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Leitlinienprogramm Onkologie

Evidenztabellen der S3-Leitlinie Endometriumkarzinom

Version 2.0 – September 2022
AWMF-Registernummer: 032/034OL

Evidenztabellen

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
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Inhalt

1. Informationen zum Dokument

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1.2. Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF), Deutschen Krebsgesellschaft e. V. (DKG) und der Stiftung Deutsche Krebshilfe (DKH).

1.3. Federführende Fachgesellschaft(en)

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

Deutsche Krebsgesellschaft (DKG)

Vertreten durch die Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)

1.4. Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

1.5. Kontakt

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1.6. Zitierweise des Dokuments

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Evidenztabellen der S3-Leitlinie Endometriumkarzinom, Version 2.0, 2022, AWMF-Registernummer: 032/034OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/ ; Zugriff am TT.MM.JJJJ).

1.7. Weitere Dokumente zu dieser Leitlinie

Dieses Dokument führt als eine gesonderte Anlage zum Leitlinienreport der S3-Leitlinie Diagnose, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom die Ergebnisse der Evidenzbewertung auf, welche auf Grundlage, der im Leitlinienreport 2.01 dargelegten Recherchen erfolgte. Die Bewertung der Evidenz findet sich hier in den Evidenztabellen ab Kapitel 2
Neben der Langversion der Leitlinie wird es die folgenden ergänzende Dokumente geben:

- Langversion der Leitlinie
- Leitlinienreport zur Leitlinie
- Kurzversion der Leitlinie
- Patientinnenleitlinie
- englische Übersetzung

Alle Dokumente zur Leitlinie sind über die folgenden Seiten zugänglich:

- Leitlinienprogramm Onkologie (https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/)
- AWMF (http://www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- Guidelines International Network (www.g-i-n.net)

1.8. Hinweise zur Evidenzbewertung

In dieser Leitlinie wurde zur Klassifikation der Evidenz das Schema des Oxford Centre for Evidence-Based Medicine in der Version von 2011 verwendet.
Quelle: Howick, J., et al. *The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document)*. 2011; Available from: http://www.cebm.net/index.aspx?o=5653.

Tabelle 1: Schema der Evidenzgradierung nach Oxford 2011

Frage	Level 1*	Level 2*	Level 3*	Level 4*	Level 5
Wie verbreitet ist das Problem?	Lokale und aktuelle Zufallsstichprobe oder Zählung (Vollerhebung)	Systematische Übersichtsarbeit von Erhebungen, die auf die lokalen Umstände übertragen werden können**	Lokale Erhebung, die nicht auf einer Zufallsstich-probe basiert**	Fallserie**	Nicht anwendbar
Ist dieser diagnostische oder kontrollierende Test genau? (Diagnose)	Systematische Übersichtsarbeit von Querschnittsstudien mit durchgehend angewandtem Referenzstandard und Verblindung	Einzelne Querschnittsstudie mit durchgehend angewandtem Referenzstandard und Verblindung	Nicht-konsekutive*** Studie oder Studie ohne angewandten Referenz-standard**	Fall-Kontroll-Studie oder Studie mit ungeeignetem oder nicht unabhängigem Referenz-standard**	Experten-meinung basierend auf pathophysio-logischen Überlegungen
Was würde passieren, wenn wir keine Therapie anwenden würden? (Prognose)	Systematische Übersichtsarbeit von Kohortenstudien, die Patienten im Anfangsstadium der Erkrankung beobachten (Inception cohort study)	Einzelne Kohortenstudie von Patienten im Anfangsstadium der Erkrankung (Inception cohort study)	Kohortenstudie oder Kontrollarm einer randomisierten Studie*	Fallserie oder Fall-Kontroll-Studie oder eine prognostische Kohorten-studie mit niedriger methodischer Qualität[1]**	Nicht anwendbar
Hilft dieses Vorgehen? (Nutzen der Intervention)	Systematische Übersichtsarbeit von randomisierten Studien oder N-von-1-Studien[2]	Randomisierte Studie oder Beobachtungs-studie mit dramatischen Effekten	Kontrollierte Kohortenstudie/Follow-up-Studie[3]**	Fallserien oder Fall-Kontroll-Studien oder Studien mit historischen Kontrollen**	Experten-meinung basierend auf pathophysio-logischen Überlegungen
Was sind häufige Nebenwir-kungen? (Schaden der Intervention	Systematische Übersichtsarbeit von entweder randomisierten Studien oder eingebetteten Fall-Kontroll-Studien[4]. Oder N-von-1-Studie mit zur Fragestellung passenden Patienten oder beobachtende Studie mit dramatischen Effekten	Randomisierte Studie oder (ausnahms-weise) Beobachtungsstudie mit dramatischen Effekten	Kontrollierte Kohortenstudie/Follow-up- Studie (Post-Marketing-Überwachung), mit ausreichender Fallzahl, um eine häufige Nebenwirkung zu identifizieren. Sollen Langzeitneben-wirkungen erfasst werden, muss das Follow-up ausreichend sein**		
Was sind seltene Nebenwir-kungen? (Nebenwir-kungen)	Systematischer Überblick über randomisierte Studien oder N-von-1-Studien	Randomisierte Studie oder (ausnahms-weise) Beobachtungsstudie mit dramatischen Effekten			
Ist dieser Früherkennungs-Test sinnvoll? (Screening)	Systematische Übersichtsarbeit von randomisierten Studien	Randomisierte Studie	Kontrollierte Kohortenstudie/Follow-up-Studie**		

Frage	Level 1*	Level 2*	Level 3*	Level 4*	Level 5

*Level kann ggf. wegen der Studienqualität, wegen ausgedehnter Konfidenzintervalle (unpräzise Effektschätzer), Inkonsistenzen zwischen Studien, oder weil der absolute Effektwert sehr klein ist, sowie wegen mangelnder Übertragbarkeit (Fragestellung der Studie entspricht nicht der klinisch relevanten Frage) abgewertet werden. Eine Aufwertung des Evidenzlevels ist möglich bei großen oder sehr großen Effekten.
** Grundsätzlich gilt: Ein systematischer Überblick ist immer besser als eine Einzelstudie.
*** Konsekutiver Einschluss = Patienten werden fortlaufend rekrutiert.
1 Zur Qualitätsbeurteilung kann u.a. das STROBE-Statement verwendet werden: http://www.strobe-statement.org/index.php?id=strobe-aims.
2 Einzelpatientenstudien, bei denen die Patienten abwechselnd Intervention und Kontrollintervention erhalten.
3 Nachbeobachtungsstudie einer Population aus einem abgeschlossenen RCT.
4 Studie, bei der aus einer laufenden Kohortenstudie Fälle und Kontrollen gezogen werden.

2. Evidenzbewertung nach Schlüsselfragen geordnet

2.1. Schlüsselfrage 01: Beeinflussen Alter, Hormonexposition, reproduktive/metabolische/physikalische/ethnische /genetische Faktoren, Körpergewicht, Rauchen und/oder Arbeitsbedingungen das Risiko für das Auftreten eines Endometriumkarzinoms?

Inhalt: *11 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Collaborative Group on Epidemiological Studies on Endometrial Cancer ,2015	3	Systematic review and meta-analysis. To investigate the association between use of oral contraceptives and the subsequent risk of endometrial cancer.
Constantine, G. D. 2019	2	Systematic review (38 studies) The aim of the study was to systematically review studies that evaluated endometrial hyperplasia or cancer incidence with unopposed vaginal estrogens.
Formoso, G. 2016	1	Systematic review and meta-analysis (42 studies) To evaluate the effectiveness and safety of tibolone for treatment of postmenopausal and perimenopausal women.
Kohler, L. N. 2016	3	Systematic review (12 studies, 3 reported endometrial cancer) to examine associations between adherence to established cancer prevention guidelines for diet and physical activity and overall cancer incidence and mortality.
Ma, X. 2018	4	Systematic review (14 studies) To assess the impact of breastfeeding and its duration on the development of endometrial cancer.
Marjoribanks, J. 2017	1	Systemtic review and meta-analysis. (22 studies) To assess effects of long-term HT (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in

Literaturstelle	Evidenzlevel	Studientyp
		perimenopausal and postmenopausal women during and after cessation of treatment.
Sjögren, L. L. 2016	2	Systematic review (28 studies) To assess the safety of estrogen plus progestin therapy according to the risk of enomtrial cnacer, while considering both regimen and type of progestin.
Skalkidou, A. 2017	3	Systematic review and meta-analysis To evaluate the association between the use of ovary-stimulating drugs for the treatment of subfertility and the risk of endometrial cancer.
Tempfer, Clemens B. 2020	2	Systematic Review of cohort studies (15), case-control studies (10) and RCT (2)
Wise, M. R. 2016	3	Systematic review and meta-analysis (9 studiees) To systematically review the literature on the association between obesity and endometrial hyperplasia or cancer in premenopausal women
Zhang, X. 2019	2	Systematic review and meta-analysis (13 studies) To assess the hypotheses that intentional weight loss is associated with lower endometrial cancer risk while weight cycling after intentional weight loss is associated with increased endometrial cancer risk.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *11 Bewertung(en)*

Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 16. 1061-1070. 2015			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis. To investigate the association between use of oral contraceptives and the subsequent risk of endometrial cancer. **Databases:** PubMed and Medline (up to Jan 31, 2012) and from review articles. **Search period:** Inception - 01/2012 **Inclusion Criteria:** Epidemiological studies were eligible for inclusion if they collected individual data about use of hormonal contraceptives and reproductive history from at least 400 women with endometrial cancer in retrospective studies, and at least 200 women in prospective studies. **Exclusion Criteria:** -	**Population:** Cases: Women with cancer (any histological type of the body of the uterus who were without previous cancer (except non-melanoma skin cancer) and controls without endometrial cancer. **Intervention:** Oral contraceptive use **Comparison:** Non-use of contraceptives.	**Primary:** Cancer risk attributed to contraceptives. **Secondary:** - **Results:** Only summary reported here, rest see article. **Study overview:**The median age of cases was 63 years (IQR 57–68) and the median year of cancer diagnosis was 2001 (IQR 1994–2005). 9459 (35%) of 27.276 cases and 45.625 (39%) of 115.743 controls had ever used oral contraceptives, for median durations of 3.0 years (IQR 1–7) and 4.4 years (IQR 2–9), respectively. **Results:** The longer that women had used oral contraceptives, the greater the reduction in risk of endometrial cancer; every 5 years of use was associated with a risk ratio of 0.76 (95% CI 0.73–0.78; p **Author's Conclusion:** Use of oral	BCDDP 2005, Netherlands Cohort 2004, NHS 1994, CNBSS 2002, IWHS 2001, Shanghai Breast Self-Examination 2006, MEC 2007 , NIH-AARP 2013, EPIC 2010, Women's Health Study 2005, MISS 2009, Swedish Women's Lifestyle and Health Cohort 2007 , Swedish Mammography Cohort 2009, Million Women Study 2005, CASH 1987, Brinton 1993, Pike 1997, Newcomb 2003, Weiderpass 1 1999 Weiderpass 2 2000, Rebbeck 2006, Shu 2006, Brinton/Lissowska 2007, Friedenreich 2014, ANECS 2011, Antunes 1979, Rosenberg 1980, WHO 1988, La Vecchia 1984, Moysich 2005, Levi 1991, Negri 1998, Dal Maso 2005, Urban 2012 , Aichi 1999.

Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 16. 1061-1070. 2015			
		contraceptives confers long-term protection against endometrial cancer. These results suggest that, in developed countries, about 400 000 cases of endometrial cancer before the age of 75 years have been prevented over the past 50 years (1965–2014) by oral contraceptives, including 200 000 in the past decade (2005-2014)	
Methodical Notes			
Funding Sources: Medical Research Council, Cancer Research UK. **COI:** "We declare no competing interests." **Study Quality:** Not investigated. **Heterogeneity:** Investigated, but not with I2 statistics. Significant heterogeneity for The proportional reduction in risk of endometrial cancer per 5 years of oral contraceptive analysis. **Publication Bias:** Not investigated "Only a third of the eligible studies have published on oral contraceptives and endometrial cancer so a review based solely on these studies could be aff ected by publication bias." **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies **Downgrade to evidence level 3.** No evaluation of study quality or publication bias. Heterogeneity present in some analyses, but not quantified by I2 statistic.			

Constantine, G. D. et al. Endometrial safety of low-dose vaginal estrogens in menopausal women: a systematic evidence review. Menopause. 26. 800-807. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review (38 studies) The aim of the study was to systematically review studies that evaluated endometrial hyperplasia or cancer incidence with unopposed vaginal estrogens. **Databases:** PubMed, EMBASE, and Clinicaltrials.gov searched for for journal articles, conference abstracts in the English language. **Search period:** Inception -08/2017. **Inclusion Criteria:** Studies (RCTs and observatioal) using vaginal estrogens in menopausal women for any reason (eg, vulvar and vaginal atrophy, urinary incontinence, pelvic organ prolapse, and recurrent urinary tract infections). Endometrial histology was required to identify cases of endometrial cancer or endometrial hyperplasia, except for larger cohort studies in which incidence rates were reported. Citations were included for	**Population:** Menopausal women. **Intervention:** Vaginal estrogens products (indications vulvar and vaginal atrophy, urinary incontinence, pelvic organ prolapse, and recurrent urinary tract infections). Different applications and formulations. **Comparison:** Placebo or non-exposure	**Primary:** endometrial cancer or endometrial hyperplasia identified by histology. **Secondary:** - **Results:** Only summary described here due to length: **Study overview:** Of 5,593 abstracts from the literature search and 47 articles from other sources, 36 articles and 2 abstracts were eligible, describing 20 randomized controlled studies, 8 interventional studies, and 10 observational studies. **Results:** Rates of endometrial cancer and hyperplasia were 0.03% and 0.4%, respectively, from 20 randomized controlled trials (2,983 women) of vaginal estrogens. Overall, reports of endometrial hyperplasia were observed with various doses and durations and appeared sporadic (except 1.25mg conjugated equine estrogens), consistent with endometrial hyperplasia rates in the general population.	Constantine 2017, Rahn 2014, Bachmann 2009, Freedman 2009, Simon 2008, Simon 2010, Study VAG 2195, Bachmann 2008, Vesna 2006, Weisberg 2005, Pinkerton 2003, Manonai 2001, Cardozo 2001, Rioux 2000, Barentsen 1997, Henriksson 1996, Nachtigall 1995.

Constantine, G. D. et al. Endometrial safety of low-dose vaginal estrogens in menopausal women: a systematic evidence review. Menopause. 26. 800-807. 2019			
full-text review if it was not stated or clear from the abstract if any endometrial histologic data were reported, including but not limited to endometrial cancer, hyperplasia, or proliferation. From the full text review, primary studies were eligible for review if they reported endometrial histology data obtained from a biopsy in menopausal women using vaginal estrogens, or incidence of endometrial cancer and/or hyperplasia in menopausal women who used vaginal estrogens from larger cohort studies. **Exclusion Criteria:** Articles were excluded if they reported no use of vaginal estrogen, use of vaginal ring with a progestogen, exclusive use of estriol or other non-US-approved estrogen, no endometrial histology, or unrelated content. General reviews or editorials, abstracts of studies now fully published, or duplicate publications were also excluded. No studies reporting endometrial histology in women using vaginal estrogens were excluded.		A Denmark registry study was an exception and may be of limited applicability to the United States. The Women's Health Initiative Observational Study showed no association (1.3 cases/1,000 women-years with vaginal estrogens versus 1.0/1,000 women-years for nonuse). Collectively, the studies did not support an increased risk of endometrial hyperplasia or cancer with low-dose vaginal estrogens. **Author's Conclusion:** The evidence assessed as part of this systematic literature review does not support an increased risk of endometrial hyperplasia or endometrial cancer with vaginal estrogens. Longer-term data may help confirm the endometrial safety profile of vaginal estrogens found in this systematic review.	
Methodical Notes			

Constantine, G. D. et al. Endometrial safety of low-dose vaginal estrogens in menopausal women: a systematic evidence review. Menopause. 26. 800-807. 2019

Funding Sources: None reported.

COI: Research support and stock options of pharmaceutical companies. See article.

Study Quality: Quality of primary studies not investigated.

Heterogeneity: Not applicable.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of RCTS and cohort studies. (no seperate RCT analysis)
Quality of primary studies not investigated.

Formoso, G. et al. Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and meta-analysis (42 studies) To evaluate the effectiveness and safety of tibolone for treatment of postmenopausal and perimenopausal women. **Databases:** Gynaecology and	**Population:** Menopausal and perimenopausal women with or without vasomotor and/or genital symptoms, defined as women with surgical menopause or with spontaneous menopause, or women who had menstruated irregularly over the past 12 months.	**Primary:** · Vasomotor symptoms measured as occurrences or through scales, defined as any otherwise unexplained sensation of flushing/sweating experienced by the participant. We included studies that measured hot flushes, provided that they measured hot flushes as an outcome of efficacy in	42 studies included: Al-Azzaqi 1999, Archer 2007, Baracat 2002, Benedek-Jaszmann 1987, Berning 2000, Bouchard 2012, Cummings 2008, de Aloysio 1998, Doren 1999, Egarter 1996, Elfituri 2005, Gallagher 2001, Gupta

Formoso, G. et al. Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016			
Fertility Group (CGF) Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and PsycINFO (from inception), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and clinicaltrials.gov. We checked the reference lists in articles retrieved. **Search period:** Inception - 10/2015 **Inclusion Criteria:** We included randomised controlled trials (RCTs) comparing tibolone versus placebo, oestrogens and/or combined hormone therapy (HT) in postmenopausal and perimenopausal women. **Exclusion Criteria:** Quasi-randomised studies. Trials with alternating allocation.	**Intervention:** Tibolone **Comparison:** · placebo, · oestrogens · combined HT (referring to two different formulations: sequential combined and continuous combined)	populations including symptomatic women · Unscheduled bleeding (vaginal bleeding and/or spotting) · Long-term adverse events: endometrial cancer, breast cancer, venous thromboembolic events, cardiovascular events, cerebrovascular events, mortality from any cause **Secondary:** · Insomnia (frequency or continuous outcome) · Genital symptoms: vaginal dryness and painful sexual intercourse (measured as frequency or severity), vaginal infection (inflammation of the vagina usually related to one of three infectious conditions: bacterial vaginosis, vulvovaginal candidiasis, trichomoniasis), urinary tract infection · Endometrial hyperplasia **Results:** Only summary reported, rest see article. **Study characteristics** 46 RCTs	2013, Hammar 1998 Hammaer 2007, Hänggi 1997, Huber 2002, Jacobson 2012, Kenemans 2009, Kökcü 2000, Kroiss 2005, Kubista 2007, Landgren 2002, Langer 2006, Meeuwsen 2002, Mendoza 2000, Mendoza 2002, Morais-Socorro 2012, Nappi 2006, Nathorst-Böös 1997, Niljand 2009, Okon 2005, Osmanagaoglu 2006, Polisseni 2013, Ross 1999, Roux 2002, Siseles 1995, Swanson 2006, Uygur 2005, Vieira 2009, Volpe 1986, Wender 2004, Winkler 2000, Wu 2001, Ziaei 2010.

Formoso, G. et al. Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		included, which included 19,976 postmenopausal women. Most studies evaluated tibolone for treatment of menopausal vasomotor symptoms. Some studies reported other objectives: Four RCTs aimed to assess endometrial safety, four bleeding patterns, five bone loss or fracture prevention, one sexual outcomes and three safety in women with a history of breast cancer; two studies examined use of tibolone in women with fibroids or lupus erythematosus. **Key results:** Moderate-quality evidence suggests that tibolone is more effective than placebo and less effective than combined hormone therapy (HT) in reducing vasomotor symptoms in postmenopausal women. Data suggest that if 67% of women taking placebo experience vasomotor symptoms, then between 35% and 45% of women taking tibolone will do so; and if 7% of women taking combined HT experience vasomotor symptoms, then between 8% and		

Formoso, G. et al. Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		14% of women taking tibolone will do so. Moderate-quality evidence also suggests that tibolone is associated with a higher rate of unscheduled bleeding than placebo, but a lower rate than HT. Compared with placebo, tibolone increases the risk of recurrent breast cancer in women with a history of breast cancer, and may increase the risk of stroke in women over 60 years of age. No evidence suggests that tibolone increases the risk of other serious adverse events, and no evidence shows differences between tibolone and HT with respect to long-term adverse events. Nearly all evidence on adverse events was of very low quality, and reported events were scarce. **Quality of the evidence:** Much of the evidence obtained was of low or very low quality. Limitations included high risk of bias in the included trials, very low event rates and potential conflicts of interest. 26 of the studies were financed by drug manufacturers, and another 14		

Formoso, G. et al. Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		studies failed to disclose their source of funding. **Author's Conclusion:** Moderate-quality evidence suggests that tibolone is more effective than placebo and is less effective than combined hormone therapy (HT) in treating vasomotor symptoms. Tibolone is associated with a higher rate of unscheduled bleeding than placebo but a lower rate than combined HT. Compared with placebo, tibolone increases the risk of recurrent breast cancer in women with a history of breast cancer, and may increase the risk of stroke in women over 60 years of age. No evidence indicates that tibolone increases the risk of other longterm adverse events, and no evidence has revealed a difference between tibolone and HT with respect to long-term adverse events. Many of the included randomised controlled trials (RCTs) were of low or very low quality. Limitations		

Formoso, G. et al. Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		included high risk of bias in the included trials, very low event rates and potential conflicts of interest. Twenty-four studies were financed by drug manufacturers, and another 10 failed to disclose their source of funding.		
Methodical Notes				
Funding Sources: Internal sources · Emilia-Romagna Health and Social Policies Directorate, Italy. Emilia-Romagna Health and Social Policies Directorate, Italy, provided the salary for reviewers External sources · Cochrane Gynaecology and Fertility Group, New Zealand. Provided feedback and support during the whole review process; provided bibliographic support **COI:** None known. **Study Quality:** Cochrane risk of bias tool was used to assess individual study quality. Overall quality of the body of evidence for each outcome was assesed by GRADE. "Much of the evidence obtained was of low or very low quality. Limitations included high risk of bias in the included trials, very low event rates and potential conflicts of interest. Twenty-six of the studies were financed by drug manufacturers, and another 14 studies failed to disclose their source of funding." **Heterogeneity:** We included in the meta-analysis all outcomes reported by individual studies, noting heterogeneity by using Chi2 and I2 statistics (Higgins 2002). We stated that the Chi2 statistic was statistically significant if P < 0.10. The I2statistic indicated the percent of variability due to between-study (or interstudy) variability, as opposed to within-study (or intrastudy) variability. We considered an I2value greater than 50% to be large.				

Formoso, G. et al. Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016			
"Heterogeneity among studies is notable, but for the comparison versus placebo, we appear to explain much of it as the result of dose e,ects and artificially large estimates due to attrition bias in several studies. Substantial heterogeneity remains for the comparison versus HT, which we cannot explain." **Publication Bias:** Funnel plot analyses were not helpful to review authors in assessing the presence of publication bias, given the relative scarcity of studies and data. Vasomotor symptoms and unscheduled bleeding were the only outcomes with sufficient RCTs to permit such an assessment, which revealed no evidence of bias for this outcome. As for the other outcomes, we cannot exclude the occurrence of publication bias because the drug manufacturer, who sponsored almost all of the published RCTs, was asked for possibly unpublished data but provided no written response **Notes:** Oxford level of evidence: 1 Systematic review and meta-analysis. A large amount of unclear/high risk of bias in the included studies, overall quality of evidence was very low-moderate.			
Kohler, L. N. et al. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. Cancer Epidemiol Biomarkers Prev. 25. 1018-28. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review (12 studies, 3 reported endometrial cancer) to examine associations between adherence to established cancer prevention guidelines for diet and physical activity and overall	**Population:** No description in the inclusion criteria. Included studies report men and women. **Intervention:** physical activity and diet. generated	**Primary:** Overall cancer incidence and cancer mortality. **Secondary:** **Results:** Only endometrial cancer reported here, rest see article:	12 studies (3 reported endometrial cancer). McCullough 2011, Thomson 2014, Kabat 2015, Hastert 2013, Hastert 2014,

Kohler, L. N. et al. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. Cancer Epidemiol Biomarkers Prev. 25. 1018-28. 2016			
cancer incidence and mortality. **Databases:** PubMed, Google Scholar, and Cochrane Reviews databases were searched following the current recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis Approach (PRISMA). **Search period:** inception -03/2016. **Inclusion Criteria:** Only prospective cohort studies were eligible for inclusion, as the focus was to ascertain cancer incidence and cancer mortality. Minimally, studies must have collected data for physical activity and diet, generated an adherence score on the basis of either ACS or WCRF/AICR cancer prevention guidelines (2, 12), and reported cancer outcomes of incidence and/or mortality to be deemed eligible for this review. Overall cancer incidence and cancer mortality were the primary outcomes of interest. However, sitespecific cancer risks were also considered when data were available from at least two studies meeting the eligibility criteria.	an adherence score on the basis of either ACS or WCRF/AICR cancer prevention guidelines **Comparison:**	**Results:**Endometrial cancer To date, 3 prospective studies have reported results for the association between nutrition and physical activity guideline adherence and endometrial cancer incidence. The large NIHAARP and EPIC cohorts both found significant inverse associations demonstrated by higher adherence and lower risk of endometrial cancer (HR, 0.40; 95% CI, 0.34–0.46; HR, 0.77; 95% CI, 0.62–0.94), respectively (27, 28); whereas findings from the WHI cohort suggest no significant association (HR, 0.73;95%CI, 0.49– 1.09; ref. 25). Although analysis of the adherence score as a categorical variable (high vs. low) in the latter study was not statistically significant for risk of endometrial cancer, the overall trend using ACS score as an ordinal variable (0–8 points) suggested a significant 7% reduction in endometrial cancer incidence (HR, 0.93; 95% CI, 0.87–0.98; ref. 25). **Author's Conclusion:** "In conclusion,	Makarem 2015, Harris 2016, Catsburg 2014, Vergnaud 2013, Romaguera 2012.

Kohler, L. N. et al. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. Cancer Epidemiol Biomarkers Prev. 25. 1018-28. 2016				
Exclusion Criteria: Commentaries and summary documents were excluded unless they presented additional data.		strong and consistent evidence from 10 large prospective cohorts in 12 publications indicates that adherence to ACS and WCRF/AICR cancer prevention guidelines was associated with significant reductions in cancer incidence and cancer mortality for both men and women. In addition, significant inverse associations were consistently found between guideline adherence and breast, colorectal, and endometrial cancer incidence. Adherence to a pattern of healthy behaviors, as outlined in cancer prevention guidelines from either the ACS or WCRF/AICR, may reduce cancer incidence and mortality."		
Methodical Notes				
Funding Sources: L.N. Kohler, D.J. Roe, and E.T. Jacobs were supported by NCI Cancer Center Support Grant No. CA023074 at the University of Arizona (Principal Investigator: Dr. Andrew Kraft, Director, Cancer Center Division, University of Arizona, Tuscon, AZ) for this work. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact. **COI:** No potential conflicts of interest were disclosed				

Kohler, L. N. et al. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. Cancer Epidemiol Biomarkers Prev. 25. 1018-28. 2016

Study Quality: The Critical Appraisal Skills Programme's Making sense of evidence was the predetermined tool used to assess the risk of bias. The tool was used to assess recruitment procedures, measurement of exposure, confounding variables, study outcomes, and generalizability.
Outcomes of this assesment are not reported in the article.

Heterogeneity: not applicable, no meta-analysis was performed.

Publication Bias: "Finally, the potential for publication bias is always of concern. Studies with significant findings are more likely to be published than those with null or unimportant findings. Grey literature was included in the search via Google Scholar in an attempt to capture any work that hasn't been formally published

Notes:
Oxford level of evidence: 2 Systematic review of cohort studies
Downgrade to evidence level 3
Lacking description of inclusion criteria (what is the population?); study quality assesed but not reported.

Ma, X. et al. Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies. Eur J Cancer Prev. 27. 144-151. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic review (14 studies) To assess the impact of breastfeeding	Population: Women Intervention: breastfeeding	**Primary:** Endometrial cancer **Secondary:** - **Results:** Only summary presented here, rest	14 studies included: Sugawara 2013, Dossus 2010, Zuchetto 2009, Brinton 2007 Okamura 2006, Wernli

Ma, X. et al. Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies. Eur J Cancer Prev. 27. 144-151. 2018				
and its duration on the development of endometrial cancer. **Databases:** We performed a systematic literature search of articles published in PubMed, Embase, and Web of Knowledge. We also searched the reference lists of relevant publications for more studies. **Search period:** Inception - 02/ 2015. **Inclusion Criteria:** Studie were included if they (i) had a case–control or cohort design; (ii) evaluated the association between breastfeeding and the risk of EC; and (iii) presented relative risks (RRs), odds ratios (ORs) or hazard ratios, and corresponding 95% confidence intervals (CIs). **Exclusion Criteria:** Excluded if studies (i) non-English language; (ii) not an original article, such as review, letters, comments, etc.; and (iii) repetitive data on the same population; we used the publication	Comparison: No breastfeeding	see article. **Study overview:** A total of 14 articles, comprising 11 case–control and three cohort studies, were included in the final analysis **Results:** Dose–response analysis was carried out for every 6-month increase in the duration of breastfeeding in relation to the risk of endometrial cancer. Three prospective and 11 case–control studies were included in this meta-analysis. The pooled estimates for ever compared with never breastfeeding and the longest duration of breastfeeding compared with the shortest were 0.91 [95% confidence interval (CI): 0.75–1.09] and 0.76 (95% CI: 0.59–0.98). The risk of endometrial cancer decreased by 7% for every 6-month increase in the duration of breastfeeding (relative risk: 0.93; 95% CI: 0.88–0.97). This study provides evidence that ever breastfeeding, particularly a longer duration of breastfeeding, is associated with a lower risk of endometrial cancer. **Author's Conclusion:** In conclusion, findings from this meta-analysis suggest that breastfeeding, particularly a longer duration	2006, Herrinton 2001, Newcomb and Trentham-Dietz 2000, Hirose 1999, Salazar-Martinez 1999, Rossenblatt and Thomas 1995, Brinton 1992, Cusimano 1989, Elwood 1977.	

Ma, X. et al. Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies. Eur J Cancer Prev. 27. 144-151. 2018				
with the most applicable information or the largest number of cases.		of breastfeeding, was associated inversely with the risk of EC. Furthermore, the inverse association occurs in a duration-dependent manner. These results add to the evidence that women with a longer duration of breastfeeding are likely to gain beneficial health consequences.		
Methodical Notes				
Funding Sources: This work was supported by the fund of the Shanghai Health Bureau Key Disciplines and Specialties Foundation. **COI:** There are no conflicts of interest. **Study Quality:** To assess each study quality, a nine-star system on the basis of the Newcastle–Ottawa Scale. A high-quality study was defined with a score of at least 7. 6 case–control studies and 2 cohort studies were considered high-quality studies. **Heterogeneity:** We evaluated the heterogeneity using the Cochrane Q statistic, where a P-value less than 0.1 was indicative of statistically significant heterogeneity, and the I2 statistic (Higgins and Thompson, 2002). Summary RRs and 95% CIs were calculated using a random-effects model when the heterogeneity was significant and a fixed-effects model was used otherwise. Heterogeneity between subgroups was evaluated by a meta-regression. Significant heterogeneity among the results of the studies was found in our analysis. There may be two potential explanations for the heterogeneity observed between studies. First, the longest and the shortest category of duration of breastfeeding varied between studies. The longest category varied from greater than 12 months to more than 72 months and the shortest category varied from never to up to 12 months **Publication Bias:** Potential publication bias was detected using Egger's regression asymmetry test.				

Ma, X. et al. Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies. Eur J Cancer Prev. 27. 144-151. 2018			
Publication bias may have influenced the results. We could not detect any evidence of publication bias. However, tests for publication bias have low statistical power, especially when the number of studies is limited (n=14) **Notes:** Oxford level of evidence: 3 Systematic review and meta-analysis of case control and cohort studies **Downgrade to evidence level 4.** Missing description of the aim of the study. Analysis of ever vs. never breastfeeeding was not significantly in favor of breastfeeding with CI overlapping 1, which the authors do not discuss. Results for study quality/risk of bias were assessed but not reported for each individual study. Heterogeneity of I2>50% present in both analyses.			
Marjoribanks, J. et al. Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. . . 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systemtic review and meta-analysis. (22 studies) To assess effects of long-term HT (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women during	**Population:** Perimenopausal or postmenopausal women recruited from any healthcare setting or a populationbased sample. Perimenopausal women were defined as women who had not yet had their finalmenstrual period but were in the transitional period between more-or-less regular cycles of ovulation andmenstruation and complete cessation of these cycles. Postmenopausal women were defined as	**Primary:** 1. Death from any cause (total mortality). 2. Cause-specific mortality. 3. Coronary events (myocardial infarction or coronary death). 4. Stroke (ischaemic or haemorrhagic) or transient ischaemic attack (TIA). 5. Venous thromboembolism (pulmonary embolism or deep vein thrombosis). 6. Breast cancer. 7. Colorectal cancer. 8. Lung cancer.	22 total included with the previous verrsion: Barakat 2006, ELITE 2014, EPAT 2001, EPHT 2006, ERA 2000, ESPRIT 2002, EVTET 2000, Ferenczy 2002, Greenspan 2005, HERS 1998, KEEPS 2012, Mlnard 2000, Nachtigall

Marjoribanks, J. et al. Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. . . 2017				
and after cessation of treatment. **Databases:** We searched the following databases to September 2016: Cochrane Gynaecology and Fertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and PsycINFO. We searched the registers of ongoing trials and reference lists provided in previous studies and systematic reviews. **Search period:** Inception - 09/2016. **Inclusion Criteria:** Randomised double-blinded studies of HT versus placebo, taken for at least 1 year by perimenopausal or postmenopausal women. HT included oestrogens, with or without progestogens, via the oral, transdermal, subcutaneous or intranasal route. **Exclusion Criteria:** We excluded studies with co-interventions that	women with surgical menopause (removal of both ovaries) and women with spontaneous menopause and amenorrhoea for longer than 12 months. Studies included women both with and without a prior history of disease (e.g. cardiovascular disease, fracture, osteoporosis). **Intervention:** All oestrogens, with and without progestogens, administered by oral, transdermal, subcutaneous or intranasal routes, and given as perimenopausal or postmenopausal therapy for any reason for 12 months or longer **Comparison:** Placebo.	9. Endometrial cancer. 10. Ovarian cancer. 11. Gallbladder disease. 12. Fractures (hip fracture, clinically diagnosed vertebral fracture, total clinically diagnosed fracture). 13. Cognitive function (using global measures) or dementia (including Alzheimer's disease) as measured in the included studies. **Secondary:** - **Results: Study overview:** This review included 22 double-blinded randomised controlled trials (RCTs) (43,637 women). **Results:** In relatively healthy postmenopausal women, using combined continuous HT for 1 year increased the risk of a heart attack from about 2 per 1000 to between 3 and 7 per 1000, and increased the risk of venous thrombosis (blood clot) from about 2 per 1000 to between 4 and 11 per 1000. With longer use, HT also increased the risk of stroke, breast cancer, gallbladder disease and death from	1979, Notelovitz 2002, Obel 1993, PEPI 1995, Tierney 2009, WAVE 2002, WEST 2001, WHI 1998, WISDOM 2007, Yaffe 2006	

Marjoribanks, J. et al. Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. . . 2017				
might potentially affect the outcomes being measured and studies of topical vaginal HT creams, topical tablets and rings. These interventions are covered in another Cochrane review (Suckling 2006). Our rationale for excluding trials of less than 1 year's duration is that we considered such trials unlikely to be long enough for investigators to report intervention-related clinical events.		lung cancer. Oestrogen-only HT increased the risk of venous thrombosis after 1 to 2 years' use: from 2 per 1000 to 2 to 10 per 1000. With longer use, it also increased the risk of stroke and gallbladder disease, but it reduced the risk of breast cancer (after 7 years' use) from 25 per 1000 to between 15 and 25 per 1000. Among women over 65 years of age taking continuous combined HT, the incidence of dementia was increased. Risk of fracture was the only outcome for which results showed strong evidence of clinical benefit from HT (both types). Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of		

Marjoribanks, J. et al. Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. . . 2017				
		cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with a uterus). The risk of endometrial cancer for women with a uterus who take oestrogen-only HT is well documented. HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HT is considered effective for prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable. Data are insufficient for assessment of the risk of long-term HT use in perimenopausal women or postmenopausal women younger than 50 years of age. **Quality of the evidence** For most		

Marjoribanks, J. et al. Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. . . 2017				
		studies, risk of bias was low in most domains and the overall quality of the evidence was moderate. The main limitation was that only about 30% of women were 50 to 59 years old at baseline - the age at which women are likely to consider HT for vasomotor symptoms. **Author's Conclusion:** HT for women with menopausal symptoms Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harmarising fromshort-termuse of low-dose HT, provided they do not have specific contraindications. HTmay be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (e.g. obesity, history of venous thrombosis) or increased risk of some types of cancer (e.g. breast cancer in women with a uterus).		

Marjoribanks, J. et al. Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. . . 2017				
		The risk of endometrial cancer among women with a uterus taking oestrogenonly HT is well documented. Although none of the studies included in this review focused specifically on women in the age group most likely to require menopausal symptom relief, subgroup analyses inWHI 1998 suggested that among relatively healthy women in their 50s taking oestrogen-only or combined HT, the only significant risk was increased incidence of venous thromboembolism in those taking combinedHT.Absolute risk of venous thromboembolismwas low, at 0.5% overall for a woman taking HT for 5 years. For women in their 50s without a uterus, taking oestrogen-only HT for 5 to 6 years appears relatively safe and may even confer some health benefits. However, safety over longer-term use is unknown.		

Marjoribanks, J. et al. Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. . . 2017

Methodical Notes

Funding Sources: Internal sources
· University of Auckland, New Zealand.
External sources
· None, Other.

COI: Declared. One author is sharholder /director of a gynaecological clinica and received expenses from ESHRE OR ASRM.

Study Quality: Two review authors independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool.
We prepared 'Summary of findings' tables using GRADEpro and Cochrane methods.
For most studies, risk of bias was low in most domains and the overall quality of the evidence was moderate. The main limitation was that only about 30% of women were 50 to 59 years old at baseline - the age at which women are likely to consider HT for vasomotor symptoms.
GRADE quality was considered to be moderate for all outcomes.

Heterogeneity: We consideredwhether clinical andmethodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary, and if this was not the case, we planned to refrain from pooling the data.We assessed statistical heterogeneity by measuring the I2statistic. We regarded I2 greater than 50% as indicating substantial heterogeneity.

Publication Bias: Investigated and considere in the GRADE summary of finding.grade

Notes:
Oxford level of evidence: 1 Systemtic review and meta-analysis.
Publication bias was considered for the GRADE summary of findings, but not reported.

Sjögren, L. L. et al. Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Maturitas. 91. 25-35. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review (28 studies) To assess the safety of estrogen plus progestin therapy according to the risk of enomtrial cnacer, while considering both regimen and type of progestin. **Databases:** PubMed, Embase, Cochrane library. **Search period:** 2012 - 03/2016. **Inclusion Criteria:** Women with an intact uterus being treated with systemic hormone therapy for menopausal symptoms. Studies on any combination of unopposed estrogen, continous and sequential combined estrogen, plus progestin, tibolone compared with placebo or never-users were incluede. Only oral regimens and treatment lasting at east a year were considered in this review. Outcome was risk of endometrial cancer,	**Population:** Women with an intact uterus being treated with systemic hormone therapy for menopausal symptoms. **Intervention:** Studies on any combination of unopposed estrogen, continous and sequential combined estrogen plus progestin, tibolone compared with placebo or never-users were inclueded. **Comparison:** See interventions.	**Primary:** Risk of endometrial cancer, meaasured as relative risk, odds or hazard ratio. **Secondary:** - **Results: Study overview:** PubeMed, Embase and Cochrane library were seraches, resulting in the identification of 527 published articles on menopausal women with intact uteri treated with estrogen only, estrogen plus progestin or tibolone for a minimum of one years. Risk of endometrail cancer was compered to placebo or never users and measured as relative risk, hazard or odds ratio. 28 studies were included. **Results:** The observational literautre found an increased risk amoing users of estrogen alone. Continous combined therapy showed a lower risk than sequentail combined therapy. The newer marked micronized progsterone increased the risk	RCTs (n=11) Cherry, Kenemans, Cummings, Langer, Ferenczy, Gallagher, Byarlsen, Hulley, Rossouw, PEPI, Nachtigall, Observational studies (n=14): Morch, Fournier, Trabert, Allen, Canchola, Karageorgi, Lacey, Beral, de Vries, Bakken, Pukkala, Persson, Sourander, Paganini-Hill.

Sjögren, L. L. et al. Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Maturitas. 91. 25-35. 2016				
meaasured as relative risk, odds or hazard ratio. All Cochrane relevant reviews as well as all randomized controlled trials published hereafter and all obervational studies were included. Studies in English, French, Spanish or the Scandinavian languages were considered. UNpublished literature was not achieved. **Exclusion Criteria:** Participants were exluded if carrier of BRCA1 and 2 genes or if history of current or prior gynecological cancers, breast cancers, hysterectomy or hormonal therapy within one month prior to the beginning of the study. SERM and anstiestrogens were not considered. Studies with no disctinction between unopposed estrogen and combined estrogen plus progestin hterapy were excluded. Case control studies were excluded.		notably, also when administered continously. In most studies, tibolone was associated with an increased risk. **Author's Conclusion:** The literature indicates that use of estrogen alone, tibolone and sequential combined therapy increases risk of cancer, even when treatment lasts less than 5 years. Continous combined therapy might present a lower risk than never use, and therapy for more than 10 years dies not increase risk. Micronized progesterone increases the risk of endometrial cancer regardless of regimen.		
Methodical Notes				
Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. **COI:** The co-authors have authored one of the studies included in this review.				

Sjögren, L. L. et al. Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Maturitas. 91. 25-35. 2016

Study Quality: Study quality was evaluated by SIGN50 chekclist for RCTs or cohort studies. Quality was also assesed by GRADE.
Quality of RCTs: 5 studies were considered high, 5 as moderate and one of low quality of evidence. Cohort studies: 3 high, 10 moderate and 1 low quality study.

Heterogeneity: no meta-analysis was performed.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review of RCTs and oberservational studies.
Selection and extraction of study data was only performed by a single author.

Skalkidou, A. et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3. Cd010931. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis To evaluate the association between the use of ovary-stimulating drugs for the treatment of subfertility	**Population:** Women 18 years of age or older, with existing endometrium/uterine body. Women with preexisting cancer diagnoses of any type were excluded, along with women who had undergone fertility preservation treatment after receiving a cancer diagnosis.	**Primary:** Incidence of endometrial (uterine) cancer, clinically or histologically confirmed, at any time following treatment for subfertility. **Secondary:** Incidence of endometrial hyperplasia (complex, simple atypical, and complex atypical).	Benshushan 2001, Brinton 2013a, Brinton 2013b, Calderon-Margalit 2009, Dor 2002, Dos Santos Silva 2009, Doyle 2002, Jensen 2009, Kessous 2016, Klip 2004, Kristiansson 2007, Lerner-Geva 2012, Luke

Skalkidou, A. et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3. Cd010931. 2017			
and the risk of endometrial cancer. **Databases:** A search was performed in CENTRAL, MEDLINE (Ovid) and Embase (Ovid), OpenGrey, ProQuest, ClinicalTrials.gov, ZETOC and reports of major conferences was also performed. **Search period:** Inception - 07/2016 **Inclusion Criteria:** Cohort and case-control studies reporting on the association between endometrial cancer and exposure to ovary-stimulating drugs for subfertility in adult women were deemed eligible. **Exclusion Criteria:** Case series, case reports and in	**Intervention:** Any of the following regimens, offered alone or in combination, was considered as the exposure: clomiphene citrate (CC), gonadotropins, hCG and GnRH agonists/antagonists. Outcomes in subfertile women treated with these agents were compared with those of subfertile women who received no intervention and with those of control groups of women who had no fertility problems **Comparison:** see intervention.	**Results:** Summary results displayed here due to length, rest see article. **Study overview:** 19 studies were eligible for inclusion (1,937,880 participants). Overall, the quality of evidence was very low, due to serious risk of bias and indirectness (non-randomised studies (NRS), which was reflected on the GRADE assessment. **Results:** 6 eligible studies, including subfertile women, without a general population control group, found that exposure to any ovarystimulating drug was not associated with an increased risk of endometrial cancer (RR 0.96, 95% CI 0.67 to 1.37; 156,774 participants; very low quality evidence). Fifteen eligible studies, using a general population as the control group, found an increased risk after exposure to any ovary-stimulating drug (RR 1.75, 95% CI 1.18 to 2.61; 1,762,829 participants; very low quality evidence). 5 eligible studies, confined to subfertile women (92,849 participants), reported on exposure to clomiphene citrate; the	2015, Parazzini 2001, Parazzini 2010, Potashnik 1999, Reigstad 2015, Venn 1999, Yli-Kuha 2012.

Skalkidou, A. et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3. Cd010931. 2017				
vitro and animal studies were excluded.		pooled studies indicated a positive association (RR 1.32; 95% CI 1.01 to 1.71; 88,618 participants; very low quality evidence), although only at high dosage (RR 1.69, 95% CI 1.07 to 2.68; two studies; 12,073 participants) and at a high number of cycles (RR 1.69, 95% CI 1.16 to 2.47; three studies; 13,757 participants). Four studies found an increased risk of endometrial cancer in subfertile women who required clomiphene citrate compared to a general population control group (RR 1.87, 95% CI 1.00 to 3.48; four studies, 19,614 participants; very low quality evidence). These data do not tell us whether the association is due to the underlying conditions requiring clomiphene or the treatment itself. Using unexposed subfertile women as controls, exposure to gonadotropins was associated with an increased risk of endometrial cancer (RR 1.55, 95% CI 1.03 to 2.34; four studies; 17,769 participants; very low quality evidence). The respective analysis of two studies (1595 participants) versus the general		

Skalkidou, A. et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3. Cd010931. 2017				
		population found no difference in risk (RR 2.12, 95%CI 0.79 to 5.64: very low quality evidence). Exposure to a combination of clomiphene citrate and gonadotropins, compared to unexposed subfertile women, produced no difference in risk of endometrial cancer (RR 1.18, 95% CI 0.57 to 2.44; two studies; 6345 participants; very low quality evidence). However, when compared to the general population, an increased risk was found , suggesting that the key factor might be subfertility, rather than treatment (RR 2.99, 95% CI 1.53 to 5.86; three studies; 7789 participants; very low quality evidence). **Author's Conclusion:** "The available data was of very low quality and at significant risk of bias, since it is known that subfertile women have risk factors for endometrial cancer that are independent of treatment for subfertility. It seems that the exposure to clomiphene citrate as an ovarystimulating drug in subfertile	

Skalkidou, A. et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3. Cd010931. 2017				
		women may be associated with an increased risk of endometrial cancer, especially at higher doses (more than 2000 mg) and higher number of cycles (7 or more cycles). Evidence regarding exposure to gonadotropins is even less conclusive. It is therefore difficult to give any certainty about the safety of subfertility treatments. Contemporary guidelines already recommend treatment with clomiphene citrate as the first line of treatment for up to 12 months only for women with World Health Organization Group II ovulation disorders (hypothalamic pituitary dysfunction), such as PCOS (NICE 2013). These data should not prevent women from seeking treatment of subfertility, but they should be aware of their underlying increased risk of endometrial cancer and adopt lifestyle changes to reduce their risk, such as weight loss and adequate endometrial protection with progesterones, should they have oligomenorrhoea due to PCOS."		

Skalkidou, A. et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3. Cd010931. 2017

Methodical Notes

Funding Sources: Internal sources
· None, Other.
External sources
· None, Other.

COI: declared, academic interests only.

Study Quality: The risk of bias was assessed in accordance with relevant sections of the Cochrane Handbook, which includes assesment of individual study quality with the Cochrane risk ob bias tool and the evluation of the body of evidence for each endpoint using GRADE.
Study risk of bias was considered to be high for almost every single included study. Overall, the quality of evidence was very low, due to serious risk of bias and indirectness (non-randomised studies (NRS), which was reflected on the GRADE assessment.

Heterogeneity: Inconsistency among studies was quantified by estimating I2 (Higgins 2011). When considerable heterogeneity was noted (I2 > 80%), the pooled estimates were suppressed in the forest plot, and results were reported as narrative text or in descriptive tables. For levels of I2 between 50% and 80%, heterogeneity was considered as moderate, and pooled analysis was attempted by using a RE model to allow for heterogeneity.Heterogeneity was also explored by means of a priori agreed subgroup analyses, by type of effect estimate.
Significant heterogeneity was present in some analyses, but was investigated and considered for the overall GRADE quality assesment.

Publication Bias: As we included more than 10 studies in the review, we assessed publication bias using Egger's formal statistical test and a funnel plot was constructed.
"No evidence of publication bias was documented in the only analysis with more than ten study arms."

Notes:
Oxford level of evidence: 3 Systematic review and meta-analysis of case control and cohort studies.

Skalkidou, A. et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3. Cd010931. 2017			
Overall, the quality of evidence was very low, due to serious risk of bias and indirectness (non-randomised studies (NRS), which was reflected on the GRADE assessment.			
Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic Review of cohort studies (15), case-control studies (10) and RCT (2) **Databases:** PubMed and Cochrane Central Register of Controlled Trials **Search period:** January 2000 until May 2020 **Inclusion Criteria:** Studies reporting on the incidence and prevalence of EC among women undergoing MHT. MHT was defined for the purpose of this systematic review as systemic (oral, transdermal or vaginal) use of estradiol or conjugated equine estrogens or estradiol or conjugated	**Population:** Peri- or postmenopausal women **Intervention:** Menopausal Hormone Therapy with estrogens/ or estrogens combined with progestin **Comparison:** /	**Primary:** Risk of EC in relation to different forms of peri- and postmenopausal MHT **Secondary:** **Results:** 31 publications reporting on 21,306 women with EC diagnosed during or after MHT were identified. **Risk of EC among continuous-combined MHT users with synthetic progestins** A significantly reduced risk of EC among continuous-combined (cc)MHT users with synthetic progestins (SPs) was demonstrated in 10/19 studies with odds ratios (ORs)/hazard ratios (HRs) between 0.24 and 0.71. In the remaining studies,	See full text article.

Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020				
equine estrogens combined with a synthetic progestin (norethisterone acetate, medroxyprogesterone acetate, megestrol acetate, chlomadinone acetate, medrogestone, levonorgestrel, cyproterone acetate, drospirenone, dienogest) or combined with progesterone (natural progesterone or dydrogesterone) in a continuous combined therapy scheme (ccMHT) or in a sequentially-combined therapy scheme (scMHT) **Exclusion Criteria:** Studies not reporting individual patient data and studies containing no extractable clinical data were excluded. We also excluded studies reporting on MHT with dehydroepiandrosterone, tibolone, or androgens with or without estrogens		neither a risk reduction nor a risk increase was observed. Only one study documented an increased risk of EC among long-term users (10 years), not confirmed in three other sub-group analyses of women with 6, 5, and >10 years of ccMHT use. **Risk of EC among users of sequential-combined MHT** A significantly increased risk of EC among users of sequential-combined (sc)MHT with SPs was demonstrated in 6/12 studies with ORs/HRs between 1.38 and 4.35. In the remaining six studies, no effect on EC risk was observed. Number of days of progestin per month was a significant modulator of EC risk. A decreased risk of EC was seen in obese women. **Risk of EC among users of cc/scMHT with micronized progesterone** Two studies documented an increased risk of EC among users of cc/scMHT with micronized progesterone. Short-term use (≤5 years) of MP and ever use of dydrogesterone and progesterone derivatives were not associated with an increased risk of EC.		

Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020				
		Risk of EC among estrogens-only MHT A significantly increased risk of EC among estrogen-only MHT users was demonstrated in 9/12 studies with ORs/HRs between 1.45 and 4.46. No study documented a decreased risk of EC. The adverse effect of estrogen-only MHT was greatest among obese women. Both past and current use and type of estradiol (estradiol, conjugated estrogens, non-conjugated estrogens) increased EC risk. **Author's Conclusion:** ccMHT with SPs reduces the risk of EC, whereas estrogen-only MHT increases the risk. scMHT with SPs and cc/scMHT with micronized progesterone increase the risk of EC depending on type of progestin, progestin dosage, and duration of MHT use.		
Methodical Notes				
Funding Sources: None. **COI:** None.				

Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020			
Study Quality: Bias of the individual studies were not assessed. **Heterogeneity:** Meta-Analysis was not performed due to the heterogeneity of the included studies. **Publication Bias:** Publication bias was not investigated. **Notes:** **Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review of cohort studies, case-control studies and RCT** Article submitted by hand search. Limitations: -Quality of the included studies was not investigated -Publication bias was not investigated			

Wise, M. R. et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review. Am J Obstet Gynecol. 214. 689.e1-689.e17. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (9 studiees) To systematically review the literature on the association between obesity and endometrial hyperplasia or cancer in premenopausal	**Population:** Post-menopausal women. **Intervention:** Exposure to obesity.	**Primary:** Endometrial Hyperplasia. **Secondary:** - **Results:** 9 case-control studies of moderate quality were included. Quantitative analysis of 5 studies showed a dose-response	Dahlgren 1991, Epplein 2008, Hosono 2011, Iatrakis 2006, La Vecchia 1991, Parslov 2000, Thomas 2009, XU

Wise, M. R. et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review. Am J Obstet Gynecol. 214. 689.e1-689.e17. 2016				
women **Databases:** MEDLINE, EMBASE, PubMed, and CINAHL and checked reference lists of included studies and systematic reviews. **Search period:** Inception - 05/2015. **Inclusion Criteria:** Studies were included if they assessed obesity (eg, BMI, Quetelet's index, both measured as kg/m2) and EH and/or EC specifically in women who were premenopausal at the time of diagnosis. Where menopausal status was not explicitly stated, then age **Exclusion Criteria:** Studies that did not include a comparative group (women who did not develop EH and/or EC, or were not exposed to the primary risk factor) were excluded (for example, case series). Studies of less than 50 women were excluded. Studies in which the only obesity measure was weight were excluded. Studies that did not report menopausal status, or that reported only menopausal status at the time of study recruitment, were excluded.	**Comparison:** Non-exposure to obesity.	relationship of body mass index and increased risk of endometrial cancer. For studies of women with body mass index of ≥25, the pooled odds ratio was 3.85 (95% confidence interval 2.53-5.84); body mass index of ≥30 was 5.25 (4.00-6.90); and body mass index of ≥40 was 19.79 (11.18-35.03). **Author's Conclusion:** In conclusion, this systematic review found that BMI was a risk factor for the diagnosis of complex EH and EC in premenopausal women. To reflect this finding, we would encourage the inclusion of BMI as a risk factor in the updating of clinical guidelines related to the diagnosis and management of abnormal uterine bleeding in premenopausal women.	2006, Yamazawa 2003.	

Wise, M. R. et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review. Am J Obstet Gynecol. 214. 689.e1-689.e17. 2016

Methodical Notes

Funding Sources: The Mercia Barnes Trust of the Royal Australian and New Zealand College of Obstetrics and Gynaecology funded 1 of the research assistants (S.L.). The University of Auckland Summer Studentship program funded 1 of the research assistants (N.W.). The funders were not involved in the study selection criteria, data analysis, or development of conclusions.

COI: The authors report no conflict of interest.

Study Quality: Each study was assessed by 2 authors using the Newcastle Ottawa Quality Assessment scale, which is a tool used for assessing quality of observational studies.
"Overall the study quality was assessed as good; 2 studies had a high risk of bias in 1 domain each, and 3 studies had a high risk of bias in 2 domains. Most studies had some missing data. "

Heterogeneity: Heterogeneity was reported using the I2 statistic.

Publication Bias: "Publication bias was reduced by the use of a comprehensive search strategy conducted by an experienced information specialist."

Notes:
Oxford level of evidence: 3 Systematic review and meta-analysis of case control studies.
Insufficient description of the publication bias assesment. I2 was 0% for the BMI ≥ 25 and 91% for the BMI ≥ 30 group.

Zhang, X. et al. Intentional weight loss, weight cycling, and endometrial cancer risk: a systematic review and meta-analysis. Int J Gynecol Cancer. 29. 1361-1371. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (13 studies) To assess the hypotheses that intentional weight loss is associated with lower endometrial cancer risk while weight cycling after intentional weight loss is associated with increased endometrial cancer risk. **Databases:** MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases **Search period:** 01/2000 - 11/2018. **Inclusion Criteria:** All published RCTS, non-randomized trials, and observational studies evaluating any intentional weight loss (bariatric surgery or self-reported intentional weight loss) and endometrial cancer risk. Eligible studies were those that included female participants aged 18 years or older and those that excluded participants who had	**Population:** Female participants aged 18 years or older **Intervention:** Self-reported intentional weight loss, self-reported weight cycling after intentional weight loss, bariatric surgery, **Comparison:** -	**Primary:** Endometrial cancer risk **Secondary:** - **Results:** Only summary presented due to lenght, rest see article. **Sutdy overview:** A total of 127 full-text articles were reviewed, and 13 were included (bariatric surgery n=7, self-reported intentional weight loss n=2, self-reported weight cycling n=4). **Results:** Qualitative synthesis suggested that compared to stable weight, self-reported intentional weight loss was associated with lower endometrial cancer risk (RR range=0.61–0.96), whereas self-reported weight cycling was associated with higher endometrial cancer risk (OR range=1.07–2.33). The meta-analysis yielded a 59% lower risk of endometrial cancer following bariatric surgery (OR=0.41, 95% CI=0.22, 0.74) in five studies, with high heterogeneity of I2=89%.	13 articles included out of which 5 went into the qualitative analysis: Mackenzie 2018, Anveden 2017 Ward 2014, Adams 2009, Christou 2008.

Zhang, X. et al. Intentional weight loss, weight cycling, and endometrial cancer risk: a systematic review and meta-analysis. Int J Gynecol Cancer. 29. 1361-1371. 2019				
preexisting endometrial or uterine cancer before intentional weight loss. Our original plan was to classify intentional weight loss as a result of surgical procedures (bariatric surgery) or behavioral interventions (caloric restricted diet with or without increased physical activity). However, the lack of long-term follow-up after behavioral weight loss interventions hindered our ability to assess the risk of developing endometrial cancer. Therefore, this systematic review and meta-analysis evaluated the relationship between self-reported intentional weight loss, self-reported weight cycling after intentional weight loss, bariatric surgery, and endometrial cancer risk. Information on self-reported intentional weight loss and weight cycling were collected through self-reported questionnaire. Bariatric procedures included Roux-en-Y gastric bypass, gastric banding, vertical banded gastroplasty, vertical sleeve gastrectomy, jejunoileal bypass, and biliopancreatic diversion. **Exclusion Criteria:** We excluded studies if: 1)the weight loss was through pharmaceutical interventions; 2)the study endpoint was not a			**Author's Conclusion:** "Current evidence from studies assessing intentional weight loss and weight cycling suggest that intentional weight loss is associated with lower endometrial cancer risk and weight cycling is associated with increased risk of endometrial cancer. Our study identified important research gaps which suggest future research to address current limitations. Strategies to improve awareness and maintenance of weight loss among women with obesity are needed to reduce endometrial cancer risk."	

Zhang, X. et al. Intentional weight loss, weight cycling, and endometrial cancer risk: a systematic review and meta-analysis. Int J Gynecol Cancer. 29. 1361-1371. 2019				
diagnosis of endometrial cancer (e.g. endometrial cancer-related biomarkers); 3) the diagnosis of endometrial cancer was prior to or during bariatric surgery or weight loss; and 4) did not include a control group. The primary outcomes of incidence, risk ratio, odds ratio, hazard ratio, or risk difference for endometrial cancer were assessed for each study. Also Reviews, case reports, letters, commentaries, editorials, unpublished studies, or any studies not published in English were not included.				
Methodical Notes				
Funding Sources: This work was supported by the National Cancer Institute (K01CA21845701A1 to ASF) and Susan G. Komen Foundation (GTDR15334082 to XZ). **COI:** All authors declare no conflicts of interest. **Study Quality:** The quality and risk of bias of each study were assessed using the Newcastle-Ottawa quality assessment scale for cohort or case-control studies. Study quality assessments were conducted independently by two reviewers. Any discrepancies regarding inclusion, exclusion and risk assessment were resolved by consensus. "In this review, the total scores of the 13 studies ranged from 6–9. Overall, studies of bariatric surgery and endometrial cancer risk were generally of higher quality compared with studies of self-reported intentional weight loss or weight cycling."				

Zhang, X. et al. Intentional weight loss, weight cycling, and endometrial cancer risk: a systematic review and meta-analysis. Int J Gynecol Cancer. 29. 1361-1371. 2019

Heterogeneity: The heterogeneity of effect size estimates across studies was quantified using the I2 statistic.(no treshold given)
The only meta-analysis performed has a high heterogeneity of I2=89%.

Publication Bias: Publication bias was assessed using the Egger's and Begg's tests (despite analyzing only 4 studies). Was not signficant.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of RCTs and cohort studies.
High heterogeneity in the only meta-analysis I2=89% which was not investigated by sensitivity or subgroup analysis.

2.2. Schlüsselfrage 02: Kann durch Modifikation der o.g. Risikofaktoren bzw. präventive medikamentöse oder operative Intervention das Risiko für das Auftreten eines Endometriumkarzinoms gesenkt werden?

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
2015	3	Systematic review and meta-analysis. To investigate the association between use of oral contraceptives and the subsequent risk of endometrial cancer.
Clement, N. S. 2017	1	Systematic review and meta-analysis (3 studies) To determine the effectiveness and safety of metformin in treating women with endometrial hyperplasia.
Lethaby, A. 2016	1	Systematic review and meta-analysis (24 studies) The objective of this review was to compare the eLicacy and safety of intra-vaginal oestrogenic preparations in relieving the symptoms of vaginal atrophy in postmenopausal women
Mirkin, S. 2016	3	Pooled analysis of 5 randomized controlled trials.
Tempfer, Clemens B. 2020	2	Systematic Review of cohort studies (15), case-control studies (10) and RCT (2)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *4 Bewertung(en)*

. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 16. 1061-1070. 2015			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 Study type: Systematic review and meta-analysis. To investigate the association between use of oral contraceptives and the subsequent risk of endometrial cancer. Databases: PubMed and Medline (up to Jan 31, 2012) and from review articles. Search period: Inception - 01/2012 Inclusion Criteria: Epidemiological studies were eligible for inclusion if they collected individual data about use of hormonal contraceptives and reproductive history from at least 400 women with endometrial cancer in retrospective studies, and at least 200 women in prospective studies. Exclusion Criteria: -	Population: Cases: Women with cancer (any histological type of the body of the uterus who were without previous cancer (except non-melanoma skin cancer) and controls without endometrial cancer. Intervention: Oral contraceptive use Comparison: Non-use of contraceptives.	Primary: Cancer risk attributed to contraceptives. Secondary: - Results: Only summary reported here, rest see article. Study overview:The median age of cases was 63 years (IQR 57–68) and the median year of cancer diagnosis was 2001 (IQR 1994–2005). 9459 (35%) of 27.276 cases and 45.625 (39%) of 115.743 controls had ever used oral contraceptives, for median durations of 3.0 years (IQR 1–7) and 4.4 years (IQR 2–9), respectively. Results: The longer that women had used oral contraceptives, the greater the reduction in risk of endometrial cancer; every 5 years of use was associated with a risk ratio of 0.76 (95% CI 0.73–0.78; p Author's Conclusion: Use of oral	BCDDP 2005, Netherlands Cohort 2004, NHS 1994, CNBSS 2002, IWHS 2001, Shanghai Breast Self-Examination 2006, MEC 2007 , NIH-AARP 2013, EPIC 2010, Women's Health Study 2005, MISS 2009, Swedish Women's Lifestyle and Health Cohort 2007 , Swedish Mammography Cohort 2009, Million Women Study 2005, CASH 1987, Brinton 1993, Pike 1997, Newcomb 2003, Weiderpass 1 1999 Weiderpass 2 2000, Rebbeck 2006, Shu 2006, Brinton/Lissowska 2007, Friedenreich 2014, ANECS 2011, Antunes 1979, Rosenberg 1980, WHO 1988, La Vecchia 1984, Moysich 2005, Levi 1991, Negri 1998, Dal Maso 2005, Urban 2012 , Aichi 1999.

. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 16. 1061-1070. 2015			
		contraceptives confers long-term protection against endometrial cancer. These results suggest that, in developed countries, about 400 000 cases of endometrial cancer before the age of 75 years have been prevented over the past 50 years (1965–2014) by oral contraceptives, including 200 000 in the past decade (2005-2014)	
Methodical Notes			
Funding Sources: Medical Research Council, Cancer Research UK. **COI:** "We declare no competing interests." **Study Quality:** Not investigated. **Heterogeneity:** Investigated, but not with I2 statistics. Significant heterogeneity for The proportional reduction in risk of endometrial cancer per 5 years of oral contraceptive analysis. **Publication Bias:** Not investigated "Only a third of the eligible studies have published on oral contraceptives and endometrial cancer so a review based solely on these studies could be aff ected by publication bias." **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies **Downgrade to evidence level 3.** No evaluation of study quality or publication bias. Heterogeneity present in some analyses, but not quantified by I2 statistic.			

Clement, N. S. et al. Metformin for endometrial hyperplasia. Cochrane Database Syst Rev. 10. Cd012214. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and meta-analysis (3 studies) To determine the effectiveness and safety of metformin in treating women with endometrial hyperplasia. **Databases:** Cochrane Gynaecology and Fertility Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, Google Scholar, OpenGrey, Latin American Caribbean Health Sciences Literature (LILACS), and two trials registers . We searched the bibliographies of all included studies and reviews on this topic. We also handsearched the conference abstracts of the European Society of Human Reproduction and Embryology (ESHRE) 2015 and the American Society for Reproductive Medicine (ASRM) 2015.	**Population:** We included women with histologically confirmed endometrial hyperplasia of any type. **Intervention:** Metformin. We also included trials that provided co-interventions (e.g. metformin plus progesterone vs progesterone), but we planned to analyse results of these studies separately. **Comparison:** with placebo or no treatment, conventional medical treatment (typically progestogens, e.g. oral or intrauterine), or any other active intervention	**Primary:** 1. Regression of endometrial hyperplasia histology (with or without atypia) towards normal histology **Secondary:** 2. Recurrence of endometrial hyperplasia 3. Progression of endometrial hyperplasia to endometrial cancer 4. Hysterectomy rate 5. Abnormal uterine bleeding 6.Health-related quality of life, as reported in the included studies 7. Adverse effects during treatment, as reported in the included studies. **Results:** Only summary results described here, due to length. **Study overview:** 3 RCTs were included in which a total of 77 women took part. We rated the quality of the evidence as very low for all outcomes owing to very serious risk of bias (associated with poor reporting, attrition, and limitations in study design) and imprecision. **Results:** We performed a meta-analysis of two trials with 59 participants.	3 studies included: Shan 2014, Sharifzadeh 2016, Tabiriz 2014.

Clement, N. S. et al. Metformin for endometrial hyperplasia. Cochrane Database Syst Rev. 10. Cd012214. 2017				
Search period: Inception to 01/2017. **Inclusion Criteria:** Randomised controlled trials (RCTs) and cross-over trials comparing metformin (used alone or in combination with other medical therapies) versus placebo or no treatment, any conventional medical treatment, or any other active intervention for women with histologically confirmed endometrial hyperplasia of any type. **Exclusion Criteria:** Not meeting inclusion criteria.		Whenmetformin was compared with megestrol acetate in women with endometrial hyperplasia, we found insufficient evidence to determine whether there were differences between groups for the following outcomes: regression of endometrial hyperplasia histology towards normal histology (odds ratio (OR) 3.34, 95% confidence interval (CI) 0.97 to 11.57, two RCTs, n = 59, very low-quality evidence), hysterectomy rates (OR 0.91, 95% CI 0.05 to 15.52, two RCTs, n = 59, very low-quality evidence), and rates of abnormal uterine bleeding (OR 0.91, 95% CI 0.05 to 15.52, two RCTs, n = 44 , very lowquality evidence). We found no data for recurrence of endometrial hyperplasia or health-related quality of life. Both studies (n = 59) provided data on progression of endometrial hyperplasia to endometrial cancer as well as one (n = 16) reporting some adverse effects in the metformin arm, notably nausea, thrombosis, lactic acidosis, abnormal liver and renal function among others. Another trial including 16 participants compared metformin plus megestrol acetate versus megestrol acetate alone in women with endometrial hyperplasia.We found		

Clement, N. S. et al. Metformin for endometrial hyperplasia. Cochrane Database Syst Rev. 10. Cd012214. 2017				
		insufficient evidence to determine whether there were differences between groups for the following outcomes: regression of endometrial hyperplasia histology towards normal histology (OR 9.00, 95% CI 0.94 to 86.52, one RCT, n = 16, very low-quality evidence), recurrence of endometrial hyperplasia among women who achieve regression (OR not estimable, no events recorded, one RCT, n = 8, very low-quality evidence), progression of endometrial hyperplasia to endometrial cancer (OR not estimable, no events recorded, one RCT, n = 13, very low-quality evidence), or hysterectomy rates (OR 0.29, 95% CI 0.01 to 8.37, one RCT, n = 16, very low-quality evidence). Investigators provided no data on abnormal uterine bleeding or health-related quality of life. In terms of adverse effects, three of eight participants (37.5%) in the metformin plus megestrol acetate study arm reported nausea. Authors' conclusions **Author's Conclusion:** Implications for practice: Review authors found insufficient evidence to support or refute the use ofmetformin given alone or in combination with standard therapy, specifically megestrol		

Clement, N. S. et al. Metformin for endometrial hyperplasia. Cochrane Database Syst Rev. 10. Cd012214. 2017				
		acetate, for treatment of women with endometrial hyperplasia.		
Methodical Notes				
Funding Sources: Internal sources · No sources of support, UK. External sources · No sources of support, UK. **COI:** Declared, see article. **Study Quality:** Study quality was evaluated by Cochrane risk of bias tool and the overall quality of evidence was evaluated using GRADE. "Using GRADE, review authors determined that the evidence was of very low quality both for the main comparison of metformin versus megestrol acetate and for the additional comparison of metformin plus megestrol acetate versus megestrol acetate alone. For both comparisons, we downgraded the quality of evidence owing to very serious risk of bias (associated with poor reporting, attrition, and limitations in study design) and imprecision as major factors. All studies had very small sample sizes, especially when assessing relatively rare events such as progression of endometrial hyperplasia to endometrial cancer. Confidence intervals were compatible with a large effect in one or both groups, or with a null effect." **Heterogeneity:** We assessed statistical heterogeneity using themeasure of I^2. We considered an I^2 greater than 50% to indicate substantial heterogeneity. No significant heterogeneity present in the analyses. **Publication Bias:** Planned but not executed due to feasibility, due to n **Notes:**				

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic review and meta-analysis (24 studies) The objective of this review was to compare the eLicacy and safety of intra-vaginal oestrogenic preparations in relieving the symptoms of vaginal atrophy in postmenopausal women **Databases:** Cochrane Gynaecology and Fertility Group Register of trials, The Cochrane Central Register of Controlled Trials (CENTRAL; 2016 issue 4), MEDLINE, Embase, PsycINFO, DARE, the Web of Knowledge, OpenGrey, LILACS, PubMed and reference lists of articles. We also contacted experts and researchers in the field. **Search period:** Inception - 04/2016	**Population:** Postmenopausal women, who had not menstruated for more than 12 months or who had a serum follicle stimulating hormone (FSH) level >= 40 IU/L were eligible for inclusion. Women who had undergone bilateral oophorectomy (removal of both ovaries) were also eligible for inclusion. **Intervention:** Oestrogen supplementation administered intravaginally. These included creams or gels, tablets, vagitories, ovules, pessaries, and an oestradiol-releasing ring. Duration of treatment must have been at least three months, as this treatment duration should be suLicient to improve vaginal symptoms. For the purpose of the review vagitories, ovules and pessaries were termed as vaginal tablets. **Comparison:** any other active intervention of placebo.	**Primary:** 1. Improvement in symptoms as assessed by participants 2. Endometrial thickness **Secondary:** 3. Improvement in symptoms as assessed visually by clinicians 4. Improvement in symptoms as assessed by clinicians using laboratory parameters 5. Other adverse events 6. Adherence to treatment **Results:** Only summary displayed here: **Study overview:** We included 30 RCTs (6235 women) comparing different intra-vaginal oestrogenic preparations with each other and with placebo. The evidence was low to moderate quality; limitations were poor reporting of study methods and serious imprecision (effect estimates with wide confidence intervals)	24 studies included: Ayton 1996, Bachmann 2008, Bachmann 2009, Barentsen 1997, Bygdeman 1996, Cano 2012, Casper 1999 study 1, Casper 1999 study 2, Dessole 2004, Dugal 2000, Eriksen 1992, Fernandes 2014, Foidart 1991, Garcia Lara 1993, Griesser 2012, Henriksson 1994, Hosseinzadeh 2015, Karp 2012, Lima 2013, Lose 2000, Mac Bride 2014, Manonai 2001, Nachtigall 1994, Nachtigall 1995, Raghunandan 2010, Rioux 2000, Simon 2008, Simunic 2003, Speroff 2003, Weisberg 2000.

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
Inclusion Criteria: The inclusion criteria were randomised comparisons of oestrogenic preparations administered intravaginally in postmenopausal women for at least 12 weeks for the treatment of symptoms resulting from vaginal atrophy or vaginitis. **Exclusion Criteria:** Exclusion criteria for most studies included: known to have hormone-dependent neoplasia and women who had taken systemic or vaginal oestrogens within three to six months of commencement of the study. Women with intercurrent major disease or who had had previous hormone therapy (HT) within three months of commencement of the study were excluded.		**Results: 1. Oestrogen ring versus other regimens Other regimens** included oestrogen cream, oestrogen tablets and placebo. There was no evidence of a diLerence in improvement in symptoms (participant assessment) either between oestrogen ring and oestrogen cream (odds ratio (OR) 1.33, 95% CI 0.80 to 2.19, two RCTs, n = 341, I2 = 0%, low-quality evidence) or between oestrogen ring and oestrogen tablets (OR 0.78, 95% CI 0.53 to 1.15, three RCTs, n = 567, I2 = 0%, low-quality evidence). However, a higher proportion of women reported improvement in symptoms following treatment with oestrogen ring compared with placebo (OR 12.67, 95% CI 3.23 to 49.66, one RCT, n = 67). With respect to endometrial thickness, a higher proportion of women who received oestrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with oestrogen ring (OR 0.36, 95% CI 0.14 to 0.94, two RCTs,		

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		n = 273; I2 = 0%, low-quality evidence). This may have been due to the higher doses of cream used. **2. Oestrogen tablets versus other regimens** Other regimens in this comparison included oestrogen cream, and placebo. There was no evidence of a difference in the proportions of women who reported improvement in symptoms between oestrogen tablets and oestrogen cream (OR 1.06, 95% CI 0.55 to 2.01, two RCTs, n = 208, I2 = 0% low-quality evidence). A higher proportion of women who were treated with oestrogen tablets reported improvement in symptoms compared to those who received placebo using a fixed-effect model (OR 12.47, 95% CI 9.81 to 15.84, two RCTs, n = 1638, I2 = 83%, low-quality evidence); however, using a random-effect model did not demonstrate any evidence of a difference in the proportions of women who reported improvement between the two treatment groups (OR 5.80, 95% CI 0.88 to 38.29). There was no		

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		evidence of a difference in the proportions of women with increase in endometrial thickness between oestrogen tablets and oestrogen cream (OR 0.31, 95% CI 0.06 to 1.60, two RCTs, n = 151, I2 = 0%, low-quality evidence). **3. Oestrogen cream versus other regimens** Other regimens identified in this comparison included isoflavone gel and placebo. There was no evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and isoflavone gel (OR 2.08, 95% CI 0.08 to 53.76, one RCT, n = 50, low-quality evidence). However, there was evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and placebo with more women who received oestrogen cream reporting improvement in symptoms compared to those who were treated with placebo (OR 4.10, 95% CI 1.88 to 8.93, two RCTs, n = 198, I2 = 50%, low-quality evidence). None of the		

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		included studies in this comparison reported data on endometrial thickness. **Author's Conclusion: Implications for practice:** There is no conclusive evidence of a diLerence in efficacy between the various intravaginal oestrogenic preparations when compared with each other. However, there is low-quality evidence that intra-vaginal oestrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo. There is low-quality evidence that oestrogen cream may be associated with increase in endometrial thickness compared to oestrogen ring, but this may have been due to the higher doses used. However there is no conclusive evidence of a diLerence in the overall body of evidence in adverse events between the various oestrogenic preparations compared with each other or with placebo. As previously noted, the low quality of		

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		the evidence resulted from poor reporting, with the review authors assessing a majority of the included studies as unclear in most risk of bias domains, due to insuLicient information; and imprecision, due to small sample sizes or eLect estimates with wide confidence intervals, or both. These results should be applied in the context of improvement of the symptoms of vaginal atrophy. Intra-vaginal oestrogenic preparations in the forms of creams, pessaries, tablets and the oestradiol-releasing ring are shown to be eLective for the symptoms of vaginal atrophy. There are few trials comparing an intervention with placebo. The oestradiol vaginal ring can be considered as an eLective and practical alternative to creams, pessaries and tablets. Dienoestrol cream has been withdrawn worldwide, and conjugated equine oestrogen cream has been withdrawn in New Zealand and Australia; 17ß oestradiol tablets in the dose of 25		

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016				
		Vg have also been withdrawn worldwide and replaced with the lower dose 10 Vg tablet. This is not available in New Zealand. Women using intra-vaginal oestrogenic preparations who have postmenopausal bleeding should have endometrial investigation.		
Methodical Notes				
Funding Sources: Internal sources · Department of Obstetrics and Gynaecology, University of Auckland, New Zealand. External sources · Health Research Council, Auckland, New Zealand. **COI:** No conflicts of interest to declare. **Study Quality:** Cochrane risk of bias for evaluation of individual study risk.'Summary of findings' tables to evaluate the overall quality of the body of evidence for the main review outcomes. GRADE Quality was low (6 outcomes) and moderate (1 outcome). **Heterogeneity:** "We considered whether the clinical and methodological characteristics of the included studies were suLiciently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the measure of the I2 statistic (Higgins 2003). An I2 measurement greater than 50% was taken to indicate substantial heterogeneity" **Publication Bias:** "In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we minimised their potential				

Lethaby, A. et al. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. . . 2016			
impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. Where there were 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention eLect to be more beneficial in smaller studies) (Sterne 2011). However, this was not undertaken because none of the analyses included 10 or more studies." **Notes:** Oxfor level of evidence: 1 Systematic review and meta-analysis.			
Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic Review of cohort studies (15), case-control studies (10) and RCT (2) **Databases:** PubMed and Cochrane Central Register of Controlled Trials **Search period:** January 2000 until May 2020 **Inclusion Criteria:** Studies reporting on the incidence and prevalence of EC among women undergoing MHT. MHT was defined for the purpose of this	**Population:** Peri- or postmenopausal women **Intervention:** Menopausal Hormone Therapy with estrogens/ or estrogens combined with progestin **Comparison:** /	**Primary:** Risk of EC in relation to different forms of peri- and postmenopausal MHT **Secondary:** **Results:** 31 publications reporting on 21,306 women with EC diagnosed during or after MHT were identified. **Risk of EC among continuous-combined MHT users with synthetic progestins** A significantly reduced risk of EC among continuous-combined (cc)MHT users with synthetic progestins (SPs) was	See full text article.

Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020				
systematic review as systemic (oral, transdermal or vaginal) use of estradiol or conjugated equine estrogens or estradiol or conjugated equine estrogens combined with a synthetic progestin (norethisterone acetate, medroxyprogesterone acetate, megestrol acetate, chlomadinone acetate, medrogestone, levonorgestrel, cyproterone acetate, drospirenone, dienogest) or combined with progesterone (natural progesterone or dydrogesterone) in a continuous combined therapy scheme (ccMHT) or in a sequentially-combined therapy scheme (scMHT) **Exclusion Criteria:** Studies not reporting individual patient data and studies containing no extractable clinical data were excluded. We also excluded studies reporting on MHT with dehydroepiandrosterone, tibolone, or androgens with or without estrogens		demonstrated in 10/19 studies with odds ratios (ORs)/hazard ratios (HRs) between 0.24 and 0.71. In the remaining studies, neither a risk reduction nor a risk increase was observed. Only one study documented an increased risk of EC among long-term users (10 years), not confirmed in three other sub-group analyses of women with 6, 5, and >10 years of ccMHT use. **Risk of EC among users of sequential-combined MHT** A significantly increased risk of EC among users of sequential-combined (sc)MHT with SPs was demonstrated in 6/12 studies with ORs/HRs between 1.38 and 4.35. In the remaining six studies, no effect on EC risk was observed. Number of days of progestin per month was a significant modulator of EC risk. A decreased risk of EC was seen in obese women. **Risk of EC among users of cc/scMHT with micronized progesterone** Two studies documented an increased risk of EC among users of cc/scMHT with micronized progesterone. Short-term use (≤5 years) of MP and ever use of		

Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020				
		dydrogesterone and progesterone derivatives were not associated with an increased risk of EC. **Risk of EC among estrogens-only MHT** A significantly increased risk of EC among estrogen-only MHT users was demonstrated in 9/12 studies with ORs/HRs between 1.45 and 4.46. No study documented a decreased risk of EC. The adverse effect of estrogen-only MHT was greatest among obese women. Both past and current use and type of estradiol (estradiol, conjugated estrogens, non-conjugated estrogens) increased EC risk. **Author's Conclusion:** ccMHT with SPs reduces the risk of EC, whereas estrogen-only MHT increases the risk. scMHT with SPs and cc/scMHT with micronized progesterone increase the risk of EC depending on type of progestin, progestin dosage, and duration of MHT use.		
Methodical Notes				

Tempfer, Clemens B. et al. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. Cancers. 12. . 2020

Funding Sources: None.

COI: None.

Study Quality: Bias of the individual studies were not assessed.

Heterogeneity: Meta-Analysis was not performed due to the heterogeneity of the included studies.

Publication Bias: Publication bias was not investigated.

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review of cohort studies, case-control studies and RCT
Article submitted by hand search.
Limitations:
-Quality of the included studies was not investigated
-Publication bias was not investigated

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Mirkin, S. et al. Gynecologic Safety of Conjugated Estrogens Plus Bazedoxifene: Pooled Analysis of Five Phase 3 Trials. J Womens Health (Larchmt). 25. 431-42. 2016		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Pooled analysis of 5 randomized controlled trials. **Number of Patient:** 4409 from five trials. **Recruitung Phase:** not described. **Inclusion Criteria:** The SMART studies enrolled generally healthy postmenopausal women with a uterus. Postmenopausal status was defined as at least 12 months of spontaneous amenorrhea or at least 6 months of spontaneous amenorrhea with follicle folliclestimulating hormone (FSH) levels >40mIU/mL in all but SMART-1. Postmenopausal status in SMART-1 was defined as at least 1 year since lastmenstrual cycle, FSH ‡30 mIU/mL, and 17 b-estradiol £183.5 pmol/L (£50 pg/mL). Depending on the specific study or substudy (Table 1), some enrolleeswere at risk for osteoporosis (based on T-score or risk factors) or were seeking treatment for vasomotor symptoms or vulva vulvar-vaginal atrophy.	**Intervention:** Conjugated estrogens 0.625 mg/bazedoxifene 20 mg, conjugated estrogens 0.45 mg/bazedoxifene 20 mg (n = 1585). **Comparison:** Placebo	**Primary:** Incidence of endometrial hyperplasia; incidence of proliferative endometrium; incidence of other endometrial, ovarian, cervical, vaginal, and breast AEs; risk of endometrial, ovarian, and breast cancers; rates of amenorrhea; and percentage of women with breast pain/tenderness **Secondary:** Gynecologic safety outcomes. **Results:** Endometrial hyperplasia occurred in There were seven cases of breast cancer: four with conjugated estrogens 0.45 mg/bazedoxifene 20 mg (1.00/1000 woman-years [95% CI, 0.00–3.21] RR 1.11 [95% CI, 0.33–3.78]), two with placebo, and one with conjugated estrogens/ medroxyprogesterone acetate. Unlike conjugated estrogens/medroxyprogesterone acetate, conjugated estrogens/bazedoxifene did not increase breast density, breast pain/tenderness, or vaginal bleeding versus placebo. No active treatment increased ovarian cysts. **Author's Conclusion:** In conclusion, this pooled analysis of the SMART trials provides encouraging safety data on use of conjugated estrogens/ bazedoxifene for up to 2 years. Longer safety data will be beneficial to confirm current safety findings in healthy women, those at risk, and those of minority

Mirkin, S. et al. Gynecologic Safety of Conjugated Estrogens Plus Bazedoxifene: Pooled Analysis of Five Phase 3 Trials. J Womens Health (Larchmt). 25. 431-42. 2016		
Exclusion Criteria: unresolved or abnormal cervical cytologic smear report, unresolved breast examination findings, nonmeasurable endometrial thickness or unacceptable transvaginal ultrasound findings (e.g., complex ovarian cyst, double-walled endometrial thickness >4 mm), endometrial biopsy with insufficient tissue or unacceptable findings confirmed by two pathologists (e.g., hyperplasia, malignancy), any history of a gynecologic or breast malignancy, and history of any malignancy except basal cell carcinoma of the skin within the prior 5 years (10 years in SMART-1).		populations. In the meantime, healthy postmenopausal women with a uterus can be offered conjugated estrogens/bazedoxifene for treatment of menopausal symptoms and prevention of bone loss with reassurance regarding its gynecologic and breast safety profile, as tested in clinical trials of up to 2 years in duration.
Methodical Notes		
Funding Sources: Medical writing support was provided by Lauren Cerruto at Peloton Advantage, LLC, and was funded by Pfizer. **COI:** Extensive list, see article. **Randomization:** not described. **Blinding:** Double-blind studies. no details provided. **Dropout Rate/ITT-Analysis:** No information provided. **Notes:** Oxford level of evidence: 2 Randomized controlled trial.		

Mirkin, S. et al. Gynecologic Safety of Conjugated Estrogens Plus Bazedoxifene: Pooled Analysis of Five Phase 3 Trials. J Womens Health (Larchmt). 25. 431-42. 2016
Downgrade to evidence level 3. Article does not allow evaluation of risk of bias as a RCT by the reviewer since important descriptions are missing. On the other hand, this is not a meta-analysis either. Important data are not provied regarding randomization, dropouts, group differences and treatment,

Literaturstelle	Evidenzlevel	Studientyp
Alcázar, J. L. 2018	2	Systematic review and meta-analysis (9 studies) To evaluate the risk of endometrial cancer and/or endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ≥ 11 mm.
Bosse, T. 2018	4	Genetic association study (cohort of patients from 6 centers) To investigate whether molecular classification can be used to refine prognosis in grade 3 endometrioid endometrial carcinomas (EECs).
Bourdel, N. 2016	2	Systematic review and meta-analysis (27 studies) to identify the most accurate method of endometrial sampling for the diagnosis of complex atypical hyperplasia (CAH), and the related risk of underestimation of endometrial cancer.
Cheewakriangkrai, C. 2020	2	Systematic review and meta-analysis (0 articles included.) To assess the effectiveness of health education interventions targeting healthcare providers, or individuals, or both, to promote early presentation and referral for women with endometrial cancer symptoms.
Clarke, M. A. 2018	2	Systematic review and meta-analysis (92 studies) To provide a reference of the prevalence of postmenopausal bleeding (PMB) in endometrial cancers and the risk of endometrial cancer in women with PMB.
Li, J. 2019	2	Meta-analysis of diagnostic studies (12 studies). To estimate the diagnostic accuracy of HE4 and CA125 and compared their performance as surrogates for EC detection.
Narice, B. F. 2018	2	Systematic review and meta-synthesis (60 studies) To identify existing evidence about the effectiveness of Pipelle compared with other ES techniques for assessing low-risk women with AUB which could inform the development of new care pathways in primary care.

Literaturstelle	Evidenzlevel	Studientyp
Nieuwenhuis, L. L. 2017	2	Systematic review of diagnostic studies (13 studies) To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS for the diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test.
Verdoodt, F. 2016	3	Systematic review and diagnostic meta-analysis (12 studies) To evaluate the usefulness of hrHPV testing in the management of women with a cytological diagnosis of AGC is evaluated.
Visser, N. C. M. 2017	3	Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma.

2.3. Schlüsselfrage 03: Welche Verfahren wie beispielsweise transvaginale Sonographie, zytologische Beurteilung, Endometriumbiopsie mittels Aspiration, Hysteroskopie oder Tumormarker-Bestimmung an Aspiraten, HPV-Bestimmung, Familienanamnese sind bei der asymptomatischen Frau mit normalem Risiko geeignet zur Früherkennung des Endometriumkarzinoms im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *10 Literaturstellen*

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *9 Bewertung(en)*

Alcázar, J. L. et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ?11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 46. 565-570. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (9 studies) To evaluate the risk of endometrial cancer and/or endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ≥ 11 mm. **Databases:** Systematic review of literature using database search (PubMed and Web of Science) **Search period:** 01/1990 to 12/2016 **Inclusion Criteria:** Prospective or retrospective cohort observational studies reporting on ET in asymptomatic postmenopausal women, as measured by the “double layer technique,” and data from histological diagnosis after	**Population:** Asymptomatic postmenopausal women. **Intervention:** Exposure/ risk factor endometrial thickness (ET) ≥ 11 mm measured by transvaginal ultrasound (double layer) and histopathological findings. **Comparison:** Endometrial thickness 5-10 mm.	**Primary:** Risk of endometrial cancer and or hyperplasia with atypia. **Secondary:** - **Results:** Only summary result described here, rest see article. **Study overview:** The search identified 289 studies. After exclusions, nine articles that met all the inclusion criteria were included, comprising data from 4751 women. **Results:** The prevalence of endometrial cancer and/or endometrial hyperplasia with atypia was 2.4%. The relative risk of endometrial cancer and/or endometrial hyperplasia with atypia in the ≥11 mm group was 2.59 (95% CI: 1.66-4.05). High heterogeneity was observed between studies (I2: 57.3%,	9 studies included: leischer 2001, Martinez-Rubio 2003, Tsikouras 2007, Schmidt 2008, Kalampokas, Gianella 2014, Yasa 2016, Louie 2016, Seckim 2016.

Alcázar, J. L. et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ?11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 46. 565-570. 2018				
endometrial sampling (whatever the method used for endometrial sampling). **Exclusion Criteria:** Studies that included patients with hormone replacement therapy, tamoxifen, or aromatase inhibitors were excluded. Studies not reporting on histological data and studies not reporting on data about ET in enough detail that we could stratified the patients in two groups (ET ≥11 mm and ET < 11 mm) were further excluded.		P = .016). **Author's Conclusion:** The risk for endometrial cancer and/or endometrial hyperplasia with atypia in asymptomatic postmenopausal women is 2.59 times higher in women with endometrial thickness ≥ 11 mm as compared with those with endometrial thickness between 5 mm and 10 mm, although there was significant heterogeneity in estimates across studies.		
Methodical Notes				
Funding Sources: not described. **COI:** All authors declare have no conflict of interest. **Study Quality:** Three investigators did quality assessment of the studies using the risk of bias tool for observational studies using the Newcastle- Otawa Scales.The quality of included studies was considered to be acceptable, although most suffered from selection bias and were retrospective. **Heterogeneity:** Heterogeneity among studies was investigated using the I2 statistics. 10 I2 values of 25%, 50% and 75% correspond to cut-off points for low, moderate, and high heterogeneity. In case of heterogeneity, we performed a meta-regression analysis for identifying potential sources. "High heterogeneity was observed between studies (I2: 57.3%, P = .016)."				

Alcázar, J. L. et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ?11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 46. 565-570. 2018

Publication Bias: Publication bias was assessed using Egger's funnel plot. We did not observe publication bias.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies
No search for grey literature was performed; initia study selection was performed by one reviewer.

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (27 studies) to identify the most accurate method of endometrial sampling for the diagnosis of complex atypical hyperplasia (CAH), and the related risk of underestimation of endometrial cancer. **Databases:** PubMed and EMBASE was performed to identify all registered articles on this subject published	**Population:** Premenopausal and postmenopausal women submitted to endometrial sampling because of a suspicion of endometrial disease (with or without symptoms) with a diagnosis of atypical endometrial hyperplasia and who underwent hysterectomy. **Intervention:** The diagnostic tests were uterine curettage (group 1), hysteroscopically guided biopsy (group	**Primary:** Percentage of unexpected cancer cases diagnosed at hysterectomy and missed during endometrial sampling (endometrial sampling with histologic diagnosis of atypical endometrial hyperplasia). **Secondary:** - **Results: Study overview:** We selected 27 studies, taking into consideration the comparison between histology of	27 studies included: see article.

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016				
restricted to English, French, Italian, or Spanish languages. In addition, cross-references of all selected articles were checked. **Search period:** 01/1999 and 09-2013 **Inclusion Criteria:** Clinical trials, comparative studies, controlled clinical trials, randomized controlled trials, and multicenter studies in which the results of the diagnostic test of interest were compared with the results of a reference standard. The population of interest was premenopausal and postmenopausal women submitted to endometrial sampling because of a suspicion of endometrial disease (with or without symptoms) with a diagnosis of atypical endometrial hyperplasia and who underwent hysterectomy. The diagnostic tests were uterine curettage (group 1), hysteroscopically guided biopsy (group 2), and endometrial hysteroscopic resection (group 3), and the reference standard	2), and endometrial hysteroscopic resection (group 3) **Comparison:** Reference standard was hysterectomy.	endometrial hyperplasia obtained by diagnostic tests of interest (uterine curettage, hysteroscopically guided biopsy, or hysteroscopic endometrial resection) and subsequent results of hysterectomy. **Results:** Analysis of the studies reviewed focused on 1106 patients with a preoperative diagnosis of atypical endometrial hyperplasia. The mean risk of finding endometrial cancer at hysterectomy after atypical endometrial hyperplasia diagnosed by uterine curettage was 32.7% (95% confidence interval [CI], 26.2–39.9), with a risk of 45.3% (95% CI, 32.8–58.5) after hysteroscopically guided biopsy and 5.8% (95% CI, 0.8–31.7) after hysteroscopic resection. In total, the risk of underestimation of endometrial cancer reaches a very high rate in patients with CAH using the classic method of evaluation (i.e., uterine curettage or hysteroscopically guided biopsy). This rate of underdiagnosed endometrial cancer leads to the risk of inappropriate surgical procedures (31.7%		

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016				
was hysterectomy. The primary outcome measure was the percentage of unexpected cancer cases diagnosed at hysterectomy and missed during endometrial sampling (endometrial sampling with histologic diagnosis of atypical endometrial hyperplasia). **Exclusion Criteria:** We excluded populations consisting entirely of patients treated by tamoxifen or affected by familiar diseases (i.e., HNPCC [Hereditary Non-Polyposis Colorectal Cancer] syndrome) because of the different prevalence of EC in this population influencing outcome measures. We also excluded studies in which the histologic findings were not compared with the reference standard (i.e., hysterectomy), the sampling methods were different from the 3 diagnostic tests, and hysterectomy was realized for other indications.		of tubal conservation in the data available and no abdominal exploration in 24.6% of the cases). Hysteroscopic resection seems to reduce the risk of underdiagnosed endometrial cancer. **Author's Conclusion:** "A review of the literature shows that hysteroscopically guided biopsy and uterine curettage may have a high risk of underestimation of EC, and this rate of underdiagnosed EC could lead to inappropriate surgical procedures. Hysteroscopic endometrial resection seems to lower this risk. However, this review highlights the need for a larger amount of data to confirm this observation, and the standard approach for evaluation of the uterine cavity could change in favor of operative hysteroscopic techniques, especially in cases of women at risk of serious endometrial disease."		
Methodical Notes				

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016

Funding Sources: Not stated.

COI: The authors declare that they have no conflict of interest.

Study Quality: For appraisal of the methodologic quality of the studies, we used the Canadian Task Force classification, a measurement tool to assess the methodologic quality of studies.
"Most of the studies included were classified II-2 (n 5 19/27) (i.e., evidence obtained from well-designed cohort or case-control studies), and 8 were classified II-3 (i.e., evidence obtained from several timed series with or without the intervention). All studies included were retrospective, and subjects were always included when they had a preoperative diagnosis of atypical endometrial hyperplasia followed by hysterectomy with pathological analysis."

Heterogeneity: Heterogeneity in the study results was evaluated by examining forest plots and confidence intervals and by using formal tests for homogeneity based on the I2 statistics. Heterogeneity was quantified by I2.
"A limitation of this review is the heterogeneity of populations and groups, which may impact the generalizability of the findings. There are 22 studies (n5984 patients) in group 1, 6 in group 2 (n= 99), and only 3 in group 3 (n =23). This difference causes a high heterogeneity (total I2 = 67.8 with I2 = 72.0 for group 1, I2 = 30.6 for group 2, and I2 = 0.0 for group 3). However, we used a random-effects analysis to take account of this heterogeneity, and the results indicated a statistically significant difference."

Publication Bias: Publication bias was assessed by a funnel plot, but results and implications were not discussed. Unclear wether bias is present or not.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis studies without consistently applied reference standard / cohort studies
Searches were carried out in 2013, while the article was published in 2016, therfor the presented evidence is not recent. High heterogeneity present in results, which limits generalzability.

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (0 articles included.) To assess the effectiveness of health education interventions targeting healthcare providers, or individuals, or both, to promote early presentation and referral for women with endometrial cancer symptoms. **Databases:** CENTRAL, MEDLINE and Embase. We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of review articles. **Search period:** Inception-02/2020. **Inclusion Criteria:** Randomised controlled trials (RCTs), both individually randomised and cluster-RCTs. In the absence of RCTs we planned to include well-designed non-	**Population:** Woman aged 18 years or older in any setting who experienced symptoms suspicious for endometrial cancer. We planned to include any healthcare providers of any age, gender, or profession (e.g. nurse, doctor, allied staF), in any public or private healthcare facility. In addition, as we planned to recruit cluster- RCTs to this review, participants could thus be communities or healthcare institutions or other units. We planned to perform a separate analysis for diFerent types of participants (individuals who experienced suspicious symptoms of endometrial cancer and healthcare providers). **Intervention:** Interventions of interest were any health education interventions performed with the aim of promoting the early presentation and referral of women with symptoms suspicious of endometrial cancer. Interventions could target individuals,	**Primary:** · Overall survival: defined as survival of women with endometrial cancer from diagnosis from all causes · Disease-free survival: defined as survival of women with endometrial cancer until the appearance of a new lesion of disease **Secondary:** Definitions see article: · Delayed referral · Delayed presentation · Referral time · Presentation time or time of help-seeking · Conversion rate · Detection rate: · Time from presentation to receiving definite treatment (days) · Women's satisfaction with the referral process · Physicians' satisfaction with the referral process: · Quality of life	No studies included.

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020				
randomised studies (NRS) with a parallel comparison assessing the benefits of any type of health education interventions. **Exclusion Criteria:** We planned to exclude cross-over RCTs due to the nature of the question of the review. If we identified no RCTs, we planned to include non-randomised studies (NRS) with a parallel comparison. We intended to include NRS that analysed results for intervention eFects adjusted for baseline characteristics, that is, participants'age and menopausal status. We planned to exclude NRS without a concurrent comparison group.	healthcare providers, or both. We planned to include studies regardless of their level of delivery of the intervention (individual or public or community). Interventions aimed at the individual level could be health education outreach visits, meetings, or printed educational materials. Communitybased health education interventions could be mass media campaigns, health education website, or posters distributed indiscriminately in public areas. **Comparison:** Control (presumably usual or standard practice), or directed, head-to-head educational interventions.	· Cost-effectiveness of the intervention **Results:** "We planned to include randomised controlled trials (studies in which people or groups of people are allocated by chance to two or more groups, treating them differently). In the absence of randomised controlled trials, we planned to include studies where participants were not randomised but that included an assessment of the benefits of health education compared to no health education. We searched scientific databases and checked the titles and abstracts of 4880 possibly relevant articles and assessed the full text of 16 of these references. However, we found no studies that met our inclusion criteria." **Author's Conclusion:** Implications for practice: At present, there is an absence of evidence to indicate the effectiveness of health education interventions involving healthcare providers or individuals, or both, to promote the early presentation		

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020

		and early referral for women with symptoms suspicious of endometrial cancer. This again highlights that endometrial cancer is under-resourced, in terms of funding and research, given its relatively high incidence in high-income countries, compared to other cancer types.		

Methodical Notes

Funding Sources: Internal sources
· Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiang Mai University, Thailand.
· Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
· Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Thailand.
· Campbell South Asia, New Delhi, India.
· Cochrane Thailand, Thailand.
External sources
· Thailand Research Fund (Distinguished Professor Award), Thailand.
· Long-term Institutional Development HUBs (LID-HUBs), the Human Reproduction Programme (HRP) Alliance for Research Capacity Strengthening, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland.

COI: Declared, none known.

Study Quality: No quality was evaluated, because no studies were included.

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020

Heterogeneity: no meta-analysis was performed.

Publication Bias: Investigation not possible

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of randomozed or non-randomized studies.
Although the article is well written it does no include any results, due to no studies meeting the inclusion criteria. Therfor this articles' implications are limited. No studies are included in this recent article (last searches 02/2020) which points toward no literature being available investigating the described relation).

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (92 studies) To provide a reference of the prevalence of postmenopausal bleeding (PMB) in endometrial cancers and the risk of endometrial cancer in women with PMB.	**Population:** Postmenopausal women. **Intervention:** Exposure to PMB or Endometrial cancer. **Comparison:** Non-exposure.	**Primary:** Prevalence of post-menopausal bleeding (PMB) in women with endometrial cancer. Risk of endometrial cancer in women with PMB. **Secondary:** Subgroup analyses f.e. for regions in which the studies were conducted. **Results:** Only summary described here, rest see article.	92 studies included: see article.

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018				
Databases: PubMed and Embase, reference lists of articles identified in the primary search for additional relevant studies. English-language studies only. **Search period:** 01/1977 - 01/2017. **Inclusion Criteria:** Original studies with primary data reporting the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer among women with PMB. English-language, peer-reviewed studies. **Exclusion Criteria:** Studies that included special populations (eg, defined by comorbid conditions or specific histologic findings), lacked detailed inclusion criteria, and/or included 25 or fewer women.		**Study overview:** A total of 129 unique studies, including 34 432 unique patients with PMB and 6358 with endometrial cancer (40 790 women), were analyzed. **Results:** The pooled prevalence of PMB among women with endometrial cancer was 91% (95%CI, 87%-93%), irrespective of tumor stage. The pooled risk of endometrial cancer among women with PMB was 9%(95%CI, 8%-11%), with estimates varying by use of hormone therapy (range, 7%[95%CI, 6%-9%] to 12%[95%CI, 9%-15%]; P < .001 for heterogeneity) and geographic region (range, 5%[95% CI, 3%-11%] in North America to 13%[95%CI, 9%-19%] in Western Europe; P = .09 for heterogeneity). **Author's Conclusion:** "The widespread practice of referring allwomenwith PMB for TVUS and/or endometrial biopsy carries a considerable burden and cost. Given the rise in endometrial cancer incidence and mortality, our findings raise the important question of how to best manage PMB to optimize the benefit of early detection approaches while avoiding unnecessary harms. Interest has increased in the use of biomarkers, such as DNA methylation, to improve early detection of endometrial cancer. To obtain reliable estimates of the clinical performance of molecular assays,		

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018				
		diagnostic tests, and management algorithms, we must know the prior risk of endometrial cancer in the population. Our study represents an important and timely evaluation of the risk of endometrial cancer in women with PMB and can serve as a reliable reference for the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer inwomenwith PMB, 2 requisite prior probabilities for prediction of endometrial cancer risk and secondary and tertiary prevention. As new markers are discovered or new clinical management strategies are evaluated, our results can aid in the assessment of their potential clinical value andwill help to inform clinical and epidemiologic risk prediction models to support clinical decision making."		
Methodical Notes				
Funding Sources: This study was supported by grant 603019 via the COHEAHR Network, 7th Framework Programme of DG Research and Innovation, European Commission (Dr Arbyn). The funding source had no role in the design and conduct of the study. **COI:** Reported, but no conflicts were declared. **Study Quality:** Two independent reviewers evaluated study quality and risk of bias using items from the Newcastle-Ottawa Quality Assessment Scale and the Quality Assessment of Diagnostic Accuracy Studies tool.				

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018

Study quality reported in the supplementary section.

Heterogeneity: We estimated pooled prevalence and 95%CIs using multilevel logistic-normal random-effects models to account for interstudy heterogeneity. Between-study variance was quantified using the τ2 statistic.

Publication Bias: We conducted sensitivity analyses to assess the influence of clinical setting (tertiary center vs other), study design, and the potential for publication bias using Egger regression analyses.
"No evidence of publication bias was found among studies reporting the prevalence of PMB in women with endometrial cancer (Egger regression intercept, 0.15; P = .90)."

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies.
Significant heterogeneity was reported for the two main outocmes.

Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Meta-analysis of diagnostic studies (12 studies). To estimate the diagnostic accuracy	**Population:** Endometrium carcinoma patients and controls (usually healthy postmenopausal women).	**Primary:** Sensitivity, Specificity, PLR, NLR., diagnostic oodds ratio. **Secondary:** Subgroup analysis.	Moore 2008, Bignotti 2011, Cong 2011, Liang 2011, Zhan 2011, Wu 2011, Zhao

Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019			
of HE4 and CA125 and compared their performance as surrogates for EC detection. **Databases:** "A literature search was performed in Medline, Cochrane Literature Library and CNKI. There was no language restriction." **Search period:** No description of search period. **Inclusion Criteria:** Only studies that fulfilled the following criteria were included for analyses: 1) evaluating the sensitivity and specificity of serum HE4 in EC detection; 2) histopathology as the reference test; 3) sufficient data to calculate TP (true-positive), FP (false-positive), FN (false-negative), TN (true-negative). **Exclusion Criteria:** Exclusion criteria were as follows: review, letter, and duplicated publication, to make sure only primary publications of original studies were included.	**Intervention:** HE4 or CNKI biomarkers. **Comparison:** Histopathology.	**Results: Study overview:** After filtering, twelve studies evaluating the diagnostic value of serum HE4, alone or in comparison with CA125, were included. The total sample size was 1106 patients and 1480 controls. **Results:** Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) were calculated and summary receiver operating characteristic (SROC) curves were plotted to assess the diagnostic accuracy. Results: The pooled estimates for HE4 were sensitivity: 0.71 (95%CI 0.56–0.82), specificity: 0.87 (95%CI 0.80–0.92), and area under ROC curve: 0.88 (0.85–0.91), compared to 0.35 (95% CI 0.25–0.46), 0.83 (95% CI 0.71–0.91), and 0.58 (95% CI 0.54–0.63), respectively, of CA125. Subgroup analysis demonstrated a better performance of HE4 in Caucasian population, compared to Chinese population. **Author's Conclusion:** "In summary, our meta-analysis demonstrated that, compared to CA125, serum HE4 has a	2012, Zanotti 2012, Anioli 2012, Omer 2013, Yu 2013, Zhang 2013.

Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019				
		higher sensitivity and overall accuracy in the diagnosis of all EC cases, when stage and histological types are not specifically considered. Furthermore, for some unidentified reasons, HE4 tends to perform better in Caucasian population than in Chinese population. It remains to be investigated if the combination of the two markers could significantly improve the outcome in medical practice."		
Methodical Notes				
Funding Sources: This project is supported by the Zhejiang Provincial Natural Science Foundation (LY18H040012), and (LY18H160052). **COI:** "None." **Study Quality:** The quality of individual studies was assessed using the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) tool. All these studies were in moderate to high quality (≥6 scores). Individual results are not displayed. **Heterogeneity:** The heterogeneity between studies was analyzed by Q test I2 test. If no significant heterogeneity existed (p > .1, I2 < 50%), a fixed-effect model was used. Otherwise, a random-effect model was applied. "Among studies assessing the diagnosis performance of HE4, high level heterogeneity existed in sensitivity (I2=92.08%) and specificity (I2=90.13%). Similarly, high between-study heterogeneity was observed in sensitivity (I2=94.22%) and specificity (I2=94.03%) of the CA125 assays." **Publication Bias:** Publication bias was assessed using Deeks' funnel plot asymmetry test. The plot was basically symmetrical (p=.82), indicating there				

Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019			
was no obvious publication bias in meat-analysis relating to the diagnostic performance of HE4. **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of diagnostic studies without consisntely applied reference standard. No description of search period. High heterogeneity (I2>90%) for sensitivity and specificity for both markers. Individual results for study quality are not reported.			
Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-synthesis (60 studies) To identify existing evidence about the effectiveness of Pipelle compared with other ES techniques for assessing low-risk women with AUB which could inform the development of new care pathways in primary care. **Databases:** MEDLINE via OvidSP, Scopus, and Web of Science for relevant English-language articles.	**Population:** Women with abnormal uterine bleeding (AUB) **Intervention:** endometrial sampling (ES) Pipelle device. **Comparison:** ES other devices	**Primary:** Sample adequacy, test performance, pain/discomfort, costs out outpatient endometrial sampling, barriers and complications.a **Secondary:** - **Results:** "Pipelle seems to perform as well as dilation and curettage and, as well or better than other ES devices in terms of sampling adequacy and sensitivity. It also seems to be better regarding pain/discomfort and costs.	60 study included: see article.

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018				
Search period: 1984 to 2016. **Inclusion Criteria:** We included papers investigating ES in women with AUB. We also considered studies in patients with known cancer; although these studies do not inform the indication of ES in primary care, they were an important source to evaluate test performance. We included review articles and opinion pieces. **Exclusion Criteria:** We excluded papers exclusively analysing postmenopausal patients, papers where the indication was assessment of fertility or recurrent miscarriage and papers where ES was assisted by hysteroscopy (unless this was used as a comparator to blind ES).		However, Pipelle can disrupt the sonographic appearance of the endometrium and may be limited by cervical stenosis, pelvic organ prolapse and endometrial atrophy." **Author's Conclusion:** The evidence we analysed suggests that performing ES in the outpatient setting may allow effective management of low-risk women with AUB in primary care without referral to a hospital. But the false negative rate, health economics and implications of such a change in practice are still unknown and more research is required.		
Methodical Notes				
Funding Sources: not described. **COI:** The authors declare that they have no competing interests.				

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018

Study Quality: The quality of the RCTs was assessed using the standard Cochrane Risk of Bias tool, and the quality of observational studies was analysed with the modified Agency for Healthcare Research and Quality (AHRQ) quality assessment criteria.
"The overall quality of the RCTs was poor (n = 4) to moderate (n = 12), no high quality studies were identified. For observational studies, the risk of bias ranged from 31 to 79% with a mean weighted score 52.8% SD ± 11.8% which again suggests overall moderate quality"

Heterogeneity: no meta-analysis was performed.

Publication Bias: not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of RCTs and oberservational studies.
No a priori clear aim or outcomes of interest. Not a meta-analysis but synthesis of qualitative data.

Nieuwenhuis, L. L. et al. Three?dimensional saline infusion sonography compared to two?dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database of Systematic Reviews. . . 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review of diagnostic studies (13 studies) To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS for the	**Population:** Populations of interest were premenopausal women with AUB or subfertility and postmenopausal women with AUB. **Intervention:** Studies comparing the diagnostic accuracy of 3D SIS alone	**Primary:** Diagnostic accuracy for diagnosis of focally growing lesions. **Secondary:** type of abnormality and discrimination between uterine polyps and submucous fibroids in with hysteroscopy and histology used as the	13 studies included: Aboulghar 2011, Adel 2014, de Kroon 2004, El-Sherbiny 2011, El-Sherbiny 2015, Katsetos 2013, Kowalsky 2012,

Nieuwenhuis, L. L. et al. Three?dimensional saline infusion sonography compared to two?dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database of Systematic Reviews. . . 2017				
diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test. **Databases:** We searched the following databases: Cochrane Central Register of Studies Online (CENTRAL CRSO), MEDLINE, Embase, PubMed, Cochrane Gynaecology and Fertility Group (CGF) Specialised Register and CGFG Diagnostic Test Accuracy (DTA) Specialised Register, clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Screening reference lists of appropriate studies was also performed. We performed searches with no language restrictions. **Search period:** Inception - 03/2016.	(index test 1) or 2D+3D SIS (index test 2) versus 2D SIS (comparator test). We defined SIS as positive for a focal intrauterine lesion when any distortion of the endometrial lining was visualised (see below). We preferred that time between index test and reference standard was less than one month. **Comparison:** see intervention	reference. **Results:** Only summary described here, rest see article. **Study overview:** 13 studies (1053 women) reported the accuracy of 3D SIS for focal uterine abnormalities; 11 of these (846 women) were suitable for meta-analysis, and eight reported accuracy according to the type of focal abnormality. The design of the included studies seems applicable. The main problem involving the quality of included studies is insufficient reporting of study methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, we considered the overall quality of the evidence as low. **Results:** The summary estimate (11 studies reporting absence or presence of abnormality at 3D SIS) for sensitivity was 94.5% (95% confidence interval (CI) 90.6% to 96.9%) and for specificity 99.4% (95% CI 96.2% to 99.9%). Meta-analysis of the eight studies (N = 716) directly comparing 2D SIS versus 3D SIS	Kupesich 2007, La Torre 1999, Makris 2007, Nieuwenhuis 2014, Sconfienza 2010, Sylvestre 2003.	

Nieuwenhuis, L. L. et al. Three?dimensional saline infusion sonography compared to two?dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database of Systematic Reviews. . . 2017				
Inclusion Criteria: The population of interest consisted of premenopausal women with AUB or subfertility and postmenopausal women with AUB. Diagnostic test accuracy studies, randomised controlled trials (RCTs) and prospective cohort studies were eligible for inclusion if they evaluated the accuracy of both 2D SIS and 3D SIS for the diagnosis of acquired intracavitary abnormalities with hysteroscopy used as the reference standard. In light of the lack of data for 3D SIS, we also included studies that evaluated the accuracy of 3D SIS alone. **Exclusion Criteria:** We excluded case control, case report and retrospective cohort studies.		showed summary sensitivity of 96.9% (95% CI 91.9% to 98.8%) and summary specificity of 99.5% (95% CI 96.1% to 100%) for 3D SIS. For 2D SIS, summary sensitivity was 90.9% (95% CI 81.2% to 95.8%) and summary specificity was 96.3% (95% CI 86.1% to 99.1%). The diJerence in accuracy between 2D SIS and 3D SIS was non-significant (P values of 0.07 for sensitivity and 0.10 for specificity). **Author's Conclusion:** Implications for practice: Low-quality evidence showed that 3D SIS is highly accurate in detecting intracavitary abnormalities. Meta-analysis revealed no statistically significant diJerences between 2D SIS and 3D SIS. Summary sensitivity and specificity are higher for 3D SIS, but margins of improvement are limited in that 2D SIS is already very accurate. 3D SIS is an alternative to 2D SIS when the technology and appropriate expertise are available. Both 2D SIS and 3D SIS should be considered alternatives to		

Nieuwenhuis, L. L. et al. Three?dimensional saline infusion sonography compared to two?dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database of Systematic Reviews. . . 2017				
		diagnostic hysteroscopy when intracavitary pathology is suspected in both subfertile women and those with abnormal uterine bleeding.		
Methodical Notes				
Funding Sources: Internal sources · VU University Medical Center, Netherlands. External sources · None, Other. **COI:** The review authors have no conflicts of interest and no financial ties to disclose. **Study Quality:** Two review authors extracted data and assessed studies for methodological quality using the QUADAS-2 tool. The overall quality of the evidence was considered to be low. **Heterogeneity:** We addressed heterogeneity by adding variables to the bivariate model as covariates if both subgroups included at least three studies. We performed these analyses for clinical symptoms (bleeding vs subfertility); prior testing (prior testing or not); and whether evaluation of 2D or 3D SIS was blinded for clinical information. We also assessed heterogeneity with forest plots and ROC plot. "This review included a broad spectrum of patients and methodological diJerences that resulted in a heterogeneous group, impeding meta-analysis." **Publication Bias:** not investigated, no meta-analysis was performed. **Notes:**				

Nieuwenhuis, L. L. et al. Three?dimensional saline infusion sonography compared to two?dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database of Systematic Reviews. . . 2017			
Oxford level of Evidence: 2 Systematic review and meta-analysis of RCTs and cohort studies. No meta-analysis was performed due to heterogeneity. Quality of studies was considered to be low.			
Verdoodt, F. et al. High-risk HPV testing in the management of atypical glandular cells: A systematic review and meta-analysis. Int J Cancer. 138. 303-10. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and diagnostic meta-analysis (12 studies) To evaluate the usefulness of hrHPV testing in the management of women with a cytological diagnosis of AGC is evaluated. **Databases:** Medline, EMBASE, and CENTRAL. No language or publication date restrictions were applied. Additionally, studies that cited, and were cited by a previous metaanalysis on AGC and other pertinent studies were browsed for additional relevant references using Scopus.	**Population:** Specimens from women participating in cytological screening with AGC or AGUS. **Intervention:** hrHPV testing was performed by HC2, **Comparison:** reference standard.	**Primary:** Sensitivity, Specificity, disease rate, diagnosis of extra-cervical cancer. **Secondary:** - **Results: Study overview:** A bibliographic database search identified 12 eligible studies. **Results:** The occurrence of cervical intraepithelial neoplasia grade two or worse including AIS1 (CIN21/AIS1), was 19.8% among women with AGC, and 55.7% among women with AGC and concurrent squamous lesions (atypical squamous cells of undetermined significance or worse, ASC-US1). The pooled sensitivity and specificity of hrHPV-testing with	12 studies included: Ronnett 1999, Derchain 2004, Chen 2005, Irvin 2005, Fetterman 2006, Saqi 2006, deOliveira 2006, Liao 2009, Schnatz 2009, Castle 2010, Zhao 2010, Anderson 2012.

Verdoodt, F. et al. High-risk HPV testing in the management of atypical glandular cells: A systematic review and meta-analysis. Int J Cancer. 138. 303-10. 2016				
Search period: Search period not mentioned. **Inclusion Criteria:** (i) specimens from women participating in cytological screening, with AGC or AGUS were included, (ii) hrHPV testing was performed by HC2, and (iii) all specimens were verified with a reference standard. In this systematic review, studies were eligible whether or not a distinction was made between subtypes of AGC. Clinical evaluation including colposcopy and directed biopsy, with or without endocervical curettage was considered as the reference standard. Follow-up cytology of women with a normal colposcopy was accepted as a valid outcome. **Exclusion Criteria:** No clear definition of a priori exclusion criteria. Studies were excluded due to (i) no primary data (n=11); (ii) no AGC/AGUS or		Hybrid Capture 2 (HC2) to detect CIN21/AIS1 in women with AGC was 90.0% (95% CI 85.1–93.4%) and 75.1% (95% CI 64.8–83.2%), respectively. Women who were hrHPV-negative, demonstrated an increased risk for extra-cervical malignancy (endometrium, fallopian tube, ovary). In women of 50y and older, a hrHPV-negative result was linked with a 18.0% chance of extra-cervical malignancy, while the chance of cervical pre-cancer and cancer was 0.4 and 0.0%, respectively. **Author's Conclusion:** "In summary, our meta-analysis shows that a diagnosis of AGC on cytology has a high predictive value for high-grade histological abnormalities, which justifies the policy of immediate referral for colposcopy and endocervical sampling. However, our findings support the usefulness of hrHPV test results in combination with age as a guidance to put emphasis on extra-cervical areas during the work-up. Particularly, a negative hrHPV test result in women 50 years of age or older can raise		

Verdoodt, F. et al. High-risk HPV testing in the management of atypical glandular cells: A systematic review and meta-analysis. Int J Cancer. 138. 303-10. 2016				
		caution regarding endometrial, or extra-uterine, disease."		

Methodical Notes

Funding Sources: DG Research of the European Commission through the CoheaHr network (603019); International Agency for Research on Cancer (IARC, Lyon, France); European Federation for Colposcopy (Birmingham, UK); German Guideline Program in Oncology (German Cancer Aid project #110163)

COI: Not stated.

Study Quality: An evaluation of the quality of each study was performed using the second version of the checklist for quality assessment of diagnostic accuracy studies (QUADAS-2). "Overall, no concerns were raised concerning blinding of the triage-test, because of the automatic reading of HC2 test results."
Results of quality assesment reported in supplementals, no overall statement regarding quality of studies.

Heterogeneity: No description of methodology, or treshold. High heterogeneity in the specificity analysis (I2= 90%).

Publication Bias: Publication bias not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive studies or studies without consistently applied reference standards.
Downgrade to evidence level 3.
Search period not mentioned. Unclear definition of outcomes. No declaration of conflicts of interest. Publication bias not investigated. High heterogeneity in the specificity analysis, without extensive discussion."

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma. **Databases:** MEDLINE, EMBASE, ClinicalTrials.gov, and the Cochrane library **Search period:** Inception to 01/2017 **Inclusion Criteria:** In eligible studies, the index test included office endometrial biopsy, hysteroscopic biopsy, or dilatation and curettage; the reference standard was hysterectomy. Outcome measures included tumor grade, histologic subtype, or both. **Exclusion Criteria:** Conference abstracts, case reports and papers containing less	**Population:** Women with endometrial carcinoma **Intervention:** Preoperative endomentrial sampling: Index test included office endometrial biopsy, hysteroscopic biopsy, or D&C; **Comparison:** Hysterectomy as reference standard.	**Primary:** Accuracy of diagnosis of tumor grade and histologica subtype, Inter rater Kappa. **Secondary:** - **Results: Study overview:** A total of 45 studies (12,459 patients) met the inclusion criteria. **Results:** The pooled agreement rate on tumor grade was 0.67 (95% CI 0.60– 0.75) and Cohen's k was 0.45 (95% CI 0.34–0.55). Agreement between hysteroscopic biopsy and final diagnosis was higher (0.89, 95% CI 0.80–0.98) than for dilatation and curettage (0.70, 95% CI 0.60–0.79; P5.02); however, it was not significantly higher than for office endometrial biopsy (0.73, 95% CI 0.60–0.86; P5.08). The lowest agreement rate was found for grade 2 carcinomas (0.61, 95% CI 0.53–0.69). Downgrading was found in 25% and upgrading was found in 21% of the endometrial samples. Agreement on	45 studies included: see article.

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017				
than five patients, review articles, absence of hysterectomy or preoperative histology, intraoperative frozen biopsies, not in English, lack of the percentage of agreement, and absence of possibilities to calculate these from available data.		histologic subtypes was 0.95 (95% CI 0.94–0.97) and 0.81 (95% CI 0.69–0.92) for preoperative endometrioid and nonendometrioid carcinomas, respectively. **Author's Conclusion:** "Overall there is only moderate agreement on tumor grade between preoperative endometrial sampling and final diagnosis with the lowest agreement for grade 2 carcinomas."		
Methodical Notes				
Funding Sources: none declared. **COI:** The authors did not report any potential conflicts of interest. **Study Quality:** Risk of bias was assessed (Quality Assessment of Diagnostic Accuracy Studies). "Overall, the risk of bias was unclear in most studies, which was mainly attributable to patient selection and interpretation of the index test and reference standard" **Heterogeneity:** To test the amount of heterogeneity between the studies, I 2 statistic was used. Our outcomes are characterized by high heterogeneity. 59-95%. **Publication Bias:** Investigated but not shown. "Funnel plots for the primary outcome did not indicate any publication bias (data not shown)."				

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive diagnostic study or studies without consistently applied reference standard.
Downgrade to evidence level 3.
Unclear definition of population. Predominantly unclear risk of bias in included studies. HIgh heterogeneity in all analyses. Publication bias investigated but not shown.

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018			
Population	Intervention	Outcomes/Results	
Evidence level: 4 **Study type:** Genetic association study (cohort of patients from 6 centers) To investigate whether molecular classification can be used to refine prognosis in grade 3 endometrioid endometrial carcinomas (EECs). **Number of Patient:** 381 **Recruitung Phase:** not described. **Inclusion Criteria:** Institutional approval for this study was obtained from each of the participating centers. FIGO grade 3 EECs with clinical follow-up data were collected from 6 institutions in Europe and North America (Table 1). Strict diagnostic criteria were applied, as follows: 1) tumors demonstrated endometrioid lineage evidenced by a component of low-grade endometrioid adenocarcinoma with low-intermediate nuclear grade and/or metaplasias	**Intervention:** POLE sequencing for hotspots in the exonuclease domain (exons 9–14) was performed using either Sanger or next-generation approaches, as described previously. Either 2 (PMS2 and MSH6) or 4 (MLH1, PMS2, MSH2, MSH6) DNA mismatch repair IHC markers were performed on representative sections at the referring institution, as well as p53 IHC staining. Grade 3 EECs were classified into four subgroups: p53-abnormal, based on mutant-like immunostaining (p53abn); MMR-deficient, based on loss of mismatch repair protein expression (MMRd); presence of POLE exonuclease domain hotspot mutation (POLE); no specific molecular profile (NSMP), in which none of these aberrations were present. **Comparison:** -	**Primary:** Overall (OS), and recurrence-free survival (RFS) rates were compared using the Kaplan-Meier method (Log-Rank test) and univariable and multivariable Cox proportional hazard models. **Secondary:** - **Results: Study population:** 281 patients met the inclusion criteria. Median follow-up was 6.1 years (range 0.2–17.0). Median age was 66 years (range 33–96). The FIGO 2009 stage distribution was as follows: IA, 44.9%; IB, 31.5%; II, 6.3%; III, 13.1%; IV, 2.9%. Results: There were 49 (12.9%) POLE, 79 (20.7%) p53abn, 115 (30.2%) NSMP, and 138 (36.2%) MMRd tumors. Median follow-up of patients was 6.1 years (range 0.2–17.0). Compared to patients with NSMP, patients with POLE mutant grade 3 EEC (OS: Hazard Ratio [HR] 0.36 [95%CI: 0.18–0.70], p=0.003; RFS: HR 0.17 [0.05–0.54], p=0.003) had a	

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018

typical of endometrioid differentiation. **Exclusion Criteria:** Exclusion of histological mimics (i.e. "confirmatory endometrioid features"); 2) tumors were characterized by predominantly solid architecture exclusive of squamous differentiation, or mixtures of glandular and solid architecture with diffusely distributed high-grade nuclei.		significantly better prognosis; patients with p53abn tumors had a significantly worse RFS (HR 1.73 [1.09–2.74], p0.021); patients with MMRd tumors showed a trend towards better RFS. Estimated 5-year OS rates were as follows: POLE 89%, MMRd 75%, NSMP 69%, p53abn 55% (Log Rank p=0.001). Five-year RFS rates were as follows: POLE 96%, MMRd 77%, NSMP 64%, p53abn 47% (p=0.000001), respectively. In a multivariable Cox model that included age and FIGO stage, POLE and MMRd status remained independent prognostic factors for better RFS; p53 status was an independent prognostic factor for worse RFS. Molecular classification of grade 3 EECs reveals that these tumors are a mixture of molecular subtypes of endometrial carcinoma, rather than a homogeneous group. **Author's Conclusion:** In summary, we have shown that the pathologic entity typically recognized as "FIGO grade 3 endometrioid carcinoma" is, in reality, a collection of at least four distinct disease types. In this era of increasingly individualized patient care, the elucidation and recognition of these	

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018			
		subgroups will contribute significantly to prognostication and the selection of novel therapeutics.	
Methodical Notes			
Funding Sources: Funding: This study was funded in part by the Dutch Cancer Society (KWF-UL2012-5719) (Dr. Bosse, Dr. Nout). This study was funded in part through the NIH/NCI Support Grant P30 CA008748 (Dr. Abu-Rustum, Dr. Levine, Dr. Soslow). **COI:** The authors have no conflicts of interest to disclose. **Randomization:** - **Blinding:** - **Dropout Rate/ITT-Analysis:** - **Notes:** Oxford level of evidence: 3 Cohort study. **Downgrade to evidence level 4.** Lacking description of the cohort and participating centers. Lack of replication cohort.			

2.4. Schlüsselfrage 04: Welche Verfahren wie beispielsweise transvaginale Sonographie, zytologische Beurteilung, Endometriumbiopsie mittels Aspiration, Hysteroskopie oder Tumormarker-Bestimmung an Aspiraten, HPV-Bestimmung, Familienanamnese sind bei der asymptomatischen Frau mit hohem Risiko geeignet zur Früherkennung des Endometriumkarzinoms im Hinblick auf Lebensqualität, Kurzzeit-/ Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Kahn, R. M. 2019	2	Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 2 **Study type:** Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer. **Databases:** PubMed, EMBASE, MEDLINE, and the Cochrane Library was performed. **Search period:** 1990-2018. **Inclusion Criteria:** 1) prospective studies, 2) studies of patients with known endometrial cancer, 3) studies whose patients underwent germline genetic testing for Lynch syndrome after positive screening, and 4) studies whose patients underwent tumor testing with MMR IHC with or without MLH1 methylation and/or	**Population:** Patients with known endometrial cancer **Intervention:** MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI). **Comparison:** each other intervention	**Primary:** Prevalence of lynch syndrome, MSI germline mutation, IHC Abnormality. **Secondary:** - **Results: Study overview:** The comprehensive search produced 4400 publications. 29 peer-reviewed studies met the inclusion criteria. **Results:** Patients with endometrial cancer (n = 6649) were identified, and 206 (3%) were confirmed to have Lynch syndrome through germline genetic testing after positive universal tumor molecular screening. Among 5917 patients who underwent tumor IHC, 28% had abnormal staining. Among 3140 patients who underwent MSI analysis, 31% had MSI. Among patients with endometrial cancer, the weighted prevalence of Lynch syndrome germline mutations was 15% (95% confidence interval [CI], 11%-18%) with deficient IHC staining and 19% (95% CI, 13%-26%) with a	29 studies included, see article.	

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019				
MSI analysis. **Exclusion Criteria:** 1) retrospective studies, 2) studies without endometrial cancer, 3) studies whose subjects had confirmed Lynch syndrome before the study, and 4) studies whose subjects did not undergo genetic testing for Lynch syndrome after positive screening.		positive MSI analysis. Among 1159 patients who exhibited a loss of MLH1 staining, 143 (13.7%) were found to be MLH1 methylation-negative among those who underwent methylation testing, and 32 demonstrated a germline MLH1 mutation (2.8% of all absent MLH1 staining cases and 22.4% of all MLH1 methylation-negative cases). Forty-three percent of patients with endometrial cancer who were diagnosed with Lynch syndrome via tumor typing would have been missed by family history-based screening alone. **Author's Conclusion:** "Overall, this study demonstrates that a significant proportion of patients with endometrial cancer have abnormal tumor IHC/MSI. Medical practitioners counseling patients about these results should be aware of the risk of identifying a Lynch syndrome germline mutation among patients with abnormal tumor testing. We found that a large number of the patients and families diagnosed with Lynch syndrome would have been missed by traditional methods such as family history-based screening. This study provides evidence to further support the widespread implementation of molecular		

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019

		screening for all women diagnosed with endometrial cancer. Furthermore, once patients are found to be at risk for Lynch syndrome through positive screening, a greater effort to counsel them during follow-up with genetic counseling and testing is imperative."		

Methodical Notes

Funding Sources: Gulce Askin and Paul J. Christos report funding from the Weill Cornell Medicine Clinical and Translational Science Center (grant 1-UL1-TR002384-01) during the conduct of this study.

COI: Kevin Holcomb reports other from Johnson and Johnson and funding from Fujirebio Diagnostics, Inc, outside the submitted work. The other authors made no disclosures.

Study Quality: "All 29 selected studies that met the inclusion criteria underwent a quality assessment with the Cochrane risk-of-bias tool. On the basis of the consensus of 2 independent reviewers for each individual study, the risk of bias for sequence generation was low, the risk of bias for incomplete outcome data was low, the risk of bias for selective outcome reporting was low, and the risk of bias for other sources of bias was low."

Heterogeneity: Statistical heterogeneity was assessed with the Cochran Q test and the I2 statistic, and heterogeneity was considered present when $P < .20$ and $I2 \geq 50\%$, respectively.
"Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history."

Publication Bias: The presence of a publication bias was evaluated with funnel plots and the Begg-Mazumdar rank-correlation test.

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies.
Unclear definition of outcomes. Heterogeneity investigated but not reported (supposedly high "Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history."). Study quality investigated, but not reported.

Literaturstelle	Evidenzlevel	Studientyp
Adar, T. 2018	3	Multicentric prospective cohort study for genetic screening "To determine the added value of screening both CRC and EC tumors in the same population."
Bellido, F. 2016	3	Genetic association cohort study To gain a better understanding of the phenotypic characteristics of this syndrome to establish specific criteria for POLE and POLD1 mutation screening and to help define the clinical management of mutation carriers.
Cheewakriangkrai, C. 2020	1	Systematic review and meta-analysis (0 articles included.) To assess the effectiveness of health education interventions targeting healthcare providers, or individuals, or both, to promote early presentation and referral for women with endometrial cancer symptoms.
Dominguez-Valentin, M. 2020	3	Genetic association cohort study with validation cohort To provide age and organspecific cancer risks according to gene and gender and to determine survival after cancer.
Helder-Woolderink, J. M. 2016	3	Systematic review (49 studies). "The aim of this systematic review was to analyse all published studies on ovarian cancer in women with LS, regarding the age of onset of ovarian cancer, the histopathological type and FIGO stage and evaluate the role of surveillance in the detection of (early stage) ovarian cancer in LS."
Kahn, R. M. 2019	2	Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer.
Le, D. T. 2017	3	Non-randomized open-label phase 2 trial
Møller, P. 2017	3	Genetic association in a prospective, multicentric cohort study.
Ryan, N. A. J. 2019	2	Systematic review and meta-analysis. (59 studies) To provide accurate data estimating the outcomes of testing for LS in EC patients.

2.5. Schlüsselfrage 05: Beeinflussen genetische Faktoren das Risiko für das Auftreten eines Endometriumkarzinoms?

Inhalt: *9 Literaturstellen*

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *4 Bewertung(en)*

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 **Study type:** Systematic review and meta-analysis (0 articles included.) To assess the effectiveness of health education interventions targeting healthcare providers, or individuals, or both, to promote early presentation and referral for women with endometrial cancer symptoms. **Databases:** CENTRAL, MEDLINE and Embase. We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of review articles. **Search period:** Inception-02/2020. **Inclusion Criteria:** Randomised controlled trials (RCTs), both individually randomised and cluster-	**Population:** Woman aged 18 years or older in any setting who experienced symptoms suspicious for endometrial cancer. We planned to include any healthcare providers of any age, gender, or profession (e.g. nurse, doctor, allied staF), in any public or private healthcare facility. In addition, as we planned to recruit cluster- RCTs to this review, participants could thus be communities or healthcare institutions or other units. We planned to perform a separate analysis for diFerent types of participants (individuals who experienced suspicious symptoms of endometrial cancer and healthcare providers). **Intervention:** Interventions of interest were any health education interventions performed with the aim of promoting the early presentation and referral of women with symptoms suspicious of endometrial	**Primary:** · Overall survival: defined as survival of women with endometrial cancer from diagnosis from all causes · Disease-free survival: defined as survival of women with endometrial cancer until the appearance of a new lesion of disease **Secondary:** Definitions see article: · Delayed referral · Delayed presentation · Referral time · Presentation time or time of help-seeking · Conversion rate · Detection rate: · Time from presentation to receiving definite treatment (days) · Women's satisfaction with the referral process · Physicians' satisfaction with the referral	No studies included.	

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020				
RCTs. In the absence of RCTs we planned to include well-designed non-randomised studies (NRS) with a parallel comparison assessing the benefits of any type of health education interventions. **Exclusion Criteria:** We planned to exclude cross-over RCTs due to the nature of the question of the review. If we identified no RCTs, we planned to include non-randomised studies (NRS) with a parallel comparison. We intended to include NRS that analysed results for intervention eFects adjusted for baseline characteristics, that is, participants'age and menopausal status. We planned to exclude NRS without a concurrent comparison group.	cancer. Interventions could target individuals, healthcare providers, or both. We planned to include studies regardless of their level of delivery of the intervention (individual or public or community). Interventions aimed at the individual level could be health education outreach visits, meetings, or printed educational materials. Communitybased health education interventions could be mass media campaigns, health education website, or posters distributed indiscriminately in public areas. **Comparison:** Control (presumably usual or standard practice), or directed, head-to-head educational interventions.	process: · Quality of life · Cost-effectiveness of the intervention **Results:** "We planned to include randomised controlled trials (studies in which people or groups of people are allocated by chance to two or more groups, treating them differently). In the absence of randomised controlled trials, we planned to include studies where participants were not randomised but that included an assessment of the benefits of health education compared to no health education. We searched scientific databases and checked the titles and abstracts of 4880 possibly relevant articles and assessed the full text of 16 of these references. However, we found no studies that met our inclusion criteria." **Author's Conclusion:** Implications for practice: At present, there is an absence of evidence to indicate the effectiveness of health education interventions involving		

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020				
		healthcare providers or individuals, or both, to promote the early presentation and early referral for women with symptoms suspicious of endometrial cancer. This again highlights that endometrial cancer is under-resourced, in terms of funding and research, given its relatively high incidence in high-income countries, compared to other cancer types.		
Methodical Notes				
Funding Sources: Internal sources · Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiang Mai University, Thailand. · Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand. · Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Thailand. · Campbell South Asia, New Delhi, India. · Cochrane Thailand, Thailand. **External sources** · Thailand Research Fund (Distinguished Professor Award), Thailand. · Long-term Institutional Development HUBs (LID-HUBs), the Human Reproduction Programme (HRP) Alliance for Research Capacity Strengthening, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland. **COI:** Declared, none known.				

Cheewakriangkrai, C. et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database of Systematic Reviews. . . 2020

Study Quality: No quality was evaluated, because no studies were included.

Heterogeneity: no meta-analysis was performed.

Publication Bias: Investigation not possible

Notes:
Oxford level of evidence: 1 Systematic review and meta-analysis.
Although the article is well written it does no include any results, due to no studies meeting the inclusion criteria. Therfor this articles' implications are limited. No studies are included in this recent article (last searches 02/2020) which points toward no literature being available investigating the described relation).

Helder-Woolderink, J. M. et al. Ovarian cancer in Lynch syndrome; a systematic review. Eur J Cancer. 55. 65-73. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review (49 studies). "The aim of this systematic review was to analyse all published studies on ovarian cancer in women with LS, regarding the age of onset of ovarian cancer, the	**Population:** Ovarian cancer patients with LS mutation or who are a first degree relative of a family member with LS or patients that fulfilled the Amsterdam II criteria **Intervention:** -	**Primary:** diagnosis, histological type, FIGO stage, age of onset. **Secondary:** - **Results: Study overview:** The quality score of the 49 identified studies was at least 6 out of 8 and provide clinical information on 747 LS women with	49 studies included, see article for list.

Helder-Woolderink, J. M. et al. Ovarian cancer in Lynch syndrome; a systematic review. Eur J Cancer. 55. 65-73. 2016				
histopathological type and FIGO stage and evaluate the role of surveillance in the detection of (early stage) ovarian cancer in LS." **Databases:** MEDLINE database. In addition, the references of the included publications were screened to evaluate if relevant articles might have been missed. **Search period:** 01/1979 until 04/2015. **Inclusion Criteria:** Studies were included if they contained information on ovarian cancer patients that carry an LS mutation or patients who are a first degree relative of a family member with LS or patients that fulfilled the Amsterdam II criteria and if they presented data on the women's age of onset of ovarian cancer, and/or the histopathology, and/or FIGO stage. **Exclusion Criteria:** Excluded were studies describing ovarian cancer in women without LS mutation or first degree relatives. Also excluded were studies with ovarian cancer in women with LS or first degree relatives without information on any of the following items:	**Comparison:** -	ovarian cancer. The mean age at diagnosis was 45.3 (range 19.82) years. **Results:** Most frequent mutations were MSH2 (47%) and MLH1 (38%). Histopathological data were available for 445 women. The most frequently reported histological type was mixed type (mucinous/endometrioid/clear cell carcinomas) (n Z 136; 31%). Most tumours (281, 65%) were diagnosed at an early stage (FIGO I/ II). Six studies evaluating the effect of surveillance of ovarian cancer, reported that seven of 22 (32%) ovarian cancers were found during surveillance, 6/7 (86%) were detected at an early stage. **Author's Conclusion:** "In conclusion, ovarian cancer in women with LS may develop < age of 35 years, although with a wide agerange and is often (65%) diagnosed at an early stage with most often endometrioid/clear cell histology and a good overall survival. The role of surveillance in early detection could not be elucidated due to scares data however detection at an early stage seems possible."		

Helder-Woolderink, J. M. et al. Ovarian cancer in Lynch syndrome; a systematic review. Eur J Cancer. 55. 65-73. 2016				
age of onset, histopathology or FIGO stage.				
Methodical Notes				
Funding Sources: none delcared. **COI:** The authors declare that there are no conflicts of interest. **Study Quality:** The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). The quality of the included studies using the NOS was high. The 31 cohort studies and 11 case control studies scored 6 out of 8 or more. **Heterogeneity:** not investigated, no meta-analysis was performed. **Publication Bias:** not investigated, no meta-analysis was performed. **Notes:** Oxford level of evidence: 3 Systematic review of cohort, family, case-control and case reports Only one database was searched, which is not considered to be a comprehensive literature search. Lacking description of study aim.				
Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019			
Evidence level: 2 **Study type:** Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer. **Databases:** PubMed, EMBASE, MEDLINE, and the Cochrane Library was performed. **Search period:** 1990-2018. **Inclusion Criteria:** 1) prospective studies, 2) studies of patients with known endometrial cancer, 3) studies whose patients underwent germline genetic testing for Lynch syndrome after positive screening, and 4) studies whose patients underwent tumor testing with MMR IHC with or without MLH1 methylation and/or MSI analysis. **Exclusion Criteria:** 1) retrospective studies, 2) studies without endometrial cancer, 3) studies whose subjects had confirmed Lynch syndrome before the study, and 4) studies	**Population:** Patients with known endometrial cancer **Intervention:** MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI). **Comparison:** each other intervention	**Primary:** Prevalence of lynch syndrome, MSI germline mutation, IHC Abnormality. **Secondary:** - **Results: Study overview:** The comprehensive search produced 4400 publications. 29 peer-reviewed studies met the inclusion criteria. **Results:** Patients with endometrial cancer (n = 6649) were identified, and 206 (3%) were confirmed to have Lynch syndrome through germline genetic testing after positive universal tumor molecular screening. Among 5917 patients who underwent tumor IHC, 28% had abnormal staining. Among 3140 patients who underwent MSI analysis, 31% had MSI. Among patients with endometrial cancer, the weighted prevalence of Lynch syndrome germline mutations was 15% (95% confidence interval [CI], 11%-18%) with deficient IHC staining and 19% (95% CI, 13%-26%) with a positive MSI analysis. Among 1159 patients who exhibited a loss of MLH1 staining, 143 (13.7%) were found to be MLH1 methylation–negative among those who underwent methylation testing, and 32 demonstrated a germline MLH1 mutation (2.8% of all absent	29 studies included, see article.

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019				
whose subjects did not undergo genetic testing for Lynch syndrome after positive screening.		MLH1 staining cases and 22.4% of all MLH1 methylation–negative cases). Forty-three percent of patients with endometrial cancer who were diagnosed with Lynch syndrome via tumor typing would have been missed by family history–based screening alone. **Author's Conclusion:** "Overall, this study demonstrates that a significant proportion of patients with endometrial cancer have abnormal tumor IHC/MSI. Medical practitioners counseling patients about these results should be aware of the risk of identifying a Lynch syndrome germline mutation among patients with abnormal tumor testing. We found that a large number of the patients and families diagnosed with Lynch syndrome would have been missed by traditional methods such as family history–based screening. This study provides evidence to further support the widespread implementation of molecular screening for all women diagnosed with endometrial cancer. Furthermore, once patients are found to be at risk for Lynch syndrome through positive screening, a greater effort to counsel them during follow-		

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019

		up with genetic counseling and testing is imperative."		

Methodical Notes

Funding Sources: Gulce Askin and Paul J. Christos report funding from the Weill Cornell Medicine Clinical and Translational Science Center (grant 1-UL1-TR002384-01) during the conduct of this study.

COI: Kevin Holcomb reports other from Johnson and Johnson and funding from Fujirebio Diagnostics, Inc, outside the submitted work. The other authors made no disclosures.

Study Quality: "All 29 selected studies that met the inclusion criteria underwent a quality assessment with the Cochrane risk-of-bias tool. On the basis of the consensus of 2 independent reviewers for each individual study, the risk of bias for sequence generation was low, the risk of bias for incomplete outcome data was low, the risk of bias for selective outcome reporting was low, and the risk of bias for other sources of bias was low."

Heterogeneity: Statistical heterogeneity was assessed with the Cochran Q test and the I2 statistic, and heterogeneity was considered present when $P < .20$ and $I2 \geq 50\%$, respectively.
"Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history."

Publication Bias: The presence of a publication bias was evaluated with funnel plots and the Begg-Mazumdar rank-correlation test.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies.
Unclear definition of outcomes. Heterogeneity investigated but not reported (supposedly high "Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history."). Study quality investigated, but not reported.

Ryan, N. A. J. et al. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 21. 2167-2180. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis. (59 studies) To provide accurate data estimating the outcomes of testing for LS in EC patients. **Databases:** Medline, Embase, Cochrane CENTRAL, and Web of Science were searched. Citation searching was utilized to augment the initial results. **Search period:** Inception - 07/2018. **Inclusion Criteria:** Only studies investigating LS in an EC population were included. Initial searches were limited by English language, human adults (>18 years), and female subjects. Only studies that used either direct germline analysis for pathogenic variants of MMR genes or proxy tumor-based molecular diagnostic methods (IHC, MSI with or without MLH1 promoter hypermethylation), or any combination of these were included.	**Population:** Human adult females (>18 years) with endometrial cancer(EC). **Intervention:** Direct germline analysis for pathogenic variants of MMR genes or proxy tumor-based molecular diagnostic methods (IHC, MSI with or without MLH1 promoter hypermethylation). **Comparison:** -	**Primary:** The proportion of EC patients who were identified as being likely lynch syndrome (LS) (aberrant MMR IHC expression, MSI-H with or without MLH1 promoter hypermethylation) or as carrying a germline MMR pathogenic variant. **Secondary:** - **Results: Study overview:** 53 studies, including 12,633 EC patients, met the inclusion criteria. **Results:** The overall proportion of endometrial tumors with microsatellite instability or mismatch repair (MMR) deficiency by immunohistochemistry (IHC) was 0.27 (95% confidence interval [CI] 0.25–0.28, I2: 71%) and 0.26 (95% CI 0.25–0.27, I2: 88%), respectively. Of those women with abnormal tumor testing, 0.29 (95% CI 0.25–0.33, I2: 83%) had LS-associated pathogenic variants on germline testing; therefore around 3% of ECs can be attributed to LS. Preselection of EC cases did increase the proportion of germline LS diagnoses.	53 studies included. List see article.

Ryan, N. A. J. et al. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 21. 2167-2180. 2019				
Microsatellite instability-high (MSI-H) was defined, where possible, as involving ≥30% of the included microsatellite markers. An IHC positive result was taken as loss of expression of one of the MMR proteins. Pathogenic variants of MMR genes were defined as per the authors' analysis. To avoid double counting data, authors of more than one study were contacted for clarification and/or registry analysis was crosschecked. Only articles that contributed at least 15 participants were included. **Exclusion Criteria:** Where there was overlapping data, the larger study was included and the smaller excluded.		**Author's Conclusion:** "In summary, ours is the first meta-analysis to examine the proportion of EC cases that are associated with LS. Different tumor triage methods did not affect estimates of the proportion of EC associated with LS, which remained constant at around 3%. Our findings suggest that a similar proportion of EC patients will test positive for LS as seen in CRC LS screening. This supports the move toward the introduction of universal screening for LS in EC."		
Methodical Notes				
Funding Sources: declared, see article for extensive list. **COI:** The authors declare no conflicts of interest. **Study Quality:** Assessment of bias analysis was conducted by three reviewers independently using Review Manager. Quality was reported in supplemental section, which is not available. No overall assesment of quality available.				

Ryan, N. A. J. et al. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 21. 2167-2180. 2019

Heterogeneity: I2 score was used to assess heterogeneity across studies. "The heterogeneity across the studies included in our review was high, and limits the strength of our conclusions. This is a reflection of the varying quality and rigor of the included studies, some of which had small numbers of participants, and were subject to bias."

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-randomized controlled or follow-up studies.
The grey literature and nonelectronic literature were not included. Assessment of study quality was reported in supplemental section, which is not available. No overall assesment of quality available. Heterogeneity present in all analyeses with I2 ranging from 60-90%.

NEWCASTLE - OTTAWA Checklist: Cohort: *5 Bewertung(en)*

Adar, T. et al. Universal screening of both endometrial and colon cancers increases the detection of Lynch syndrome. Cancer. 124. 3145-3153. 2018

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Multicentric prospective cohort study for genetic screening "To determine the added value of	**Funding sources:** No specific funding was disclosed. **Conflict of Interests:** Tomer Adar received fellowship grants from the American Physicians Fellowship for Medicine in Israel, the Israel Cancer Association, and the Israel Gastroenterology Association. Anthony J. Iafrate reports personal fees from ArcherDx	**Total no. patients:** 1290 with CRC and 484 with EC. **Recruiting Phase:** 2013-2015. **Inclusion criteria:** All patients who had newly diagnosed CRC and EC at 2 sites: Massachusetts General Hospital (a tertiary care	**Interventions:** An IHC-based universal screening program for LS using 4 MMR proteins (MLH1, MSH2, MSH6, and PMS2), **Comparison:** Amsterdam criteria,

Adar, T. et al. Universal screening of both endometrial and colon cancers increases the detection of Lynch syndrome. Cancer. 124. 3145-3153. 2018			
screening both CRC and EC tumors in the same population."	and Roche outside the submitted work. The remaining authors made no disclosures. **Randomization:** - **Blinding:** - **Dropout rates:** -	center in Boston, MA) and North Shore Medical Center (a community hospital in Danvers, MA). **Exclusion criteria:** -	revised Bethesda criteria, PREMM model, updated PREMM model.
Notes:	Oxford level of evidence: 3 Non -randomized cohort study. **Author's conclusion:** Expanding a universal screening program for LS to include patients who had EC identified 50% more patients with LS, and many of these patients would have been missed by risk assessment tools (including PREMM5). Universal screening programs for LS should include both CRC and EC.		
Outcome Measures/results	**Primary** Detection of LS using screening. **Secondary** -	**Results:** In total, 1290 patients with CRC and 484 with EC were screened for LS, and genetic testing was recommended for 137 patients (10.6%) and 32 patients (6.6%), respectively (P5.01). LS was identified in 16 patients (1.2%) with CRC and in 8 patients (1.7%) with EC. Among patients for whom genetic testing was recommended, the LS diagnosis rate was higher among those with EC (25.0% vs 11.7%, P5.052). The Amsterdam II criteria, revised Bethesda criteria, and both PREMM calculators would have missed 62.5%, 50.0%, and 12.5% of the identified patients with LS, respectively.	

Bellido, F. et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med. 18. 325-32. 2016			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Genetic association cohort study To gain a better understanding of the phenotypic characteristics of this syndrome to establish specific criteria for POLE and POLD1 mutation screening and to help define the clinical management of mutation carriers.	Funding sources: Declared, list see article. Conflict of Interests: The authors declare no conflict of interest. Randomization: - Blinding: - Dropout rates: -	Total no. patients: 544 Recruiting Phase: 1999-2012 Inclusion criteria: CRC or polyposis cases. Exclusion criteria: not described.	**Interventions:** Genetic phenotyping of exonuclease domains of POLE and POLD1 using pooled DNA amplification and massively parallel sequencing. **Comparison:**
Notes:	Oxford level of evidence: 3 cohort study. Unclear if patient group is representative of the general patient collective. No validation cohort was investigated. **Author's conclusion:** Our results widen the phenotypic spectrum of the POLE/POLD1-associated syndrome and identify novel pathogenic variants. We propose guidelines for genetic testing and surveillance recommendations.		

Bellido, F. et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med. 18. 325-32. 2016		
Outcome Measures/results	**Primary** Identification of novel and or rare genetic variants. **Secondary** -	**Results: Population:** 529 kindred, 441 with familial nonpolyposis CRC and 88 with polyposis. **Results:** 7 novel or rare genetic variants were identified. In addition to the POLE p.L424V recurrent mutation in a patient with polyposis, CRC and oligodendroglioma, six novel or rare POLD1 variants (four of them, p.D316H, p.D316G, p.R409W, and p.L474P with strong evidence for pathogenicity) were identified in nonpolyposis CRC families. Phenotypic data from these and previously reported POLE/POLD1 carriers point to an associated phenotype characterized by attenuated or oligo-adenomatous colorectal polyposis, CRC, and probably brain tumors. In addition, POLD1 mutations predispose to endometrial and breast tumors.

Dominguez-Valentin, M. et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 22. 15-25. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Genetic association cohort study with validation cohort To provide age and organspecific cancer risks according to gene and	Funding sources: not described. Conflict of Interests: The authors declare no conflicts of interest. Randomization: -	**Total no. patients:** 6350 combined from test and validation cohort. **Recruiting Phase:** not reported. **Inclusion criteria:** The PLSD database design and its inclusion criteria have been described previously in detail.6–8 This study was a	**Interventions:** Exposure to pathogenic variants in each of the MMR genes path_MLH1, path_MSH2, path_MSH6, and path_PMS2 **Comparison:** Non-exposure.

Dominguez-Valentin, M. et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 22. 15-25. 2020			
gender and to determine survival after cancer.	Blinding: - Dropout rates: -	prospective observational study without a control group in which we counted cancers detected during follow-up in 6350 carriers of path_MMR variants. **Exclusion criteria:** not reported.	
Notes:	Oxford level of evidence: 3 cohort study No mention of patients lost to follow up or avarage length of follow up. **Author's conclusion:** Management guidelines for Lynch syndrome may require revision in light of these different gene and gender-specific risks and the good prognosis for the most commonly associated cancers.		
Outcome Measures/results	**Primary** Age- and organspecific cancer risks according to gene and gender, survival after diagnosis. **Secondary** -	**Results: Cohort description:** The newly recruited validation cohort included 3527 path_MMR carriers and 26,682 observation years while the original cohort included 2823 path_MMR carriers and 24,964 follow-up years after updating. In the validation cohort, neither cumulative risk for any cancer (penetrance) nor cumulative risk for CRC for each MMR gene differed significantly from those in the original PLSD cohort6–8 ($P > 0.05$ at all ages, see Fig. 1 and Table S2). Upon merger of the new and original cohorts, the combined data set comprised 6350 path_MMR carriers, 3480 females and 2870 males, who were included from a mean age of 46.8 years (range 25–74 years, Fig. 2) providing 51,646 observation years **Results:** There were 1808 prospectively observed cancers. Pathogenic MLH1 and MSH2 variants caused high penetrance dominant cancer syndromes sharing similar colorectal, endometrial, and ovarian cancer risks, but older MSH2 carriers had higher risk of cancers of the upper urinary tract, upper gastrointestinal tract, brain, and particularly prostate.	

Dominguez-Valentin, M. et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 22. 15-25. 2020			
		Pathogenic MSH6 variants caused a sex-limited trait with high endometrial cancer risk but only modestly increased colorectal cancer risk in both genders. We did not demonstrate a significantly increased cancer risk in carriers of pathogenic PMS2 variants. Ten-year crude survival was over 80% following colon, endometrial, or ovarian cancer.	

Le, D. T. et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 357. 409-413. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Non-randomized open-label phase 2 trial	**Funding sources:** The Swim Across America Laboratory at Johns Hopkins, The Ludwig Center for Cancer Genetics and Therapeutics, The Howard Hughes Medical Institutes, The Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, The 2017 Stand Up To Cancer Colon Cancer Dream Team, The Commonwealth Fund, The Banyan Gate Foundation, The Lustgarten Foundation for Pancreatic Cancer Research, The Bloomberg Foundation, The Sol Goldman Pancreatic Cancer Research Center, Merck & Co., Inc., Kenilworth, NJ USA, Gastrointestinal SPORE grant P50CA062924 and NIH grants P30CA006973, CA163672, CA43460, CA203891, CA67941, CA16058 and CA57345 **Conflict of Interests:** LD, DL, BV, NP and KWK are	**Total no. patients:** 68 patients with advanced MMR-deficient cancers **Recruiting Phase:** September 2013 and September 2016 **Inclusion criteria:** n.a. **Exclusion criteria:** n.a.	**Interventions:** PD-1 blockade (using the anti-PD-1 antibody pembrolizumab) **Comparison:** /

Le, D. T. et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 357. 409-413. 2017			
	inventors on patent application (PCT/US2015/060331 or WO 2016077553 A1) submitted by Johns Hopkins University that covers checkpoint blockade and microsatellite instability. LD, BV, NP and KWK are founders of PapGene and Personal Genome Diagnostics (PGDx). LD is a consultant for Merck, Illumina, PGDx and Cell Design Labs. PGDx and PapGene, as well as other companies, have licensed technologies from Johns Hopkins University, on which LD, BV, NP and KWK are inventors. Some of these licenses and relationships are associated with equity or royalty payments. **Randomization:** Single-group **Blinding:** Open-label **Dropout rates:** /		
Notes:	**Oxford CEBM Level of Evidence 2011: EL 3 Non-randomized trial** Article submitted by hand search Limitations: -Inclusion and exclusion criteria were not specified		

Le, D. T. et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 357. 409-413. 2017		
	Author's conclusion: These data support the hypothesis that the large proportion of mutant neoantigens in MMR-deficient cancers make them sensitive to immune checkpoint blockade, regardless of the cancers' tissue of origin.	
Outcome Measures/results	**Primary** Objective radiographic responses, disease control, PFS, OS, adverse events **Secondary**	**Results: Objective radiographic responses** Objective radiographic responses were noted in 53% of patients (46 of 86 patients; 95% CI, 42–64%), with 21% (n = 18) achieving a complete radiographic response. **Disease control** Disease control (measured as partial response + complete response + stable disease) was achieved in 66 (77%) of the 86 patients (95% CI, 66–85%). **Progression-free survival and overall survival** Neither median progression-free survival (PFS) nor median overall survival (OS) has yet been reached (median follow-up time of 12.5 months; Fig. 1) and the study is ongoing. However the estimates of PFS at 1- and 2-years were 64% and 53%, respectively. The estimates of OS at 1- and 2-years were 76% and 64%, respectively, which is markedly higher than expected based on the advanced state of disease in this cohort (21). The PFS and OS was not significantly different in patients with colorectal cancers as compared to those with other cancer types (fig. S1). Neither PFS (HR 1.2; 95% CI of 0.582 to 2.512, p = 0.61) or OS (HR 1.71; 95% CI of 0.697 to 4.196; p = 0.24) were influenced by tumors associated with Lynch Syndrome. **Adverse events** The adverse events to treatment were manageable, and similar to

Le, D. T. et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 357. 409-413. 2017			
		those found in other clinical studies employing pembrolizumab. While 74% of patients experienced an adverse effect, most were low grade. Endocrine disorders, mostly hypothyroidism, occurred in 21% of patients and was easily managed with thyroid hormone replacement.	

Møller, P. et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 66. 464-472. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Genetic association in a prospective, multicentric cohort study.	**Funding sources:** Extensive list declared, see article. **Conflict of Interests:** JB has a patent for high-speed low-cost tumour profiling pending to JB and QuantuMDx. DGE is a NIHR senior investigator. **Randomization:** - **Blinding:** - **Dropout rates:** -	**Total no. patients:** 1942 **Recruiting Phase:** not described. **Inclusion criteria:** Patients with Lynch syndrom (carriers of Mutations in the MMR genes, MSH2, MLH1, PMS2, MSH6, or deletion in EPCAM gene. All analysed observations were prospective, commencing when the patients were subjected to their first prospectively planned colonoscopy after being identified as at risk for colon cancer.a **Exclusion criteria:** Cases with any cancer prior to or at the same age as first colonoscopy (prevalent cancers) were excluded, as were all cases with	Interventions: - Comparison: -

Møller, P. et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 66. 464-472. 2017		
Notes:	Oxford level of evidence: 2 Inception cohort study. **Downgrade to evidence level 3.** Unclear if population is representative of the avarage. No description of mean follow-up length or study dropouts. **Author's conclusion:** "The four Lynch syndrome-associated genes had different penetrance and expression. Colorectal cancer occurred frequently despite colonoscopic surveillance but resulted in few deaths. Using our data, a website has been established at http://LScarisk.org enabling calculation of cumulative cancer risks as an aid to genetic counselling in Lynch syndrome."	
Outcome Measures/results	**Primary** Cumulative incidences for colorectal adenomas or early CRC, endometrial cancer and ovarian cancer (not all centers), as well as cancer awareness for all cancers known to be associated with LS. **Secondary** 10 year crude survival.	**Results:** 1942 mutation carriers without previous cancer had follow-up including colonoscopic surveillance for 13.782 observation years. 314 patients developed cancer, mostly colorectal (n=151), endometrial (n=72) and ovarian (n=19). Cancers were detected from 25 years onwards in MLH1 and MSH2 mutation carriers, and from about 40 years in MSH6 and PMS2 carriers. Among first cancer detected in each patient the colorectal cancer cumulative incidences at 70 years by gene were 46%, 35%, 20% and 10% for MLH1, MSH2, MSH6 and PMS2 mutation carriers, respectively. The equivalent cumulative incidences for endometrial cancer were 34%, 51%, 49% and 24%; and for ovarian cancer 11%, 15%, 0% and 0%. Ten-year crude survival was 87% after any cancer, 91% if the first cancer was colorectal, 98% if endometrial and 89% if ovarian.

Literaturstelle	Evidenzlevel	Studientyp
Alblas, M. 2018	4	Systematic review (14 studies) To provide an overview of prediction models for the risk of developing endometrial cancer in women of the general population or for the presence of endometrial cancer in symptomatic women.
Bittencourt, C. A. 2017	2	Systematic review and meta-analysis of diagnostic studies (5 studies) To analyze the diagnostic accuracy of two- (2D) and three- (3D) dimensional saline contrast sonohysterography (SCSH) in the detection of endometrial polyps and submucosal uterine leiomyomas in women of reproductive age with abnormal uterine bleeding compared with gold standard hysteroscopy.
Clarke, M. A. 2018	2	Systematic review and meta-analysis (92 studies) To provide a reference of the prevalence of postmenopausal bleeding (PMB) in endometrial cancers and the risk of endometrial cancer in women with PMB.
D. E. Franciscis P 2017	3	Randomized controlled trial. To compare resectoscopic and small-diameter hysteroscopic techniques for endometrial polypectomy in patients with unfavorable cervix.
de Rijk, S. R. 2016	3	Systematic review (10 studies) To estimate the risk of concurrent endometrial cancer in nonpolypoid endometrium when atypia was diagnosed within an endometrial polyp.
Nieuwenhuis, L. L. 2017	2	Systematic review and meta-analysis · To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS for the diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test.
Uglietti, A. 2019	3	Systmatic review and meta-analysis (51 studies) To estimate the prevalence of premalignant and malignant lesions in women undergoing hysteroscopic polypectomy.
van Hanegem, N. 2017	2	Randomized controlled open-label trial. "To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling."
van Hanegem, N. 2016	3	Systematic review and meta-analysis (12 studies) To study the diagnostic accuracy of endometrial sampling in women with PMB regarding the diagnoses of endometrial

Literaturstelle	Evidenzlevel	Studientyp
		cancer and atypical hyperplasia compared to two different reference standards: blind D&C and the current reference standard: hysteroscopy with histology or hysterectomy.
Visser, N. C. M. 2017	3	Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma.
Vroom, A. J. 2019	2	Systematic review and meta-analysis (5 studies) To assess the accuracy of saline contrast sonohysterography (SCSH) for diagnosis of endometrial polyps in women with postmenopausal bleeding.

2.6. Schlüsselfrage 07: Welchen Stellenwert hat die transvaginale Sonographie in der Diagnostik der symptomatischen Frau mit normalem Risiko zum Nachweis eines Endometriumkarzinoms im Hinblick auf Lebensqualität, Kurzzeit-/ Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *11 Literaturstellen*

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *9 Bewertung(en)*

Alblas, M. et al. Prediction models for endometrial cancer for the general population or symptomatic women: A systematic review. Crit Rev Oncol Hematol. 126. 92-99. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic review (14 studies) To provide an overview of prediction models for the risk of developing endometrial cancer in women of the general population or for the presence of endometrial cancer in symptomatic women. **Databases:** We systematically searched the Embase and Pubmed database **Search period:** Unclear - 09/2017 **Inclusion Criteria:** Papers with the main aim of developing, validating or updating a model predicting the risk of endometrial cancer in the general population or presence in symptomatic women. Any multivariable (at least two predictors) prediction model was eligible	**Population:** General population or EC patients. **Intervention:** Exposure to risk-factors. **Comparison:** Non-exposure to risk factors.	**Primary:** Diagnosis of endometrial cancer **Secondary:** - **Results: Study overview:** 14 studies were included. We found two prediction models for developing endometrial cancer in the general population (risk models) and one extension. Eight studies described the development of models for symptomatic women (diagnostic models), one comparison of the performance of two diagnostic models and two external validation. Sample size varied from 60 (10 with cancer) to 201,811 (855 with cancer) women. **Results:** The age of the women was included as a predictor in almost all models. The risk models included epidemiological variables related to the reproductive history of women, hormone use, BMI, and smoking history. The	Fortner 2017, Husing 2016, Pfeiffer 2013, Madkour 2017, Plotti 2017, Sladkevicius 2016, Wong 2016, Gianella 2014, Angioli 2013, Opolskiene 2011, Burbos 2011, Burbos 2010, Weber 1999, Masonda 2011.

Alblas, M. et al. Prediction models for endometrial cancer for the general population or symptomatic women: A systematic review. Crit Rev Oncol Hematol. 126. 92-99. 2018

for inclusion, including prediction scores or prediction tools. Only papers written in the English language were included. There was no restriction on publication date. **Exclusion Criteria:** -		diagnostic models also included clinical predictors, such as endometrial thickness and recurrent bleeding. The concordance statistic (c), assessing the discriminative ability, varied from 0.68 to 0.77 in the risk models and from 0.73 to 0.957 in the diagnostic models. Methodological information was often limited, especially on the handling of missing data, and the selection of predictors. One risk model and four diagnostic models were externally validated. **Author's Conclusion:** "In conclusion, only a few models have been developed to predict endometrial cancer in asymptomatic or symptomatic women. The usefulness of most of the models is unclear considering methodological shortcomings and lack of external validation and head to head comparisons of models. Developed risk models should be externally validated and extended with new predictors, such as genetic and epigenetic risk predictors, to improve model performance. Future research on diagnostic models should focus on		

Alblas, M. et al. Prediction models for endometrial cancer for the general population or symptomatic women: A systematic review. Crit Rev Oncol Hematol. 126. 92-99. 2018

		external validation and creating models with larger sample sizes, which could be realized with individual patients data meta-analysis"		

Methodical Notes

Funding Sources: The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 634570 (FORECEE).

COI: Declared, for list see article.

Study Quality: Not investigated.

Heterogeneity: no meta-analysis was performed.

Publication Bias: not investigated.

Notes:
Oxford level of evidence: 3 Systematic review of cohort, case-cohort, case control studies.
Downgrade to evidence level 4:
Insufficient description of performed searches and inclusion criteria or outcomes. No evaluation of study quality.

Bittencourt, C. A. et al. Accuracy of saline contrast sonohysterography in detection of endometrial polyps and submucosal leiomyomas in women of reproductive age with abnormal uterine bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 50. 32-39. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis of diagnostic studies (5 studies) To analyze the diagnostic accuracy of two- (2D) and three- (3D) dimensional saline contrast sonohysterography (SCSH) in the detection of endometrial polyps and submucosal uterine leiomyomas in women of reproductive age with abnormal uterine bleeding compared with gold standard hysteroscopy. **Databases:** MEDLINE, EMBASE and The Cochrane Library. **Search period:** Inception - 03/2016 **Inclusion Criteria:** Patients of reproductive age with AUB who underwent 2D- or 3D-SCSH and hysteroscopy with anatomopathology. Studies presenting absolute values, allowing calculation of sensitivity and specificity.	**Population:** Patients with AUB. **Intervention:** 2D- and/or 3D-SCSH **Comparison:** Hysteroscopy and anatomopathology	**Primary:** Sensitivity, specificity and positive (LR+) and negative (LR–) likelihood ratios of SCSH in the detection of uterine cavity abnormalities (endometrial polyp or submucosal uterine leiomyoma) **Secondary:** - **Results: Study overview:** A total of 1398 citations were identified and five studies were included in the systematic review and meta-analysis. **Results:** Pooled sensitivity and specificity of 2D-SCSH in detecting endometrial polyps were 93% (95% CI, 89–96%) and 81% (95% CI, 76–86%), respectively, with pooled LR+ of 5.41 (95% CI, 2.60–11.28) and LR– of 0.10 (95% CI, 0.06–0.17). In the detection of submucosal uterine leiomyomas, pooled sensitivity and specificity were 94% (95% CI, 89–97%) and 81% (95% CI, 76–86%), respectively, with pooled LR+ of 4.25 (95% CI, 2.20–8.21) and LR– of 0.11 (95% CI, 0.05–	5 studies included: Cepni 2005, Jansen 2006, Kamel 2000, de Vries 2000, Soguktas 2012.no

Bittencourt, C. A. et al. Accuracy of saline contrast sonohysterography in detection of endometrial polyps and submucosal leiomyomas in women of reproductive age with abnormal uterine bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 50. 32-39. 2017				
Exclusion Criteria: Retrospective baseline studies or those for which we did not have access to the full text were excluded.		0.22). 2D-SCSH had good accuracy in detecting endometrial polyps and submucosal uterine leiomyomas, with areas under the SROC curves of 0.97±0.02 and 0.97±0.03, respectively. Studies that analyzed the diagnostic accuracy of 3D-SCSH could not be compared due to high heterogeneity related to menopausal status, type of technique used and primary outcome being investigation of infertility **Author's Conclusion:** In conclusion, 2D-SCSH has high diagnostic accuracy for the detection of endometrial polyps and submucosal uterine leiomyomas in women of reproductive age with AUB. More studies are needed on 3D-SCSH in this population of women.		
Methodical Notes				
Funding Sources: Not declared. **COI:** Not declared. **Study Quality:** The methodological assessment of included studies according to QUADAS-2. Quality assessment showed one study with a low risk of				

Bittencourt, C. A. et al. Accuracy of saline contrast sonohysterography in detection of endometrial polyps and submucosal leiomyomas in women of reproductive age with abnormal uterine bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 50. 32-39. 2017

bias for all four items, two studies with a high risk of bias for two of the items , while four studies had an unclear risk of bias for the description of flow and timing. Three studies had low risk for the three items of applicability.

Heterogeneity: Heterogeneity was explored by visual analysis of the SROC curve.
I2 was high (>80%) for specificty and positive LR.

Publication Bias: Not investigated. Not feasible with 5 included studies.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive studies or studies without consistently applied reference standard.
No declaration of funding or conflicts of interest. High heterogeneity (I2 was >80%) for specificty and positive LR.)

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (92 studies) To provide a reference of the prevalence of postmenopausal bleeding (PMB) in endometrial cancers	**Population:** Postmenopausal women. **Intervention:** Exposure to PMB or Endometrial cancer. **Comparison:** Non-exposure.	**Primary:** Prevalence of post-menopausal bleeding (PMB) in women with endometrial cancer. Risk of endometrial cancer in women with PMB. **Secondary:** Subgroup analyses f.e. for regions in which the studies were conducted.	92 studies included: see article.

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018				
and the risk of endometrial cancer in women with PMB. **Databases:** PubMed and Embase, reference lists of articles identified in the primary search for additional relevant studies. English-language studies only. **Search period:** 01/1977 - 01/2017. **Inclusion Criteria:** Original studies with primary data reporting the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer among women with PMB. English-language, peer-reviewed studies. **Exclusion Criteria:** Studies that included special populations (eg, defined by comorbid conditions or specific histologic findings), lacked detailed inclusion criteria, and/or included 25 or fewer women.		**Results:** Only summary described here, rest see article. **Study overview:** A total of 129 unique studies, including 34 432 unique patients with PMB and 6358 with endometrial cancer (40 790 women), were analyzed. **Results:** The pooled prevalence of PMB among women with endometrial cancer was 91% (95%CI, 87%-93%), irrespective of tumor stage. The pooled risk of endometrial cancer among women with PMB was 9%(95%CI, 8%-11%), with estimates varying by use of hormone therapy (range, 7%[95%CI, 6%-9%] to 12%[95%CI, 9%-15%]; P < .001 for heterogeneity) and geographic region (range, 5%[95% CI, 3%-11%] in North America to 13%[95%CI, 9%-19%] in Western Europe; P = .09 for heterogeneity). **Author's Conclusion:** "The widespread practice of referring allwomenwith PMB for TVUS and/or endometrial biopsy carries a considerable burden and cost. Given the rise in endometrial cancer incidence and mortality, our findings raise the important question of how to best manage PMB to optimize the benefit of early detection approaches while avoiding unnecessary harms. Interest has increased in the use of biomarkers, such as DNA methylation, to improve early detection of		

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018				
		endometrial cancer. To obtain reliable estimates of the clinical performance of molecular assays, diagnostic tests, and management algorithms, we must know the prior risk of endometrial cancer in the population. Our study represents an important and timely evaluation of the risk of endometrial cancer in women with PMB and can serve as a reliable reference for the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer inwomenwith PMB, 2 requisite prior probabilities for prediction of endometrial cancer risk and secondary and tertiary prevention. As new markers are discovered or new clinical management strategies are evaluated, our results can aid in the assessment of their potential clinical value andwill help to inform clinical and epidemiologic risk prediction models to support clinical decision making."		
Methodical Notes				
Funding Sources: This study was supported by grant 603019 via the COHEAHR Network, 7th Framework Programme of DG Research and Innovation, European Commission (Dr Arbyn). The funding source had no role in the design and conduct of the study. **COI:** Reported, but no conflicts were declared.				

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018

Study Quality: Two independent reviewers evaluated study quality and risk of bias using items from the Newcastle-Ottawa Quality Assessment Scale and the Quality Assessment of Diagnostic Accuracy Studies tool.
Study quality reported in the supplementary section.

Heterogeneity: We estimated pooled prevalence and 95%CIs using multilevel logistic-normal random-effects models to account for interstudy heterogeneity. Between-study variance was quantified using the $\tau 2$ statistic.

Publication Bias: We conducted sensitivity analyses to assess the influence of clinical setting (tertiary center vs other), study design, and the potential for publication bias using Egger regression analyses.
"No evidence of publication bias was found among studies reporting the prevalence of PMB in women with endometrial cancer (Egger regression intercept, 0.15; P = .90)."

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies.
Significant heterogeneity was reported for the two main outocmes.

de Rijk, S. R. et al. Atypical Endometrial Polyps and Concurrent Endometrial Cancer: A Systematic Review. Obstet Gynecol. 128. 519-25. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review (10 studies) To estimate the risk of concurrent	**Population:** Women diagnosed with an atypical endometrial polyp with or without consecutive	**Primary:** Risk of concurrent endometrial cancer **Secondary:** -	10 studies included: Agostini 2002, Hahn 2010, Kelly

de Rijk, S. R. et al. Atypical Endometrial Polyps and Concurrent Endometrial Cancer: A Systematic Review. Obstet Gynecol. 128. 519-25. 2016			
endometrial cancer in nonpolypoid endometrium when atypia was diagnosed within an endometrial polyp. **Databases:** MEDLINE, EMBASE, Web of Science, and ClinicalTrials.gov **Search period:** 1990 and January 2015. **Inclusion Criteria:** Studies of women diagnosed with an atypical endometrial polyp with a consecutive hysterectomy or studies evaluating the natural behavior of the endometrium when atypical endometrial polyps were diagnosed were included. Initially, there were no restrictions on age, menopausal status, diagnostic techniques, or hormonal therapy. However, in the final selection, we did not include patients specified to be undergoing hormonal treatment for atypical endometrial polyps or women who were using tamoxifen. When reporting was insufficient concerning initial pathology diagnosis, diagnostic techniques, and final pathology diagnosis on hysterectomy specimen, studies were not included. No other selection on study type or language was performed. Frequently cited articles from before 1990 were selectively	hysterectomy. **Intervention:** - **Comparison:** -	**Results: Study overview:** Broad searches yielded 2,922 authentic citations, 307 met criteria for full-text evaluation, and 10 met inclusion criteria. **Results:** The final selection included eight retrospective studies reporting on concurrent endometrial cancer in case of atypical endometrial polyps and two follow-up studies on patients conserving their uterus after hysteroscopic resection of atypical endometrial polyps. In total, 127 patients were included with an initial diagnosis of atypical endometrial hyperplasia within polyps. Meta-analysis showed a pooled risk estimate of 5.6% (95%CI 0.2–17.6%) on concurrent endometrial cancer after resection of an atypical endometrial polyp. **Author's Conclusion:** "The pooled risk estimate of 5.6% (95% CI 0.2–17.6%) on endometrial cancer when atypia is found within an endometrial polyp differs from the well-established risk of nonpolypoid atypical endometrial hyperplasia on endometrial cancer of up to 42%. This risk of endometrial cancer is important in the	2007, Leitao 2010, Litta 2013, Mittal 2008, Naaman 2014, Obeidat 2009, Scrimin 2006, Scrimin 2008.

de Rijk, S. R. et al. Atypical Endometrial Polyps and Concurrent Endometrial Cancer: A Systematic Review. Obstet Gynecol. 128. 519-25. 2016				
included. **Exclusion Criteria:** Case reports and series, conference abstracts, and letters to editors were excluded.		process of shared decision-making regarding follow-up and further treatment."		
Methodical Notes				
Funding Sources: The authors did not report any potential conflicts of interest. **COI:** The authors did not report any potential conflicts of interest. **Study Quality:** Study quality not investigated. **Heterogeneity:** Not investigated /applicable, no meta-analysis was performed. **Publication Bias:** Not investigated /applicable, no meta-analysis was performed. **Notes:** Oxford level of evidence: 2 Systematic review of cohort studies Downgrade to evidence level 3. Insufficient description of inclusion criteria. No evaluation of study quality.				

Nieuwenhuis, L. L. et al. Three-dimensional saline infusion sonography compared to two-dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database Syst Rev. 5. Cd011126. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis · To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS for the diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test. **Databases:** PubMed, Ovid, MEDLINE, Embase; Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (Appendix 3), ProCite. Handsearch by screening the reference lists of all included articles. We screened available online conference abstracts in the	**Population:** Populations of interest were premenopausal women with AUB or subfertility and postmenopausal women with AUB. **Intervention: Index tests**: We included studies comparing the diagnostic accuracy of 3D SIS alone (index test 1) or 2D+3D SIS (index test 2) versus 2D SIS (comparator test). We defined SIS as positive for a focal intrauterine lesion when any distortion of the endometrial lining was visualised (see below). We preferred that time between index test and reference standard was less than one month. **Comparison: Reference standards:** Diagnostic hysteroscopy was the reference standard for confirmation of the absence or presence of the target condition. Absence of an intracavitary abnormality was seen as clear vision	**Primary:** Diagnostic accuracy. **Secondary:** - **Results: Study overview:** 13 studies (1053 women) reported the accuracy of 3D SIS for focal uterine abnormalities; 11 of these (846 women) were suitable for meta-analysis, and eight reported accuracy according to the type of focal abnormality. The design of the included studies seems applicable. The main problem involving the quality of included studies is insufficient reporting of study methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, we considered the overall quality of the evidence as low. **Results:** The summary estimate (11 studies reporting absence or presence of abnormality at 3D SIS) for sensitivity was 94.5% (95% confidence interval (CI) 90.6% to 96.9%) and for specificity	13 studies included: Aboulghar 2011, Adek 2014, de Kroon 2004, El-Sherbiny 2011, El-Sherbiny 2015, Katsetos 2013, Kowalczyk 2012, Kupesic 20077, La Torre 1999, Makris 2007, Nieuwenhuis 2014, Scofienza 2010, Sylvestre 2003.

Nieuwenhuis, L. L. et al. Three-dimensional saline infusion sonography compared to two-dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database Syst Rev. 5. Cd011126. 2017				
field of gynaecology **Search period:** Inception 03/2016. **Inclusion Criteria:** The population of interest consisted of premenopausal women with AUB or subfertility and postmenopausal women with AUB. Diagnostic test accuracy studies, randomised controlled trials (RCTs) and prospective cohort studies were eligible for inclusion if they evaluated the accuracy of both 2D SIS and 3D SIS for the diagnosis of acquired intracavitary abnormalities with hysteroscopy used as the reference standard. In light of the lack of data for 3D SIS, we also included studies that evaluated the accuracy of 3D SIS alone. **Exclusion Criteria:** -	of the entire cavity without disruption of the endometrial lining. When reported, we also used histology as a reference standard to diJerentiate the type of abnormality (polyp or fibroid	99.4% (95% CI 96.2% to 99.9%). Meta-analysis of the eight studies (N = 716) directly comparing 2D SIS versus 3D SIS showed summary sensitivity of 96.9% (95% CI 91.9% to 98.8%) and summary specificity of 99.5% (95% CI 96.1% to 100%) for 3D SIS. For 2D SIS, summary sensitivity was 90.9% (95% CI 81.2% to 95.8%) and summary specificity was 96.3% (95% CI 86.1% to 99.1%). The diJerence in accuracy between 2D SIS and 3D SIS was non-significant (P values of 0.07 for sensitivity and 0.10 for specificity). **Author's Conclusion: Implications for practice:** Low-quality evidence showed that 3D SIS is highly accurate in detecting intracavitary abnormalities. Meta-analysis revealed no statistically significant diJerences between 2D SIS and 3D SIS. Summary sensitivity and specificity are higher for 3D SIS, but margins of improvement are limited in that 2D SIS is already very accurate. 3D SIS is an alternative to 2D SIS when the technology and appropriate expertise		

Nieuwenhuis, L. L. et al. Three-dimensional saline infusion sonography compared to two-dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database Syst Rev. 5. Cd011126. 2017

		are available. Both 2D SIS and 3D SIS should be considered alternatives to diagnostic hysteroscopy when intracavitary pathology is suspected in both subfertile women and those with abnormal uterine bleeding.		

Methodical Notes

Funding Sources: Internal sources
· VU University Medical Center, Netherlands.
External sources
· None, Other.

COI: The review authors have no conflicts of interest and no financial ties to disclose.

Study Quality: Two review authors worked independently to assess studies for methodological quality using QUADAS-2 (revised tool for quality assessment of diagnostic accuracy studies).
"The main problem involving the quality of included studies is insuJicient reporting of study methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, we considered the overall quality of the evidence as low"

Heterogeneity: We addressed heterogeneity by adding variables to the bivariate model as covariates if both subgroups included at least three studies. We performed these analyses for clinical symptoms (bleeding vs subfertility); prior testing (prior testing or not); and whether evaluation of 2D or 3D SIS was blinded for clinical information. We also wanted to evaluate the effect of menopausal state (premenopausal or postmenopausal), but the models did not converge when we added this information as a covariate. We also assessed heterogeneity with forest plots and ROC plots.
"This review included a broad spectrum of patients and methodological differences that resulted in a heterogeneous group, impeding meta-analysis."

Nieuwenhuis, L. L. et al. Three-dimensional saline infusion sonography compared to two-dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database Syst Rev. 5. Cd011126. 2017			
Publication Bias: Not investigated. **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive studies or studies without consistently applied reference standard. Overall quality of evidence was considered to be low. Due to the high heterogeneity no meta-analysis was performed.			
Uglietti, A. et al. The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 237. 48-56. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systmatic review and meta-analysis (51 studies) To estimate the prevalence of premalignant and malignant lesions in women undergoing hysteroscopic polypectomy. **Databases:** PubMed/Medline, Embase **Search period:** 2000-01/2019. **Inclusion Criteria:** Observational retrospective and prospective studies meeting the following	**Population:** Premenopausal and postmenopausal women. **Intervention:** - **Comparison:** -	**Primary:** Prevalence of endometrial premalignant or malignant polyps in the total series. **Secondary:** Subgroup analysis. **Results: Study overview:** A total of 51 studies reporting data on 35,345 women were included in this review. **Results:** The prevalence of malignant polyps was 2.73% (95% CI 2.57-2.91) with very high heterogeneity among studies. The rates were lower for premenopausal women	51 studies included, see article for list.

Uglietti, A. et al. The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 237. 48-56. 2019				
criteria: pre-operative diagnosis of benign-looking endometrial polyps at ultrasound examination (TVS,SIS) or at hysteroscopy, excision of endometrial polyps via surgical hysteroscopy, histopathological diagnosis of benign polyps, or hyperplasia withou atypia, or premalignancy (atypical hyperplasia) or malignancy (endometrial cancer). Moreover studies were included, if number or percentage of subjects with and without malignancy was provided and if they reported data about menoüausal and / or bleeding status. **Exclusion Criteria:** Data presented exclusively as abstracts in national and international meetings, or case report or review articles, that did not include original data, and papers published in other than english language.		(1.12%) than post-menopausal ones (4.93%) and the difference was statistically significant (chi-square = 397.21. p < .0001). The risk of malignancy was higher among symptomatic (5.14%) than asymptomatic ones (1.89%) (chi-square = 133.13 p < .001). We observed higher rate of malignant polyps in prospective studies. In the meta-analysis selecting 10 prospective studies the random pooled estimate was 5.88 (95% CI: 4.06-7.97) with heterogeneity among studies (heterogeneity chi square = 17.55 P = .025) whereas in retrospective studies the random pooled estimate was 2.94 (95% CI:2.24-3.71) with high heterogeneity among studies (P < .001). This finding can be due to more strict diagnostic criteria in prospective studies. **Author's Conclusion:** Symptomatic vaginal bleeding and postmenopausal status in women with endometrial polyps increased the risk of malignancy. This finding could be an useful evidence to select patients who need to undergo hysteroscopic resection of endometrial polyps and women to whom, instead, an expectant management can be offer.		

Uglietti, A. et al. The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 237. 48-56. 2019

Methodical Notes

Funding Sources: This work was partially funded by Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico.

COI: The author's declare that they have no conflict of interest.

Study Quality: Information on the methodological quality of selected studies was assessed using the Methodological Index for Non-randomized studies (MINORS), a validated instrument which is designed for assessment of methodological quality of non-randomized studies in surgery. Briefly, the studies were judged on eight pre-defined items and maximum score was 16.
"Their quality was generally good, the MINORS criteria score ranged from 4-10, being 8 or 10 in 29 papers out of 51." Individual study qualit not reported.

Heterogeneity: To evaluate heterogeneity among studies, heterogeneity chi square value was reported.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systmatic review and meta-analysis of cohort studies
Downgrade to evidence level 3.
NO search for gray literature or literature in languages other than english. No investigation of publication bias. Individual study quality not reported.
High heterogeneity in all analyses and subgrouops, no display of forest plots.

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (12 studies) To study the diagnostic accuracy of endometrial sampling in women with PMB regarding the diagnoses of endometrial cancer and atypical hyperplasia compared to two different reference standards: blind D&C and the current reference standard: hysteroscopy with histology or hysterectomy. **Databases:** Medline, Embase, Science direct. **Search period:** 01/1965 - 03/2015. **Inclusion Criteria:** Observational studies on the evaluation of the diagnostic accuracy of endometrial sampling in women with PMB. Histology results of endometrial sampling were compared with the	**Population:** Women with postmenopausal uterine bleeding. **Intervention:** Endometrial sampling (histology). **Comparison:** Endometrial histological findings from (blind) D&C, diagnostic hysteroscopy with histology by targeted biopsy or D&C or hysterectomy.	**Primary:** Diagnostic accuracy for detection of endometrial cancer, atypical hyperplasia and endometrial disease. **Secondary:** - **Results: Study overview:** 12 studies reporting 1029 women with PMB: 5 with dilatation and curettage and 7 with hysteroscopy as a reference test. **Results:** "The weighted sensitivity of endometrial sampling with D&C as a reference fro the diagnosis of endometrial cancer was 100%(100-100) and 92%(71-100) for the diagnosis of atypical hyperplasia. Only ine study reported sensitivity for endometrial disease, which was 76%. When hysteroscopy was used as a referen, weighted sensitivities of endometrial sampling were 90%(50-100), 82%(56-94) and 39%(21-69) for the diagnosis of endometrial cancer,	12 studies included: Goldberg 1982, Batool 1994, Ben-Baruch 1994, vdBosch 1995, vdBosch 1996, Giusa-Chifieri 1996, Gupta 1996, De Silva 1997, Mortakis 1997, Bunyavejchevin 2001, Epstein 2001, Spicer 2006.

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016				
results of a reference standards. The articles had to study women with postmenopausal uterine bleeding, the diagnostic test of interest was endometrial sampling (histology), the reference standard had to be endometrial histology findings from (blind) D&C, diagnostic hysteroscopy with histology by targeted biopsy of D&C or hysterectomy. **Exclusion Criteria:** -		atypical hyperplasia and endometrial disease, respectively. For all diagnosis studie and the reference test used, specificity was 98-100%. The weighted failure rate of endometrial sampling was 11% (1-53%), while insufficient samples were found in 31%(7-76%). In these women with insufficient or failed samples, an endometrial (pre) cancer was found in % (range 0-18%)." **Author's Conclusion:** "In women with postmenopausal bleeding, the sensitivity of endometrial sampling to detect endometrial cancer and especially atypical hyperplasia and endometrial disease, including endometrial polyps, is lower than previously thought. Thereffore, further diagnostic work-up for focal pathology is warranted, after a benign result of endometrial sampling."		
Methodical Notes				

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016

Funding Sources: Declared, no grants or funding received.

COI: Not declared.

Study Quality: Two reviewers independently assessed the the methodological quality of each article using QUADAS-2 tool for diagnostic studies, modified to conform to this review. low risk of bias in 4 studies; high risk of bias in 3 studies; unclear risk of bias in 8 studies.

Heterogeneity: No investigation of heterogeneity.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive studies or studies without consistently applied reference standard. Downgrade to evidence level 3.
Conflict of interest not declared. No investigation of heterogeneity or publication bias. ROC curves do not provide relevant information.

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017			
Evidence level: 3 **Study type:** Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma. **Databases:** MEDLINE, EMBASE, ClinicalTrials.gov, and the Cochrane library **Search period:** Inception to 01/2017 **Inclusion Criteria:** In eligible studies, the index test included office endometrial biopsy, hysteroscopic biopsy, or dilatation and curettage; the reference standard was hysterectomy. Outcome measures included tumor grade, histologic subtype, or both. **Exclusion Criteria:** Conference abstracts, case reports and papers containing less than five patients, review articles, absence of hysterectomy or preoperative histology, intraoperative frozen biopsies, not in English, lack of the percentage of	**Population:** Women with endometrial carcinoma **Intervention:** Preoperative endomentrial sampling: Index test included office endometrial biopsy, hysteroscopic biopsy, or D&C; **Comparison:** Hysterectomy as reference standard.	**Primary:** Accuracy of diagnosis of tumor grade and histologica subtype, Inter rater Kappa. **Secondary:** - **Results: Study overview:** A total of 45 studies (12,459 patients) met the inclusion criteria. **Results:** The pooled agreement rate on tumor grade was 0.67 (95% CI 0.60– 0.75) and Cohen's k was 0.45 (95% CI 0.34–0.55). Agreement between hysteroscopic biopsy and final diagnosis was higher (0.89, 95% CI 0.80–0.98) than for dilatation and curettage (0.70, 95% CI 0.60–0.79; P5.02); however, it was not significantly higher than for office endometrial biopsy (0.73, 95% CI 0.60–0.86; P5.08). The lowest agreement rate was found for grade 2 carcinomas (0.61, 95% CI 0.53–0.69). Downgrading was found in 25% and upgrading was found in 21% of the endometrial samples. Agreement on histologic subtypes was 0.95 (95% CI 0.94–0.97) and 0.81 (95% CI 0.69–0.92) for preoperative endometrioid and nonendometrioid carcinomas, respectively.	45 studies included: see article.

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017				
agreement, and absence of possibilities to calculate these from available data.		**Author's Conclusion:** "Overall there is only moderate agreement on tumor grade between preoperative endometrial sampling and final diagnosis with the lowest agreement for grade 2 carcinomas."		
Methodical Notes				
Funding Sources: none declared. **COI:** The authors did not report any potential conflicts of interest. **Study Quality:** Risk of bias was assessed (Quality Assessment of Diagnostic Accuracy Studies). "Overall, the risk of bias was unclear in most studies, which was mainly attributable to patient selection and interpretation of the index test and reference standard" **Heterogeneity:** To test the amount of heterogeneity between the studies, I 2 statistic was used. Our outcomes are characterized by high heterogeneity. 59-95%. **Publication Bias:** Investigated but not shown. "Funnel plots for the primary outcome did not indicate any publication bias (data not shown)." **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive diagnostic study or studies without consistently applied reference standard. **Downgrade to evidence level 3.**				

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017			
Unclear definition of population. Predominantly unclear risk of bias in included studies. HIgh heterogeneity in all analyses. Publication bias investigated but not shown.			
Vroom, A. J. et al. Diagnostic accuracy of saline contrast sonohysterography in detecting endometrial polyps in women with postmenopausal bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 54. 28-34. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (5 studies) To assess the accuracy of saline contrast sonohysterography (SCSH) for diagnosis of endometrial polyps in women with postmenopausal bleeding. **Databases:** MEDLINE, EMBASE and Web of Science databases to identify all diagnostic studies in which SCSH was used to detect endometrial polyps in postmenopausal women (Appendix S1). The search was not limited to women with PMB in order to ensure that the search was as comprehensive as possible. The search was	**Population:** Postmenopausal women with postmenopausal bleeding (PMB). **Intervention:** Saline contrast sonohysterography (SCSH) **Comparison:** Reference standard (Hysteroscopy and/or histopathology)	**Primary:** Diagnostic accuracy for detection of endometrial polyps. **Secondary:** - **Results:** After selection and quality assessment, five studies were included. Using ‘polyps diagnosed with histopathology’ as the reference standard, the pooled sensitivity of SCSH was 86.5% (95% CI, 63.6–100%) and the pooled specificity was 91.1% (95% CI, 63.2–100%). Using ‘polyps seen on hysteroscopy’ as the reference standard, the pooled sensitivity of SCSH was 85.1% (95% CI, 66.9–100%) and the pooled specificity was 84.5% (95% CI,	5 studies included (after exclusion of one due to quality concerns): van Hanegem 2017, Bingol 2011, Karageyim Karsidag 2010, Epstein 2001, Cohen 1994.

Vroom, A. J. et al. Diagnostic accuracy of saline contrast sonohysterography in detecting endometrial polyps in women with postmenopausal bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 54. 28-34. 2019				
limited to studies in humans; language restrictions were not applied. All known synonyms for the following phrases were used: 'saline contrast sonohysterography', 'postmenopausal women', 'endometrial pathology' and 'polyps'. Reference lists of the selected articles were searched manually for further relevant articles not identified by the electronic search. Several trial registers were searched (ClinicalTrial .gov, The European Union Clinical Trials Register and The Dutch Trial Register) but no eligible studies with unpublished results were found. **Search period:** Inception - 08/2018. **Inclusion Criteria:** Studies were included if SCSH was performed to detect endometrial polyps in women with PMB and if detection of a polyp on hysteroscopy or histopathological diagnosis was used as the reference standard. Studies on both pre- and postmenopausal women were included if data on women with PMB could be extracted separately		68.1–100%). Excluding the one study that included women in whom the SCSH examination was reported to be suboptimal, the pooled sensitivity increased to 90.7% (95% CI, 72.8–100%) using hysteroscopy as the reference standard. The sensitivity of hysteroscopy to detect polyps, as reported in two studies, was 81–98%. **Author's Conclusion:** "Provided that the SCSH examination is of optimal quality, it can be considered as a method to stratify women with PMB for further diagnostic workup and treatment with hysteroscopy. In women without suspicion of a polypoid lesion on SCSH and with a benign endometrial sample, expectant management should be considered."	

Vroom, A. J. et al. Diagnostic accuracy of saline contrast sonohysterography in detecting endometrial polyps in women with postmenopausal bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 54. 28-34. 2019

Exclusion Criteria: Studies that used dilatation and curettage (D&C) or endometrial aspiration as a reference standard, as well as those in which more than 5% of women were taking tamoxifen, were excluded.				

Methodical Notes

Funding Sources: Not declared.

COI: Not declared.

Study Quality: Methodological quality was assessed independently by two reviewers using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool.
One study was excluded because of high risk of bias in two dmains and questionable applicability. The remaining studies were considered to be of low or unclear risk of bias with one exception.

Heterogeneity: Heterogeneity was calculated using the intraclass correlation coefficient for multilevel logistic regression.
Heterogeneity in analyses using histopathology as the reference standard was 7.6% for sensitivity and 27.7% for specificity. For analyses using hysteroscopy as the reference standard, heterogeneity was 11% for sensitivity and 6.5% for specificity. This shows that there was limited heterogeneity between the studies.

Publication Bias: Described in the strenghts and limitations section. Not investigated, but not applicable due to low study number.

Notes:

Vroom, A. J. et al. Diagnostic accuracy of saline contrast sonohysterography in detecting endometrial polyps in women with postmenopausal bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 54. 28-34. 2019
Oxford level of evidence: 2 Systematic review and meta-analysis of diagnostic studies non-consecutive studies or studies without consistently applie reference standard. No declaration of conflict of interests or funding.

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

D. E. Franciscis P et al. Resectoscope versus small diameter hysteroscopy for endometrial polypectomy in patients with "unfavorable" cervix. Minerva Ginecol. 69. 239-244. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Randomized controlled trial. To compare resectoscopic and small-diameter hysteroscopic techniques for endometrial polypectomy in patients with unfavorable cervix. **Number of Patient:** 80 **Recruitung Phase:** 1 year recruitment, year not specified. **Inclusion Criteria:** Women attending our Endoscopic centers presenting abnormal uterine bleeding and a single endometrial polyp was suspected. Inclusion criteria were verified during diagnostisc hysteroscopy and gynaelogical examination: single 2-4cm sized endometrial polyp, stenosis of cervical canal, small cervix melted with the vaginal wall, ventral fixation of the uterus.	**Intervention:** 26F resectoscope equipped with bipolar knife (group A) **Comparison:** 5mm diameter hysteroscope equipped with a bipolar electrode (group B)	**Primary:** Operative time, fluid absorption, complications, instrument failure, postoperative pain, operative pain, operative difficulty, overall surgeon's satifsfaction. **Secondary:** - **Results: Study population:** 80 woment with a single 2-4 cm sized endometrial polyp, with unfavorable cervical anatomical conditions were enrolled in the study and randomized to group A 26F resectoscope requiring cervical dilation or group B 5mm hysteroscope requiring vaginoscopic approach. **Results:** Operative time was significanlty longer in group A than in group B (18.3±7.4 vs 11.3±5.2 minutes), the cumulative complication rate and the need pf postoperative analgesics were higher in group A than in group B. VAS of surgical difficulty and surgeon's satisfaction were higher in group B than in group A. **Author's Conclusion:** "The indications for small-diameter operative hysteroscopy are expanding and not yet completely defined, in experienced hands a small-diameter hysteroscopy is a safe and effective approach for endometrial polyp up to 4

D. E. Franciscis P et al. Resectoscope versus small diameter hysteroscopy for endometrial polypectomy in patients with "unfavorable" cervix. Minerva Ginecol. 69. 239-244. 2017			
Exclusion Criteria: Non-organic cause of abnormal uterine bleeding, concomittant endomtrial pathology, multiple endometrial polyps, endometrial polyps bigger than 4cm or less than 2cm, other surgical procedure planned.		cm in patients with unfavorable cervical canal at risk of cervical injury.	
Methodical Notes			
Funding Sources: see conflicts of interest. **COI:** The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. **Randomization:** not described. **Blinding:** not described, likely not blinded. **Dropout Rate/ITT-Analysis:** not described. **Notes:** Oxford level of evidence: 2 Randomized controlled trial **Downgrade to evidence level 3.** Randomization and allocation not described. Groups appear similar, but few baseline characteristics are described. No description of patient or statistician blinding.			

van Hanegem, N. et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. Bjog. 124. 231-240. 2017		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized controlled open-label trial. "To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling." **Number of Patient:** 200 **Recruitung Phase:** Betweeen January 2010 and October 2013. **Inclusion Criteria:** Women with PMB, an endometrial thickness >4 mm and benign result from endometrial sampling **Exclusion Criteria:** Women with complex hyperplasia. Other exclusion criteria were cervical cytology showing an abnormality which warranted treatment, an endometrial biopsy showing a (pre)malignancy (i.e. atypical endometrial hyperplasia or endometrial cancer) or an insufficient sample or if endometrial sampling had failed due to technical	**Intervention:** workup by hysteroscopy, preceded by saline infusion sonography (SIS) **Comparison:** Expectant management	**Primary:** Recurrence of PMB within a year after randomisation. **Secondary:** Time to recurrent bleeding and recurrent bleeding after more than 1 year. **Results: Study population:** Between January 2010 and October 2013, 200 women were randomised; 98 to hysteroscopy and 102 to expectant management. **Results:** Within 1 year a total of 15 women (15.3%) in the hysteroscopy group experienced recurrent bleeding, versus 18 (18.0%) in the expectant management group (relative risk 0.85 (95% CI 0.46–1.59). In the hysteroscopy group, 50/98 (51%) polyps were diagnosed of which 6/98 (6%) showed evidence of endometrial (pre)malignancy; final pathology results after hysterectomy showed three women with hyperplasia with atypia and three women with endometrial cancer. **Author's Conclusion:** "In women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent bleeding. Hysteroscopy detected focal endometrial (pre)malignancy in 6% of women who had benign

van Hanegem, N. et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. Bjog. 124. 231-240. 2017			
problems. Women using an aromataseinhibitor or anti-oestrogen medication were also excluded.		endometrial sampling. This finding indicates that in these women, further diagnostic workup is warranted to detect focal (pre)malignancies, missed by blind endometrial sampling."	
Methodical Notes			
Funding Sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. **COI:** Declared, only available online. **Randomization:** Block randomisation with a block size of four, an allocation ratio of 1:1 and stratification for hospital. The web-based program generated a unique number with allocation code after entry of the patient's initials and date of birth. Neither recruiting doctors nor members of the trial project group could access the randomisation sequence. **Blinding:** Open-label study. Statistician performed the analysis was masked to assigned intervention. **Dropout Rate/ITT-Analysis:** Statistical analysis was performed according to the intention- to-treat principle. 0 and 2 patients were lost to follow up per group out of 98 and 102. **Notes:** Oxford level of evidence: 2 Randomized controlled open-label trial. No tests for group differences, but groups appear similar.			

2.7. Schlüsselfrage 09: Welche Bedeutung hat die Endometriumbiopsie mittels Aspiration in der Diagnostik zum Nachweis des Endometriumkarzinoms im Vergleich zur frakt. Abrasio +/- HSK im Hinblick auf Sensitivität/Spezifität/prädiktiven Wert und die möglichen Nebenwirkungen und Risiken?

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bourdel, N. 2016	3	Systematic review and meta-analysis (27 studies) to identify the most accurate method of endometrial sampling for the diagnosis of complex atypical hyperplasia (CAH), and the related risk of underestimation of endometrial cancer.
Narice, B. F. 2018	2	Systematic review and meta-synthesis (60 studies) To identify existing evidence about the effectiveness of Pipelle compared with other ES techniques for assessing low-risk women with AUB which could inform the development of new care pathways in primary care.
van Hanegem, N. 2017	2	Randomized controlled open-label trial. "To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling."
van Hanegem, N. 2016	3	Systematic review and meta-analysis (12 studies) To study the diagnostic accuracy of endometrial sampling in women with PMB regarding the diagnoses of endometrial cancer and atypical hyperplasia compared to two different reference standards: blind D&C and the current reference standard: hysteroscopy with histology or hysterectomy.
Visser, N. C. M. 2017	3	Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial

Literaturstelle	Evidenzlevel	Studientyp
		sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *4 Bewertung(en)*

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic review and meta-analysis (27 studies) to identify the most accurate method of endometrial sampling for the diagnosis of complex atypical hyperplasia (CAH), and the related risk of underestimation of endometrial cancer. **Databases:** PubMed and EMBASE was performed to identify all registered articles on this subject published restricted to English, French, Italian, or Spanish languages. In addition, cross-references of all selected articles were checked. **Search period:** 01/1999 and 09-2013 **Inclusion Criteria:** Clinical trials, comparative studies, controlled clinical	**Population:** Premenopausal and postmenopausal women submitted to endometrial sampling because of a suspicion of endometrial disease (with or without symptoms) with a diagnosis of atypical endometrial hyperplasia and who underwent hysterectomy. **Intervention:** The diagnostic tests were uterine curettage (group 1), hysteroscopically guided biopsy (group 2), and endometrial hysteroscopic resection (group 3) **Comparison:** Reference standard was hysterectomy.	**Primary:** Percentage of unexpected cancer cases diagnosed at hysterectomy and missed during endometrial sampling (endometrial sampling with histologic diagnosis of atypical endometrial hyperplasia). **Secondary:** - **Results: Study overview:** We selected 27 studies, taking into consideration the comparison between histology of endometrial hyperplasia obtained by diagnostic tests of interest (uterine curettage, hysteroscopically guided biopsy, or hysteroscopic endometrial resection) and subsequent results of hysterectomy. **Results:** Analysis of the studies reviewed focused on 1106 patients with a preoperative diagnosis of atypical	27 studies included: see article.	

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016				
trials, randomized controlled trials, and multicenter studies in which the results of the diagnostic test of interest were compared with the results of a reference standard. The population of interest was premenopausal and postmenopausal women submitted to endometrial sampling because of a suspicion of endometrial disease (with or without symptoms) with a diagnosis of atypical endometrial hyperplasia and who underwent hysterectomy. The diagnostic tests were uterine curettage (group 1), hysteroscopically guided biopsy (group 2), and endometrial hysteroscopic resection (group 3), and the reference standard was hysterectomy. The primary outcome measure was the percentage of unexpected cancer cases diagnosed at hysterectomy and missed during endometrial sampling (endometrial sampling with histologic diagnosis of atypical endometrial hyperplasia).		endometrial hyperplasia. The mean risk of finding endometrial cancer at hysterectomy after atypical endometrial hyperplasia diagnosed by uterine curettage was 32.7% (95% confidence interval [CI], 26.2–39.9), with a risk of 45.3% (95% CI, 32.8–58.5) after hysteroscopically guided biopsy and 5.8% (95% CI, 0.8–31.7) after hysteroscopic resection. In total, the risk of underestimation of endometrial cancer reaches a very high rate in patients with CAH using the classic method of evaluation (i.e., uterine curettage or hysteroscopically guided biopsy). This rate of underdiagnosed endometrial cancer leads to the risk of inappropriate surgical procedures (31.7% of tubal conservation in the data available and no abdominal exploration in 24.6% of the cases). Hysteroscopic resection seems to reduce the risk of underdiagnosed endometrial cancer. **Author's Conclusion:** "A review of the literature shows that hysteroscopically guided biopsy and uterine curettage may		

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016				
Exclusion Criteria: We excluded populations consisting entirely of patients treated by tamoxifen or affected by familiar diseases (i.e., HNPCC [Hereditary Non-Polyposis Colorectal Cancer] syndrome) because of the different prevalence of EC in this population influencing outcome measures. We also excluded studies in which the histologic findings were not compared with the reference standard (i.e., hysterectomy), the sampling methods were different from the 3 diagnostic tests, and hysterectomy was realized for other indications.		have a high risk of underestimation of EC, and this rate of underdiagnosed EC could lead to inappropriate surgical procedures. Hysteroscopic endometrial resection seems to lower this risk. However, this review highlights the need for a larger amount of data to confirm this observation, and the standard approach for evaluation of the uterine cavity could change in favor of operative hysteroscopic techniques, especially in cases of women at risk of serious endometrial disease."		
Methodical Notes				
Funding Sources: Not stated. **COI:** The authors declare that they have no conflict of interest. **Study Quality:** For appraisal of the methodologic quality of the studies, we used the Canadian Task Force classification, a measurement tool to assess the methodologic quality of studies. "Most of the studies included were classified II-2 (n 5 19/27) (i.e., evidence obtained from well-designed cohort or case-control studies), and 8 were classified II-3 (i.e., evidence obtained from several timed series with or without the intervention). All studies included were retrospective, and subjects				

Bourdel, N. et al. Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 23. 692-701. 2016			
were always included when they had a preoperative diagnosis of atypical endometrial hyperplasia followed by hysterectomy with pathological analysis." **Heterogeneity:** Heterogeneity in the study results was evaluated by examining forest plots and confidence intervals and by using formal tests for homogeneity based on the I2 statistics. Heterogeneity was quantified by I2. "A limitation of this review is the heterogeneity of populations and groups, which may impact the generalizability of the findings. There are 22 studies (n5984 patients) in group 1, 6 in group 2 (n= 99), and only 3 in group 3 (n =23). This difference causes a high heterogeneity (total I2 = 67.8 with I2 = 72.0 for group 1, I2 = 30.6 for group 2, and I2 = 0.0 for group 3). However, we used a random-effects analysis to take account of this heterogeneity, and the results indicated a statistically significant difference." **Publication Bias:** Publication bias was assessed by a funnel plot, but results and implications were not discussed. Unclear wether bias is present or not. **Notes:** Oxford level of evidence: 3 Systematic review and meta-analysis of cohort or case control studies. Searches were carried out in 2013, while the article was published in 2016, therfor the presented evidence is not recent. High heterogeneity present in results, which limits generalzability.			

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-	**Population:** Women with abnormal uterine bleeding (AUB)	**Primary:** Sample adequacy, test performance, pain/discomfort, costs out outpatient endometrial sampling, barriers and	60 study included: see article.

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018				
synthesis (60 studies) To identify existing evidence about the effectiveness of Pipelle compared with other ES techniques for assessing low-risk women with AUB which could inform the development of new care pathways in primary care. **Databases:** MEDLINE via OvidSP, Scopus, and Web of Science for relevant English-language articles. **Search period:** 1984 to 2016. **Inclusion Criteria:** We included papers investigating ES in women with AUB. We also considered studies in patients with known cancer; although these studies do not inform the indication of ES in primary care, they were an important source to evaluate test performance. We included review articles and opinion pieces. **Exclusion Criteria:** We excluded papers exclusively analysing postmenopausal patients, papers where the indication was assessment of fertility or recurrent miscarriage and papers where ES was assisted by	**Intervention:** endometrial sampling (ES) Pipelle device. **Comparison:** ES other devices	complications.a **Secondary:** - **Results:** "Pipelle seems to perform as well as dilation and curettage and, as well or better than other ES devices in terms of sampling adequacy and sensitivity. It also seems to be better regarding pain/discomfort and costs. However, Pipelle can disrupt the sonographic appearance of the endometrium and may be limited by cervical stenosis, pelvic organ prolapse and endometrial atrophy." **Author's Conclusion:** The evidence we analysed suggests that performing ES in the outpatient setting may allow effective management of low-risk women with AUB in primary care without referral to a hospital. But the false negative rate, health economics and implications of such a change in practice are still unknown and more research is required.		

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018				
hysteroscopy (unless this was used as a comparator to blind ES).				
Methodical Notes				
Funding Sources: not described. **COI:** The authors declare that they have no competing interests. **Study Quality:** The quality of the RCTs was assessed using the standard Cochrane Risk of Bias tool, and the quality of observational studies was analysed with the modified Agency for Healthcare Research and Quality (AHRQ) quality assessment criteria. "The overall quality of the RCTs was poor (n = 4) to moderate (n = 12), no high quality studies were identified. For observational studies, the risk of bias ranged from 31 to 79% with a mean weighted score 52.8% SD ± 11.8% which again suggests overall moderate quality" **Heterogeneity:** no meta-analysis was performed. **Publication Bias:** not investigated. **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of RCTs and oberservational studies. No a priori clear aim or outcomes of interest. Not a meta-analysis but synthesis of qualitative data.				

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (12 studies) To study the diagnostic accuracy of endometrial sampling in women with PMB regarding the diagnoses of endometrial cancer and atypical hyperplasia compared to two different reference standards: blind D&C and the current reference standard: hysteroscopy with histology or hysterectomy. **Databases:** Medline, Embase, Science direct. **Search period:** 01/1965 - 03/2015. **Inclusion Criteria:** Observational studies on the evaluation of the diagnostic accuracy of endometrial sampling in women with PMB. Histology results of endometrial sampling were compared with the	**Population:** Women with postmenopausal uterine bleeding. **Intervention:** Endometrial sampling (histology). **Comparison:** Endometrial histological findings from (blind) D&C, diagnostic hysteroscopy with histology by targeted biopsy or D&C or hysterectomy.	**Primary:** Diagnostic accuracy for detection of endometrial cancer, atypical hyperplasia and endometrial disease. **Secondary:** - **Results: Study overview:** 12 studies reporting 1029 women with PMB: 5 with dilatation and curettage and 7 with hysteroscopy as a reference test. **Results:** "The weighted sensitivity of endometrial sampling with D&C as a reference fro the diagnosis of endometrial cancer was 100%(100-100) and 92%(71-100) for the diagnosis of atypical hyperplasia. Only ine study reported sensitivity for endometrial disease, which was 76%. When hysteroscopy was used as a referen, weighted sensitivities of endometrial sampling were 90%(50-100), 82%(56-94) and 39%(21-69) for the diagnosis of endometrial cancer,	12 studies included: Goldberg 1982, Batool 1994, Ben-Baruch 1994, vdBosch 1995, vdBosch 1996, Giusa-Chifieri 1996, Gupta 1996, De Silva 1997, Mortakis 1997, Bunyavejchevin 2001, Epstein 2001, Spicer 2006.

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016				
results of a reference standards. The articles had to study women with postmenopausal uterine bleeding, the diagnostic test of interest was endometrial sampling (histology), the reference standard had to be endometrial histology findings from (blind) D&C, diagnostic hysteroscopy with histology by targeted biopsy of D&C or hysterectomy. **Exclusion Criteria:** -		atypical hyperplasia and endometrial disease, respectively. For all diagnosis studie and the reference test used, specificity was 98-100%. The weighted failure rate of endometrial sampling was 11% (1-53%), while insufficient samples were found in 31%(7-76%). In these women with insufficient or failed samples, an endometrial (pre) cancer was found in % (range 0-18%)." **Author's Conclusion:** "In women with postmenopausal bleeding, the sensitivity of endometrial sampling to detect endometrial cancer and especially atypical hyperplasia and endometrial disease, including endometrial polyps, is lower than previously thought. Thereffore, further diagnostic work-up for focal pathology is warranted, after a benign result of endometrial sampling."		
Methodical Notes				

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016

Funding Sources: Declared, no grants or funding received.

COI: Not declared.

Study Quality: Two reviewers independently assessed the the methodological quality of each article using QUADAS-2 tool for diagnostic studies, modified to conform to this review. low risk of bias in 4 studies; high risk of bias in 3 studies; unclear risk of bias in 8 studies.

Heterogeneity: No investigation of heterogeneity.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive studies or studies without consistently applied reference standard. Downgrade to evidence level 3.
Conflict of interest not declared. No investigation of heterogeneity or publication bias. ROC curves do not provide relevant information.

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017			
Evidence level: 3 **Study type:** Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma. **Databases:** MEDLINE, EMBASE, ClinicalTrials.gov, and the Cochrane library **Search period:** Inception to 01/2017 **Inclusion Criteria:** In eligible studies, the index test included office endometrial biopsy, hysteroscopic biopsy, or dilatation and curettage; the reference standard was hysterectomy. Outcome measures included tumor grade, histologic subtype, or both. **Exclusion Criteria:** Conference abstracts, case reports and papers containing less than five patients, review articles, absence of hysterectomy or preoperative histology, intraoperative frozen biopsies, not in English, lack of the percentage of	**Population:** Women with endometrial carcinoma **Intervention:** Preoperative endomentrial sampling: Index test included office endometrial biopsy, hysteroscopic biopsy, or D&C; **Comparison:** Hysterectomy as reference standard.	**Primary:** Accuracy of diagnosis of tumor grade and histologica subtype, Inter rater Kappa. **Secondary:** - **Results: Study overview:** A total of 45 studies (12,459 patients) met the inclusion criteria. **Results:** The pooled agreement rate on tumor grade was 0.67 (95% CI 0.60– 0.75) and Cohen's k was 0.45 (95% CI 0.34–0.55). Agreement between hysteroscopic biopsy and final diagnosis was higher (0.89, 95% CI 0.80–0.98) than for dilatation and curettage (0.70, 95% CI 0.60–0.79; P5.02); however, it was not significantly higher than for office endometrial biopsy (0.73, 95% CI 0.60–0.86; P5.08). The lowest agreement rate was found for grade 2 carcinomas (0.61, 95% CI 0.53–0.69). Downgrading was found in 25% and upgrading was found in 21% of the endometrial samples. Agreement on histologic subtypes was 0.95 (95% CI 0.94–0.97) and 0.81 (95% CI 0.69–0.92) for preoperative endometrioid and nonendometrioid carcinomas, respectively.	45 studies included: see article.

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017				
agreement, and absence of possibilities to calculate these from available data.		**Author's Conclusion:** "Overall there is only moderate agreement on tumor grade between preoperative endometrial sampling and final diagnosis with the lowest agreement for grade 2 carcinomas."		
Methodical Notes				
Funding Sources: none declared. **COI:** The authors did not report any potential conflicts of interest. **Study Quality:** Risk of bias was assessed (Quality Assessment of Diagnostic Accuracy Studies). "Overall, the risk of bias was unclear in most studies, which was mainly attributable to patient selection and interpretation of the index test and reference standard" **Heterogeneity:** To test the amount of heterogeneity between the studies, I 2 statistic was used. Our outcomes are characterized by high heterogeneity. 59-95%. **Publication Bias:** Investigated but not shown. "Funnel plots for the primary outcome did not indicate any publication bias (data not shown)." **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive diagnostic study or studies without consistently applied reference standard. **Downgrade to evidence level 3.**				

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017	
Unclear definition of population. Predominantly unclear risk of bias in included studies. HIgh heterogeneity in all analyses. Publication bias investigated but not shown.	

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

van Hanegem, N. et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. Bjog. 124. 231-240. 2017		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized controlled open-label trial. "To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling." **Number of Patient:** 200 **Recruitung Phase:** Betweeen January 2010 and October 2013. **Inclusion Criteria:** Women with PMB, an endometrial thickness >4 mm and benign result from endometrial sampling **Exclusion Criteria:** Women with complex hyperplasia. Other exclusion criteria were cervical cytology showing an abnormality which warranted treatment, an endometrial biopsy showing a (pre)malignancy (i.e. atypical endometrial hyperplasia	**Intervention:** workup by hysteroscopy, preceded by saline infusion sonography (SIS) **Comparison:** Expectant management	**Primary:** Recurrence of PMB within a year after randomisation. **Secondary:** Time to recurrent bleeding and recurrent bleeding after more than 1 year. **Results: Study population:** Between January 2010 and October 2013, 200 women were randomised; 98 to hysteroscopy and 102 to expectant management. **Results:** Within 1 year a total of 15 women (15.3%) in the hysteroscopy group experienced recurrent bleeding, versus 18 (18.0%) in the expectant management group (relative risk 0.85 (95% CI 0.46–1.59). In the hysteroscopy group, 50/98 (51%) polyps were diagnosed of which 6/98 (6%) showed evidence of endometrial (pre)malignancy; final pathology results after hysterectomy showed three women with hyperplasia with atypia and three women with endometrial cancer. **Author's Conclusion:** "In women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent

van Hanegem, N. et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. Bjog. 124. 231-240. 2017			
or endometrial cancer) or an insufficient sample or if endometrial sampling had failed due to technical problems. Women using an aromataseinhibitor or anti-oestrogen medication were also excluded.		bleeding. Hysteroscopy detected focal endometrial (pre)malignancy in 6% of women who had benign endometrial sampling. This finding indicates that in these women, further diagnostic workup is warranted to detect focal (pre)malignancies, missed by blind endometrial sampling."	
Methodical Notes			
Funding Sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. **COI:** Declared, only available online. **Randomization:** Block randomisation with a block size of four, an allocation ratio of 1:1 and stratification for hospital. The web-based program generated a unique number with allocation code after entry of the patient's initials and date of birth. Neither recruiting doctors nor members of the trial project group could access the randomisation sequence. **Blinding:** Open-label study. Statistician performed the analysis was masked to assigned intervention. **Dropout Rate/ITT-Analysis:** Statistical analysis was performed according to the intention- to-treat principle. 0 and 2 patients were lost to follow up per group out of 98 and 102. **Notes:** Oxford level of evidence: 2 Randomized controlled open-label trial. No tests for group differences, but groups appear similar.			

2.8. Schlüsselfrage 10: Gibt es bei V.a. Endometriumkarzinom einen sinnvollen Algorithmus von transvaginaler Sonographie, Endometriumbiopsie mittels Aspiration, Abrasio uteri oder Hysteroskopie für die Diagnostik zum Nachweis eines Endometriumkarzinoms bei Frauen mit normalem Risiko?

Inhalt: *9 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Alblas, M. 2018	4	Systematic review (14 studies) To provide an overview of prediction models for the risk of developing endometrial cancer in women of the general population or for the presence of endometrial cancer in symptomatic women.
Alcázar, J. L. 2018	2	Systematic review and meta-analysis (9 studies) To evaluate the risk of endometrial cancer and/or endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ≥ 11 mm.
Clarke, M. A. 2018	2	Systematic review and meta-analysis (92 studies) To provide a reference of the prevalence of postmenopausal bleeding (PMB) in endometrial cancers and the risk of endometrial cancer in women with PMB.
de Rijk, S. R. 2016	3	Systematic review (10 studies) To estimate the risk of concurrent endometrial cancer in nonpolypoid endometrium when atypia was diagnosed within an endometrial polyp.
Li, J. 2019	2	Meta-analysis of diagnostic studies (12 studies). To estimate the diagnostic accuracy of HE4 and CA125 and compared their performance as surrogates for EC detection.
Narice, B. F. 2018	2	Systematic review and meta-synthesis (60 studies) To identify existing evidence about the effectiveness of Pipelle compared with other ES techniques for assessing low-

Literaturstelle	Evidenzlevel	Studientyp
		risk women with AUB which could inform the development of new care pathways in primary care.
van Hanegem, N. 2017	2	Randomized controlled open-label trial. "To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling."
van Hanegem, N. 2016	3	Systematic review and meta-analysis (12 studies) To study the diagnostic accuracy of endometrial sampling in women with PMB regarding the diagnoses of endometrial cancer and atypical hyperplasia compared to two different reference standards: blind D&C and the current reference standard: hysteroscopy with histology or hysterectomy.
Visser, N. C. M. 2017	3	Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *8 Bewertung(en)*

Alblas, M. et al. Prediction models for endometrial cancer for the general population or symptomatic women: A systematic review. Crit Rev Oncol Hematol. 126. 92-99. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic review (14 studies) To provide an overview of prediction models for the risk of developing endometrial cancer in women of the general population or for the presence of endometrial cancer in symptomatic women. **Databases:** We systematically searched the Embase and Pubmed database **Search period:** Unclear - 09/2017 **Inclusion Criteria:** Papers with the main aim of developing, validating or updating a model predicting the risk of endometrial cancer in the general population or presence in symptomatic women. Any multivariable (at least two predictors) prediction model was eligible	**Population:** General population or EC patients. **Intervention:** Exposure to risk-factors. **Comparison:** Non-exposure to risk factors.	**Primary:** Diagnosis of endometrial cancer **Secondary:** - **Results: Study overview:** 14 studies were included. We found two prediction models for developing endometrial cancer in the general population (risk models) and one extension. Eight studies described the development of models for symptomatic women (diagnostic models), one comparison of the performance of two diagnostic models and two external validation. Sample size varied from 60 (10 with cancer) to 201,811 (855 with cancer) women. **Results:** The age of the women was included as a predictor in almost all models. The risk models included epidemiological variables related to the reproductive history of women, hormone use, BMI, and smoking history. The	Fortner 2017, Husing 2016, Pfeiffer 2013, Madkour 2017, Plotti 2017, Sladkevicius 2016, Wong 2016, Gianella 2014, Angioli 2013, Opolskiene 2011, Burbos 2011, Burbos 2010, Weber 1999, Masonda 2011.

Alblas, M. et al. Prediction models for endometrial cancer for the general population or symptomatic women: A systematic review. Crit Rev Oncol Hematol. 126. 92-99. 2018

for inclusion, including prediction scores or prediction tools. Only papers written in the English language were included. There was no restriction on publication date. **Exclusion Criteria:** -		diagnostic models also included clinical predictors, such as endometrial thickness and recurrent bleeding. The concordance statistic (c), assessing the discriminative ability, varied from 0.68 to 0.77 in the risk models and from 0.73 to 0.957 in the diagnostic models. Methodological information was often limited, especially on the handling of missing data, and the selection of predictors. One risk model and four diagnostic models were externally validated. **Author's Conclusion:** "In conclusion, only a few models have been developed to predict endometrial cancer in asymptomatic or symptomatic women. The usefulness of most of the models is unclear considering methodological shortcomings and lack of external validation and head to head comparisons of models. Developed risk models should be externally validated and extended with new predictors, such as genetic and epigenetic risk predictors, to improve model performance. Future research on diagnostic models should focus on		

Alblas, M. et al. Prediction models for endometrial cancer for the general population or symptomatic women: A systematic review. Crit Rev Oncol Hematol. 126. 92-99. 2018				
		external validation and creating models with larger sample sizes, which could be realized with individual patients data meta-analysis"		
Methodical Notes				
Funding Sources: The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 634570 (FORECEE). **COI:** Declared, for list see article. **Study Quality:** Not investigated. **Heterogeneity:** no meta-analysis was performed. **Publication Bias:** not investigated. **Notes:** Oxford level of evidence: 3 Systematic review of cohort, case-cohort, case control studies. **Downgrade to evidence level 4:** Insufficient description of performed searches and inclusion criteria or outcomes. No evaluation of study quality.				

Alcázar, J. L. et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ?11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 46. 565-570. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (9 studies) To evaluate the risk of endometrial cancer and/or endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ≥ 11 mm. **Databases:** Systematic review of literature using database search (PubMed and Web of Science) **Search period:** 01/1990 to 12/2016 **Inclusion Criteria:** Prospective or retrospective cohort observational studies reporting on ET in asymptomatic postmenopausal women, as measured by the “double layer technique,” and data from histological diagnosis after endometrial sampling (whatever the method used for endometrial sampling).	**Population:** Asymptomatic postmenopausal women. **Intervention:** Exposure/ risk factor endometrial thickness (ET) ≥ 11 mm measured by transvaginal ultrasound (double layer) and histopathological findings. **Comparison:** Endometrial thickness 5-10 mm.	**Primary:** Risk of endometrial cancer and or hyperplasia with atypia. **Secondary:** - **Results:** Only summary result described here, rest see article. **Study overview:** The search identified 289 studies. After exclusions, nine articles that met all the inclusion criteria were included, comprising data from 4751 women. **Results:** The prevalence of endometrial cancer and/or endometrial hyperplasia with atypia was 2.4%. The relative risk of endometrial cancer and/or endometrial hyperplasia with atypia in the ≥11 mm group was 2.59 (95% CI: 1.66-4.05). High heterogeneity was observed between studies (I2: 57.3%, P = .016).	9 studies included: leischer 2001, Martinez-Rubio 2003, Tsikouras 2007, Schmidt 2008, Kalampokas, Gianella 2014, Yasa 2016, Louie 2016, Seckim 2016.

Alcázar, J. L. et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ?11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 46. 565-570. 2018

Exclusion Criteria: Studies that included patients with hormone replacement therapy, tamoxifen, or aromatase inhibitors were excluded. Studies not reporting on histological data and studies not reporting on data about ET in enough detail that we could stratified the patients in two groups (ET ≥11 mm and ET < 11 mm) were further excluded.		**Author's Conclusion:** The risk for endometrial cancer and/or endometrial hyperplasia with atypia in asymptomatic postmenopausal women is 2.59 times higher in women with endometrial thickness ≥ 11 mm as compared with those with endometrial thickness between 5 mm and 10 mm, although there was significant heterogeneity in estimates across studies.	

Methodical Notes

Funding Sources: not described.

COI: All authors declare have no conflict of interest.

Study Quality: Three investigators did quality assessment of the studies using the risk of bias tool for observational studies using the Newcastle- Otawa Scales.The quality of included studies was considered to be acceptable, although most suffered from selection bias and were retrospective.

Heterogeneity: Heterogeneity among studies was investigated using the I2 statistics. 10 I2 values of 25%, 50% and 75% correspond to cut-off points for low, moderate, and high heterogeneity. In case of heterogeneity, we performed a meta-regression analysis for identifying potential sources.
"High heterogeneity was observed between studies (I2: 57.3%, P = .016)."

Publication Bias: Publication bias was assessed using Egger's funnel plot. We did not observe publication bias.

Alcázar, J. L. et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ?11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 46. 565-570. 2018			
Notes: Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies No search for grey literature was performed; initia study selection was performed by one reviewer.			
Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (92 studies) To provide a reference of the prevalence of postmenopausal bleeding (PMB) in endometrial cancers and the risk of endometrial cancer in women with PMB. **Databases:** PubMed and Embase, reference lists of articles identified in the primary search for additional relevant studies. English-language studies only.	**Population:** Postmenopausal women. **Intervention:** Exposure to PMB or Endometrial cancer. **Comparison:** Non-exposure.	**Primary:** Prevalence of post-menopausal bleeding (PMB) in women with endometrial cancer. Risk of endometrial cancer in women with PMB. **Secondary:** Subgroup analyses f.e. for regions in which the studies were conducted. **Results:** Only summary described here, rest see article. **Study overview:** A total of 129 unique studies, including 34 432 unique patients with PMB and 6358 with endometrial cancer (40 790 women), were analyzed. **Results:** The pooled prevalence of PMB among women with endometrial cancer was	92 studies included: see article.

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018				
Search period: 01/1977 - 01/2017. **Inclusion Criteria:** Original studies with primary data reporting the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer among women with PMB. English-language, peer-reviewed studies. **Exclusion Criteria:** Studies that included special populations (eg, defined by comorbid conditions or specific histologic findings), lacked detailed inclusion criteria, and/or included 25 or fewer women.		91% (95%CI, 87%-93%), irrespective of tumor stage. The pooled risk of endometrial cancer among women with PMB was 9%(95%CI, 8%-11%), with estimates varying by use of hormone therapy (range, 7%[95%CI, 6%-9%] to 12%[95%CI, 9%-15%]; P < .001 for heterogeneity) and geographic region (range, 5%[95% CI, 3%-11%] in North America to 13%[95%CI, 9%-19%] in Western Europe; P = .09 for heterogeneity). **Author's Conclusion:** "The widespread practice of referring allwomenwith PMB for TVUS and/or endometrial biopsy carries a considerable burden and cost. Given the rise in endometrial cancer incidence and mortality, our findings raise the important question of how to best manage PMB to optimize the benefit of early detection approaches while avoiding unnecessary harms. Interest has increased in the use of biomarkers, such as DNA methylation, to improve early detection of endometrial cancer. To obtain reliable estimates of the clinical performance of molecular assays, diagnostic tests, and management algorithms, we must know the prior risk of endometrial cancer in the population. Our study represents an important and timely evaluation of the risk of endometrial cancer in women with PMB and can serve as a		

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018

		reliable reference for the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer inwomenwith PMB, 2 requisite prior probabilities for prediction of endometrial cancer risk and secondary and tertiary prevention. As new markers are discovered or new clinical management strategies are evaluated, our results can aid in the assessment of their potential clinical value andwill help to inform clinical and epidemiologic risk prediction models to support clinical decision making."		

Methodical Notes

Funding Sources: This study was supported by grant 603019 via the COHEAHR Network, 7th Framework Programme of DG Research and Innovation, European Commission (Dr Arbyn). The funding source had no role in the design and conduct of the study.

COI: Reported, but no conflicts were declared.

Study Quality: Two independent reviewers evaluated study quality and risk of bias using items from the Newcastle-Ottawa Quality Assessment Scale and the Quality Assessment of Diagnostic Accuracy Studies tool.
Study quality reported in the supplementary section.

Heterogeneity: We estimated pooled prevalence and 95%CIs using multilevel logistic-normal random-effects models to account for interstudy heterogeneity. Between-study variance was quantified using the $\tau 2$ statistic.

Clarke, M. A. et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 178. 1210-1222. 2018			
Publication Bias: We conducted sensitivity analyses to assess the influence of clinical setting (tertiary center vs other), study design, and the potential for publication bias using Egger regression analyses. "No evidence of publication bias was found among studies reporting the prevalence of PMB in women with endometrial cancer (Egger regression intercept, 0.15; P = .90)." **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies. Significant heterogeneity was reported for the two main outocmes.			
de Rijk, S. R. et al. Atypical Endometrial Polyps and Concurrent Endometrial Cancer: A Systematic Review. Obstet Gynecol. 128. 519-25. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review (10 studies) To estimate the risk of concurrent endometrial cancer in nonpolypoid endometrium when atypia was diagnosed within an endometrial polyp. **Databases:** MEDLINE, EMBASE, Web of Science, and ClinicalTrials.gov **Search period:** 1990 and January 2015.	**Population:** Women diagnosed with an atypical endometrial polyp with or without consecutive hysterectomy. **Intervention:** - **Comparison:** -	**Primary:** Risk of concurrent endometrial cancer **Secondary:** - **Results: Study overview:** Broad searches yielded 2,922 authentic citations, 307 met criteria for full-text evaluation, and 10 met inclusion criteria. **Results:** The final selection included eight retrospective studies reporting on	10 studies included: Agostini 2002, Hahn 2010, Kelly 2007, Leitao 2010, Litta 2013, Mittal 2008, Naaman 2014, Obeidat 2009, Scrimin 2006, Scrimin 2008.

de Rijk, S. R. et al. Atypical Endometrial Polyps and Concurrent Endometrial Cancer: A Systematic Review. Obstet Gynecol. 128. 519-25. 2016				
Inclusion Criteria: Studies of women diagnosed with an atypical endometrial polyp with a consecutive hysterectomy or studies evaluating the natural behavior of the endometrium when atypical endometrial polyps were diagnosed were included. Initially, there were no restrictions on age, menopausal status, diagnostic techniques, or hormonal therapy. However, in the final selection, we did not include patients specified to be undergoing hormonal treatment for atypical endometrial polyps or women who were using tamoxifen. When reporting was insufficient concerning initial pathology diagnosis, diagnostic techniques, and final pathology diagnosis on hysterectomy specimen, studies were not included. No other selection on study type or language was performed. Frequently cited articles from before 1990 were selectively included. **Exclusion Criteria:** Case reports and series, conference abstracts, and letters to editors were excluded.		concurrent endometrial cancer in case of atypical endometrial polyps and two follow-up studies on patients conserving their uterus after hysteroscopic resection of atypical endometrial polyps. In total, 127 patients were included with an initial diagnosis of atypical endometrial hyperplasia within polyps. Meta-analysis showed a pooled risk estimate of 5.6% (95%CI 0.2–17.6%) on concurrent endometrial cancer after resection of an atypical endometrial polyp. **Author's Conclusion:** "The pooled risk estimate of 5.6% (95% CI 0.2–17.6%) on endometrial cancer when atypia is found within an endometrial polyp differs from the well-established risk of nonpolypoid atypical endometrial hyperplasia on endometrial cancer of up to 42%. This risk of endometrial cancer is important in the process of shared decision-making regarding follow-up and further treatment."		

de Rijk, S. R. et al. Atypical Endometrial Polyps and Concurrent Endometrial Cancer: A Systematic Review. Obstet Gynecol. 128. 519-25. 2016			
Methodical Notes			
Funding Sources: The authors did not report any potential conflicts of interest. **COI:** The authors did not report any potential conflicts of interest. **Study Quality:** Study quality not investigated. **Heterogeneity:** Not investigated /applicable, no meta-analysis was performed. **Publication Bias:** Not investigated /applicable, no meta-analysis was performed. **Notes:** Oxford level of evidence: 2 Systematic review of cohort studies Downgrade to evidence level 3. Insufficient description of inclusion criteria. No evaluation of study quality.			
Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2	**Population:** Endometrium carcinoma patients and controls	**Primary:** Sensitivity, Specificity, PLR, NLR., diagnostic oodds ratio.	Moore 2008, Bignotti 2011,

Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019			
Study type: Meta-analysis of diagnostic studies (12 studies). To estimate the diagnostic accuracy of HE4 and CA125 and compared their performance as surrogates for EC detection. **Databases:** "A literature search was performed in Medline, Cochrane Literature Library and CNKI. There was no language restriction." **Search period:** No description of search period. **Inclusion Criteria:** Only studies that fulfilled the following criteria were included for analyses: 1) evaluating the sensitivity and specificity of serum HE4 in EC detection; 2) histopathology as the reference test; 3) sufficient data to calculate TP (true-positive), FP (false-positive), FN (false-negative), TN (true-negative). **Exclusion Criteria:** Exclusion criteria were as follows: review, letter, and	(usually healthy postmenopausal women). **Intervention:** HE4 or CNKI biomarkers. **Comparison:** Histopathology.	**Secondary:** Subgroup analysis. **Results: Study overview:** After filtering, twelve studies evaluating the diagnostic value of serum HE4, alone or in comparison with CA125, were included. The total sample size was 1106 patients and 1480 controls. **Results:** Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) were calculated and summary receiver operating characteristic (SROC) curves were plotted to assess the diagnostic accuracy. Results: The pooled estimates for HE4 were sensitivity: 0.71 (95%CI 0.56–0.82), specificity: 0.87 (95%CI 0.80–0.92), and area under ROC curve: 0.88 (0.85–0.91), compared to 0.35 (95% CI 0.25–0.46), 0.83 (95% CI 0.71–0.91), and 0.58 (95% CI 0.54–0.63), respectively, of CA125. Subgroup analysis demonstrated a better performance of HE4 in Caucasian population, compared to Chinese population.	Cong 2011, Liang 2011, Zhan 2011, Wu 2011, Zhao 2012, Zanotti 2012, Anioli 2012, Omer 2013, Yu 2013, Zhang 2013.

Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019				
duplicated publication, to make sure only primary publications of original studies were included.		**Author's Conclusion:** "In summary, our meta-analysis demonstrated that, compared to CA125, serum HE4 has a higher sensitivity and overall accuracy in the diagnosis of all EC cases, when stage and histological types are not specifically considered. Furthermore, for some unidentified reasons, HE4 tends to perform better in Caucasian population than in Chinese population. It remains to be investigated if the combination of the two markers could significantly improve the outcome in medical practice."		
Methodical Notes				
Funding Sources: This project is supported by the Zhejiang Provincial Natural Science Foundation (LY18H040012), and (LY18H160052). **COI:** "None." **Study Quality:** The quality of individual studies was assessed using the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) tool. All these studies were in moderate to high quality (≥6 scores). Individual results are not displayed. **Heterogeneity:** The heterogeneity between studies was analyzed by Q test I2 test. If no significant heterogeneity existed ($p > .1$, $I2 < 50\%$), a fixed-effect model was used. Otherwise, a random-effect model was applied. "Among studies assessing the diagnosis performance of HE4, high level heterogeneity existed in sensitivity (I2=92.08%) and specificity (I2=90.13%).				

Li, J. et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta. 488. 215-220. 2019

Similarly, high between-study heterogeneity was observed in sensitivity (I2=94.22%) and specificity (I2=94.03%) of the CA125 assays."

Publication Bias: Publication bias was assessed using Deeks' funnel plot asymmetry test. The plot was basically symmetrical (p=.82), indicating there was no obvious publication bias in meat-analysis relating to the diagnostic performance of HE4.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of diagnostic studies without consisntely applied reference standard.
No description of search period. High heterogeneity (I2>90%) for sensitivity and specificity for both markers. Individual results for study quality are not reported.

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-synthesis (60 studies) To identify existing evidence about the effectiveness of Pipelle compared with other ES techniques for assessing low-risk women with AUB which could inform the development of new care pathways in primary care.	**Population:** Women with abnormal uterine bleeding (AUB) **Intervention:** endometrial sampling (ES) Pipelle device. **Comparison:** ES other devices	**Primary:** Sample adequacy, test performance, pain/discomfort, costs out outpatient endometrial sampling, barriers and complications.a **Secondary:** - **Results:** "Pipelle seems to perform as well as dilation and curettage and, as well or better	60 study included: see article.

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018				
Databases: MEDLINE via OvidSP, Scopus, and Web of Science for relevant English-language articles. **Search period:** 1984 to 2016. **Inclusion Criteria:** We included papers investigating ES in women with AUB. We also considered studies in patients with known cancer; although these studies do not inform the indication of ES in primary care, they were an important source to evaluate test performance. We included review articles and opinion pieces. **Exclusion Criteria:** We excluded papers exclusively analysing postmenopausal patients, papers where the indication was assessment of fertility or recurrent miscarriage and papers where ES was assisted by hysteroscopy (unless this was used as a comparator to blind ES).		than other ES devices in terms of sampling adequacy and sensitivity. It also seems to be better regarding pain/discomfort and costs. However, Pipelle can disrupt the sonographic appearance of the endometrium and may be limited by cervical stenosis, pelvic organ prolapse and endometrial atrophy." **Author's Conclusion:** The evidence we analysed suggests that performing ES in the outpatient setting may allow effective management of low-risk women with AUB in primary care without referral to a hospital. But the false negative rate, health economics and implications of such a change in practice are still unknown and more research is required.		
Methodical Notes				

Narice, B. F. et al. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract. 19. 135. 2018

Funding Sources: not described.

COI: The authors declare that they have no competing interests.

Study Quality: The quality of the RCTs was assessed using the standard Cochrane Risk of Bias tool, and the quality of observational studies was analysed with the modified Agency for Healthcare Research and Quality (AHRQ) quality assessment criteria.
"The overall quality of the RCTs was poor (n = 4) to moderate (n = 12), no high quality studies were identified. For observational studies, the risk of bias ranged from 31 to 79% with a mean weighted score 52.8% SD ± 11.8% which again suggests overall moderate quality"

Heterogeneity: no meta-analysis was performed.

Publication Bias: not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of RCTs and oberservational studies.
No a priori clear aim or outcomes of interest. Not a meta-analysis but synthesis of qualitative data.

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and	**Population:** Women with postmenopausal uterine bleeding.	**Primary:** Diagnostic accuracy for detection of endometrial cancer, atypical hyperplasia and endometrial	12 studies included: Goldberg 1982, Batool 1994, Ben-Baruch 1994,

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016			
meta-analysis (12 studies) To study the diagnostic accuracy of endometrial sampling in women with PMB regarding the diagnoses of endometrial cancer and atypical hyperplasia compared to two different reference standards: blind D&C and the current reference standard: hysteroscopy with histology or hysterectomy. **Databases:** Medline, Embase, Science direct. **Search period:** 01/1965 - 03/2015. **Inclusion Criteria:** Observational studies on the evaluation of the diagnostic accuracy of endometrial sampling in women with PMB. Histology results of endometrial sampling were compared with the results of a reference standards. The articles had to study women with postmenopausal uterine bleeding, the diagnostic test of interest was endometrial sampling (histology), the reference standard had to be	**Intervention:** Endometrial sampling (histology). **Comparison:** Endometrial histological findings from (blind) D&C, diagnostic hysteroscopy with histology by targeted biopsy or D&C or hysterectomy.	disease. **Secondary:** - **Results: Study overview:** 12 studies reporting 1029 women with PMB: 5 with dilatation and curettage and 7 with hysteroscopy as a reference test. **Results:** "The weighted sensitivity of endometrial sampling with D&C as a reference fro the diagnosis of endometrial cancer was 100%(100-100) and 92%(71-100) for the diagnosis of atypical hyperplasia. Only ine study reported sensitivity for endometrial disease, which was 76%. When hysteroscopy was used as a referen, weighted sensitivities of endometrial sampling were 90%(50-100), 82%(56-94) and 39%(21-69) for the diagnosis of endometrial cancer, atypical hyperplasia and endometrial disease, respectively. For all diagnosis studie and the reference test used, specificity was 98-100%. The weighted failure rate of endometrial sampling was 11% (1-53%), while insufficient	vdBosch 1995, vdBosch 1996, Giusa-Chifieri 1996, Gupta 1996, De Silva 1997, Mortakis 1997, Bunyavejchevin 2001, Epstein 2001, Spicer 2006.

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016				
endometrial histology findings from (blind) D&C, diagnostic hysteroscopy with histology by targeted biopsy of D&C or hysterectomy. **Exclusion Criteria:** -		samples were found in 31%(7-76%). In these women with insufficient or failed samples, an endometrial (pre) cancer was found in % (range 0-18%)." **Author's Conclusion:** "In women with postmenopausal bleeding, the sensitivity of endometrial sampling to detect endometrial cancer and especially atypical hyperplasia and endometrial disease, including endometrial polyps, is lower than previously thought. Thereffore, further diagnostic work-up for focal pathology is warranted, after a benign result of endometrial sampling."		
Methodical Notes				
Funding Sources: Declared, no grants or funding received. **COI:** Not declared. **Study Quality:** Two reviewers independently assessed the the methodological quality of each article using QUADAS-2 tool for diagnostic studies, modified to conform to this review. low risk of bias in 4 studies; high risk of bias in 3 studies; unclear risk of bias in 8 studies.				

van Hanegem, N. et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 197. 147-55. 2016			
Heterogeneity: No investigation of heterogeneity. **Publication Bias:** Not investigated. **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive studies or studies without consistently applied reference standard. Downgrade to evidence level 3. Conflict of interest not declared. No investigation of heterogeneity or publication bias. ROC curves do not provide relevant information.			

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (45 studies). To assess the agreement between preoperative endometrial sampling and final diagnosis for tumor grade and subtype in patients with endometrial carcinoma. **Databases:** MEDLINE, EMBASE,	**Population:** Women with endometrial carcinoma **Intervention:** Preoperative endomentrial sampling: Index test included office endometrial biopsy, hysteroscopic biopsy, or D&C; **Comparison:** Hysterectomy as reference standard.	**Primary:** Accuracy of diagnosis of tumor grade and histologica subtype, Inter rater Kappa. **Secondary:** - **Results: Study overview:** A total of 45 studies (12,459 patients) met the inclusion criteria. **Results:** The pooled agreement rate on	45 studies included: see article.

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017				
ClinicalTrials.gov, and the Cochrane library **Search period:** Inception to 01/2017 **Inclusion Criteria:** In eligible studies, the index test included office endometrial biopsy, hysteroscopic biopsy, or dilatation and curettage; the reference standard was hysterectomy. Outcome measures included tumor grade, histologic subtype, or both. **Exclusion Criteria:** Conference abstracts, case reports and papers containing less than five patients, review articles, absence of hysterectomy or preoperative histology, intraoperative frozen biopsies, not in English, lack of the percentage of agreement, and absence of possibilities to calculate these from available data.		tumor grade was 0.67 (95% CI 0.60– 0.75) and Cohen's k was 0.45 (95% CI 0.34–0.55). Agreement between hysteroscopic biopsy and final diagnosis was higher (0.89, 95% CI 0.80–0.98) than for dilatation and curettage (0.70, 95% CI 0.60–0.79; P5.02); however, it was not significantly higher than for office endometrial biopsy (0.73, 95% CI 0.60–0.86; P5.08). The lowest agreement rate was found for grade 2 carcinomas (0.61, 95% CI 0.53–0.69). Downgrading was found in 25% and upgrading was found in 21% of the endometrial samples. Agreement on histologic subtypes was 0.95 (95% CI 0.94–0.97) and 0.81 (95% CI 0.69–0.92) for preoperative endometrioid and nonendometrioid carcinomas, respectively. **Author's Conclusion:** "Overall there is only moderate agreement on tumor grade between preoperative endometrial sampling and final diagnosis with the lowest agreement for grade 2 carcinomas."		
Methodical Notes				

Visser, N. C. M. et al. Accuracy of Endometrial Sampling in Endometrial Carcinoma: A Systematic Review and Meta-analysis. Obstet Gynecol. 130. 803-813. 2017

Funding Sources: none declared.

COI: The authors did not report any potential conflicts of interest.

Study Quality: Risk of bias was assessed (Quality Assessment of Diagnostic Accuracy Studies).
"Overall, the risk of bias was unclear in most studies, which was mainly attributable to patient selection and interpretation of the index test and reference standard"

Heterogeneity: To test the amount of heterogeneity between the studies, I 2 statistic was used. Our outcomes are characterized by high heterogeneity. 59-95%.

Publication Bias: Investigated but not shown. "Funnel plots for the primary outcome did not indicate any publication bias (data not shown)."

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive diagnostic study or studies without consistently applied reference standard.
Downgrade to evidence level 3.
Unclear definition of population. Predominantly unclear risk of bias in included studies. HIgh heterogeneity in all analyses. Publication bias investigated but not shown.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

van Hanegem, N. et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. Bjog. 124. 231-240. 2017		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized controlled open-label trial. "To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling." **Number of Patient:** 200 **Recruitung Phase:** Betweeen January 2010 and October 2013. **Inclusion Criteria:** Women with PMB, an endometrial thickness >4 mm and benign result from endometrial sampling **Exclusion Criteria:** Women with complex hyperplasia. Other exclusion criteria were cervical cytology showing an abnormality which warranted treatment, an endometrial biopsy showing a (pre)malignancy (i.e. atypical endometrial hyperplasia	**Intervention:** workup by hysteroscopy, preceded by saline infusion sonography (SIS) **Comparison:** Expectant management	**Primary:** Recurrence of PMB within a year after randomisation. **Secondary:** Time to recurrent bleeding and recurrent bleeding after more than 1 year. **Results: Study population:** Between January 2010 and October 2013, 200 women were randomised; 98 to hysteroscopy and 102 to expectant management. **Results:** Within 1 year a total of 15 women (15.3%) in the hysteroscopy group experienced recurrent bleeding, versus 18 (18.0%) in the expectant management group (relative risk 0.85 (95% CI 0.46–1.59). In the hysteroscopy group, 50/98 (51%) polyps were diagnosed of which 6/98 (6%) showed evidence of endometrial (pre)malignancy; final pathology results after hysterectomy showed three women with hyperplasia with atypia and three women with endometrial cancer. **Author's Conclusion:** "In women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent

van Hanegem, N. et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. Bjog. 124. 231-240. 2017			
or endometrial cancer) or an insufficient sample or if endometrial sampling had failed due to technical problems. Women using an aromataseinhibitor or anti-oestrogen medication were also excluded.		bleeding. Hysteroscopy detected focal endometrial (pre)malignancy in 6% of women who had benign endometrial sampling. This finding indicates that in these women, further diagnostic workup is warranted to detect focal (pre)malignancies, missed by blind endometrial sampling."	
Methodical Notes			
Funding Sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. **COI:** Declared, only available online. **Randomization:** Block randomisation with a block size of four, an allocation ratio of 1:1 and stratification for hospital. The web-based program generated a unique number with allocation code after entry of the patient's initials and date of birth. Neither recruiting doctors nor members of the trial project group could access the randomisation sequence. **Blinding:** Open-label study. Statistician performed the analysis was masked to assigned intervention. **Dropout Rate/ITT-Analysis:** Statistical analysis was performed according to the intention- to-treat principle. 0 and 2 patients were lost to follow up per group out of 98 and 102. **Notes:** Oxford level of evidence: 2 Randomized controlled open-label trial. No tests for group differences, but groups appear similar.			

2.9. Schlüsselfrage 11: Gibt es bei V.a. Endometriumkarzinom einen sinnvollen Algorithmus von transvaginaler Sonographie, Endometriumbiopsie mittels Aspiration, Abrasio uteri oder Hysteroskopie für die Diagnostik zum Nachweis eines Endometriumkarzinoms bei Frauen mit hohem Risiko?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Fleming, C. A. 2018	2	Systematic review and meta-analysis (4 studies) To identify the risk of endometrial malignancy in the setting of extended tamoxifen therapy.
Kahn, R. M. 2019	2	Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer.
Raffone, A. 2019	2	Systematic review and meta-analysis (12 studies) To assess the reliability of WHO system, D score and subjective EIN system in stratifying the risk of progression to cancer in EH.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *3 Bewertung(en)*

Fleming, C. A. et al. Meta-analysis of the cumulative risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy. Br J Surg. 105. 1098-1106. 2018				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 2 **Study type:** Systematic review and meta-analysis (4 studies) To identify the risk of endometrial malignancy in the setting of extended tamoxifen therapy. **Databases:** Cochrane Library, PubMed and MEDLINE. **Search period:** Inception March 2016. **Inclusion Criteria:** Inclusion criteria comprised English-language studies, and those that reported outcomes related to endometrial abnormalities and pathologically confirmed malignancy. Publications reporting on the same series of patients were identified and only the most recent data were included. **Exclusion Criteria:** Studies describing 'one-off' endometrial screening in a cross-sectional	**Population:** Unclear definition: likely patients receiving tamoxifen. **Intervention:** Exposure to extended tamoxifen treatment. **Comparison:** Exposure to standard tamoxifen treatment.	**Primary:** Breast cancer local recurrence, Disease specific mortality, overall mortality, endometrial malignancy incidence. **Secondary:** - **Results:** Study overview: 4 RCTs reported on endometrial risk in extended tamoxifen therapy.In total, these trials included 21 361 patients, of whom 7652 (35·8 per cent) received extended therapy. All studies scored highly on quality assessment. Results: The cumulative risk of endometrial malignancy increased twofold from 1·5 to 3·2 per cent with extended therapy compared with the standard 5 years of tamoxifen (RR 2·29, 95 percent c.i. 1·60 to 3·28; P **Author's Conclusion:** "Extended adjuvant tamoxifen is associated with an increase in	4 studies included: ATLAS, aTTom, Scottish, NSABP B-14.	

Fleming, C. A. et al. Meta-analysis of the cumulative risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy. Br J Surg. 105. 1098-1106. 2018				
design were excluded. Studies that did not report on endometrial malignancy rates were excluded.		endometrial cancer. No clear benefit has been shown for routine endometrial surveillance in asymptomatic patients on tamoxifen therapy."		
Methodical Notes				
Funding Sources: not reported. **COI:** The authors declare no conflict of interest. **Study Quality:** Themethodological quality of included RCTs was assessed using the Cochrane Collaboration's tool for assessing RCT risk of bias. The Newcastle-Ottawa quality assessment scale for non-randomized cohort studies was applied to determine the quality of each eligible study objectively. "All studies scored highly on quality assessment." but the scores are not reported. **Heterogeneity:** The degree of heterogeneity between studies was expressed as the I2 statistic. An I2 value of 0 per cent corresponds to no heterogeneity, 25–49 per cent represents low heterogeneity, 50–74 per cent moderate heterogeneity and 75 per cent or more indicates high heterogeneity between included studies. **Publication Bias:** Not investigated, but not feasible for the number of included studies. **Notes:** Oxofrd level of evidence: 1 Systematic review and meta-analysis of randomized trials. **Downgrade to evidence level 2** Unclear definition of study population. High heterogeneity in some analysis but not for the outcome of interest (Combined analysis of endometrial risk				

Fleming, C. A. et al. Meta-analysis of the cumulative risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy. Br J Surg. 105. 1098-1106. 2018			
was subject to low to moderate heterogeneity (I2 =41 per cent)). All scores of study quality were high, but are not reported in the article.			
Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer. **Databases:** PubMed, EMBASE, MEDLINE, and the Cochrane Library was performed. **Search period:** 1990-2018. **Inclusion Criteria:** 1) prospective studies, 2) studies of patients with known endometrial	**Population:** Patients with known endometrial cancer **Intervention:** MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI). **Comparison:** each other intervention	**Primary:** Prevalence of lynch syndrome, MSI germline mutation, IHC Abnormality. **Secondary:** - **Results: Study overview:** The comprehensive search produced 4400 publications. 29 peer-reviewed studies met the inclusion criteria. **Results:** Patients with endometrial cancer (n = 6649) were identified, and 206 (3%) were confirmed to have Lynch syndrome through germline genetic testing after positive universal tumor molecular screening. Among 5917 patients who underwent tumor IHC, 28% had abnormal staining. Among 3140 patients who underwent MSI analysis, 31% had MSI.	29 studies included, see article.

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019				
cancer, 3) studies whose patients underwent germline genetic testing for Lynch syndrome after positive screening, and 4) studies whose patients underwent tumor testing with MMR IHC with or without MLH1 methylation and/or MSI analysis. **Exclusion Criteria:** 1) retrospective studies, 2) studies without endometrial cancer, 3) studies whose subjects had confirmed Lynch syndrome before the study, and 4) studies whose subjects did not undergo genetic testing for Lynch syndrome after positive screening.		Among patients with endometrial cancer, the weighted prevalence of Lynch syndrome germline mutations was 15% (95% confidence interval [CI], 11%-18%) with deficient IHC staining and 19% (95% CI, 13%-26%) with a positive MSI analysis. Among 1159 patients who exhibited a loss of MLH1 staining, 143 (13.7%) were found to be MLH1 methylation–negative among those who underwent methylation testing, and 32 demonstrated a germline MLH1 mutation (2.8% of all absent MLH1 staining cases and 22.4% of all MLH1 methylation–negative cases). Forty-three percent of patients with endometrial cancer who were diagnosed with Lynch syndrome via tumor typing would have been missed by family history–based screening alone. **Author's Conclusion:** "Overall, this study demonstrates that a significant proportion of patients with endometrial cancer have abnormal tumor IHC/MSI. Medical practitioners counseling patients about these results should be aware of the risk of identifying a Lynch syndrome germline mutation among patients with abnormal tumor testing. We found that a large number of the patients and families		

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019				
		diagnosed with Lynch syndrome would have been missed by traditional methods such as family history–based screening. This study provides evidence to further support the widespread implementation of molecular screening for all women diagnosed with endometrial cancer. Furthermore, once patients are found to be at risk for Lynch syndrome through positive screening, a greater effort to counsel them during follow-up with genetic counseling and testing is imperative."		
Methodical Notes				
Funding Sources: Gulce Askin and Paul J. Christos report funding from the Weill Cornell Medicine Clinical and Translational Science Center (grant 1-UL1-TR002384-01) during the conduct of this study. **COI:** Kevin Holcomb reports other from Johnson and Johnson and funding from Fujirebio Diagnostics, Inc, outside the submitted work. The other authors made no disclosures. **Study Quality:** "All 29 selected studies that met the inclusion criteria underwent a quality assessment with the Cochrane risk-of-bias tool. On the basis of the consensus of 2 independent reviewers for each individual study, the risk of bias for sequence generation was low, the risk of bias for incomplete outcome data was low, the risk of bias for selective outcome reporting was low, and the risk of bias for other sources of bias was low." **Heterogeneity:** Statistical heterogeneity was assessed with the Cochran Q test and the I2 statistic, and heterogeneity was considered present when P <				

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019			
.20 and I2 ≥ 50%, respectively. "Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history." **Publication Bias:** The presence of a publication bias was evaluated with funnel plots and the Begg-Mazumdar rank-correlation test. **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies. Unclear definition of outcomes. Heterogeneity investigated but not reported (supposedly high "Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history."). Study quality investigated, but not reported.			
Raffone, A. et al. Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis. Arch Gynecol Obstet. 299. 1233-1242. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (12 studies) To assess the reliability of WHO system, D score and subjective EIN system in stratifying the risk of progression to cancer in EH. **Databases:** MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID,	**Population:** Women with endometrial hyperplasia **Intervention:** WHO classification system **Comparison:** EIN system	**Primary:** Relative risk of Progression to endometrial cancer. **Secondary:** - **Results: Results:** 12 cohort studies and one case–control study, assessing 3629 EH, were included. Relative risk (RR) for cancer progression was calculated with 95% confidence interval (CI), and results were	12 studies included: Kurman 1985, Baak 1988, Baak 1992, Ho 1997, Orbo 2000, Baak 2001, Horn 2004, Baak 2005, Baak 2005 (multicentre), Hecht 2005, Reed 2010, Steinbakk 2011.

Raffone, A. et al. Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis. Arch Gynecol Obstet. 299. 1233-1242. 2019				
Cochrane Library and Google Scholar. **Search period:** Inception to 08/2018. **Inclusion Criteria:** Peer-reviewed, retrospective or prospective studies assessing the rates of progression of EH to cancer. **Exclusion Criteria:** 1. Assessment of only those EH undergone hysterectomy as primary treatment. 2. Inclusion of only benign or only premalignant EH. 3. EH not classified. 4. Classification system other than WHO or EIN. 5. Reviews. 6. Same cohort of patients as a study already included.		compared using Chi-square test (significant p value < 0.05). WHO system showed a RR of 8.74 (95% CI 6.66–11.47). Objective D score showed a RR of 29.22 (95% CI 13.24–64.51), significantly higher than WHO (p = 0.005). Subjective EIN system showed a RR of 19.37 (95% CI 5.86–64.01), intermediate between WHO and D score, without significant differences (p = 0.20 and p = 0.57, respectively). **Author's Conclusion:** "Among the classification systems of EH, objective EIN criteria with D score calculation are significantly more reliable than WHO criteria in stratifying the risk of progression of EH to cancer. Subjective EIN criteria, which are more applicable in the common practice than D score, did not show significant superiority over WHO instead. Further studies are necessary to determine if subjective EIN system should replace WHO system in the routine diagnosis of EH."		
Methodical Notes				

Raffone, A. et al. Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis. Arch Gynecol Obstet. 299. 1233-1242. 2019

Funding Sources: not described.

COI: The authors declare that they have no conflict of interest.

Study Quality: The risk of bias was assessed following the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).
Predominantly low or unclear risk of bias. One study was considered to be of high risk of bias in one domain. This study was excluded from the analysis.

Heterogeneity: Statistical heterogeneity among studies was assessed using the inconsistency index I2: heterogeneity was considered insignificant for I2 < 25%, low for I2 < 50%, moderate for I2 < 75% and high for I2 ≥ 75%. The random effect model of DerSimonian and Laird was used only.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies.
Lacking definition of inclusion criteria. Publication bias not investigated.

2.10. Schlüsselfrage 12: Gibt es bei V.a. Endometriumkarzinom einen sinnvollen Algorithmus von transvaginaler Sonographie, Endometriumbiopsie mittels Aspiration, Abrasio uteri oder Hysteroskopie für die Diagnostik zum Nachweis eines Endometriumkarzinoms bei Frauen mit genetischer Disposition?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Coelho, H. 2017	3	Systematic review (7 studies) To assess the diagnostic test accuracy of polymerase chain reaction (PCR)-based microsatellite instability (MSI) testing for identifying Lynch syndrome in patients with colorectal cancer.
Kahn, R. M. 2019	2	Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer.
Menko, F. H. 2019	3	Systematic review (30 studies) to critically evaluate studies on the uptake of presymptomatic genetic testing in the two most common hereditary cancer syndromes, (1) after at-risk family members were informed by the proband and (2) when at-risk family members were directly contacted by a genetics centre.
Ryan, N. A. J. 2019	2	Systematic review and meta-analysis. (59 studies) To provide accurate data estimating the outcomes of testing for LS in EC patients.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *4 Bewertung(en)*

Coelho, H. et al. A systematic review of test accuracy studies evaluating molecular micro-satellite instability testing for the detection of individuals with lynch syndrome. BMC Cancer. 17. 836. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic review (7 studies) To assess the diagnostic test accuracy of polymerase chain reaction (PCR)-based microsatellite instability (MSI) testing for identifying Lynch syndrome in patients with colorectal cancer. **Databases:** Cochrane Database of Systematic Reviews, CENTRAL and HTA, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase and the Health Management Information Consortium; Web of Science [including conference proceedings, via Thomson Reuters]. **Search period:** 2006 to current (unspecified). **Inclusion Criteria:** Studies had to be single-gate (also known as diagnostic cohort	**Population:** Patients with colorectal cancer **Intervention:** polymerase chain reaction (PCR)-based microsatellite instability (MSI) testing **Comparison:** best practice for the reference standard	**Primary:** Lynch syndrome diagnosis accuracy **Secondary:** - **Results:** 9 study samples were included. When MSI-Low results were considered to be negative, sensitivity estimates ranged from 67% (95% CI 47, 83) to 100% (95% CI 94, 100). Three studies contributed to estimates of both sensitivity and specificity, with specificity ranging from 61% (95% CI 57, 65), to 93% (95% CI 89, 95). Good sensitivity was achieved at the expense of specificity. When MSI-L was considered to be positive (effectively lowering the threshold for a positive index test result) sensitivity increased and specificity decreased. Between-study heterogeneity in both the MSI and reference standard testing, combined	8 studies included: Barnetson 2006, Southey 2005, Poynter 2008, Caldes 2004, Mueller 2009, Overbeek 2007, Poynter 2008, Shia 2005.	

Coelho, H. et al. A systematic review of test accuracy studies evaluating molecular micro-satellite instability testing for the detection of individuals with lynch syndrome. BMC Cancer. 17. 836. 2017

studies) or two-gate (also known as diagnostic case-control studies) diagnostic test accuracy studies. They had to recruit individuals with colorectal cancer and investigate the diagnostic test accuracy of molecular MSI testing. MSI must have been compared with the reference standard, which was constitutional MMR mutation testing, by providing sufficient data for at least sensitivity to be estimated. Other outcomes were: specificity, likelihood ratios, predictive values, concordance (with the reference standard), diagnostic yield, and test failure rates. To be included in the review, studies must have been designed for all participants to receive both the index test and reference standard. However, studies recruiting a representative sample of all patients with CRC (including where an age limit was applied), the reference standard may have been applied to all MSI positive-tumours and to a representative (e.g., random) sample of MSI negative-tumours. Abstracts were included if they reported data from an included study that was published in full. **Exclusion Criteria:** -		with the low number of studies contributing to both sensitivity and specificity estimates, precluded pooling by meta-analysis. **Author's Conclusion:** MSI testing is an effective screening test for Lynch syndrome. However, there is a paucity of studies that evaluate test accuracy in unselected, population-based samples. In addition, the studies that were identified in this review displayed heterogeneity in both the MSI and reference standard testing methods. As such, there is significant uncertainty surrounding what balance of sensitivity and specificity will be achieved in clinical practice and how this relates to specific characteristics of the test (such as the panel of markers used or the thresholds used to denote a positive test).		

Coelho, H. et al. A systematic review of test accuracy studies evaluating molecular micro-satellite instability testing for the detection of individuals with lynch syndrome. BMC Cancer. 17. 836. 2017

Methodical Notes

Funding Sources: Declared, see article for list.

COI: The authors declare that they have no competing interests.

Study Quality: Risk of bias in individual studies was assessed according to criteria in Phase 3 of the QUADAS-2 tool.
None of the included studies displayed any evidence to suggest that they were at high-risk of bias.

Heterogeneity: Between-study heterogeneity in both the MSI and reference standard testing, combined with the low number of studies contributing to both sensitivity and specificity estimates, precluded pooling by meta-analysis.

Publication Bias: not investigated.

Notes:
Oxford level of evidence: 3 Systematic review of diagnostic cohort or diagnostic case control studies.
End of search period not disclosed (current). No meta-analysis was performed due to high heterogeneity.

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019

Evidence level: 2 **Study type:** Systematic review and meta-analysis (29 studies) The aim of this study was to evaluate outcomes of MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI) analysis among patients with endometrial cancer. **Databases:** PubMed, EMBASE, MEDLINE, and the Cochrane Library was performed. **Search period:** 1990-2018. **Inclusion Criteria:** 1) prospective studies, 2) studies of patients with known endometrial cancer, 3) studies whose patients underwent germline genetic testing for Lynch syndrome after positive screening, and 4) studies whose patients underwent tumor testing with MMR IHC with or without MLH1 methylation and/or MSI analysis. **Exclusion Criteria:** 1) retrospective studies, 2) studies without endometrial cancer, 3) studies whose subjects had confirmed Lynch syndrome before the study, and 4) studies	**Population:** Patients with known endometrial cancer **Intervention:** MMR immunohistochemistry (IHC), mutL homolog 1 (MLH1) methylation, and microsatellite instability (MSI). **Comparison:** each other intervention	**Primary:** Prevalence of lynch syndrome, MSI germline mutation, IHC Abnormality. **Secondary:** - **Results: Study overview:** The comprehensive search produced 4400 publications. 29 peer-reviewed studies met the inclusion criteria. **Results:** Patients with endometrial cancer (n = 6649) were identified, and 206 (3%) were confirmed to have Lynch syndrome through germline genetic testing after positive universal tumor molecular screening. Among 5917 patients who underwent tumor IHC, 28% had abnormal staining. Among 3140 patients who underwent MSI analysis, 31% had MSI. Among patients with endometrial cancer, the weighted prevalence of Lynch syndrome germline mutations was 15% (95% confidence interval [CI], 11%-18%) with deficient IHC staining and 19% (95% CI, 13%-26%) with a positive MSI analysis. Among 1159 patients who exhibited a loss of MLH1 staining, 143 (13.7%) were found to be MLH1 methylation–negative among those who underwent methylation testing, and 32 demonstrated a germline MLH1 mutation (2.8% of all absent	29 studies included, see article.

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019				
whose subjects did not undergo genetic testing for Lynch syndrome after positive screening.		MLH1 staining cases and 22.4% of all MLH1 methylation–negative cases). Forty-three percent of patients with endometrial cancer who were diagnosed with Lynch syndrome via tumor typing would have been missed by family history–based screening alone. **Author's Conclusion:** "Overall, this study demonstrates that a significant proportion of patients with endometrial cancer have abnormal tumor IHC/MSI. Medical practitioners counseling patients about these results should be aware of the risk of identifying a Lynch syndrome germline mutation among patients with abnormal tumor testing. We found that a large number of the patients and families diagnosed with Lynch syndrome would have been missed by traditional methods such as family history–based screening. This study provides evidence to further support the widespread implementation of molecular screening for all women diagnosed with endometrial cancer. Furthermore, once patients are found to be at risk for Lynch syndrome through positive screening, a greater effort to counsel them during follow-		

Kahn, R. M. et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?. Cancer. 125. 3172-3183. 2019

		up with genetic counseling and testing is imperative."		

Methodical Notes

Funding Sources: Gulce Askin and Paul J. Christos report funding from the Weill Cornell Medicine Clinical and Translational Science Center (grant 1-UL1-TR002384-01) during the conduct of this study.

COI: Kevin Holcomb reports other from Johnson and Johnson and funding from Fujirebio Diagnostics, Inc, outside the submitted work. The other authors made no disclosures.

Study Quality: "All 29 selected studies that met the inclusion criteria underwent a quality assessment with the Cochrane risk-of-bias tool. On the basis of the consensus of 2 independent reviewers for each individual study, the risk of bias for sequence generation was low, the risk of bias for incomplete outcome data was low, the risk of bias for selective outcome reporting was low, and the risk of bias for other sources of bias was low."

Heterogeneity: Statistical heterogeneity was assessed with the Cochran Q test and the I2 statistic, and heterogeneity was considered present when $P < .20$ and $I2 \geq 50\%$, respectively.
"Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history."

Publication Bias: The presence of a publication bias was evaluated with funnel plots and the Begg-Mazumdar rank-correlation test.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of cohort studies.
Unclear definition of outcomes. Heterogeneity investigated but not reported (supposedly high "Another limitation is the large heterogeneity noted in the meta-analysis data regarding family history."). Study quality investigated, but not reported.

Menko, F. H. et al. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. Fam Cancer. 18. 127-135. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review (30 studies) to critically evaluate studies on the uptake of presymptomatic genetic testing in the two most common hereditary cancer syndromes, (1) after at-risk family members were informed by the proband and (2) when at-risk family members were directly contacted by a genetics centre. **Databases:** PubMed, Embase and PsycINFO databases. **Search period:** 2001 -2017. **Inclusion Criteria:** Studies informing relatives, family communication, genetic counselling, genetic testing, presymptomatic testing, uptake of testing, cascade screening, duty to warn, disclosure, direct contact, proactive approach, in combination with (genetic predisposition for) hereditary breast-ovarian cancer (BRCA1, BRCA2) and Lynch	**Population:** Hereditary breast-ovarian cancer and Lynch syndrome patients with BRCA1/BRCA2 mutation or DNA mismatch repair gene. **Intervention:** - **Comparison:** -	**Primary:** Uptake of presymptomati genetic testing for at-risk family members. **Secondary:** - **Results:** Based on information provided by the proband (15 studies) the uptake of presymptomatic genetic testing ranged from 15 to 57% in HBOC, while one study in LS kindreds reported an uptake of 70%. Based on information provided by genetics centres (the remaining 15 studies) the uptake ranged from 21 to 44% in HBOC and from 41 to 94% in LS. However, when genetics centres contacted relatives directly a substantial number of additional family members could be tested. **Author's Conclusion:** Proband-mediated provision of information to at-risk relatives is a standard procedure in hereditary breast-ovarian cancer and Lynch syndrome. However, the resulting uptake of presymptomatic testing is disappointing—an issue that is now	15 studies, see article.

Menko, F. H. et al. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. Fam Cancer. 18. 127-135. 2019				
syndrome (DNA mismatch repair genes). **Exclusion Criteria:** not described.		urgent due to the increased use of genetic testing in clinical oncology. We propose that additional strategies should be introduced including the geneticist directly contacting relatives. The outcomes of these strategies should be carefully monitored and evaluated		
Methodical Notes				
Funding Sources: Funding was provided by the Dutch Cancer Society (Grant No. NKI 2014-6944). **COI:** not declared. **Study Quality:** not investigated. **Heterogeneity:** not applicable, no meta-analysis was performed. **Publication Bias:** not applicable, no meta-analysis was performed. **Notes:** Oxford level of evidence: 2 Systematic review of cohort studies **Downgrade to evidence level 3.** Unclear aim of the study. No searches in study registries or grey literatur. Unclear inclusion criteria. No evaluation of study quality. No declaration of conflict of interest.				

Ryan, N. A. J. et al. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 21. 2167-2180. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis. (59 studies) To provide accurate data estimating the outcomes of testing for LS in EC patients. **Databases:** Medline, Embase, Cochrane CENTRAL, and Web of Science were searched. Citation searching was utilized to augment the initial results. **Search period:** Inception - 07/2018. **Inclusion Criteria:** Only studies investigating LS in an EC population were included. Initial searches were limited by English language, human adults (>18 years), and female subjects. Only studies that used either direct germline analysis for pathogenic variants of MMR genes or proxy tumor-based molecular diagnostic methods (IHC, MSI with or without MLH1 promoter hypermethylation), or any combination of these were included.	**Population:** Human adult females (>18 years) with endometrial cancer(EC). **Intervention:** Direct germline analysis for pathogenic variants of MMR genes or proxy tumor-based molecular diagnostic methods (IHC, MSI with or without MLH1 promoter hypermethylation). **Comparison:** -	**Primary:** The proportion of EC patients who were identified as being likely lynch syndrome (LS) (aberrant MMR IHC expression, MSI-H with or without MLH1 promoter hypermethylation) or as carrying a germline MMR pathogenic variant. **Secondary:** - **Results: Study overview:** 53 studies, including 12,633 EC patients, met the inclusion criteria. **Results:** The overall proportion of endometrial tumors with microsatellite instability or mismatch repair (MMR) deficiency by immunohistochemistry (IHC) was 0.27 (95% confidence interval [CI] 0.25–0.28, I2: 71%) and 0.26 (95% CI 0.25–0.27, I2: 88%), respectively. Of those women with abnormal tumor testing, 0.29 (95% CI 0.25–0.33, I2: 83%) had LS-associated pathogenic variants on germline testing; therefore around 3% of ECs can be attributed to LS. Preselection of EC cases did increase the proportion of germline LS diagnoses.	53 studies included. List see article.

Ryan, N. A. J. et al. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 21. 2167-2180. 2019				
Microsatellite instability-high (MSI-H) was defined, where possible, as involving ≥30% of the included microsatellite markers. An IHC positive result was taken as loss of expression of one of the MMR proteins. Pathogenic variants of MMR genes were defined as per the authors' analysis. To avoid double counting data, authors of more than one study were contacted for clarification and/or registry analysis was crosschecked. Only articles that contributed at least 15 participants were included. **Exclusion Criteria:** Where there was overlapping data, the larger study was included and the smaller excluded.		**Author's Conclusion:** "In summary, ours is the first meta-analysis to examine the proportion of EC cases that are associated with LS. Different tumor triage methods did not affect estimates of the proportion of EC associated with LS, which remained constant at around 3%. Our findings suggest that a similar proportion of EC patients will test positive for LS as seen in CRC LS screening. This supports the move toward the introduction of universal screening for LS in EC."		
Methodical Notes				
Funding Sources: declared, see article for extensive list. **COI:** The authors declare no conflicts of interest. **Study Quality:** Assessment of bias analysis was conducted by three reviewers independently using Review Manager. Quality was reported in supplemental section, which is not available. No overall assesment of quality available.				

Ryan, N. A. J. et al. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 21. 2167-2180. 2019

Heterogeneity: I2 score was used to assess heterogeneity across studies. "The heterogeneity across the studies included in our review was high, and limits the strength of our conclusions. This is a reflection of the varying quality and rigor of the included studies, some of which had small numbers of participants, and were subject to bias."

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-randomized controlled or follow-up studies.
The grey literature and nonelectronic literature were not included. Assessment of study quality was reported in supplemental section, which is not available. No overall assesment of quality available. Heterogeneity present in all analyeses with I2 ranging from 60-90%.

2.11. Schlüsselfrage 13: Welchen Stellenwert haben bildgebende Verfahren wie MRT, CT, PET-CT, PET-MRT und US präoperativ für die lokale und systemische Ausbreitungsdiagnostik des histologisch gesicherten primären Endometriumkarzinoms im Hinblick auf eine Änderung der operativen Strategie sowie auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Alcázar, J. L. 2017	2	Systematic review and meta-analysis (8 studies) To compare the diagnostic accuracy of transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI) for detecting myometrial infiltration (MI) in endometrial carcinoma
Alcázar, J. L. 2015	2	Systematic review and meta-analysis (24 studies) To review the diagnostic accuracy of transvaginal ultrasound (TVS) in the preoperative detection of deep myometrial infiltration in patients with endometrial cancer, comparing subjective and objective methods.
Alcázar, J. L. 2019	3	Systematic review and meta-analysis (17 studies) To evaluate the role of transvaginal ultrasound (TVUS) for diagnosing cervical invasion in the preoperative assessment of endometrial carcinoma.
Bollineni, V. R. 2016	4	SR and META (21 studies, 13 for MA)
Hu, J. 2019	2	Systematic review and meta-analysis. (19 studies) To assess the diagnostic accuracy of preoperative 18F-FDG PET or PET/CT in detecting pelvic lymph node (PLN) and para-aortic lymph node (PALN) metastasis in patients with

Literaturstelle	Evidenzlevel	Studientyp
		endometrial cancer (EC) in systematic review and meta-analysis format.
Stewart, K. I. 2019	3	Prospective diagnostic study (without consistently applied reference standard)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *5 Bewertung(en)*

Alcázar, J. L. et al. Transvaginal ultrasound versus magnetic resonance imaging for preoperative assessment of myometrial infiltration in patients with endometrial cancer: a systematic review and meta-analysis. J Gynecol Oncol. 28. e86. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 2 **Study type:** Systematic review and meta-analysis (8 studies) To compare the diagnostic accuracy of transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI) for detecting myometrial infiltration (MI) in endometrial carcinoma **Databases:** MEDLINE (PubMed), Web of Science, and Cochrane Database **Search period:** 1989 - 01/2017. **Inclusion Criteria:** 1) Prospective or retrospective cohort study including patients who underwent both techniques, MRI and TVS, for evaluating MI in endometrial carcinoma as index tests.	**Population:** Endometrial carcinoma patients. **Intervention:** transvaginal ultrasound (TVS) **Comparison:** magnetic resonance imaging (MRI)	**Primary:** Detection of myometrial infiltration (MI) **Secondary:** - **Results:** Our extended search identified 747 citations but after exclusions we finally included in the meta-analysis 8 articles. The risk of bias for most studies was low for most 4 domains assessed in QUADAS-2. Overall, pooled estimated sensitivity and specificity for diagnosing deep MI were 75% (95% confidence interval [CI]=67%–82%) and 82% (95% CI=75%–93%) for TVS, and 83% (95% CI=76%–89%) and 82% (95% CI=72%–89%) for MRI, respectively. No statistical differences were found when comparing both methods (p=0.314). Heterogeneity was low for sensitivity and high for specificity for TVS and MRI. **Author's Conclusion:** MRI showed a better sensitivity than TVS for detecting deep MI in women with endometrial cancer. However, the	8 studies included: Cagnazzo 1992, DeMaschio 1993, Yamashita 1993, Kim 1995, Yahata 2007, Savelli 2008, Özdermir 2009, Antonsen 2013.	

Alcázar, J. L. et al. Transvaginal ultrasound versus magnetic resonance imaging for preoperative assessment of myometrial infiltration in patients with endometrial cancer: a systematic review and meta-analysis. J Gynecol Oncol. 28. e86. 2017				
2) Surgical assessment of the presence of MI according to histopathological permanent frozen section as reference standard. 3) Presence of results sufficient to construct the 2×2 table of diagnostic performance as minimum data requirement **Exclusion Criteria:** not declared.		difference observed was not statistically significant.		
Methodical Notes				
Funding Sources: not declared. **COI:** No potential conflict of interest relevant to this article was reported. **Study Quality:** Quality was assessed using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Study design was clearly stated as prospective in 6 studies. In 2 studies, design was not clear. Regarding risk of bias and the domain patient selection, 1 study was not clear regarding patient inclusion criteria and 3 were considered as high risk for patient selection. Concerning the domain index test, with regard to TVS 5 studies adequately described the method of index text as well as how it was performed and interpreted, 2 studies were unclear and one was considered as high risk since MI was estimated “subjectively” by the examiner. With regard MRI, 5 studies adequately described the method of index text as well as how it was performed and interpreted, 3 studies were unclear. Concerning the domain flow and timing, the time elapsed between the index test and reference standard was unclear in 2 studies. For the domain reference standard, all studies were likely to correctly classify the target condition by the reference standard. However, in 3 studies it was not clearly specified. Only 2 studies reported specifically that pathologists were blinded to imaging results, in the rest of the studies this was unclear. Regarding applicability, for the domain patient selection, all studies were deemed to				

Alcázar, J. L. et al. Transvaginal ultrasound versus magnetic resonance imaging for preoperative assessment of myometrial infiltration in patients with endometrial cancer: a systematic review and meta-analysis. J Gynecol Oncol. 28. e86. 2017

include patients that matched the review question. For the domain index test, most studies were considered as having low concerns for applicability as the index tests were described well enough for study replication, as was the reference standard domain.

Heterogeneity: We assessed the presence of heterogeneity for sensitivity and specificity using Cochran's Q statistic and the I2 index [16]. A p-value Heterogeneity was low for sensitivity and high for specificity for TVS and MRI.

Publication Bias: Publication bias was assessed by a regression of diagnostic log odds ratio against 1/√(effective sample size), weighted by effective sample size, with p
No publication bias was found, neither for TVS (p=0.650) nor for MRI (p=0.090).

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of non-consecutive diagnostic studies or studies without consistently applied reference standard.
No methodgological flaws observed.

Alcázar, J. L. et al. Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 46. 405-13. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (24 studies) To review the diagnostic accuracy of	**Population:** Adult participants with biopsy-proven primary adenocarcinoma of the endometrium, at any stage of the disease, undergoing preoperative	**Primary:** Detection of deep myometrial infiltration (MI) **Secondary:** -	24 studies included: Artner 1994, Prömpeller 1994, Weber 1995, Osmers 1995, Gabrielli 1996, Valsecchi 1997,

Alcázar, J. L. et al. Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 46. 405-13. 2015			
transvaginal ultrasound (TVS) in the preoperative detection of deep myometrial infiltration in patients with endometrial cancer, comparing subjective and objective methods. **Databases:** MEDLINE (PubMed) and EMBASE **Search period:** 1989 - 12/2014. **Inclusion Criteria:** 1) prospective cohort study with≥50 patients; 2) adult participants with biopsy-proven primary adenocarcinoma of the endometrium, at any stage of the disease, undergoing preoperative staging prior to surgery; 3) presurgical detection of deep MI in primary endometrial adenocarcinoma by TVS as the target condition; 4) TVS as the index test, using both subjective impression and objective methods, the latter consisting of Gordon's approach, i.e. ratio of distance between maximum tumor depth and total myometrial thickness10	staging prior to surgery. **Intervention:** Transvaginal ultrasound TVS as the index test **Comparison:** subjective and objective methods (Gordon's approach, Karlsso's approach). Pathological assesment of deep MI removed at surgery as reference standard.	**Results: Study overview:** Our extended search identified a total of 184 citations, among which we examined the full text of 24 articles. **Results:** Overall pooled sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR–) of TVS for detecting deep myometrial infiltration were 82% (95% CI, 76–87%), 81% (95% CI, 76–85%), 4.3 (95% CI, 3.6–5.3) and 0.22 (95% CI, 0.16–0.30), respectively. We did not observe differences among the three methods in terms of diagnostic performance. Significant heterogeneity was found for sensitivity and specificity of all three methods (I2 range, 60.6–95.0). The main limitation was that very few studies compared different approaches in the same set of patients. **Author's Conclusion:** "Diagnostic performance of TVS for detecting deep myometrial infiltration in women with endometrial cancer is moderate."	Olaya 1998, Alcazar 1999, Arko 2000, Van Doorn 2002, Sawicki 2003, De Smet 2006, Takac 2007, Yahata 2007, Savelli 2008, Alcazar 2009, Ozdemir 2009, Savelli 2012, Ortoft 2013, Mascilini 2013, Antonsen 2013, Miklos 2004, Van Holsbeke 2014, Fischerova 2014.

Alcázar, J. L. et al. Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 46. 405-13. 2015				
and/or Karlsson's approach, i.e. ratio between maximum anteroposterior diameter of the endometrial lesion and the uterine anteroposterior diameter, both measured in the sagittal plane11; 5) pathological assessment of the presence of deep MI in the uterus removed at surgery as reference standard; 6) presence of results sufficient to construct the 2×2 table of diagnostic performance as minimum data requirement. **Exclusion Criteria:** -				
Methodical Notes				
Funding Sources: not declared. **COI:** not declared. **Study Quality:** Study quality was assessed using the QUADAS-2 tool. Quality was reported, but no overall assesment was provided. No studies were excluded from the analysis because of quality. **Heterogeneity:** "We explored graphically heterogeneity of all studies, drawing forest plots of sensitivity and specificity. We then formally assessed the				

Alcázar, J. L. et al. Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 46. 405-13. 2015			
presence of heterogeneity for sensitivity and specificity using Cochran's Q test and the I2 index for all three approaches." Significant heterogeneity across studies in terms of sensitivity and specificity. **Publication Bias:** Not investigated. **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of non consecutive studies or studies without consitently applied reference standard (no blinding in this case) No declaration of conflicts of interest/funding. No investigation of publication bias. High heterogeneity observed for sensitivity and specificity.			
Alcázar, J. L. et al. Diagnostic Performance of Transvaginal Ultrasound for Detecting Cervical Invasion In Women With Endometrial Carcinoma: A Systematic Review and Meta-analysis. J Ultrasound Med. 38. 179-189. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (17 studies) To evaluate the role of transvaginal ultrasound (TVUS) for diagnosing cervical invasion in the preoperative assessment of endometrial carcinoma. **Databases:** PubMed/MEDLINE, Web of Science, www. ClinicalTrials.gov, and	**Population:** Patients with a diagnosis of endometrial carcinoma . **Intervention:** TVUS examinations for evaluating cervical invasion before surgery as the index test. **Comparison:** pathologic	**Primary:** Diagnostic accuracy for detection of cervical invasion. **Secondary:** - **Results: Study overview:** We identified 211 citations. Ultimately, 17 studies comprising 1751 women were included. The mean prevalence of cervical invasion was 16.3%. The risk of bias was	17 studies included: Artner 1994, Gabrielli 1996, Toki 1998, Sawicki 2003, Köse 2003, Cicinelli 2008, Savelli 2008, Fotopoulou 2008, Calik 2010, Akbayir 2011, Antonsen 2013, Mascilini 2013,

Alcázar, J. L. et al. Diagnostic Performance of Transvaginal Ultrasound for Detecting Cervical Invasion In Women With Endometrial Carcinoma: A Systematic Review and Meta-analysis. J Ultrasound Med. 38. 179-189. 2019				
www.who.int/trialsearch. **Search period:** 1990 - 12/2016. **Inclusion Criteria:** (1) prospective and retrospective cohort studies including patients with a diagnosis of endometrial carcinoma who underwent TVUS examinations for evaluating cervical invasion before surgery as the index test; (2) pathologic assessment of cervical involvement in the uterus removed at surgery as the reference standard; and (3) presence of data reported that would allow construction of a 232 table to estimate the diagnostic performance of TVUS. **Exclusion Criteria:** -	assessment of cervical involvement in the uterus removed at surgery as the reference standard.	high in 7 studies for the domains “patient selection” and “index test,” whereas it was considered low for the “reference test” domain. **Results:** Overall, the pooled estimated sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of TVUS for detecting cervical invasion were 63% (95% confidence interval [CI], 51%–74%), 91% (95% CI, 87%–94%), 10.2 (95% CI, 5.7–18.3), and 0.38 (95% CI, 0.28–0.53), respectively. Heterogeneity was high for both sensitivity and specificity. **Author's Conclusion:** "Transvaginal ultrasound has acceptable diagnostic performance for detecting cervical invasion in women with endometrial carcinoma."	Fischerova 2014, Yin 2015, Eriksson 2015, Christensen 2016, Angiolo 2016.	
Methodical Notes				
Funding Sources: Not declared. **COI:** Not declared.				

Alcázar, J. L. et al. Diagnostic Performance of Transvaginal Ultrasound for Detecting Cervical Invasion In Women With Endometrial Carcinoma: A Systematic Review and Meta-analysis. J Ultrasound Med. 38. 179-189. 2019

Study Quality: A quality assessment of studies included in the metaanalysis was conducted by using the tool provided by the Quality Assessment of Diagnostic Accuracy Studies 2. Quality was assessed and reported, but no overall statement of quality was provided.

Heterogeneity: Heterogeneity for sensitivity and specificity was assessed by the Cochran Q statistic and the I2 index.11 P<.1 indicated heterogeneity. i2 values of and were considered to indicate low moderate high significant heterogeneity was found for sensitivity cochran q p specificity

Publication Bias: Publication bias was assessed by the method of Deeks et al. We did not observe a publication bias.

Notes:
Oxford level of evidence: 3 Systematic review and meta-analysis of prospective and retrospective cohort studies.
No declaration of potential conflicts of interest/funding. Significant heterogeneity was found for sensitivity and specificity.

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** SR and META (21 studies, 13 for MA) **Databases:** Pubmed	**Population:** 861 endometrial cancer patients were included for MA. **Intervention:** Diagnostic incidence of 18F-FDG PET/CT	**Primary:** preoperative prediction of PLN, Disease recurrence. **Secondary:** - **Results: Preoperative prediction PLN:**	see publication

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016				
Search period: inception to August 17, 2015. **Inclusion Criteria:** - Studies that reported the diagnostic performance of 18F-FDG PET/CT in detecting LNM preoperatively or disease recurrence in endometrial cancer patients after primary surgery; - clinical studies that included at least 10 patients; - studies that applied 18F-FDG as a tracer on a dedicated device and were published after peer review. **Exclusion Criteria:** Studies on animals or in vitro studies, studies not available in full text or not written in English, and non original articles (e.g., reviews, editorials, letters, legal cases, interviews, case reports).	for preoperative prediction of pelvic lymph node metastases (PLN). **Comparison:** n.a.	The pooled sensitivity and specificity values were 0.72 (95% CI, 0.63–0.80) and 0.94 (95% CI, 0.93–0.96) respectively. The pooled PLR was 10.9 (95% CI, 7.9–15.1), the pooled NLR was 0.36 (95% CI, 0.27–0.48), and the DOR was 39.7 (95% CI, 21.4–73.6). The SROC representing a global summary score for the test performance yielded an AUC of 0.94 and a Q* value of 0.88 (Fig. 3C), indicating a relatively high level of overall accuracy. Detection of ECR: 8 studies comprising 378 patients have been included. The pooled sensitivity was 0.95 (95% CI, 0.91–0.98), and the pooled specificity was 0.91 (95% CI,0.86–0.94). The pooled PLR was 8.8 (95% CI, 6.0– 12.7), NLR was 0.08 (95% CI, 0.05–0.15), and DOR was 171.7 (95% CI, 67.9–434.3). The SROC curve for the 18F-FDG PET/CT in the detection of ECR yielded an AUC and Q* values of 0.97 and 0.93, respectively, suggesting that the level of overall accuracy was high. **Author's Conclusion:** Overall, 18F-FDG PET/CT demonstrated a high diagnostic performance in identifying LNM preoperatively and in detecting recurrence after endometrial carcinoma surgery with		

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016				
		curative intent. Larger prospective studies are needed to validate this high diagnostic performance of 18F-FDG PET/CT in endometrial cancer and further assess patient subgroups with particular clinical benefit from applying this advanced imaging procedure.		

Methodical Notes

Funding Sources: The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This study was supported by funding from the Norwegian Cancer Society. No other potential conflict of interest relevant to this article was reported.

COI: See funding.

Study Quality: n.a.

Heterogeneity: The I-square index was used to test for heterogeneity between studies.

Publication Bias: Evaluated publication bias in our meta-analysis using funnel plot asymmetry, finding the funnel plots to be symmetric for both sensitivity and specificity pooling, implying no large bias in our study.

Notes:
OXford CEBM Level of evidence 2011: EL 3 diagnostic retrospective nonconsectutive studies or studies without consistently applied reference standards. (systematic review, downgraded one Level due to methodological flaws -see notes).

Notes:

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016			
- only one database searched - no quality analysis of the included studies -			
Hu, J. et al. Diagnostic accuracy of preoperative (18)F-FDG PET or PET/CT in detecting pelvic and para-aortic lymph node metastasis in patients with endometrial cancer: a systematic review and meta-analysis. Arch Gynecol Obstet. 300. 519-529. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis. (19 studies) To assess the diagnostic accuracy of preoperative 18F-FDG PET or PET/CT in detecting pelvic lymph node (PLN) and para-aortic lymph node (PALN) metastasis in patients with endometrial cancer (EC) in systematic review and meta-analysis format. **Databases:** PubMed, Cochrane Library, EMBASE, Web of science, SpringerLink and Science Direct **Search period:** Inception - 08/2018	**Population:** Patients were diagnosed with EC. **Intervention:** 18F-FDG **Comparison:** PET/CT	**Primary:** Diagnostic accuracy for detection of pelvic and para-aortic lymph node metastasis **Secondary:** - **Results:** Nineteen studies (1431 patients in total) were included in the analysis. On a lymph node basis, the overall pooled sensitivity, specificity, AUC and overall diagnostic accuracy (Q* index) of 18F-FDG PET or PET/CT in detecting total lymph node metastasis were 0.68 (95% CI 0.63–0.73), 0.96 (95% CI 0.96–0.97), 0.82, and 0.75, respectively. The corresponding indices for detecting PLN	19 studies included: Ansonsen 2012, Bese 2016, Chao 2005, Crivellaro 2013, Horowitz 2015, Husby 2015, Hyun Jeong Kim 2015, Inubarashi 2008, Jeong-Yeol Park 2008, Kitjima 2007, Kitajima 2013, KLAR 2009, Mayoral 2016, Nakamura 2011, Nayot 2008, Nogami 2014, Picchio 2010, Suga 2010, SUZUKI 2007.

Hu, J. et al. Diagnostic accuracy of preoperative (18)F-FDG PET or PET/CT in detecting pelvic and para-aortic lymph node metastasis in patients with endometrial cancer: a systematic review and meta-analysis. Arch Gynecol Obstet. 300. 519-529. 2019				
Inclusion Criteria: (1) evaluated patients were diagnosed with EC in any stage; (2) 18F-FDG was used as tracer; (3) a dedicated device was performed to assess the status of lymph nodes; (4) the data were sufficient to construct or reconstruct a 2 × 2 contingency table to assess the diagnostic accuracy of 18F-FDG PET or PET/CT; (5) at least ten patients were included; (6) pathological results were used as the gold standard; (7) studies belonged to prospective or retrospective studies. **Exclusion Criteria:** Studies on animals and in vitro studies, not available in full text or not written in English, and unoriginal articles (e.g., reviews, letter to editors, legal cases, interviews, case reports) were excluded in this review. But meeting abstracts with enough information to abstract valid data were also included.		metastasis were 0.61 (95% CI 0.52–0.69), 0.96 (95% CI 0.95–0.97), 0.79, and 0.73, respectively. And the corresponding value for detection of PALN were 0.70 (95% CI 0.58–0.79), 0.92 (95% CI 0.9–0.94), 0.84, and 0.77, respectively. Data based on patients also performed well. **Author's Conclusion:** 18F-FDG PET and PET/CT both have excellent diagnostic performance for detecting lymph node metastasis, including PLN and PALN metastasis, in patients with endometrial cancer preoperatively. Though the utility of this method is limited due to its moderate sensitivity, it can help surgeons make better-tailored surgical decision for its high specificity.		
Methodical Notes				

Hu, J. et al. Diagnostic accuracy of preoperative (18)F-FDG PET or PET/CT in detecting pelvic and para-aortic lymph node metastasis in patients with endometrial cancer: a systematic review and meta-analysis. Arch Gynecol Obstet. 300. 519-529. 2019

Funding Sources: This study was supported by grants from the Natural Science Foundation of China (No. 81772790 and No. 81572568).

COI: The authors have no conflicts of interest to declare.

Study Quality: Methodological quality of each included article was assigned using QUADAS-2 which comprises four domains: patient selection, index test, flow and timing, and gold standard. Each domain was assessed in terms of risk of bias, and the first three domains were also assessed in terms of concerns regarding applicability.
4/17 studies were judged to be at high risk of bias.

Heterogeneity: I-square index was used to quantify the heterogeneity.
"Heterogeneity in our study does not seem to be a major issue except for the pooled specificity of lymph node metastasis on a patient basis (I-square index for pooled specificity of LN, PLN and PALN metastasis were 98.4%, 97.8% and 97.6%)."

Publication Bias: Deeks' Funnel plots asymmetry test was used for evaluating publication bias; shows no significant publication bias in our study.

Notes:
Systematic review and meta-analysis of diagnostic non-consecutive studies or studies without consistently applied reference standard (no blinding in this case)
The authors claim that "Heterogeneity in our study does not seem to be a major issue except for the pooled specificity of lymph node metastasis on a patient basis (I-square index for pooled specificity of LN, PLN and PALN metastasis were 98.4%, 97.8% and 97.6%).", which I do not support.

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *1 Bewertung(en)*

Stewart, K. I. et al. Preoperative PET/CT does not accurately detect extrauterine disease in patients with newly diagnosed high-risk endometrial cancer: A prospective study. Cancer. 125. 3347-3353. 2019				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 3 **Study type:** Prospective diagnostic study (without consistently applied reference standard)	**Number of patients / samples:** 112 Women with high-risk endometrial cancer. Likely representative sample. **Reference standard:** Lymph node pathology. **Validation:** Index test was preoperative PET/CT surgery, including sentinel lymph node biopsy and lymphadenectomy. **Blinding:** For the current study, two nuclear medicine physicians (B.C. and F.W.) who were blinded to the surgical results independently reviewed each scan. **Inclusion of clinical information:** Not specified.	**Results:** A total of 112 patients were enrolled and underwent PET/CT between April 2013 and May 2016, 108 of whom were evaluable. On PET/CT, 21 patients (19.4%) were found to have extrauterine disease, 18 (17%) had positive lymph nodes, and 8 (7%) had peritoneal disease. A total of 108 patients underwent surgery, 103 of whom (95%) underwent lymphadenectomy. The sensitivity of PET/CT to detect positive lymph nodes was 45.8%, with a specificity of 91.1%, positive predictive value of 61.1%, and negative predictive value of 84.7%. The false-negative rate was 54.2%. There was no difference in primary tumor characteristics on imaging noted between patients with positive and negative lymph nodes. The sensitivity of PET/CT to detect peritoneal disease was 37.5%, with a specificity of 97.8%, positive predictive value of 75%, and negative predictive value of 90.0%. The false-negative rate was 62.5%. **Author conclusions:** Preoperative PET/CT did not reliably predict the presence of extrauterine disease in women with high-risk endometrial cancer. Given the high false-negative rates, PET/CT should not be used in the preoperative treatment planning of these patients.		

Stewart, K. I. et al. Preoperative PET/CT does not accurately detect extrauterine disease in patients with newly diagnosed high-risk endometrial cancer: A prospective study. Cancer. 125. 3347-3353. 2019				
	Dealing with ambiguous clinical findings: Not specified.			
Methodical Notes				
Funding Sources: Declared, see article. **COI:** Declared, list see article. **Notes:** Oxford level of evidence: 3 studies without consistently applied reference standards** According to fig.1 the reference test was only applied to positive index patients. Nevertheless a false negative rate was calculated, which is confusing.				

2.12. Schlüsselfrage 14: Welches operative Standardverfahren ist bei Vorliegen einer atypischen Hyperplasie indiziert?

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Travaglino, A. 2019	3	Systematic review and meta-analysis (12 studies) To assess the risk of coexistent cancer in complex EH and simple EH without atypia, through a systematic review and meta-analysis.
Uglietti, A. 2019	4	Systmatic review and meta-analysis (51 studies) To estimate the prevalence of premalignant and malignant lesions in women undergoing hysteroscopic polypectomy.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Travaglino, A. et al. Significant risk of occult cancer in complex non-atypical endometrial hyperplasia. Arch Gynecol Obstet. 300. 1147-1154. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (12 studies) To assess the risk of coexistent cancer in complex EH and simple EH without atypia, through a systematic review and meta-analysis. **Databases:** Scopus, MEDLINE, Ovid, Web of Sciences; EMBASE, ClinicalTrial.gov, Cochrane Library and Google Scholar. **Search period:** Inception - 01/2019 **Inclusion Criteria:** All studies assessing the rate of occult endometrial cancer in women diagnosed with SEH and CEH were included. Occult endometrial cancer was defined as a cancer diagnosed on hysterectomy specimen after a preoperative diagnosis of endometrial	**Population:** Women diagnosed with non-atypical EH who underwent hysterectomy after a preoperative diagnosis of EH; **Intervention:** Presence of a complex glandular architecture (CEH diagnosis). **Comparison:** simple non-atypical EH (SEH)	**Primary:** Presence of endometrial cancer on histologic examination of hysterectomy specimen after the diagnosis of EH. **Secondary:** - **Results: Study population:** Twelve retrospective studies assessing a total of 804 EH were included. **Results:** Out of these, 566 were SEH and 238 were CEH Among non-atypical EH, a diagnosis of CEH was significantly associated with the presence of occult cancer on histologic examination of hysterectomy specimen (p = 0.0002), with an OR of 6.02 (95% CI 2.35–15.42) and null statistical heterogeneity among studies (I2 = 0%) (Fig. 1). Among SEH, the pooled rate of coexistent cancer on hysterectomy specimen was 0.020 (95% CI 0.010–0.038), with null statistical heterogeneity among studies	12 studie included: Dunton 1996, Bettochi 2001, Xie 2002, Obeidat 2008, Yarandi 2010, Daud 2011, Yang 2012, Sirimusika 2014, Dolanbay 20015, Kadirogullari 2015, Matsuo 2015, Boyraz 2016.

Travaglino, A. et al. Significant risk of occult cancer in complex non-atypical endometrial hyperplasia. Arch Gynecol Obstet. 300. 1147-1154. 2019				
hyperplasia. **Exclusion Criteria:** Overlapping patient data, case reports, reviews, and presence of endometrial cancer not assessed on hysterectomy sample.		(I2 = 0%). Among CEH, the pooled rate of coexistent cancer was 0.124 (95% CI 0.084–0.181), with low heterogeneity among studies (I2 = 27%). **Author's Conclusion:** CEH is associated with a significant risk of coexistent endometrial cancer, about six times higher than SEH. Considering such category as benign may cause many patients to be undertreated. Therefore, a revision in the 2014 WHO classification criteria might be advisable; they do not consider complexity of glandular architecture in non-atypical EH.		
Methodical Notes				
Funding Sources: No financial support was received for this study. **COI:** The authors report no conflict of interest. **Study Quality:** The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) were used to assess the risk of bias within studies. "For the domain 1 (patient selection), all studies were considered at low risk of bias. Domain 2 (index test), 5 studies were considered at low risk and the other ones at unclear risk. High concern about applicability was raised for one study, due to the possibility of SEH (non-atypical) being lumped together with simple atypical EH. For the domain 3 (reference standard), the risk of bias was low in five studies and unclear in the other ones. For the domain 4 (flow and timing), the risk of bias was low for 8 studies (all patients underwent hysterectomy within 1 year from index diagnosis) and unclear for 4				

Travaglino, A. et al. Significant risk of occult cancer in complex non-atypical endometrial hyperplasia. Arch Gynecol Obstet. 300. 1147-1154. 2019			
studies (time to hysterectomy not specified, or inclusion of some patients with a time-to-hysterectomy > 1 year)" **Heterogeneity:** Statistical heterogeneity among studies was categorized based on the inconsistency index (I2) as follows: I2 = 0: null; 0 < I2 < 25: minimal; 25 < I2 < 50: low; 50 < I2 < 75: moderate; I2 > 75%: high. A fixed effect model was adopted in the case of I2 < 50, while a random effect model was used in the case of I2 > 50. Heterogeneity was low for all outcomes. **Publication Bias:** The risk of bias across studies (publication bias) was assessed by reporting the studies on funnel plots of the logarithm of the OR by the standard error and of the rate of cancer by the standard error. The funnel plot of OR, CEH, SEH were symmetrical, excluding a significant risk of publication bias. **Notes:** Oxford level of evidence: 3 Systematic review and meta-analysis of retrospective cohort studies No methodological flaws observed.			

Uglietti, A. et al. The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 237. 48-56. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systmatic review and meta-analysis (51 studies) To estimate the prevalence of premalignant and malignant lesions in women undergoing	**Population:** Premenopausal and postmenopausal women. **Intervention:** - **Comparison:** -	**Primary:** Prevalence of endometrial premalignant or malignant polyps in the total series. **Secondary:** Subgroup analysis.	51 studies included, see article for list.

Uglietti, A. et al. The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 237. 48-56. 2019				
hysteroscopic polypectomy. **Databases:** PubMed/Medline, Embase **Search period:** 2000-01/2019. **Inclusion Criteria:** Observational retrospective and prospective studies meeting the following criteria: pre-operative diagnosis of benign-looking endometrial polyps at ultrasound examination (TVS,SIS) or at hysteroscopy, excision of endometrial polyps via surgical hysteroscopy, histopathological diagnosis of benign polyps, or hyperplasia withou atypia, or premalignancy (atypical hyperplasia) or malignancy (endometrial cancer). Moreover studies were included, if number or percentage of subjects with and without malignancy was provided and if they reported data about menoüausal and / or bleeding status. **Exclusion Criteria:** Data presented exclusively as abstracts in national and international meetings, or case report or review articles, that did not include original data, and papers published in other than english language.		**Results: Study overview:** A total of 51 studies reporting data on 35,345 women were included in this review. **Results:** The prevalence of malignant polyps was 2.73% (95% CI 2.57-2.91) with very high heterogeneity among studies. The rates were lower for premenopausal women (1.12%) than post-menopausal ones (4.93%) and the difference was statistically significant (chi-square = 397.21. p < .0001). The risk of malignancy was higher among symptomatic (5.14%) than asymptomatic ones (1.89%) (chi-square = 133.13 p < .001). We observed higher rate of malignant polyps in prospective studies. In the meta-analysis selecting 10 prospective studies the random pooled estimate was 5.88 (95% CI: 4.06-7.97) with heterogeneity among studies (heterogeneity chi square = 17.55 P = .025) whereas in retrospective studies the random pooled estimate was 2.94 (95% CI:2.24-3.71) with high heterogeneity among studies (P < .001). This finding can be due to more strict diagnostic criteria in prospective studies. **Author's Conclusion:** Symptomatic vaginal bleeding and postmenopausal status in women with endometrial polyps increased		

Uglietti, A. et al. The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 237. 48-56. 2019				
		the risk of malignancy. This finding could be an useful evidence to select patients who need to undergo hysteroscopic resection of endometrial polyps and women to whom, instead, an expectant management can be offer.		

Methodical Notes

Funding Sources: This work was partially funded by Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico.

COI: The author's declare that they have no conflict of interest.

Study Quality: Information on the methodological quality of selected studies was assessed using the Methodological Index for Non-randomized studies (MINORS), a validated instrument which is designed for assessment of methodological quality of non-randomized studies in surgery. Briefly, the studies were judged on eight pre-defined items and maximum score was 16.
"Their quality was generally good, the MINORS criteria score ranged from 4-10, being 8 or 10 in 29 papers out of 51." Individual study qualit not reported.

Heterogeneity: To evaluate heterogeneity among studies, heterogeneity chi square value was reported.

Publication Bias: Not investigated.

Notes:
Oxford level of evidence: 3 Systmatic review and meta-analysis of retrospective cohort studies
Downgrade to evidence level 4.

Uglietti, A. et al. The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 237. 48-56. 2019	
NO search for gray literature or literature in languages other than english. No investigation of publication bias. Individual study quality not reported. High heterogeneity in all analyses and subgrouops, no display of forest plots.	

2.13. Schlüsselfrage 16: Welches operative Standardverfahren ist bei Vorliegen eines frühen Endometriumkarzinoms (Typ 1, G1, G2, pT1a) indiziert?

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Asher, R. 2018	1	Systematic Review and Meta-Analysis (9 RCTs, 4405 patients)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Asher, R. et al. Disease-Free and Survival Outcomes for Total Laparoscopic Hysterectomy Compared With Total Abdominal Hysterectomy in Early-Stage Endometrial Carcinoma: A Meta-analysis. Int J Gynecol Cancer. 28. 529-538. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis (9 RCTs, 4405 patients) **Databases:** Medline, Embase, Cochrane Central Register of Controlled Trials, clinical trials.gov **Search period:** 1996 to 2017 **Inclusion Criteria:** RCTs comparing laparoscopic hysterectomy with TAH in patients with endometrial cancer **Exclusion Criteria:**	**Population:** Patients with endometrial cancer **Intervention:** Total laparoscopic hysterectomy (TLH) or laparoscopic-assisted vaginal hyterectomy **Comparison:** Total abdominal hysterectomy (TAH)	**Primary:** 3 year disease free survival **Secondary:** overall survial, local recurrence, conversion of TLH to TAH, intraoperative and postoperative complications **Results:** Nine studies (4405 patients) were identified in which DFS was reported in 5 studies. The difference in 3-year DFS was 1.44% (95% CI -0,65% to 3,53%) in favor of total abdominal hysterectomy, consistent with a noninferiority margin of 5%. Differences in DFS (HR 1.10, 95% 0.92 – 1.32), overall survival (HR 1.16, 95% CI 0.81 – 1.66) and local recurrence (difference, 0,42%, 95% CI -0.41% to 1.25%) were not significant. Rates of intraoperative complications showed no difference (0.5%, 95% CI, -1.1 to 2.0%) based on 7 studies. There was no significant reduction in postoperative complications with the laparoscopic procedure (-6,83%, 95% CI -9.19% - -4,47%). **Author's Conclusion:** Noninferiority of laparoscopy was demonstrated on clinical outcomes and was	9 RCTs (4405 patients) included: Tozzi 2005, Fram 2002, Zorlu 2005, Lu 2016, LAP-2 2012, Zullo 2009, Malzoni 2009, LACE 2017, Mouritis 2010

Asher, R. et al. Disease-Free and Survival Outcomes for Total Laparoscopic Hysterectomy Compared With Total Abdominal Hysterectomy in Early-Stage Endometrial Carcinoma: A Meta-analysis. Int J Gynecol Cancer. 28. 529-538. 2018

		associated with a reduction in postoperative complications. These results support continued treatment by laparoscopic hysterectomy for early-stage endometrial cancer.		

Methodical Notes

Funding Sources: This work was supported by the National Health and Medical research program.

COI: None.

Study Quality: Risks of individual study bias were examined using the Cochrane Collaboration tool. The authors state that 6 trials are deemed to be at a low risk of bias. All studies were at risk of bias because of lack of blinding; however as all studies were comparing vastly different surgical procedures, having a unblinded study was unavoidable and impractical.

Heterogeneity: X2 and I2 statistics were used to assess statistical heterogeneity. Heterogeneity was low for the following outcomes: 3-year-DFS (I2= 2%), DFS HR (I2=0%), Local recurrence (I2= 14%), OS HR (I2=0%. Moderate heterogeneity was present for Intraoperative complication (I2= 32%) and postoperative complications (I2=56%).

Publication Bias: Publication bias was examined with the "file drawer problem" method and approach of Gleser and Olkin. Publication bias was not detected.

Notes:
Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs
Title/Abstract Screening and data extraction was only performed by one reviewer.
Population was not described sufficiently.

Asher, R. et al. Disease-Free and Survival Outcomes for Total Laparoscopic Hysterectomy Compared With Total Abdominal Hysterectomy in Early-Stage Endometrial Carcinoma: A Meta-analysis. Int J Gynecol Cancer. 28. 529-538. 2018
Quality of the included studies was assessed but not reported in detail (detailed quality assessment was provided in supplementary material, which is not accesible). Moderate heterogeneity was present for the secondary outcomes intraoperative complication (I2= 32%) and postoperative complications (I2=56%), but not for the primary outcome.

2.14. Schlüsselfrage 17: Unter welchen Voraussetzungen können bei prä-, peri- und postmenopausalen Frauen mit Endometriumkarzinom die Ovarien belassen werden im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Gu, H. 2017	3	Systematic review and meta-analysis (7 studies) To investigate the survival impact of ovarian preservation in surgically treated patientswith early-stage endometrial cancer using a meta-analysis.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Gu, H. et al. Survival Impact of Ovarian Preservation on Women With Early-Stage Endometrial Cancer: A Systematic Review and Meta-analysis. Int J Gynecol Cancer. 27. 77-84. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic review and meta-analysis (7 studies) To investigate the survival impact of ovarian preservation in surgically treated patientswith early-stage endometrial cancer using a meta-analysis. **Databases:** PubMed, EMBASE, Web of Science, and the Cochrane Library **Search period:** Inception - 04/2016. **Inclusion Criteria:** The inclusion criteria for this meta-analysis were studies including International Federation of Gynecology and Obstetrics (FIGO) stage I and II EC patients who underwent surgical treatment and comparison of survivals between ovarian preservation group and BSO group, which contained sufficient data to calculate a hazards ratio (HR)	**Population:** Stage I and II EC patients **Intervention:** Ovarian preservation **Comparison:** Bilateral salpingo-oophorectomy (BSO)	**Primary:** Overall survival. **Secondary:** Disease free survival **Results: Study population:** Totally, 7 retrospective cohort studies including 1419 patients in ovarian preservation group and 15,826 patients in BSO group were enrolled. **Results:** Meta-analysis showed that there was no significant difference in overall survival between the patients treated with ovarian preservation and BSO (hazards ratio [HR], 1.00; 95% confidence interval [CI], 0.72-1.39; P = 1.00). Similar result was achieved in the young and premenopausal women (HR, 0.99; 95% CI, 0.70-1.39; P = 0.39). Furthermore, the disease-free survival of patients whose ovaries were preserved was slightly compromised but with no statistical significance (HR, 1.49; 95% CI, 0.56-3.93; P = 0.42).	7 studies included: Wright 2016, Sun 2015, Lau 2014, Li 2014, Lee 2013, Sun 2013, Richter 2009.	

Gu, H. et al. Survival Impact of Ovarian Preservation on Women With Early-Stage Endometrial Cancer: A Systematic Review and Meta-analysis. Int J Gynecol Cancer. 27. 77-84. 2017

and a 95% confidence interval (CI). **Exclusion Criteria:** Conference abstracts were excluded due to the lack of details. If no comparison of survivals was preformed, if it was impossible to calculate the outcomes from the published results, or if the patients with EC were all FIGO stage III or IV, the articles were excluded. When more than 1 article was published from the same study, either the higher-quality or more detailed publication was included in the analysis to avoid including the same patients.		**Author's Conclusion:** "Ovarian preservation may be safe in patients with early-stage endometrial cancer, and it could be cautiously considered in treating young and premenopausal women because it is not associated with an adverse impact on the patients' survival. Given the inherent limitations of the included studies, further well-designed randomized controlled trial are needed to confirm and update this analysis."		

Methodical Notes

Funding Sources: not declared.

COI: The authors declare no conflicts of interest.

Study Quality: The quality of study was assessed using the Newcastle-Ottawa Scale (NOS) for quality assessment. For the purpose of this study, we defined as high-quality studies those works that scored 9 or 8 points on the NOS, medium-quality studies those that scored 7 or 6 points, and low-quality studies those that scored less than 6.
All the studies were scored 7 or 6 (medium quality) according to the NOS.

Heterogeneity: A test of heterogeneity of combined HRs was conducted using Cochran Q test and I2 statistic. A random-effect model was applied if

Gu, H. et al. Survival Impact of Ovarian Preservation on Women With Early-Stage Endometrial Cancer: A Systematic Review and Meta-analysis. Int J Gynecol Cancer. 27. 77-84. 2017

heterogeneity was observed (I2 > 35%); otherwise, the fixed-effect model was used in the absence of between-study heterogeneity (I2 ≤ 35%). Heterogeneity was low for all outcomes.

Publication Bias: Funnel plots were used to screen for potential publication bias. As shown in the funnel plot, no publication bias was observed in the meta-analysis for OS and DFS (OS: Egger test P = 0.095, Begg test P = 1.00; DFS: Egger test P = 0.930, Begg test P = 1.00)

Notes:
Oxford level of evidence: 3 Systematic review and meta-analysis of retrospective cohort studies

2.15. Schlüsselfrage 18: Unter welchen Voraussetzungen können bei Vorliegen eines frühen Endometriumkarzinoms (Typ 1, G1, G2, pT1a) Uterus und Adnexe belassen werden im Hinblick auf Lebensqualität, Kurzzeit/-Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Greenwald, Z. R. 2017	3	Retrospective cohort study. to investigate the overall and cancer-specific survival for HT compared with primary surgery in young women with localized endometrial cancer of favorable histology.
Guillon, S. 2019	4	Systematic review and meta-analysis (65 studies) To identify remission rates and associated prognostic factors in patients undergoing fertility-sparing management for endometrial cancer and atypical hyperplasia
Mandelbaum, R. S. 2020	3	Retrospective cohort study to examine differences in treatment response between local progestin therapy with the levonorgestrel-releasing intrauterine device and systemic progestin therapy in women with complex atypical hyperplasi
Raffone, A. 2019	3	Systematic review and meta-analysis (13 studies) To assess whether immunohistochemical expression of estrogens and progesterone receptors (ER and PR) predicts the treatment response.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Guillon, S. et al. A systematic review and meta-analysis of prognostic factors for remission in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma. Int J Gynaecol Obstet. 146. 277-288. 2019				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 4 **Study type:** Systematic review and meta-analysis (65 studies) To identify remission rates and associated prognostic factors in patients undergoing fertility-sparing management for endometrial cancer and atypical hyperplasia **Databases:** MEDLINE **Search period:** 1950 - 07/2017. **Inclusion Criteria:** Studies evaluating fertility-sparing management in patients aged between 19 and 44 years for the histologic diagnosis of atypical hyperplasia or stage I endometrial cancer. **Exclusion Criteria:** Studies that included fewer than five patients, patients with deep	**Population:** Patients aged 19-44 with histologic diagnosis of atypical hyperplasia or stage I endometrial cancer undergoing fertility-sparing management **Intervention:** Exposure to risk or protective factors **Comparison:** Non-exposure.	**Primary:** Remission rate. **Secondary:** - **Results:** A total of 3673 studies were screened; 65 studies including 1604 patients met the inclusion criteria. The remission rate was 0.75 (95% CI, 0.73–0.77). Operative hysteroscopy for endometrial sampling was associated with higher remission rates (OR 2.31; 95% CI, 1.10–4.84; P=0.03). Studies with higher ratios of infertile women were associated with higher remission rates (OR 4.21; 95% CI, 1.44– 12.33; P<0.01). **Author's Conclusion:** Operative hysteroscopy is the preferred endometrial sampling method for patients with atypical hyperplasia or endometrial cancer undergoing fertility-sparing management.	65 studies included, see article.	

Guillon, S. et al. A systematic review and meta-analysis of prognostic factors for remission in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma. Int J Gynaecol Obstet. 146. 277-288. 2019				
myometrial invasion tumor, conservation because of high risk for perioperative morbidity, unextractable data, endometrial cancer other than type 1 adenocarcinoma, simple hyperplasia, atypical treatment (i.e. photodynamic therapy), and redundant articles were excluded.				
Methodical Notes				
Funding Sources: Not declared. **COI:** The authors have no conflicts of interest to declare. **Study Quality:** All studies obtained were independently reviewed by three investigators. The following criteria were considered for quality assessments: (1) clear definition of inclusion and exclusion criteria or appropriate selection of study participant; and (2) adequate measurement of outcome variables (prognostic factors and remission). Results for quality assesment were reported for each individual study, but no widely accepted assessment method was used. **Heterogeneity:** We used the I2 statistic to assess the heterogeneity across the studies, with I2 >50% indicating large heterogeneity across studies beyond that expected by chance. No signifcant heteroeneity was observed. **Publication Bias:** We built a funnel plot to investigate the remission rate against the measure of study size and to estimate possible publication or disclosure bias. Funnel plot analysis showed an asymmetrical plot for overall remission rate. There were 10 studies at the bottom right that were not symmetrical due to				

Guillon, S. et al. A systematic review and meta-analysis of prognostic factors for remission in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma. Int J Gynaecol Obstet. 146. 277-288. 2019			
the small populations and a bias of publication. **Notes:** Oxford level of evidence: 3 Systematic review and meta-analysis of retrospective and prospective cohort studies **Downgrade to evidence level 4.** Only one database search was performed is not considered a comprehensive search only english studies are included. Insufficient definition of PICO (Outcome?). Results for quality assesment were reported for each individual study, but no widely accepted assessment method was used; overall quality judgement was not provided.. Publication bias was present for overall remission rate.			
Raffone, A. et al. Should progesterone and estrogen receptors be assessed for predicting the response to conservative treatment of endometrial hyperplasia and cancer? A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 98. 976-987. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (13 studies) To assess whether immunohistochemical expression of estrogens and progesterone receptors (ER and PR) predicts the treatment response.	**Population:** Women diagnosed with endometrial hyperplasia (EH) or early endometrialc cancer (EEC) and conservatively treated with progestins **Intervention:** immunohistochemical expression of estrogens and progesterone receptors **Comparison:** -	**Primary:** Prediction oftreatment response. **Secondary:** - **Results:** Thirteen studies with 635 patients were included in the systematic review. Studies at high risk of bias were excluded from the meta-analysis. Negative ER expression did not significantly predict poor response (P =	13 studies included: Utsunomiyaa 2003, Vereide 2006, Minaguchi 2007, Kashima 2009, Akesson 2010, Kamoi 2011, Upson 2012, Gallos 2013, Gunderson 2014, Yang 2015, Reyes, Orbo;

Raffone, A. et al. Should progesterone and estrogen receptors be assessed for predicting the response to conservative treatment of endometrial hyperplasia and cancer? A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 98. 976-987. 2019				
Databases: MEDLINE, Embase, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library as electronic databases. **Search period:** Inception - 06/2018 **Inclusion Criteria:** · study population constituted of women diagnosed with EH or EEC and conservatively treated with progestins; · assessment of the expression of the marker (ER or PR) on pretreatment endometrial specimens by immunohistochemistry; · assessment of the association between the expression of the marker and the response to therapy. **Exclusion Criteria:** Studies at high risk of bias were		0.16), with low predictive accuracy (AUC = 0.637). Negative PR significantly predicted poor response (P = 0.01), with moderate accuracy (AUC = 0.806). In the oral progestin subgroup, neither ER (P = 0.55) nor PR (P = 0.18) had significant predictive value. In the levonorgestrel-intrauterine device subgroup, both ER (P < 0.0001) and PR (P = 0.02) were significantly predictive of good response, although the accuracy was suboptimal (LR+ 6.02 and 2.48, respectively; LR− 0.59 and 0.55, respectively). The atypical EH/EEC subgroup showed non-significant results. Data about non-atypical EH were not extractable. **Author's Conclusion:** ER and PR expressions are significantly predictive of response in EH and EEC treated with a levonorgestrel-intrauterine device but not with oral progestins. However, their accuracy is insufficient to be determining in the clinical practice.		

Raffone, A. et al. Should progesterone and estrogen receptors be assessed for predicting the response to conservative treatment of endometrial hyperplasia and cancer? A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 98. 976-987. 2019				
excluded from the meta-analysis.				
Methodical Notes				
Funding Sources: not declared. **COI:** The authors have stated explicitly that there are no conflicts of interest in connection with this article. **Study Quality:** The revised tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews (QUADAS-2)26 was used to assess the risk of bias in each study. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk of bias. Quality was assesed but not reported for individual studies. **Heterogeneity:** The statistical heterogeneity among studies was assessed using the inconsistency index (I2): heterogeneity was considered insignificant for I2 Low to moderate heterogeneity in moste analyses. **Publication Bias:** The risk of bias across studies (publication bias) was assessed by reporting the results on a funnel plot. In the assessment of the risk of bias across studies for ER, although the funnel plot showed an evident asymmetry, the studies with higher accuracy were those showing the higher RR results (Figure 6a). Thus, publication bias was absent. **Notes:** Oxford level of evidence: 3 Systematic review and meta-analysis of retrospective and prospective cohort studies. Results of the assessment of study quality was not reported for individual studies.				

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Greenwald, Z. R. et al. Does hormonal therapy for fertility preservation affect the survival of young women with early-stage endometrial cancer?. Cancer. 123. 1545-1554. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Retrospective cohort study. to investigate the overall and cancer-specific survival for HT compared with primary surgery in young women with localized endometrial cancer of favorable histology.	**Funding sources:** The data set for the current study (Surveillance, Epidemiology, and End Results database from the US National Cancer Institute) were obtained without cost via a direct requisition to the provider. The US National Cancer Institute had no influence on the content of this article. **Conflict of Interests:** The authors made no disclosures. **Randomization:** - **Blinding:** - **Dropout rates:** -	**Total no. patients:** 6339 patients with a diagnosis of localized (stage I), grade 1 or 2 endometrial cancer **Recruiting Phase:** 1993-2012 **Inclusion criteria:** HT patients from the SEER programo; only patients aged **Exclusion criteria:** FIGO stage I not further specified. We excluded patients with tumors of grade 3 or 4 or unknown histology and ICD-O-3 morphological codes considered ineligible for HT.	**Interventions:** Hormone therapy n=161 **Comparison:** Surgery n=6178
Notes:	Oxford level of evidence: 3 Non-randomized controlled cohort/follow-up study Insufficient description of PICO research question and inclusion criteria. **Author's conclusion:** "Based on this population-based cohort, young patients with low-grade endometrial cancer appear to have excellent survival, regardless of the primary therapy chosen (HT vs primary surgery). The current		

Greenwald, Z. R. et al. Does hormonal therapy for fertility preservation affect the survival of young women with early-stage endometrial cancer?. Cancer. 123. 1545-1554. 2017		
	selection of patients for HT to preserve fertility, which is managed carefully by experienced clinicians, does not appear to significantly worsen clinical outcomes."	
Outcome Measures/results	**Primary** All-cause mortality **Secondary** -	**Results:** A total of 6339 women were included in the current study cohort, 161 of whom initially received HT and 6178 of whom received primary surgery. After 15 years of follow-up, all-cause mortality did not differ between the groups (HT group: 14.1% [95% CI, 6.7%-28.4%] and propensity score-matched primary surgery group: 9.3% [95% CI, 4.1%-20.5%]). Cancer-specific mortality appeared higher in patients treated with HT compared with those treated with primary surgery (9.2% [95% CI, 3.4%-24.0%] vs 2.1% [95% CI, 1.5%-2.8%]). However, this difference was driven by 3 late deaths in the HT group. Sensitivity analyses using a broader definition of cancer-specific mortality provided no statistical evidence of a survival difference between the treatment groups. The hazard ratio for the overall risk of death was 1.45 (95% CI, 0.44-4.74).

Mandelbaum, R. S. et al. Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing intrauterine device vs systemic therapy. Am J Obstet Gynecol. 223. 103.e1-103.e13. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Retrospective cohort study	**Funding sources:** was received from the Ensign Endowment for Gynecologic Cancer Research (K.M.). The authors disclose the following: L.D.R.:	**Total no. patients:** 245 women with complex atypical hyperplasia **Recruiting Phase:** 2003 - 2018.	**Interventions:** Local progestin therapy via levonorgestrel-releasing intrauterine device n = 69

Mandelbaum, R. S. et al. Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing intrauterine device vs systemic therapy. Am J Obstet Gynecol. 223. 103.e1-103.e13. 2020			
to examine differences in treatment response between local progestin therapy with the levonorgestrel-releasing intrauterine device and systemic progestin therapy in women with complex atypical hyperplasi	consultant, Quantgene; K.M.: honorarium, Chugai, textbook editorial expense, Springer, and investigator meeting attendance expense, VBL therapeutics; S.M.: research funding, MSD; none for other authors. Ethical committee approval: HS-11- 00131, HS-13-00674. **Conflict of Interests:** Not declared. **Randomization:** - **Blinding:** - **Dropout rates:** -	**Inclusion criteria:** Women with CAH who received medical treatment with progestin were eligible for the study criteria. Women with nonatypical or simple hyperplasia as well as those with an endometrial cancer diagnosis prior to the start of progestin therapy were excluded. Of women with CAH, only those who had received at least 1 month of systemic or local progestin therapy following the diagnosis of CAH and who did not initiate progestin therapy before CAH diagnosis were included. Patients on multiple progestin agents were also excluded. **Exclusion criteria:** Women were excluded if they did not have a follow-up biopsy performed at least 1 month following treatment initiation.	**Comparison:** Systemic progestin therapy n = 176
Notes:	Oxford level of evidence: 3 Non-randomized controlled cohort/follow-up study** Dropout rates not described. **Author's conclusion:** Our study suggests that local therapy with the levonorgestrel-releasing intrauterine device may		

Mandelbaum, R. S. et al. Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing intrauterine device vs systemic therapy. Am J Obstet Gynecol. 223. 103.e1-103.e13. 2020		
	be more effective than systemic therapy for women with complex atypical hyperplasia who opt for nonsurgical treatment, particularly in morbidly obese women. Shifts in treatment paradigm during the study period toward increased levonorgestrel-releasing intrauterine device use also led to improved complete response rates despite increasing rates of obesity.	
Outcome Measures/results	**Primary** complete response, ogression to cancer **Secondary** -	**Results: Study population:** A total of 245 women with complex atypical hyperplasia received progestin therapy (levonorgestrel-releasing intrauterine device n = 69 and systemic therapy n = 176). The mean age and body mass index were 36.9 years and 40.0 kg/m2, respectively. Median follow-up 42 months. **Results:** In the patient-level analysis, women who received the levonorgestrel-releasing intrauterine device had higher rates of complete response (78.7% vs 46.7%; adjusted hazard ratio, 3.32; 95% confidence interval, 2.39e4.62) and a lower likelihood of progression to cancer (4.5% vs 15.7%; adjusted hazard ratio, 0.28; 95% confidence interval, 0.11-0.73) compared to those who received systemic therapy. In particular, women with class III obesity derived a higher relative benefit from levonorgestrel-releasing intrauterine device therapy in achieving complete response compared to systemic therapy: class III obesity, adjusted hazard ratio 4.72, 95% confidence interval 2.83-7.89; class IeII obesity, adjusted hazard ratio 1.83, 95% confidence interval 1.09-3.09; and nonobese, adjusted hazard ratio 1.26, 95% confidence interval 0.40-3.95. In the cohort-level analysis, the obesity rate increased during the study period (77.8% to 88.2%, 13.4% relative increase, P = .033) and levonorgestrel-releasing intrauterine device use significantly increased after 2007 (6.3% to 82.7%, 13.2-fold increase, P <

Mandelbaum, R. S. et al. Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing intrauterine device vs systemic therapy. Am J Obstet Gynecol. 223. 103.e1-103.e13. 2020		
		.001), both concomitant with a higher proportion of women achieving complete response (32.9% to 81.4%, 2.5-fold increase, P = .005).

2.16. Schlüsselfrage 19: Ist beim Endometriumkarzinom Stadium pT2 die radikale (Piver II oder III) oder einfache Hysterektomie (Piver I) sinnvoller im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Liu, T. 2019	3	Systematic review and meta-analysis (10 studies) To investigate the impact of radical hysterectomy (RH) versus simple hysterectomy (SH) on survival of patients with stage 2 EC.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Liu, T. et al. Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis. Ann Surg Oncol. 26. 2933-2942. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic review and meta-analysis (10 studies) To investigate the impact of radical hysterectomy (RH) versus simple hysterectomy (SH) on survival of patients with stage 2 EC. **Databases:** PUBMED, MEDLINE, EMBASE, Cochrane Library, and Web of Science. **Search period:** Inception - 07/2018 **Inclusion Criteria:** The study included all observational and experimental studies that compared survival between RH and SH among FIGO stage 2 EC patients with surgical treatment and had sufficient data to obtain the hazard ratio (HR) with a 95% confidence interval (CI) for at least one of the quantitative survival outcomes, including overall survival	**Population:** Stage 2 EC patients with surgical treatment **Intervention:** Radical hysterectomy (RH) **Comparison:** Simple hysterectomy (SH)	**Primary:** Overall survival, progression-free survival **Secondary:** - **Results:** The study included 10 retrospective cohort studies enrolling 2866 patients. Patients who received RH did not show a significant survival benefit for either overall survival (pooled HR 0.92; 95% CI 0.72–1.16; P = 0.484) or progression-free survival (pooled HR 0.75; 95% CI 0.39–1.42; P = 0.378). The result remained consistent after it was balanced with possible impact from adjuvant radiotherapy (pooled HR 0.85; 95% CI 0.62–1.16; P = 0.300). In earlier studies that staged patients according to FIGO 1988, RH showed a 27% survival benefit (pooled HR 0.73; 95% CI 0.53–1.00; P = 0.050), whereas in newly published studies based on FIGO 2009	10 studies included: Ayhan 2004, Boente 1993, Cohn 2007, Cornelison 1999, Fu 2018, Lemin 1995, Orezzoli 2009, Phelippeau 2016, Sartori 2001, Takano 2013.

Liu, T. et al. Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis. Ann Surg Oncol. 26. 2933-2942. 2019				
(OS) and progression-free survival (PFS). We did not distinguish between mRH and RH (Piver–Rutledge classes 2 and 3). For staging, both FIGO 2009 and FIGO 1988 were allowed. We considered Kaplan–Meier curves or Cox proportional hazards regression models to calculate HR for survival comparison between groups. **Exclusion Criteria:** In case of two or more studies possibly including overlapping patients, we selected the one with higher quality or more detailed publication.		staging, it reversely showed increased risk of death (pooled HR 1.24; 95% CI 0.86–1.77; P = 0.245). However, no statistical significance was reached under either staging criterion. **Author's Conclusion:** Based on the results of this meta-analysis, RH does not significantly improve survival in stage 2 EC. The choice of RH remains controversial and should be considered carefully in clinical practice. More qualified studies are needed to determine the best treatment strategy for stage 2 EC.		
Methodical Notes				
Funding Sources: Not declared. **COI:** The authhors declare that they have no conflict of interest. **Study Quality:** The quality of the included studies was assessed independently by two reviewers according to the Newcastle– Ottawa Quality Assessment Scale (NOS) for cohort studies (see Supplementary Methods). According to the NOS for cohort studies, the median score of the included studies was 7.5 (Table S1). Five studies were graded as 9 or 8 (high quality), and the remaining five studies were graded as 7 or 6 (medium quality).				

Liu, T. et al. Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis. Ann Surg Oncol. 26. 2933-2942. 2019

Heterogeneity: Statistical heterogeneity was assessed using the I2 statistic and Q statistic. A random-effect model was applied when significant heterogeneity existed (I2 value [50%). Otherwise, a fixed-effect model was used.
No significant heterogeneity was found between studies.

Publication Bias: Publication bias was assessed by inspection of funnel plots, Egger test, and Begg test.
"No significant publication bias was found in OS comparison (Egger test, P = 0.079; Begg test, P = 0.152) or PFS comparison (Egger test, P = 0.387; Begg test, P = 1.000)."

Notes:
Oxford level of evidence: 3 Systematic review and meta-analysis of retrospective cohort studies.

2.17. Schlüsselfrage 20: Ist beim Endometriumkarzinom (Typ I, pT1a, G1/2) die systematische pelvine bzw. pelvine plus paraaortale Lymphonodektomie (LNE) bei makroskopisch unauffälligen LK sinnvoll im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bogani, G. 2020	4	Retrospective cohort study
Frost, J. A. 2017	1	Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.
Guo, W. 2018	3	Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis
Shisler, R. 2018	4	SR (27 studies)
Wright, J. D. 2016	4	Retrospective cohort study
Zheng, Y. 2019	4	Retrospective cohort study (SEER database)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *3 Bewertung(en)*

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase **Search period:** Inception to June 2017 **Inclusion Criteria:** RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer.	**Population:** Adult women diagnosed with endometrial cancer **Intervention:** Pelvic lymphadenectomy versus no lymphadenectomy Pelvic lymphadenectomy versus pelvic lymph node sampling Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy Removal of bulky pelvic lymph nodes versus no removal of lymph nodes **Comparison:**	**Primary:** Overall survival (OS) **Secondary:** Progression-free survival (PFS) QOL measured by a validated scale Adverse events, for example, direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection); surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism) cardiac events (cardiac ischaemia and cardiac failure) cerebrovascular accident recovery: delayed discharge, unscheduled re-admission lymphoedema and lymphocyst formation; other side effects not categorised above. **Results:** 978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria;	3 studies included: Fayallah 2011, Kitchener 2009, Panici 2008

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
Exclusion Criteria: We excluded cross-over trials and clusterrandomised trials, women with other concurrent malignancies.		for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence). We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst		

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
		formation, respectively) (1922 participants, two studies; high-quality evidence). **Author's Conclusion:** This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.		
Methodical Notes				
Funding Sources: None **COI:** None **Study Quality:** We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. **Heterogeneity:** We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between				

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this. The two trials included in the meta-analysis showed no heterogeneity (I2 = 0). **Publication Bias:** Not investigated, because only three studies were included **Notes:** Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs Update of an previous Cochrane Review			

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis **Databases:** PubMed, Embase, and	**Population:** Patients with endometrial cancer **Intervention:** Pelvic lymphadenectomy (PLND) **Comparison:** Pelvic and para-aortic	**Primary:** Overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS) **Secondary:** **Results:** Eight studies with a total of 2793 patients were included. OS was significantly longer in PPaLND group than in	8 retrospective cohort studies (2793 patients): Eggemann 2016, Toptas 2015, Tong 2011, Todo 2010, Chang 2008, May 2013, Okazawa 2012, Fujimoto 2007

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018				
Cochrane Library **Search period:** n January 1, 1990, and January 1, 2017 **Inclusion Criteria:** Studies exploring endometrial cancer; studies comparing 2 treatment modalities and reporting overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS); studies providing hazard ratio (HR) directly or key information to calculate HR indirectly, such as Kaplan-curves and original survival data **Exclusion Criteria:** Abstracts of meetings, duplicate publication, review articles, and case reports; studies explored new surgical techniques or evaluated operation outcomes without comparison of survival effects; and full text or valid data not accessed. To avoid overlapping patient data in publications on the same cohort, we included articles with the latest data.	lymphadenectomy (PPaLND)	pelviclymphadenectomy (PLND) group for patients with endometrial cancer [HR 0.68; 95% confidence interval (CI) 0.55–0.84, P lower .001 i subgroup analysis by recurrence risk explored the same association in patients at intermediate- or high-risk ci p but not for low-risk ppalnd with systematic resection of all para-aortic nodes up to renal vein also improved pfs compared plnd. **Author's Conclusion:** PPaLND is associated with favorable survival outcomes in endometrial cancer patients with intermediate- or high-risk of recurrence compared with PLND, particularly with regards to OS. PPaLND with systematic resection of all para-aortic nodes up to renal vein also improve PFS compared with PLND. Further large-scale randomized clinical trials are required to validate our findings.		

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018

Methodical Notes

Funding Sources: This study was funded by National Natural Science Foundation of China (grant number: 81201720).

COI: None.

Study Quality: Quality assessments were performed according to the Newcastle– Ottawa Quality Assessment Scale (NOS),[19] which contains 3 aspects: selection, comparability, and outcome. The quality score ranged from 7 to 9 with a median score of 8 for all cohort studies, which suggested the relatively high quality of the studies included in the meta-analysis

Heterogeneity: Forest plots were generated for graphical presentations, and heterogeneity among different studies was appraised by Q statistics and I 2 estimates. Fixed effects model was conducted to aggregate data if there were no statistical heterogeneity (I 2

Publication Bias: Publication bias was examined using Begg funnel plot and Egger linear regression test. Two-sided P lower .05 was considered statistically significant. no publication bias observed among included studies.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of retropective cohort studies

No search for grey literature or unpublished articles was performed
Heterogeneity was present for some analyses, but the authors are aware of this and performed sub-group analyses to explore the heterogeneity.
Overall, the quality of the included studies was considered as high by the authors, but details of the quality assessment are not described.

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** SR (27 studies) **Databases:** Medline, Embase, Scopus, CINAHL. **Search period:** not specified. **Inclusion Criteria:** Observational studies (i.e. no drug intervention) reporting patient-related outcomes (PRO) among EC survivors; original data collection, use of validated scales. **Exclusion Criteria:** Studies with outcomes other than PRO, studies that did not include EC survivors, pilot studies and clinical trials assessing drug effects, studies of gynecological cancer survivors that did not report estimates separately for EC patients.	**Population:** Women diagnosed with EC **Intervention:** Questionnaires used to assess PROs: for example the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) used in 9 of the 27 observational studies. **Comparison:** Two studies included non-cancer control groups	**Primary:** Association between - BMI and/or physical activity and PROs - Treatment and PROs - predictors of sexual function - catch-all "other" category. 19 studies assessed the PROs at some point in time after EC diagnosis; whereas 8 studies prospectively evaluated changes in PROs over time with the use of multiple assessements. **Secondary:** - **Results:** Sample size range between 38 and 666 women. **BMI and/or physical activity and PROs** (8 studies): QoL: 6 studies: lower overall QoL among obese EC survivors relative to their normal counterparts. 5 Studies reported that physical functioning was	see publication.

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018				
		lower in obese patients relative to non-obese patients. **Treatment and PROs:** Treatment type affected several outcomes. Laparoscopy generally resulted in better QoL outcomes than laparotomy. Vaginal brachytherapy was associated with better outcomes compared to external beam radiation. **Predictors of sexual function:** Sexual function outcomes were dependent on age, time since diagnosis and having consulted a physician before engaging in sexual activities. In addition, a physical activity intervention was associated with improved sexual interest but not sexual function. **Catch-all "other" category** (five studies): one study evaluating psychosocial factors and mortality found a significant association between active coping (which consists of putting effort into improving one's situation)		

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018				
		with lower all-cause mortality. **Author's Conclusion:** Our review provides insights into the experiences of EC survivors from patient perspective. Factors that contribute to QoL such as pain, fatigue, emotional and social functioning should be monitored following an EG diagnosis.		
Methodical Notes				
Funding Sources: n.s. **COI:** None. **Study Quality:** Quality assessment is mentioned in the title of a paragraph, but no further details are mentioned. Thus the assumption is, that a quality assessment of the included studies is missing. **Heterogeneity:** not assessed. **Publication Bias:** not assessed.				

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018
Notes: Oxfrod Level of evidence 2011: EL 3 Systematic review of cross-sectional and retrospective cohort studies (downgraded from EL 3 one level EL 4 due to methodological flaws). - the search range is not specified - no methodological quality of the included studies was performed - no analysis regarding heterogeneity, bias assessment ... was performed.

NEWCASTLE - OTTAWA Checklist: Cohort: *3 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients.	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
		Exclusion criteria: Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3) presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	
Notes:	Oxford CEBM Level of Evidence: 4 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy. Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.		
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.	

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	**Funding sources:** Not described **Conflict of Interests:** The authors did not report any potential conflicts of interest. **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 151,089 women **Recruiting Phase:** 1998-2011 **Inclusion criteria:** Women with endometrioid adenocarcinoma of the endometrium diagnosed from 1998–2011 who underwent hysterectomy were selected. **Exclusion criteria:** Patient who received preoperative radiation and those who had another primary tumor prior to the diagnosis of uterine cancer were excluded. Women with primary tumor spread beyond the uterus (>T2) or metastatic disease were excluded.	**Interventions:** Lymphadenectomy **Comparison:** No Lymphadenectomy
Notes:	Oxford CEBM Level of Evidence 2011: EL 4 Retrospective, cohort study Retrospective analysis of a national wide cancer database Funding sources were not described **Author's conclusion:** Lymphadenectomy is associated with a modest, if any, effect on survival for women with endometrial cancer.		

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016		
Outcome Measures/results	Primary Overall survival Secondary	**Results:** A total of 151,089 women treated at 1336 hospitals were identified; 99,052 (65.6%) patients underwent lymphadenectomy while 52,037 (34.4%) did not. In a multivariable regression model, lymphadenectomy was associated with a 16% reduction in mortality (HR=0.84; 95% CI, 0.81–0.87). The results were similar after adjustment for adjuvant therapy (HR=0.85; 95% CI, 0.82–0.87). The results were largely unchanged and suggested that lymphadenectomy was associated with improved survival after application of a propensity score analysis. In contrast, in the instrumental variable analysis there was not a statistically significant association between lymphadenectomy and survival (HR=0.75; 95% CI, 0.53–1.06), even after adjustment for adjuvant treatment (HR=0.76; 95% CI, 0.54–1.06). The results were unchanged for women with T1A and T1B tumors.

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study (SEER database)	**Funding sources:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.	**Total no. patients:** 103,103 patients with endometrial cancer identified from the SEER database of the National Cancer Institute (USA) were identified. Analysed were 11.603 patients. **Recruiting Phase:** 2004-2013 **Inclusion criteria:** Patients with endometrium as the primary site and	**Interventions:** Lymphadenectomy (total hysterectomy – with/without bilateral salpingo-oophorectomy) **Comparison:** -

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
	Conflict of Interests: see funding surces **Randomization:** - **Blinding:** - **Dropout rates:** -	endometrial cancer malignancy as the disease classification; grade 1 endometrial cancer; focused on early-stage endometrial cancer, in which total hysterectomy – with/without bilateral salpingo-oophorectomy – is the most common type of surgery. **Exclusion criteria:** Patients with more than one primary site, only a clinical diagnosis, other disease stages and survival times less than 3 months.	
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective, cohort study) Limitations: - The authors stated, that the lack of significance after matching may be due to the small number of patients after matching. - high loss rate (not specified by the authors) - some relevant medical information (depth of myometrial invasion, time to recurrence, and subsequent surgical and medical therapies) are noch available due to the retrospective approach - number of patients for lymph node biopsies ist very small - only one cohort (patient group)- not a cohort study in the original meaning. **Author's conclusion:** In conclusion, using SEER database, we found that for all stage IA patients, most patients died of cardiovascular disease (27%) and diabetes (8%); lymphadenectomy has no influence on survival and sentinel lymph node biopsies can reduce the number of lymph node removed but have no effect in survival. Given that practice patterns have shifted in the		

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
	world to predominantly sentinel node biopsy, we think our manuscript applicable to current clinical practice	
Outcome Measures/results	**Primary** Survival **Secondary** cause of death spectrum, the effect of sentinel lymph node biopsy and adjuvant therapies.	**Results:** Mean age at diagnosis was 56.5 years old. 22.83% of the women analyzed died from endometrial cancer; other sources were: cardiovascular disease (27%), diabetes (8%) and respiratory diseases (3%). But as the differentiation of the cancer became worse, more women died from the cancer. Overall survival - multivariant analysis: - age and grade were crucial factors in terms of survival, and a younger age and lower grade were associated with a better prognosis ($p < 0.0001$). - Asian women had better survival times than white women and black women ($p < 0.0001$) - no significant influence can be found for geographic region or number of removed lymph nodes. - lymphadenectomy can increase survival in grade 3/4 stage I patients ($p = 0.013$). **Sentinel lymph nodes biopsies:** Sentinel lymph nodes biopsy could reduce the number of lymph node removed (12 vs 6, $p = 8.387e-10$ in Wilcox test), but had no effect on survival (n=102 patients). Propensity score Matching: no difference was observed in survival between the lymphadenectomy group & the nonlymphadenectomy group ($p = 0.93$ and 0.65 respectively).

2.18. Schlüsselfrage 21: Ist beim Endometriumkarzinom (Typ I, pT1a, G1/2) die SLN bei makroskopisch unauffälligen LK sinnvoll im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben? (S. Schlüsselfrage 34)

Inhalt: *10 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Body, N. 2018	4	Retrospective Cohort Study
Bogani, G. 2020	4	Retrospective cohort study
Bogani, G. 2019	4	Systematic Review and Meta-Analysis (5 studies, 3536 patients)
Cusimano, M. C. 2021	3	Prospective multicenter cohort study
El-Agwany, A. S. 2018	3	Randomized Trial
Kogan, L. 2020	4	Retrospective Cohort study
Plante, M. 2017	3	Prospective cohort study.
Rossi, E. C. 2017	2	Prospective cohort study
Zheng, Y. 2019	4	Retrospective cohort study (SEER database)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic Review	**Population:** Patients with endometrial cancer	**Primary:** Positive node detection rate, survival outcomes (overall survival and disease free survival)	5 studies (3536 patients) included: Eriksson 2015,

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
and Meta-Analysis (5 studies, 3536 patients) **Databases:** Pubmed, Scopus, Web of Sciences, Clinicaltrials.gov **Search period:** Inception to December 2018 **Inclusion Criteria:** Comparative studies, English language, and >10 cases **Exclusion Criteria:** Case reports, in vitro or cadaveric studies, technical notes, review articles not reporting original data, duplicate publications, and single arm studies	**Intervention:** Sentinel node mapping **Comparison:** Lymphadenectomy	**Secondary:** Mean operative time, mean blood loss, blood transfusion rate, procedure conversion rate, complication rate, in hospital stay, postoperative complications **Results:** Six comparative studies were included. Overall, 3536 patients were included: 1249 (35,3%) and 2287 (64,7%), undergoing sentinel node mapping and lymphadenectomy, respectively. Pooled data suggested that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03 (95% CI 1.30 – 3.18); p=0.002). No difference in detection of positive nodes located in the paraaortic was observed (OR: 0.93 (95% CI 0.30 to 2.18), p= 0.086). Overall recurrence rate was 4.3% and 7.3% after sentinel node mapping and lymphadenectomy, respectively (OR: 0.90 (95% CI 0.58 – 1.38), p = 0.63). Similarly, nodal recurrences were statistically similar between group (1.2% vs. 1.7%; OR 1.51 (95% CI 0.70 to 3.29), p=0.29). **Author's Conclusion:** In conclusion, our	Holloway 2016, Baiocchi 2017, Buda 2017, Ducie 2017, Buda 2018	

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

		meta-analysis underlines that sentinel node mapping is non-inferior to standard lymphadenectomy in term of detection of paraaortic nodal involvement and recurrence rates (any site and nodal recurrence); while, focusing on the ability to detect positive pelvic nodes, sentinel node mapping could be consider superior to lymphadenectomy. Further randomized studies are needed to assess long term effectiveness of sentinel node mapping.		

Methodical Notes

Funding Sources: None.

COI: None.

Study Quality: Cochrane Collaboration Risks of Bias assessment tool was used to assess the quality of the included studies. Assessment of the study quality is displayed in the supplementary material, which is not accessible.

Heterogeneity: Heterogeneity was measured using I2 statistic, in which I2 > 50% suggests high heterogeneity. High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%)

Publication Bias: Publication bias was not investigated (less than ten studies included)

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of Retrospective cohort studies
Downgraded to Level 4 due to methodical weakness:
Inclusion criteria and Population were not described sufficiently
No search for grey literature or reference lists was conducted. Non-English articles were excluded. Insufficient description of the performed searches.
Publication bias was not investigated (less than ten studies included)
High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%)
Assessment of the study quality is displayed in the supplementary material, which is not accessible.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Randomized Trial **Number of Patient:** 120 **Recruitung Phase:** Between June 2016 and June 2017 **Inclusion Criteria:** Patients with low-risk endometrial cancer for nodal metastasis were included in this study. Low risk was defined as stage Ia, type I, grade a,b endometrial cancer confirmed clinically and histologically by fractional curettage. **Exclusion Criteria:**	**Intervention:** Group A included hysteroscopic guided methylene blue injection, Group B included transcervical injection, Group C included uterine subserosal injection and Group D included combined transcervical and subserosal injection. We used 1 ml injection of methylene blue per site after sterilization of the methylene blue powder by autoclave or autoclaving of the diluted solution in autoclavable bottle or using sterilized ampules. Cervical injection was done by insulin syringe (one ml) inserting full needle length (1 cm) at 3, 9 o'clock. Subserosal myometrial injection was done at eight points, four anterior and four posterior in the midline with insulin syringe **Comparison:**	**Primary:** **Secondary:** **Results:** Clinical and pathological SLN detection were more with hysteroscopic technique than others and pathological detection was lower than clinical detection in all techniques. Metastatic disease was more common in nodes with suspicious appearance. About 10% of negative suspicious and mapped nodes were associated with positive other nodes for metastasis. **Author's Conclusion:** SLN in endometrial cancer has a role in staging of endometrial cancer with best technique for detection, hysteroscopic guided blue dye injection. SLN can be used in patients with low risk for lymph node metastasis for selective lymphadenectomy. Blue dye labelling using methylene blue dye is good in low resource countries as it is cheap. We recommended the following algorithm for surgical staging in early

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

		endometrial cancer with better results than using SLN alone. Stage I type 1, grade 1,2 endometrial cancer should undergo surgical staging with initial evaluation of the peritoneum which if affected, it is stage III with no need for lymphadenectomy. Then, dissection of the blue and suspicious nodes which if any is positive on frozen section, selective same side pelvic and paraaortic nodal dissection should be done. If they are negative, no need for lymphadenectomy. This approach can help patients to avoid the side effects associated with a complete lymphadenectomy. The higher rate of detection using this algorithm is related to combining the suspicions nodes with the stained ones.	
Methodical Notes			
Funding Sources: None **COI:** None **Randomization:** Method unclear **Blinding:** Not described			

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Dropout Rate/ITT-Analysis:

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized trial
Downgraded to Level 3 due to methodical weakness:
Inclusion and exclusion criteria were not described sufficiently.
Outcomes were not described.
Method of randomization was not described.
Blinding was not described.
Reference standard was not applied.

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective Cohort Study	**Number of patients / samples:** 119 patients with endometrial cancer **Reference standard:** No reference standard **Validation:** Detection rate, sensitivity and negative predictive value (NPV) **Blinding:** Not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	**Results:** Sentinel lymph node mapping with Indocyanin green A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection (p = 0.01). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymphe node. **Author conclusions:** ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection (p = 0.01). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.		
Methodical Notes				

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018		
Funding Sources: Not stated. COI: None. Notes: Oxford CEBM Level of Evidence 2011: EL 4 Retrospective cohort study without blinding or reference standard Articles submitted by hand search.		
Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective multicenter cohort study	**Number of patients / samples:** 156 patients **Reference standard:** Lymphadenectomy as the reference standard **Validation:** Sensitivity of the SLNB algorithm in detecting metastatic disease, False negative rate and negative predictive value Additional measures of diagnostic accuracy, sentinel lymph node detection rates, and adverse events	**Results:** Performance characteristics of Sentinel Lymph Node Biopsy (SLNB) using indocyanine green (ICG) The study enrolled 156 patients (median age, 65.5 years; range, 40-86 years; median body mass index [calculated as weight in kilograms divided by height in meters squared], 27.5; range, 17.6-49.3), including 126 with high-grade EC. All patients underwent SLNB and PLND, and 101 patients (80%) with high-grade EC also underwent PALND. Sentinel lymph node detection rates were 97.4%per patient (95%CI, 93.6%-99.3%), 87.5%per hemipelvis (95%CI, 83.3%-91.0%), and 77.6%bilaterally (95%CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the SLNB algorithm, yielding a sensitivity of 96%(95%CI, 81%-100%), a false-negative rate of 4%(95%CI,

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021				
	Blinding: Blinding was not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	0%-19%), and a negative predictive value of 99%(95%CI, 96%-100%). Only 1 patient (0.6%) was misclassified by the SLNB algorithm. Seven of 27 patients with node-positive cancer (26%) were identified outside traditional PLND boundaries or required immunohistochemistry for diagnosis. **Author conclusions:** In this study, SLNB had acceptable diagnostic accuracy compared with lymphadenectomy for the detection of nodal metastatic disease in high-grade EC. On the basis of this study and the existing literature, SLNB appears to be a viable option for the surgical staging of both low- and high-grade EC.		
Methodical Notes				
Funding Sources: Dr Clarke reported receiving personal fees from AstraZeneca outside the submitted work. No other disclosures were reported. **COI:** This study was supported by the Princess Margaret Cancer Foundation of Princess Margaret Cancer Centre (Toronto, Ontario) and the McArthur Research Fund of the Department of Obstetrics and Gynecology at the University of Toronto (Toronto, Ontario). Dr Cusimano is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship and American College of Surgeons Resident Research Scholarship. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Prospective cohort study with consistently applied reference standard but without blinding** Article submitted by hand search.				

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021

Limitations:
-Blinding was not performed

NEWCASTLE - OTTAWA Checklist: Cohort: *5 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients. **Exclusion criteria:** Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3)	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
		presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	
Notes:	Oxford CEBM Level of Evidence: 4 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy. Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.		
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.	

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective Cohort study	**Funding sources:** This study was supported by grants from the Israel Cancer Research Fund, the Azrieli Foundation, the Gloria's Girls Fund, the Susan and Jonathan Wener Fund and the Anne-Marie and Mitch Garber Fund **Conflict of Interests:** None **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 343 **Recruiting Phase:** December 2007- September 2010 **Inclusion criteria:** Patients with endometrial cancer who underwent surgical staging **Exclusion criteria:** Patients with sarcomas or neoadjuvant chemotherapy were excluded	**Interventions:** All patients diagnosed from December 2007 until November 2010 underwent complete pelvic LND (LND cohort) **Comparison:** All patients from December 2010 until September 2014 underwent SLN mapping followed by complete pelvic LND (SLN cohort)
Notes:	Oxford CEBM Level of Evidence 2011: 4, Retrospective Cohort Study Retrospective evaluation of prospective gathered data Inclusion criteria were not described sufficiently No description of where patients were recruited Blinding not described **Author's conclusion:** Addition of SLN to LND was ultimately associated with improved clinical outcomes compared to LND		

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020		
	alone in patients with endometrial cancer undergoing surgical staging, suggesting that the data provided by the analysis of the SLN added relevant clinical information and improved the decision on adjuvant therapy.	
Outcome Measures/results	**Primary** Positive and negative predictive value **Secondary**	**Results:** From 2007 to 2010, 193 patients underwent LND and from December 2010 to 2014, 250 patients had SLN mapping with completion LND. Both groups had similar clinical characteristics. During a median follow-up period of 6.9 years, addition of SLN was associated with more favorable oncological outcomes compared to LND with 6-year overall survival (OS) of 90% compared to 81% (p=0.009), and progression free survival (PFS) of 85% compared to 75% (p=0.01) respectively. SLN was associated with improved OS (HR 0.5, 95% CI 0.3 – 0.8, p=0.004) and PFS (HR 0.6, 95% CI 0.4-0.9, p=0.03) in a multivariable analysis, adjusted for age, ASA score, stage, grade, non-endometrioid histology, and LVSI. Patients who were staged with SLN were less likely to have a recurrence in the pelvis or lymph node basins compared to patients who underwent LND only (6-year recurrence-free survival 95% vs. 90%, p=0.04).

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study	Funding sources: None. Conflict of Interests: None. Randomization: -	**Total no. patients:** 519 patients with early stage endometrial cancer **Recruiting Phase:** November 2010 to December 2015	**Interventions:** adjuvant treatment (chemotherapy and radiotherapy)

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
type: Prospective cohort study.	Blinding: - Dropout rates: n.s.	**Inclusion criteria:** Histological diagnosis of endometrial carcinoma who underwent SLN mapping procedure followed by surgical staging at L`Hotel-Dieu de Quebec Hospital **Exclusion criteria:** -	**Comparison:** Brachytherapy
Notes:	Oxford CEBM Level of evidence: EL 3 Limitations/Notes: - small groups - one study group, results based on staging (not a cohort study in the original design) - no stratification **Author's conclusion:** Patients with endometrial cancer found to have SLN ITCs have an excellent outcome. The use of adjuvant treatment should be tailored to uterine factors and histology and not solely based on the presence of ITCs. Patients with ITCs and otherwise low risk uterine disease probably derive little benefit from receiving additional treatments. More studies are needed to confirm our data.		
Outcome Measures/results	**Primary** progression free survival (PFS), overall survival (OS)	**Results:** Median age was 64 years. All patients were staged surgically (by laprotomy (47%), laparoscopy or laparoscopy assisted vaginal surgery (33%), robotic surgery (20%). Cancer type: 86% endometrial cancer, 6.9% serous cancer, 4.2% carcinosarcoma. Grade: 79% either grade 1 or 2, 21% grade 3.	

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017		
	Secondary -	FIGO stage: 62.4% stage IA, 20.2% stage IB, 2.5% stage II, 3.2% IIIA, 0.4 IIIB, 6.9% IIIC1, 2.1% IIIC2, 2.1% stage IV. 85 patients (16.4%) had SLN metastases (43 (51%) macrometastasis, 11 (13%) micrometastasis, 31 (36%) ITC. ITC patients received significant less chemotherapy (p=0.0001) and WRT (p=0.007) compared to patients with macrometastasis. Median follow up was: 29 months (0-67): PFS for ITC patients was 95.5%, similar to node negative (87.6%) and micrometastasis patients (85.5%) at three years. And it was statistically better than patients with macrometastasis (58,5%) (p=0.0012). Only 1 of 31 patient with ITC recurred despite adjuvant treatment. None of the ITC patients with endometrioid histology recurred and none of the ITC patients who did not received adjuvant treatment or VBT recurred.

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2 Study type: Prospective cohort study	**Funding sources:** Indiana University Health, Indiana University Health Simon Cancer Center, and the Indiana University Department of Obstetrics and Gynecology.	**Total no. patients:** 385 patients **Recruiting Phase:** Between Aug 1, 2012, and Oct 20, 2015 **Inclusion criteria:** Patients were eligible if they had documented endometrial cancer of	**Interventions:** Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Each patient served as their own control,

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
	Conflict of Interests: We declare no competing interests **Randomization:** **Blinding:** Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens **Dropout rates:** ITT analysis was performed	any histology on pathology specimens from endometrial sampling, and if they had clinically determined stage 1 disease, defined as having no physical examination findings or radiographical suspicion of extrauterine disease. There was no age limit for eligibility. Patients were included in the study if they met the performance status and life expectancy to tolerate a surgical staging procedure. Patients who were pregnant based on urine choriogonadotropin assessments were excluded. **Exclusion criteria:** Patients were excluded if they had evidence of extrauterine disease, had undergone previous hysterectomy or treatment for their endometrial cancer (such as radiotherapy, chemotherapy, or hormonal therapy), had received a previous retroperitoneal surgery or lymphadenectomy, or had contraindications for receiving the ICG tracer, including a history of hepatic impairment or an iodine allergy. If patients were recognised to have gross extra-uterine disease at the time of surgery after tracer injection, they were ineligible for the sentinel-lymph-node mapping	with sentinel lymph node results compared with nonsentinel lymph node results within the same patient. **Comparison:** Complete lymphadenectomy as gold standard

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017		
Notes:	Oxford CEBM Level of Evidence 2011: Prospective Cohort Study Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens Intention to treat analysis was performed **Author's conclusion:** Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.	
Outcome Measures/results	**Primary** Sensitivity and negative predictive value **Secondary**	**Results:** Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Sentinel-lymph-node mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97·2% (95% CI 85·0–100), and a negative predictive value of 99·6% (97·9–100). The most common grade 3–4 adverse events or serious adverse events were postoperative neurological disorders (4 patients) and postoperative respiratory distress or failure (4 patients). 22 patients had serious adverse events, with one related to the study intervention: a ureteral injury incurred during sentinel-lymph-node dissection.

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study (SEER database)	**Funding sources:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. **Conflict of Interests:** see funding surces **Randomization:** - **Blinding:** - **Dropout rates:** -	**Total no. patients:** 103,103 patients with endometrial cancer identified from the SEER database of the National Cancer Institute (USA) were identified. Analysed were 11.603 patients. **Recruiting Phase:** 2004-2013 **Inclusion criteria:** Patients with endometrium as the primary site and endometrial cancer malignancy as the disease classification; grade 1 endometrial cancer; focused on early-stage endometrial cancer, in which total hysterectomy – with/without bilateral salpingo-oophorectomy – is the most common type of surgery. **Exclusion criteria:** Patients with more than one primary site, only a clinical diagnosis, other disease stages and survival times less than 3 months.	**Interventions:** Lymphadenectomy (total hysterectomy – with/without bilateral salpingo-oophorectomy) **Comparison:** -

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective, cohort study) Limitations: - The authors stated, that the lack of significance after matching may be due to the small number of patients after matching. - high loss rate (not specified by the authors) - some relevant medical information (depth of myometrial invasion, time to recurrence, and subsequent surgical and medical therapies) are noch available due to the retrospective approach - number of patients for lymph node biopsies ist very small - only one cohort (patient group)- not a cohort study in the original meaning. **Author's conclusion:** In conclusion, using SEER database, we found that for all stage IA patients, most patients died of cardiovascular disease (27%) and diabetes (8%); lymphadenectomy has no influence on survival and sentinel lymph node biopsies can reduce the number of lymph node removed but have no effect in survival. Given that practice patterns have shifted in the world to predominantly sentinel node biopsy, we think our manuscript applicable to current clinical practice	
Outcome Measures/results	**Primary** Survival **Secondary** cause of death spectrum, the effect of sentinel lymph node biopsy and adjuvant therapies.	**Results:** Mean age at diagnosis was 56.5 years old. 22.83% of the women analyzed died from endometrial cancer; other sources were: cardiovascular disease (27%), diabetes (8%) and respiratory diseases (3%). But as the differentiation of the cancer became worse, more women died from the cancer. <u>Overall survival - multivariant analysis:</u> - age and grade were crucial factors in terms of survival, and a younger age and lower grade were associated with a better prognosis ($p < 0.0001$). - Asian women had better survival times than white women and black women ($p < 0.0001$) - no significant influence can be found for geographic region or number of

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
		removed lymph nodes. - lymphadenectomy can increase survival in grade 3/4 stage I patients (p = 0.013). **Sentinel lymph nodes biopsies:** Sentinel lymph nodes biopsy could reduce the number of lymph node removed (12 vs 6, p = 8.387e-10 in Wilcox test), but had no effect on survival (n=102 patients). Propensity score Matching: no difference was observed in survival between the lymphadenectomy group & the nonlymphadenectomy group (p = 0.93 and 0.65 respectively).

2.19. Schlüsselfrage 22: Ist beim Endometriumkarzinom (Typ I, pT1a, G3; pT1 b, G1/2) die systematische pelvine bzw. pelvine plus paraaortale Lymphonodektomie (LNE) bei makroskopisch unauffälligen LK sinnvoll im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bogani, G. 2020	4	Retrospective cohort study
Frost, J. A. 2017	1	Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.
Guo, W. 2018	3	Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis
Salehi, S. 2019	2	follow-up analysis of a randomized trial (RASHEC)
Wright, J. D. 2016	4	Retrospective cohort study
Zheng, Y. 2019	4	Retrospective cohort study (SEER database)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase **Search period:** Inception to June 2017 **Inclusion Criteria:** RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer.	**Population:** Adult women diagnosed with endometrial cancer **Intervention:** Pelvic lymphadenectomy versus no lymphadenectomy Pelvic lymphadenectomy versus pelvic lymph node sampling Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy Removal of bulky pelvic lymph nodes versus no removal of lymph nodes **Comparison:**	**Primary:** Overall survival (OS) **Secondary:** Progression-free survival (PFS) QOL measured by a validated scale Adverse events, for example, direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection); surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism) cardiac events (cardiac ischaemia and cardiac failure) cerebrovascular accident recovery: delayed discharge, unscheduled re-admission lymphoedema and lymphocyst formation; other side effects not categorised above. **Results:** 978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria;	3 studies included: Fayallah 2011, Kitchener 2009, Panici 2008

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
Exclusion Criteria: We excluded cross-over trials and clusterrandomised trials, women with other concurrent malignancies.		for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence). We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst		

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
		formation, respectively) (1922 participants, two studies; high-quality evidence). **Author's Conclusion:** This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.		
Methodical Notes				
Funding Sources: None **COI:** None **Study Quality:** We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. **Heterogeneity:** We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between				

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this. The two trials included in the meta-analysis showed no heterogeneity (I2 = 0). **Publication Bias:** Not investigated, because only three studies were included **Notes:** Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs Update of an previous Cochrane Review			

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis **Databases:** PubMed, Embase, and	**Population:** Patients with endometrial cancer **Intervention:** Pelvic lymphadenectomy (PLND) **Comparison:** Pelvic and para-aortic	**Primary:** Overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS) **Secondary:** **Results:** Eight studies with a total of 2793 patients were included. OS was significantly longer in PPaLND group than in	8 retrospective cohort studies (2793 patients): Eggemann 2016, Toptas 2015, Tong 2011, Todo 2010, Chang 2008, May 2013, Okazawa 2012, Fujimoto 2007

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018				
Cochrane Library **Search period:** n January 1, 1990, and January 1, 2017 **Inclusion Criteria:** Studies exploring endometrial cancer; studies comparing 2 treatment modalities and reporting overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS); studies providing hazard ratio (HR) directly or key information to calculate HR indirectly, such as Kaplan-curves and original survival data **Exclusion Criteria:** Abstracts of meetings, duplicate publication, review articles, and case reports; studies explored new surgical techniques or evaluated operation outcomes without comparison of survival effects; and full text or valid data not accessed. To avoid overlapping patient data in publications on the same cohort, we included articles with the latest data.	lymphadenectomy (PPaLND)	pelviclymphadenectomy (PLND) group for patients with endometrial cancer [HR 0.68; 95% confidence interval (CI) 0.55–0.84, P lower .001 i subgroup analysis by recurrence risk explored the same association in patients at intermediate- or high-risk ci p but not for low-risk ppalnd with systematic resection of all para-aortic nodes up to renal vein also improved pfs compared plnd. **Author's Conclusion:** PPaLND is associated with favorable survival outcomes in endometrial cancer patients with intermediate- or high-risk of recurrence compared with PLND, particularly with regards to OS. PPaLND with systematic resection of all para-aortic nodes up to renal vein also improve PFS compared with PLND. Further large-scale randomized clinical trials are required to validate our findings.		

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018

Methodical Notes

Funding Sources: This study was funded by National Natural Science Foundation of China (grant number: 81201720).

COI: None.

Study Quality: Quality assessments were performed according to the Newcastle– Ottawa Quality Assessment Scale (NOS),[19] which contains 3 aspects: selection, comparability, and outcome. The quality score ranged from 7 to 9 with a median score of 8 for all cohort studies, which suggested the relatively high quality of the studies included in the meta-analysis

Heterogeneity: Forest plots were generated for graphical presentations, and heterogeneity among different studies was appraised by Q statistics and I 2 estimates. Fixed effects model was conducted to aggregate data if there were no statistical heterogeneity (I 2

Publication Bias: Publication bias was examined using Begg funnel plot and Egger linear regression test. Two-sided P lower .05 was considered statistically significant. no publication bias observed among included studies.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of retropective cohort studies

No search for grey literature or unpublished articles was performed
Heterogeneity was present for some analyses, but the authors are aware of this and performed sub-group analyses to explore the heterogeneity.
Overall, the quality of the included studies was considered as high by the authors, but details of the quality assessment are not described.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Salehi, S. et al. Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial. Int J Gynecol Cancer. 29. 86-93. 2019			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** follow-up analysis of a randomized trial (RASHEC) **Number of Patient:** 24 patients of the RALS group and 24 patients of the laparotomy group received drainage. **Recruitung Phase:** Between 2013 and 2016. **Inclusion Criteria:** Patients from the RASHEC trial further randomized to abdominal drainage or no drainage. **Exclusion Criteria:** -	**Intervention:** Abdominal drainage. **Comparison:** No drainage.	**Primary:** Self-reported lower limb lymphedema, imaging, Long-term serious adverse events and admission to hospital for any reason. **Secondary:** see primary. **Results:** At 12 months after laparotomy and RALS, 61% and 50%, respectively, reported LLL (p=0.31). In univariate analysis, the mean score of LLL at 12 months was significantly higher for laparotomy than for RALS (p **Author's Conclusion:** In conclusion, the majority of women with high-risk endometrial cancer subjected to pelvic and infrarenal para-aortic lymphadenectomy report symptoms of LLL 1 year after surgery. The route of abdominal access does not appear to affect long term morbidity, since no differences were observe between robot-assisted laparoscopy and laparotomy.	
Methodical Notes			

Salehi, S. et al. Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial. Int J Gynecol Cancer. 29. 86-93. 2019

Funding Sources: None.

COI: HH is a proctor for intuitive surgical. the others declare no conflict of interest.

Randomization: yes

Blinding: no.

Dropout Rate/ITT-Analysis: -

Notes:
This study is a follow-up analysis of the RASHEC trial (study of Salehi S et al, 2017 and 2018).

Oxford CEBM Level of evidence 2011: EL 2 (Randomized trial)

Limitations:
- due to the second randomization step in this study the study groups are very small (24 patients per group) and
- the study was not designed (powered) to analyse differences in complications.

The results should be interpreted with care.

NEWCASTLE - OTTAWA Checklist: Cohort: *3 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients. **Exclusion criteria:** Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3) presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**
Notes:	Oxford CEBM Level of Evidence: 3 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy.		

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020		
	Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.	
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study**	**Funding sources:** Not described **Conflict of Interests:** The authors	**Total no. patients:** 151,089 women **Recruiting Phase:** 1998-2011 **Inclusion criteria:** Women with endometrioid	**Interventions:** Lymphadenectomy

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016			
type: Retrospective cohort study	did not report any potential conflicts of interest. **Randomization:** **Blinding:** **Dropout rates:**	adenocarcinoma of the endometrium diagnosed from 1998–2011 who underwent hysterectomy were selected. **Exclusion criteria:** Patient who received preoperative radiation and those who had another primary tumor prior to the diagnosis of uterine cancer were excluded. Women with primary tumor spread beyond the uterus (>T2) or metastatic disease were excluded.	**Comparison:** No Lymphadenectomy
Notes:	Oxford CEBM Level of Evidence 2011: EL 4 Retrospective, cohort study Retrospective analysis of a national wide cancer database Funding sources were not described **Author's conclusion:** Lymphadenectomy is associated with a modest, if any, effect on survival for women with endometrial cancer.		
Outcome Measures/results	Primary Overall survival Secondary	**Results:** A total of 151,089 women treated at 1336 hospitals were identified; 99,052 (65.6%) patients underwent lymphadenectomy while 52,037 (34.4%) did not. In a multivariable regression model, lymphadenectomy was associated with a 16% reduction in mortality (HR=0.84; 95% CI, 0.81–0.87). The results were similar after adjustment for adjuvant therapy (HR=0.85; 95% CI, 0.82–0.87). The results were largely unchanged and suggested that lymphadenectomy was associated with improved survival after application of a propensity score analysis. In contrast, in the instrumental variable analysis there was not a statistically significant association between lymphadenectomy and survival (HR=0.75; 95% CI, 0.53–1.06), even after adjustment for	

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016			
		adjuvant treatment (HR=0.76; 95% CI, 0.54–1.06). The results were unchanged for women with T1A and T1B tumors.	

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study (SEER database)	**Funding sources:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. **Conflict of Interests:** see funding surces **Randomization:** - **Blinding:** -	**Total no. patients:** 103,103 patients with endometrial cancer identified from the SEER database of the National Cancer Institute (USA) were identified. Analysed were 11.603 patients. **Recruiting Phase:** 2004-2013 **Inclusion criteria:** Patients with endometrium as the primary site and endometrial cancer malignancy as the disease classification; grade 1 endometrial cancer; focused on early-stage endometrial cancer, in which total hysterectomy – with/without bilateral salpingo-oophorectomy – is the most common type of surgery.	**Interventions:** Lymphadenectomy (total hysterectomy – with/without bilateral salpingo-oophorectomy) **Comparison:** -

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
	Dropout rates: -	**Exclusion criteria:** Patients with more than one primary site, only a clinical diagnosis, other disease stages and survival times less than 3 months.	
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective, cohort study) Limitations: - The authors stated, that the lack of significance after matching may be due to the small number of patients after matching. - high loss rate (not specified by the authors) - some relevant medical information (depth of myometrial invasion, time to recurrence, and subsequent surgical and medical therapies) are noch available due to the retrospective approach - number of patients for lymph node biopsies ist very small - only one cohort (patient group)- not a cohort study in the original meaning. **Author's conclusion:** In conclusion, using SEER database, we found that for all stage IA patients, most patients died of cardiovascular disease (27%) and diabetes (8%); lymphadenectomy has no influence on survival and sentinel lymph node biopsies can reduce the number of lymph node removed but have no effect in survival. Given that practice patterns have shifted in the world to predominantly sentinel node biopsy, we think our manuscript applicable to current clinical practice		
Outcome Measures/results	**Primary** Survival **Secondary** cause of death spectrum, the effect of sentinel lymph node	**Results:** Mean age at diagnosis was 56.5 years old. 22.83% of the women analyzed died from endometrial cancer; other sources were: cardiovascular disease (27%), diabetes (8%) and respiratory diseases (3%). But as the differentiation of the cancer became worse, more women died from the cancer.	

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
	biopsy and adjuvant therapies.	Overall survival - multivariant analysis: - age and grade were crucial factors in terms of survival, and a younger age and lower grade were associated with a better prognosis ($p < 0.0001$). - Asian women had better survival times than white women and black women ($p < 0.0001$) - no significant influence can be found for geographic region or number of removed lymph nodes. - lymphadenectomy can increase survival in grade 3/4 stage I patients ($p = 0.013$). **Sentinel lymph nodes biopsies:** Sentinel lymph nodes biopsy could reduce the number of lymph node removed (12 vs 6, $p = 8.387e-10$ in Wilcox test), but had no effect on survival (n=102 patients). Propensity score Matching: no difference was observed in survival between the lymphadenectomy group & the nonlymphadenectomy group ($p = 0.93$ and 0.65 respectively).

2.20. Schlüsselfrage 23: Ist beim Endometriumkarzinom (Typ I, pT1a, G3; pT1 b, G1/2) die SLN bei makroskopisch unauffälligen LK sinnvoll im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *11 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Body, N. 2018	4	Retrospective Cohort Study
Bogani, G. 2020	4	Retrospective cohort study
Cusimano, M. C. 2021	3	Prospective multicenter cohort study
Davidson, B. A. 2018	2	Randomized controlled trial
El-Agwany, A. S. 2018	3	Randomized Trial
Kogan, L. 2020	4	Retrospective Cohort study
Plante, M. 2017	3	Prospective cohort study.
Rossi, E. C. 2017	2	Prospective cohort study
Staley, A. 2017	1	
Zheng, Y. 2019	4	Retrospective cohort study (SEER database)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Staley, A. et al. Sentinel Lymph Node Technique in Endometrial Cancer. Obstet Gynecol Surv. 72. 289-295. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Databases:	Intervention: Comparison:	Primary: Secondary: Results:	

Staley, A. et al. Sentinel Lymph Node Technique in Endometrial Cancer. Obstet Gynecol Surv. 72. 289-295. 2017				
Search period: Inclusion Criteria: Exclusion Criteria:		Author's Conclusion:		
Methodical Notes				
Funding Sources: **COI:** **Study Quality:** **Heterogeneity:** **Publication Bias:** **Notes:** Exclusion of article Not a systematic review, but a narrative summary with database search. No evaluation is possible.				

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 120 **Recruitung Phase:** January 2009 and March 2015 **Inclusion Criteria:** Woman with high-grade EC on preoperative sampling (grade 3 endometrioid, clear cell, serous, carcinosarcoma or mixed histologies) who were appropriate surgical candidates and deemed medically eligible for a lymph node dissection **Exclusion Criteria:** Exclusion criteria were patients with low-grade histologies on preoperative assessment or advanced disease at diagnosis.	**Intervention:** Collection of LNs into nodal basin-specific containers on the randomized side **Comparison:** Simple labeling on the non-randomized side	**Primary:** Total number of LNs and total number of LNs with metastases on the randomized versus the nonrandomized side were compared. The remaining adipose tissue from each LN specimen was submitted for histologic examination. Wen analyzed the number of LNs with and without metastases identified from additional adipose tissue. **Secondary:** **Results:** Of 120 consented subjects, 56 had sufficient data for analysis. The additional adipose tissue contained 7.5 LNs per patient on average (range: 0-26). In 2/54 total cases (3.7%) and 2/5 cases with nodal metastases (40%), the additional adipose tissue contained LNs with metastases. In both cases, metastases were also detected in grossly identified LN candidates. The mean number of LNs identified was not significantly different based on method of collection (p=0.22). The mean number of LNs containing metastases per side was not significantly different (p=0.58). **Author's Conclusion:** Processing of adipose tissue does increase the total number of LNs identified, however, it does	

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
		not influence EC stage. No difference in LN counts was noted with basin-specific collection.	
Methodical Notes			
Funding Sources: Not stated **COI:** None **Randomization:** Randomization was performed using a random number generator with block randomization (block size 6) stratified by site. **Blinding:** No blinding **Dropout Rate/ITT-Analysis:** Not performed **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 No test for group differences Blinding was not performed Small number of patients included in the analysis. Nearly half of the patients initially consented were not included in the final analysis			

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Randomized Trial **Number of Patient:** 120 **Recruitung Phase:** Between June 2016 and June 2017 **Inclusion Criteria:** Patients with low-risk endometrial cancer for nodal metastasis were included in this study. Low risk was defined as stage Ia, type I, grade a,b endometrial cancer confirmed clinically and histologically by fractional curettage. **Exclusion Criteria:**	**Intervention:** Group A included hysteroscopic guided methylene blue injection, Group B included transcervical injection, Group C included uterine subserosal injection and Group D included combined transcervical and subserosal injection. We used 1 ml injection of methylene blue per site after sterilization of the methylene blue powder by autoclave or autoclaving of the diluted solution in autoclavable bottle or using sterilized ampules. Cervical injection was done by insulin syringe (one ml) inserting full needle length (1 cm) at 3, 9 o'clock. Subserosal myometrial injection was done at eight points, four anterior and four posterior in the midline with insulin syringe **Comparison:**	**Primary:** **Secondary:** **Results:** Clinical and pathological SLN detection were more with hysteroscopic technique than others and pathological detection was lower than clinical detection in all techniques. Metastatic disease was more common in nodes with suspicious appearance. About 10% of negative suspicious and mapped nodes were associated with positive other nodes for metastasis. **Author's Conclusion:** SLN in endometrial cancer has a role in staging of endometrial cancer with best technique for detection, hysteroscopic guided blue dye injection. SLN can be used in patients with low risk for lymph node metastasis for selective lymphadenectomy. Blue dye labelling using methylene blue dye is good in low resource countries as it is cheap. We recommended the following algorithm for surgical staging in early endometrial cancer with better results than using SLN alone. Stage I type 1, grade 1,2 endometrial

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

		cancer should undergo surgical staging with initial evaluation of the peritoneum which if affected, it is stage III with no need for lymphadenectomy. Then, dissection of the blue and suspicious nodes which if any is positive on frozen section, selective same side pelvic and paraaortic nodal dissection should be done. If they are negative, no need for lymphadenectomy. This approach can help patients to avoid the side effects associated with a complete lymphadenectomy. The higher rate of detection using this algorithm is related to combining the suspicions nodes with the stained ones.	

Methodical Notes

Funding Sources: None

COI: None

Randomization: Method unclear

Blinding: Not described

Dropout Rate/ITT-Analysis:

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized trial
Downgraded to Level 3 due to methodical weakness:
Inclusion and exclusion criteria were not described sufficiently.
Outcomes were not described.
Method of randomization was not described.
Blinding was not described.
Reference standard was not applied.

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective Cohort Study	**Number of patients / samples:** 119 patients with endometrial cancer **Reference standard:** No reference standard **Validation:** Detection rate, sensitivity and negative predictive value (NPV) **Blinding:** Not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	**Results:** Sentinel lymph node mapping with Indocyanin green A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection (p = 0.01). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymphe node. **Author conclusions:** ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection (p = 0.01). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.		
Methodical Notes				

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018		
Funding Sources: Not stated. COI: None. Notes: Oxford CEBM Level of Evidence 2011: EL 4 Retrospective cohort study without blinding or reference standard Articles submitted by hand search.		
Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective multicenter cohort study	**Number of patients / samples:** 156 patients **Reference standard:** Lymphadenectomy as the reference standard **Validation:** Sensitivity of the SLNB algorithm in detecting metastatic disease, False negative rate and negative predictive value Additional measures of diagnostic accuracy, sentinel lymph node detection rates, and adverse events	**Results:** Performance characteristics of Sentinel Lymph Node Biopsy (SLNB) using indocyanine green (ICG) The study enrolled 156 patients (median age, 65.5 years; range, 40-86 years; median body mass index [calculated as weight in kilograms divided by height in meters squared], 27.5; range, 17.6-49.3), including 126 with high-grade EC. All patients underwent SLNB and PLND, and 101 patients (80%) with high-grade EC also underwent PALND. Sentinel lymph node detection rates were 97.4%per patient (95%CI, 93.6%-99.3%), 87.5%per hemipelvis (95%CI, 83.3%-91.0%), and 77.6%bilaterally (95%CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the SLNB algorithm, yielding a sensitivity of 96%(95%CI, 81%-100%), a false-negative rate of 4%(95%CI,

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021				
	Blinding: Blinding was not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	0%-19%), and a negative predictive value of 99%(95%CI, 96%-100%). Only 1 patient (0.6%) was misclassified by the SLNB algorithm. Seven of 27 patients with node-positive cancer (26%) were identified outside traditional PLND boundaries or required immunohistochemistry for diagnosis. **Author conclusions:** In this study, SLNB had acceptable diagnostic accuracy compared with lymphadenectomy for the detection of nodal metastatic disease in high-grade EC. On the basis of this study and the existing literature, SLNB appears to be a viable option for the surgical staging of both low- and high-grade EC.		
Methodical Notes				
Funding Sources: Dr Clarke reported receiving personal fees from AstraZeneca outside the submitted work. No other disclosures were reported. **COI:** This study was supported by the Princess Margaret Cancer Foundation of Princess Margaret Cancer Centre (Toronto, Ontario) and the McArthur Research Fund of the Department of Obstetrics and Gynecology at the University of Toronto (Toronto, Ontario). Dr Cusimano is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship and American College of Surgeons Resident Research Scholarship. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Prospective cohort study with consistently applied reference standard but without blinding** Article submitted by hand search.				

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021

Limitations:
-Blinding was not performed

NEWCASTLE - OTTAWA Checklist: Cohort: *5 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients. **Exclusion criteria:** Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3)	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
		presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	
Notes:	Oxford CEBM Level of Evidence: 4 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy. Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.		
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.	

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective Cohort study	**Funding sources:** This study was supported by grants from the Israel Cancer Research Fund, the Azrieli Foundation, the Gloria's Girls Fund, the Susan and Jonathan Wener Fund and the Anne-Marie and Mitch Garber Fund **Conflict of Interests:** None **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 343 **Recruiting Phase:** December 2007- September 2010 **Inclusion criteria:** Patients with endometrial cancer who underwent surgical staging **Exclusion criteria:** Patients with sarcomas or neoadjuvant chemotherapy were excluded	**Interventions:** All patients diagnosed from December 2007 until November 2010 underwent complete pelvic LND (LND cohort) **Comparison:** All patients from December 2010 until September 2014 underwent SLN mapping followed by complete pelvic LND (SLN cohort)
Notes:	Oxford CEBM Level of Evidence 2011: 4, Retrospective Cohort Study Retrospective evaluation of prospective gathered data Inclusion criteria were not described sufficiently No description of where patients were recruited Blinding not described **Author's conclusion:** Addition of SLN to LND was ultimately associated with improved clinical outcomes compared to LND		

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020		
	alone in patients with endometrial cancer undergoing surgical staging, suggesting that the data provided by the analysis of the SLN added relevant clinical information and improved the decision on adjuvant therapy.	
Outcome Measures/results	**Primary** Positive and negative predictive value **Secondary**	**Results:** From 2007 to 2010, 193 patients underwent LND and from December 2010 to 2014, 250 patients had SLN mapping with completion LND. Both groups had similar clinical characteristics. During a median follow-up period of 6.9 years, addition of SLN was associated with more favorable oncological outcomes compared to LND with 6-year overall survival (OS) of 90% compared to 81% (p=0.009), and progression free survival (PFS) of 85% compared to 75% (p=0.01) respectively. SLN was associated with improved OS (HR 0.5, 95% CI 0.3 – 0.8, p=0.004) and PFS (HR 0.6, 95% CI 0.4-0.9, p=0.03) in a multivariable analysis, adjusted for age, ASA score, stage, grade, non-endometrioid histology, and LVSI. Patients who were staged with SLN were less likely to have a recurrence in the pelvis or lymph node basins compared to patients who underwent LND only (6-year recurrence-free survival 95% vs. 90%, p=0.04).

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study	Funding sources: None. Conflict of Interests: None. Randomization: -	**Total no. patients:** 519 patients with early stage endometrial cancer **Recruiting Phase:** November 2010 to December 2015	**Interventions:** adjuvant treatment (chemotherapy and radiotherapy)

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
type: Prospective cohort study.	Blinding: - Dropout rates: n.s.	**Inclusion criteria:** Histological diagnosis of endometrial carcinoma who underwent SLN mapping procedure followed by surgical staging at L`Hotel-Dieu de Quebec Hospital **Exclusion criteria:** -	**Comparison:** Brachytherapy
Notes:	Oxford CEBM Level of evidence: EL 3 Limitations/Notes: - small groups - one study group, results based on staging (not a cohort study in the original design) - no stratification **Author's conclusion:** Patients with endometrial cancer found to have SLN ITCs have an excellent outcome. The use of adjuvant treatment should be tailored to uterine factors and histology and not solely based on the presence of ITCs. Patients with ITCs and otherwise low risk uterine disease probably derive little benefit from receiving additional treatments. More studies are needed to confirm our data.		
Outcome Measures/results	**Primary** progression free survival (PFS), overall survival (OS)	**Results:** Median age was 64 years. All patients were staged surgically (by laprotomy (47%), laparoscopy or laparoscopy assisted vaginal surgery (33%), robotic surgery (20%). Cancer type: 86% endometrial cancer, 6.9% serous cancer, 4.2% carcinosarcoma. Grade: 79% either grade 1 or 2, 21% grade 3.	

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017		
	Secondary -	FIGO stage: 62.4% stage IA, 20.2% stage IB, 2.5% stage II, 3.2% IIIA, 0.4 IIIB, 6.9% IIIC1, 2.1% IIIC2, 2.1% stage IV. 85 patients (16.4%) had SLN metastases (43 (51%) macrometastasis, 11 (13%) micrometastasis, 31 (36%) ITC. ITC patients received significant less chemotherapy (p=0.0001) and WRT (p=0.007) compared to patients with macrometastasis. Median follow up was: 29 months (0-67): PFS for ITC patients was 95.5%, similar to node negative (87.6%) and micrometastasis patients (85.5%) at three years. And it was statistically better than patients with macrometastasis (58,5%) (p=0.0012). Only 1 of 31 patient with ITC recurred despite adjuvant treatment. None of the ITC patients with endometrioid histology recurred and none of the ITC patients who did not received adjuvant treatment or VBT recurred.

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2 Study type: Prospective cohort study	**Funding sources:** Indiana University Health, Indiana University Health Simon Cancer Center, and the Indiana University Department of Obstetrics and Gynecology.	**Total no. patients:** 385 patients **Recruiting Phase:** Between Aug 1, 2012, and Oct 20, 2015 **Inclusion criteria:** Patients were eligible if they had documented endometrial cancer of	**Interventions:** Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Each patient served as their own control,

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
	Conflict of Interests: We declare no competing interests **Randomization:** **Blinding:** Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens **Dropout rates:** ITT analysis was performed	any histology on pathology specimens from endometrial sampling, and if they had clinically determined stage 1 disease, defined as having no physical examination findings or radiographical suspicion of extrauterine disease. There was no age limit for eligibility. Patients were included in the study if they met the performance status and life expectancy to tolerate a surgical staging procedure. Patients who were pregnant based on urine choriogonadotropin assessments were excluded. **Exclusion criteria:** Patients were excluded if they had evidence of extrauterine disease, had undergone previous hysterectomy or treatment for their endometrial cancer (such as radiotherapy, chemotherapy, or hormonal therapy), had received a previous retroperitoneal surgery or lymphadenectomy, or had contraindications for receiving the ICG tracer, including a history of hepatic impairment or an iodine allergy. If patients were recognised to have gross extra-uterine disease at the time of surgery after tracer injection, they were ineligible for the sentinel-lymph-node mapping	with sentinel lymph node results compared with nonsentinel lymph node results within the same patient. **Comparison:** Complete lymphadenectomy as gold standard

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017		
Notes:	Oxford CEBM Level of Evidence 2011: Prospective Cohort Study Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens Intention to treat analysis was performed **Author's conclusion:** Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.	
Outcome Measures/results	**Primary** Sensitivity and negative predictive value **Secondary**	**Results:** Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Sentinel-lymph-node mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97·2% (95% CI 85·0–100), and a negative predictive value of 99·6% (97·9–100). The most common grade 3–4 adverse events or serious adverse events were postoperative neurological disorders (4 patients) and postoperative respiratory distress or failure (4 patients). 22 patients had serious adverse events, with one related to the study intervention: a ureteral injury incurred during sentinel-lymph-node dissection.

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study (SEER database)	**Funding sources:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. **Conflict of Interests:** see funding surces **Randomization:** - **Blinding:** - **Dropout rates:** -	**Total no. patients:** 103,103 patients with endometrial cancer identified from the SEER database of the National Cancer Institute (USA) were identified. Analysed were 11.603 patients. **Recruiting Phase:** 2004-2013 **Inclusion criteria:** Patients with endometrium as the primary site and endometrial cancer malignancy as the disease classification; grade 1 endometrial cancer; focused on early-stage endometrial cancer, in which total hysterectomy – with/without bilateral salpingo-oophorectomy – is the most common type of surgery. **Exclusion criteria:** Patients with more than one primary site, only a clinical diagnosis, other disease stages and survival times less than 3 months.	**Interventions:** Lymphadenectomy (total hysterectomy – with/without bilateral salpingo-oophorectomy) **Comparison:** -

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective, cohort study) Limitations: - The authors stated, that the lack of significance after matching may be due to the small number of patients after matching. - high loss rate (not specified by the authors) - some relevant medical information (depth of myometrial invasion, time to recurrence, and subsequent surgical and medical therapies) are noch available due to the retrospective approach - number of patients for lymph node biopsies ist very small - only one cohort (patient group)- not a cohort study in the original meaning. **Author's conclusion:** In conclusion, using SEER database, we found that for all stage IA patients, most patients died of cardiovascular disease (27%) and diabetes (8%); lymphadenectomy has no influence on survival and sentinel lymph node biopsies can reduce the number of lymph node removed but have no effect in survival. Given that practice patterns have shifted in the world to predominantly sentinel node biopsy, we think our manuscript applicable to current clinical practice	
Outcome Measures/results	**Primary** Survival **Secondary** cause of death spectrum, the effect of sentinel lymph node biopsy and adjuvant therapies.	**Results:** Mean age at diagnosis was 56.5 years old. 22.83% of the women analyzed died from endometrial cancer; other sources were: cardiovascular disease (27%), diabetes (8%) and respiratory diseases (3%). But as the differentiation of the cancer became worse, more women died from the cancer. <u>Overall survival - multivariant analysis:</u> - age and grade were crucial factors in terms of survival, and a younger age and lower grade were associated with a better prognosis ($p < 0.0001$). - Asian women had better survival times than white women and black women ($p < 0.0001$) - no significant influence can be found for geographic region or number of

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
		removed lymph nodes. - lymphadenectomy can increase survival in grade 3/4 stage I patients (p = 0.013). **Sentinel lymph nodes biopsies:** Sentinel lymph nodes biopsy could reduce the number of lymph node removed (12 vs 6, p = 8.387e-10 in Wilcox test), but had no effect on survival (n=102 patients). Propensity score Matching: no difference was observed in survival between the lymphadenectomy group & the nonlymphadenectomy group (p = 0.93 and 0.65 respectively).

2.21. Schlüsselfrage 24: Ist beim Endometriumkarzinom (Typ I, pT1b, G3) die systematische pelvine bzw. pelvine plus paraaortale Lymphonodektomie (LNE) sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Davidson, B. A. 2018	2	Randomized controlled trial
Frost, J. A. 2017	1	Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.
Guo, W. 2018	3	Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis
Wright, J. D. 2016	4	Retrospective cohort study

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase **Search period:** Inception to June 2017 **Inclusion Criteria:** RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer.	**Population:** Adult women diagnosed with endometrial cancer **Intervention:** Pelvic lymphadenectomy versus no lymphadenectomy Pelvic lymphadenectomy versus pelvic lymph node sampling Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy Removal of bulky pelvic lymph nodes versus no removal of lymph nodes **Comparison:**	**Primary:** Overall survival (OS) **Secondary:** Progression-free survival (PFS) QOL measured by a validated scale Adverse events, for example, direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection); surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism) cardiac events (cardiac ischaemia and cardiac failure) cerebrovascular accident recovery: delayed discharge, unscheduled re-admission lymphoedema and lymphocyst formation; other side effects not categorised above. **Results:** 978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria;	3 studies included: Fayallah 2011, Kitchener 2009, Panici 2008

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
Exclusion Criteria: We excluded cross-over trials and clusterrandomised trials, women with other concurrent malignancies.		for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence). We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst		

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
		formation, respectively) (1922 participants, two studies; high-quality evidence). **Author's Conclusion:** This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.		
Methodical Notes				
Funding Sources: None **COI:** None **Study Quality:** We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. **Heterogeneity:** We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between				

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this. The two trials included in the meta-analysis showed no heterogeneity (I2 = 0). **Publication Bias:** Not investigated, because only three studies were included **Notes:** Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs Update of an previous Cochrane Review			

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis **Databases:** PubMed, Embase, and	**Population:** Patients with endometrial cancer **Intervention:** Pelvic lymphadenectomy (PLND) **Comparison:** Pelvic and para-aortic	**Primary:** Overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS) **Secondary:** **Results:** Eight studies with a total of 2793 patients were included. OS was significantly longer in PPaLND group than in	8 retrospective cohort studies (2793 patients): Eggemann 2016, Toptas 2015, Tong 2011, Todo 2010, Chang 2008, May 2013, Okazawa 2012, Fujimoto 2007

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018				
Cochrane Library **Search period:** n January 1, 1990, and January 1, 2017 **Inclusion Criteria:** Studies exploring endometrial cancer; studies comparing 2 treatment modalities and reporting overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS); studies providing hazard ratio (HR) directly or key information to calculate HR indirectly, such as Kaplan-curves and original survival data **Exclusion Criteria:** Abstracts of meetings, duplicate publication, review articles, and case reports; studies explored new surgical techniques or evaluated operation outcomes without comparison of survival effects; and full text or valid data not accessed. To avoid overlapping patient data in publications on the same cohort, we included articles with the latest data.	lymphadenectomy (PPaLND)	pelviclymphadenectomy (PLND) group for patients with endometrial cancer [HR 0.68; 95% confidence interval (CI) 0.55–0.84, P lower .001 i subgroup analysis by recurrence risk explored the same association in patients at intermediate- or high-risk ci p but not for low-risk ppalnd with systematic resection of all para-aortic nodes up to renal vein also improved pfs compared plnd. **Author's Conclusion:** PPaLND is associated with favorable survival outcomes in endometrial cancer patients with intermediate- or high-risk of recurrence compared with PLND, particularly with regards to OS. PPaLND with systematic resection of all para-aortic nodes up to renal vein also improve PFS compared with PLND. Further large-scale randomized clinical trials are required to validate our findings.		

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018

Methodical Notes

Funding Sources: This study was funded by National Natural Science Foundation of China (grant number: 81201720).

COI: None.

Study Quality: Quality assessments were performed according to the Newcastle– Ottawa Quality Assessment Scale (NOS),[19] which contains 3 aspects: selection, comparability, and outcome. The quality score ranged from 7 to 9 with a median score of 8 for all cohort studies, which suggested the relatively high quality of the studies included in the meta-analysis

Heterogeneity: Forest plots were generated for graphical presentations, and heterogeneity among different studies was appraised by Q statistics and I 2 estimates. Fixed effects model was conducted to aggregate data if there were no statistical heterogeneity (I 2

Publication Bias: Publication bias was examined using Begg funnel plot and Egger linear regression test. Two-sided P lower .05 was considered statistically significant. no publication bias observed among included studies.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of retropective cohort studies

No search for grey literature or unpublished articles was performed
Heterogeneity was present for some analyses, but the authors are aware of this and performed sub-group analyses to explore the heterogeneity.
Overall, the quality of the included studies was considered as high by the authors, but details of the quality assessment are not described.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 120 **Recruitung Phase:** January 2009 and March 2015 **Inclusion Criteria:** Woman with high-grade EC on preoperative sampling (grade 3 endometrioid, clear cell, serous, carcinosarcoma or mixed histologies) who were appropriate surgical candidates and deemed medically eligible for a lymph node dissection **Exclusion Criteria:** Exclusion criteria were patients with low-grade histologies on preoperative assessment or advanced disease at diagnosis.	**Intervention:** Collection of LNs into nodal basin-specific containers on the randomized side **Comparison:** Simple labeling on the non-randomized side	**Primary:** Total number of LNs and total number of LNs with metastases on the randomized versus the nonrandomized side were compared. The remaining adipose tissue from each LN specimen was submitted for histologic examination. Wen analyzed the number of LNs with and without metastases identified from additional adipose tissue. **Secondary:** **Results:** Of 120 consented subjects, 56 had sufficient data for analysis. The additional adipose tissue contained 7.5 LNs per patient on average (range: 0-26). In 2/54 total cases (3.7%) and 2/5 cases with nodal metastases (40%), the additional adipose tissue contained LNs with metastases. In both cases, metastases were also detected in grossly identified LN candidates. The mean number of LNs identified was not significantly different based on method of collection (p=0.22). The mean number of LNs containing metastases per side was not significantly different (p=0.58). **Author's Conclusion:** Processing of adipose tissue does increase the total number of LNs identified, however, it does	

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
		not influence EC stage. No difference in LN counts was noted with basin-specific collection.	
Methodical Notes			
Funding Sources: Not stated **COI:** None **Randomization:** Randomization was performed using a random number generator with block randomization (block size 6) stratified by site. **Blinding:** No blinding **Dropout Rate/ITT-Analysis:** Not performed **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 No test for group differences Blinding was not performed Small number of patients included in the analysis. Nearly half of the patients initially consented were not included in the final analysis			

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	**Funding sources:** Not described **Conflict of Interests:** The authors did not report any potential conflicts of interest. **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 151,089 women **Recruiting Phase:** 1998-2011 **Inclusion criteria:** Women with endometrioid adenocarcinoma of the endometrium diagnosed from 1998–2011 who underwent hysterectomy were selected. **Exclusion criteria:** Patient who received preoperative radiation and those who had another primary tumor prior to the diagnosis of uterine cancer were excluded. Women with primary tumor spread beyond the uterus (>T2) or metastatic disease were excluded.	**Interventions:** Lymphadenectomy **Comparison:** No Lymphadenectomy
Notes:	Oxford CEBM Level of Evidence 2011: EL 4 Retrospective, cohort study Retrospective analysis of a national wide cancer database Funding sources were not described **Author's conclusion:** Lymphadenectomy is associated with a modest, if any, effect on survival for women with endometrial cancer.		

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016		
Outcome Measures/results	Primary Overall survival Secondary	**Results:** A total of 151,089 women treated at 1336 hospitals were identified; 99,052 (65.6%) patients underwent lymphadenectomy while 52,037 (34.4%) did not. In a multivariable regression model, lymphadenectomy was associated with a 16% reduction in mortality (HR=0.84; 95% CI, 0.81–0.87). The results were similar after adjustment for adjuvant therapy (HR=0.85; 95% CI, 0.82–0.87). The results were largely unchanged and suggested that lymphadenectomy was associated with improved survival after application of a propensity score analysis. In contrast, in the instrumental variable analysis there was not a statistically significant association between lymphadenectomy and survival (HR=0.75; 95% CI, 0.53–1.06), even after adjustment for adjuvant treatment (HR=0.76; 95% CI, 0.54–1.06). The results were unchanged for women with T1A and T1B tumors.

2.22. Schlüsselfrage 25: Ist beim Endometriumkarzinom (Typ I, pT1b, G3) die SLN sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *8 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Body, N. 2018	4	Retrospective Cohort Study
Bogani, G. 2020	4	Retrospective cohort study
Cusimano, M. C. 2021	3	Prospective multicenter cohort study
Davidson, B. A. 2018	2	Randomized controlled trial
El-Agwany, A. S. 2018	3	Randomized Trial
Rossi, E. C. 2017	2	Prospective cohort study
Wang, L. 2018	3	Systematic Review and Meta-Analysis (8 studies, 366 patients) To explore sentinel lymph node mapping in laparoscopy surgery in EC

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis (8 studies, 366 patients)	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage one or higher EC	**Primary:** Detection rate and/or sensitivity. The sensitivity associated with the sentinel lymph node procedure was described as the total number of true	8 studies (366 patients) included: Anne-Sophie 2008,

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018				
To explore sentinel lymph node mapping in laparoscopy surgery in EC **Databases:** Pubmed, Embase, Medline and the Cochrane Library **Search period:** Inception to February 2018 **Inclusion Criteria:** (1) included ten or more women diagnosed with International Federation of Gynecology and Obstetrics stage one or higher EC; (2) Laparoscopy SLN mapping was the study's primary focus; (3) Studies validated by pelvic with/without parasitic lymph node dissection and pathological examination including H&E (hematoxylin–eosin) staining or immunohistochemistry (IHC) were taken as the reference standard; (4) Total number of included patients, as well as those with detected sentinel nodes were both reported; (6) Studies that reported the total number of patients with a positive lymph node diagnosis, as well as those with false negative results. (7) Articles published by the same author with the latest	**Intervention:** Laparoscopy SLN mapping **Comparison:** Studies validated by pelvic with/without parasitic lymph node dissection and pathological examination including H&E (hematoxylin–eosin) staining or immunohistochemistry (IHC) were taken as the reference standard	positives in patients with a positive histopathology. The SLN detection rate can be defned as the percentage of patients in which at least one SLN was identifed. **Secondary:** **Results:** The overall detection rate of sentinel lymph node mapping was included in 389 patients of 8 studies, ranging from 25 to 71 patients, which was 96% (95% confidence interval 95–98). 366 patients were included in bilateral sentinel node detection rate, ranging from 30 to 71 patients; it was 73% (95% confidence interval, 69–77). The sensitivity of the overall detection rate of sentinel lymph node mapping was 96.3% with a sensitivity of 73.1% bilateral sentinel node detection rate. **Author's Conclusion:** Laparoscopy sentinel lymph node localization is feasible and accurately predicts lymph node status in patients with EC. For patients with early stage clinical disease, it is very important to screen patients	Barranger 2009, Favero 2015, Taskin 2017, Holub 2004, Papadia 2016, Ballester 2008, Vidal 2013	

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018				
published **Exclusion Criteria:** We excluded studies with fewer than ten women with EC, as well as robot-assisted surgery laparoscopy and meeting abstracts, reviews, case reports, or editorials		with no lymph node metastasis, reduce the range of surgical resection, reduce the incidence of the corresponding complications, and improve the quality of patients.		
Methodical Notes				
Funding Sources: **COI:** None **Study Quality:** Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool. **Heterogeneity:** Tests of heterogeneity were conducted to decide which method would be used to pool the results. Results were considered homogenous when the I2 statistic (the percentage of variance due to heterogeneity) was less than 50% and the p value for the test of heterogeneity was≥0.10, in these cases, a fixed-effect model was used to compute the pooled estimate of detection rate. In all other cases (I2>50% or p Overall detection rate of sentinel lymph node mapping (I2=91%), Bilateral sentinel node detection rate of sentinel lymph node mapping (I2=94%), **Publication Bias:** Egger's regression intercepts were used for the evaluation of publication bias. Publication bias is an important issue which should be addressed in all systematic reviews, funnel plots of detection rate and sensitivity pooling showed some asymmetry, although Egger's test was not statistically signifcant in either one, Egger's regression intercepts to make the was 0.043 (p				

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018

important limitation

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review and Meta-Analysis of diagnostic non-consecutive studies or studies without consistently applied reference standard.

Downgraded to EL 3 due to methodical weakness:

No search for grey literature, reference lists and unpublished articles was performed.
Publication bias may be present
Overall, the number of included patients was small
Heterogeneity was present for the main outcomes overall detection rate of sentinel lymph node mapping (I2=91%), Bilateral sentinel node detection rate of sentinel lymph node mapping (I2=94%). Heterogeneity was not explained.
Quality was assessed but the results were not reported

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 120 **Recruitung Phase:** January 2009 and March 2015 **Inclusion Criteria:** Woman with high-grade EC on preoperative sampling (grade 3 endometrioid, clear cell, serous, carcinosarcoma or mixed histologies) who were appropriate surgical candidates and deemed medically eligible for a lymph node dissection **Exclusion Criteria:** Exclusion criteria were patients with low-grade histologies on preoperative assessment or advanced disease at diagnosis.	**Intervention:** Collection of LNs into nodal basin-specific containers on the randomized side **Comparison:** Simple labeling on the non-randomized side	**Primary:** Total number of LNs and total number of LNs with metastases on the randomized versus the nonrandomized side were compared. The remaining adipose tissue from each LN specimen was submitted for histologic examination. Wen analyzed the number of LNs with and without metastases identified from additional adipose tissue. **Secondary:** **Results:** Of 120 consented subjects, 56 had sufficient data for analysis. The additional adipose tissue contained 7.5 LNs per patient on average (range: 0-26). In 2/54 total cases (3.7%) and 2/5 cases with nodal metastases (40%), the additional adipose tissue contained LNs with metastases. In both cases, metastases were also detected in grossly identified LN candidates. The mean number of LNs identified was not significantly different based on method of collection (p=0.22). The mean number of LNs containing metastases per side was not significantly different (p=0.58). **Author's Conclusion:** Processing of adipose tissue does increase the total number of LNs identified, however, it does	

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
		not influence EC stage. No difference in LN counts was noted with basin-specific collection.	
Methodical Notes			
Funding Sources: Not stated **COI:** None **Randomization:** Randomization was performed using a random number generator with block randomization (block size 6) stratified by site. **Blinding:** No blinding **Dropout Rate/ITT-Analysis:** Not performed **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 No test for group differences Blinding was not performed Small number of patients included in the analysis. Nearly half of the patients initially consented were not included in the final analysis			

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Randomized Trial **Number of Patient:** 120 **Recruitung Phase:** Between June 2016 and June 2017 **Inclusion Criteria:** Patients with low-risk endometrial cancer for nodal metastasis were included in this study. Low risk was defined as stage Ia, type I, grade a,b endometrial cancer confirmed clinically and histologically by fractional curettage. **Exclusion Criteria:**	**Intervention:** Group A included hysteroscopic guided methylene blue injection, Group B included transcervical injection, Group C included uterine subserosal injection and Group D included combined transcervical and subserosal injection. We used 1 ml injection of methylene blue per site after sterilization of the methylene blue powder by autoclave or autoclaving of the diluted solution in autoclavable bottle or using sterilized ampules. Cervical injection was done by insulin syringe (one ml) inserting full needle length (1 cm) at 3, 9 o'clock. Subserosal myometrial injection was done at eight points, four anterior and four posterior in the midline with insulin syringe **Comparison:**	**Primary:** **Secondary:** **Results:** Clinical and pathological SLN detection were more with hysteroscopic technique than others and pathological detection was lower than clinical detection in all techniques. Metastatic disease was more common in nodes with suspicious appearance. About 10% of negative suspicious and mapped nodes were associated with positive other nodes for metastasis. **Author's Conclusion:** SLN in endometrial cancer has a role in staging of endometrial cancer with best technique for detection, hysteroscopic guided blue dye injection. SLN can be used in patients with low risk for lymph node metastasis for selective lymphadenectomy. Blue dye labelling using methylene blue dye is good in low resource countries as it is cheap. We recommended the following algorithm for surgical staging in early endometrial cancer with better results than using SLN alone. Stage I type 1, grade 1,2 endometrial

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

		cancer should undergo surgical staging with initial evaluation of the peritoneum which if affected, it is stage III with no need for lymphadenectomy. Then, dissection of the blue and suspicious nodes which if any is positive on frozen section, selective same side pelvic and paraaortic nodal dissection should be done. If they are negative, no need for lymphadenectomy. This approach can help patients to avoid the side effects associated with a complete lymphadenectomy. The higher rate of detection using this algorithm is related to combining the suspicions nodes with the stained ones.	
Methodical Notes			
Funding Sources: None **COI:** None **Randomization:** Method unclear **Blinding:** Not described **Dropout Rate/ITT-Analysis:**			

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized trial
Downgraded to Level 3 due to methodical weakness:
Inclusion and exclusion criteria were not described sufficiently.
Outcomes were not described.
Method of randomization was not described.
Blinding was not described.
Reference standard was not applied.

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective Cohort Study	**Number of patients / samples:** 119 patients with endometrial cancer **Reference standard:** No reference standard **Validation:** Detection rate, sensitivity and negative predictive value (NPV) **Blinding:** Not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	**Results:** Sentinel lymph node mapping with Indocyanin green A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection (p = 0.01). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymphe node. **Author conclusions:** ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection (p = 0.01). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.		
Methodical Notes				

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018		
Funding Sources: Not stated. COI: None. Notes: Oxford CEBM Level of Evidence 2011: EL 4 Retrospective cohort study without blinding or reference standard Articles submitted by hand search.		
Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective multicenter cohort study	**Number of patients / samples:** 156 patients **Reference standard:** Lymphadenectomy as the reference standard **Validation:** Sensitivity of the SLNB algorithm in detecting metastatic disease, False negative rate and negative predictive value Additional measures of diagnostic accuracy, sentinel lymph node detection rates, and adverse events	**Results:** Performance characteristics of Sentinel Lymph Node Biopsy (SLNB) using indocyanine green (ICG) The study enrolled 156 patients (median age, 65.5 years; range, 40-86 years; median body mass index [calculated as weight in kilograms divided by height in meters squared], 27.5; range, 17.6-49.3), including 126 with high-grade EC. All patients underwent SLNB and PLND, and 101 patients (80%) with high-grade EC also underwent PALND. Sentinel lymph node detection rates were 97.4%per patient (95%CI, 93.6%-99.3%), 87.5%per hemipelvis (95%CI, 83.3%-91.0%), and 77.6%bilaterally (95%CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the SLNB algorithm, yielding a sensitivity of 96%(95%CI, 81%-100%), a false-negative rate of 4%(95%CI,

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021				
	Blinding: Blinding was not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	0%-19%), and a negative predictive value of 99%(95%CI, 96%-100%). Only 1 patient (0.6%) was misclassified by the SLNB algorithm. Seven of 27 patients with node-positive cancer (26%) were identified outside traditional PLND boundaries or required immunohistochemistry for diagnosis. **Author conclusions:** In this study, SLNB had acceptable diagnostic accuracy compared with lymphadenectomy for the detection of nodal metastatic disease in high-grade EC. On the basis of this study and the existing literature, SLNB appears to be a viable option for the surgical staging of both low- and high-grade EC.		
Methodical Notes				
Funding Sources: Dr Clarke reported receiving personal fees from AstraZeneca outside the submitted work. No other disclosures were reported. **COI:** This study was supported by the Princess Margaret Cancer Foundation of Princess Margaret Cancer Centre (Toronto, Ontario) and the McArthur Research Fund of the Department of Obstetrics and Gynecology at the University of Toronto (Toronto, Ontario). Dr Cusimano is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship and American College of Surgeons Resident Research Scholarship. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Prospective cohort study with consistently applied reference standard but without blinding** Article submitted by hand search.				

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021

Limitations:
-Blinding was not performed

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients. **Exclusion criteria:** Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3)	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
		presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	
Notes:	Oxford CEBM Level of Evidence: 4 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy. Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.		
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.	

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2 Study type: Prospective cohort study	**Funding sources:** Indiana University Health, Indiana University Health Simon Cancer Center, and the Indiana University Department of Obstetrics and Gynecology. **Conflict of Interests:** We declare no competing interests **Randomization:** **Blinding:** Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens **Dropout rates:** ITT analysis was performed	**Total no. patients:** 385 patients **Recruiting Phase:** Between Aug 1, 2012, and Oct 20, 2015 **Inclusion criteria:** Patients were eligible if they had documented endometrial cancer of any histology on pathology specimens from endometrial sampling, and if they had clinically determined stage 1 disease, defined as having no physical examination findings or radiographical suspicion of extrauterine disease. There was no age limit for eligibility. Patients were included in the study if they met the performance status and life expectancy to tolerate a surgical staging procedure. Patients who were pregnant based on urine choriogonadotropin assessments were excluded. **Exclusion criteria:** Patients were excluded if they had evidence of extrauterine disease, had undergone previous hysterectomy or treatment for their endometrial cancer (such	**Interventions:** Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Each patient served as their own control, with sentinel lymph node results compared with nonsentinel lymph node results within the same patient. **Comparison:** Complete lymphadenectomy as gold standard

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
		as radiotherapy, chemotherapy, or hormonal therapy), had received a previous retroperitoneal surgery or lymphadenectomy, or had contraindications for receiving the ICG tracer, including a history of hepatic impairment or an iodine allergy. If patients were recognised to have gross extra-uterine disease at the time of surgery after tracer injection, they were ineligible for the sentinel-lymph-node mapping	
Notes:	Oxford CEBM Level of Evidence 2011: Prospective Cohort Study Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens Intention to treat analysis was performed **Author's conclusion:** Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.		
Outcome Measures/results	**Primary** Sensitivity and negative predictive value **Secondary**	**Results:** Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Sentinel-lymph-node mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive	

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017		
		nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97·2% (95% CI 85·0–100), and a negative predictive value of 99·6% (97·9–100). The most common grade 3–4 adverse events or serious adverse events were postoperative neurological disorders (4 patients) and postoperative respiratory distress or failure (4 patients). 22 patients had serious adverse events, with one related to the study intervention: a ureteral injury incurred during sentinel-lymph-node dissection.

2.23. Schlüsselfrage 26: Ist beim Endometriumkarzinom (Typ I, pT2 bis pTIV b, G1-3) die systematische pelvine bzw. pelvine plus paraaortale Lymphonodektomie (LNE) sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Davidson, B. A. 2018	2	Randomized controlled trial
Frost, J. A. 2017	1	Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.
Guo, W. 2018	3	Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer. Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase Search period: Inception to June 2017 Inclusion Criteria: RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer. Exclusion Criteria: We excluded cross-over trials and clusterrandomised trials, women with other concurrent malignancies.	Population: Adult women diagnosed with endometrial cancer Intervention: Pelvic lymphadenectomy versus no lymphadenectomy Pelvic lymphadenectomy versus pelvic lymph node sampling Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy Removal of bulky pelvic lymph nodes versus no removal of lymph nodes Comparison:	Primary: Overall survival (OS) Secondary: Progression-free survival (PFS) QOL measured by a validated scale Adverse events, for example, direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection); surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism) cardiac events (cardiac ischaemia and cardiac failure) cerebrovascular accident recovery: delayed discharge, unscheduled re-admission lymphoedema and lymphocyst formation; other side effects not categorised above. Results: 978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria; for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of	3 studies included: Fayallah 2011, Kitchener 2009, Panici 2008

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
		the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence). We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation, respectively) (1922 participants, two studies; high-quality evidence). Author's Conclusion: This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence	

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
		shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.	

Methodical Notes

Funding Sources: None

COI: None

Study Quality: We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting.

Heterogeneity: We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this. The two trials included in the meta-analysis
showed no heterogeneity (I2 = 0).

Publication Bias: Not investigated, because only three studies were included

Notes:
Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs
Update of an previous Cochrane Review

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis **Databases:** PubMed, Embase, and Cochrane Library **Search period:** n January 1, 1990, and January 1, 2017 **Inclusion Criteria:** Studies exploring endometrial cancer; studies comparing 2 treatment modalities and reporting overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS); studies providing hazard ratio (HR) directly or key information to calculate HR indirectly, such	**Population:** Patients with endometrial cancer **Intervention:** Pelvic lymphadenectomy (PLND) **Comparison:** Pelvic and para-aortic lymphadenectomy (PPaLND)	**Primary:** Overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS) **Secondary:** **Results:** Eight studies with a total of 2793 patients were included. OS was significantly longer in PPaLND group than in pelviclymphadenectomy (PLND) group for patients with endometrial cancer [HR 0.68; 95% confidence interval (CI) 0.55–0.84, P lower .001 i subgroup analysis by recurrence risk explored the same association in patients at intermediate- or high-risk ci p but not for low-risk ppalnd with systematic resection of all para-aortic nodes up to renal vein also improved pfs compared plnd. **Author's Conclusion:** PPaLND is associated with favorable survival outcomes in endometrial cancer patients with intermediate- or high-risk of recurrence	8 retrospective cohort studies (2793 patients): Eggemann 2016, Toptas 2015, Tong 2011, Todo 2010, Chang 2008, May 2013, Okazawa 2012, Fujimoto 2007

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018				
as Kaplan-curves and original survival data **Exclusion Criteria:** Abstracts of meetings, duplicate publication, review articles, and case reports; studies explored new surgical techniques or evaluated operation outcomes without comparison of survival effects; and full text or valid data not accessed. To avoid overlapping patient data in publications on the same cohort, we included articles with the latest data.		compared with PLND, particularly with regards to OS. PPaLND with systematic resection of all para-aortic nodes up to renal vein also improve PFS compared with PLND. Further large-scale randomized clinical trials are required to validate our findings.		
Methodical Notes				
Funding Sources: This study was funded by National Natural Science Foundation of China (grant number: 81201720). **COI:** None. **Study Quality:** Quality assessments were performed according to the Newcastle– Ottawa Quality Assessment Scale (NOS),[19] which contains 3 aspects: selection, comparability, and outcome. The quality score ranged from 7 to 9 with a median score of 8 for all cohort studies, which suggested the relatively high quality of the studies included in the meta-analysis **Heterogeneity:** Forest plots were generated for graphical presentations, and heterogeneity among different studies was appraised by Q statistics and I 2 estimates. Fixed effects model was conducted to aggregate data if there were no statistical heterogeneity (I 2				

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018

Publication Bias: Publication bias was examined using Begg funnel plot and Egger linear regression test. Two-sided P lower .05 was considered statistically significant. no publication bias observed among included studies.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of retropective cohort studies

No search for grey literature or unpublished articles was performed
Heterogeneity was present for some analyses, but the authors are aware of this and performed sub-group analyses to explore the heterogeneity.
Overall, the quality of the included studies was considered as high by the authors, but details of the quality assessment are not described.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 120 **Recruitung Phase:** January 2009 and March 2015 **Inclusion Criteria:** Woman with high-grade EC on preoperative sampling (grade 3 endometrioid, clear cell, serous, carcinosarcoma or mixed histologies) who were appropriate surgical candidates and deemed medically eligible for a lymph node dissection **Exclusion Criteria:** Exclusion criteria were patients with low-grade histologies on preoperative assessment or advanced disease at diagnosis.	**Intervention:** Collection of LNs into nodal basin-specific containers on the randomized side **Comparison:** Simple labeling on the non-randomized side	**Primary:** Total number of LNs and total number of LNs with metastases on the randomized versus the nonrandomized side were compared. The remaining adipose tissue from each LN specimen was submitted for histologic examination. Wen analyzed the number of LNs with and without metastases identified from additional adipose tissue. **Secondary:** **Results:** Of 120 consented subjects, 56 had sufficient data for analysis. The additional adipose tissue contained 7.5 LNs per patient on average (range: 0-26). In 2/54 total cases (3.7%) and 2/5 cases with nodal metastases (40%), the additional adipose tissue contained LNs with metastases. In both cases, metastases were also detected in grossly identified LN candidates. The mean number of LNs identified was not significantly different based on method of collection (p=0.22). The mean number of LNs containing metastases per side was not significantly different (p=0.58). **Author's Conclusion:** Processing of adipose tissue does increase the total number of LNs identified, however, it does	

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
		not influence EC stage. No difference in LN counts was noted with basin-specific collection.	
Methodical Notes			
Funding Sources: Not stated **COI:** None **Randomization:** Randomization was performed using a random number generator with block randomization (block size 6) stratified by site. **Blinding:** No blinding **Dropout Rate/ITT-Analysis:** Not performed **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 No test for group differences Blinding was not performed Small number of patients included in the analysis. Nearly half of the patients initially consented were not included in the final analysis			

2.24. Schlüsselfrage 27: Ist beim Endometriumkarzinom (Typ I, pT2 bis pTIV b, G1-3) die SLN sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/ Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *10 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Body, N. 2018	4	Retrospective Cohort Study
Bogani, G. 2020	4	Retrospective cohort study
Bogani, G. 2019	4	Systematic Review and Meta-Analysis (5 studies, 3536 patients)
Cusimano, M. C. 2021	3	Prospective multicenter cohort study
Davidson, B. A. 2018	2	Randomized controlled trial
Kogan, L. 2020	4	Retrospective Cohort study
Plante, M. 2017	3	Prospective cohort study.
Rossi, E. C. 2017	2	Prospective cohort study
Wang, L. 2018	3	Systematic Review and Meta-Analysis (8 studies, 366 patients) To explore sentinel lymph node mapping in laparoscopy surgery in EC

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *3 Bewertung(en)*

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

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measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic Review	**Population:** Patients with endometrial cancer	**Primary:** Positive node detection rate, survival outcomes (overall survival and disease free survival)	5 studies (3536 patients) included: Eriksson 2015,

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
and Meta-Analysis (5 studies, 3536 patients) **Databases:** Pubmed, Scopus, Web of Sciences, Clinicaltrials.gov **Search period:** Inception to December 2018 **Inclusion Criteria:** Comparative studies, English language, and >10 cases **Exclusion Criteria:** Case reports, in vitro or cadaveric studies, technical notes, review articles not reporting original data, duplicate publications, and single arm studies	**Intervention:** Sentinel node mapping **Comparison:** Lymphadenectomy	**Secondary:** Mean operative time, mean blood loss, blood transfusion rate, procedure conversion rate, complication rate, in hospital stay, postoperative complications **Results:** Six comparative studies were included. Overall, 3536 patients were included: 1249 (35,3%) and 2287 (64,7%), undergoing sentinel node mapping and lymphadenectomy, respectively. Pooled data suggested that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03 (95% CI 1.30 – 3.18); p=0.002). No difference in detection of positive nodes located in the paraaortic was observed (OR: 0.93 (95% CI 0.30 to 2.18), p= 0.086). Overall recurrence rate was 4.3% and 7.3% after sentinel node mapping and lymphadenectomy, respectively (OR: 0.90 (95% CI 0.58 – 1.38), p = 0.63). Similarly, nodal recurrences were statistically similar between group (1.2% vs. 1.7%; OR 1.51 (95% CI 0.70 to 3.29), p=0.29). **Author's Conclusion:** In conclusion, our	Holloway 2016, Baiocchi 2017, Buda 2017, Ducie 2017, Buda 2018	

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019				
		meta-analysis underlines that sentinel node mapping is non-inferior to standard lymphadenectomy in term of detection of paraaortic nodal involvement and recurrence rates (any site and nodal recurrence); while, focusing on the ability to detect positive pelvic nodes, sentinel node mapping could be consider superior to lymphadenectomy. Further randomized studies are needed to assess long term effectiveness of sentinel node mapping.		
Methodical Notes				
Funding Sources: None. **COI:** None. **Study Quality:** Cochrane Collaboration Risks of Bias assessment tool was used to assess the quality of the included studies. Assessment of the study quality is displayed in the supplementary material, which is not accessible. **Heterogeneity:** Heterogeneity was measured using I2 statistic, in which I2 > 50% suggests high heterogeneity. High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%) **Publication Bias:** Publication bias was not investigated (less than ten studies included)				

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
Notes: Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of Retrospective cohort studies Downgraded to Level 4 due to methodical weakness: Inclusion criteria and Population were not described sufficiently No search for grey literature or reference lists was conducted. Non-English articles were excluded. Insufficient description of the performed searches. Publication bias was not investigated (less than ten studies included) High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%) Assessment of the study quality is displayed in the supplementary material, which is not accessible.			
Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis (8 studies, 366 patients) To explore sentinel lymph node mapping in laparoscopy surgery in EC **Databases:** Pubmed, Embase, Medline and the Cochrane Library	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage one or higher EC **Intervention:** Laparoscopy SLN mapping **Comparison:** Studies validated by	**Primary:** Detection rate and/or sensitivity. The sensitivity associated with the sentinel lymph node procedure was described as the total number of true positives in patients with a positive histopathology. The SLN detection rate can be defned as the percentage of patients in which at least one SLN was identifed.	8 studies (366 patients) included: Anne-Sophie 2008, Barranger 2009, Favero 2015, Taskin 2017, Holub 2004, Papadia 2016,

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018			
Search period: Inception to February 2018 **Inclusion Criteria:** (1) included ten or more women diagnosed with International Federation of Gynecology and Obstetrics stage one or higher EC; (2) Laparoscopy SLN mapping was the study's primary focus; (3) Studies validated by pelvic with/without parasitic lymph node dissection and pathological examination including H&E (hematoxylin–eosin) staining or immunohistochemistry (IHC) were taken as the reference standard; (4) Total number of included patients, as well as those with detected sentinel nodes were both reported; (6) Studies that reported the total number of patients with a positive lymph node diagnosis, as well as those with false negative results. (7) Articles published by the same author with the latest published **Exclusion Criteria:** We excluded studies with fewer than ten women with EC, as well as robot-assisted	pelvic with/without parasitic lymph node dissection and pathological examination including H&E (hematoxylin–eosin) staining or immunohistochemistry (IHC) were taken as the reference standard	**Secondary:** **Results:** The overall detection rate of sentinel lymph node mapping was included in 389 patients of 8 studies, ranging from 25 to 71 patients, which was 96% (95% confidence interval 95–98). 366 patients were included in bilateral sentinel node detection rate, ranging from 30 to 71 patients; it was 73% (95% confidence interval, 69–77). The sensitivity of the overall detection rate of sentinel lymph node mapping was 96.3% with a sensitivity of 73.1% bilateral sentinel node detection rate. **Author's Conclusion:** Laparoscopy sentinel lymph node localization is feasible and accurately predicts lymph node status in patients with EC. For patients with early stage clinical disease, it is very important to screen patients with no lymph node metastasis, reduce the range of surgical resection, reduce the incidence of the corresponding complications, and improve the quality of patients.	Ballester 2008, Vidal 2013

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018				
surgery laparoscopy and meeting abstracts, reviews, case reports, or editorials				
Methodical Notes				
Funding Sources: **COI:** None **Study Quality:** Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool. **Heterogeneity:** Tests of heterogeneity were conducted to decide which method would be used to pool the results. Results were considered homogenous when the I2 statistic (the percentage of variance due to heterogeneity) was less than 50% and the p value for the test of heterogeneity was≥0.10, in these cases, a fixed-effect model was used to compute the pooled estimate of detection rate. In all other cases (I2>50% or p Overall detection rate of sentinel lymph node mapping (I2=91%), Bilateral sentinel node detection rate of sentinel lymph node mapping (I2=94%), **Publication Bias:** Egger's regression intercepts were used for the evaluation of publication bias. Publication bias is an important issue which should be addressed in all systematic reviews, funnel plots of detection rate and sensitivity pooling showed some asymmetry, although Egger's test was not statistically signifcant in either one, Egger's regression intercepts to make the was 0.043 (p important limitation **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review and Meta-Analysis of diagnostic non-consecutive studies or studies without consistently				

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018	
applied reference standard. Downgraded to EL 3 due to methodical weakness: No search for grey literature, reference lists and unpublished articles was performed. Publication bias may be present Overall, the number of included patients was small Heterogeneity was present for the main outcomes overall detection rate of sentinel lymph node mapping (I2=91%), Bilateral sentinel node detection rate of sentinel lymph node mapping (I2=94%). Heterogeneity was not explained. Quality was assessed but the results were not reported	

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 120 **Recruitung Phase:** January 2009 and March 2015 **Inclusion Criteria:** Woman with high-grade EC on preoperative sampling (grade 3 endometrioid, clear cell, serous, carcinosarcoma or mixed histologies) who were appropriate surgical candidates and deemed medically eligible for a lymph node dissection **Exclusion Criteria:** Exclusion criteria were patients with low-grade histologies on preoperative assessment or advanced disease at diagnosis.	**Intervention:** Collection of LNs into nodal basin-specific containers on the randomized side **Comparison:** Simple labeling on the non-randomized side	**Primary:** Total number of LNs and total number of LNs with metastases on the randomized versus the nonrandomized side were compared. The remaining adipose tissue from each LN specimen was submitted for histologic examination. Wen analyzed the number of LNs with and without metastases identified from additional adipose tissue. **Secondary:** **Results:** Of 120 consented subjects, 56 had sufficient data for analysis. The additional adipose tissue contained 7.5 LNs per patient on average (range: 0-26). In 2/54 total cases (3.7%) and 2/5 cases with nodal metastases (40%), the additional adipose tissue contained LNs with metastases. In both cases, metastases were also detected in grossly identified LN candidates. The mean number of LNs identified was not significantly different based on method of collection (p=0.22). The mean number of LNs containing metastases per side was not significantly different (p=0.58). **Author's Conclusion:** Processing of adipose tissue does increase the total number of LNs identified, however, it does	

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018

		not influence EC stage. No difference in LN counts was noted with basin-specific collection.	

Methodical Notes

Funding Sources: Not stated

COI: None

Randomization: Randomization was performed using a random number generator with block randomization (block size 6) stratified by site.

Blinding: No blinding

Dropout Rate/ITT-Analysis: Not performed

Notes:
Oxford CEBM Level of Evidence 2011: EL 2
No test for group differences
Blinding was not performed
Small number of patients included in the analysis. Nearly half of the patients initially consented were not included in the final analysis

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective Cohort Study	**Number of patients / samples:** 119 patients with endometrial cancer **Reference standard:** No reference standard **Validation:** Detection rate, sensitivity and negative predictive value (NPV) **Blinding:** Not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	**Results:** Sentinel lymph node mapping with Indocyanin green A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection (p = 0.01). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymphe node. **Author conclusions:** ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection (p = 0.01). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.		
Methodical Notes				

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018		
Funding Sources: Not stated. COI: None. Notes: Oxford CEBM Level of Evidence 2011: EL 4 Retrospective cohort study without blinding or reference standard Articles submitted by hand search.		
Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective multicenter cohort study	**Number of patients / samples:** 156 patients **Reference standard:** Lymphadenectomy as the reference standard **Validation:** Sensitivity of the SLNB algorithm in detecting metastatic disease, False negative rate and negative predictive value Additional measures of diagnostic accuracy, sentinel lymph node detection rates, and adverse events	**Results:** Performance characteristics of Sentinel Lymph Node Biopsy (SLNB) using indocyanine green (ICG) The study enrolled 156 patients (median age, 65.5 years; range, 40-86 years; median body mass index [calculated as weight in kilograms divided by height in meters squared], 27.5; range, 17.6-49.3), including 126 with high-grade EC. All patients underwent SLNB and PLND, and 101 patients (80%) with high-grade EC also underwent PALND. Sentinel lymph node detection rates were 97.4%per patient (95%CI, 93.6%-99.3%), 87.5%per hemipelvis (95%CI, 83.3%-91.0%), and 77.6%bilaterally (95%CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the SLNB algorithm, yielding a sensitivity of 96%(95%CI, 81%-100%), a false-negative rate of 4%(95%CI,

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021				
	Blinding: Blinding was not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	0%-19%), and a negative predictive value of 99%(95%CI, 96%-100%). Only 1 patient (0.6%) was misclassified by the SLNB algorithm. Seven of 27 patients with node-positive cancer (26%) were identified outside traditional PLND boundaries or required immunohistochemistry for diagnosis. **Author conclusions:** In this study, SLNB had acceptable diagnostic accuracy compared with lymphadenectomy for the detection of nodal metastatic disease in high-grade EC. On the basis of this study and the existing literature, SLNB appears to be a viable option for the surgical staging of both low- and high-grade EC.		
Methodical Notes				
Funding Sources: Dr Clarke reported receiving personal fees from AstraZeneca outside the submitted work. No other disclosures were reported. **COI:** This study was supported by the Princess Margaret Cancer Foundation of Princess Margaret Cancer Centre (Toronto, Ontario) and the McArthur Research Fund of the Department of Obstetrics and Gynecology at the University of Toronto (Toronto, Ontario). Dr Cusimano is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship and American College of Surgeons Resident Research Scholarship. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Prospective cohort study with consistently applied reference standard but without blinding** Article submitted by hand search.				

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021

Limitations:
-Blinding was not performed

NEWCASTLE - OTTAWA Checklist: Cohort: *4 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients. **Exclusion criteria:** Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3)	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
		presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	
Notes:	Oxford CEBM Level of Evidence: 4 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy. Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.		
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.	

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective Cohort study	**Funding sources:** This study was supported by grants from the Israel Cancer Research Fund, the Azrieli Foundation, the Gloria's Girls Fund, the Susan and Jonathan Wener Fund and the Anne-Marie and Mitch Garber Fund **Conflict of Interests:** None **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 343 **Recruiting Phase:** December 2007- September 2010 **Inclusion criteria:** Patients with endometrial cancer who underwent surgical staging **Exclusion criteria:** Patients with sarcomas or neoadjuvant chemotherapy were excluded	**Interventions:** All patients diagnosed from December 2007 until November 2010 underwent complete pelvic LND (LND cohort) **Comparison:** All patients from December 2010 until September 2014 underwent SLN mapping followed by complete pelvic LND (SLN cohort)
Notes:	Oxford CEBM Level of Evidence 2011: 4, Retrospective Cohort Study Retrospective evaluation of prospective gathered data Inclusion criteria were not described sufficiently No description of where patients were recruited Blinding not described **Author's conclusion:** Addition of SLN to LND was ultimately associated with improved clinical outcomes compared to LND		

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020		
	alone in patients with endometrial cancer undergoing surgical staging, suggesting that the data provided by the analysis of the SLN added relevant clinical information and improved the decision on adjuvant therapy.	
Outcome Measures/results	**Primary** Positive and negative predictive value **Secondary**	**Results:** From 2007 to 2010, 193 patients underwent LND and from December 2010 to 2014, 250 patients had SLN mapping with completion LND. Both groups had similar clinical characteristics. During a median follow-up period of 6.9 years, addition of SLN was associated with more favorable oncological outcomes compared to LND with 6-year overall survival (OS) of 90% compared to 81% (p=0.009), and progression free survival (PFS) of 85% compared to 75% (p=0.01) respectively. SLN was associated with improved OS (HR 0.5, 95% CI 0.3 – 0.8, p=0.004) and PFS (HR 0.6, 95% CI 0.4-0.9, p=0.03) in a multivariable analysis, adjusted for age, ASA score, stage, grade, non-endometrioid histology, and LVSI. Patients who were staged with SLN were less likely to have a recurrence in the pelvis or lymph node basins compared to patients who underwent LND only (6-year recurrence-free survival 95% vs. 90%, p=0.04).

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study	Funding sources: None. Conflict of Interests: None. Randomization: -	**Total no. patients:** 519 patients with early stage endometrial cancer **Recruiting Phase:** November 2010 to December 2015	**Interventions:** adjuvant treatment (chemotherapy and radiotherapy)

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
type: Prospective cohort study.	Blinding: - Dropout rates: n.s.	**Inclusion criteria:** Histological diagnosis of endometrial carcinoma who underwent SLN mapping procedure followed by surgical staging at L`Hotel-Dieu de Quebec Hospital **Exclusion criteria:** -	**Comparison:** Brachytherapy
Notes:	Oxford CEBM Level of evidence: EL 3 Limitations/Notes: - small groups - one study group, results based on staging (not a cohort study in the original design) - no stratification **Author's conclusion:** Patients with endometrial cancer found to have SLN ITCs have an excellent outcome. The use of adjuvant treatment should be tailored to uterine factors and histology and not solely based on the presence of ITCs. Patients with ITCs and otherwise low risk uterine disease probably derive little benefit from receiving additional treatments. More studies are needed to confirm our data.		
Outcome Measures/results	**Primary** progression free survival (PFS), overall survival (OS)	**Results:** Median age was 64 years. All patients were staged surgically (by laprotomy (47%), laparoscopy or laparoscopy assisted vaginal surgery (33%), robotic surgery (20%). Cancer type: 86% endometrial cancer, 6.9% serous cancer, 4.2% carcinosarcoma. Grade: 79% either grade 1 or 2, 21% grade 3.	

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
	Secondary -	FIGO stage: 62.4% stage IA, 20.2% stage IB, 2.5% stage II, 3.2% IIIA, 0.4 IIIB, 6.9% IIIC1, 2.1% IIIC2, 2.1% stage IV. 85 patients (16.4%) had SLN metastases (43 (51%) macrometastasis, 11 (13%) micrometastasis, 31 (36%) ITC. ITC patients received significant less chemotherapy (p=0.0001) and WRT (p=0.007) compared to patients with macrometastasis. Median follow up was: 29 months (0-67): PFS for ITC patients was 95.5%, similar to node negative (87.6%) and micrometastasis patients (85.5%) at three years. And it was statistically better than patients with macrometastasis (58,5%) (p=0.0012). Only 1 of 31 patient with ITC recurred despite adjuvant treatment. None of the ITC patients with endometrioid histology recurred and none of the ITC patients who did not received adjuvant treatment or VBT recurred.	

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2 Study type: Prospective cohort study	**Funding sources:** Indiana University Health, Indiana University Health Simon Cancer Center, and the Indiana University Department of Obstetrics and Gynecology.	**Total no. patients:** 385 patients **Recruiting Phase:** Between Aug 1, 2012, and Oct 20, 2015 **Inclusion criteria:** Patients were eligible if they had documented endometrial cancer of	**Interventions:** Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Each patient served as their own control,

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
	Conflict of Interests: We declare no competing interests **Randomization:** **Blinding:** Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens **Dropout rates:** ITT analysis was performed	any histology on pathology specimens from endometrial sampling, and if they had clinically determined stage 1 disease, defined as having no physical examination findings or radiographical suspicion of extrauterine disease. There was no age limit for eligibility. Patients were included in the study if they met the performance status and life expectancy to tolerate a surgical staging procedure. Patients who were pregnant based on urine choriogonadotropin assessments were excluded. **Exclusion criteria:** Patients were excluded if they had evidence of extrauterine disease, had undergone previous hysterectomy or treatment for their endometrial cancer (such as radiotherapy, chemotherapy, or hormonal therapy), had received a previous retroperitoneal surgery or lymphadenectomy, or had contraindications for receiving the ICG tracer, including a history of hepatic impairment or an iodine allergy. If patients were recognised to have gross extra-uterine disease at the time of surgery after tracer injection, they were ineligible for the sentinel-lymph-node mapping	with sentinel lymph node results compared with nonsentinel lymph node results within the same patient. **Comparison:** Complete lymphadenectomy as gold standard

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017		
Notes:	Oxford CEBM Level of Evidence 2011: Prospective Cohort Study Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens Intention to treat analysis was performed **Author's conclusion:** Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.	
Outcome Measures/results	**Primary** Sensitivity and negative predictive value **Secondary**	**Results:** Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Sentinel-lymph-node mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97·2% (95% CI 85·0–100), and a negative predictive value of 99·6% (97·9–100). The most common grade 3–4 adverse events or serious adverse events were postoperative neurological disorders (4 patients) and postoperative respiratory distress or failure (4 patients). 22 patients had serious adverse events, with one related to the study intervention: a ureteral injury incurred during sentinel-lymph-node dissection.

2.25. Schlüsselfrage 28: Ist beim Endometriumkarzinom Typ II die systematische pelvine bzw. pelvine plus paraaortale Lymphonodektomie (LNE) sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *7 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Bogani, G. 2020	4	Retrospective cohort study
Bogani, G. 2019	4	Systematic Review and Meta-Analysis (5 studies, 3536 patients)
Kogan, L. 2020	4	Retrospective Cohort study
Rossi, E. C. 2017	2	Prospective cohort study
Schlappe, B. A. 2020	4	Retrospective cohort study
Wang, L. 2018	3	Systematic Review and Meta-Analysis (8 studies, 366 patients) To explore sentinel lymph node mapping in laparoscopy surgery in EC

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *3 Bewertung(en)*

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic Review	**Population:** Patients with endometrial cancer	**Primary:** Positive node detection rate, survival outcomes (overall survival and disease free survival)	5 studies (3536 patients) included: Eriksson 2015,

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
and Meta-Analysis (5 studies, 3536 patients) **Databases:** Pubmed, Scopus, Web of Sciences, Clinicaltrials.gov **Search period:** Inception to December 2018 **Inclusion Criteria:** Comparative studies, English language, and >10 cases **Exclusion Criteria:** Case reports, in vitro or cadaveric studies, technical notes, review articles not reporting original data, duplicate publications, and single arm studies	**Intervention:** Sentinel node mapping **Comparison:** Lymphadenectomy	**Secondary:** Mean operative time, mean blood loss, blood transfusion rate, procedure conversion rate, complication rate, in hospital stay, postoperative complications **Results:** Six comparative studies were included. Overall, 3536 patients were included: 1249 (35,3%) and 2287 (64,7%), undergoing sentinel node mapping and lymphadenectomy, respectively. Pooled data suggested that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03 (95% CI 1.30 – 3.18); p=0.002). No difference in detection of positive nodes located in the paraaortic was observed (OR: 0.93 (95% CI 0.30 to 2.18), p= 0.086). Overall recurrence rate was 4.3% and 7.3% after sentinel node mapping and lymphadenectomy, respectively (OR: 0.90 (95% CI 0.58 – 1.38), p = 0.63). Similarly, nodal recurrences were statistically similar between group (1.2% vs. 1.7%; OR 1.51 (95% CI 0.70 to 3.29), p=0.29). **Author's Conclusion:** In conclusion, our	Holloway 2016, Baiocchi 2017, Buda 2017, Ducie 2017, Buda 2018	

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019				
		meta-analysis underlines that sentinel node mapping is non-inferior to standard lymphadenectomy in term of detection of paraaortic nodal involvement and recurrence rates (any site and nodal recurrence); while, focusing on the ability to detect positive pelvic nodes, sentinel node mapping could be consider superior to lymphadenectomy. Further randomized studies are needed to assess long term effectiveness of sentinel node mapping.		
Methodical Notes				
Funding Sources: None. **COI:** None. **Study Quality:** Cochrane Collaboration Risks of Bias assessment tool was used to assess the quality of the included studies. Assessment of the study quality is displayed in the supplementary material, which is not accessible. **Heterogeneity:** Heterogeneity was measured using I2 statistic, in which I2 > 50% suggests high heterogeneity. High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%) **Publication Bias:** Publication bias was not investigated (less than ten studies included)				

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
Notes: Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of Retrospective cohort studies Downgraded to Level 4 due to methodical weakness: Inclusion criteria and Population were not described sufficiently No search for grey literature or reference lists was conducted. Non-English articles were excluded. Insufficient description of the performed searches. Publication bias was not investigated (less than ten studies included) High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%) Assessment of the study quality is displayed in the supplementary material, which is not accessible.			
Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis (8 studies, 366 patients) To explore sentinel lymph node mapping in laparoscopy surgery in EC **Databases:** Pubmed, Embase, Medline and the Cochrane Library	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage one or higher EC **Intervention:** Laparoscopy SLN mapping **Comparison:** Studies validated by	**Primary:** Detection rate and/or sensitivity. The sensitivity associated with the sentinel lymph node procedure was described as the total number of true positives in patients with a positive histopathology. The SLN detection rate can be defned as the percentage of patients in which at least one SLN was identifed.	8 studies (366 patients) included: Anne-Sophie 2008, Barranger 2009, Favero 2015, Taskin 2017, Holub 2004, Papadia 2016,

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018				
Search period: Inception to February 2018 **Inclusion Criteria:** (1) included ten or more women diagnosed with International Federation of Gynecology and Obstetrics stage one or higher EC; (2) Laparoscopy SLN mapping was the study's primary focus; (3) Studies validated by pelvic with/without parasitic lymph node dissection and pathological examination including H&E (hematoxylin–eosin) staining or immunohistochemistry (IHC) were taken as the reference standard; (4) Total number of included patients, as well as those with detected sentinel nodes were both reported; (6) Studies that reported the total number of patients with a positive lymph node diagnosis, as well as those with false negative results. (7) Articles published by the same author with the latest published **Exclusion Criteria:** We excluded studies with fewer than ten women with EC, as well as robot-assisted	pelvic with/without parasitic lymph node dissection and pathological examination including H&E (hematoxylin–eosin) staining or immunohistochemistry (IHC) were taken as the reference standard	**Secondary:** **Results:** The overall detection rate of sentinel lymph node mapping was included in 389 patients of 8 studies, ranging from 25 to 71 patients, which was 96% (95% confidence interval 95–98). 366 patients were included in bilateral sentinel node detection rate, ranging from 30 to 71 patients; it was 73% (95% confidence interval, 69–77). The sensitivity of the overall detection rate of sentinel lymph node mapping was 96.3% with a sensitivity of 73.1% bilateral sentinel node detection rate. **Author's Conclusion:** Laparoscopy sentinel lymph node localization is feasible and accurately predicts lymph node status in patients with EC. For patients with early stage clinical disease, it is very important to screen patients with no lymph node metastasis, reduce the range of surgical resection, reduce the incidence of the corresponding complications, and improve the quality of patients.	Ballester 2008, Vidal 2013	

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018				
surgery laparoscopy and meeting abstracts, reviews, case reports, or editorials				
Methodical Notes				
Funding Sources: **COI:** None **Study Quality:** Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool. **Heterogeneity:** Tests of heterogeneity were conducted to decide which method would be used to pool the results. Results were considered homogenous when the I2 statistic (the percentage of variance due to heterogeneity) was less than 50% and the p value for the test of heterogeneity was≥0.10, in these cases, a fixed-effect model was used to compute the pooled estimate of detection rate. In all other cases (I2>50% or p Overall detection rate of sentinel lymph node mapping (I2=91%), Bilateral sentinel node detection rate of sentinel lymph node mapping (I2=94%), **Publication Bias:** Egger's regression intercepts were used for the evaluation of publication bias. Publication bias is an important issue which should be addressed in all systematic reviews, funnel plots of detection rate and sensitivity pooling showed some asymmetry, although Egger's test was not statistically signifcant in either one, Egger's regression intercepts to make the was 0.043 (p important limitation **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review and Meta-Analysis of diagnostic non-consecutive studies or studies without consistently				

Wang, L. et al. Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer. Arch Gynecol Obstet. 298. 505-510. 2018			
applied reference standard. Downgraded to EL 3 due to methodical weakness: No search for grey literature, reference lists and unpublished articles was performed. Publication bias may be present Overall, the number of included patients was small Heterogeneity was present for the main outcomes overall detection rate of sentinel lymph node mapping (I2=91%), Bilateral sentinel node detection rate of sentinel lymph node mapping (I2=94%). Heterogeneity was not explained. Quality was assessed but the results were not reported			

NEWCASTLE - OTTAWA Checklist: Cohort: *4 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
	Dropout rates:	lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients. **Exclusion criteria:** Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3) presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	
Notes:	Oxford CEBM Level of Evidence: 4 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy. Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.		
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up	

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020			
		time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.	

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective Cohort study	**Funding sources:** This study was supported by grants from the Israel Cancer Research Fund, the Azrieli Foundation, the Gloria's Girls Fund, the Susan and Jonathan Wener Fund and the Anne-Marie and Mitch Garber Fund **Conflict of Interests:** None **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 343 **Recruiting Phase:** December 2007- September 2010 **Inclusion criteria:** Patients with endometrial cancer who underwent surgical staging **Exclusion criteria:** Patients with sarcomas or neoadjuvant chemotherapy were excluded	**Interventions:** All patients diagnosed from December 2007 until November 2010 underwent complete pelvic LND (LND cohort) **Comparison:** All patients from December 2010 until September 2014 underwent SLN mapping followed by complete pelvic LND (SLN cohort)

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020		
Notes:	Oxford CEBM Level of Evidence 2011: 4, Retrospective Cohort Study Retrospective evaluation of prospective gathered data Inclusion criteria were not described sufficiently No description of where patients were recruited Blinding not described **Author's conclusion:** Addition of SLN to LND was ultimately associated with improved clinical outcomes compared to LND alone in patients with endometrial cancer undergoing surgical staging, suggesting that the data provided by the analysis of the SLN added relevant clinical information and improved the decision on adjuvant therapy.	
Outcome Measures/results	**Primary** Positive and negative predictive value **Secondary**	**Results:** From 2007 to 2010, 193 patients underwent LND and from December 2010 to 2014, 250 patients had SLN mapping with completion LND. Both groups had similar clinical characteristics. During a median follow-up period of 6.9 years, addition of SLN was associated with more favorable oncological outcomes compared to LND with 6-year overall survival (OS) of 90% compared to 81% (p=0.009), and progression free survival (PFS) of 85% compared to 75% (p=0.01) respectively. SLN was associated with improved OS (HR 0.5, 95% CI 0.3 – 0.8, p=0.004) and PFS (HR 0.6, 95% CI 0.4-0.9, p=0.03) in a multivariable analysis, adjusted for age, ASA score, stage, grade, non-endometrioid histology, and LVSI. Patients who were staged with SLN were less likely to have a recurrence in the pelvis or lymph node basins compared to patients who underwent LND only (6-year recurrence-free survival 95% vs. 90%, p=0.04).

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 2 Study type: Prospective cohort study	**Funding sources:** Indiana University Health, Indiana University Health Simon Cancer Center, and the Indiana University Department of Obstetrics and Gynecology. **Conflict of Interests:** We declare no competing interests **Randomization:** **Blinding:** Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens **Dropout rates:** ITT analysis was performed	**Total no. patients:** 385 patients **Recruiting Phase:** Between Aug 1, 2012, and Oct 20, 2015 **Inclusion criteria:** Patients were eligible if they had documented endometrial cancer of any histology on pathology specimens from endometrial sampling, and if they had clinically determined stage 1 disease, defined as having no physical examination findings or radiographical suspicion of extrauterine disease. There was no age limit for eligibility. Patients were included in the study if they met the performance status and life expectancy to tolerate a surgical staging procedure. Patients who were pregnant based on urine choriogonadotropin assessments were excluded. **Exclusion criteria:** Patients were excluded if they had evidence of extrauterine disease, had undergone previous hysterectomy or treatment for their endometrial cancer (such	**Interventions:** Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Each patient served as their own control, with sentinel lymph node results compared with nonsentinel lymph node results within the same patient. **Comparison:** Complete lymphadenectomy as gold standard

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
		as radiotherapy, chemotherapy, or hormonal therapy), had received a previous retroperitoneal surgery or lymphadenectomy, or had contraindications for receiving the ICG tracer, including a history of hepatic impairment or an iodine allergy. If patients were recognised to have gross extra-uterine disease at the time of surgery after tracer injection, they were ineligible for the sentinel-lymph-node mapping	
Notes:	Oxford CEBM Level of Evidence 2011: Prospective Cohort Study Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens Intention to treat analysis was performed **Author's conclusion:** Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.		
Outcome Measures/results	**Primary** Sensitivity and negative predictive value **Secondary**	**Results:** Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Sentinel-lymph-node mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive	

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
		nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97·2% (95% CI 85·0–100), and a negative predictive value of 99·6% (97·9–100). The most common grade 3–4 adverse events or serious adverse events were postoperative neurological disorders (4 patients) and postoperative respiratory distress or failure (4 patients). 22 patients had serious adverse events, with one related to the study intervention: a ureteral injury incurred during sentinel-lymph-node dissection.

Schlappe, B. A. et al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. Gynecol Oncol. 156. 62-69. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	**Funding sources:** This study was funded in part through the NIH/NCI Support Grant P30 CA008748 (Drs. Nadeem R. Abu-Rustum and Mario M. Leitao Jr). **Conflict of Interests:** Outside the submitted work, Dr. Abu-Rustum reports grants from Stryker/Novadaq, Olympus, and GRAIL. Outside the submitted work, Dr. Leitao is an ad hoc speaker for Intuitive	**Total no. patients:** 214 patients **Recruiting Phase:** 2006 through 2013 (SLN cohort), and the Mayo Clinic database review encompassed the years 2004 through 2008 (LND cohort). **Inclusion criteria:** Patients with newly diagnosed, apparently uterine-confined serous or clear cell endometrial carcinoma with any	**Interventions:** SLN algorithm **Comparison:** Comprehensive pelvic and paraaortic LND

Schlappe, B. A. et al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. Gynecol Oncol. 156. 62-69. 2020			
	Surgical, Inc. The other authors have no potential conflicts to disclose. **Randomization:** No randomization **Blinding:** Not described **Dropout rates:**	degree of myometrial invasion **Exclusion criteria:**	
Notes:	Oxford CEBM Level of Evidence 2011: EL 4 Retrospective, cohort study Retrospective analysis Patients were recruited from two centers Adjuvant therapy differed between the cohorts Inclusion and exclusion criteria were not described Number of included patients was small Follow-up was relatively short (2.3 years) **Author's conclusion:** In conclusion, OS is not compromised with the use of an SLN algorithm in serous or clear cell endometrial cancer. In the cohort of patients with negative lymph nodes, OS was similar but RFS shorter with the use of the algorithm, despite more patients receiving adjuvant chemotherapy. This may be due to differences in surveillance between the two cohorts; however, more investigation is needed into this subgroup.		
Outcome Measures/results	**Primary** Three-year recurrence-free survival (RFS) and overall survival	**Results:** 214 patients were identified (118 SLN cohort, 96 LND cohort). Adjuvant therapy differed between the cohorts; 84% and 40% in the SLN and	

Schlappe, B. A. et al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. Gynecol Oncol. 156. 62-69. 2020		
	Secondary	LND cohorts, respectively, received chemotherapy ± radiation therapy. The IPTW-adjusted 3-year RFS rates were 69% and 80%, respectively. The IPTW-adjusted 3-year OS rates were 88% and 77%, respectively. The IPTW-adjusted hazard ratio (HR) for the association of surgical approach (SLN vs LND) with progression and death was 1.46 (95% CI: 0.70e3.04) and 0.44 (95% CI: 0.19e1.02), respectively. In the 168 node-negative cases, the IPTW-adjusted 3-year RFS rates were 73% and 91%, respectively. The IPTW-adjusted 3-year OS rates were 88% and 86%, respectively. In this subgroup, IPTW-adjusted HR for the association of surgical approach (SLN vs LND) with progression and death was 3.12 (95% CI: 1.02e9.57) and 0.69 (95% CI: 0.24e1.95), respectively.

2.26. Schlüsselfrage 29: Ist beim Endometriumkarzinom Typ II die SLN sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamtüberleben?

Inhalt: 7 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Bogani, G. 2020	4	Retrospective cohort study
Bogani, G. 2019	4	Systematic Review and Meta-Analysis (5 studies, 3536 patients)
Davidson, B. A. 2018	2	Randomized controlled trial
Kogan, L. 2020	4	Retrospective Cohort study
Rossi, E. C. 2017	3	Prospective cohort study
Schlappe, B. A. 2020	4	Retrospective cohort study

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic Review	**Population:** Patients with endometrial cancer	**Primary:** Positive node detection rate, survival outcomes (overall survival and disease free survival)	5 studies (3536 patients) included: Eriksson 2015,

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
and Meta-Analysis (5 studies, 3536 patients) **Databases:** Pubmed, Scopus, Web of Sciences, Clinicaltrials.gov **Search period:** Inception to December 2018 **Inclusion Criteria:** Comparative studies, English language, and >10 cases **Exclusion Criteria:** Case reports, in vitro or cadaveric studies, technical notes, review articles not reporting original data, duplicate publications, and single arm studies	**Intervention:** Sentinel node mapping **Comparison:** Lymphadenectomy	**Secondary:** Mean operative time, mean blood loss, blood transfusion rate, procedure conversion rate, complication rate, in hospital stay, postoperative complications **Results:** Six comparative studies were included. Overall, 3536 patients were included: 1249 (35,3%) and 2287 (64,7%), undergoing sentinel node mapping and lymphadenectomy, respectively. Pooled data suggested that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03 (95% CI 1.30 – 3.18); p=0.002). No difference in detection of positive nodes located in the paraaortic was observed (OR: 0.93 (95% CI 0.30 to 2.18), p= 0.086). Overall recurrence rate was 4.3% and 7.3% after sentinel node mapping and lymphadenectomy, respectively (OR: 0.90 (95% CI 0.58 – 1.38), p = 0.63). Similarly, nodal recurrences were statistically similar between group (1.2% vs. 1.7%; OR 1.51 (95% CI 0.70 to 3.29), p=0.29). **Author's Conclusion:** In conclusion, our	Holloway 2016, Baiocchi 2017, Buda 2017, Ducie 2017, Buda 2018	

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019				
		meta-analysis underlines that sentinel node mapping is non-inferior to standard lymphadenectomy in term of detection of paraaortic nodal involvement and recurrence rates (any site and nodal recurrence); while, focusing on the ability to detect positive pelvic nodes, sentinel node mapping could be consider superior to lymphadenectomy. Further randomized studies are needed to assess long term effectiveness of sentinel node mapping.		
Methodical Notes				
Funding Sources: None. **COI:** None. **Study Quality:** Cochrane Collaboration Risks of Bias assessment tool was used to assess the quality of the included studies. Assessment of the study quality is displayed in the supplementary material, which is not accessible. **Heterogeneity:** Heterogeneity was measured using I2 statistic, in which I2 > 50% suggests high heterogeneity. High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%) **Publication Bias:** Publication bias was not investigated (less than ten studies included)				

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of Retrospective cohort studies
Downgraded to Level 4 due to methodical weakness:
Inclusion criteria and Population were not described sufficiently
No search for grey literature or reference lists was conducted. Non-English articles were excluded. Insufficient description of the performed searches.
Publication bias was not investigated (less than ten studies included)
High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%)
Assessment of the study quality is displayed in the supplementary material, which is not accessible.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 120 **Recruitung Phase:** January 2009 and March 2015 **Inclusion Criteria:** Woman with high-grade EC on preoperative sampling (grade 3 endometrioid, clear cell, serous, carcinosarcoma or mixed histologies) who were appropriate surgical candidates and deemed medically eligible for a lymph node dissection **Exclusion Criteria:** Exclusion criteria were patients with low-grade histologies on preoperative assessment or advanced disease at diagnosis.	**Intervention:** Collection of LNs into nodal basin-specific containers on the randomized side **Comparison:** Simple labeling on the non-randomized side	**Primary:** Total number of LNs and total number of LNs with metastases on the randomized versus the nonrandomized side were compared. The remaining adipose tissue from each LN specimen was submitted for histologic examination. Wen analyzed the number of LNs with and without metastases identified from additional adipose tissue. **Secondary:** **Results:** Of 120 consented subjects, 56 had sufficient data for analysis. The additional adipose tissue contained 7.5 LNs per patient on average (range: 0-26). In 2/54 total cases (3.7%) and 2/5 cases with nodal metastases (40%), the additional adipose tissue contained LNs with metastases. In both cases, metastases were also detected in grossly identified LN candidates. The mean number of LNs identified was not significantly different based on method of collection (p=0.22). The mean number of LNs containing metastases per side was not significantly different (p=0.58). **Author's Conclusion:** Processing of adipose tissue does increase the total number of LNs identified, however, it does	

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
		not influence EC stage. No difference in LN counts was noted with basin-specific collection.	
Methodical Notes			
Funding Sources: Not stated **COI:** None **Randomization:** Randomization was performed using a random number generator with block randomization (block size 6) stratified by site. **Blinding:** No blinding **Dropout Rate/ITT-Analysis:** Not performed **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 No test for group differences Blinding was not performed Small number of patients included in the analysis. Nearly half of the patients initially consented were not included in the final analysis			

NEWCASTLE - OTTAWA Checklist: Cohort: *4 Bewertung(en)*

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 180 **Recruiting Phase:** 01/01 2006 and 12/31/2016 **Inclusion criteria:** Inclusion criteria were: (1) age > 18 years old, (2) execution of hysterectomy plus nodal dissection (including (1) lymphadenectomy, (2) SLNM followed by lymphadenectomy and (3) SLNM alone), (3) at least 3-year follow-up for non-recurring patients. **Exclusion criteria:** Exclusion criteria: (1) consent withdraw, (2) preoperative suspicious or intraoperative finding of bulky nodes, (3) presence of peritoneal disease (i.e., stage IV EC), (4) personal history of non-gynecological cancer.	**Interventions:** Lymphadenectomy, sentinel lymphe mapping followed by lymphadenectomy, SLNM alone **Comparison:**
Notes:	Oxford CEBM Level of Evidence: 4 Retrospective, cohort Study Multi-institutional retrospective cohort study **Author's conclusion:** Our study highlighted that SLNM provides similar long-term oncologic outcomes than lymphadenectomy.		

Bogani, G. et al. Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis. Gynecol Oncol. 158. 77-83. 2020		
	Further evidence is warranted to assess the prognostic value of low-volume disease detected by ultrastaging in patients following SLNM.	
Outcome Measures/results	**Primary** Long-term survival, adverse events, prevalence of nodal involvement and low volume disease **Secondary**	**Results:** Applying a propensity score matching algorithm we selected 180 patients having SLNM (90 SLNM vs. 90 SLNM followed by lymphadenectomy). Additional, a control group of 180 patients having a lymphadenectomy was selected using the same criteria. Overall, 10% of patients were diagnosed with positive nodes. Low volume disease was observed in 16 cases (5 micrometastasis and 11 isolated tumor cells). Patients having SLNM followed by lymphadectonomy had a higher possibility to be diagnosed with a stage IIIC disease in comparison to lymphadenectomy alone (p=0.02); while we did not observe difference in the diagnostic value of SLNM followed by lymphadenectomy and SLNM (p=0.389). Median follow-up time was 69 months (range 7-206). The survival analysis comparing the three techniques did not show statistical differences in terms disease-free (p=0.579, log-rank test) and overall survival (p=0.911, log-rank test). Similarly, they did not impact on survival outcomes after stratification by low, intermediate and high risk patients.

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study**	**Funding sources:** This study was supported by grants from the Israel Cancer Research Fund, the Azrieli Foundation, the Gloria's Girls Fund, the Susan and Jonathan Wener Fund and the	**Total no. patients:** 343 **Recruiting Phase:** December 2007- September 2010	**Interventions:** All patients diagnosed from December 2007 until November 2010 underwent complete pelvic LND (LND cohort)

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020			
type: Retrospective Cohort study	Anne-Marie and Mitch Garber Fund **Conflict of Interests:** None **Randomization:** **Blinding:** **Dropout rates:**	**Inclusion criteria:** Patients with endometrial cancer who underwent surgical staging **Exclusion criteria:** Patients with sarcomas or neoadjuvant chemotherapy were excluded	**Comparison:** All patients from December 2010 until September 2014 underwent SLN mapping followed by complete pelvic LND (SLN cohort)
Notes:	Oxford CEBM Level of Evidence 2011: 4, Retrospective Cohort Study Retrospective evaluation of prospective gathered data Inclusion criteria were not described sufficiently No description of where patients were recruited Blinding not described **Author's conclusion:** Addition of SLN to LND was ultimately associated with improved clinical outcomes compared to LND alone in patients with endometrial cancer undergoing surgical staging, suggesting that the data provided by the analysis of the SLN added relevant clinical information and improved the decision on adjuvant therapy.		
Outcome Measures/results	**Primary** Positive and negative predictive value **Secondary**	**Results:** From 2007 to 2010, 193 patients underwent LND and from December 2010 to 2014, 250 patients had SLN mapping with completion LND. Both groups had similar clinical characteristics. During a median follow-up period of 6.9 years, addition of SLN was associated with more favorable oncological outcomes compared to LND with 6-year overall survival (OS) of 90% compared to 81% (p=0.009), and progression free survival (PFS) of 85% compared to 75%	

Kogan, L. et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 158. 84-91. 2020			
		(p=0.01) respectively. SLN was associated with improved OS (HR 0.5, 95% CI 0.3 – 0.8, p=0.004) and PFS (HR 0.6, 95% CI 0.4-0.9, p=0.03) in a multivariable analysis, adjusted for age, ASA score, stage, grade, non-endometrioid histology, and LVSI. Patients who were staged with SLN were less likely to have a recurrence in the pelvis or lymph node basins compared to patients who underwent LND only (6-year recurrence-free survival 95% vs. 90%, p=0.04).	

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study type: Prospective cohort study	**Funding sources:** Indiana University Health, Indiana University Health Simon Cancer Center, and the Indiana University Department of Obstetrics and Gynecology. **Conflict of Interests:** We declare no competing interests **Randomization:** **Blinding:** Pathologists were not blinded to the results of the H&E	**Total no. patients:** 385 patients **Recruiting Phase:** Between Aug 1, 2012, and Oct 20, 2015 **Inclusion criteria:** Patients were eligible if they had documented endometrial cancer of any histology on pathology specimens from endometrial sampling, and if they had clinically determined stage 1 disease, defined as having no physical examination findings or radiographical suspicion of extrauterine disease. There was no age limit for eligibility. Patients were included in the study if they	**Interventions:** Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Each patient served as their own control, with sentinel lymph node results compared with nonsentinel lymph node results within the same patient. **Comparison:** Complete lymphadenectomy as gold standard

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017			
	staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens **Dropout rates:** ITT analysis was performed	met the performance status and life expectancy to tolerate a surgical staging procedure. Patients who were pregnant based on urine choriogonadotropin assessments were excluded. **Exclusion criteria:** Patients were excluded if they had evidence of extrauterine disease, had undergone previous hysterectomy or treatment for their endometrial cancer (such as radiotherapy, chemotherapy, or hormonal therapy), had received a previous retroperitoneal surgery or lymphadenectomy, or had contraindications for receiving the ICG tracer, including a history of hepatic impairment or an iodine allergy. If patients were recognised to have gross extra-uterine disease at the time of surgery after tracer injection, they were ineligible for the sentinel-lymph-node mapping	
Notes:	Oxford CEBM Level of Evidence 2011: Prospective Cohort Study Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens Intention to treat analysis was performed		

Rossi, E. C. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18. 384-392. 2017		
	Author's conclusion: Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.	
Outcome Measures/results	**Primary** Sensitivity and negative predictive value **Secondary**	**Results:** Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Sentinel-lymph-node mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97·2% (95% CI 85·0–100), and a negative predictive value of 99·6% (97·9–100). The most common grade 3–4 adverse events or serious adverse events were postoperative neurological disorders (4 patients) and postoperative respiratory distress or failure (4 patients). 22 patients had serious adverse events, with one related to the study intervention: a ureteral injury incurred during sentinel-lymph-node dissection.

Schlappe, B. A. et al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. Gynecol Oncol. 156. 62-69. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study**	**Funding sources:** This study was funded in part through the NIH/NCI Support Grant P30 CA008748 (Drs. Nadeem R. Abu-	**Total no. patients:** 214 patients **Recruiting Phase:** 2006 through	**Interventions:** SLN algorithm

Schlappe, B. A. et al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. Gynecol Oncol. 156. 62-69. 2020			
type: Retrospective cohort study	Rustum and Mario M. Leitao Jr). **Conflict of Interests:** Outside the submitted work, Dr. Abu-Rustum reports grants from Stryker/Novadaq, Olympus, and GRAIL. Outside the submitted work, Dr. Leitao is an ad hoc speaker for Intuitive Surgical, Inc. The other authors have no potential conflicts to disclose. **Randomization:** No randomization **Blinding:** Not described **Dropout rates:**	2013 (SLN cohort), and the Mayo Clinic database review encompassed the years 2004 through 2008 (LND cohort). **Inclusion criteria:** Patients with newly diagnosed, apparently uterine-confined serous or clear cell endometrial carcinoma with any degree of myometrial invasion **Exclusion criteria:**	**Comparison:** Comprehensive pelvic and paraaortic LND
Notes:	Oxford CEBM Level of Evidence 2011: EL 4 Retrospective, cohort study Retrospective analysis Patients were recruited from two centers Adjuvant therapy differed between the cohorts Inclusion and exclusion criteria were not described Number of included patients was small Follow-up was relatively short (2.3 years)		

Schlappe, B. A. et al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. Gynecol Oncol. 156. 62-69. 2020		
	Author's conclusion: In conclusion, OS is not compromised with the use of an SLN algorithm in serous or clear cell endometrial cancer. In the cohort of patients with negative lymph nodes, OS was similar but RFS shorter with the use of the algorithm, despite more patients receiving adjuvant chemotherapy. This may be due to differences in surveillance between the two cohorts; however, more investigation is needed into this subgroup.	
Outcome Measures/results	**Primary** Three-year recurrence-free survival (RFS) and overall survival **Secondary**	**Results:** 214 patients were identified (118 SLN cohort, 96 LND cohort). Adjuvant therapy differed between the cohorts; 84% and 40% in the SLN and LND cohorts, respectively, received chemotherapy ± radiation therapy. The IPTW-adjusted 3-year RFS rates were 69% and 80%, respectively. The IPTW-adjusted 3-year OS rates were 88% and 77%, respectively. The IPTW-adjusted hazard ratio (HR) for the association of surgical approach (SLN vs LND) with progression and death was 1.46 (95% CI: 0.70e3.04) and 0.44 (95% CI: 0.19e1.02), respectively. In the 168 node-negative cases, the IPTW-adjusted 3-year RFS rates were 73% and 91%, respectively. The IPTW-adjusted 3-year OS rates were 88% and 86%, respectively. In this subgroup, IPTW-adjusted HR for the association of surgical approach (SLN vs LND) with progression and death was 3.12 (95% CI: 1.02e9.57) and 0.69 (95% CI: 0.24e1.95), respectively.

2.27. Schlüsselfrage 30: Ist bei Karzinosarkomen die systematische pelvine bzw. pelvine plus paraaortale Lymphonodektomie (LNE) sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Frost, J. A. 2017	1	Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.
Versluis, M. A. C. 2018	3	Retrospective Cohort Study

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase **Search period:** Inception to June 2017 **Inclusion Criteria:** RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer.	**Population:** Adult women diagnosed with endometrial cancer **Intervention:** Pelvic lymphadenectomy versus no lymphadenectomy Pelvic lymphadenectomy versus pelvic lymph node sampling Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy Removal of bulky pelvic lymph nodes versus no removal of lymph nodes **Comparison:**	**Primary:** Overall survival (OS) **Secondary:** Progression-free survival (PFS) QOL measured by a validated scale Adverse events, for example, direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection); surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism) cardiac events (cardiac ischaemia and cardiac failure) cerebrovascular accident recovery: delayed discharge, unscheduled re-admission lymphoedema and lymphocyst formation; other side effects not categorised above. **Results:** 978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria;	3 studies included: Fayallah 2011, Kitchener 2009, Panici 2008

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
Exclusion Criteria: We excluded cross-over trials and clusterrandomised trials, women with other concurrent malignancies.		for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence). We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst		

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
		formation, respectively) (1922 participants, two studies; high-quality evidence). **Author's Conclusion:** This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.		
Methodical Notes				
Funding Sources: None **COI:** None **Study Quality:** We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. **Heterogeneity:** We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between				

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017
trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this. The two trials included in the meta-analysis showed no heterogeneity (I2 = 0). **Publication Bias:** Not investigated, because only three studies were included **Notes:** Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs Update of an previous Cochrane Review

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Retrospective Cohort Study	Funding sources: n.s. Conflict of Interests: None Randomization: - Blinding: -	**Total no. patients:** 1.140 patients diagnosed with UCS undergoing primary surgery with a curative intent - from the Netherlands Cancer Registry (NCR) and PALGA (Nationwide Network and registry of histo- and cytopathology in the Netherlands. **Recruiting Phase:** January 1, 1993, and December 31, 2012.	**Interventions:** LND with or without RT and/or CT LND was defined as the removal of any number of nodes.

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018			
	Dropout rates: -	**Inclusion criteria:** Patients diagnosed with uterine carcinoma as identified by corresponding ICD-O-3 codes (C54; C55 combined with morphological code 8950, 8951, or 8980) **Exclusion criteria:** Patients who did not undergo primary surgery defined as TAH-BSO with or without LND.	**Comparison:** see intervention.
Notes:	Oxford CEBM Level of Evidence: EL 3 (Non-randomized cohort) Limitations: -Patients are noch equally distributed over the analyzed groups, this may influence the results. - only one cohort group (not a cohort study in the original design) **Author's conclusion:** Conclusion: LND is related to improved survival when more than 10 nodes are removed. Adjuvant therapy improves survival when LND is omitted, or when nodes are positive.		
Outcome Measures/results	**Primary** Overall survival (OS) was defined as the time until death, with a maximum of 5 years. Disease free survival (DFS) was defined as the time until recurrence or death, with a maximum of 5 years.	**Results:** Median age at diagnosis was 70 years. The majority (64%) of the patients was diagnosed with early-stage disease (FIGO stage 1–2). The median number of nodes removed was 12 (IQR 3–18). LND was related to higher FIGO stage and age below 70 years ($p < 0.001$). 622 patients received adjuvant treatment (77.8% received RT, 16.7% received CT, and 5.5% received RCT).	

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018		
	Secondary -	Survival analysis: Multivariant analysis (Corrected for adjuvant therapy, FIGO stage, age below/above 70 years, myometrial invasion, and distant metastasis) LND >10 was an independent predictor of OS (HR 0.65, 95% CI 0.48–0.87). LND ≤10 was not related to OS (HR 0.83, 95% CI 0.65–1.05). Adjuvant therapy was also related to improved OS. RT and CT had similar HRs of 0.64 (95% CI 0.54–0.75) and 0.65 (95% CI 0.48–0.88), respectively. RCT had an HR of 0.25 (95% CI 0.13–0.46). The results were similar for DFS, with LND > 10 and adjuvant treatment related to improved DFS. Stratified by lymph node status: Adjuvant treatment was not related to OS when the nodes were negative. Positive nodes: adjuvant treatment was related to improved OS, with an HR of 0.17 (95% CI 0.07–0.39) for RT, an HR of 0.40 (95% CI 0.19– 0.84) for CT, and an HR of 0.04 (95% CI 0.03–0.18) for RCT.

2.28. Schlüsselfrage 31: Ist bei Karzinosarkomen die SLN sinnvoll, wenn makroskopisch Tumorfreiheit erzielt werden kann im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Body, N. 2018	4	Retrospective Cohort Study
Cusimano, M. C. 2021	3	Prospective multicenter cohort study
Frost, J. A. 2017	1	Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.
Versluis, M. A. C. 2018	3	Retrospective Cohort Study

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase **Search period:** Inception to June 2017 **Inclusion Criteria:** RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer.	**Population:** Adult women diagnosed with endometrial cancer **Intervention:** Pelvic lymphadenectomy versus no lymphadenectomy Pelvic lymphadenectomy versus pelvic lymph node sampling Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy Removal of bulky pelvic lymph nodes versus no removal of lymph nodes **Comparison:**	**Primary:** Overall survival (OS) **Secondary:** Progression-free survival (PFS) QOL measured by a validated scale Adverse events, for example, direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection); surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism) cardiac events (cardiac ischaemia and cardiac failure) cerebrovascular accident recovery: delayed discharge, unscheduled re-admission lymphoedema and lymphocyst formation; other side effects not categorised above. **Results:** 978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria;	3 studies included: Fayallah 2011, Kitchener 2009, Panici 2008

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
Exclusion Criteria: We excluded cross-over trials and clusterrandomised trials, women with other concurrent malignancies.		for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence). We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst		

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
		formation, respectively) (1922 participants, two studies; high-quality evidence). **Author's Conclusion:** This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.		
Methodical Notes				
Funding Sources: None **COI:** None **Study Quality:** We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. **Heterogeneity:** We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between				

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017

trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this. The two trials included in the meta-analysis
showed no heterogeneity (I2 = 0).

Publication Bias: Not investigated, because only three studies were included

Notes:
Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs
Update of an previous Cochrane Review

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective Cohort Study	**Number of patients / samples:** 119 patients with endometrial cancer **Reference standard:** No reference standard **Validation:** Detection rate, sensitivity and negative predictive value (NPV) **Blinding:** Not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	**Results:** Sentinel lymph node mapping with Indocyanin green A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection (p = 0.01). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymphe node. **Author conclusions:** ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection (p = 0.01). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.		
Methodical Notes				

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018		
Funding Sources: Not stated. COI: None. Notes: Oxford CEBM Level of Evidence 2011: EL 4 Retrospective cohort study without blinding or reference standard Articles submitted by hand search.		
Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective multicenter cohort study	**Number of patients / samples:** 156 patients **Reference standard:** Lymphadenectomy as the reference standard **Validation:** Sensitivity of the SLNB algorithm in detecting metastatic disease, False negative rate and negative predictive value Additional measures of diagnostic accuracy, sentinel lymph node detection rates, and adverse events	**Results:** Performance characteristics of Sentinel Lymph Node Biopsy (SLNB) using indocyanine green (ICG) The study enrolled 156 patients (median age, 65.5 years; range, 40-86 years; median body mass index [calculated as weight in kilograms divided by height in meters squared], 27.5; range, 17.6-49.3), including 126 with high-grade EC. All patients underwent SLNB and PLND, and 101 patients (80%) with high-grade EC also underwent PALND. Sentinel lymph node detection rates were 97.4%per patient (95%CI, 93.6%-99.3%), 87.5%per hemipelvis (95%CI, 83.3%-91.0%), and 77.6%bilaterally (95%CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the SLNB algorithm, yielding a sensitivity of 96%(95%CI, 81%-100%), a false-negative rate of 4%(95%CI,

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021				
	Blinding: Blinding was not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	0%-19%), and a negative predictive value of 99%(95%CI, 96%-100%). Only 1 patient (0.6%) was misclassified by the SLNB algorithm. Seven of 27 patients with node-positive cancer (26%) were identified outside traditional PLND boundaries or required immunohistochemistry for diagnosis. **Author conclusions:** In this study, SLNB had acceptable diagnostic accuracy compared with lymphadenectomy for the detection of nodal metastatic disease in high-grade EC. On the basis of this study and the existing literature, SLNB appears to be a viable option for the surgical staging of both low- and high-grade EC.		
Methodical Notes				
Funding Sources: Dr Clarke reported receiving personal fees from AstraZeneca outside the submitted work. No other disclosures were reported. **COI:** This study was supported by the Princess Margaret Cancer Foundation of Princess Margaret Cancer Centre (Toronto, Ontario) and the McArthur Research Fund of the Department of Obstetrics and Gynecology at the University of Toronto (Toronto, Ontario). Dr Cusimano is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship and American College of Surgeons Resident Research Scholarship. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Prospective cohort study with consistently applied reference standard but without blinding** Article submitted by hand search.				

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021

Limitations:
-Blinding was not performed

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Retrospective Cohort Study	Funding sources: n.s. Conflict of Interests: None Randomization: - Blinding: - Dropout rates: -	**Total no. patients:** 1.140 patients diagnosed with UCS undergoing primary surgery with a curative intent - from the Netherlands Cancer Registry (NCR) and PALGA (Nationwide Network and registry of histo- and cytopathology in the Netherlands. **Recruiting Phase:** January 1, 1993, and December 31, 2012. **Inclusion criteria:** Patients diagnosed with uterine carcinoma as identified by corresponding ICD-O-3 codes (C54; C55 combined with morphological code 8950, 8951, or 8980)	**Interventions:** LND with or without RT and/or CT LND was defined as the removal of any number of nodes. **Comparison:** see intervention.

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018			
		Exclusion criteria: Patients who did not undergo primary surgery defined as TAH-BSO with or without LND.	
Notes:	Oxford CEBM Level of Evidence: EL 3 (Non-randomized cohort) Limitations: -Patients are noch equally distributed over the analyzed groups, this may influence the results. - only one cohort group (not a cohort study in the original design) **Author's conclusion:** Conclusion: LND is related to improved survival when more than 10 nodes are removed. Adjuvant therapy improves survival when LND is omitted, or when nodes are positive.		
Outcome Measures/results	**Primary** Overall survival (OS) was defined as the time until death, with a maximum of 5 years. Disease free survival (DFS) was defined as the time until recurrence or death, with a maximum of 5 years. **Secondary** -	**Results:** Median age at diagnosis was 70 years. The majority (64%) of the patients was diagnosed with early-stage disease (FIGO stage 1–2). The median number of nodes removed was 12 (IQR 3–18). LND was related to higher FIGO stage and age below 70 years ($p < 0.001$). 622 patients received adjuvant treatment (77.8% received RT, 16.7% received CT, and 5.5% received RCT). Survival analysis: Multivariant analysis (Corrected for adjuvant therapy, FIGO stage, age below/above 70 years, myometrial invasion, and distant metastasis) LND >10 was an independent predictor of OS (HR 0.65, 95% CI 0.48–0.87). LND ≤10 was not related to OS (HR 0.83, 95% CI 0.65–1.05). Adjuvant therapy was also related to improved OS.	

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018		
		RT and CT had similar HRs of 0.64 (95% CI 0.54–0.75) and 0.65 (95% CI 0.48–0.88), respectively. RCT had an HR of 0.25 (95% CI 0.13–0.46). The results were similar for DFS, with LND > 10 and adjuvant treatment related to improved DFS. Stratified by lymph node status: Adjuvant treatment was not related to OS when the nodes were negative. Positive nodes: adjuvant treatment was related to improved OS, with an HR of 0.17 (95% CI 0.07–0.39) for RT, an HR of 0.40 (95% CI 0.19– 0.84) for CT, and an HR of 0.04 (95% CI 0.03–0.18) for RCT.

2.29. Schlüsselfrage 32: Wie sollte beim Endometriumkarzinom eine LNE durchgeführt werden, um eine Verbesserung zu erreichen im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Frost, J. A. 2017	1	Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer.
Guo, W. 2018	3	Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis
Wright, J. D. 2016	4	Retrospective cohort study
Zheng, Y. 2019	4	Retrospective cohort study (SEER database)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis To evaluate the effectiveness and safety of lymphadenectomy for the management of endometrial cancer. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase **Search period:** Inception to June 2017 **Inclusion Criteria:** RCTs and quasi-RCTs that compared lymphadenectomy versus no lymphadenectomy in adult women diagnosed with endometrial cancer.	**Population:** Adult women diagnosed with endometrial cancer **Intervention:** Pelvic lymphadenectomy versus no lymphadenectomy Pelvic lymphadenectomy versus pelvic lymph node sampling Pelvic and para-aortic lymphadenectomy versus no lymphadenectomy Pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy Removal of bulky pelvic lymph nodes versus no removal of lymph nodes **Comparison:**	**Primary:** Overall survival (OS) **Secondary:** Progression-free survival (PFS) QOL measured by a validated scale Adverse events, for example, direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel (or colon); presence and complications of adhesions; febrile morbidity; intestinal obstruction; haematoma; local infection); surgery-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism) cardiac events (cardiac ischaemia and cardiac failure) cerebrovascular accident recovery: delayed discharge, unscheduled re-admission lymphoedema and lymphocyst formation; other side effects not categorised above. **Results:** 978 unique references were identified via the search strategy. All but 50 were excluded by title and abstract screening. Three RCTs met the inclusion criteria;	3 studies included: Fayallah 2011, Kitchener 2009, Panici 2008

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
Exclusion Criteria: We excluded cross-over trials and clusterrandomised trials, women with other concurrent malignancies.		for one small RCT, data were insufficient for inclusion in the meta-analysis. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. Results of the meta-analysis remained unchanged from the previous versions of this review and indicated no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43; HR 1.23, 95% CI 0.96 to 1.58 for overall and recurrence-free survival, respectively) (1851 participants, two studies; moderate-quality evidence). We found no difference in risk of direct surgical morbidity between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. However, women who underwent lymphadenectomy had a significantly higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formation than those who did not undergo lymphadenectomy (RR 3.72, 95% CI 1.04 to 13.27; RR 8.39, 95% CI 4.06 to 17.33 for risk of surgery-related systemic morbidity and lymphoedema/lymphocyst		

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017				
		formation, respectively) (1922 participants, two studies; high-quality evidence). **Author's Conclusion:** This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.		
Methodical Notes				
Funding Sources: None **COI:** None **Study Quality:** We assessed risk of bias in included RCTs by using the Cochrane 'risk of bias' tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. The two RCTs included in the analysis randomly assigned 1945 women, reported HRs for survival adjusted for prognostic factors and based on 1851 women and had an overall low risk of bias, as they satisfied four of the assessment criteria. The third study had an overall unclear risk of bias, as information provided was not adequate concerning random sequence generation, allocation concealment, blinding, or completeness of outcome reporting. **Heterogeneity:** We assessed heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between				

Frost, J. A. et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 10. Cd007585. 2017			
trials that could not be ascribed to sampling variation (Higgins 2003), by conducting a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by performing subgroup analyses (see below). If we found evidence of substantial heterogeneity, we investigated and reported possible reasons for this. The two trials included in the meta-analysis showed no heterogeneity (I2 = 0). **Publication Bias:** Not investigated, because only three studies were included **Notes:** Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs Update of an previous Cochrane Review			

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies The aim of this work is to evaluate the survival benefits or risks in endometrial cancer patients who underwent surgical staging with or without para-aortic lymphadenectomy using meta-analysis **Databases:** PubMed, Embase, and	**Population:** Patients with endometrial cancer **Intervention:** Pelvic lymphadenectomy (PLND) **Comparison:** Pelvic and para-aortic	**Primary:** Overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS) **Secondary:** **Results:** Eight studies with a total of 2793 patients were included. OS was significantly longer in PPaLND group than in	8 retrospective cohort studies (2793 patients): Eggemann 2016, Toptas 2015, Tong 2011, Todo 2010, Chang 2008, May 2013, Okazawa 2012, Fujimoto 2007

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018				
Cochrane Library **Search period:** n January 1, 1990, and January 1, 2017 **Inclusion Criteria:** Studies exploring endometrial cancer; studies comparing 2 treatment modalities and reporting overall survival (OS)/progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS)/disease-related survival (DRS); studies providing hazard ratio (HR) directly or key information to calculate HR indirectly, such as Kaplan-curves and original survival data **Exclusion Criteria:** Abstracts of meetings, duplicate publication, review articles, and case reports; studies explored new surgical techniques or evaluated operation outcomes without comparison of survival effects; and full text or valid data not accessed. To avoid overlapping patient data in publications on the same cohort, we included articles with the latest data.	lymphadenectomy (PPaLND)	pelviclymphadenectomy (PLND) group for patients with endometrial cancer [HR 0.68; 95% confidence interval (CI) 0.55–0.84, P lower .001 i subgroup analysis by recurrence risk explored the same association in patients at intermediate- or high-risk ci p but not for low-risk ppalnd with systematic resection of all para-aortic nodes up to renal vein also improved pfs compared plnd. **Author's Conclusion:** PPaLND is associated with favorable survival outcomes in endometrial cancer patients with intermediate- or high-risk of recurrence compared with PLND, particularly with regards to OS. PPaLND with systematic resection of all para-aortic nodes up to renal vein also improve PFS compared with PLND. Further large-scale randomized clinical trials are required to validate our findings.		

Guo, W. et al. Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis. Medicine (Baltimore). 97. e9520. 2018

Methodical Notes

Funding Sources: This study was funded by National Natural Science Foundation of China (grant number: 81201720).

COI: None.

Study Quality: Quality assessments were performed according to the Newcastle– Ottawa Quality Assessment Scale (NOS),[19] which contains 3 aspects: selection, comparability, and outcome. The quality score ranged from 7 to 9 with a median score of 8 for all cohort studies, which suggested the relatively high quality of the studies included in the meta-analysis

Heterogeneity: Forest plots were generated for graphical presentations, and heterogeneity among different studies was appraised by Q statistics and I 2 estimates. Fixed effects model was conducted to aggregate data if there were no statistical heterogeneity (I 2

Publication Bias: Publication bias was examined using Begg funnel plot and Egger linear regression test. Two-sided P lower .05 was considered statistically significant. no publication bias observed among included studies.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of retropective cohort studies

No search for grey literature or unpublished articles was performed
Heterogeneity was present for some analyses, but the authors are aware of this and performed sub-group analyses to explore the heterogeneity.
Overall, the quality of the included studies was considered as high by the authors, but details of the quality assessment are not described.

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	**Funding sources:** Not described **Conflict of Interests:** The authors did not report any potential conflicts of interest. **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 151,089 women **Recruiting Phase:** 1998-2011 **Inclusion criteria:** Women with endometrioid adenocarcinoma of the endometrium diagnosed from 1998–2011 who underwent hysterectomy were selected. **Exclusion criteria:** Patient who received preoperative radiation and those who had another primary tumor prior to the diagnosis of uterine cancer were excluded. Women with primary tumor spread beyond the uterus (>T2) or metastatic disease were excluded.	**Interventions:** Lymphadenectomy **Comparison:** No Lymphadenectomy
Notes:	Oxford CEBM Level of Evidence 2011: EL 4 Retrospective, cohort study Retrospective analysis of a national wide cancer database Funding sources were not described **Author's conclusion:** Lymphadenectomy is associated with a modest, if any, effect on survival for women with endometrial cancer.		

Wright, J. D. et al. Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer. Obstet Gynecol. 127. 109-18. 2016		
Outcome Measures/results	Primary Overall survival Secondary	**Results:** A total of 151,089 women treated at 1336 hospitals were identified; 99,052 (65.6%) patients underwent lymphadenectomy while 52,037 (34.4%) did not. In a multivariable regression model, lymphadenectomy was associated with a 16% reduction in mortality (HR=0.84; 95% CI, 0.81–0.87). The results were similar after adjustment for adjuvant therapy (HR=0.85; 95% CI, 0.82–0.87). The results were largely unchanged and suggested that lymphadenectomy was associated with improved survival after application of a propensity score analysis. In contrast, in the instrumental variable analysis there was not a statistically significant association between lymphadenectomy and survival (HR=0.75; 95% CI, 0.53–1.06), even after adjustment for adjuvant treatment (HR=0.76; 95% CI, 0.54–1.06). The results were unchanged for women with T1A and T1B tumors.

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study (SEER database)	**Funding sources:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.	**Total no. patients:** 103,103 patients with endometrial cancer identified from the SEER database of the National Cancer Institute (USA) were identified. Analysed were 11.603 patients. **Recruiting Phase:** 2004-2013 **Inclusion criteria:** Patients with endometrium as the primary site and	**Interventions:** Lymphadenectomy (total hysterectomy – with/without bilateral salpingo-oophorectomy) **Comparison:** -

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
	Conflict of Interests: see funding surces **Randomization:** - **Blinding:** - **Dropout rates:** -	endometrial cancer malignancy as the disease classification; grade 1 endometrial cancer; focused on early-stage endometrial cancer, in which total hysterectomy – with/without bilateral salpingo-oophorectomy – is the most common type of surgery. **Exclusion criteria:** Patients with more than one primary site, only a clinical diagnosis, other disease stages and survival times less than 3 months.	
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective, cohort study) Limitations: - The authors stated, that the lack of significance after matching may be due to the small number of patients after matching. - high loss rate (not specified by the authors) - some relevant medical information (depth of myometrial invasion, time to recurrence, and subsequent surgical and medical therapies) are noch available due to the retrospective approach - number of patients for lymph node biopsies ist very small - only one cohort (patient group)- not a cohort study in the original meaning. **Author's conclusion:** In conclusion, using SEER database, we found that for all stage IA patients, most patients died of cardiovascular disease (27%) and diabetes (8%); lymphadenectomy has no influence on survival and sentinel lymph node biopsies can reduce the number of lymph node removed but have no effect in survival. Given that practice patterns have shifted in the		

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
	world to predominantly sentinel node biopsy, we think our manuscript applicable to current clinical practice	
Outcome Measures/results	**Primary** Survival **Secondary** cause of death spectrum, the effect of sentinel lymph node biopsy and adjuvant therapies.	**Results:** Mean age at diagnosis was 56.5 years old. 22.83% of the women analyzed died from endometrial cancer; other sources were: cardiovascular disease (27%), diabetes (8%) and respiratory diseases (3%). But as the differentiation of the cancer became worse, more women died from the cancer. Overall survival - multivariant analysis: - age and grade were crucial factors in terms of survival, and a younger age and lower grade were associated with a better prognosis ($p < 0.0001$). - Asian women had better survival times than white women and black women ($p < 0.0001$) - no significant influence can be found for geographic region or number of removed lymph nodes. - lymphadenectomy can increase survival in grade 3/4 stage I patients ($p = 0.013$). **Sentinel lymph nodes biopsies:** Sentinel lymph nodes biopsy could reduce the number of lymph node removed (12 vs 6, $p = 8.387e-10$ in Wilcox test), but had no effect on survival (n=102 patients). Propensity score Matching: no difference was observed in survival between the lymphadenectomy group & the nonlymphadenectomy group ($p = 0.93$ and 0.65 respectively).

2.30. Schlüsselfrage 33: Wie sollte beim Endometriumkarzinom eine SLN durchgeführt werden, um eine Verbesserung zu erreichen im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *11 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Body, N. 2018	4	Retrospective Cohort Study
Bogani, G. 2019	4	Systematic Review and Meta-Analysis (5 studies, 3536 patients)
Cusimano, M. C. 2021	3	Prospective multicenter cohort study
Davidson, B. A. 2018	2	Randomized controlled trial
El-Agwany, A. S. 2018	3	Randomized Trial
Frumovitz, M. 2018	2	Randomized controlled phase 3 trial
Holloway, R. W. 2017	3	Prospective cohort study
Rocha, A. 2016	4	Systematic Review

Literaturstelle	Evidenzlevel	Studientyp
Rozenholc, A. 2019	2	Randomized controlled trial
Ruscito, I. 2016	3	Systematic Review and Meta-Analysis of retrospective and prospective studies The purpose of this meta-analysis was to compare the efficacy of ICG versus other conventional tracers (99Tc, blue dyes or a combination of the two) in terms of overall and bilateral detection rates and false negative rates, in cervical and endometrial cancer patients undergoing SLN mapping.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *4 Bewertung(en)*

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic Review	**Population:** Patients with endometrial cancer	**Primary:** Positive node detection rate, survival outcomes (overall survival and disease free survival)	5 studies (3536 patients) included: Eriksson 2015,

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
and Meta-Analysis (5 studies, 3536 patients) **Databases:** Pubmed, Scopus, Web of Sciences, Clinicaltrials.gov **Search period:** Inception to December 2018 **Inclusion Criteria:** Comparative studies, English language, and >10 cases **Exclusion Criteria:** Case reports, in vitro or cadaveric studies, technical notes, review articles not reporting original data, duplicate publications, and single arm studies	**Intervention:** Sentinel node mapping **Comparison:** Lymphadenectomy	**Secondary:** Mean operative time, mean blood loss, blood transfusion rate, procedure conversion rate, complication rate, in hospital stay, postoperative complications **Results:** Six comparative studies were included. Overall, 3536 patients were included: 1249 (35,3%) and 2287 (64,7%), undergoing sentinel node mapping and lymphadenectomy, respectively. Pooled data suggested that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03 (95% CI 1.30 – 3.18); p=0.002). No difference in detection of positive nodes located in the paraaortic was observed (OR: 0.93 (95% CI 0.30 to 2.18), p= 0.086). Overall recurrence rate was 4.3% and 7.3% after sentinel node mapping and lymphadenectomy, respectively (OR: 0.90 (95% CI 0.58 – 1.38), p = 0.63). Similarly, nodal recurrences were statistically similar between group (1.2% vs. 1.7%; OR 1.51 (95% CI 0.70 to 3.29), p=0.29). **Author's Conclusion:** In conclusion, our	Holloway 2016, Baiocchi 2017, Buda 2017, Ducie 2017, Buda 2018	

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

		meta-analysis underlines that sentinel node mapping is non-inferior to standard lymphadenectomy in term of detection of paraaortic nodal involvement and recurrence rates (any site and nodal recurrence); while, focusing on the ability to detect positive pelvic nodes, sentinel node mapping could be consider superior to lymphadenectomy. Further randomized studies are needed to assess long term effectiveness of sentinel node mapping.		

Methodical Notes

Funding Sources: None.

COI: None.

Study Quality: Cochrane Collaboration Risks of Bias assessment tool was used to assess the quality of the included studies. Assessment of the study quality is displayed in the supplementary material, which is not accessible.

Heterogeneity: Heterogeneity was measured using I2 statistic, in which I2 > 50% suggests high heterogeneity. High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%)

Publication Bias: Publication bias was not investigated (less than ten studies included)

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of Retrospective cohort studies
Downgraded to Level 4 due to methodical weakness:
Inclusion criteria and Population were not described sufficiently
No search for grey literature or reference lists was conducted. Non-English articles were excluded. Insufficient description of the performed searches.
Publication bias was not investigated (less than ten studies included)
High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%)
Assessment of the study quality is displayed in the supplementary material, which is not accessible.

Rocha, A. et al. Indocyanine green and infrared fluorescence in detection of sentinel lymph nodes in endometrial and cervical cancer staging - a systematic review. Eur J Obstet Gynecol Reprod Biol. 206. 213-219. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic Review **Databases:** Pubmed **Search period:** January 2010 up to May 2015	**Population:** Patients with endometrial and cervical cancer **Intervention:** Indocyanine green (ICG) during SLN biopsy, using robotic and laparoscopic assisted surgery and laparotomy	**Primary:** Detection rate, Sensitivity, specificity and negative predictive value **Secondary:** **Results:** 422 patients were included in 10 studies, ranging from 1 to 227 patients. The main surgical approach used in ICG SLN biopsy was	10 studies (422 patients): Crane et al., 2010, Furukawa et al., 2010, Van der Vorst et al., 2011, Rossi et al., 2012, Holloway et al., 2012, Schaafsma et al., 2012, Rossi et

Rocha, A. et al. Indocyanine green and infrared fluorescence in detection of sentinel lymph nodes in endometrial and cervical cancer staging - a systematic review. Eur J Obstet Gynecol Reprod Biol. 206. 213-219. 2016				
Inclusion Criteria: Publications using ICG as a tracer were selected **Exclusion Criteria:**	**Comparison:**	robotic-assisted surgery in 368 patients. Laparotomy was performed in 39 patients and laparoscopy in 15. The detection rate in SLN mapping using ICG ranged from 78% to 100% for cervical injection and from 33% to 100% for hysteroscopic injection. Sensitivity and negative predictive value (NPV) vary from 50% to 100% and 88% to 100%, respectively. The most common site of injection was the cervix (two quadrants); this technique is correlated with a high detection rate (ranging from 78% to 95%). The cervical submucosal and stromal injections were the most frequent sites used. No complications related to ICG administration were described. **Author's Conclusion:** NIR fluorescence imaging using ICG is performed in robotic-assisted surgery in laparoscopy and in laparotomy, being a feasible, safe, time-efficient and seemingly reliable method for lymphatic mapping in early stage of CC and EC. Although it has promising results in SLN mapping, randomized studies, with larger patient samples, are needed.	al., 2013, Sinno et al., 2014, Jewell et al., 2014, Ditto et al., 2015	
Methodical Notes				

Rocha, A. et al. Indocyanine green and infrared fluorescence in detection of sentinel lymph nodes in endometrial and cervical cancer staging - a systematic review. Eur J Obstet Gynecol Reprod Biol. 206. 213-219. 2016

Funding Sources: None

COI: None

Study Quality: Not investigated

Heterogeneity: No meta-analysis was performed

Publication Bias: Not investigated

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review of retrospective cohort studies

Downgrading to Level 4 due to methodical weakness:
Only one database (Pubmed) was searched.
No search for grey literature or unpublished articles
No search for articles in languages other than english
Insufficient description of inclusion and exclusion criteria and PICO
Quality of the included studies was not investigated
Publication bias was not investigated

Ruscito, I. et al. Sentinel Node Mapping in Cervical and Endometrial Cancer: Indocyanine Green Versus Other Conventional Dyes-A Meta-Analysis. Ann Surg Oncol. 23. 3749-3756. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective and prospective studies The purpose of this meta-analysis was to compare the efficacy of ICG versus other conventional tracers (99Tc, blue dyes or a combination of the two) in terms of overall and bilateral detection rates and false negative rates, in cervical and endometrial cancer patients undergoing SLN mapping. **Databases:** PubMed, MEDLINE, and Scopus **Search period:** Inception to January 2016 **Inclusion Criteria:** All English language original reports evaluating the efficacy of SLN mapping with ICG or other conventional dyes (99Tc, blue dyes or a combination of these two) in patients affected by cervical or endometrial cancer were considered for inclusion. Studies reporting laparotomy,	**Population:** Cervical and endometrial cancer patients undergoing SLN mapping. **Intervention:** Indocyanine green (ICG) **Comparison:** Other conventional tracers (99Tc, blue dyes or a combination of the two)	**Primary:** Overall and bilateral detection rates of the different mapping tracers (ICG vs. conventional dyes), expressed in terms of risk failure in detecting at least one SLN and at least one SLN per hemipelvis respectively. We assessed overall and bilateral detection rates of different SLN mapping tracers comparing ICG versus blue dyes only, ICG versus 99Tc only, and ICG versus the combination of blue dyes and 99Tc. **Secondary:** SLN false-negative rate using different mapping tracers. We assessed the SLN false-negative rate comparing ICG versus blue dyes only, ICG versus 99Tc only, and ICG versus the combination of blue dyes and 99Tc **Results:** Forty-five studies were retrieved. Six studies including 538 patients met selection criteria. Compared with blue dyes, ICG SLN mapping had	6 studies (538 patients) included: Holloway 2012, Sinno 2014, Tanner 2015, How 2015, Imboden 2015, Buda 2015

Ruscito, I. et al. Sentinel Node Mapping in Cervical and Endometrial Cancer: Indocyanine Green Versus Other Conventional Dyes-A Meta-Analysis. Ann Surg Oncol. 23. 3749-3756. 2016				
laparoscopic, or robotic surgery for SLN biopsy were all assessed for inclusion. In endometrial cancer, intracervical, hysteroscopic, and subserosal tracer injections for SLN mapping have been described. However, only series in which the tracer for the SLN mapping was injected intracervically were selected due to the overwhelming diffusion of this procedure and its proven correlation with higher detection rates **Exclusion Criteria:** Review articles, case reports, video articles, and letters were excluded. Only studies reporting SLN false-negative rates on fully staged patients were considered. Studies reporting SLN false-negative rates based on patients who were not subjected to both SLN biopsy and complete lymphadenectomy were excluded.		higher overall (odds ratio [OR] 0.27; 95 % confidence interval [CI] 0.15–0.50; p **Author's Conclusion:** In cervical and endometrial cancer, ICG SLN mapping seems to be equivalent to the combination of blue dyes and 99TC in terms of overall and bilateral detection rates. Its safety profile and ease of use may favor its employment respect to conventional tracers.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None				

Ruscito, I. et al. Sentinel Node Mapping in Cervical and Endometrial Cancer: Indocyanine Green Versus Other Conventional Dyes-A Meta-Analysis. Ann Surg Oncol. 23. 3749-3756. 2016

Study Quality: Quality of the included studies was not investigated.

Heterogeneity: A x2 test for heterogeneity among proportions was performed to assess the presence of statistical heterogeneity between studies. A fixed-effects model was used if statistical heterogeneity was not significant (I 2 value ≤50 %); differently, a random-effects model was adopted. Heterogeneity was not present.

Publication Bias: Publication bias was not investigated (less than ten studies included)

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective studies without consistently applied reference standard.
No search for unpublished articles was performed
Quality of the included studies was not investigated

OXFORD (2011) Appraisal Sheet: RCT: *4 Bewertung(en)*

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 120 **Recruitung Phase:** January 2009 and March 2015 **Inclusion Criteria:** Woman with high-grade EC on preoperative sampling (grade 3 endometrioid, clear cell, serous, carcinosarcoma or mixed histologies) who were appropriate surgical candidates and deemed medically eligible for a lymph node dissection **Exclusion Criteria:** Exclusion criteria were patients with low-grade histologies on preoperative assessment or advanced disease at diagnosis.	**Intervention:** Collection of LNs into nodal basin-specific containers on the randomized side **Comparison:** Simple labeling on the non-randomized side	**Primary:** Total number of LNs and total number of LNs with metastases on the randomized versus the nonrandomized side were compared. The remaining adipose tissue from each LN specimen was submitted for histologic examination. Wen analyzed the number of LNs with and without metastases identified from additional adipose tissue. **Secondary:** **Results:** Of 120 consented subjects, 56 had sufficient data for analysis. The additional adipose tissue contained 7.5 LNs per patient on average (range: 0-26). In 2/54 total cases (3.7%) and 2/5 cases with nodal metastases (40%), the additional adipose tissue contained LNs with metastases. In both cases, metastases were also detected in grossly identified LN candidates. The mean number of LNs identified was not significantly different based on method of collection (p=0.22). The mean number of LNs containing metastases per side was not significantly different (p=0.58). **Author's Conclusion:** Processing of adipose tissue does increase the total number of LNs identified, however, it does	

Davidson, B. A. et al. Prospective Evaluation of Lymph Node Processing at Staging Surgery for High-grade Endometrial Cancer. Int J Gynecol Pathol. 37. 252-255. 2018			
		not influence EC stage. No difference in LN counts was noted with basin-specific collection.	
Methodical Notes			
Funding Sources: Not stated **COI:** None **Randomization:** Randomization was performed using a random number generator with block randomization (block size 6) stratified by site. **Blinding:** No blinding **Dropout Rate/ITT-Analysis:** Not performed **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 No test for group differences Blinding was not performed Small number of patients included in the analysis. Nearly half of the patients initially consented were not included in the final analysis			

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Randomized Trial **Number of Patient:** 120 **Recruitung Phase:** Between June 2016 and June 2017 **Inclusion Criteria:** Patients with low-risk endometrial cancer for nodal metastasis were included in this study. Low risk was defined as stage Ia, type I, grade a,b endometrial cancer confirmed clinically and histologically by fractional curettage. **Exclusion Criteria:**	**Intervention:** Group A included hysteroscopic guided methylene blue injection, Group B included transcervical injection, Group C included uterine subserosal injection and Group D included combined transcervical and subserosal injection. We used 1 ml injection of methylene blue per site after sterilization of the methylene blue powder by autoclave or autoclaving of the diluted solution in autoclavable bottle or using sterilized ampules. Cervical injection was done by insulin syringe (one ml) inserting full needle length (1 cm) at 3, 9 o'clock. Subserosal myometrial injection was done at eight points, four anterior and four posterior in the midline with insulin syringe **Comparison:**	**Primary:** **Secondary:** **Results:** Clinical and pathological SLN detection were more with hysteroscopic technique than others and pathological detection was lower than clinical detection in all techniques. Metastatic disease was more common in nodes with suspicious appearance. About 10% of negative suspicious and mapped nodes were associated with positive other nodes for metastasis. **Author's Conclusion:** SLN in endometrial cancer has a role in staging of endometrial cancer with best technique for detection, hysteroscopic guided blue dye injection. SLN can be used in patients with low risk for lymph node metastasis for selective lymphadenectomy. Blue dye labelling using methylene blue dye is good in low resource countries as it is cheap. We recommended the following algorithm for surgical staging in early endometrial cancer with better results than using SLN alone. Stage I type 1, grade 1,2 endometrial

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

		cancer should undergo surgical staging with initial evaluation of the peritoneum which if affected, it is stage III with no need for lymphadenectomy. Then, dissection of the blue and suspicious nodes which if any is positive on frozen section, selective same side pelvic and paraaortic nodal dissection should be done. If they are negative, no need for lymphadenectomy. This approach can help patients to avoid the side effects associated with a complete lymphadenectomy. The higher rate of detection using this algorithm is related to combining the suspicions nodes with the stained ones.	
Methodical Notes			
Funding Sources: None **COI:** None **Randomization:** Method unclear **Blinding:** Not described **Dropout Rate/ITT-Analysis:**			

El-Agwany, A. S. et al. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 225. 35-39. 2018

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized trial
Downgraded to Level 3 due to methodical weakness:
Inclusion and exclusion criteria were not described sufficiently.
Outcomes were not described.
Method of randomization was not described.
Blinding was not described.
Reference standard was not applied.

Frumovitz, M. et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol. 19. 1394-1403. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized controlled phase 3 trial **Number of Patient:** 180 **Recruitung Phase:** Between Dec 21, 2015, and June 19, 2017 **Inclusion Criteria:** Participating surgeons were required to have completed at least ten lymphatic	**Intervention:** Lymph node mapping with isosulfan blue dye followed by lymph node mapping with indocyanine green dye and near-infrared imaging (PINPOINT) **Comparison:** Lymph node mapping with indocyanine green dye and near-infrared imaging (PINPOINT) followed by lymph	**Primary:** Efficacy of intraoperative indocyanine green with near-infrared fluorescence imaging versus that of blue dye in the identification of lymph nodes, defined as the number of lymph nodes identified by each dye (and confirmed as lymphoid tissue by histology) divided by the number of lymph nodes identified intraoperatively and excised. **Secondary:** Secondary endpoints were the rate of intraoperative detection of at least one sentinel node per patient and the rate of detection of bilateral

Frumovitz, M. et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol. 19. 1394-1403. 2018		
mapping procedures, including at least three with the PINPOINT near-infrared fluorescence imaging system, before the initiation of enrolment. Patients were eligible for enrolment if they were 18 years of age or older, diagnosed with International Federation of Gynecology and Obstetrics clinical stage I cervical or uterine cancer (any histology), and were scheduled for curative surgery that included lymph node assessment. Any patient felt to be a safe surgical candidate was considered eligible irrespective of Eastern Cooperative Oncology Group performance status or life expectancy. Other eligibility criteria included negative nodes and absence of metastatic disease by clinical evaluation and radiological imaging. **Exclusion Criteria:** Patients were ineligible if they had previous pelvic dissection or irradiation, advanced cervical or uterine cancer, T3 or T4 lesions, cervical tumour size larger than 2 cm, hepatic dysfunction defined as a Model for End-Stage Liver Disease score of 10 or greater, renal dysfunction defined as serum creatinine of 2·0 mg/dL or greater, or a known allergy to indocyanine green, iodine, iodine dyes, isosulfan blue, or triphenylmethane.	node mapping with isosulfan blue dye	sentinel nodes with indocyanine green compared with isosulfan blue dye, and the safety of each detection method. Two other secondary endpoints (the proportion of lymph nodes identified from following lymphatic channels and the anatomical distribution of lymph nodes) will be reported in a separate publication. **Results:** Between Dec 21, 2015, and June 19, 2017, 180 patients were enrolled and randomly assigned to the two groups (90 to each group); 176 patients received the intervention and were evaluable (modified intention-totreat population). 13 patients with major protocol violations were subsequently excluded from the per-protocol population. 517 sentinel nodes were identified in the per-protocol population (n=163), of which 478 (92%) were confirmed to be lymph nodes on pathological processing: 219 (92%) of 238 nodes that were both blue and green, all seven nodes that were blue only, and 252 (95%) of 265 nodes that were green only (p=0.33). Seven sentinel lymph nodes were neither blue nor green but were removed for appearing suspicious or enlarged on visual examination. In total, 471 (97%) of 485 lymph nodes were identified with the green dye and 226 (47%) with the blue dye (difference

Frumovitz, M. et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol. 19. 1394-1403. 2018

		50%, 95% CI 39–62; p<0·0001). **Author's Conclusion:** Indocyanine green dye with near-infrared fluorescence imaging identified more sentinel nodes than isosulfan blue dye in women with cervical and uterine cancers, with no difference in the pathological confirmation of nodal tissue between the two mapping substances.	

Methodical Notes

Funding Sources: Novadaq.

COI: None

Randomization: Randomisation was stratified by study site, with permuted block randomisation within strata. To minimise the opportunity for the sequence to be predicted, the block size was variable and randomly chosen from small multiples of two (ie, two, four, or six). The randomisation schedules were generated in advance using a computerised random number generator

Blinding: All participants were masked to their randomisation assignment
until after the procedure; however, investigators were not masked to the procedure used.

Dropout Rate/ITT-Analysis: Modified intention-to-treat analysis was performed

Frumovitz, M. et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol. 19. 1394-1403. 2018

Notes:
Oxford CEBM Level of Evidence: EL 2 Randomized controlled trial
The trial design was a non-inferiority, within-patient comparison study. Because of the study design, investigators could not be blinded.

Rozenholc, A. et al. Green versus blue: Randomized controlled trial comparing indocyanine green with methylene blue for sentinel lymph node detection in endometrial cancer. Gynecol Oncol. 153. 500-504. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** 135 **Recruitung Phase:** March 2016 to April 2017 **Inclusion Criteria:** All patients with endometrial carcinoma diagnosed by endometrial biopsy or curettage and with preoperative FIGO stage I who were intended for staging via laparoscopic or robotic surgery were eligible. **Exclusion Criteria:** Exclusion criteria included the following: age < 18 years, previous pelvic or paraaortic lymphadenectomy/radiotherapy/surgery that could change uterine	**Intervention:** Blue dye (2 ml of a 10 mg/ml solution) on the left (ICG on the right, 2 ml of a 1.25 mg/ml solution) **Comparison:** Blue dye (2 ml of a 10 mg/ml solution) on the right (ICG on the left, 2 ml of a 1.25 mg/ml solution)	**Primary:** Difference in SLN detection rates per HP according to the dye used. **Secondary:** Number of SLNs and the proportion of sides with cross-mapping (defined as a blue SLN on the side mapped with ICG or a NIR fluorescent SLN on the side mapped with blue dye) **Results:** This trial included 132 patients, and 46 patients underwent robotic-assisted surgery while 86 had standard laparoscopic surgery. Successful detection of SLN was 90,9% using ICG and 64,4% using blue dye (p

Rozenholc, A. et al. Green versus blue: Randomized controlled trial comparing indocyanine green with methylene blue for sentinel lymph node detection in endometrial cancer. Gynecol Oncol. 153. 500-504. 2019			
lymphatic drainage, iodine allergy and pregnancy. Patients were also excluded when SLN procedure was not completed per protocol due to reasons unrelated to the dye such as inadvertent injection of dye on wrong side of the cervix, intraoperative find of suspicious lymph nodes or advanced disease or surgical complications interrupting SLN procedure.		**Author's Conclusion:** The use of ICG instead of blue dye results in a 26,5% (95% CI 17,4%-35,6%) increase of SLN detection rates per HP in women with endometrial cancer.	
Methodical Notes			
Funding Sources: Not stated **COI:** None **Randomization:** The unit of randomization was the side that received each dye. Block randomization with computer generated random block size was used. **Blinding:** The allocation sequence was concealed from the surgeons in sequentially numbered opaque and sealed envelopes that were opened at the time of surgery in the operating room **Dropout Rate/ITT-Analysis:** Per protocol analysis **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled trial Per protocol analysis was performed			

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective Cohort Study	**Number of patients / samples:** 119 patients with endometrial cancer **Reference standard:** No reference standard **Validation:** Detection rate, sensitivity and negative predictive value (NPV) **Blinding:** Not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	**Results:** Sentinel lymph node mapping with Indocyanin green A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection (p = 0.01). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymphe node. **Author conclusions:** ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection (p = 0.01). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.		
Methodical Notes				

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018		
Funding Sources: Not stated. COI: None. Notes: Oxford CEBM Level of Evidence 2011: EL 4 Retrospective cohort study without blinding or reference standard Articles submitted by hand search.		
Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective multicenter cohort study	**Number of patients / samples:** 156 patients **Reference standard:** Lymphadenectomy as the reference standard **Validation:** Sensitivity of the SLNB algorithm in detecting metastatic disease, False negative rate and negative predictive value Additional measures of diagnostic accuracy, sentinel lymph node detection rates, and adverse events	**Results:** Performance characteristics of Sentinel Lymph Node Biopsy (SLNB) using indocyanine green (ICG) The study enrolled 156 patients (median age, 65.5 years; range, 40-86 years; median body mass index [calculated as weight in kilograms divided by height in meters squared], 27.5; range, 17.6-49.3), including 126 with high-grade EC. All patients underwent SLNB and PLND, and 101 patients (80%) with high-grade EC also underwent PALND. Sentinel lymph node detection rates were 97.4%per patient (95%CI, 93.6%-99.3%), 87.5%per hemipelvis (95%CI, 83.3%-91.0%), and 77.6%bilaterally (95%CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the SLNB algorithm, yielding a sensitivity of 96%(95%CI, 81%-100%), a false-negative rate of 4%(95%CI,

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021				
	Blinding: Blinding was not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	0%-19%), and a negative predictive value of 99%(95%CI, 96%-100%). Only 1 patient (0.6%) was misclassified by the SLNB algorithm. Seven of 27 patients with node-positive cancer (26%) were identified outside traditional PLND boundaries or required immunohistochemistry for diagnosis. **Author conclusions:** In this study, SLNB had acceptable diagnostic accuracy compared with lymphadenectomy for the detection of nodal metastatic disease in high-grade EC. On the basis of this study and the existing literature, SLNB appears to be a viable option for the surgical staging of both low- and high-grade EC.		
Methodical Notes				
Funding Sources: Dr Clarke reported receiving personal fees from AstraZeneca outside the submitted work. No other disclosures were reported. **COI:** This study was supported by the Princess Margaret Cancer Foundation of Princess Margaret Cancer Centre (Toronto, Ontario) and the McArthur Research Fund of the Department of Obstetrics and Gynecology at the University of Toronto (Toronto, Ontario). Dr Cusimano is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship and American College of Surgeons Resident Research Scholarship. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Prospective cohort study with consistently applied reference standard but without blinding** Article submitted by hand search.				

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021

Limitations:
-Blinding was not performed

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Holloway, R. W. et al. A Prospective Cohort Study Comparing Colorimetric and Fluorescent Imaging for Sentinel Lymph Node Mapping in Endometrial Cancer. Ann Surg Oncol. 24. 1972-1979. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study type: Prospective cohort study	**Funding sources:** Not described **Conflict of Interests:** Dr. Robert W. Holloway has received compensation for advanced training programs from Intuitive Surgical, Inc., Sunnyvale, CA. All the other authors declare no conflict of interest. **Randomization:** Randomization was performed **Blinding:** Randomization envelopes were prepared by a third-party statistician. These were kept secure and unavailable to the investigators until blue dye results were recorded in the operating room. After the blue dye results were recorded, the randomization envelopes were opened, and 180 subjects were randomized to NIR imaging	**Total no. patients:** 200 **Recruiting Phase:** September 2012 to January 2015 **Inclusion criteria:** All the patients with clinical stage 1 uterine malignancies (types 1 and 2 histologies) who were candidates for RALH with lymphadenectomy were screened and offered inclusion in the study. **Exclusion criteria:** The exclusion criteria ruled out suspected allergies to blue dyes, iodine, or	**Interventions:** Sentinel lymph node mapping using Isosulfan blue (ISB) + indocyanine green (ICG) **Comparison:** Sentinel lymph node mapping using isosulfan blue (ISB) alone

Holloway, R. W. et al. A Prospective Cohort Study Comparing Colorimetric and Fluorescent Imaging for Sentinel Lymph Node Mapping in Endometrial Cancer. Ann Surg Oncol. 24. 1972-1979. 2017			
	Dropout rates:	ICG dye, as well as inability to undergo robotically assisted hysterectomy for any reason.	
Notes:	Oxford CEBM Level of Evidence: 3 Prospective cohort study Single-center analysis Prospective design with a 10% (20-case) randomized ISB dye control group Reference standard was not described Blinding of the patients was not described Fundin was not described **Author's conclusion:** In this prospective study, ISB + ICG and NIR detected more SLNs and more LN metastases than ISB alone. Assessment of SLN with ICG + ISB/NIR imaging had excellent sensitivity for detection of metastasis and no safety issues.		
Outcome Measures/results	**Primary** Bilateral mapping, Unilateral mapping, Mapping failure, Side-specific success, Sensitivity and negative predictive value (NPV) for the detection of lymph node metastasis using SLN mapping. **Secondary**	**Results:** The mean age of the patients was 64.5 ± 8.4 years, and the mean body mass index (BMI) was 33 ± 7.6 kg/m2. The histologies were endometrioid G1 (43%), G2 (30%), G3 (7%), and type 2 (20%). The mean time from dye injection to initiation of mapping was 13.4 ± 6.2 min, and the time to removal of SLN was 17.4 ± 11.2 min. Detection of SLN for the 20 ISB control cases did not differ from that for the 180 ISB + ICG cases (p>0.05). The rates of SLN detection for ISB + ICG/ NIR (n =	

Holloway, R. W. et al. A Prospective Cohort Study Comparing Colorimetric and Fluorescent Imaging for Sentinel Lymph Node Mapping in Endometrial Cancer. Ann Surg Oncol. 24. 1972-1979. 2017		
		180) versus ISB (n = 200) were as follows: bilateral (83.9 vs. 40%), unilateral (12.2 vs. 36%), and none (3.9 vs. 24%) (p

2.31. Schlüsselfrage 34: Sollte beim Endometriumkarzinom bei positivem Sentinel eine anschließende systematische LNE durchgeführt werden, um eine Verbesserung zu erreichen im Hinblick auf Lebensqualität, Kurzzeit-/ Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bodurtha Smith, A. J. 2017	3	Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer
Bogani, G. 2019	4	Systematic Review and Meta-Analysis (5 studies, 3536 patients)
Zheng, Y. 2019	4	Retrospective cohort study (SEER database)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis To evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer **Databases:** Medline, Embase, and the Cochrane Central Registry of Controlled Trials **Search period:** Inception to March 25, 2016 **Inclusion Criteria:** Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes	**Population:** Women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer **Intervention:** Sentinel lymph node mapping **Comparison:**	**Primary:** Detection rate, sensitivity, and/or impact on treatment or survival **Secondary:** **Results:** We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77-84) with a 50% (95% confidence interval, 44-56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11-23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection	55 studies (4915 patients), see full text article.	

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017				
measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival. We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. **Exclusion Criteria:** We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials		techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91-98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment. **Author's Conclusion:** Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.		
Methodical Notes				
Funding Sources: Funding not described **COI:** None.				

Bodurtha Smith, A. J. et al. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 216. 459-476.e10. 2017

Study Quality: Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool.

Heterogeneity: We assessed heterogeneity among the studies using the I 2 statistic and visual inspection of funnel plots. Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%). Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Publication Bias: The investigation of publication bias was not described but the authors state that publication bias may be present.

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of prospective and retrospective cohort studies.
The investigation of publication bias was not described but the authors state that publication bias may be present.
Substantial heterogeneity was present for the main outcomes: Overall SLN detection rate (I2=97,9%), Bilateral SLN detection rate (I2=98,4%).
Heterogeneity was explained by the SLN mapping variables that were included and controlled for in meta-regressions.

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** Systematic Review	**Population:** Patients with endometrial cancer	**Primary:** Positive node detection rate, survival outcomes (overall survival and disease free survival)	5 studies (3536 patients) included: Eriksson 2015,

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019			
and Meta-Analysis (5 studies, 3536 patients) **Databases:** Pubmed, Scopus, Web of Sciences, Clinicaltrials.gov **Search period:** Inception to December 2018 **Inclusion Criteria:** Comparative studies, English language, and >10 cases **Exclusion Criteria:** Case reports, in vitro or cadaveric studies, technical notes, review articles not reporting original data, duplicate publications, and single arm studies	**Intervention:** Sentinel node mapping **Comparison:** Lymphadenectomy	**Secondary:** Mean operative time, mean blood loss, blood transfusion rate, procedure conversion rate, complication rate, in hospital stay, postoperative complications **Results:** Six comparative studies were included. Overall, 3536 patients were included: 1249 (35,3%) and 2287 (64,7%), undergoing sentinel node mapping and lymphadenectomy, respectively. Pooled data suggested that positive pelvic nodes were detected in 184 out of 1249 (14.7%) patients having sentinel node mapping and 228 out of 2287 (9.9%) patients having lymphadenectomy (OR: 2.03 (95% CI 1.30 – 3.18); p=0.002). No difference in detection of positive nodes located in the paraaortic was observed (OR: 0.93 (95% CI 0.30 to 2.18), p= 0.086). Overall recurrence rate was 4.3% and 7.3% after sentinel node mapping and lymphadenectomy, respectively (OR: 0.90 (95% CI 0.58 – 1.38), p = 0.63). Similarly, nodal recurrences were statistically similar between group (1.2% vs. 1.7%; OR 1.51 (95% CI 0.70 to 3.29), p=0.29). **Author's Conclusion:** In conclusion, our	Holloway 2016, Baiocchi 2017, Buda 2017, Ducie 2017, Buda 2018

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019				
		meta-analysis underlines that sentinel node mapping is non-inferior to standard lymphadenectomy in term of detection of paraaortic nodal involvement and recurrence rates (any site and nodal recurrence); while, focusing on the ability to detect positive pelvic nodes, sentinel node mapping could be consider superior to lymphadenectomy. Further randomized studies are needed to assess long term effectiveness of sentinel node mapping.		
Methodical Notes				
Funding Sources: None. **COI:** None. **Study Quality:** Cochrane Collaboration Risks of Bias assessment tool was used to assess the quality of the included studies. Assessment of the study quality is displayed in the supplementary material, which is not accessible. **Heterogeneity:** Heterogeneity was measured using I2 statistic, in which I2 > 50% suggests high heterogeneity. High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%) **Publication Bias:** Publication bias was not investigated (less than ten studies included)				

Bogani, G. et al. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 153. 676-683. 2019

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of Retrospective cohort studies
Downgraded to Level 4 due to methodical weakness:
Inclusion criteria and Population were not described sufficiently
No search for grey literature or reference lists was conducted. Non-English articles were excluded. Insufficient description of the performed searches.
Publication bias was not investigated (less than ten studies included)
High heterogeneity was present for positive pelvic nodes: (I2=73%), positive paraaortic nodes (I2=74%), while no heterogeneity was present for recurrence (any site) (I2=0%) and nodal recurrence (I2=0%)
Assessment of the study quality is displayed in the supplementary material, which is not accessible.

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study (SEER database)	**Funding sources:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert	**Total no. patients:** 103,103 patients with endometrial cancer identified from the SEER database of the National Cancer Institute (USA) were identified. Analysed were 11.603 patients. **Recruiting Phase:** 2004-2013	**Interventions:** Lymphadenectomy (total hysterectomy – with/without bilateral salpingo-oophorectomy) **Comparison:** -

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
	testimony, grants or patents received or pending, or royalties. **Conflict of Interests:** see funding surces **Randomization:** - **Blinding:** - **Dropout rates:** -	**Inclusion criteria:** Patients with endometrium as the primary site and endometrial cancer malignancy as the disease classification; grade 1 endometrial cancer; focused on early-stage endometrial cancer, in which total hysterectomy – with/without bilateral salpingo-oophorectomy – is the most common type of surgery. **Exclusion criteria:** Patients with more than one primary site, only a clinical diagnosis, other disease stages and survival times less than 3 months.	
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective, cohort study) Limitations: - The authors stated, that the lack of significance after matching may be due to the small number of patients after matching. - high loss rate (not specified by the authors) - some relevant medical information (depth of myometrial invasion, time to recurrence, and subsequent surgical and medical therapies) are noch available due to the retrospective approach - number of patients for lymph node biopsies ist very small - only one cohort (patient group)- not a cohort study in the original meaning. **Author's conclusion:** In conclusion, using SEER database, we found that for all stage IA patients, most patients died of cardiovascular disease (27%) and diabetes (8%); lymphadenectomy has no influence on survival and sentinel lymph node biopsies		

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
	can reduce the number of lymph node removed but have no effect in survival. Given that practice patterns have shifted in the world to predominantly sentinel node biopsy, we think our manuscript applicable to current clinical practice	
Outcome Measures/results	**Primary** Survival **Secondary** cause of death spectrum, the effect of sentinel lymph node biopsy and adjuvant therapies.	**Results:** Mean age at diagnosis was 56.5 years old. 22.83% of the women analyzed died from endometrial cancer; other sources were: cardiovascular disease (27%), diabetes (8%) and respiratory diseases (3%). But as the differentiation of the cancer became worse, more women died from the cancer. <u>Overall survival - multivariant analysis:</u> - age and grade were crucial factors in terms of survival, and a younger age and lower grade were associated with a better prognosis ($p < 0.0001$). - Asian women had better survival times than white women and black women ($p < 0.0001$) - no significant influence can be found for geographic region or number of removed lymph nodes. - lymphadenectomy can increase survival in grade 3/4 stage I patients ($p = 0.013$). **Sentinel lymph nodes biopsies:** Sentinel lymph nodes biopsy could reduce the number of lymph node removed (12 vs 6, $p = 8.387e-10$ in Wilcox test), but had no effect on survival (n=102 patients). <u>Propensity score Matching:</u> no difference was observed in survival between the lymphadenectomy group & the nonlymphadenectomy group ($p = 0.93$ and 0.65 respectively).

2.32. Schlüsselfrage 35: Wie ist der Stellenwert laparoskopischer Verfahren beim Endometriumkarzinom im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Asher, R. 2018	1	Systematic Review and Meta-Analysis (9 RCTs, 4405 patients)
Behbehani, S. 2019	3	SR and Meta (of 18 Retrospective Cohort Studies, 2 Prospective Cohort Studies and 1 RCT)
Cusimano, M. C. 2019	3	SR and Meta (of 51 Observational Studies)
Galaal, K. 2018	1	Systematic Review and Meta-Analysis of 9 RCTs (4389 patients)
Marra, A. R. 2019	3	SR and Meta (of 50 retrospective cohort, prospective cohort, RCT and case-control studies)
Wang, Y. R. 2018	1	Network Meta-Analysis of RCTs (9 RCTs, 2263 patients) In the present study, 3 different operative approaches (laparoscopy, laparotomy, and LAVH) for EC were searched out from relevant databases to compare their operative time and complications by performing this network meta-analysis.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *6 Bewertung(en)*

Asher, R. et al. Disease-Free and Survival Outcomes for Total Laparoscopic Hysterectomy Compared With Total Abdominal Hysterectomy in Early-Stage Endometrial Carcinoma: A Meta-analysis. Int J Gynecol Cancer. 28. 529-538. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis (9 RCTs, 4405 patients) **Databases:** Medline, Embase, Cochrane Central Register of Controlled Trials, clinical trials.gov **Search period:** 1996 to 2017 **Inclusion Criteria:** RCTs comparing laparoscopic hysterectomy with TAH in patients with endometrial cancer **Exclusion Criteria:**	**Population:** Patients with endometrial cancer **Intervention:** Total laparoscopic hysterectomy (TLH) or laparoscopic-assisted vaginal hyterectomy **Comparison:** Total abdominal hysterectomy (TAH)	**Primary:** 3 year disease free survival **Secondary:** overall survial, local recurrence, conversion of TLH to TAH, intraoperative and postoperative complications **Results:** Nine studies (4405 patients) were identified in which DFS was reported in 5 studies. The difference in 3-year DFS was 1.44% (95% CI -0,65% to 3,53%) in favor of total abdominal hysterectomy, consistent with a noninferiority margin of 5%. Differences in DFS (HR 1.10, 95% 0.92 – 1.32), overall survival (HR 1.16, 95% CI 0.81 – 1.66) and local recurrence (difference, 0,42%, 95% CI -0.41% to 1.25%) were not significant. Rates of intraoperative complications showed no difference (0.5%, 95% CI, -1.1 to 2.0%) based on 7 studies. There was no significant reduction in postoperative complications with the laparoscopic procedure (-6,83%, 95% CI -9.19% - -4,47%). **Author's Conclusion:** Noninferiority of laparoscopy was demonstrated on clinical outcomes and was	9 RCTs (4405 patients) included: Tozzi 2005, Fram 2002, Zorlu 2005, Lu 2016, LAP-2 2012, Zullo 2009, Malzoni 2009, LACE 2017, Mouritis 2010

Asher, R. et al. Disease-Free and Survival Outcomes for Total Laparoscopic Hysterectomy Compared With Total Abdominal Hysterectomy in Early-Stage Endometrial Carcinoma: A Meta-analysis. Int J Gynecol Cancer. 28. 529-538. 2018

		associated with a reduction in postoperative complications. These results support continued treatment by laparoscopic hysterectomy for early-stage endometrial cancer.		

Methodical Notes

Funding Sources: This work was supported by the National Health and Medical research program.

COI: None.

Study Quality: Risks of individual study bias were examined using the Cochrane Collaboration tool. The authors state that 6 trials are deemed to be at a low risk of bias. All studies were at risk of bias because of lack of blinding; however as all studies were comparing vastly different surgical procedures, having a unblinded study was unavoidable and impractical.

Heterogeneity: X2 and I2 statistics were used to assess statistical heterogeneity. Heterogeneity was low for the following outcomes: 3-year-DFS (I2= 2%), DFS HR (I2=0%), Local recurrence (I2= 14%), OS HR (I2=0%. Moderate heterogeneity was present for Intraoperative complication (I2= 32%) and postoperative complications (I2=56%).

Publication Bias: Publication bias was examined with the "file drawer problem" method and approach of Gleser and Olkin. Publication bias was not detected.

Notes:
Oxford CEBM Level of Evidence 2011: EL 1 Systematic Review and Meta-Analysis of RCTs.
Title/Abstract Screening and data extraction was only performed by one reviewer.
Population was not described sufficiently.

Asher, R. et al. Disease-Free and Survival Outcomes for Total Laparoscopic Hysterectomy Compared With Total Abdominal Hysterectomy in Early-Stage Endometrial Carcinoma: A Meta-analysis. Int J Gynecol Cancer. 28. 529-538. 2018			
Quality of the included studies was assessed but not reported in detail (detailed quality assessment was provided in supplementary material, which is not accesible). Moderate heterogeneity was present for the secondary outcomes intraoperative complication (I2= 32%) and postoperative complications (I2=56%), but not for the primary outcome.			
Behbehani, S. et al. Mortality Rates in Laparoscopic and Robotic Gynecologic Oncology Surgery: A Systemic Review and Meta-analysis. J Minim Invasive Gynecol. 26. 1253-1267.e4. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** SR and Meta (of 18 Retrospective Cohort Studies, 2 Prospective Cohort Studies and 1 RCT) **Databases:** Pubmed, Embase, Scopus, Web of Science, and Cochrane Database **Search period:** in the last 10 years. **Inclusion Criteria:** All MIS articles in benign gynecology reporting operative mortality (within 30 days) were reviewed	**Intervention:** laparoscopic and robotic surgery (MIS) **Comparison:** commonly performed MIS	**Primary:** mortality rates in benign gynecologic laparoscopic and robotic surgery (MIS), **Secondary:** **Results:** These results are represented as odds, or number needed to treat, which are calculated as the reciprocal of the estimated mortality rate. 21 articles (124,216 patients) were included. Operative mortality from any benign MIS (laparoscopy and robotics) procedure was 1:6456 (95 % CI 1:3946, 1:10562). Studies were then grouped based on surgical procedure. Mortality rate for hysterectomy (119,721	see publication

Behbehani, S. et al. Mortality Rates in Laparoscopic and Robotic Gynecologic Oncology Surgery: A Systemic Review and Meta-analysis. J Minim Invasive Gynecol. 26. 1253-1267.e4. 2019				
Exclusion Criteria: If mortality was not specifically documented as occurring in the postoperative period, the article was excluded.If mortality rates reported included laparotomy cases, and mortality for MIS procedures of interest (laparoscopy and robotic) could not be extracted, the articles were excluded. Reports of less than 5 MIS cases, duplicate data presented in multiple manuscripts, and data presented in review articles were also excluded.		patients) was 1:6814 (95% CI 1:4119, 1:11275); for sacrocolpopexy was 1:1246 (95% CI 1:36, 1:44700); and for adnexal surgery and diagnostic laparoscopy was 1:2245 (95% CI 1:45, 1:113372). Eighteen articles reported operative mortality for laparoscopic surgery, and 4 for robotic surgery.The mortality in laparoscopic and robotic surgery was 1:6512 (95% CI 1:3971, 1:10680) and 1:5430 (95% CI 1:69-1:435052) respectively. **Author's Conclusion:** Operative mortality in benign minimally invasive gynecologic surgery is low, and mortality for laparoscopic and robotic approaches appear to be similar		
Methodical Notes				
Funding Sources: **COI:** J.M received a speaker honorarium intuitive November 2018. The remaining authors report no conflict of interest. **Study Quality:** The Newcastle-Ottawa scale for observational studies was used to assess the quality of nonrandomized studies for potential risk of bias. For randomized controlled trials Cochrane risk of bias assessment tool (www.training.cochrane.org/handbook) was used. **Heterogeneity:** Due to heterogeneity in study-designs (prospective, retrospective, single site, multicenter, etc.) the random-effects model is fitted for each analysis. Measures of between-study heterogeneity and consistency measured as tau-squared and I^2 are provided in every forest plot. Since the				

Behbehani, S. et al. Mortality Rates in Laparoscopic and Robotic Gynecologic Oncology Surgery: A Systemic Review and Meta-analysis. J Minim Invasive Gynecol. 26. 1253-1267.e4. 2019

probability of observing mortality is very small, a variety of confidence interval formulations, such as the normal approximation, might have negative values for the lower limit of mortality rate. This would not make sense. To avoid this, the confidence intervals in the forest plots are calculated using the Wilson Score method with continuity correction, which sets the lower confidence interval equal to 0 in the case where no mortalities were observed. A continuity correction of 0.50 was added to articles that reported no events.

Mortality in benign MIS gynecological procedures: I2=0%, t2=0, p=1.00
Mortality in benign laparoscopic gynecological procedures: I2=0%, t2=0, p=0.99
Mortality in benign robotic gynecological procedures: I2=0%, t2=0, p=0.88
Mortality in MIS hysterectomy:I2=0%, t2=0, p=0.70
Mortality in laparoscopic hysterectomy:I2=0%, t2=0, p=0.73

Publication Bias:

Notes:
SR and Meta based on only RCTs, prospective and retrospective cohort studies: EL 3
Heterogeneity is low but mortality cases are rare (see heterogeneity)
Although comparison was stated to be commonly performed MIS

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** SR and Meta (of 51 Observational Studies) **Databases:** MEDLINE, EMBASE, and Evidence-Based Medicine Reviews **Search period:** January 1, 2000, to July 18, 2018 **Inclusion Criteria:** Studies of patients with endometrial cancer and obesity (body mass index, 30 kg/m2) who underwent primary hysterectomy. **Exclusion Criteria:** exclusion of studies that evaluated hysterectomy with panniculectomy only.	**Population:** patients with endometrial cancer and obesity (body mass index, ≥30 kg/m2). **Intervention:** robotic hysterectomy **Comparison:** laparoscopic hysterectomy	**Primary:** rates of conversion **Secondary:** perioperative complications **Results:** **51 observational studies** that reported on **10,800 patients** with **endometrial cancer and obesity** (study-level body mass index, 31.0-56.3 kg/m2). The pooled proportions of conversion from laparoscopic and robotic hysterectomy were 6.5% (95% confidence interval, 4.3-9.9) and 5.5% (95% confidence interval, 3.3-9.1), respectively, among patients with a body mass index of ≥30 kg/m2, and 7.0% (95% confidence interval, 3.2-14.5) and 3.8% (95% confidence interval, 1.4-9.9) among patients with body mass index of ≥40 kg/m2. Inadequate exposure because of adhesions/ visceral adiposity was the most common reason for conversion for both laparoscopic (32%) and robotic hysterectomy (61%); however, intolerance of the Trendelenburg position caused 31% of laparoscopic conversions and 6% of robotic hysterectomy conversions. The pooled proportions of organ/vessel injury (laparoscopic, 3.5% [95% confidence interval, 2.2-5.5]; robotic hysterectomy,	see publication

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019				
		1.2% [95% confidence interval, 0.4-3.4]), venous thromboembolism (laparoscopic, 0.5% [95% confidence interval, 0.2-1.2]; robotic hysterectomy, 0.5% [95% confidence interval, 0.1-2.0]), and blood transfusion (laparoscopic, 2.8% [95% confidence interval, 1.5-5.1]; robotic hysterectomy, 2.1% [95% confidence interval, 1.6-3.8]) were low and not appreciably different between arms. **Author's Conclusion:** In conclusion, our review of moderate quality observational data suggests that LH and RH have similar rates of conversion to laparotomy and selected perioperative complications in patients with endometrial cancer and obesity. However, RH may offer benefit specifically in patients with morbid obesity by reducing conversions because of positional intolerance. Given the influence of selection and confounding bias, randomized trials in this patient population are needed to confirm our results and direct practice standards in this high-risk patient population.		
Methodical Notes				

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019

Funding Sources: Supported in part by the American College of Surgeons Resident Research Scholarship (M.C.C. and F.D.) and by the Ontario Women's Health Scholars Award funded by the Ontario Ministry of Health and Long-Term Care (M.C.C).

COI: The authors report no conflict of interest.

Study Quality: We assessed risk of bias with the Institute of Health Economics Quality Appraisal Checklist for single-arm studies. In keeping with prior work, we gave 1 point for "yes" answers, 0.5 points for "partial/unclear" answers, and 0 points for "no" answers and classified studies as being at low (80-100%), moderate (60-79%), or high risk (0-59%) of bias based on their overall percentage score.
Newcastle-Ottawa Quality Scale for double-arm studies. Studies were classified as being at low (7-9), moderate (4-6), or high (0e3) risk of bias based on their overall point score. Both scales evaluate broad sources of bias that include selection and attrition bias, exposure/ outcome ascertainment bias, and confounding bias, rather than topic-specific issues (eg, whether reasons forc onversion were documented).

We assessed all full-text articles for methodologic quality. Of the double-arm studies, 79% (23/29) were at low risk of bias, and 21% (6/29) were at moderate risk of bias. Of the single-arm studies, 41% (9/22) were at low risk of bias, and 59% (13/22) were at moderate risk of bias.

Heterogeneity: We evaluated statistical heterogeneity with the use of the I2 statistic and defined heterogeneity as notable when I2>50%.
There was considerable across-study heterogeneity for this outcome: conversion to laparotomy (I2: 82% LH; 79% RH). Heterogeneity was notable and the meta-analytic approach used in this study does not permit direct statistical comparisons between LH and RH, this difference is physiologically plausible and consistent with our data on the underlying reasons for conversion.

Publication Bias: Publication bias for our primary outcome (conversion to laparotomy) was evaluated with the use of funnel plots with the proportion of conversions on the x-axis and standard error on the y-axis.
The funnel plots for our primary outcome were asymmetric, which indicates that small studies with high proportions of patients who require conversion to laparotomy were not represented in the literature. However, this pattern was similar for both LH and RH, which suggests that publication bias may have affected the magnitude of our pooled estimates but
may have had less impact on differences between approaches.

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019			
Notes: SR auf Basis von retrospektiven Observationsstudien: CEBM Level of Evidence (Oxford): EL 3 This systematic review is limited primarily by the heterogeneity and observational design of included studies.			
Galaal, K. et al. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev. 10. Cd006655. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis of 9 RCTs (4389 patients) **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 5) in the Cochrane Library, MEDLINE via Ovid (April 2012 to June 2018) and Embase via Ovid (April 2012 to June 2018). **Search period:** **Inclusion Criteria:** Adult women diagnosed with endometrial cancer undergoing surgery as primary treatment. Since staging of endometrial cancer is	**Population:** Adult women diagnosed with endometrial cancer undergoing surgery as primary treatment. **Intervention:** Laparotomy, total abdominal hysterectomy (TAH) Laparoscopy; laparoscopically assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH) **Comparison:**	**Primary:** Overall survival (OS): survival until death from all causes. Survival was assessed from the time when women were enrolled in the trial. Recurrence free survival (RFS): length of time after treatment during which a woman survived with no sign of disease recurrence. **Secondary:** Local recurrence (port site, vaginal vault at laparoscopy and abdominal incision at laparotomy), Distant recurrence, Severe adverse events: perioperative death within 30 days; injuries (urinary tract, vascular,	9 RCTs (4389 patients) included: Fram 2002; Janda 2017; Lu 2013; Malzoni 2009; Mourits 2010; Tozzi 2005; Walker 2012; Zorlu 2005; Zullo 2009

Galaal, K. et al. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev. 10. Cd006655. 2018				
surgical, cases included were identified on the basis of no evidence of extrauterine disease preoperatively. We included studies with at least 70% of women with stage I to IIA disease, as it was expected that some studies would have small percentages of women with more advanced (stage IIb, III and IV) disease. **Exclusion Criteria:** We excluded women without a preoperative diagnosis of endometrial cancer(e.g. diagnosed with endometrial hyperplasia).		bowel); lymphoedema; venous thromboembolism; grade III or IV early and late complications. Blood loss including need for transfusion. Length of hospital stay/delayed discharge. Quality of life (QoL) after six months or more post operation, measured using a scale that was validated through reporting of norms in a peer-reviewed publication. **Results:** We identified one new study in this update of the review. The review contains nine RCTs comparing laparoscopy with laparotomy for the surgical management of early stage endometrial cancer. All nine studies met the inclusion criteria and assessed 4389 women at the end of the studies. Six studies assessing 3993 participants with early stage endometrial cancer found no significant difference in the risk of death between women who underwent laparoscopy and women who underwent laparotomy (HR 1.04, 95% 0.86 to 1.25; moderate-certainty evidence) and five studies assessing 3710 participants found no significant		

Galaal, K. et al. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev. 10. Cd006655. 2018				
		difference in the risk of recurrence between the laparoscopy and laparotomy groups (HR 1.14, 95% CI 0.90 to 1.43; moderate-certainty evidence). There was no significant difference in the rate of perioperative death; women requiring a blood transfusion; and bladder, ureteric, bowel and vascular injury. However, one meta-analysis of three studies found that women in the laparoscopy group lost significantly less blood than women in the laparotomy group (MD −106.82 mL, 95% CI −141.59 to −72.06; low-certainty evidence). A further meta-analysis of two studies, which assessed 3344 women and included one very large trial of over 2500 participants, found that there was no clinical difference in the risk of severe postoperative complications in women in the laparoscopy and laparotomy groups (RR 0.78, 95% CI 0.44 to 1.38). Most studies were at moderate risk of bias. All nine studies reported hospital stay and results showed that on average, laparoscopy was associated with a significantly shorter hospital stay.		

Galaal, K. et al. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev. 10. Cd006655. 2018				
		Author's Conclusion: This review found low to moderate-certainty evidence to support the role of laparoscopy for the management of early endometrial cancer. For presumed early stage primary endometrioid adenocarcinoma of the endometrium, laparoscopy is associated with similar OS and DFS. Furthermore, laparoscopy is associated with reduced operative morbidity and hospital stay. There is no significant difference in severe postoperative morbidity between the two modalities.		
Methodical Notes				
Funding Sources: Northern Gynaecology Oncology Centre, Queen Elizabeth Hospital, Gateshead, UK; Department of Health, UK; NHS Cochrane Collaboration programme Grant Scheme CPG-506 **COI:** None. **Study Quality:** Two review authors (KG, AB) independently used the Cochrane 'Risk of bias' tool to assess risk of bias of the included studies. The certainty of evidence for OS and RFS was moderate and was downgraded for unclear risk of bias profiles and imprecision in effect estimates. However, most studies used adequate methods of sequence generation and concealment of allocation so studies were not prone to selection bias. Adverse event outcomes were downgraded for the same reasons and additionally for low event rates and low power thus these outcomes provided low-certainty				

Galaal, K. et al. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev. 10. Cd006655. 2018			
evidence. **Heterogeneity:** We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between studies which could not be ascribed to sampling variation, by a formal statistical test of the significance of the heterogeneity and, where possible, by subgroup analyses. When there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this. No heterogeneity was present for the main outcomes overall survial (I 2 = 0%), Recurrence free survival (I 2 = 0%). **Publication Bias:** We examined funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects. When there was evidence of small-study effects, we considered publication bias as only one of several possible explanations. Where these plots suggested that treatment effects may not have be sampled from a symmetric distribution, as assumed by the random-effects model, we performed sensitivity analyses using fixed-effect models. The greatest threat to the validity of the review was likely to be the possibility of publication bias (i.e. studies that did found the treatment ineffective may not have been published). We were unable to assess this possibility as all the treatment comparisons were restricted to meta-analyses of up to seven trials. **Notes:** Oxford CEBM Level of Evidence 2011: EL 1 Systematic review and Meta-Analysis of RCTs Publication bias may be present.			
Marra, A. R. et al. Infectious complications of laparoscopic and robotic hysterectomy: a systematic literature review and meta-analysis. Int J Gynecol Cancer. 29. 518-530. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3	**Population:** Women who underwent hysterectomy (benign	**Primary:** infectious compications	see publication

Marra, A. R. et al. Infectious complications of laparoscopic and robotic hysterectomy: a systematic literature review and meta-analysis. Int J Gynecol Cancer. 29. 518-530. 2019				
Study type: SR and Meta (of 50 retrospective cohort, prospective cohort, RCT and case-control studies) **Databases:** PubMed, CINAHL, CDSR, and EMBASE **Search period:** Inception to July 15 2018 **Inclusion Criteria:** Studies evaluating robotic-assisted hysterectomy, laparoscopic-assisted hysterectomy, and infectious complications. Original research manuscripts; published in peer-reviewed, scientific journals; conducted in acute care settings that implemented robotic-assisted hysterectomy and compared data on infectious complications with laparoscopic-assisted hysterectomy; and controlled trial or observational study design. **Exclusion Criteria:** Studies in which open abdominal hysterectomy was compared only to laparoscopic- or only to robotic-assisted hysterectomy and studies that did not report infectious complications were also excluded.	disease, endometrial cancer, and cervical cancer patients) **Intervention:** Robotic-assisted hysterectomy **Comparison:** Conventional laparoscopic-assisted hysterectomy	**Secondary:** **Results:** **50** studies were included in the final review for the meta-analysis with **176016** patients undergoing hysterectomy. There was no statistically significant difference in the number of infectious complication events between robotic-assisted hysterectomy and laparoscopicassisted hysterectomy (pooled OR 0.97; 95 % CI 0.74 to 1.28). When we performed a stratified analysis, similar results were found with no statistically significant difference in infectious complications comparing robotic-assisted hysterectomy to laparoscopic-assisted hysterectomy among patients with benign uterine disease (pooled OR 1.10; 95 % CI 0.70 to 1.73), endometrial cancer (pooled OR 0.97; 95 % CI 0.55 to 1.73), or cervical cancer (pooled OR 1.09; 95 % CI 0.60 to 1.97). In addition, stratified analyzes among studies in academic vs community hospitals; in earlier studies (published between 2008 and 2012, vs published later (between 2013 and 2018)); and body mass index		

Marra, A. R. et al. Infectious complications of laparoscopic and robotic hysterectomy: a systematic literature review and meta-analysis. Int J Gynecol Cancer. 29. 518-530. 2019

		Author's Conclusion: In conclusion, our meta-analysis shows that robotic-assisted hysterectomy demonstrated no benefit in decreasing infectious complications in comparison to laparoscopic-assisted hysterectomy.		

Methodical Notes

Funding Sources: None reported

COI: None reported

Study Quality: Infectious complications were assessed using a random-effects model to estimate pooled ORs and 95% CIs with weights.We used the scale employed by Downs and Black16 to evaluate study quality. Each reviewed paper was assessed and the total score calculated. We used all the questions as written except for
question #27 (a single item on the Power subscale, which was scored 0 to 5), which we changed to a yes/no answer. The authors (two of them) performed component quality analysis independently, reviewed all inconsistent assessments, and achieved consensus by discussion.

Heterogeneity: Heterogeneity was evaluated with I2 estimation and the Cochran Q statistic.
infectious complications: Tau2= 0.26; Chi2=121,92; df=49 (P
infectious complications in patients with endometrial cancer (n=15 studies) with robotic hysterectomy (RH) and laparoscopichysterectomy (LH): Tau2=0.00; Chi2=8.46; df=10 (p=0.58); I2=0%

Publication Bias: Publication bias was assessed using the Egger test and the Durval and Tweedie's trim and fill test with Comprehensive Meta-Analysis Version 3 software

Marra, A. R. et al. Infectious complications of laparoscopic and robotic hysterectomy: a systematic literature review and meta-analysis. Int J Gynecol Cancer. 29. 518-530. 2019			
(Englewood, NJ).The funnel plot appeared fairly symmetrical, but the Egger test showed some evidence for publication bias among our included studies (P=0.028). However, using Duval and Tweedie's trim and fill to remove the most extreme studies from the funnel plot, did not substantially change the meta-analysis results (adjusted values using Duval and Tweedie's trim and fill OR=0.81; 95% CI 0.61 to 1.06). **Notes:** CEBM Level of Evidence (Oxford): EL 3 (Systematic review of retrospective cohort, prospective cohort, RCT and case-control studies)			
Wang, Y. R. et al. A network meta-analysis of comparison of operative time and complications of laparoscopy, laparotomy, and laparoscopic-assisted vaginal hysterectomy for endometrial carcinoma. Medicine (Baltimore). 97. e0474. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** Network Meta-Analysis of RCTs (9 RCTs, 2263 patients) In the present study, 3 different operative approaches (laparoscopy, laparotomy, and LAVH) for EC were searched out from relevant databases to compare their operative time and complications by performing this network meta-analysis. **Databases:** The Cochrane Library,	**Population:** EC patients aged from 27 to 89 years **Intervention:** Laparoscopy, laparotomy, and LAVH **Comparison:**	**Primary:** Operative time, incidences of bowel injury, and wound infection **Secondary:** **Results:** A total of 9 qualified RCTs were included into the study. The results showed that laparotomy had a shorter-operative time than LAVH (WMD=-40.36, 95% confidence interval=-75.03 to -2.57). However, there was no significant difference in the incidence of bowel	9 RCTs (2263 patients) included: Malur et al. 2001, Lu et al. 2013, Janda et al. 2010, Tozzi et al. 2005, Obermair et al. 2012, Nezhat et al. 2008, Kalogiannidis et al. 2007, Ghezzi et al. 2006, Bijen et al. 2011

Wang, Y. R. et al. A network meta-analysis of comparison of operative time and complications of laparoscopy, laparotomy, and laparoscopic-assisted vaginal hysterectomy for endometrial carcinoma. Medicine (Baltimore). 97. e0474. 2018				
PubMed, and Embase **Search period:** Inception to October 2017 **Inclusion Criteria:** Inclusion criteria were as follows: study design should be randomized controlled trials (RCTs); operative approaches included laparoscopy, laparotomy, and LAVH; the age of EC patients should be from 27 to 89 years old; outcomes included operative time, incidences of bowel injury, and wound infection **Exclusion Criteria:** Exclusion criteria were as follows: the studies lack data integrity; non-RCTs, non-English studies, nonhuman studies; and duplicate studies, conference reports, systematic reviews, and summaries.		injury and wound infection among 3 operative approaches. Besides, the SUCRA values indicated that laparotomy had the shortest operative time, but the incidence of bowel injury and wound infection was relatively higher. **Author's Conclusion:** The results from this study indicate that laparotomy had highest incidence of bowel injury and wound infection but shortest operative time among 3 operative approaches in the treatment of EC.		
Methodical Notes				
Funding Sources: None.				

Wang, Y. R. et al. A network meta-analysis of comparison of operative time and complications of laparoscopy, laparotomy, and laparoscopic-assisted vaginal hysterectomy for endometrial carcinoma. Medicine (Baltimore). 97. e0474. 2018

COI: None.

Study Quality: The risk of bias of included RCTs was assessed by 2 investigators according to the Cochrane Collaboration's tool. All included studies were in line with adequate
sequence generation and allocation concealment. Only a few studies were confirmed that blind method was not adopted. Most of the literatures conform to complete outcome data addressed, free of selective reporting, and free of other bias

Heterogeneity: I2 test and chi-squared test were used to test heterogeneity among the studies. Inconsistency tests showed that the results of the direct and indirect evidence of all outcomes were consistent, so the consistency model was adopted (both P>.05)

Publication Bias: Review Manager 5 (RevMan 5.2.3, Cochrane Collaboration, Oxford, UK) was used to carry out the quality assessment and investigation of publication bias. The funnel plot reveals that the scattered points are located in the funnel and distributed evenly on both sides of the central line, which further shows that there is no obvious bias in the included studies.

Notes:
Oxford CEBM Level of Evidence 2011: EL 1 Network Meta-Analysis
No search for grey literature or unpublished literature was performed.

2.33. Schlüsselfrage 36: Wie ist der Stellenwert robotergestützter operativer Verfahren beim Endometriumkarzinom im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *11 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Behbehani, S. 2019	3	SR and Meta (of 18 Retrospective Cohort Studies, 2 Prospective Cohort Studies and 1 RCT)
Cusimano, M. C. 2019	3	SR and Meta (of 51 Observational Studies)
Iavazzo, C. 2016	4	SR of 16 studies (15 case series and one case report)
Ind, T. 2017	3	SR and Meta (of 33 retrospective studies, 2 matched case-control studies and 1 RCT)
Jørgensen, S. L. 2019	3	nationwide prospective cohort study (6 national cancer centers)
Kristensen, S. E. 2017	4	SR (of 76 predominantly non-randomized retrospective observational studies)
Lawrie, T. A. 2019	1	SR and Meta (of 12 RCTs) This is an updated review of two originally separate Cochrane reviews concerning the use of robot-assisted surgery for benign gynaecological disease - in Liu 2012 - and for gynaecological cancer - in Lu 2012.
Machida, H. 2018	4	Retrospective cohort study

Literaturstelle	Evidenzlevel	Studientyp
Marra, A. R. 2019	3	SR and Meta (of 50 retrospective cohort, prospective cohort, RCT and case-control studies)
Salehi, S. 2018	2	Randomized controlled trial
Salehi, S. 2019	2	follow-up analysis of a randomized trial (RASHEC)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *7 Bewertung(en)*

Behbehani, S. et al. Mortality Rates in Laparoscopic and Robotic Gynecologic Oncology Surgery: A Systemic Review and Meta-analysis. J Minim Invasive Gynecol. 26. 1253-1267.e4. 2019				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Study type:** SR and Meta (of 18 Retrospective Cohort Studies, 2 Prospective Cohort Studies and 1 RCT) **Databases:** Pubmed, Embase, Scopus, Web of Science, and Cochrane Database **Search period:** in the last 10 years. **Inclusion Criteria:** All MIS articles in benign gynecology reporting operative mortality (within 30 days) were reviewed **Exclusion Criteria:** If mortality was not specifically documented as occurring in the postoperative period, the article was excluded.If mortality rates reported included laparotomy cases, and mortality for MIS procedures of interest (laparoscopy and robotic) could	**Intervention:** laparoscopic and robotic surgery (MIS) **Comparison:** commonly performed MIS	**Primary:** mortality rates in benign gynecologic laparoscopic and robotic surgery (MIS), **Secondary:** **Results:** These results are represented as odds, or number needed to treat, which are calculated as the reciprocal of the estimated mortality rate. 21 articles (124,216 patients) were included. Operative mortality from any benign MIS (laparoscopy and robotics) procedure was 1:6456 (95 % CI 1:3946, 1:10562). Studies were then grouped based on surgical procedure. Mortality rate for hysterectomy (119,721 patients) was 1:6814 (95% CI 1:4119, 1:11275); for sacrocolpopexy was 1:1246 (95% CI 1:36, 1:44700); and for adnexal surgery and diagnostic laparoscopy was 1:2245 (95% CI 1:45, 1:113372). Eighteen articles reported operative mortality for laparoscopic surgery, and 4 for robotic surgery.The mortality in laparoscopic and robotic surgery was 1:6512 (95% CI	see publication	

Behbehani, S. et al. Mortality Rates in Laparoscopic and Robotic Gynecologic Oncology Surgery: A Systemic Review and Meta-analysis. J Minim Invasive Gynecol. 26. 1253-1267.e4. 2019

not be extracted, the articles were excluded. Reports of less than 5 MIS cases, duplicate data presented in multiple manuscripts, and data presented in review articles were also excluded.		1:3971, 1:10680) and 1:5430 (95% CI 1:69-1:435052) respectively. **Author's Conclusion:** Operative mortality in benign minimally invasive gynecologic surgery is low, and mortality for laparoscopic and robotic approaches appear to be similar		

Methodical Notes

Funding Sources:

COI: J.M received a speaker honorarium intuitive November 2018. The remaining authors report no conflict of interest.

Study Quality: The Newcastle-Ottawa scale for observational studies was used to assess the quality of nonrandomized studies for potential risk of bias. For randomized controlled trials Cochrane risk of bias assessment tool (www.training.cochrane.org/handbook) was used.

Heterogeneity: Due to heterogeneity in study-designs (prospective, retrospective, single site, multicenter, etc.) the random-effects model is fitted for each analysis. Measures of between-study heterogeneity and consistency measured as tau-squared and I^2 are provided in every forest plot. Since the probability of observing mortality is very small, a variety of confidence interval formulations, such as the normal approximation, might have negative values for the lower limit of mortality rate. This would not make sense. To avoid this, the confidence intervals in the forest plots are calculated using the Wilson Score method with continuity correction, which sets the lower confidence interval equal to 0 in the case where no mortalities were observed. A continuity correction of 0.50 was added to articles that reported no events.

Mortality in benign MIS gynecological procedures: I2=0%, t2=0, p=1.00
Mortality in benign laparoscopic gynecological procedures: I2=0%, t2=0, p=0.99

Behbehani, S. et al. Mortality Rates in Laparoscopic and Robotic Gynecologic Oncology Surgery: A Systemic Review and Meta-analysis. J Minim Invasive Gynecol. 26. 1253-1267.e4. 2019

Mortality in benign robotic gynecological procedures: I2=0%, t2=0, p=0.88
Mortality in MIS hysterectomy:I2=0%, t2=0, p=0.70
Mortality in laparoscopic hysterectomy:I2=0%, t2=0, p=0.73

Publication Bias:

Notes:
SR and Meta based on only RCTs, prospective and retrospective cohort studies: EL 3
Heterogeneity is low but mortality cases are rare (see heterogeneity)
Although comparison was stated to be commonly performed MIS

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** SR and Meta (of 51 Observational Studies)	**Population:** patients with endometrial cancer and obesity (body mass index, ≥30 kg/m2).	**Primary:** rates of conversion **Secondary:** perioperative complications	see publication

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019				
Databases: MEDLINE, EMBASE, and Evidence-Based Medicine Reviews **Search period:** January 1, 2000, to July 18, 2018 **Inclusion Criteria:** Studies of patients with endometrial cancer and obesity (body mass index, 30 kg/m2) who underwent primary hysterectomy. **Exclusion Criteria:** exclusion of studies that evaluated hysterectomy with panniculectomy only.	**Intervention:** robotic hysterectomy **Comparison:** laparoscopic hysterectomy	**Results:** **51 observational studies** that reported on **10,800 patients** with **endometrial cancer and obesity** (study-level body mass index, 31.0-56.3 kg/m2). The pooled proportions of conversion from laparoscopic and robotic hysterectomy were 6.5% (95% confidence interval, 4.3-9.9) and 5.5% (95% confidence interval, 3.3-9.1), respectively, among patients with a body mass index of ≥30 kg/m2, and 7.0% (95% confidence interval, 3.2-14.5) and 3.8% (95% confidence interval, 1.4-9.9) among patients with body mass index of ≥40 kg/m2. Inadequate exposure because of adhesions/ visceral adiposity was the most common reason for conversion for both laparoscopic (32%) and robotic hysterectomy (61%); however, intolerance of the Trendelenburg position caused 31% of laparoscopic conversions and 6% of robotic hysterectomy conversions. The pooled proportions of organ/vessel injury (laparoscopic, 3.5% [95% confidence interval, 2.2-5.5]; robotic hysterectomy, 1.2% [95% confidence interval, 0.4-3.4]), venous thromboembolism (laparoscopic, 0.5% [95% confidence interval, 0.2-1.2]; robotic hysterectomy, 0.5% [95% confidence interval, 0.1-2.0]), and blood transfusion (laparoscopic, 2.8% [95% confidence interval, 1.5-5.1]; robotic hysterectomy, 2.1% [95% confidence interval,		

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019				
		1.6-3.8]) were low and not appreciably different between arms. **Author's Conclusion:** In conclusion, our review of moderate quality observational data suggests that LH and RH have similar rates of conversion to laparotomy and selected perioperative complications in patients with endometrial cancer and obesity. However, RH may offer benefit specifically in patients with morbid obesity by reducing conversions because of positional intolerance. Given the influence of selection and confounding bias, randomized trials in this patient population are needed to confirm our results and direct practice standards in this high-risk patient population.		
Methodical Notes				
Funding Sources: Supported in part by the American College of Surgeons Resident Research Scholarship (M.C.C. and F.D.) and by the Ontario Women's Health Scholars Award funded by the Ontario Ministry of Health and Long-Term Care (M.C.C). **COI:** The authors report no conflict of interest.				

Cusimano, M. C. et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 221. 410-428.e19. 2019

Study Quality: We assessed risk of bias with the Institute of Health Economics Quality Appraisal Checklist for single-arm studies. In keeping with prior work, we gave 1 point for "yes" answers, 0.5 points for "partial/unclear" answers, and 0 points for "no" answers and classified studies as being at low (80-100%), moderate (60-79%), or high risk (0-59%) of bias based on their overall percentage score.
Newcastle-Ottawa Quality Scale for double-arm studies. Studies were classified as being at low (7-9), moderate (4-6), or high (0e3) risk of bias based on their overall point score. Both scales evaluate broad sources of bias that include selection and attrition bias, exposure/ outcome ascertainment bias, and confounding bias, rather than topic-specific issues (eg, whether reasons forc onversion were documented).

We assessed all full-text articles for methodologic quality. Of the double-arm studies, 79% (23/29) were at low risk of bias, and 21% (6/29) were at moderate risk of bias. Of the single-arm studies, 41% (9/22) were at low risk of bias, and 59% (13/22) were at moderate risk of bias.

Heterogeneity: We evaluated statistical heterogeneity with the use of the I2 statistic and defined heterogeneity as notable when I2>50%.
There was considerable across-study heterogeneity for this outcome: conversion to laparotomy (I2: 82% LH; 79% RH). Heterogeneity was notable and the meta-analytic approach used in this study does not permit direct statistical comparisons between LH and RH, this difference is physiologically plausible and consistent with our data on the underlying reasons for conversion.

Publication Bias: Publication bias for our primary outcome (conversion to laparotomy) was evaluated with the use of funnel plots with the proportion of conversions on the x-axis and standard error on the y-axis.
The funnel plots for our primary outcome were asymmetric, which indicates that small studies with high proportions of patients who require conversion to laparotomy were not represented in the literature. However, this pattern was similar for both LH and RH, which suggests that publication bias may have affected the magnitude of our pooled estimates but
may have had less impact on differences between approaches.

Notes:
SR auf Basis von retrospektiven Observationsstudien: CEBM Level of Evidence (Oxford): EL 3
This systematic review is limited primarily by the heterogeneity and observational design of included studies.

Iavazzo, C. et al. Robotic assisted hysterectomy in obese patients: a systematic review. Arch Gynecol Obstet. 293. 1169-83. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** SR of 16 studies (15 case series and one case report) **Databases:** PubMed and in Scopus **Search period:** 05 October 2015 **Inclusion Criteria:** Studies that reported data on the robotic assisted hysterectomy on obese patients were included in this review. **Exclusion Criteria:** Letters to the editor, abstracts in scientific conferences, editorials and studies published in languages other than English, German, French, Italian and Spanish were excluded from this study.	**Population:** Obese and morbidly obese patients. **Intervention:** Robotic hysterectomy. **Comparison:** None.	**Primary:** Conversion rates, blood loss and transfusion rate or on complication rates and patients outcomes. **Secondary:** Not depicted. **Results:** In total, 3986 patients were included in this study, while robotic assisted hysterectomy was performed on 2769 patients. The most frequent indication for robotic hysterectomy was endometrial carcinoma (1832 out of 2769 patients, 66.2 %). Hypertension, diabetes mellitus, obstructive sleep apnea, chronic obstructive pulmonary disease and venous thromboembolism were the most common comorbidities reported. The conversion rate to laparotomy was 92 out of 2226 patients (4.1 %). The most frequent intraoperative complications for robotic hysterectomy were gastrointestinal injury (17 out of 2769 patients, 0.6 %), haemorrhage (five out of 2769 patients, 0.2 %) and bladder injury (five out of 2769 patients, 0.2 %). Wound infections/dehiscence (66 out of 2769 patients, 2.4 %), fever (56 out of 2769 patients, 2 %), pulmonary complications (55 out of 2769 patients, 1.9 %), urogenital complications (36 out of 2769 patients, 1.3 %) and postoperative ileus (28 out of 2769 patients, 1 %)	See publication.

Iavazzo, C. et al. Robotic assisted hysterectomy in obese patients: a systematic review. Arch Gynecol Obstet. 293. 1169-83. 2016				
		were the most common postoperative complications. Death was reported in three out of 2769 patients (0.1 %). The ICU admitted patients were eight of 2226 patients (0.4 %). **Author's Conclusion:** Robotic hysterectomy is an alternative approach to the management of female genital tract pathology. In this review, we showed that the robotic assisted technique can optimize the surgical approach and post operative recovery, presenting advantages in the treatment of such patients. In conclusion, the use of robotics seems apparently to have equally if not better outcomes compared to open and/or laparoscopic techniques.		
Methodical Notes				
Funding Sources: None. **COI:** The authors do not have any financial relationship/interest. **Study Quality:** Not depicted. **Heterogeneity:** Not depicted. **Publication Bias:** Not depicted.				

Iavazzo, C. et al. Robotic assisted hysterectomy in obese patients: a systematic review. Arch Gynecol Obstet. 293. 1169-83. 2016			
Notes: CEBM Level of Evidence (Oxford): EL 4 (Systematic review of 16 studies (15 case series and one case report)) with no discription of study quality assessment or heterogeneity. No comparison reported.			
Ind, T. et al. A comparison of operative outcomes between standard and robotic laparoscopic surgery for endometrial cancer: A systematic review and meta-analysis. Int J Med Robot. 13. . 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** SR and Meta (of 33 retrospective studies, 2 matched case-control studies and 1 RCT) **Databases:** Medline, Embase and Cochrane databases **Search period:** 1st January 1991 until 30th October 2016 **Inclusion Criteria:** Studies that compared a standard laparoscopic approach to endometrial cancer with a robotic approach within a discrete cohort were included.	**Population:** Endometrial cancer patients. **Intervention:** Robot assisted laparoscopy. **Comparison:** Standard laparoscopy.	**Primary:** Duration of surgery or operating room times, blood loss, total number of lymph nodes removed, Conversion to Laparotomy, All Complications. **Secondary:** Not depicted. **Results:** Dichotomous data were presented as Risk Ratios using the Mantel-Haenszel method with random effects. Continuous data were presented as means with standard deviations and analysed using the Inverse Variance metho using random effects. 36 studies with 8075 patients (3830 robotic and 4245 laparoscopic). **Author's Conclusion:** In summary, this study demonstrates that the current evidence is in favour of	See publication.

Ind, T. et al. A comparison of operative outcomes between standard and robotic laparoscopic surgery for endometrial cancer: A systematic review and meta-analysis. Int J Med Robot. 13. . 2017				
Exclusion Criteria: If data extraction for endometrial cancer patients from other diagnoses was not possible.		robotic assisted laparoscopy for endometrial cancer over standard laparoscopy for clinic outcomes but costs are probably greater. To date there are only 99 patients recruited to randomized controlled trials and an increase in this number will undoubtedly provide stronger evidence.		
Methodical Notes				
Funding Sources: Not stated. **COI:** Marielle Nobbenhuis and Thomas Ind have proctored for Intuitive Surgical. **Study Quality:** 33 Retrospective cohort reviews, 2 matched retrospective reviews and 1 RCT. Therefore, the quality of the evidence is low although it is bolstered by large numbers of papers and patients. One criticism is that in many of the papers, the robotic arm consists of an early series for the surgical teams. Outcomes with robotic surgery improve with numbers performed so this would potentially be biasing the results in favour of the more established standard laparoscopy arm. Furthermore, some authors have acknowledged worse co-morbidity in the robotic arms of their studies with obesity in particular associated with worse outcomes. Therefore the data in favour of robotic laparoscopy is in spite of adverse confounders. **Heterogeneity:** Duration of operations for endometrial cancer (mins): Tau2=1773.16 ; Chi2=1007.21 ; df=26 ; (P Days in hospital following surgery for endometrial cancer: Tau2=0.17 ; Chi2=156.68 ; df=24 ; (P Mean estimated blood loss (mL) following surgery for endometrial cancer: Tau2=1907.01 ; Chi2=235.23 ; df=27 ; (P Blood transfusions following surgery for endometrial cancer:				

Ind, T. et al. A comparison of operative outcomes between standard and robotic laparoscopic surgery for endometrial cancer: A systematic review and meta-analysis. Int J Med Robot. 13. . 2017			
Tau2=0.02 ; Chi2=18.74 ; df=18 ; (P=0.41) ; I2=4% All complications related to surgery for endometrial cancer: Tau2=0.01 ; Chi2=25.06 ; df=24 ; (P=0.40) ; I2=4% Conversions to laparotomy following surgery for endometrial cancer: Tau2=0.19 ; Chi2=37.05 ; df=26 ; (P=0.07) ; I2=30% **Publication Bias:** Not stated. **Notes:** CEBM Level of Evidence (Oxford): EL 3 (Systematic review of 33 Retrospective cohort reviews, 2 matched retrospective reviews and 1 RCT)			
Kristensen, S. E. et al. Robot-assisted surgery in gynecological oncology: current status and controversies on patient benefits, cost and surgeon conditions - a systematic review. Acta Obstet Gynecol Scand. 96. 274-285. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** SR (of 76 predominantly non-randomized retrospective observational studies) **Databases:** PubMed and EMBASE	Population: Human participants Intervention: n.s. Comparison: n.s.	**Primary:** n.s. **Secondary:** n.s. **Results:** Robot-assisted surgery in gynecological oncology has increased, and current knowledge supports that the oncological safety is similar, compared with previous surgical methods. Controversies arise because current knowledge does not clearly	

Kristensen, S. E. et al. Robot-assisted surgery in gynecological oncology: current status and controversies on patient benefits, cost and surgeon conditions - a systematic review. Acta Obstet Gynecol Scand. 96. 274-285. 2017				
Search period: up until 4 March 2016 **Inclusion Criteria:** Human participants and English language were the only restrictive filters applied. **Exclusion Criteria:** -		document the benefit of robot-assisted surgery, on perioperative outcome compared with the increased costs of the acquisition and application. **Author's Conclusion:** In conclusion, the current evidence suggests that RAS is safe to treat endometrial cancer, especially in obese women, but with limited data for overall survival and disease-free period.		
Methodical Notes				
Funding Sources: n.s. **COI:** No conflicts of interest. **Study Quality:** The strength of evidence in the included articles was evaluated by means of Grading of Recommendations Assessments, Development, and Evaluation (GRADE) criteria. **Heterogeneity:** high - pooling of results was not possible. **Publication Bias:** n.a. **Notes:** Oxford CEBM Level of evidence 2011: EL 3 Systematic review of retrospective cohort studies. (downgraded one level from EL 3 to 4, due to low quality)				

Kristensen, S. E. et al. Robot-assisted surgery in gynecological oncology: current status and controversies on patient benefits, cost and surgeon conditions - a systematic review. Acta Obstet Gynecol Scand. 96. 274-285. 2017			
Limitations: - no adequate population description - no inclusion/exlusion criteria - no Indication/comparison - all outcomes relevant The above mentioned factors resulted in a very divers subset of studies, all describing different aspects of robot-assisted surgery.			
Lawrie, T. A. et al. Robot?assisted surgery in gynaecology. Cochrane Database of Systematic Reviews. . . 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** SR and Meta (of 12 RCTs) This is an updated review of two originally separate Cochrane reviews concerning the use of robot-assisted surgery for benign gynaecological disease - in Liu 2012 - and for gynaecological cancer - in Lu 2012. **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via	**Population:** Women undergoing hysterectomy. Women requiring surgery for benign or malignant gynaecological disease at any age. **Intervention:** Robot-assisted surgery (RAS) **Comparison:** Conventional laparoscopic surgery (CLS)	**Primary:** · **Intraoperative complications** including injury to the bladder, ureters, bowel, blood vessels, and nerves · **Postoperative complications** including vascular (e.g. haemorrhage, deep vein thrombosis), wound (e.g. infection, dehiscence (wound breakdown)), gastrointestinal (e.g. bowel obstruction due to fibrous adhesions, paralytic ileus due to paralysis of intestinal muscles), incisional hernia (swelling caused by tissue poking	Anger 2014; Costantini 2017; Deimling 2017; Green 2013; LAROSE 2017; Lonnerfors

Lawrie, T. A. et al. Robot?assisted surgery in gynaecology. Cochrane Database of Systematic Reviews. . . 2019				
Ovid, and EMBASE via Ovid, on 8 January 2018. We searched www.ClinicalTrials.gov. on 16 January 2018 **Search period:** Electronic searches For this review update, we searched the following databases (**8 January 2018**). · Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 12). · MEDLINE via Ovid (June 2014 to December week 4 2018). · Embase via Ovid (June 2014 to 2018 week 2). We identified all potentially eligible articles on PubMed, and we performed searches for related articles using the 'Related articles' feature. Original searches We conducted the original searches (**14 July 2010**) for the review of 'Robotics and malignant disease' as follows (Lu 2012). · Cochrane Gynaecological Cancer Review Group Trials Register. · CENTRAL (2010, Issue 3). · MEDLINE (from 1950 to June week 5 2010). · Embase (from 1974 to week 27 2010). Similarly, we performed the **original**	Open surgery Comparison of different types of robot assistants	through a surgical scar of a previous operation), neurological, respiratory (e.g. pneumonia, embolism (blood clot in a lung blood vessel)), and urinary complications (e.g. acute urinary retention) **Secondary:** · Early and late mortality (early mortality defined as death within 30 days; late mortality defined as death within three months) · Total operating time (from skin incision to closure) · Instrument setup time · Overall and postoperative duration of hospital stay · Estimated blood loss · Blood transfusion · Rate of conversion to open surgery (for RAS vs CLS) · Quality of life (QoL) as assessed using validated scales (e.g. Quality of Life Questionnaire-Core 30 (QLQ-C30) - developed to assess the quality of life of people with cancer; Functional Assessment of Cancer Therapy - Ovarian (FACT-O)) · Postoperative pain as assessed using visual analogue or other validated scales	2014; Maenpaa 2016; Paraiso 2011; Paraiso 2013; RASHEC 2013; Sarlos 2010; Wijk 2016	

Lawrie, T. A. et al. Robot?assisted surgery in gynaecology. Cochrane Database of Systematic Reviews. . . 2019				
searches from inception to 21 November 2011, for the review of 'Robotics and benign disease.' In addition, we searched the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Trials Register, the Chinese Biomedical Literature Database (CBM), and Chinese Medical Current Contents (CMCC). **Inclusion Criteria:** RCTs comparing RAS versus CLS or open surgery in women requiring surgery for gynaecological disease. **Exclusion Criteria:** No RCT		· Total cost (including equipment costs, theatre costs, and cost of hospital stay) · Surgeon's performance and workload as assessed by investigators (e.g. using NASA Task Load Index (NASA-TLX)) Additionally, for cancer surgery: · Disease-free survival · Overall survival · Numbers of lymph nodes harvested: total, pelvic, and paraaortic lymph nodes **Results:** We included 12 RCTs involving 1016 women. Procedures performed were hysterectomy (eight studies) and sacrocolpopexy (three studies). In addition, one trial examined surgical treatment for endometriosis, which included resection or hysterectomy. Among studies of women undergoing hysterectomy procedures, two studies involved malignant disease (endometrial cancer); the rest involved non-malignant disease. · **RAS versus CLS (hysterectomy)** Low-certainty evidence suggests there might be little or no difference in any		

Lawrie, T. A. et al. Robot?assisted surgery in gynaecology. Cochrane Database of Systematic Reviews. . . 2019				
		complication rates between RAS and CLS (risk ratio (RR) 0.92, 95% confidence interval (CI) 0.54 to 1.59; participants = 585; studies = 6; IR = 51%), intraoperative complication rates (RR 1.05, 95% CI 0.31 to 3.56; participants = 487; studies = 5; IR = 28%), postoperative complications (RR 0.82, 95% CI 0.42 to 1.59; participants = 533; studies = 5; I2 = 51%), and blood transfusions (RR 2.49, 95% CI 0.75 to 8.23; participants = 346; studies = 4; I2 = 0%)). There was no statistical difference between malignant and non-malignant disease subgroups with regard to complication rates. Survival outcomes for women with malignant disease were not reported. Mean total operating time was longer on average in the RAS arm than in the CLS arm (mean diKerence (MD) 41.18 minutes, 95% CI -6.17 to 88.53; participants = 148; studies = 2; IR = 80%; very low-certainty evidence), and the mean length of hospital stay was slightly shorter with RAS than with CLS (MD -0.30 days, 95% CI -0.53 to -0.07; participants = 192; studies = 2; IR = 0%; very low-certainty evidence). · **RAS versus open abdominal surgery**		

Lawrie, T. A. et al. Robot?assisted surgery in gynaecology. Cochrane Database of Systematic Reviews. . . 2019				
		(hysterectomy) Two studies of 20 and 96 participants with non-malignant disease and malignant disease, respectively, compared RAS with open surgery. For most outcomes only one study contributed data, with most evidence assessed as very low-certainty. Low-certainty evidence from the study among women with endometrial cancer suggests that lymph node yields may be lower with RAS (MD -8.00, 95% CI -14.97 to -1.03), operating time may be longer (233 minutes (range 166 to 320 minutes) compared with 187 minutes (range 109 to 300), hospital stays may be shorter (mean of 2 days [1 to 5] versus 5 days [4 to 9]; P Author's Conclusion: Evidence on the effectiveness and safety of robot-assisted surgery (RAS) compared with conventional laparoscopic surgery (CLS) for non-malignant disease (hysterectomy and		

Lawrie, T. A. et al. Robot?assisted surgery in gynaecology. Cochrane Database of Systematic Reviews. . . 2019				
		sacrocolpopexy) is of low certainty but suggests that surgical complication rates might be comparable. Evidence on the effectiveness and safety of RAS compared with CLS or open surgery for malignant disease is more uncertain because survival data are lacking; therefore, until further evidence becomes available, its use in this context might be appropriate only in clinical trials. Other practical implications, such as the potential for under-skilling of surgical trainees and future surgeons in essential surgical skills, should be carefully considered in broader discussions around the use of RAS. The effectiveness and safety of RAS remain uncertain, so more evidence on whether it should be used for gynaecological procedures is needed, as is independent evaluation of cost-effectiveness. RAS is an operator dependent, expensive technology, meaning that independent evaluation of the safety of this technology without bias will be challenging.		
Methodical Notes				

Lawrie, T. A. et al. Robot?assisted surgery in gynaecology. Cochrane Database of Systematic Reviews. . . 2019

Funding Sources: Internal sources
· Department of Obstetrics & Gynaecology, West China Second University Hospital, Sichuan University, China, Other.
External sources
· No sources of support supplied

COI: None.

Study Quality: Risk of bias in included RCTs assesesd using the 'Risk of bias' tool of the Cochrane Collaboration. Overall, we considered one study to be at high risk of bias (Green 2013), and we considered the other studies to be at moderate risk
of bias. We downgraded evidence mainly due to concerns about risk of bias among
studies contributing data and imprecision of effect estimates.

Heterogeneity: Heterogeneity for malignant disease: Not applicable. For other disease: see result. Tests for heterogeneity using the ChiR test, with significance set at P value less than 0.1. We explored statistical heterogeneity by visually inspecting forest plots. We used the IR statistic to estimate the total variation across studies that was due to heterogeneity: less than 25% was considered as mild, 25% to 50% as moderate, and greater than 50% as substantial heterogeneity (Higgins 2011). If the primary outcome measures had substantial heterogeneity (IR > 50%), we explored possible sources of heterogeneity by performing sensitivity and subgroup analyses.

Publication Bias: As a result of the small number of included studies, we were unable to meaningfully evaluate publication bias as planned; however, one included study with significant protocol deviations remains unpublished (Green 2013).

Notes:
CEBM Level of Evidence (Oxford): EL 1
Systematic review of randomized trials

Marra, A. R. et al. Infectious complications of laparoscopic and robotic hysterectomy: a systematic literature review and meta-analysis. Int J Gynecol Cancer. 29. 518-530. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** SR and Meta (of 50 retrospective cohort, prospective cohort, RCT and case-control studies) **Databases:** PubMed, CINAHL, CDSR, and EMBASE **Search period:** Inception to July 15 2018 **Inclusion Criteria:** Studies evaluating robotic-assisted hysterectomy, laparoscopic-assisted hysterectomy, and infectious complications. Original research manuscripts; published in peer-reviewed, scientific journals; conducted in acute care settings that implemented robotic-assisted hysterectomy and compared data on infectious complications with laparoscopic-assisted hysterectomy; and controlled trial or observational study design.	**Population:** Women who underwent hysterectomy (benign disease, endometrial cancer, and cervical cancer patients) **Intervention:** Robotic-assisted hysterectomy **Comparison:** Conventional laparoscopic-assisted hysterectomy	**Primary:** infectious compications **Secondary:** **Results:** **50** studies were included in the final review for the meta-analysis with **176016** patients undergoing hysterectomy. There was no statistically significant difference in the number of infectious complication events between robotic-assisted hysterectomy and laparoscopicassisted hysterectomy (pooled OR 0.97; 95 % CI 0.74 to 1.28). When we performed a stratified analysis, similar results were found with no statistically significant difference in infectious complications comparing robotic-assisted hysterectomy to laparoscopic-assisted hysterectomy among patients with benign uterine disease (pooled OR 1.10; 95 % CI 0.70 to 1.73), endometrial cancer (pooled OR 0.97; 95 % CI 0.55 to 1.73), or cervical cancer (pooled OR 1.09; 95 % CI 0.60 to	see publication

Marra, A. R. et al. Infectious complications of laparoscopic and robotic hysterectomy: a systematic literature review and meta-analysis. Int J Gynecol Cancer. 29. 518-530. 2019				
Exclusion Criteria: Studies in which open abdominal hysterectomy was compared only to laparoscopic- or only to robotic-assisted hysterectomy and studies that did not report infectious complications were also excluded.		1.97). In addition, stratified analyzes among studies in academic vs community hospitals; in earlier studies (published between 2008 and 2012, vs published later (between 2013 and 2018)); and body mass index **Author's Conclusion:** In conclusion, our meta-analysis shows that robotic-assisted hysterectomy demonstrated no benefit in decreasing infectious complications in comparison to laparoscopic-assisted hysterectomy.		
Methodical Notes				
Funding Sources: None reported **COI:** None reported **Study Quality:** Infectious complications were assessed using a random-effects model to estimate pooled ORs and 95% CIs with weights.We used the scale employed by Downs and Black16 to evaluate study quality. Each reviewed paper was assessed and the total score calculated. We used all the questions as written except for question #27 (a single item on the Power subscale, which was scored 0 to 5), which we changed to a yes/no answer. The authors (two of them) performed component quality analysis independently, reviewed all inconsistent assessments, and achieved consensus by discussion. **Heterogeneity:** Heterogeneity was evaluated with I2 estimation and the Cochran Q statistic.				

Marra, A. R. et al. Infectious complications of laparoscopic and robotic hysterectomy: a systematic literature review and meta-analysis. Int J Gynecol Cancer. 29. 518-530. 2019

infectious complications: Tau2= 0.26; Chi2=121,92; df=49 (P
infectious complications in patients with endometrial cancer (n=15 studies) with robotic hysterectomy (RH) and laparoscopichysterectomy (LH): Tau2=0.00; Chi2=8.46; df=10 (p=0.58); I2=0%

Publication Bias: Publication bias was assessed using the Egger test and the Durval and Tweedie's trim and fill test with Comprehensive Meta-Analysis Version 3 software
(Englewood, NJ).The funnel plot appeared fairly symmetrical, but the Egger test showed some evidence for publication bias among our included studies (P=0.028).
However, using Duval and Tweedie's trim and fill to remove the most extreme studies from the funnel plot, did not substantially change the meta-analysis results (adjusted values using Duval and Tweedie's trim and fill OR=0.81; 95% CI 0.61 to 1.06).

Notes:
CEBM Level of Evidence (Oxford): EL 3 (Systematic review of retrospective cohort, prospective cohort, RCT and case-control studies)

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Salehi, S. et al. Long-term quality of life after comprehensive surgical staging of high-risk endometrial cancer - results from the RASHEC trial. Acta Oncol. 57. 1671-1676. 2018		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized controlled trial **Number of Patient:** Of 120 included women, (60 in each group). 7 women did not undergo the allocated procedure, thus 113 were part of the intention to treat analysis. **Recruitung Phase:** May 2013 and July 2016 **Inclusion Criteria:** Women with early stage EC and high-risk features; women aged between 18 and 75 years, FIGO stage I or II; PS 0-1; **Exclusion Criteria:** ongoing antitumor treatment (except treatment with tamoxifen or aromatase inhibitors), pre-operative imaging indicating extra-	**Intervention:** infrarenal para-aortic lymph node yield between RALS and LT with the intention to undergo hysterectomy, bilateral salpingo-oophorectomy, pelvic and infrarenal paraaortic lymph node dissection. **Comparison:** see intervention	**Primary:** The number of harvested paraaortic lymph nodes. **Secondary:** HRQoL was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and its endometrial cancer supplementary questionnaire module (QLQ-EN24) before and 12 months after surgery. **Results:** Original trial: Mean pelvic and paraaortic lymph node count was 22 and 20 for RALS, 28 and 22 for LT. The paraaortic lymph node count MD was within the non-inferiority margin (-1.6, 95% CI -5.78, 2.57). Mean pelvic node count was lower after RALS (28 ± 10 vs. 22 ± 8, p **Quality of Life:** There was no difference in the functional scales (including global health status) in the intention to treat analysis, though LT conferred a small clinically

Salehi, S. et al. Long-term quality of life after comprehensive surgical staging of high-risk endometrial cancer - results from the RASHEC trial. Acta Oncol. 57. 1671-1676. 2018			
uterine spread, medically unfit for extensive surgery or inability to comply to the protocol.		important difference (CID) over RALS in 'cognitive functioning' albeit not statistically significant -6 (95% CI14 to 0, p = .06). LT conferred a significantly better outcome for the 'nausea and vomiting' item though it did not reach a CID, 4 (95% CI 1 to 7, p = .01). In the EORTC-QLQ/QLQ-EN24, no significant differences were observed. Eq5D-3L questionnaire demonstrated a higher proportion of women reporting any extent of mobility impairment 12 months after surgery in the LT arm (p = .03). **Author's Conclusion:** Original trial (2017): The Robot-Assisted Surgery for High-Risk Endometrial Cancer (RASHEC) trial, robotassisted laparoscopic surgery (RALS) offers a similar infrarenal paraaortic lymph node count, lower health care cost and similar short-term complications rates compared to laparotomy (LT). In conclusion, the results of our study suggest that HRQoL 1 year after comprehensive surgical staging, including infrarenal paraaortic lymphadenectomy, in women with EC is not affected by surgical modality. From a HRQoL prespective, the choice of abdominal access should be based on patient's preference and surgeon's experience.	

Salehi, S. et al. Long-term quality of life after comprehensive surgical staging of high-risk endometrial cancer - results from the RASHEC trial. Acta Oncol. 57. 1671-1676. 2018			
Methodical Notes			
Funding Sources: This study was funded by grants from Radiumhemmets Forskningsfonder and grants from Stockholm County Council. **COI:** Henrik Falconer is a Proctor for Intuitive Surgical. The remaining authors declare no conflict of interest in regard to this paper. **Randomization:** yes (using a complete block design with 20 sealed envelopes at a time, with the patient drawing a sealed envelope. **Blinding:** Masking was not performed due to the nature of the treatment. **Dropout Rate/ITT-Analysis:** Performed for main outcome. **Notes:** Oxford CEBM Level of evidence: EL 2 (randomized trial). This evidence table combines the three studies of Salehi et al from 2017 and 2018 , both evaluating the results of the RASHEC trial with different outcomess.			
Salehi, S. et al. Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial. Int J Gynecol Cancer. 29. 86-93. 2019			
Population	Intervention - Comparison	Outcomes/Results	

Salehi, S. et al. Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial. Int J Gynecol Cancer. 29. 86-93. 2019

Evidence level: 2

Study type: follow-up analysis of a randomized trial (RASHEC)

Number of Patient: 24 patients of the RALS group and 24 patients of the laparotomy group received drainage.

Recruitung Phase: Between 2013 and 2016.

Inclusion Criteria: Patients from the RASHEC trial further randomized to abdominal drainage or no drainage.

Exclusion Criteria: -

Intervention: Abdominal drainage.

Comparison: No drainage.

Primary: Self-reported lower limb lymphedema, imaging, Long-term serious adverse events and admission to hospital for any reason.

Secondary: see primary.

Results: At 12 months after laparotomy and RALS, 61% and 50%, respectively, reported LLL (p=0.31). In univariate analysis, the mean score of LLL at 12 months was significantly higher for laparotomy than for RALS (p

Author's Conclusion: In conclusion, the majority of women with high-risk endometrial cancer subjected to pelvic and infrarenal para-aortic lymphadenectomy report symptoms of LLL 1 year after surgery. The route of abdominal access does not appear to affect long term morbidity, since no differences were observe between robot-assisted laparoscopy and laparotomy.

Methodical Notes

Funding Sources: None.

COI: HH is a proctor for intuitive surgical. the others declare no conflict of interest.

Salehi, S. et al. Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial. Int J Gynecol Cancer. 29. 86-93. 2019

Randomization: yes

Blinding: no.

Dropout Rate/ITT-Analysis: -

Notes:
This study is a follow-up analysis of the RASHEC trial (study of Salehi S et al, 2017 and 2018).

Oxford CEBM Level of evidence 2011: EL 2 (Randomized trial)

Limitations:
- due to the second randomization step in this study the study groups are very small (24 patients per group) and
- the study was not designed (powered) to analyse differences in complications.

The results should be interpreted with care.

NEWCASTLE - OTTAWA Checklist: Case Control: *1 Bewertung(en)*

Machida, H. et al. Intrauterine Manipulator Use During Minimally Invasive Hysterectomy and Risk of Lymphovascular Space Invasion in Endometrial Cancer. Int J Gynecol Cancer. 28. 208-219. 2018

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4	**Funding sources:** This study was supported by the Ensign Endowment for Gynecologic	**Total no. patients:** 687 women who underwent hysterectomy for endometrial	**Interventions:** Total laparoscopic hysterectomy

Machida, H. et al. Intrauterine Manipulator Use During Minimally Invasive Hysterectomy and Risk of Lymphovascular Space Invasion in Endometrial Cancer. Int J Gynecol Cancer. 28. 208-219. 2018			
Study type: Retrospective cohort study	Cancer Research (K.M.). **Conflict of Interests:** The authors declare no conflict of interest in this study. **Randomization:** Eligible cases were divided into 2 groups: patients who underwent TLH using an nonrandomized patient selection for hysterectomy procedure type IUM and patients who underwent TAH without IUM use. The decision to use an IUM and the type of IUM depends on surgeons. **Blinding:** None **Dropout rates:** retrospective	cancer. Of those, 419 women underwent TLH with IUM use and 194 women underwent TAH. **Patient characteristics:** January 1, 2008, and December 31, 2015 **Inclusion criteria:** Women with stage I-IV endometrial cancer who underwent hysterectomy between 2008 and 2015. **Exclusion criteria:** (i) the patient did not undergo hysterectomy-based surgical staging; (ii) the type of hysterectomy was radical or modified radical, vaginal, or supracervical; and (iii) available information on the use of IUM and/or LVSI status was insufficient.	(TLH) with intrauterine manipulator IUM. **Comparison:** Total abdominal hysterectomy (TAH).
Notes:	Oxford CEBM Level of evidence 2011: EL 4 (cohort study - retrospective) retrospective cohort: association exists between LVSI and IUM use in hysterectomy specimens with endometrial cancer SR: validation cohort for this association by using systematic literature review. **Author's conclusion:** In summary, IUM use during minimally invasive surgical staging hysterectomy is not associated with an		

Machida, H. et al. Intrauterine Manipulator Use During Minimally Invasive Hysterectomy and Risk of Lymphovascular Space Invasion in Endometrial Cancer. Int J Gynecol Cancer. 28. 208-219. 2018		
	increase in the frequency of LVSI. Intrauterine manipulator use seems acceptable in the treatment for women with early-stage endometrial cancer.	
Outcome Measures/results	**Primary** Lymphovascular space invasion (LVSI) **Secondary** Association of IUM type and survival outcome among TLH-IUM cases, and survival outcome was examined based on the diagnostic modality in this group. In a post hoc sensitivity analysis, frequency of LVSI was compared between the TLH-IUM group and the TLH without IUM group.	**Results:** There were 687 women who underwent hysterectomy for endometrial cancer. Of those, 419 women underwent TLH with IUM use and 194 women underwent TAH. The most common type of IUM was VCare (89.5%). There was no statistically significant difference in the frequency of LVSI between the 2 groups: 15.1% for TLH-IUM vs 19.9% for TAH (P = 0.14). After propensity score matching, frequencies of LVSI were similar between the 2 groups: 21.2% for TLH-IUM vs 19.6% for TAH (P = 0.78). Systematic literature review identified 1371 cases of TLH-IUM and 1246 cases of TAH performed for endometrial cancer, and frequencies of LVSI were similar between the 2 groups (15.0% vs 13.6%, P = 0.31). Survival outcome of women in the TLH-IUM group was examined. The median follow-up time was 25.6 months.nThere were 35 women who developed recurrence and 14 women who died of endometrial cancer. Type of IUM was not associated with DFS (5-year rates for VCare vs others, 85% vs 90%; P = 0.82) and CSS (5-year rates for VCare vs others, 94% vs 94%; P = 0.52). Diagnostic modality including endometrial biopsy (n = 293), Vabra aspirator\ (n = 70), dilation and curettage (n = 42), and hysteroscopy (n = 14) was not associated with survival (DFS, P = 0.65; CSS, P = 0.50).

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Jørgensen, S. L. et al. Nationwide Introduction of Minimally Invasive Robotic Surgery for Early-Stage Endometrial Cancer and Its Association With Severe Complications. JAMA Surg. 154. 530-538. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** nationwide prospective cohort study (6 national cancer centers)	**Funding sources:** Funding/Support: The project was funded by the region of Southern Denmark, the University of Southern Denmark, the Danish Cancer Society, the Department of Gynecology and Obstetrics Odense University Hospital Denmark, the Senior Consultant Research Council Odense University Hospital Denmark, the A.P. Moeller Foundation, and Carpenter Axel Kastrup-Nielsen's memorial fund. The study was granted epidemiological support by Program for Clinical Research Infrastructure, which was established by the Lundbeck Foundation and the Novo Nordisk Foundation. Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Conflict of Interests:** None reported. **Randomization:** The women were divided into 2 groups: group 1 underwent surgery before MIRS	**Total no. patients:** 5654 women **Recruiting Phase:** January 1, 2005, to June 30, 2015 **Inclusion criteria:** early-stage endometrial cancer **Exclusion criteria:** Women with an unknown disease stage, an unknown association with MIRS implementation, unknown histologic findings, sarcoma, or synchronous cancer were excluded, as were women who underwent vaginal or an unknown surgical type of hysterectomy.	**Interventions:** Minimally invasive robotic surgery, MILS. **Comparison:** Total abdominal hysterectomy.

Jørgensen, S. L. et al. Nationwide Introduction of Minimally Invasive Robotic Surgery for Early-Stage Endometrial Cancer and Its Association With Severe Complications. JAMA Surg. 154. 530-538. 2019			
	was introduced, and group 2 underwent surgery after MIRS was introduced. The date dividing the groups was set as the date of the first such procedure performed at each cancer center for early-stage endometrial cancer. The 2 groups differed significantly regarding several clinical, sociodemographic, and histopathologic characteristics (see Table 1 of publication). **Blinding:** No **Dropout rates:** -		
Notes:	Oxford CEBM Level of evidence 2011: EL 3 (Cohort study). **Author's conclusion:** The national introduction of MIRS changed the surgical approach for early-stage endometrial cancer from open surgery to MIS. This change in surgical approach was associated with a significantly reduced risk of severe complications.		
Outcome Measures/results	**Primary** Severe complications, dichotomized for each woman into absent or present. Severe complications were defined to include 30-day mortality and severe intraoperative and postoperative complications. **Secondary** -	**Results:** 3091 women (mean [SD] age, 67 [10] years) were allocated to group 1, and a total of 2563 women (mean [SD] age, 68 [10] years) were allocated to group 2.In multivariate logistic regression analyses, the odds of severe complications were significantly higher in group 1 than in group 2 (odds ratio [OR], 1.39; 95%CI, 1.11-1.74). The proportion of women undergoing MILS was 14.1% (n = 436) in group 1 and 22.2%in group 2 (n = 569). The proportion of women undergoing MIRS in group 2 was 50.0%(n = 1282). In group 2, multivariate logistic	

Jørgensen, S. L. et al. Nationwide Introduction of Minimally Invasive Robotic Surgery for Early-Stage Endometrial Cancer and Its Association With Severe Complications. JAMA Surg. 154. 530-538. 2019		
		regression analyses demonstrated that a total abdominal hysterectomy was associated with increased odds of severe complications compared with MILS (OR, 2.58; 95%CI, 1.80-3.70) and MIRS (OR, 3.87; 95%CI, 2.52-5.93). No difference was found for MILS compared with MIRS (OR, 1.50; 95%CI, 0.99-2.27).

2.34. Schlüsselfrage 37: Beeinflussen Tools des geriatrischen Assessments operative, systemtherapeutische und radioonkologische Therapieentscheidungen?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Ahmed, A. 2018	3	Prospective cohort study The primary objective was to determine whether the pre-operative GA-GYN score, performed within 14 days prior to surgery, is associated with major post-operative complications in elderly patients undergoing primary open cytoreduction surgery
Bourgin, C. 2016	4	Systematic Review The aim of the present literature review is to define the population of elderly women with this disease and to define the characteristics of this cancer in elderly people as well as its surgical treatment.
Driver, J. A. 2017	3	Cohort Study A combined frailty measure was a more robust predictor of DFS and OS than patient age, tumor characteristics and comorbidities in this cohort of older women with very good functional status.
Nadaraja, S. 2020	3	Randomized controlled trial

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Bourgin, C. et al. Endometrial cancer in elderly women: Which disease, which surgical management? A systematic review of the literature. Eur J Surg Oncol. 42. 166-75. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 4 **Study type:** Systematic Review The aim of the present literature review is to define the population of elderly women with this disease and to define the characteristics of this cancer in elderly people as well as its surgical treatment. **Databases:** Pubmed, Central Cochrane Library, EmBase, National Institute on Aging, INSEE **Search period:** January 1995 to January 2015 **Inclusion Criteria:** Inclusion criteria were studies that included adult femals with either age more than 65 years old and endometrial cancer with surgery	**Population:** Adult femals with either age more than 65 years old and endometrial cancer with surgery **Intervention:** **Comparison:**	**Primary:** The primary outcomes were rate of post-operative complications (morbidity and mortality), histo-pathological analysis of uterus and nodes and survival rate. **Secondary:** The secondary outcome was described oncogeriatric scores nevertheless kind of cancer. **Results:** Endometrial cancer is more aggressive in elderly women. However, surgical staging performed in elderly patients is often not concomitant with the disease's aggressiveness in this group. Mini-invasive surgery is performed less often, for no obvious reason. Of note, oncogeriatric evaluation was not usually ruled out to determine the most appropriate surgical modality. **Author's Conclusion:** Studies are needed to evaluate surgical management of endometrial cancer in elderly women, notably with the aid of oncogeriatric scores to predict surgical morbidity.	17 studies included, see full text article	

Bourgin, C. et al. Endometrial cancer in elderly women: Which disease, which surgical management? A systematic review of the literature. Eur J Surg Oncol. 42. 166-75. 2016

Exclusion Criteria: Exclusion criteria were patients with recurrent endometrial cancer, studies with no inclusion of women older than 65 years, duplicate data.				

Methodical Notes

Funding Sources: Not described

COI: None

Study Quality: Not investigated

Heterogeneity: No meta-analysis was performed

Publication Bias: Not investigated

Notes:
Oxford CEBM Level of Evidence 2011: EL 3 Systematic Review of RCTs, as well as prospective and retrospective studies.

Downgraded to EL 4
Intervention and Comparison not described, PICO unclear
Results regarding primary and secondary outcomes were not reported.
Publication bias not investigated

Bourgin, C. et al. Endometrial cancer in elderly women: Which disease, which surgical management? A systematic review of the literature. Eur J Surg Oncol. 42. 166-75. 2016
Quality of the included studies was not assessed Thus the relevance of the results is unclear and the implications of this article is limited.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Nadaraja, S. et al. The impact of comprehensive geriatric assessment for optimal treatment of older patients with cancer: A randomized parallel-group clinical trial. J Geriatr Oncol. 11. 488-495. 2020		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Randomized controlled trial **Number of Patient:** 96 **Recruitung Phase:** From January 2016 to June 2018 **Inclusion Criteria:** Inclusion criteria were, 1) age ≥ 70 years, 2) a diagnosis of gynecological cancer (ovarian (ICD-10 codes C56–57, C48), endometrial cancer (C54–55)), urological cancer (prostate (C61), bladder (C65–57), kidney cancer (C64)), or non-small cell lung cancer (NSCLC (C34)), 3) starting chemotherapy or targeted therapy (tyrosine kinase inhibitor) for primary or recurrent disease, 4) able to understand/speak Danish, and 5) able to give informed consent. **Exclusion Criteria:** Exclusion criteria were a previous cancer diagnosis other than recurrence of	**Intervention:** G8 screening followed by comprehensive geriatric assessment (CGA) and a multidisciplinary team conference **Comparison:** Standard assessment (SA) only	**Primary:** The primary endpoint was the rate of completion of oncologic treatment as scheduled (number of planned courses) without premature termination due to unacceptable toxicity, progression of disease, or death. Patients, who received treatment until progression, were followed for a maximum of 6 months during treatment. A maximum of 1 dose reduction and/or a maximum of 14 days of dose delay were allowed **Secondary:** Rate of severe (grade 3–4 toxicity (National Cancer Common Terminology Criteria for Adverse Events (CTCAE) version 4), Time from randomization to start of treatment, Progression-free survival (PFS) defined as time from randomization to disease progression or death, Overall survival (OS) defined as time from randomization to death **Results:** The study was closed early. 47 patients were randomized to the control group and 49 to the intervention group; 28 had a G8 ≤ 14, 24 of whom attended CGA. In the intervention group 48% completed

Nadaraja, S. et al. The impact of comprehensive geriatric assessment for optimal treatment of older patients with cancer: A randomized parallel-group clinical trial. J Geriatr Oncol. 11. 488-495. 2020			
the current cancer disease (carcinoma in situ of the cervix and non-melanoma skin cancer were allowed) and either surgery or curative intended radiation therapy within the last four weeks prior to inclusion (local radiotherapy of isolated lesions for palliative intent was allowed prior to and during the study).		treatment as planned compared to 54% in the control group (p = .208). Thirty-eight percent experienced grade 3–4 toxicity in the control group compared with only 20% in the intervention group (p = .055). Median overall survival (OS) was 14.2 months in the control group and 19.1 months in the intervention group (p = .911). Median progression-fr ree survival (PFS) was 9.0 months in the control group and 7.8 months for the intervention group (p = .838). **Author's Conclusion:** Treatment decision based on G8 screening followed by CGA had no impact on completion rate of planned oncologic treatment, OS or PFS, but resulted in a borderline significant lower incidence of grade 3–4 toxicity.	
Methodical Notes			
Funding Sources: Danish Cancer Society **COI:** None **Randomization:** Eligible patients were randomized 1:1 to intervention versus control using block randomization with random blocks of four and six with stratification for cancer diagnosis (gynecological versus urological versus lung cancer), and prior chemotherapy and/or radiation (yes/no). **Blinding:** Open-label study			

Nadaraja, S. et al. The impact of comprehensive geriatric assessment for optimal treatment of older patients with cancer: A randomized parallel-group clinical trial. J Geriatr Oncol. 11. 488-495. 2020

Dropout Rate/ITT-Analysis: Not described

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled trial

Downgraded to level 3:

Patients with urological, kidney and non small cell lung cancer were also included. Applicability to patients with endometrial carcinoma unclear. Thus the clinical impact of the results is limited.
Number of included patients was small (less than 50 patients per arm)
The study was closed early after inclusion of 50% of the patients according to the prospectively calculated patient sample. Therefore the power of the study is limited.
Patients in the control group were slightly older.
Open label study, no blinding was performed

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Ahmed, A. et al. Pre-operative assessment and post-operative outcomes of elderly women with gynecologic cancers, primary analysis of NRG CC-002: An NRG oncology group/gynecologic oncology group study. Gynecol Oncol. 150. 300-305. 2018		
Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prospective cohort study The primary objective was to determine whether the pre-operative GA-GYN score, performed within 14 days prior to surgery, is associated with major post-operative complications in elderly patients undergoing primary open cytoreduction surgery **Number of Patient:** 189 **Recruitung Phase:** February 10th, 2015 to November 2nd, 2015 **Inclusion Criteria:** Eligible patients included women 70 years or older with suspected primary peritoneal, ovarian, fallopian tube or advanced staged uterine carcinomas. Patients were included irrespective of their performance status. **Exclusion Criteria:** Patients were excluded for	**Intervention:** Pre-operative GA-GYN score **Comparison:**	**Primary:** Major post-operative complications **Secondary:** **Results:** There were 189 eligible patients, 117 patients with primary surgical intervention and 37 patients undergoing interval cytoreduction surgery. The association between higher GA-GYN score and major postoperative complications in patients undergoing primary surgery was not significant (p=0.1341). In a subgroup analysis of patients with advanced staged malignant disease who underwent primary cytoreductive surgery, there was a trend towards an association with the GA-GYN score and post-operative complications. **Author's Conclusion:** The pre-operative GA-GYN score derived from a predictive model utilizing components of an abbreviated geriatric assessment was not predictive of major post-operative complications in elderly patients undergoing primary open cytoreductive surgery. However, there was an association between GA-GYN score and post-operative complications in a subgroup of patients with advanced staged malignant disease.

Ahmed, A. et al. Pre-operative assessment and post-operative outcomes of elderly women with gynecologic cancers, primary analysis of NRG CC-002: An NRG oncology group/gynecologic oncology group study. Gynecol Oncol. 150. 300-305. 2018			
planned minimally invasive cytoreductive surgery (laparoscopy/robotic surgery).			
Methodical Notes			
Funding Sources: Not described **COI:** Dr. Robert Mannel served on Advisory Boards for Tesaro and Clovis. Dr. Mitchell Edelson states that his spouse is an employee of Merck and received stock as an employee. Dr. Susan Modesitt reports that her institution received grant funding from NRG. Dr. Anthony Evans reports his institution received standard payment for institutional support from the NRG. All other co-authors have no conflicts of interest to declare. **Randomization:** **Blinding:** The protocol specifies that the surgeon would be blinded to the results of the questionnaire from the geriatric assessment, but there was no protocoldefined enforcement or monitoring of this blinding. **Dropout Rate/ITT-Analysis:** **Notes:** Oxford CEBM Level of Evidence 2011: EL 3 Prospective Cohort Study One study group (not a cohort study in the original design) Length of follow-up may be not long enough (6 weeks) Suspected ovarian, fallopian tube, primary peritoneal or advanced stage papillary serous uterine carcinoma included. Relevance for endometrial cancer is unclear.			

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Driver, J. A. et al. Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older. Gynecol Oncol. 145. 526-530. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Cohort Study A combined frailty measure was a more robust predictor of DFS and OS than patient age, tumor characteristics and comorbidities in this cohort of older women with very good functional status.	**Funding sources:** This work was supported by National Institutes of Health MSTAR Grant 5T35AG038027-07. Dr. Driver is supported by a Veterans' Affairs Merit Review Award. Dr. Viswanathan receives National Institutes of Health funding through R21 167800. **Conflict of Interests:** None **Randomization:** **Blinding:** Not described **Dropout rates:**	**Total no. patients:** 88 **Recruiting Phase:** Between 1982 and 2011 **Inclusion criteria:** i.e., they had stage I-IV disease treated with a hysterectomy and bilateral salpingoophorectomy, with or without pelvic and para-aortic lymph node dissection, followed by radiation and chemotherapy. **Exclusion criteria:**	**Interventions:** Readily obtainable markers of frailty: albumin < 3.5 mg/dL, hemoglobin < 10 mg/dL, BMI < 20 kg/m2, unintentional weight loss, ECOG performance status ≥ 2, history of osteopenia or osteoporosis and Charlson comorbidity score **Comparison:**
Notes:	Oxford CEBM Level of Evidence 2011: EL 3 Cohort Study One study group, not a cohort study in the original design Inclusion and exclusion criteria were not described in detail		

Driver, J. A. et al. Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older. Gynecol Oncol. 145. 526-530. 2017		
	Author's conclusion: A combined frailty measure was a more robust predictor of DFS and OS than patient age, tumor characteristics and comorbidities in this cohort of older women with very good functional status.	
Outcome Measures/results	**Primary** Patients were followed for a median of 3.18 years (range 0.45 – 15 years) for disease related clinical endpoints and post-treatment adverse events. We recorded whether treatment was delayed, modified or truncated. Actuarial estimates of disease-free survival (DFS), and overall survival (OS) were assessed, and were stratified by the presence of frailty markers. **Secondary**	**Results:** The median age was 68.5 (range 60–88 years). The majority of women (65/88) had at least one frailty factor at baseline and 23/88 had two or more. All women received radiation and chemotherapy. Treatment was delayed, modified or truncated in 46% (40/88) of women due to treatment-related toxicity. Age (< 70 vs. ≥70 y) did not independently predict toxicity or recurrence risk. Women with at least one baseline frailty factor had twice the risk of disease recurrence (HR=2.21;95% CI: 1.02–4.80) when adjusted for age, stage, grade and Charlson score. The 3-year DFS was 77% in those with no frailty markers and 48% in those with at least one (p=0.02). The presence of a frailty marker also predicted shortened overall survival (HR=2.34;95%CI: 1.08–5.03) irrespective of treatment administered and stage of disease.

2.35. Schlüsselfrage 38: Bei welchen Stadien bzw. histolog. Typen des Endometriumkarzinoms ist eine adjuvante externe Strahlentherapie (perkutan allein) indiziert im Hinblick auf Lebensqualität, Kurzzeit-/ Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *9 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Boer, S. M. 2018	2	Randomized phase 3 trial
de Boer, S. M. 2016	2	Randomized phase 3 trial
de Boer, S. M. 2019	2	Randomized phase 3 trial
Matei, D. 2019	2	Randomized phase 3 trial
Narasimhulu, D. M. 2020	3	Systematic Review and Meta-Analysis of Cohort Studies
Randall, M. E. 2019	2	Randomized phase 3 trial
Stelloo, E. 2016	3	Post-Hoc Analysis of two RCTs (PORTEC-1 and -2 trials)
Wortman, B. G. 2018	2	RCT (multicentre randomised trial, PORTEC-2 trial)
Ørtoft, G. 2020	4	Prognostic retrospective cohort study

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Narasimhulu, D. M. et al. External beam radiotherapy versus vaginal brachytherapy in patients with stage II endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer. 30. 797-805. 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of Cohort Studies **Databases:** Medline, Embase, Central, Scopus **Search period:** Inception to January 2019 **Inclusion Criteria:** Not described **Exclusion Criteria:** Not described	**Population:** Woman with stage II endometrial cancer **Intervention:** Adjuvant postoperative external beam radiotherapy with or without vaginal brachytherapy **Comparison:** Brachytherapy alone	**Primary:** Locoregional recurrence rate defined as recurrence in the pelvis or vagina **Secondary:** Rate of recurrence at any site, distant recurrence rate, vaginal recurrence rate, pelvic recurrence rate, 5 year overall survival **Results:** Locoregional recurrence (pelvic and vaginal recurrence) was significantly reduced with external beam radiotherapy with or without vaginal brachytherapy compared with vaginal brachytherapy alone (14 studies, (n = 1057); OR 0.33 (95% CI 0.16 to 0.68), I2=95%) regardless of pelvic lymph node assessment. Most woman (81,8%) who recurred locoregionally had at least one uterine risk factor (grade 3 tumor, myometrial invasion >50%, or lymphovascular invasion). There was no difference overall survival with external beam radiotherapy with	15 cohort studies: Ozgul et al. 2018, Berry et al. 2018, Jung et al. 2017, Chen et al. 2017, Paydar et al. 2015, Elshaikh et al. 2015, Frandsen et al. 2014, Galper et al. 2010, Orezzoli et al. 2009, Cannon et al. 2009, Cozad 2008, Rittenberg et al. 2005, Pitson et al. 2002, MacLeod et al. 1999, Eltabbakh and Moore 1999

Narasimhulu, D. M. et al. External beam radiotherapy versus vaginal brachytherapy in patients with stage II endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer. 30. 797-805. 2020				
		or without vaginal brachytherapy compared with vaginal brachytherapy alone (five studies(n=463); OR 0.78 (95% CI 0.34 to 1.80); I2= 48%). **Author's Conclusion:** External beam radiotherapy with or without vaginal brachytherapy decreased the locoregional recurrence threefold for stage II endometrial cancer, regardless of pelvic lymph node assessment. Most women who suffered for recurrence locoregionally had at least one high risk factor. Vaginal brachytherapy alone may be sufficient therapy for node negative stage II endometrial cancer without uterine risk factors, while those with uterine risk factors should be considered for external beam radiotherapy with or without vaginal brachytherapy to improve locoregional control.		
Methodical Notes				

Narasimhulu, D. M. et al. External beam radiotherapy versus vaginal brachytherapy in patients with stage II endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer. 30. 797-805. 2020

Funding Sources: This publication was supported by CTSA grant No UL 1 TR002377 from the National Center for Advancing Translational Sciences

COI: None

Study Quality: The certainty of the evidence was assessed using the GRADE approach. All studies have a serious risk of bias due to unadjusted confounding.

Heterogeneity: I2 statistic was used to assess the heterogeneity between the studies. I2 < 50% indicated substantial heterogeneity. Moderate heterogeneity was present for the outcome overall survival (I2=48%), that was explained by lymph node assessment status.

Publication Bias: Publication bias was not detected for recurrence and could not be assessed for overall survival because of the small number of studies.

Notes:
Oxford Level of Evidence 2011: EL 3 Systematic Review and Meta-Analysis of retrospective cohort studies.
No search for grey literature or unpublished studies.
Insufficient description of the inclusion and exclusion criteria
Quality of the included primary studies was assessed but not reported in this article (reported in the online supplementary material, which is not accessible). The authors state that the certainty of evidence was low for all outcomes due to the observational nature of the evidence, the serious risk of bias and imprecision in the estimates.

OXFORD (2011) Appraisal Sheet: RCT: *6 Bewertung(en)*

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 660 **Recruitung Phase:** Between Nov 23, 2006, and Dec 20, 2013 **Inclusion Criteria:** Patients were eligible if they had endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO) 2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. WHO performance score 0–2; adequate bone marrow function (white blood cells ≥3·0×10⁹/L, platelets ≥100×10⁹/L), liver function	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival **Secondary:** Vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life (published in de Boer et al. 2016) **Results:** Median follow-up was 60.2 months (IQR 48.1–73.1). 5-year overall survival was 81.8% (95% CI 77.5–86.2) with chemoradiotherapy versus 76.7% (72.1–81.6) with radiotherapy (adjusted hazard ratio [HR] 0.76, 95% CI 0.54–1.06; p=0.11); 5-year failure-free survival was 75.5% (95% CI 70.3–79.9) versus 68.6% (63.1–73.4; HR 0.71, 95% CI 0.53–0.95; p=0.022). Grade 3 or worse adverse events during treatment occurred in 198 (60%) of 330 who received chemoradiotherapy versus 41 (12%) of 330 patients who received radiotherapy (p<0·0001). Neuropathy (grade 2 or worse) persisted significantly more often after chemoradiotherapy than after radiotherapy (20 [8%] women vs one [1%] at 3 years; p

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018		
(bilirubin ≤1·5×upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase ≤2·5×UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault10 or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). **Exclusion Criteria:** Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual macroscopic tumour; impaired renal or cardiac function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder		**Author's Conclusion:** Adjuvant chemotherapy given during and after radiotherapy for high-risk endometrial cancer did not improve 5-year overall survival, although it did increase failure-free survival. Women with high-risk endometrial cancer should be individually counselled about this combined treatment. Continued follow-up is needed to evaluate long-term survival.
Methodical Notes		
Funding Sources: Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council Project Grant and Cancer Australia, L'Agenzia Italiana del Farmaco, and Canadian Cancer Society Research Institute.		

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

COI: None.

Randomization: Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type).

Blinding: Participants and investigators were not masked to treatment allocation.

Dropout Rate/ITT-Analysis: All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled Trial
For the outcomes: adverse events, patient reported symptoms and health-related quality of life see: de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival. **Secondary:** Vaginal, pelvic, or distant recurrence;

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Number of Patient: 660 **Recruitung Phase:** Sept 15, 2006, and Dec 20, 2013, **Inclusion Criteria:** Patients were eligible for inclusion in this trial if they had International Federation of Gynecology and Obstetrics 2009 categorised stage IA grade 3 endometrial carcinoma with myometrial invasion and with documented lymph-vascular space invasion; stage IB grade 3; stage II, stage IIIA, or IIIC (or IIIB if parametrial invasion only); serous or clear cell histology with stage IA (with invasion), IB, II, or III. Eligible patients also had to have adequate WHO performance scores (WHO score 0–2); bone marrow (white blood cell count ≥3·0 cells × 10⁹/L, platelets ≥100 × 10⁹/L); liver function (bilirubin ≤1·5 × upper limit of normal [ULN], aspartate aminotransferase concentration ≤2·5 × ULN, or alanine aminotransferase concentration ≤2·5 × ULN); and kidney function (creatinine clearance >60 mL/min calculated according to Cockroft18 or >50 mL/min EDTA clearance) and be aged older than 18 years **Exclusion Criteria:** Exclusion criteria were having		treatment-related toxicity; and health-related quality of life (published elsewhere) **Results:** Between Sept 15, 2006, and Dec 20, 2013, 686 women were randomly allocated in the PORTEC-3 trial. Of these, 660 met eligibility criteria, and 570 (86%) were evaluable for health-related quality of life. Median follow-up was 42.3 months (IQR 25.8–55.1). At completion of radiotherapy and at 6 months, EORTC QLQ-C30 functioning scales were significantly lower (worse functioning) and health-related quality of life symptom scores higher (worse symptoms) for the chemoradiotherapy group compared with radiotherapy alone, improving with time. At 12 and 24 months, global health or quality of life was similar between groups, whereas physical functioning scores remained slightly lower in patients who received chemoradiotherapy compared with patients who received radiotherapy alone. At 24 months, 48 (25%) of 194 patients in the chemoradiotherapy group reported severe tingling or numbness compared with 11 (6%) of 170 patients in the radiotherapy alone group (p 42 (13%) of 326 patients in the radiotherapy alone group (p<0.0001).

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016		
uterine sarcoma, previous malignancy less than 10 years ago, receipt of previous pelvic radiotherapy, hormonal or chemotherapy, gross cervical involvement with radical hysterectomy, infl ammatory bowel disease, residual macroscopic tumour, impaired renal or cardiac function, neuropathy grade 2 or worse, hearing impairment grade 3 or worse, or congenital hearing disorder.		**Author's Conclusion:** Despite the increased physician and patient-reported toxicities, this schedule of adjuvant chemotherapy given during and after radiotherapy in patients with high-risk endometrial cancer is feasible, with rapid recovery after treatment, but with persistence of patient-reported sensory neurological symptoms in 25% of patients. We await the analysis of primary endpoints before fi nal conclusions are made.
Methodical Notes		
Funding Sources: Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council Project Grant and Cancer Australia, L'Agenzia Italiana del Farmaco, and Canadian Cancer Society Research Institute. **COI:** None. **Randomization:** Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type). **Blinding:** Participants and investigators were not masked to treatment allocation. **Dropout Rate/ITT-Analysis:** Intention to treat analysis was not performed for the outcomes described in this study.		

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled Trial

Intention to treat analysis was not performed for the outcomes described in this study.

For the outcomes: Overall survival and failure-free survival. see:
de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 660 **Recruitung Phase:** Between Nov 23, 2006, and Dec 20, 2013 **Inclusion Criteria:** Patients were eligible if they had endometrial cancer with either International	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival **Secondary:** Vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life **Results:** At a median follow-up of 72.6 months (IQR 59.9–85.6), 5-year overall survival was 81.4% (95% CI 77.2–85.8) with chemoradiotherapy versus 76.1% (71.6–80.9) with radiotherapy alone (adjusted hazard ratio [HR] 0.70 [95% CI 0.51–0.97], p=0.034), and 5-

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019

Federation of Gynecology and Obstetrics (FIGO) 2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. WHO performance score 0–2; adequate bone marrow function (white blood cells ≥3·0×10⁹/L, platelets ≥100×10⁹/L), liver function (bilirubin ≤1·5×upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase ≤2·5×UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault10 or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). **Exclusion Criteria:** Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual		year failure-free survival was 76.5% (95% CI 71.5–80.7) versus 69.1% (63.8–73.8; HR 0.70 [0.52–0.94], p=0.016). Distant metastases were the first site of recurrence in most patients with a relapse, occurring in 78 of 330 women (5-year probability 21.4%; 95% CI 17.3–26.3) in the chemoradiotherapy group versus 98 of 330 (5-year probability 29.1%; 24.4–34.3) in the radiotherapy-alone group (HR 0.74 [95% CI 0.55–0.99]; p=0.047). Isolated vaginal recurrence was the first site of recurrence in one patient (0.3%; 95% CI 0.0–2.1) in both groups (HR 0.99 [95% CI 0.06–15.90]; p=0.99), and isolated pelvic recurrence was the first site of recurrence in three women (0.9% [95% CI 0.3–2.8]) in the chemoradiotherapy group versus four (0.9% [95% CI 0.3–2.8]) in the radiotherapy-alone group (HR 0.75 [95% CI 0·17–3·33]; p=0.71). At 5 years, only one grade 4 adverse event (ileus or obstruction) was reported (in the chemoradiotherapy group). At 5 years, reported grade 3 adverse events did not differ significantly between the two groups, occurring in 16 (8%) of 201 women in the chemoradiotherapy group versus ten (5%) of 187 in the radiotherapy-alone group (p=0.24). The most common grade 3 adverse event was hypertension (in four [2%] women in both groups). At 5 years, grade 2 or worse adverse events were reported in 76 (38%) of 201 women in the chemoradiotherapy group versus

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019			
macroscopic tumour; impaired renal or cardiac function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder		43 (23%) of 187 in the radiotherapy-alone group (p=0.002). Sensory neuropathy persisted more often after chemoradiotherapy than after radiotherapy alone, with 5-year rates of grade 2 or worse neuropathy of 6% (13 of 201 women) versus 0% (0 of 187). No treatment-related deaths were reported. **Author's Conclusion:** This updated analysis shows significantly improved overall survival and failure-free survival with chemoradiotherapy versus radiotherapy alone. This treatment schedule should be discussed and recommended especially for women with stage III or serous cancers, or both, as part of shared decision making between doctors and patients. Follow-up is ongoing to evaluate long-term survival.	
Methodical Notes			
Funding Sources: Funding Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council, Project Grant, Cancer Australia Grant, Italian Medicines Agency, and the Canadian Cancer Society Research Institute. **COI:** None. **Randomization:** Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type).			

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019		
Blinding: Participants and investigators were not masked to treatment allocation. **Dropout Rate/ITT-Analysis:** All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled trial Post-hoc analysis to analyse patterns of recurrence with 1 additional year of follow-up of de Boer et al. (2018)		
Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 707 **Recruitung Phase:** June 29, 2009, and July 28, 2014 **Inclusion Criteria:** Women who were 18 years of age or older and who had surgical stage III or IVA	**Intervention:** 6 months of platinum-based chemotherapy plus radiation therapy (chemoradiotherapy) **Comparison:** Six cycles of combination chemotherapy alone	**Primary:** Relapse-free survival **Secondary:** Overall survival, acute and chronic toxic effects, and quality of life **Results:** Relapse free survival The median follow-up period was 47 months. At 60 months, the Kaplan–Meier estimate of the percentage of patients alive and relapse-free was 59% (95% confidence interval [CI], 53 to 65) in the chemoradiotherapy group and 58% (95% CI, 53 to 64) in the chemotherapy-only group (hazard ratio,

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019			
endometrial carcinoma according to FIGO 2009 staging criteria of any histologic subtype or had FIGO 2009 surgical stage I or II clear-cell or serous endometrial carcinoma and peritoneal washings that were positive for cancer cells. Hysterectomy and bilateral salpingo-oophorectomy had to have been performed within 8 weeks before trial entry. No single residual tumor mass could be larger than 2 cm in greatest dimension. Pelvic and paraaortic lymph-node biopsy or dissection was optional. Normal organ function and a GOG performance status score of 2 or lower were required (scores range from 0 to 5, with higher scores reflecting greater disability). **Exclusion Criteria:** Patients with carcinosarcoma or recurrent endometrial carcinoma were excluded.		0.90; 90% CI, 0.74 to 1.10). Therefore, the null hypothesis that chemoradiotherapy is not superior to chemotherapy alone could not be rejected (P=0.20 by one-tailed test). <u>Overall survival</u> A total of 165 deaths have been reported to date — 86 in the chemoradiotherapy group and 79 in the chemotherapy-only group. Of those deaths, 73% and 81%, respectively, were due to endometrial cancer progression. The data on overall survival are not sufficiently mature to allow comparison between the groups. <u>Recurrence</u> Chemoradiotherapy was associated with a lower 5-year incidence of vaginal recurrence (2% vs. 7%; hazard ratio, 0.36; 95% CI, 0.16 to 0.82) and pelvic and paraaortic lymph-node recurrence (11% vs. 20%; hazard ratio, 0.43; 95% CI, 0.28 to 0.66) than chemotherapy alone, but distant recurrence was more common in association with chemoradiotherapy (27% vs. 21%; hazard ratio, 1.36; 95% CI, 1.00 to 1.86). Grade 3, 4, or 5 adverse events were reported in 202 patients (58%) in the chemoradiotherapy group and 227 patients (63%) in the chemotherapy-only group. <u>Quality of life</u> After adjustment for age and baseline scores, the leastsquares mean Trial Outcome Index score at 18 weeks in the chemoradiotherapy group was 5.2 points lower (97.5% CI, 2.7 to 7.8) than that in the chemotherapy-only group. The difference in this score remained significant at 70 weeks (3.4 points lower in the chemoradiotherapy group;	

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019			
		97.5% CI, 0.7 to 6.2) but did not exceed the 6-point difference that had been preset as clinically meaningful. **Author's Conclusion:** Chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma.	
Methodical Notes			
Funding Sources: Funded by the National Cancer Institute **COI:** Disclosure forms provided by the authors are available with the full text of this article at NEJM.org **Randomization:** Randomization was stratified according to age and the presence or absence of gross residual disease. **Blinding:** Not described **Dropout Rate/ITT-Analysis:** ITT-Analysis was performed **Notes:** Oxford Level of Evidence 2011: EL 2 randomized controlled trial Blinding was not described, however measures were objective except quality of life and chemotherapy-induced neurotoxic effects.			

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 601 **Recruitung Phase:** From 2009 to 2013 **Inclusion Criteria:** After hysterectomy, patients with stage I endometrial cancer were eligible if they had endometrioid adenocarcinoma and met study criteria. A bilateral pelvic and para-aortic lymphadenectomy was recommended. Eligibility for patients with endometrioid histology was as follows: age 70 years or older with one uterine risk factor, age 50 years or older with two risk factors, or age 18 years or older with three risk factors. Uterine risk factors included grade 2 or 3 tumor, outer half depth of invasion, and lymphovascular invasion. Positive or negative peritoneal cytology was allowed. Patients with cervical stromal invasion (stage II) were eligible regardless of other risk factors. Patients with serous or clear cell tumors with stage I to II disease and with negative peritoneal cytology were eligible. Retrospective	**Intervention:** Pelvic radiation therapy (RT) (45 to 50.4 Gy over 5 weeks) **Comparison:** Vaginal cuff brachytherapy plus three cycles of carboplatin and paclitaxel repeated every 3 weeks (VCB/C)	**Primary:** Recurrence free survival (RFS) **Secondary:** **Results:** The median age of the 601 patients was 63 years, and 74% had stage I disease. Histologies included endometrioid (71%), serous (15%), and clear cell (5%). With a median follow-up of 53 months, the 60-month RFS was 0.76 (95% CI, 0.70 to 0.81) for RT and 0.76 (95% CI, 0.70 to 0.81) for VCB/C (hazard ratio, 0.92; 90% confidence limit, 0.69 to 1.23). The 60-month overall survival was 0.87 (95% CI, 0.83 to 0.91) for RT and 0.85 (95% CI, 0.81 to 0.90) for VCB/C (hazard ratio, 1.04; 90% confidence limit, 0.71 to 1.52). Vaginal and distant recurrence rates were similar between arms. Pelvic or para-aortic nodal recurrences were more common with VCB/C (9% v 4%). There was no heterogeneity of treatment effect with respect to RFS or overall survival among clinical or pathologic variables evaluated. **Author's Conclusion:** Superiority of VCB/C compared with pelvic RT was not demonstrated. Acute toxicity was greater with VCB/C; late toxicity was similar. Pelvic RT alone remains an effective, well-tolerated, and appropriate

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019			
central pathology review confirmed eligibility and established histology. Patients not undergoing node dissection had postoperative computed tomography or magnetic resonance imaging to document the absence of enlarged nodes. Patients had adequate prespecified hematologic and organ function. **Exclusion Criteria:**		adjuvant treatment in high-risk early-stage endometrial carcinomas of all histologies.	
Methodical Notes			
Funding Sources: Supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517), NRG Oncology (1 U10 CA180822), and NRG Operations (U10CA180868) and in part by Memorial Sloan Kettering Cancer Center Support Grant No. P30 CA008748 (C.A.A.). **COI:** See full text article for authors disclosures **Randomization:** Patients were randomly assigned at a ratio of one to one to treatment with either RT or VCB/C. **Blinding:** Open-label study **Dropout Rate/ITT-Analysis:** Intention to treat analysis was performed			

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019

Notes:
Oxford Level of Evidence 2011: EL 2 randomized controlled trial
Open-label study

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (multicentre randomised trial, PORTEC-2 trial) **Number of Patient:** 427 women with HIR endometrial carcinoma (214 received EBRT and 213 recieved VBT). **Recruitung Phase:** Between May 2002 and September 2006. **Inclusion Criteria:** Woman diagnosed with endometrial carcinoma with high-intermediate risk factors (HIR), HIR was defined as either (1) FIGO	**Intervention:** Vaginal brachytherapy (VBT) **Comparison:** Pelvic radiotherapy (EBRT).	**Primary:** Vaginal recurrence (VR) **Secondary:** Pelvic recurrence (PR), distant recurrence (DR), overall survival (OS, date of randomisation to death from any cause, with censoring at date of last information for patients alive), endometrial cancer-related survival (CSS, from date of randomisation to date of death related to endometrial cancer), disease-free survival (DFS, date of randomisation to date of disease recurrence or to date of death from any cause,), and toxicity and quality of life. **Results:** Patient and tumour characteristics were equally distributed over the two treatment groups. The database was frozen on May 1st 2016 and by then, the median follow-up was 116 months (range 18–163 months).

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018		
1988 stage 1C (≥50% myometrial invasion) with age greater than 60 and grade 1 or 2; or (2) FIGO 1988 stage 1B (**Exclusion Criteria:** Serous or clear cell carcinoma; staging lymphadenectomy; > 8 weeks interval between surgery and radiotherapy; history of previous malignancy; previous radiotherapy, hormonal or chemotherapy; Crohn's disease or ulcerative colitis.		The 10-year **vaginal recurrence rates** were 3.4% and 2.4% for VBT and EBRT, respectively (p = 0.55). **Pelvic recurrences** were 6.3% vs. 0.9% (p = 0.004); of these, 2.5% vs. 0.5% were isolated pelvic recurrences (p = 0.10). Ten-year rates of **distant metastases** were 10.4% vs. 8.9% for VBT vs EBRT (p = 0.45). In the <u>confirmed HIR-group</u> the 10-year vaginal recurrence rates were 2.7% vs. 3.1% (p = 0.78) and the pelvic recurrence rates 7.4% and 1.2% (p = 0.01) for VBT vs. EBRT,respectively. Ten-year **overall survival** was 69.5% vs. 67.6% (p = 0.72) and 10-year endometrial cancer-related survival 88.2% vs. 90.9% (p = 0.42) for VBT vs. EBRT groups, respectively. <u>Prognostic factors:</u> Women with tumours harbouring a POLE mutation, 10-year CSS was 100%, in contrast to 96.2% for no specific molecular profile, 84.8% for MSI and 62.3% for p53-mutant tumours (p < 0.001). Substantial LVSI (in confirmed HIR group) was found to be a very strong independent risk factor for pelvic and distant recurrence (HR 8.73 (p = 0.005) and 5.36 (p = 0.001), respectively) and for endometrial cancer-related survival (HR 7.16, p < 0.001). L1CAM expression (HR 4.18, p = 0.016) and p53-mutant expression (HR 3.35, p = 0.015) were significant prognostic factors for distant recurrence and CSS (HR 5.05, p = 0.006 and HR 3.30, p = 0.015).

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018		
		Author's Conclusion: In conclusion, long-term results of PORTEC-2 confirmed VBT as the adjuvant treatment of choice for women with high intermediate risk endometrial cancer. EBRT might provide better pelvic control in the small subgroup of women with unfavourable risk factors (substantial LVSI, L1CAM expression or p53-mutant expression).
Methodical Notes		
Funding Sources: The PORTEC-2 study was supported by a grant from the Dutch Cancer Society (CKTO 2001-04). **COI:** None. **Randomization:** Yes **Blinding:** n.s. **Dropout Rate/ITT-Analysis:** ITT yes **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 (randomized controlled trial) Long term analysis of the outcomes of PORTEC-2 trial.		

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016			
Population	Intervention	Outcomes/Results	
Evidence level: 3 **Study type:** Post-Hoc Analysis of two RCTs (PORTEC-1 and -2 trials) **Number of Patient:** 947 available early-stage endometrioid endometrial carcinomas from the PORTEC-1 and -2 trials **Recruitung Phase:** PORTEC-1 (1990–1997), PORTEC-2 (2000–2006) **Inclusion Criteria:** PORTEC-1 included patients with stage I endometrial carcinoma, grade 1 or 2 with deep myometrial invasion, or grade 2 or 3 with superficial invasion PORTEC-2 included endometrial carcinoma patients with high-intermediate risk features: stage I, age	**Intervention:** Prognostic significance of the proposed molecular classification tool in early-stage endometrioid endometrial carcinomas. Analysis of MSI, hotspot mutations in 14 genes including POLE, protein expression of p53, ARID1a, b-catenin, L1CAM, PTEN, ER, and PR **Comparison:** /	**Primary:** Prognostic value **Secondary:** / **Results:** Molecular analyses were feasible in >96% of the patients and confirmed the four molecular subgroups: p53-mutant (9%), MSI (26%), POLE-mutant (6%), and NSMP (59%). Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Approximately 15% of highintermediate risk patients had unfavorable features (substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM), 50% favorable features (POLE-mutant, NSMP being microsatellite stable, and CTNNB1 wild-type), and 35% intermediate features (MSI or CTNNB1-mutant). **Author's Conclusion:** Integrating clinicopathologic and molecular factors improves the risk assessment of patients with early-stage endometrial carcinoma. Assessment of this	

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016			
>60 years, grade 1–2 with deep invasion, or grade 3 with superficial invasion and stage IIA disease (except grade 3 with deep invasion). Post-hoc analysis: All tumor samples with confirmed endometrioid histology were included in the current analysis. **Exclusion Criteria:** n.a.		integrated risk profile is feasible in daily practice, and holds promise to reduce both overtreatment and undertreatment.	
Methodical Notes			
Funding Sources: This study was supported by the Dutch Cancer Society (UL2012-5719). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact. Clinical Trial Tissue Samples: Translational research was performed on tissue samples from two randomized clinical trials (PORTEC-1 and PORTEC-2). PORTEC-2 trial register number is ISRCTN16228756 and PORTEC-1 was conducted before time of trial registries. Both trials were supported by grants from the Dutch Cancer Society (CKTO 90-01 and CKTO 2001-04). **COI:** None. **Randomization:** Yes. **Blinding:** Blinding was performed in this post-hoc analysis.			

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016

Dropout Rate/ITT-Analysis: n.a.

Notes: Oxford CEBM Level of Evidence 2011: EL 3 Post-Hoc analysis of two RCTs
Article submitted by hand search

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Ørtoft, G. et al. Survival and recurrence in stage II endometrial cancers in relation to uterine risk stratification after introduction of lymph node resection and omission of postoperative radiotherapy: a Danish Gynecological Cancer Group Study. J Gynecol Oncol. 31. e22. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Prognostic retrospective cohort study	**Funding sources:** The study was financially supported by the Health research fund of Copenhagen University Hospital and Hans & Nora Buchard's Fond. **Conflict of Interests:** None. **Randomization:** **Blinding:** **Dropout rates:**	**Total no. patients:** 708 cases with cervical stromal invasion were included, and of these 461 were stage II cases **Recruiting Phase:** 2005-2012 **Inclusion criteria:** Not described **Exclusion criteria:** Not described	Interventions: Comparison:

Ørtoft, G. et al. Survival and recurrence in stage II endometrial cancers in relation to uterine risk stratification after introduction of lymph node resection and omission of postoperative radiotherapy: a Danish Gynecological Cancer Group Study. J Gynecol Oncol. 31. e22. 2020		
Notes:	Oxford CEBM Level of Evidence 2011: EL 4 Prognostic Retrospective Cohort study No comparison group. Outcome for stage II was compared before and after the introduction of lymph node (LN) resection and omission of all postoperative radiotherapy. Inclusion and exclusion criteria were not described sufficiently. **Author's conclusion:** Uterine risk groups are the strongest predictors for survival and recurrence in stage II patients and should be considered when advising adjuvant therapy. LN-resected stage II had increased survival and decreased recurrence. Omitting radiotherapy increase vaginal recurrence without affecting survival	
Outcome Measures/results	**Primary** Survival and recurrence **Secondary**	**Results:** Uterine risk factors (low-, intermediate-, and high-) were the strongest predictors of survival and recurrence in stage II. Stage II low-risk having a prognosis comparable to low-risk stage I (grade 1–2,

2.36. Schlüsselfrage 39: Bei welchen Stadien bzw. histolog. Typen des Endometriumkarzinoms ist eine adjuvante externe (perkutane) Strahlentherapie in Kombination mit Brachytherapie indiziert im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *8 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Boer, S. M. 2018	2	Randomized phase 3 trial
de Boer, S. M. 2016	2	Randomized phase 3 trial
de Boer, S. M. 2019	2	Randomized phase 3 trial
León-Castillo, A. 2020	2	RCT (phase-III-trial, molecular analysis)
Matei, D. 2019	2	Randomized phase 3 trial
Randall, M. E. 2019	2	Randomized phase 3 trial
Stelloo, E. 2016	3	Post-Hoc Analysis of two RCTs (PORTEC-1 and -2 trials)
Wortman, B. G. 2018	2	RCT (multicentre randomised trial, PORTEC-2 trial)

OXFORD (2011) Appraisal Sheet: RCT: *7 Bewertung(en)*

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 660 **Recruitung Phase:** Between Nov 23, 2006, and Dec 20, 2013 **Inclusion Criteria:** Patients were eligible if they had endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO) 2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. WHO performance score 0–2; adequate bone marrow function (white blood cells ≥3·0×10⁹/L, platelets ≥100×10⁹/L), liver function	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival **Secondary:** Vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life (published in de Boer et al. 2016) **Results:** Median follow-up was 60.2 months (IQR 48.1–73.1). 5-year overall survival was 81.8% (95% CI 77.5–86.2) with chemoradiotherapy versus 76.7% (72.1–81.6) with radiotherapy (adjusted hazard ratio [HR] 0.76, 95% CI 0.54–1.06; p=0.11); 5-year failure-free survival was 75.5% (95% CI 70.3–79.9) versus 68.6% (63.1–73.4; HR 0.71, 95% CI 0.53–0.95; p=0.022). Grade 3 or worse adverse events during treatment occurred in 198 (60%) of 330 who received chemoradiotherapy versus 41 (12%) of 330 patients who received radiotherapy (p<0·0001). Neuropathy (grade 2 or worse) persisted significantly more often after chemoradiotherapy than after radiotherapy (20 [8%] women vs one [1%] at 3 years; p

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018		
(bilirubin ≤1·5×upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase ≤2·5×UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault10 or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). **Exclusion Criteria:** Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual macroscopic tumour; impaired renal or cardiac function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder		**Author's Conclusion:** Adjuvant chemotherapy given during and after radiotherapy for high-risk endometrial cancer did not improve 5-year overall survival, although it did increase failure-free survival. Women with high-risk endometrial cancer should be individually counselled about this combined treatment. Continued follow-up is needed to evaluate long-term survival.
Methodical Notes		
Funding Sources: Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council Project Grant and Cancer Australia, L'Agenzia Italiana del Farmaco, and Canadian Cancer Society Research Institute.		

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

COI: None.

Randomization: Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type).

Blinding: Participants and investigators were not masked to treatment allocation.

Dropout Rate/ITT-Analysis: All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled Trial
For the outcomes: adverse events, patient reported symptoms and health-related quality of life see: de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival. **Secondary:** Vaginal, pelvic, or distant recurrence;

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Number of Patient: 660

Recruitung Phase: Sept 15, 2006, and Dec 20, 2013,

Inclusion Criteria: Patients were eligible for inclusion in this trial if they had International Federation of Gynecology and Obstetrics 2009 categorised stage IA grade 3 endometrial carcinoma with myometrial invasion and with documented lymph-vascular space invasion; stage IB grade 3; stage II, stage IIIA, or IIIC (or IIIB if parametrial invasion only); serous or clear cell histology with stage IA (with invasion), IB, II, or III. Eligible patients also had to have adequate WHO performance scores (WHO score 0–2); bone marrow (white blood cell count ≥3·0 cells × 10^9/L, platelets ≥100 × 10^9/L); liver function (bilirubin ≤1·5 × upper limit of normal [ULN], aspartate aminotransferase concentration ≤2·5 × ULN, or alanine aminotransferase concentration ≤2·5 × ULN); and kidney function (creatinine clearance >60 mL/min calculated according to Cockroft18 or >50 mL/min EDTA clearance) and be aged older than 18 years

Exclusion Criteria: Exclusion criteria were having

treatment-related toxicity;
and health-related quality of life (published elsewhere)

Results: Between Sept 15, 2006, and Dec 20, 2013, 686 women were randomly allocated in the PORTEC-3 trial. Of these, 660 met eligibility criteria, and 570 (86%) were evaluable for health-related quality of life. Median follow-up was 42.3 months (IQR 25.8–55.1). At completion of radiotherapy and at 6 months, EORTC QLQ-C30 functioning scales were significantly lower (worse functioning) and health-related quality of life symptom scores higher (worse symptoms) for the chemoradiotherapy group compared with radiotherapy alone, improving with time. At 12 and 24 months, global health or quality of life was similar between groups, whereas physical functioning scores remained slightly lower in patients who received chemoradiotherapy compared with patients who received radiotherapy alone. At 24 months, 48 (25%) of 194 patients in the chemoradiotherapy group reported severe tingling or numbness compared with 11 (6%) of 170 patients in the radiotherapy alone group (p
42 (13%) of 326 patients in the radiotherapy alone group (p<0.0001).

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016		
uterine sarcoma, previous malignancy less than 10 years ago, receipt of previous pelvic radiotherapy, hormonal or chemotherapy, gross cervical involvement with radical hysterectomy, infl ammatory bowel disease, residual macroscopic tumour, impaired renal or cardiac function, neuropathy grade 2 or worse, hearing impairment grade 3 or worse, or congenital hearing disorder.		**Author's Conclusion:** Despite the increased physician and patient-reported toxicities, this schedule of adjuvant chemotherapy given during and after radiotherapy in patients with high-risk endometrial cancer is feasible, with rapid recovery after treatment, but with persistence of patient-reported sensory neurological symptoms in 25% of patients. We await the analysis of primary endpoints before fi nal conclusions are made.
Methodical Notes		
Funding Sources: Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council Project Grant and Cancer Australia, L'Agenzia Italiana del Farmaco, and Canadian Cancer Society Research Institute. **COI:** None. **Randomization:** Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type). **Blinding:** Participants and investigators were not masked to treatment allocation. **Dropout Rate/ITT-Analysis:** Intention to treat analysis was not performed for the outcomes described in this study. **Notes:**		

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled Trial

Intention to treat analysis was not performed for the outcomes described in this study.

For the outcomes: Overall survival and failure-free survival. see:
de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 660 **Recruitung Phase:** Between Nov 23, 2006, and Dec 20, 2013 **Inclusion Criteria:** Patients were eligible if they had endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO)	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival **Secondary:** Vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life **Results:** At a median follow-up of 72.6 months (IQR 59.9–85.6), 5-year overall survival was 81.4% (95% CI 77.2–85.8) with chemoradiotherapy versus 76.1% (71.6–80.9) with radiotherapy alone (adjusted hazard ratio [HR] 0.70 [95% CI 0.51–0.97], p=0.034), and 5-year failure-free survival was 76.5% (95% CI 71.5–

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019		
2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. WHO performance score 0–2; adequate bone marrow function (white blood cells ≥3·0×10⁹/L, platelets ≥100×10⁹/L), liver function (bilirubin ≤1·5×upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase ≤2·5×UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault10 or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). **Exclusion Criteria:** Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual macroscopic tumour; impaired renal or cardiac		80.7) versus 69.1% (63.8–73.8; HR 0.70 [0.52–0.94], p=0.016). Distant metastases were the first site of recurrence in most patients with a relapse, occurring in 78 of 330 women (5-year probability 21.4%; 95% CI 17.3–26.3) in the chemoradiotherapy group versus 98 of 330 (5-year probability 29.1%; 24.4–34.3) in the radiotherapy-alone group (HR 0.74 [95% CI 0.55–0.99]; p=0.047). Isolated vaginal recurrence was the first site of recurrence in one patient (0.3%; 95% CI 0.0–2.1) in both groups (HR 0.99 [95% CI 0.06–15.90]; p=0.99), and isolated pelvic recurrence was the first site of recurrence in three women (0.9% [95% CI 0.3–2.8]) in the chemoradiotherapy group versus four (0.9% [95% CI 0.3–2.8]) in the radiotherapy-alone group (HR 0.75 [95% CI 0·17–3·33]; p=0.71). At 5 years, only one grade 4 adverse event (ileus or obstruction) was reported (in the chemoradiotherapy group). At 5 years, reported grade 3 adverse events did not differ significantly between the two groups, occurring in 16 (8%) of 201 women in the chemoradiotherapy group versus ten (5%) of 187 in the radiotherapy-alone group (p=0.24). The most common grade 3 adverse event was hypertension (in four [2%] women in both groups). At 5 years, grade 2 or worse adverse events were reported in 76 (38%) of 201 women in the chemoradiotherapy group versus 43 (23%) of 187 in the radiotherapy-alone group

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019			
function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder		(p=0.002). Sensory neuropathy persisted more often after chemoradiotherapy than after radiotherapy alone, with 5-year rates of grade 2 or worse neuropathy of 6% (13 of 201 women) versus 0% (0 of 187). No treatment-related deaths were reported. **Author's Conclusion:** This updated analysis shows significantly improved overall survival and failure-free survival with chemoradiotherapy versus radiotherapy alone. This treatment schedule should be discussed and recommended especially for women with stage III or serous cancers, or both, as part of shared decision making between doctors and patients. Follow-up is ongoing to evaluate long-term survival.	
Methodical Notes			
Funding Sources: Funding Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council, Project Grant, Cancer Australia Grant, Italian Medicines Agency, and the Canadian Cancer Society Research Institute. **COI:** None. **Randomization:** Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type).			

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019

Blinding: Participants and investigators were not masked to treatment allocation.

Dropout Rate/ITT-Analysis: All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled trial
Post-hoc analysis to analyse patterns of recurrence with 1 additional year of follow-up of de Boer et al. (2018)

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (phase-III-trial, molecular analysis) **Number of Patient:** FFPE tissue samples of 423 patients of the PORTEC-3 trial! **Recruitung Phase:** n.a.	**Intervention:** <u>Of the original PORTEC-trial:</u> Abdominal or laparoscopic hysterectomy with bilateral salpingooophorectomy was performed on all patients. Combined adjuvant chemotherapy and EBRT (CTRT, (2 cycles of cisplatin followed by 4 cycles of carboplatin and paclitaxel)) versus EBRT alone. **In this follow-up analysis:** Immunohistochemical staining for p53 and MMR proteins (MLH1, PMS2, MSH2, and MSH6) was performed on all	**Primary:** RFS, defined as time from randomization to date of first relapse or death, whichever occurred first. **Secondary:** The secondary end point was overall survival (OS), defined as the time from randomization to date of death of any cause. **Results:** Molecular testing was successful for 410 tumors (=97%). Patient and tumor

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020

Inclusion Criteria: Patients with high-risk EC (endometrioid EC [EEC] grade 3 stage IA with documented lymphovascular space invasion [LVSI]; EEC grade 3 stage IB; EEC stage II-III; and nonendometrioid invasive EC stages I, II, or III). **Exclusion Criteria:** n.s.	cases. If p53 immunohistochemistry was not evaluable, TP53 mutational status was used (n 5 9; 2.1% of the total 423 EC cases). If MMR immunohistochemistry was not evaluable, microsatellite instability (MSI) was assessed (n 5 8; 1.9%). Tumors with >1 classifying feature (multiple-classifier EC) were allocated in 1 of the 4 molecular subgroups. ECs with a pathogenic POLE EDM with p53 abnormal expression and/or MMR protein loss were classified as POLEmut EC, whereas ECs with loss of any MMR protein or MSI-high with a p53 mutant staining pattern were classified as MMRd EC. **Comparison:** See Intervention.	characteristics of these 410 ECs were comparable to the original trial population. Median follow-up was 6.1 years (range, 0.52-11.03 years). Tumors were classified: 1. 93 (22.7%) were p53abn 2. 51 (12.4%) were POLEmut 3. 137 (33.4%) were MMRd 4. 129 (31.5%) were NSMP ECs. The respective five-year RFS for patients was: - p53abn EC: 48% - POLEmut EC: 98% - MMRd EC: 72% and - NSMP EC: 74% (P ≤.001 the rfs with ctrt versus rt for p53abn ec was .019 patients polemut .637 .428 mmrd and .243 nsmp ec. **Author's Conclusion:** In conclusion, our study shows the strong prognostic information the EC molecular classification carries, as well as its great potential to guide adjuvant treatment. It is essential to implement the molecular EC classification in clinical diagnostics and decision-making. Patients with p53abn EC may be considered for adjuvant treatment including chemotherapy, whereas adjuvant treatment de-escalation should be considered for those with POLEmut EC; additional studies are needed especially

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020

		for MMRd and NSMP EC. Future clinical trials should include molecular subgroups in their design and study specific targeted adjuvant treatments.	

Methodical Notes

Funding Sources: Supported by the Dutch Cancer Society (KWF Kankerbestrijding; Grant No. 10418/2016-1 [T.B.]). E.J.C. is supported by National Institute for Health Research Manchester Biomedical Research Centre (Grant No. ISBRC-1215-20007).

COI: Declared online-

Randomization: Patient allocation in the original trial was performed randomly 1:1 to EBRT alone or CTRT.

Blinding: Sequencing and immunohistochemistry results were evaluated blinded for patient outcome.

Dropout Rate/ITT-Analysis: If ≥ 1 of the molecular features (p53, MMR, and/or POLE status) could not be determined (eg, not enough tumoral material or testing failed), and thus the molecular subgroup could not be determined, the case was classified as EC, not otherwise specified and excluded from the study (n = 13).
ITT was done, but data not shown.

Notes:
Oxford CEBM Level of Evidence (2011): EL 2 (randomized trial)

This study was not a standard RCT, but a follow up molecular analysis. Limiting factor may be the small study groups, discussed by the authors.

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 707 **Recruitung Phase:** June 29, 2009, and July 28, 2014 **Inclusion Criteria:** Women who were 18 years of age or older and who had surgical stage III or IVA endometrial carcinoma according to FIGO 2009 staging criteria of any histologic subtype or had FIGO 2009 surgical stage I or II clear-cell or serous endometrial carcinoma and peritoneal washings that were positive for cancer cells. Hysterectomy and bilateral salpingo-oophorectomy had to have been performed within 8 weeks before trial entry. No single residual tumor mass could be larger than 2 cm in greatest dimension. Pelvic and paraaortic lymph-node biopsy or dissection was optional. Normal organ function and a GOG performance status score of 2 or lower were required (scores range from 0 to 5, with higher scores reflecting greater disability).	**Intervention:** 6 months of platinum-based chemotherapy plus radiation therapy (chemoradiotherapy) **Comparison:** Six cycles of combination chemotherapy alone	**Primary:** Relapse-free survival **Secondary:** Overall survival, acute and chronic toxic effects, and quality of life **Results:** Relapse free survival The median follow-up period was 47 months. At 60 months, the Kaplan–Meier estimate of the percentage of patients alive and relapse-free was 59% (95% confidence interval [CI], 53 to 65) in the chemoradiotherapy group and 58% (95% CI, 53 to 64) in the chemotherapy-only group (hazard ratio, 0.90; 90% CI, 0.74 to 1.10). Therefore, the null hypothesis that chemoradiotherapy is not superior to chemotherapy alone could not be rejected (P=0.20 by one-tailed test). Overall survival A total of 165 deaths have been reported to date — 86 in the chemoradiotherapy group and 79 in the chemotherapy-only group. Of those deaths, 73% and 81%, respectively, were due to endometrial cancer progression. The data on overall survival are not sufficiently mature to allow comparison between the groups. Recurrence Chemoradiotherapy was associated with a lower 5-year incidence of vaginal recurrence (2% vs. 7%; hazard ratio, 0.36; 95% CI, 0.16 to 0.82) and pelvic and paraaortic lymph-

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019			
Exclusion Criteria: Patients with carcinosarcoma or recurrent endometrial carcinoma were excluded.		node recurrence (11% vs. 20%; hazard ratio, 0.43; 95% CI, 0.28 to 0.66) than chemotherapy alone, but distant recurrence was more common in association with chemoradiotherapy (27% vs. 21%; hazard ratio, 1.36; 95% CI, 1.00 to 1.86). Grade 3, 4, or 5 adverse events were reported in 202 patients (58%) in the chemoradiotherapy group and 227 patients (63%) in the chemotherapy-only group. Quality of life After adjustment for age and baseline scores, the leastsquares mean Trial Outcome Index score at 18 weeks in the chemoradiotherapy group was 5.2 points lower (97.5% CI, 2.7 to 7.8) than that in the chemotherapy-only group. The difference in this score remained significant at 70 weeks (3.4 points lower in the chemoradiotherapy group; 97.5% CI, 0.7 to 6.2) but did not exceed the 6-point difference that had been preset as clinically meaningful. **Author's Conclusion:** Chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma.	
Methodical Notes			
Funding Sources: Funded by the National Cancer Institute			

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019		
COI: Disclosure forms provided by the authors are available with the full text of this article at NEJM.org **Randomization:** Randomization was stratified according to age and the presence or absence of gross residual disease. **Blinding:** Not described **Dropout Rate/ITT-Analysis:** ITT-Analysis was performed **Notes:** Oxford Level of Evidence 2011: EL 2 randomized controlled trial Blinding was not described, however measures were objective except quality of life and chemotherapy-induced neurotoxic effects.		
Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 601 **Recruitung Phase:** From 2009 to 2013	**Intervention:** Pelvic radiation therapy (RT) (45 to 50.4 Gy over 5 weeks) **Comparison:** Vaginal cuff brachytherapy plus three cycles of carboplatin and	**Primary:** Recurrence free survival (RFS) **Secondary:** **Results:** The median age of the 601 patients was 63 years, and 74% had stage I disease. Histologies included endometrioid (71%), serous (15%), and clear cell (5%). With

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019		
Inclusion Criteria: After hysterectomy, patients with stage I endometrial cancer were eligible if they had endometrioid adenocarcinoma and met study criteria. A bilateral pelvic and para-aortic lymphadenectomy was recommended. Eligibility for patients with endometrioid histology was as follows: age 70 years or older with one uterine risk factor, age 50 years or older with two risk factors, or age 18 years or older with three risk factors. Uterine risk factors included grade 2 or 3 tumor, outer half depth of invasion, and lymphovascular invasion. Positive or negative peritoneal cytology was allowed. Patients with cervical stromal invasion (stage II) were eligible regardless of other risk factors. Patients with serous or clear cell tumors with stage I to II disease and with negative peritoneal cytology were eligible. Retrospective central pathology review confirmed eligibility and established histology. Patients not undergoing node dissection had postoperative computed tomography or magnetic resonance imaging to document the absence of enlarged nodes. Patients had adequate prespecified hematologic and organ function. **Exclusion Criteria:**	paclitaxel repeated every 3 weeks (VCB/C)	a median follow-up of 53 months, the 60-month RFS was 0.76 (95% CI, 0.70 to 0.81) for RT and 0.76 (95% CI, 0.70 to 0.81) for VCB/C (hazard ratio, 0.92; 90% confidence limit, 0.69 to 1.23). The 60-month overall survival was 0.87 (95% CI, 0.83 to 0.91) for RT and 0.85 (95% CI, 0.81 to 0.90) for VCB/C (hazard ratio, 1.04; 90% confidence limit, 0.71 to 1.52). Vaginal and distant recurrence rates were similar between arms. Pelvic or para-aortic nodal recurrences were more common with VCB/C (9% v 4%). There was no heterogeneity of treatment effect with respect to RFS or overall survival among clinical or pathologic variables evaluated. **Author's Conclusion:** Superiority of VCB/C compared with pelvic RT was not demonstrated. Acute toxicity was greater with VCB/C; late toxicity was similar. Pelvic RT alone remains an effective, well-tolerated, and appropriate adjuvant treatment in high-risk early-stage endometrial carcinomas of all histologies.

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019

Methodical Notes

Funding Sources: Supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517), NRG Oncology (1 U10 CA180822), and NRG Operations (U10CA180868) and in part by Memorial Sloan Kettering Cancer Center Support Grant No. P30 CA008748 (C.A.A.).

COI: See full text article for authors disclosures

Randomization: Patients were randomly assigned at a ratio of one to one to treatment with either RT or VCB/C.

Blinding: Open-label study

Dropout Rate/ITT-Analysis: Intention to treat analysis was performed

Notes:
Oxford Level of Evidence 2011: EL 2 randomized controlled trial
Open-label study

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (multicentre randomised trial, PORTEC-2 trial) **Number of Patient:** 427 women with HIR endometrial carcinoma (214 received EBRT and 213 recieved VBT). **Recruitung Phase:** Between May 2002 and September 2006. **Inclusion Criteria:** Woman diagnosed with endometrial carcinoma with high-intermediate risk factors (HIR), HIR was defined as either (1) FIGO 1988 stage 1C (≥50% myometrial invasion) with age greater than 60 and grade 1 or 2; or (2) FIGO 1988 stage 1B (**Exclusion Criteria:** Serous or clear cell carcinoma; staging lymphadenectomy; > 8 weeks interval between surgery and radiotherapy; history of previous malignancy; previous	**Intervention:** Vaginal brachytherapy (VBT) **Comparison:** Pelvic radiotherapy (EBRT).	**Primary:** Vaginal recurrence (VR) **Secondary:** Pelvic recurrence (PR), distant recurrence (DR), overall survival (OS, date of randomisation to death from any cause, with censoring at date of last information for patients alive), endometrial cancer-related survival (CSS, from date of randomisation to date of death related to endometrial cancer), disease-free survival (DFS, date of randomisation to date of disease recurrence or to date of death from any cause,), and toxicity and quality of life. **Results:** Patient and tumour characteristics were equally distributed over the two treatment groups. The database was frozen on May 1st 2016 and by then, the median follow-up was 116 months (range 18–163 months). The 10-year **vaginal recurrence rates** were 3.4% and 2.4% for VBT and EBRT, respectively (p = 0.55). **Pelvic recurrences** were 6.3% vs. 0.9% (p = 0.004); of these, 2.5% vs. 0.5% were isolated pelvic recurrences (p = 0.10). Ten-year rates of **distant metastases** were 10.4% vs. 8.9% for VBT vs EBRT (p = 0.45). In the confirmed HIR-group the 10-year vaginal recurrence rates

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018		
radiotherapy, hormonal or chemotherapy; Crohn's disease or ulcerative colitis.		were 2.7% vs. 3.1% (p = 0.78) and the pelvic recurrence rates 7.4% and 1.2% (p = 0.01) for VBT vs. EBRT,respectively. Ten-year **overall survival** was 69.5% vs. 67.6% (p = 0.72) and 10-year endometrial cancer-related survival 88.2% vs. 90.9% (p = 0.42) for VBT vs. EBRT groups, respectively. <u>Prognostic factors:</u> Women with tumours harbouring a POLE mutation, 10-year CSS was 100%, in contrast to 96.2% for no specific molecular profile, 84.8% for MSI and 62.3% for p53-mutant tumours (p < 0.001). Substantial LVSI (in confirmed HIR group) was found to be a very strong independent risk factor for pelvic and distant recurrence (HR 8.73 (p = 0.005) and 5.36 (p = 0.001), respectively) and for endometrial cancer-related survival (HR 7.16, p < 0.001). L1CAM expression (HR 4.18, p = 0.016) and p53-mutant expression (HR 3.35, p = 0.015) were significant prognostic factors for distant recurrence and CSS (HR 5.05, p = 0.006 and HR 3.30, p = 0.015). **Author's Conclusion:** In conclusion, long-term results of PORTEC-2 confirmed VBT as the adjuvant treatment of choice for women with high intermediate risk endometrial cancer. EBRT might provide better pelvic control in the small subgroup of women with unfavourable risk factors (substantial LVSI, L1CAM expression or p53-mutant expression).

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018

Methodical Notes

Funding Sources: The PORTEC-2 study was supported by a grant from the Dutch Cancer Society (CKTO 2001–04).

COI: None.

Randomization: Yes

Blinding: n.s.

Dropout Rate/ITT-Analysis: ITT yes

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 (randomized controlled trial)

Long term analysis of the outcomes of PORTEC-2 trial.

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016			
Population	Intervention	Outcomes/Results	
Evidence level: 3 **Study type:** Post-Hoc Analysis of two RCTs (PORTEC-1 and -2 trials) **Number of Patient:** 947 available early-stage endometrioid endometrial carcinomas from the PORTEC-1 and -2 trials **Recruitung Phase:** PORTEC-1 (1990–1997), PORTEC-2 (2000–2006) **Inclusion Criteria:** PORTEC-1 included patients with stage I endometrial carcinoma, grade 1 or 2 with deep myometrial invasion, or grade 2 or 3 with superficial invasion PORTEC-2 included endometrial carcinoma patients with high-intermediate risk features: stage I, age	**Intervention:** Prognostic significance of the proposed molecular classification tool in early-stage endometrioid endometrial carcinomas. Analysis of MSI, hotspot mutations in 14 genes including POLE, protein expression of p53, ARID1a, b-catenin, L1CAM, PTEN, ER, and PR **Comparison:** /	**Primary:** Prognostic value **Secondary:** / **Results:** Molecular analyses were feasible in >96% of the patients and confirmed the four molecular subgroups: p53-mutant (9%), MSI (26%), POLE-mutant (6%), and NSMP (59%). Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Approximately 15% of highintermediate risk patients had unfavorable features (substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM), 50% favorable features (POLE-mutant, NSMP being microsatellite stable, and CTNNB1 wild-type), and 35% intermediate features (MSI or CTNNB1-mutant). **Author's Conclusion:** Integrating clinicopathologic and molecular factors improves the risk assessment of patients with early-stage endometrial carcinoma. Assessment of this	

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016			
>60 years, grade 1–2 with deep invasion, or grade 3 with superficial invasion and stage IIA disease (except grade 3 with deep invasion). Post-hoc analysis: All tumor samples with confirmed endometrioid histology were included in the current analysis. **Exclusion Criteria:** n.a.		integrated risk profile is feasible in daily practice, and holds promise to reduce both overtreatment and undertreatment.	
Methodical Notes			
Funding Sources: This study was supported by the Dutch Cancer Society (UL2012-5719). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact. Clinical Trial Tissue Samples: Translational research was performed on tissue samples from two randomized clinical trials (PORTEC-1 and PORTEC-2). PORTEC-2 trial register number is ISRCTN16228756 and PORTEC-1 was conducted before time of trial registries. Both trials were supported by grants from the Dutch Cancer Society (CKTO 90-01 and CKTO 2001-04). **COI:** None. **Randomization:** Yes. **Blinding:** Blinding was performed in this post-hoc analysis.			

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016

Dropout Rate/ITT-Analysis: n.a.

Notes: Oxford CEBM Level of Evidence 2011: EL 3 Post-Hoc analysis of two RCTs
Article submitted by hand search

2.37. Schlüsselfrage 40: Welchen Einfluss hat die alleinige adjuvante Brachytherapie beim Endometriumkarzinom im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
AlHilli, M. 2020	4	Retrospective Cohort Study
Randall, M. E. 2019	2	Randomized phase 3 trial
Wortman, B. G. 2018	2	RCT (multicentre randomised trial, PORTEC-2 trial)

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 601 **Recruitung Phase:** From 2009 to 2013 **Inclusion Criteria:** After hysterectomy, patients with stage I endometrial cancer were eligible if they had endometrioid adenocarcinoma and met study criteria. A bilateral pelvic and para-aortic lymphadenectomy was recommended. Eligibility for patients with endometrioid histology was as follows: age 70 years or older with one uterine risk factor, age 50 years or older with two risk factors, or age 18 years or older with three risk factors. Uterine risk factors included grade 2 or 3 tumor, outer half depth of invasion, and lymphovascular invasion. Positive or negative peritoneal cytology was allowed. Patients with cervical stromal invasion (stage II) were eligible regardless of other risk factors. Patients with serous or clear cell	**Intervention:** Pelvic radiation therapy (RT) (45 to 50.4 Gy over 5 weeks) **Comparison:** Vaginal cuff brachytherapy plus three cycles of carboplatin and paclitaxel repeated every 3 weeks (VCB/C)	**Primary:** Recurrence free survival (RFS) **Secondary:** **Results:** The median age of the 601 patients was 63 years, and 74% had stage I disease. Histologies included endometrioid (71%), serous (15%), and clear cell (5%). With a median follow-up of 53 months, the 60-month RFS was 0.76 (95% CI, 0.70 to 0.81) for RT and 0.76 (95% CI, 0.70 to 0.81) for VCB/C (hazard ratio, 0.92; 90% confidence limit, 0.69 to 1.23). The 60-month overall survival was 0.87 (95% CI, 0.83 to 0.91) for RT and 0.85 (95% CI, 0.81 to 0.90) for VCB/C (hazard ratio, 1.04; 90% confidence limit, 0.71 to 1.52). Vaginal and distant recurrence rates were similar between arms. Pelvic or para-aortic nodal recurrences were more common with VCB/C (9% v 4%). There was no heterogeneity of treatment effect with respect to RFS or overall survival among clinical or pathologic variables evaluated. **Author's Conclusion:** Superiority of VCB/C compared with pelvic RT was not demonstrated. Acute toxicity was	

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019			
tumors with stage I to II disease and with negative peritoneal cytology were eligible. Retrospective central pathology review confirmed eligibility and established histology. Patients not undergoing node dissection had postoperative computed tomography or magnetic resonance imaging to document the absence of enlarged nodes. Patients had adequate prespecified hematologic and organ function. **Exclusion Criteria:**		greater with VCB/C; late toxicity was similar. Pelvic RT alone remains an effective, well-tolerated, and appropriate adjuvant treatment in high-risk early-stage endometrial carcinomas of all histologies.	
Methodical Notes			
Funding Sources: Supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517), NRG Oncology (1 U10 CA180822), and NRG Operations (U10CA180868) and in part by Memorial Sloan Kettering Cancer Center Support Grant No. P30 CA008748 (C.A.A.). **COI:** See full text article for authors disclosures **Randomization:** Patients were randomly assigned at a ratio of one to one to treatment with either RT or VCB/C. **Blinding:** Open-label study			

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019

Dropout Rate/ITT-Analysis: Intention to treat analysis was performed

Notes:
Oxford Level of Evidence 2011: EL 2 randomized controlled trial
Open-label study

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (multicentre randomised trial, PORTEC-2 trial) **Number of Patient:** 427 women with HIR endometrial carcinoma (214 received EBRT and 213 recieved VBT). **Recruitung Phase:** Between May 2002 and September 2006. **Inclusion Criteria:** Woman diagnosed with	**Intervention:** Vaginal brachytherapy (VBT) **Comparison:** Pelvic radiotherapy (EBRT).	**Primary:** Vaginal recurrence (VR) **Secondary:** Pelvic recurrence (PR), distant recurrence (DR), overall survival (OS, date of randomisation to death from any cause, with censoring at date of last information for patients alive), endometrial cancer-related survival (CSS, from date of randomisation to date of death related to endometrial cancer), disease-free survival (DFS, date of randomisation to date of disease recurrence or to date of death from any cause,), and toxicity and quality of life. **Results:** Patient and tumour characteristics were equally distributed over the two treatment groups. The database was

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018		
endometrial carcinoma with high-intermediate risk factors (HIR), HIR was defined as either (1) FIGO 1988 stage 1C (≥50% myometrial invasion) with age greater than 60 and grade 1 or 2; or (2) FIGO 1988 stage 1B (**Exclusion Criteria:** Serous or clear cell carcinoma; staging lymphadenectomy; > 8 weeks interval between surgery and radiotherapy; history of previous malignancy; previous radiotherapy, hormonal or chemotherapy; Crohn's disease or ulcerative colitis.		frozen on May 1st 2016 and by then, the median follow-up was 116 months (range 18–163 months). The 10-year **vaginal recurrence rates** were 3.4% and 2.4% for VBT and EBRT, respectively (p = 0.55). **Pelvic recurrences** were 6.3% vs. 0.9% (p = 0.004); of these, 2.5% vs. 0.5% were isolated pelvic recurrences (p = 0.10). Ten-year rates of **distant metastases** were 10.4% vs. 8.9% for VBT vs EBRT (p = 0.45). In the <u>confirmed HIR-group</u> the 10-year vaginal recurrence rates were 2.7% vs. 3.1% (p = 0.78) and the pelvic recurrence rates 7.4% and 1.2% (p = 0.01) for VBT vs. EBRT,respectively. Ten-year **overall survival** was 69.5% vs. 67.6% (p = 0.72) and 10-year endometrial cancer-related survival 88.2% vs. 90.9% (p = 0.42) for VBT vs. EBRT groups, respectively. <u>Prognostic factors:</u> Women with tumours harbouring a POLE mutation, 10-year CSS was 100%, in contrast to 96.2% for no specific molecular profile, 84.8% for MSI and 62.3% for p53-mutant tumours (p < 0.001). Substantial LVSI (in confirmed HIR group) was found to be a very strong independent risk factor for pelvic and distant recurrence (HR 8.73 (p = 0.005) and 5.36 (p = 0.001), respectively) and for endometrial cancer-related survival (HR 7.16, p < 0.001). L1CAM expression (HR 4.18, p = 0.016) and p53-mutant expression (HR 3.35, p = 0.015) were significant prognostic

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018			
		factors for distant recurrence and CSS (HR 5.05, p = 0.006 and HR 3.30, p = 0.015). **Author's Conclusion:** In conclusion, long-term results of PORTEC-2 confirmed VBT as the adjuvant treatment of choice for women with high intermediate risk endometrial cancer. EBRT might provide better pelvic control in the small subgroup of women with unfavourable risk factors (substantial LVSI, L1CAM expression or p53-mutant expression).	
Methodical Notes			
Funding Sources: The PORTEC-2 study was supported by a grant from the Dutch Cancer Society (CKTO 2001-04). **COI:** None. **Randomization:** Yes **Blinding:** n.s. **Dropout Rate/ITT-Analysis:** ITT yes **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 (randomized controlled trial) Long term analysis of the outcomes of PORTEC-2 trial.			

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

AlHilli, M. et al. Impact of vaginal brachytherapy on survival in stage I endometrioid endometrial carcinoma. Int J Gynecol Cancer. 30. 789-796. 2020			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective Cohort Study	Funding sources: None Conflict of Interests: None Randomization: Blinding: Dropout rates:	**Total no. patients:** 132.393 **Recruiting Phase:** 2004-2013 **Inclusion criteria:** Patients with stage I, type I disease (endometrioid histology) including all grades **Exclusion criteria:** Non-endometrioid histology, stage greater than IB, initial treatment non-surgical, missing post-operative treatment data or survival data, or if death occurred within 4 months of surgery and no adjuvant treatment was given, Patients with systemic therapy (with or without radiation therapy) were excluded	**Interventions:** No treatment, vaginal brachytherapy only or external beam radiation therapy only **Comparison:**
Notes:	Oxford CEBM Level of Evidence 2011: EL 3 Retrospective, cohort Study Retrospective analysis of a large population-based database. Blinding of the data analysts was not described. **Author's conclusion:** The delivery of adjuvant radiation therapy in patients with stage IA G1/2 endometrial carcinoma is not associated with improvement in overall survival. Patients with stage IB G1/2 and G3 as well as stage IA G3 are shown to benefit		

AlHilli, M. et al. Impact of vaginal brachytherapy on survival in stage I endometrioid endometrial carcinoma. Int J Gynecol Cancer. 30. 789-796. 2020		
	from improved overall survival wen adjuvant radiation therapy is administered. These findings demonstrate potential opportunities to reduce both overtreatment and undertreatment in stage I endometrial cancer patients.	
Outcome Measures/results	Primary Overall survival Secondary	**Results:** A total of 132.393 patients met inclusion criteria, and 81% of patients had stage IA and 19% had stage IB endometrial cancer. Adjuvant therapy was administered in 18% of patients: 52% received vaginal brachytherapy, 30% external beam radiation therapy and 18% chemotherapy +/- radiation therapy. External beam radiation therapy use decreased from 9% in 2004 to 4% in 2012, while vaginal brachytherapy use increased from 8% to 14%. Stage IA G1/2 patients did not benefit from either external beam radiation therapy or vaginal brachytherapy, while administration of vaginal brachytherapy improved overall survival in stage IB G1/2 compared with no treatment (p

2.38. Schlüsselfrage 41: Welchen Stellenwert hat eine adjuvante kombinierte Radiochemotherapie (sequenziell/simultan) im Vergleich zu anderen Verfahren (alleinige Radiatio, pelvin +/- paraaortale Bestrahlung, Abdomenganzbestrahlung, alleinige Chemotherapie) beim Endometriumkarzinom in Bezug auf Kurzzeit-/ Langzeitmorbidität, krankheitsspezifisches Gesamt-Überleben und Rezidivhäufigkeit?

Inhalt: *6 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Boer, S. M. 2018	2	Randomized phase 3 trial
de Boer, S. M. 2016	2	Randomized phase 3 trial
de Boer, S. M. 2019	2	Randomized phase 3 trial
Matei, D. 2019	2	Randomized phase 3 trial
Randall, M. E. 2019	2	Randomized phase 3 trial
Spirtos, N. M. 2019	2	Randomized phase III trial

OXFORD (2011) Appraisal Sheet: RCT: *6 Bewertung(en)*

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 660 **Recruitung Phase:** Between Nov 23, 2006, and Dec 20, 2013 **Inclusion Criteria:** Patients were eligible if they had endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO) 2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. WHO performance score 0–2; adequate bone marrow function (white blood cells ≥3·0×10⁹/L, platelets ≥100×10⁹/L), liver function	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival **Secondary:** Vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life (published in de Boer et al. 2016) **Results:** Median follow-up was 60.2 months (IQR 48.1–73.1). 5-year overall survival was 81.8% (95% CI 77.5–86.2) with chemoradiotherapy versus 76.7% (72.1–81.6) with radiotherapy (adjusted hazard ratio [HR] 0.76, 95% CI 0.54–1.06; p=0.11); 5-year failure-free survival was 75.5% (95% CI 70.3–79.9) versus 68.6% (63.1–73.4; HR 0.71, 95% CI 0.53–0.95; p=0.022). Grade 3 or worse adverse events during treatment occurred in 198 (60%) of 330 who received chemoradiotherapy versus 41 (12%) of 330 patients who received radiotherapy (p<0·0001). Neuropathy (grade 2 or worse) persisted significantly more often after chemoradiotherapy than after radiotherapy (20 [8%] women vs one [1%] at 3 years; p

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018		
(bilirubin ≤1·5×upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase ≤2·5×UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault10 or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). **Exclusion Criteria:** Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual macroscopic tumour; impaired renal or cardiac function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder		**Author's Conclusion:** Adjuvant chemotherapy given during and after radiotherapy for high-risk endometrial cancer did not improve 5-year overall survival, although it did increase failure-free survival. Women with high-risk endometrial cancer should be individually counselled about this combined treatment. Continued follow-up is needed to evaluate long-term survival.
Methodical Notes		
Funding Sources: Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council Project Grant and Cancer Australia, L'Agenzia Italiana del Farmaco, and Canadian Cancer Society Research Institute.		

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

COI: None.

Randomization: Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type).

Blinding: Participants and investigators were not masked to treatment allocation.

Dropout Rate/ITT-Analysis: All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled Trial
For the outcomes: adverse events, patient reported symptoms and health-related quality of life see: de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival. **Secondary:** Vaginal, pelvic, or distant recurrence;

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Number of Patient: 660 **Recruitung Phase:** Sept 15, 2006, and Dec 20, 2013, **Inclusion Criteria:** Patients were eligible for inclusion in this trial if they had International Federation of Gynecology and Obstetrics 2009 categorised stage IA grade 3 endometrial carcinoma with myometrial invasion and with documented lymph-vascular space invasion; stage IB grade 3; stage II, stage IIIA, or IIIC (or IIIB if parametrial invasion only); serous or clear cell histology with stage IA (with invasion), IB, II, or III. Eligible patients also had to have adequate WHO performance scores (WHO score 0–2); bone marrow (white blood cell count ≥3·0 cells × 10^9/L, platelets ≥100 × 10^9/L); liver function (bilirubin ≤1·5 × upper limit of normal [ULN], aspartate aminotransferase concentration ≤2·5 × ULN, or alanine aminotransferase concentration ≤2·5 × ULN); and kidney function (creatinine clearance >60 mL/min calculated according to Cockroft18 or >50 mL/min EDTA clearance) and be aged older than 18 years **Exclusion Criteria:** Exclusion criteria were having		treatment-related toxicity; and health-related quality of life (published elsewhere) **Results:** Between Sept 15, 2006, and Dec 20, 2013, 686 women were randomly allocated in the PORTEC-3 trial. Of these, 660 met eligibility criteria, and 570 (86%) were evaluable for health-related quality of life. Median follow-up was 42.3 months (IQR 25.8–55.1). At completion of radiotherapy and at 6 months, EORTC QLQ-C30 functioning scales were significantly lower (worse functioning) and health-related quality of life symptom scores higher (worse symptoms) for the chemoradiotherapy group compared with radiotherapy alone, improving with time. At 12 and 24 months, global health or quality of life was similar between groups, whereas physical functioning scores remained slightly lower in patients who received chemoradiotherapy compared with patients who received radiotherapy alone. At 24 months, 48 (25%) of 194 patients in the chemoradiotherapy group reported severe tingling or numbness compared with 11 (6%) of 170 patients in the radiotherapy alone group (p 42 (13%) of 326 patients in the radiotherapy alone group (p<0.0001).

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016		
uterine sarcoma, previous malignancy less than 10 years ago, receipt of previous pelvic radiotherapy, hormonal or chemotherapy, gross cervical involvement with radical hysterectomy, infl ammatory bowel disease, residual macroscopic tumour, impaired renal or cardiac function, neuropathy grade 2 or worse, hearing impairment grade 3 or worse, or congenital hearing disorder.		**Author's Conclusion:** Despite the increased physician and patient-reported toxicities, this schedule of adjuvant chemotherapy given during and after radiotherapy in patients with high-risk endometrial cancer is feasible, with rapid recovery after treatment, but with persistence of patient-reported sensory neurological symptoms in 25% of patients. We await the analysis of primary endpoints before fi nal conclusions are made.
Methodical Notes		
Funding Sources: Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council Project Grant and Cancer Australia, L'Agenzia Italiana del Farmaco, and Canadian Cancer Society Research Institute. **COI:** None. **Randomization:** Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type). **Blinding:** Participants and investigators were not masked to treatment allocation. **Dropout Rate/ITT-Analysis:** Intention to treat analysis was not performed for the outcomes described in this study. **Notes:**		

de Boer, S. M. et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 17. 1114-1126. 2016

Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled Trial

Intention to treat analysis was not performed for the outcomes described in this study.

For the outcomes: Overall survival and failure-free survival. see:
de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 19. 295-309. 2018

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 660 **Recruitung Phase:** Between Nov 23, 2006, and Dec 20, 2013 **Inclusion Criteria:** Patients were eligible if they had endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO)	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival **Secondary:** Vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life **Results:** At a median follow-up of 72.6 months (IQR 59.9–85.6), 5-year overall survival was 81.4% (95% CI 77.2–85.8) with chemoradiotherapy versus 76.1% (71.6–80.9) with radiotherapy alone (adjusted hazard ratio [HR] 0.70 [95% CI 0.51–0.97], p=0.034), and 5-year failure-free survival was 76.5% (95% CI 71.5–

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019

2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. WHO performance score 0–2; adequate bone marrow function (white blood cells ≥3·0×10⁹/L, platelets ≥100×10⁹/L), liver function (bilirubin ≤1·5×upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase ≤2·5×UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault10 or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). **Exclusion Criteria:** Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual macroscopic tumour; impaired renal or cardiac		80.7) versus 69.1% (63.8–73.8; HR 0.70 [0.52–0.94], p=0.016). Distant metastases were the first site of recurrence in most patients with a relapse, occurring in 78 of 330 women (5-year probability 21.4%; 95% CI 17.3–26.3) in the chemoradiotherapy group versus 98 of 330 (5-year probability 29.1%; 24.4–34.3) in the radiotherapy-alone group (HR 0.74 [95% CI 0.55–0.99]; p=0.047). Isolated vaginal recurrence was the first site of recurrence in one patient (0.3%; 95% CI 0.0–2.1) in both groups (HR 0.99 [95% CI 0.06–15.90]; p=0.99), and isolated pelvic recurrence was the first site of recurrence in three women (0.9% [95% CI 0.3–2.8]) in the chemoradiotherapy group versus four (0.9% [95% CI 0.3–2.8]) in the radiotherapy-alone group (HR 0.75 [95% CI 0·17–3·33]; p=0.71). At 5 years, only one grade 4 adverse event (ileus or obstruction) was reported (in the chemoradiotherapy group). At 5 years, reported grade 3 adverse events did not differ significantly between the two groups, occurring in 16 (8%) of 201 women in the chemoradiotherapy group versus ten (5%) of 187 in the radiotherapy-alone group (p=0.24). The most common grade 3 adverse event was hypertension (in four [2%] women in both groups). At 5 years, grade 2 or worse adverse events were reported in 76 (38%) of 201 women in the chemoradiotherapy group versus 43 (23%) of 187 in the radiotherapy-alone group

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019			
function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder		(p=0.002). Sensory neuropathy persisted more often after chemoradiotherapy than after radiotherapy alone, with 5-year rates of grade 2 or worse neuropathy of 6% (13 of 201 women) versus 0% (0 of 187). No treatment-related deaths were reported. **Author's Conclusion:** This updated analysis shows significantly improved overall survival and failure-free survival with chemoradiotherapy versus radiotherapy alone. This treatment schedule should be discussed and recommended especially for women with stage III or serous cancers, or both, as part of shared decision making between doctors and patients. Follow-up is ongoing to evaluate long-term survival.	
Methodical Notes			
Funding Sources: Funding Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council, Project Grant, Cancer Australia Grant, Italian Medicines Agency, and the Canadian Cancer Society Research Institute. **COI:** None. **Randomization:** Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type).			

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019		
Blinding: Participants and investigators were not masked to treatment allocation. **Dropout Rate/ITT-Analysis:** All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled trial Post-hoc analysis to analyse patterns of recurrence with 1 additional year of follow-up of de Boer et al. (2018)		
Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 707 **Recruitung Phase:** June 29, 2009, and July 28, 2014 **Inclusion Criteria:** Women who were 18 years of age or older and who had surgical stage III or IVA endometrial carcinoma according to FIGO 2009	**Intervention:** 6 months of platinum-based chemotherapy plus radiation therapy (chemoradiotherapy) **Comparison:** Six cycles of combination chemotherapy alone	**Primary:** Relapse-free survival **Secondary:** Overall survival, acute and chronic toxic effects, and quality of life **Results:** Relapse free survival The median follow-up period was 47 months. At 60 months, the Kaplan–Meier estimate of the percentage of patients alive and relapse-free was 59% (95% confidence interval [CI], 53 to 65) in the chemoradiotherapy group and 58% (95% CI, 53 to 64) in the chemotherapy-only group (hazard ratio, 0.90; 90% CI, 0.74 to 1.10). Therefore, the null hypothesis

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019			
staging criteria of any histologic subtype or had FIGO 2009 surgical stage I or II clear-cell or serous endometrial carcinoma and peritoneal washings that were positive for cancer cells. Hysterectomy and bilateral salpingo-oophorectomy had to have been performed within 8 weeks before trial entry. No single residual tumor mass could be larger than 2 cm in greatest dimension. Pelvic and paraaortic lymph-node biopsy or dissection was optional. Normal organ function and a GOG performance status score of 2 or lower were required (scores range from 0 to 5, with higher scores reflecting greater disability). **Exclusion Criteria:** Patients with carcinosarcoma or recurrent endometrial carcinoma were excluded.		that chemoradiotherapy is not superior to chemotherapy alone could not be rejected (P=0.20 by one-tailed test). Overall survival A total of 165 deaths have been reported to date — 86 in the chemoradiotherapy group and 79 in the chemotherapy-only group. Of those deaths, 73% and 81%, respectively, were due to endometrial cancer progression. The data on overall survival are not sufficiently mature to allow comparison between the groups. Recurrence Chemoradiotherapy was associated with a lower 5-year incidence of vaginal recurrence (2% vs. 7%; hazard ratio, 0.36; 95% CI, 0.16 to 0.82) and pelvic and paraaortic lymph-node recurrence (11% vs. 20%; hazard ratio, 0.43; 95% CI, 0.28 to 0.66) than chemotherapy alone, but distant recurrence was more common in association with chemoradiotherapy (27% vs. 21%; hazard ratio, 1.36; 95% CI, 1.00 to 1.86). Grade 3, 4, or 5 adverse events were reported in 202 patients (58%) in the chemoradiotherapy group and 227 patients (63%) in the chemotherapy-only group. Quality of life After adjustment for age and baseline scores, the leastsquares mean Trial Outcome Index score at 18 weeks in the chemoradiotherapy group was 5.2 points lower (97.5% CI, 2.7 to 7.8) than that in the chemotherapy-only group. The difference in this score remained significant at 70 weeks (3.4 points lower in the chemoradiotherapy group; 97.5% CI, 0.7 to 6.2) but did not exceed the 6-point	

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019			
		difference that had been preset as clinically meaningful. **Author's Conclusion:** Chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma.	
Methodical Notes			
Funding Sources: Funded by the National Cancer Institute **COI:** Disclosure forms provided by the authors are available with the full text of this article at NEJM.org **Randomization:** Randomization was stratified according to age and the presence or absence of gross residual disease. **Blinding:** Not described **Dropout Rate/ITT-Analysis:** ITT-Analysis was performed **Notes:** Oxford Level of Evidence 2011: EL 2 randomized controlled trial Blinding was not described, however measures were objective except quality of life and chemotherapy-induced neurotoxic effects.			

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 601 **Recruitung Phase:** From 2009 to 2013 **Inclusion Criteria:** After hysterectomy, patients with stage I endometrial cancer were eligible if they had endometrioid adenocarcinoma and met study criteria. A bilateral pelvic and para-aortic lymphadenectomy was recommended. Eligibility for patients with endometrioid histology was as follows: age 70 years or older with one uterine risk factor, age 50 years or older with two risk factors, or age 18 years or older with three risk factors. Uterine risk factors included grade 2 or 3 tumor, outer half depth of invasion, and lymphovascular invasion. Positive or negative peritoneal cytology was allowed. Patients with cervical stromal invasion (stage II) were eligible regardless of other risk factors. Patients with serous or clear cell tumors with stage I to II disease and with negative peritoneal cytology were eligible. Retrospective	**Intervention:** Pelvic radiation therapy (RT) (45 to 50.4 Gy over 5 weeks) **Comparison:** Vaginal cuff brachytherapy plus three cycles of carboplatin and paclitaxel repeated every 3 weeks (VCB/C)	**Primary:** Recurrence free survival (RFS) **Secondary:** **Results:** The median age of the 601 patients was 63 years, and 74% had stage I disease. Histologies included endometrioid (71%), serous (15%), and clear cell (5%). With a median follow-up of 53 months, the 60-month RFS was 0.76 (95% CI, 0.70 to 0.81) for RT and 0.76 (95% CI, 0.70 to 0.81) for VCB/C (hazard ratio, 0.92; 90% confidence limit, 0.69 to 1.23). The 60-month overall survival was 0.87 (95% CI, 0.83 to 0.91) for RT and 0.85 (95% CI, 0.81 to 0.90) for VCB/C (hazard ratio, 1.04; 90% confidence limit, 0.71 to 1.52). Vaginal and distant recurrence rates were similar between arms. Pelvic or para-aortic nodal recurrences were more common with VCB/C (9% v 4%). There was no heterogeneity of treatment effect with respect to RFS or overall survival among clinical or pathologic variables evaluated. **Author's Conclusion:** Superiority of VCB/C compared with pelvic RT was not demonstrated. Acute toxicity was greater with VCB/C; late toxicity was similar. Pelvic RT alone remains an effective, well-tolerated, and appropriate

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019			
central pathology review confirmed eligibility and established histology. Patients not undergoing node dissection had postoperative computed tomography or magnetic resonance imaging to document the absence of enlarged nodes. Patients had adequate prespecified hematologic and organ function. **Exclusion Criteria:**		adjuvant treatment in high-risk early-stage endometrial carcinomas of all histologies.	
Methodical Notes			
Funding Sources: Supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517), NRG Oncology (1 U10 CA180822), and NRG Operations (U10CA180868) and in part by Memorial Sloan Kettering Cancer Center Support Grant No. P30 CA008748 (C.A.A.). **COI:** See full text article for authors disclosures **Randomization:** Patients were randomly assigned at a ratio of one to one to treatment with either RT or VCB/C. **Blinding:** Open-label study **Dropout Rate/ITT-Analysis:** Intention to treat analysis was performed			

Randall, M. E. et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 37. 1810-1818. 2019

Notes:
Oxford Level of Evidence 2011: EL 2 randomized controlled trial
Open-label study

Spirtos, N. M. et al. The addition of paclitaxel to doxorubicin and cisplatin and volume-directed radiation does not improve overall survival (OS) or long-term recurrence-free survival (RFS) in advanced endometrial cancer (EC): A randomized phase III NRG/Gynecologic Oncology Gr. Gynecol Oncol. 154. 13-21. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase III trial **Number of Patient:** 552 **Recruitung Phase:** From July 3, 2000 to September 13, 2004 **Inclusion Criteria:** In July, 2000, protocol accrual was open to patients diagnosed with Stage III or IV endometrial carcinoma of any histology if the disease was limited to the pelvis and abdomen. Required surgery included hysterectomy and bilateral salpingo-	**Intervention:** Paclitaxel (P) (160 mg/m2) + Cisplatin and doxorubicin (CD) (50 mg/m2)/(45 mg/m2) **Comparison:** Cisplatin and doxorubicin (CD)(50 mg/m2)/(45 mg/m2)	**Primary:** Recurrence free survival (RFS), overall survival (OS) **Secondary:** **Results:** Since initial publication, 60 deaths occurred, leaving 311 patients alive with 290 (93.8%) recurrence-free. There was no significant decrease in the risk of recurrence or death associated with the CDP treatment regimen stratified for stage (p = 0.14, one-tail). The exploratory analysis for OS and the corresponding homogeneity tests for different effects across subgroups revealed only EFRT and EFRT & GRD status to have significantly different treatment effects (p = 0.027 and p = 0.017, respectively). Second primary malignancies were identified in 17/253 (6.4%) and 19/263 (7.0%) of patients

Spirtos, N. M. et al. The addition of paclitaxel to doxorubicin and cisplatin and volume-directed radiation does not improve overall survival (OS) or long-term recurrence-free survival (RFS) in advanced endometrial cancer (EC): A randomized phase III NRG/Gynecologic Oncology Gr. Gynecol Oncol. 154. 13-21. 2019			
oophorectomy with residual disease measuring **Exclusion Criteria:** Ineligible patients included those with co-morbid conditions precluding completion of protocol treatment; recurrent disease; prior pelvic or abdominal RT; a history of malignancy evident within the last 5 years or treatment with radiation or chemotherapy for that malignancy		treated with CD and CDP respectively. Breast (2.4%) followed by colon (1%) were the two cancers most frequently diagnosed in this setting **Author's Conclusion:** No significant difference between treatment arms was identified. Subgroup analysis both in the initial and current reports demonstrated a trend towards improved RFS and OS in patients treated with CDP and EFRT. This long-term analysis of outcomes also identified the necessity of providing on-going cancer screening to patients enrolled in trials	
Methodical Notes			
Funding Sources: **COI:** See full text article for authors disclosures **Randomization:** Following RT, the GOG Statistical and Data Center (SDC), randomly assigned the chemotherapy regimen, administered every 21 days for a maximum of six cycles, if patients were recurrence-free and agreeable. The sequence of treatment assignments, allocated with equal probability within strata using balanced blocks, was concealed from institutions and patients until randomization. Stratum levels were defined by the use of extended field radiation **Blinding:** Blinding was not described			

Spirtos, N. M. et al. The addition of paclitaxel to doxorubicin and cisplatin and volume-directed radiation does not improve overall survival (OS) or long-term recurrence-free survival (RFS) in advanced endometrial cancer (EC): A randomized phase III NRG/Gynecologic Oncology Gr. Gynecol Oncol. 154. 13-21. 2019

Dropout Rate/ITT-Analysis: ITT-analysis was performed

Notes:
Oxford CEBM Level Of Evidence: EL 2 Randomized Controlled Trial

This study displays the long term results of the initial study of Homesley HD, Filiaci V, Gibbons SK, Long HJ, Cella D, Spirtos NM, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. Gynecol. Oncol. 2009: 112:543–552.

Blinding was not described

2.39. Schlüsselfrage 43: Wie ist der Stellenwert der adjuvanten Chemotherapie beim Endometriumkarzinom im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *7 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Boer, S. M. 2019	2	Randomized phase 3 trial
de Lange, N. M. 2019	4	Retrospective, multicenter cohort study.
Latham, A. H. 2019	3	Cohort study (Database analysis).
Matei, D. 2019	2	Randomized phase 3 trial
Miller, D. S. 2020	2	Phase III randomized, open label trial (GOG0209)
Nomura, H. 2019	2	Multicenter, open label, phase 3 randomized trial.
Yi, L. 2018	1	SR and META (6 studies)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Yi, L. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 149. 612-619. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** SR and META (6 studies) **Databases:** PubMed, EMBASE, Cochrane Library, Web of Science, Clinicaltrials.gov. **Search period:** Last date of search: Dec. 9, 2017. **Inclusion Criteria:** prospective RCTs, Englisch language publications; histologically verified endometrial cancer, international FIGO stage I to III, CRT vs. RT alone, no chemotherapy or RT intervention before surgery **Exclusion Criteria:** unpublished studies and retrospective studies; studies in which antiangiogenic or endocrine drugs	**Population:** Patients with endometrial cancer randomly subjected to CRT or RT alone **Intervention:** CRT alone **Comparison:** RT alone	**Primary:** five-year OS, five-year PFS, local recurrence rate, the distant metastasis rate, five-year cancer specific survival (CSS)grade III/IV acute, late toxicities and small bowel obstruction rate. **Secondary:** see primary. **Results:** In total 2105 patients were included, 1064 underwent CRT and 1041 underwent RT. OS: CRT: 81.3%, RT: 79.8% no signif. difference (RR=1.02, 95% CI 0.98-1.06, p=0.04), (I2=32%, P=0.19). PFS: CRT: 80.2%, RT: 74.5%; PFS with CRT sign. higher (RR=1.08, 95% CI 1.02-1.13, p=0.005), (I2=42%, P=0.16). CSS: CRT: 86.1%, RT: 79.0% at late follow up; Difference was sign. (RR=1.09, 95% CI 1.01-1.08, p=0.03), (I2=0%, P=0.89). Local recurrence rate: CRT: 2.0%, RT: 4.1% no signif. difference (RR=0.48, 95% CI 0.19-1.18,	- Morrow, CP; 1990, Gynecol. Oncol. - Kuoppala, T.; 2008, Gynecol. Oncol. - Hogberg, T.; 2010, Eur. J. Cancer. - de Boer, S.M.; 2016, Lancet Oncol. - de Boer, SM; 2017, J. Clin. Oncol. (Abstract). - Randall, M; 2017, J. Radiat. Oncol. Biol. Phys. (Abstract).

Yi, L. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 149. 612-619. 2018				
or immunomodulators were used in either treatment.		p=0.11), (I2=0%, P=0.49). Distinct metastasis rate: CRT: 12.5%, RT: 13.2% no signif. difference (RR=0.94, 95% CI 0.72-1.23, p=0.67), (I2=61%, P=0.04). **Author's Conclusion:** With the deepening understanding of endometrial cancer, the roles of RT and chemotherapy have gained increasing attention. Compared with RT alone, additional chemotherapy significantly improves PFS and CSS in HRECs with FIGO stages I-III. However, CRT has no statistical significance for OS and recurrence rate. Furthermore, CRT is well tolerated without increasing long-term toxicities. Efforts should still be made to identify subgroups of patients with HRECs based on the distribution of FIGO stage, to further optimize the use of CRT in HREC.		
Methodical Notes				
Funding Sources: None. **COI:** Nothing to declare. **Study Quality:** Was assessed according to Cochrane Collaboration tool for assessing the risk of bias. Overall the studies were at low risk of bias.				

Yi, L. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 149. 612-619. 2018

Heterogeneity: Inconsistencies between studies was measured by I2 statistics (I2

Publication Bias: was determined by visual evaluating the asymmetry of the funnel plot. Begg's and Egger's test were also used to qualitatively detect publication bias. No significant publication bias could be found.

Notes:
Oxford CEBM Level of evidence 2011: EL 1 (systematic review or RTCs)

OXFORD (2011) Appraisal Sheet: RCT: *4 Bewertung(en)*

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019		
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Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 660 **Recruitung Phase:** Between Nov 23, 2006, and Dec 20, 2013 **Inclusion Criteria:** Patients were eligible if they had endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO) 2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. WHO performance score 0–2; adequate bone marrow function (white blood cells ≥3·0×10⁹/L, platelets ≥100×10⁹/L), liver function (bilirubin	**Intervention:** Chemoradiotherapy **Comparison:** Radiotherapy alone	**Primary:** Overall survival and failure-free survival **Secondary:** Vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life **Results:** At a median follow-up of 72.6 months (IQR 59.9–85.6), 5-year overall survival was 81.4% (95% CI 77.2–85.8) with chemoradiotherapy versus 76.1% (71.6–80.9) with radiotherapy alone (adjusted hazard ratio [HR] 0.70 [95% CI 0.51–0.97], p=0.034), and 5-year failure-free survival was 76.5% (95% CI 71.5–80.7) versus 69.1% (63.8–73.8; HR 0.70 [0.52–0.94], p=0.016). Distant metastases were the first site of recurrence in most patients with a relapse, occurring in 78 of 330 women (5-year probability 21.4%; 95% CI 17.3–26.3) in the chemoradiotherapy group versus 98 of 330 (5-year probability 29.1%; 24.4–34.3) in the radiotherapy-alone group (HR 0.74 [95% CI 0.55–0.99]; p=0.047). Isolated vaginal recurrence was the first site of recurrence in one patient (0.3%; 95% CI 0.0–2.1) in both groups (HR 0.99 [95% CI 0.06–15.90];

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019		
≤1·5×upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase ≤2·5×UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault10 or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). **Exclusion Criteria:** Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual macroscopic tumour; impaired renal or cardiac function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder		p=0.99), and isolated pelvic recurrence was the first site of recurrence in three women (0.9% [95% CI 0.3–2.8]) in the chemoradiotherapy group versus four (0.9% [95% CI 0.3–2.8]) in the radiotherapy-alone group (HR 0.75 [95% CI 0·17–3·33]; p=0.71). At 5 years, only one grade 4 adverse event (ileus or obstruction) was reported (in the chemoradiotherapy group). At 5 years, reported grade 3 adverse events did not differ significantly between the two groups, occurring in 16 (8%) of 201 women in the chemoradiotherapy group versus ten (5%) of 187 in the radiotherapy-alone group (p=0.24). The most common grade 3 adverse event was hypertension (in four [2%] women in both groups). At 5 years, grade 2 or worse adverse events were reported in 76 (38%) of 201 women in the chemoradiotherapy group versus 43 (23%) of 187 in the radiotherapy-alone group (p=0.002). Sensory neuropathy persisted more often after chemoradiotherapy than after radiotherapy alone, with 5-year rates of grade 2 or worse neuropathy of 6% (13 of 201 women) versus 0% (0 of 187). No treatment-related deaths were reported. **Author's Conclusion:** This updated analysis shows significantly improved overall survival and failure-free survival with chemoradiotherapy versus radiotherapy alone. This treatment schedule should be discussed

de Boer, S. M. et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 20. 1273-1285. 2019			
		and recommended especially for women with stage III or serous cancers, or both, as part of shared decision making between doctors and patients. Follow-up is ongoing to evaluate long-term survival.	
Methodical Notes			
Funding Sources: Funding Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council, Project Grant, Cancer Australia Grant, Italian Medicines Agency, and the Canadian Cancer Society Research Institute. **COI:** None. **Randomization:** Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type). **Blinding:** Participants and investigators were not masked to treatment allocation. **Dropout Rate/ITT-Analysis:** All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 Randomized controlled trial Post-hoc analysis to analyse patterns of recurrence with 1 additional year of follow-up of de Boer et al. (2018)			

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Evidence level: 2 **Study type:** Randomized phase 3 trial **Number of Patient:** 707 **Recruitung Phase:** June 29, 2009, and July 28, 2014 **Inclusion Criteria:** Women who were 18 years of age or older and who had surgical stage III or IVA endometrial carcinoma according to FIGO 2009 staging criteria of any histologic subtype or had FIGO 2009 surgical stage I or II clear-cell or serous endometrial carcinoma and peritoneal washings that were positive for cancer cells. Hysterectomy and bilateral salpingo-oophorectomy had to have been performed within 8 weeks before trial entry. No single residual tumor mass could be larger than 2 cm in greatest dimension. Pelvic and paraaortic lymph-node biopsy or dissection was optional. Normal organ function and a GOG performance status score of 2 or lower were required (scores range from 0 to 5, with higher scores reflecting greater disability).	**Intervention:** 6 months of platinum-based chemotherapy plus radiation therapy (chemoradiotherapy) **Comparison:** Six cycles of combination chemotherapy alone	**Primary:** Relapse-free survival **Secondary:** Overall survival, acute and chronic toxic effects, and quality of life **Results:** Relapse free survival The median follow-up period was 47 months. At 60 months, the Kaplan–Meier estimate of the percentage of patients alive and relapse-free was 59% (95% confidence interval [CI], 53 to 65) in the chemoradiotherapy group and 58% (95% CI, 53 to 64) in the chemotherapy-only group (hazard ratio, 0.90; 90% CI, 0.74 to 1.10). Therefore, the null hypothesis that chemoradiotherapy is not superior to chemotherapy alone could not be rejected (P=0.20 by one-tailed test). Overall survival A total of 165 deaths have been reported to date — 86 in the chemoradiotherapy group and 79 in the chemotherapy-only group. Of those deaths, 73% and 81%, respectively, were due to endometrial cancer progression. The data on overall survival are not sufficiently mature to allow comparison between the groups. Recurrence Chemoradiotherapy was associated with a lower 5-year incidence of vaginal recurrence (2% vs. 7%; hazard ratio, 0.36; 95% CI, 0.16 to 0.82) and pelvic and paraaortic lymph-

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019			
Exclusion Criteria: Patients with carcinosarcoma or recurrent endometrial carcinoma were excluded.		node recurrence (11% vs. 20%; hazard ratio, 0.43; 95% CI, 0.28 to 0.66) than chemotherapy alone, but distant recurrence was more common in association with chemoradiotherapy (27% vs. 21%; hazard ratio, 1.36; 95% CI, 1.00 to 1.86). Grade 3, 4, or 5 adverse events were reported in 202 patients (58%) in the chemoradiotherapy group and 227 patients (63%) in the chemotherapy-only group. Quality of life After adjustment for age and baseline scores, the leastsquares mean Trial Outcome Index score at 18 weeks in the chemoradiotherapy group was 5.2 points lower (97.5% CI, 2.7 to 7.8) than that in the chemotherapy-only group. The difference in this score remained significant at 70 weeks (3.4 points lower in the chemoradiotherapy group; 97.5% CI, 0.7 to 6.2) but did not exceed the 6-point difference that had been preset as clinically meaningful. **Author's Conclusion:** Chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma.	
Methodical Notes			
Funding Sources: Funded by the National Cancer Institute			

Matei, D. et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 380. 2317-2326. 2019

COI: Disclosure forms provided by the authors are available with the full text of this article at NEJM.org

Randomization: Randomization was stratified according to age and the presence or absence of gross residual disease.

Blinding: Not described

Dropout Rate/ITT-Analysis: ITT-Analysis was performed

Notes:
Oxford Level of Evidence 2011: EL 2 randomized controlled trial
Blinding was not described, however measures were objective except quality of life and chemotherapy-induced neurotoxic effects.

Miller, D. S. et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. . Jco2001076. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Phase III randomized, open label trial (GOG0209) **Number of Patient:** 1.381 patients by 266 GOG member clinical sites.	**Intervention:** Regimen I (TAP)—day 1: doxorubicin 45 mg/m2 followed immediately by cisplatin 50 mg/m2; day 2: paclitaxel 160 mg/m2 over 3 hours; day 3: filgrastim 5 mcg/kg/day for at least 10 days or pegfilgrastim 6 mg.	**Primary:** Overall Survival (OS) **Secondary:** Adverse events, PFS and patient-reported neurotoxicity and helath-related quality of life (HRQoL). **Results:** 640 patients in TAP and 664 patients in TC were included in safety analysis.

Miller, D. S. et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. . Jco2001076. 2020

Recruitung Phase: August 25, 2003 and April 20, 2009. **Inclusion Criteria:** Patients with primary stage III or IV, or recurrent endometrial cancer with poor potential for cure by surgery and/or radiation therapy; Treatment with radiation, hormones, or biologic agents must have been discontinued before enrollment. Adequate end-organ function and a GOG performance status of ≤# 2 was also required. In April 2006, eligibility was expanded from measurable only to include patients with International Federation of Gynecology and Obstetrics (FIGO) stage III, stage IV, and recurrent endometrial carcinoma who had not received prior chemotherapy. **Exclusion Criteria:** Prior cytotoxic chemotherapy, including chemotherapy used for radiation sensitization, was not allowed.	**Comparison:** Regimen II (TC)—day 1: paclitaxel 175 mg/m2 over 3 hours followed by carboplatin dosed to an area under the curve (AUC) of 6.0.	<u>Adverse events:</u> The most common toxicities (grades 3-5; TAP v TC) were leukopenia (48% v 50%), neutropenia (52% v 80%), thrombocytopenia (23% v 12%), and other hematologic adverse events (31% v 21%). Overall, the regimens were well tolerated, with 63% completing the planned seven cycles in the TAP arm, and 69% completing the TC arm. Neutropenic fever was reported in 7% of patients receiving TAP and 6% of those receiving TC. Grade > 2 sensory neuropathy was recorded in 26% of patients receiving TAP and 20% receiving TC (P = .40). More grade ≥$ 3 thrombocytopenia (23% v 12%), vomiting (7% v 4%), diarrhea (6% v 2%), and metabolic (14% v 8%) toxicities were reported with TAP. <u>PFS and OS:</u> The median follow-up was 124 months. More than 65% of the patients have died, and 28% remain alive without evidence of cancer. HR of TC relative to TAP was 1.002 (95% CI of 0.88 to 1.15) PFS: HR of TC to TAP was 1.032, (90% CI of 0.93 to 1.15). Median PFS was 14 months in the TAP-treated patients and 13 months in the TC-treated patients. Median OS

Miller, D. S. et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. . Jco2001076. 2020

		for the patients receiving TAP was 41 months and 37 months for patients receiving TC. HRQoL: Small HRQoL differences favored TC. **Author's Conclusion:** In conclusion, this trial has shown that TC is not inferior to TAP with regard to efficacy. Given its more favorable toxicity profile and the small but potentially meaningful differences in HRQoL favoring TC, TC should be considered the first-line therapy for advanced or recurrent endometrial cancer. The tolerability of the TC regimen further suggests that it should serve as a suitable backbone for combination with targeted therapies in future trials. This has been confirmed in subsequently initiated trials by the GOG and others.	
Methodical Notes			
Funding Sources: See publication **COI:** see online_publication. **Randomization:** Yes.			

Miller, D. S. et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. . Jco2001076. 2020

Blinding: Central review of patients was blinded to outcome.

Dropout Rate/ITT-Analysis: For main outcome (OS) a hazard ratio (HR) of TC to TAP exceeding 1.20 was considered inferior. This threshold required observing at least 795 events assuming proportional hazards to provide 90% statistical power with type I error limited to 0.10 (one-tail test) at the final analysis.
For all other outcomes see text.
Twenty-eight patients declined all treatment: 20 in the TAP arm and eight in the TC arm.

Notes:
Oxford CEBM Level of evidence 2011: EL 2 (randomized trial)
Article submitted by hand search

Nomura, H. et al. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomized Clinical Trial. JAMA Oncol. 5. 833-840. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Multicenter, open label, phase 3 randomized trial. **Number of Patient:** 788 patients were enrolled at 118 clinical sites.	**Intervention:** docetaxel plus cisplatin or paclitaxel plus carboplatin **Comparison:** doxorubicin plus cisplatin	**Primary:** Progression-free survival (PFS). **Secondary:** Overall survival, occurrence of adverse events (AEs), tolerability of treatment, and status of lymph node dissection. **Results:** AP: 263 patients to the doxorubicin plus

Nomura, H. et al. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomized Clinical Trial. JAMA Oncol. 5. 833-840. 2019		
Recruitung Phase: November 24, 2006, through January 7, 2011. **Inclusion Criteria:** Patients with endometrial cancer at a high risk of progression following surgery. (1)patients who had undergone total abdominal hysterectomy with bilateral salpingooophorectomy and pelvic lymph node dissection in which the residual tumor was 2 cm or less, (2) patients scheduled to receive chemotherapy within 8 weeks postsurgery, (3) patients without prior chemotherapy or radiotherapy, (4) patients aged between 20 and 74 years at registration, (5) patients having an Eastern Cooperative Oncology Group performance status of 0 to 2, and (6) patients with adequate function of major organs (eg, bone marrow, heart, liver, kidneys). **Exclusion Criteria:** Sarcomatous component, serious complications, concurrent infection, or a simultaneous cancer or a history of other cancer within the past 5 years.		cisplatin treatment group, DP: 263 patients to the docetaxel plus cisplatin treatment group, and TC: 262 patients to the paclitaxel plus carboplatin treatment group. After median of follow-up of seven years: **The 5-year PFS was** AP: 73.3% DP: 79.0% TC: 73.9% with no significant differences among the 3 groups(2-sided P = .12). **The 5-year overall survival was** AP: 82.7% DP: 88.1% TC: 86.1% with no significant differences among the 3 groups (2-sided P = .67). The number of patients who did not complete 6 cycles was 53 (20.1%) for the doxorubicin plus cisplatin group, 45 (17.1%) for the docetaxel plus cisplatin group, and 63 (24.0%) for the paclitaxel plus carboplatin group. Tolerability of these regimens were not statistically different. **Author's Conclusion:** In conclusion, taxane plus platinum regimens did not demonstrate a survival

Nomura, H. et al. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomized Clinical Trial. JAMA Oncol. 5. 833-840. 2019			
		benefit over treatment with doxorubicin plus cisplatin; therefore, doxorubicin plus cisplatin remains the standard postoperative adjuvant chemotherapy regimen for endometrial cancer at a high risk of progression. Nevertheless, considering efficacy and tolerability, taxane plus platinum regimens may be an alternative to treatment with doxorubicin plus cisplatin.	
Methodical Notes			
Funding Sources: See publication **COI:** see publication **Randomization:** 1:1:1 ratio using surgical stage (I or II vs III or IV) and tumor histology (G1 or G2 vs G3 or histology with a poor prognosis) as stratification factors. **Blinding:** n.a. **Dropout Rate/ITT-Analysis:** To robustly detect these clinical improvement swith 80% power, which is defined by the probability that the global null hypothesis and any paired null hypotheses were rejected simultaneously, under the aforementioned procedure in an enrollment period of 4 years and a follow-up period of 5 years, 250 patients per treatment group were required in 10 000 simulation studies.The recruitment target was 260 patients with 10 dropouts per treatment group.			

Nomura, H. et al. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomized Clinical Trial. JAMA Oncol. 5. 833-840. 2019			
Notes: Oxford CEBM Level of evidence 2011: EL 2 (randomized trial)			

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

de Lange, N. M. et al. Neoadjuvant chemotherapy followed by surgery for advanced-stage endometrial cancer. Curr Oncol. 26. e226-e232. 2019			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective, multicenter cohort study.	Funding sources: n.s. Conflict of Interests: Nothing to declare. Randomization: No. Blinding: No. Dropout rates: n.a.	**Total no. patients:** 102 patients with figo 2009 stage III or IV eca treated with nact. **Recruiting Phase:** January 2005 and January 2014 **Inclusion criteria:** Figo iii or iv endometrial carcinoma (eca) treated with nact, independent of histologic subtype, and adequate follow-up during treatment. **Exclusion criteria:** None applied.	**Interventions:** NACT: neoadjuvant chemotherapy **Comparison:** -
Notes:	Oxford CEBM Level of evidence 2011: EL 4 (retrospective, cohort study) Article submitted by hand search <u>Limitations:</u> - retrospective study		

de Lange, N. M. et al. Neoadjuvant chemotherapy followed by surgery for advanced-stage endometrial cancer. Curr Oncol. 26. e226-e232. 2019		
	- small cohort - no stratification The results should be interpreted with care due to the low level of methodological quality of the study and the small study groups. **Author's conclusion:** The present observational study indicates that nact followed by ids is a suitable noninferior treatment strategy for patients with advanced eca who are not considered suitable for primary surgery, regardless of histopathologic subtype. Compared with incomplete or no surgery, complete or optimal debulking after nact could lead to a survival benefit of 25–28 months; however, those data must be interpreted with care, given the retrospective nature of the study. No significant difference was evident in radiologic response rate, percentage of complete ids, recurrence rate, pfs, or os between the endometrioid and serous eca subtypes. The treatment options for this group of patients are limited and have to be explored.	
Outcome Measures/results	**Primary** Response to nact according to the recist 1.1 criteria. **Secondary** Recurrence rate, pfs, and os.	**Results:** <u>Histology_patient distribution:</u> 43% (n = 44) with endometrioid, 43% (n = 44) with serous, 4% (n = 4) with clear-cell, and 10% (n = 10) with other or mixed histologic subtypes of eca. <u>Radiological response to NACT:</u> A complete radiologic response was achieved in only 4 cases, with a partial response being achieved in 72% (64% of endometrioid cases, 80% of serous cases). <u>IDS:</u> 78% of the patients (n = 80) underwent ids, with 60% (n = 48) having a complete debulking, and 29% (n = 23) having an optimal debulking. Surgery was omitted in 22

de Lange, N. M. et al. Neoadjuvant chemotherapy followed by surgery for advanced-stage endometrial cancer. Curr Oncol. 26. e226-e232. 2019		
		patients. No difference in outcome between the histopathologic subtypes was found (surgical outcome for patients with figo stages iii and iv disease). Overall, no significant difference was evident with respect to the surgical outcome between the endometrioid and serous eca cases. <u>Adjuvant therapy after surgery:</u> - ctx: 69% (n=49)-Only 7% (n = 5) received a combination of adjuvant ctx and rt, - rt: consists of at least external-beam radiation and was in most cases combined with vaginal brachytherapy, or - hormonal therapy. <u>Recurrence and survival:</u> Median os was 41 months after complete and optimal debulking, 16 months after incomplete debulking, and 13 months for patients who did not undergo surgery. The overall recurrence rate for patients after nact and complete or optimal ids was 60.6% (n = 43). For endometrioid eca, the recurrence rate was 56% (n = 15), with a median time to recurrence of 18 months; for serous eca, the recurrence rate was 67% (n = 22), with a median time to recurrence of 13 months. The recurrence rate was not significantly different in the endometrioid and serous subgroups (p = 0.6).

Latham, A. H. et al. Sequencing of therapy in women with stage III endometrial carcinoma receiving adjuvant combination chemotherapy and radiation. Gynecol Oncol. 155. 13-20. 2019

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Cohort study (Database analysis).	**Funding sources:** n.s. **Conflict of Interests:** Dr.Wright has served as a consultant for Tesaro and Clovis Oncology. Dr. Neugut has served as a consultant to Otsuka, Hospira, and United Biosource Corporation. He is on the scientific advisory board of EHE, Intl. No other authors have any conflicts of interest or disclosures. **Randomization:** - **Blinding:** - **Dropout rates:** -	**Total no. patients:** 6981 patients. **Recruiting Phase:** 2004 to 2015 (National Cancer database) **Inclusion criteria:** Women with stage IIIC endometrial carcinoma who underwent hysterectomy and were treated with both adjuvant chemotherapy (CT) and external beam radiation (RT). Tumor histology was limited to carcinomas (endometrioid, serous, clear cell, endometrial not otherwise specified (NOS), and other). **Exclusion criteria:** Exclusion of carcinosarcomas and sarcomas. Women who had received any neoadjuvant therapy (CT or RT) prior to hysterectomy were excluded. exclusion of brachytherapy alone. Any patients with missing CT or RT day variables or unknown adjuvant therapy status were also excluded.	**Interventions:** - CT before RT, - RT before CT, and - concurrent therapy (a window of 21 days between first day of CT and first day of RT was used to define concurrent therapy regardless of whether CT or RT was initiated first). **Comparison:** See intervention.

Latham, A. H. et al. Sequencing of therapy in women with stage III endometrial carcinoma receiving adjuvant combination chemotherapy and radiation. Gynecol Oncol. 155. 13-20. 2019		
Notes:	Oxford CEBM Level of evidence 2011: EL 3 (cohort study) **Author's conclusion:** In summary, our data suggest that the use of CT before RT is increasing among women with stage IIIC endometrial cancer. While there was no clear difference in survival whether chemotherapy or radiation was initiated first, concurrent therapy is associated with decreased survival. Further data to develop individualized adjuvant treatment strategies for women with stage IIIC endometrial cancer is clearly needed.	
Outcome Measures/results	**Primary** The association between the type of adjuvant therapy sequence and overall survival. **Secondary** Five-year survival.	**Results:** <u>Patients:</u> - CT before RT: 5116 (73.3%) - RT before CT: 696 (10.0%) - concurrent therapy: 1169 (16.7%). <u>Overall survival:</u> The median follow-up of the cohort was 43 months (IQR 25–71), while 5-year survival was 69.2% (67.8–70.6%). Compared to those who received CT before RT, there was no difference in risk of mortality with RT then CT (HR = 1.01; 95% CI, 0.86–1.19) while concurrent therapy was associated with a 47% increased risk of mortality (HR = 1.47; 95% CI, 1.31–1.66)(p <u>Five-year survival</u> was - 70.8% (95% CI, 69.1–72.4%) among women who received CT before RT, - 69.9% (95% CI, 64.7–74.5%) for those treated with RT before CT, and - 61.2% (95% CI, 57.4–64.8%) for those who received concurrent therapy. In a sensitivity analysis comparing all women who received RT first (RT first then CT or

Latham, A. H. et al. Sequencing of therapy in women with stage III endometrial carcinoma receiving adjuvant combination chemotherapy and radiation. Gynecol Oncol. 155. 13-20. 2019		
		concurrent RT-CT), mortality was 25% higher (HR = 1.25; 95% CI, 1.13–1.39) compared to a strategy of CT followed by RT.

2.40. Schlüsselfrage 45: Welchen Stellenwert haben gynäkologische Untersuchung, zytologischer Abstrich, vaginale/abdominale/retroperitoneale Sonographie, Bestimmung von Tumormarkern, MRT, CT und PET-CT, PET-MRT in der Nachsorge der asymptomatischen Patientin im Hinblick auf Lebensqualität, Kurzzeit-/ Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bollineni, V. R. 2016	4	SR and META (21 studies, 13 for MA)
Høeg, B. L. 2019	2	SR and META (53 trials)
Nomura, H. 2019	2	follow-up analysis of a phase III randomized trial
Oaknin, A. 2020	3	Nonrandomized Phase 1 Clinical Trial (GARNET trial (NCT02715284))

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 4 **Study type:** SR and META (21 studies, 13 for MA) **Databases:** Pubmed **Search period:** inception to August 17, 2015. **Inclusion Criteria:** - Studies that reported the diagnostic performance of 18F-FDG PET/CT in detecting LNM preoperatively or disease recurrence in endometrial cancer patients after primary surgery; - clinical studies that included at least 10 patients; - studies that applied 18F-FDG as a tracer on a dedicated device and were published after peer review.	**Population:** 861 endometrial cancer patients were included for MA. **Intervention:** Diagnostic incidence of 18F-FDG PET/CT for preoperative prediction of pelvic lymph node metastases (PLN). **Comparison:** n.a.	**Primary:** preoperative prediction of PLN, Disease recurrence. **Secondary:** - **Results: Preoperative prediction PLN:** The pooled sensitivity and specificity values were 0.72 (95% CI, 0.63–0.80) and 0.94 (95% CI, 0.93–0.96) respectively. The pooled PLR was 10.9 (95% CI, 7.9–15.1), the pooled NLR was 0.36 (95% CI, 0.27–0.48), and the DOR was 39.7 (95% CI, 21.4–73.6). The SROC representing a global summary score for the test performance yielded an AUC of 0.94 and a Q* value of 0.88 (Fig. 3C), indicating a relatively high level of overall accuracy. Detection of ECR: 8 studies comprising 378 patients have been included. The pooled sensitivity was 0.95 (95% CI, 0.91–0.98), and the pooled specificity was 0.91 (95% CI,0.86–	see publication	

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016				
Exclusion Criteria: Studies on animals or in vitro studies, studies not available in full text or not written in English, and non original articles (e.g., reviews, editorials, letters, legal cases, interviews, case reports).		0.94). The pooled PLR was 8.8 (95% CI, 6.0– 12.7), NLR was 0.08 (95% CI, 0.05–0.15), and DOR was 171.7 (95% CI, 67.9–434.3). The SROC curve for the 18F-FDG PET/CT in the detection of ECR yielded an AUC and Q* values of 0.97 and 0.93, respectively, suggesting that the level of overall accuracy was high. **Author's Conclusion:** Overall, 18F-FDG PET/CT demonstrated a high diagnostic performance in identifying LNM preoperatively and in detecting recurrence after endometrial carcinoma surgery with curative intent. Larger prospective studies are needed to validate this high diagnostic performance of 18F-FDG PET/CT in endometrial cancer and further assess patient subgroups with particular clinical benefit from applying this advanced imaging procedure.		
Methodical Notes				
Funding Sources: The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This study was supported by funding from the Norwegian Cancer Society. No other potential conflict of interest relevant to this article was reported. **COI:** See funding.				

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016

Study Quality: n.a.

Heterogeneity: The I-square index was used to test for heterogeneity between studies.

Publication Bias: Evaluated publication bias in our meta-analysis using funnel plot asymmetry, finding the funnel plots to be symmetric for both sensitivity and specificity pooling, implying no large bias in our study.

Notes:
OXford CEBM Level of evidence 2011: EL 3 diagnostic retrospective nonconsectutive studies or studies without consistently applied reference standards. (systematic review, downgraded one Level due to methodological flaws -see notes).

Notes:
- only one database searched
- no quality analysis of the included studies
-

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** SR and META (53	**Population:** Adult cancer survivors from the following cancer sites: breast, colon, colorectal, endometrial, ovarian,	**Primary:** OS and time to detection of recurrence.	Two studies with endometrial

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019			
trials) **Databases:** Cochrane CENTRAL, MEDLINE, Embase, PsycINFO Ovid, CINAHL EBSCO; www.clinicaltrials.com and www.who.int/ **Search period:** until 11 December 2018 **Inclusion Criteria:** Randomised trials comparing different follow-up strategies for adult cancer survivors following completion of curatively intended primary cancer treatment, which included at least one of the outcomes listed. **Exclusion Criteria:** We excluded studies testing only psychosocial or rehabilitation components or studies investigating diagnostic components that were not integrated as part of clinical cancer follow-up.	cervical, melanoma and oesophageal. **Intervention:** 1) nonspecialist-led follow-up (i.e. general practitioner(GP)-led, nurse-led, patient-initiated or shared care) versus specialist-led follow-up; 2) less intensive versus more intensive follow-up (based on clinical visits, examinations and diagnostic procedures) and 3) follow-up integrating additional care components relevant for detection of recurrence (e.g.patient symptom education or monitoring or survivorship care plans) versus usual care. **Comparison:** See intervention.	**Secondary:** · Health-related quality of life · Anxiety (including fear of recurrence) · Depression · Cost **Results:** 20.832 participants in 15 countries. Seventeen studies compared non-specialist-led followup with specialist-led follow-up, 24 studies compared intensity of follow-up and 12 studies compared patient symptom education or monitoring, or survivorship care plans with usual care. Only two studies were included with endometrial cancer. Non-specialist-led vs. specialist-led follow-up: <u>Time to detection of recurrence - endometrial cancer:</u> One study (Beaver 2017; 259 participants), investigated follow-up after endometrial cancer and reported median time to recurrence in the nurse led arm (307 days; range 48 to 662) versus the hospital arm (172 days; range 99 to 436) but did not carry out any statistical analysis. We judged	cancer patients: Beaver 2017 and Jeppesen 2018.

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019

		the certainty of evidence to be very low and downgraded by three levels for serious concerns regarding inconsistency, indirectness and imprecision due to few studies, reporting of results by different estimates that could not be pooled and high variance of the result estimates. EORTC-C30: Beaver 2017 reported little or no effect of nurse-led telephone follow-up after endometrial cancer on all six subscales at time points ranging from 3 to 12 months after baseline data collection. For the overall results: there are no significant differences between non-speccialist-led vs. specialist-led follow-up regarding OS, time to detection or the secondary outomes. For details see publication. Comparing less intensive follow-up vs. more intensive follow-up theres is little or no difference to OS and probably an slight increase in time to detection of recurrence (HR 0.85, 95% CI 0.79 to 0.92; 12 studies; 11,276 participants; moderate-		

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019				
		certainty evidence). **Author's Conclusion:** Evidence regarding the effectiveness of the different follow-up strategies varies substantially. Less intensive follow-up may make little or no difference to overall survival but probably delays detection of recurrence. However, as we did not analyse the two outcomes together, we cannot make direct conclusions about the effect of interventions on survival after detection of recurrence. The effects of nonspecialist-led follow-up on survival and detection of recurrence, and how intensity of follow-up affects health-related quality of life, anxiety and depression, are uncertain. There was little evidence for the effects of follow-up integrating additional patient symptom education/ monitoring and survivorship care plans.		
Methodical Notes				

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019

Funding Sources: Danish Cancer Society Research Foundation, Denmark (intern).

COI: Klaus Kaae Andersen (KKA), afer completing the work on the review and near to its final publication, KKA started working at Astra Zeneca. The other authors stated "none known".

Study Quality: Certainty of evidence was assessed by GRADE approach and risk of bias using the criteria described in Chapter 8 of Cochrane Handbook for Systematic Reviews of Intervention.
Risk of bias was generally low or unclear in most of the studies, with a higher risk of bias in the smaller trials.

Heterogeneity: We used the Chi2 test and the I2 statistic, to measure statistical heterogeneity among the trials in the analysis for each outcome.

Publication Bias: Where applicable, visuell inspection of funel plot revealed no evidence for publication bias.

Notes:
Oxford CEBM Level of evidence 2011: EL 2 (systematic review) randomized trials, but without blinding

Notes:
- endometrial cancer was evaluated in two of the 53 trials. Thus the overall impact of the study results is not clear.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Nomura, H. et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 155. 413-419. 2019			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** follow-up analysis of a phase III randomized trial **Number of Patient:** 788 patients were registered in the JGOG2043 study and in 196 of those, relapse occurred. 3 were excluded because they didn't received chemotherapy. The other 193 were analyzed here. **Recruitung Phase:** n.s. **Inclusion Criteria:** Patients with histopathological confirmation of endometrial cancer who were considered to have a high risk of progression following surgery; patients who had undergone total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and maximal residual tumor of ≤ 2cm, as well as no prior anticancer therapy; age ≥20 years to < 75 years at registration, ECOG performance status (PS) of 0-2, adequate of vital organ function, no serious	**Intervention:** AP-Therapy: doxorubicin + cisplatin(263 patients) DP-therapy: docetaxel + cisplatin (263 patients) TC-therapy: paclitaxel + carboplatin (262 patients). 6 cycles of treatment **Comparison:** see intervention	**Primary:** Site of relapse, method of detecting relapse, CA125 prior to relapse, disease-free interval (DFI), and treatment following relapse. Overall survival (OS) **Secondary:** see primary. **Results:** <u>Pattern of relapse:</u> - local relapse: 50% of the patients (96/193) - distant relapse: 63% (121/193) - both types: 12% (24/193). Local relapse involved regional lymph nodes in 30% and distant relapse the abdominal cavity in 42%. Median DFI was 11.5 months (0-86.3 months): 9.7 months with AP, 9.5 with DP and 18.8 months with TC therapy. Thus, treatment with paclitaxel and carboplatin showed a significant correlation with DFI > 12 months (p=0.04). Factors showing a significant correlation with DFI ≤ 12 months were: - residual tumor at surgery (p<0.01), - Grade 3 histology (p< 0.01)	

Nomura, H. et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 155. 413-419. 2019			
complications. **Exclusion Criteria:** Patients without chemotherapy and lost to follow-up.		- lymph node metastasis (p= 0.03). Median post-relapse OS was 23.9 months. In multivariate analysis, CA125 ≥ 100 U/ml prior to relapse ((p **Author's Conclusion:** Relapse frequently occurred at 1 year after treatment in patients receiving adjuvant chemotherapy, and distant metastasis was less frequent, while local relapse was more frequent than reported previously after adjuvant chemotherapy. DFI >12 months was correlated with no residual tumor at surgery and with use of TC therapy, while the factors correlated with better RS were performing para-aortic lyphadenectomy and DFI >12 months.	
Methodical Notes			
Funding Sources: yes, see publication. **COI:** yes, see publication. **Randomization:** Random allocation 1:1:1 **Blinding:** No.			

Nomura, H. et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 155. 413-419. 2019

Dropout Rate/ITT-Analysis: Patients lost to follow-up were censored on the last day when survival was confirmed.

Notes:
Oxford CEBM Level of evidence 2011: EL 2 (randomized trial)

Limits:
- follow-up analysis
- it was not specified if the analyzing persons were blinded
- "Patients lost to follow-up were censored on the last day when survival was confirmed".

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Nonrandomized Phase 1 Clinical Trial (GARNET trial (NCT02715284))	**Funding sources:** This study was funded by GlaxoSmithKline. **Conflict of Interests:** Disclosures are provided in the article. **Randomization:** Non-randomized single-group trial.	**Total no. patients:** 104 patients with dMMR EC **Recruiting Phase:** Trial started March 7, 2016 and is still ongoing. Date of this preliminary analysis: July 8, 2019. **Inclusion criteria:** Eligible patients	**Interventions:** Part 1 was a dose-escalation study to evaluate weightbased doses of dostarlimab monotherapy. Part 2A was an extension of part 1 to evaluate the safety of non-weight-based fixed doses of dostarlimab.

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020			
	Blinding: Open-label trial, outcome assessors were blinded **Dropout rates:** /	were aged 18 years or older with histologically or cytologically proven recurrent or advanced EC with measurable lesion(s) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Patients could be screened on the basis of local MSI and/or MMR testing results, including dMMR as assessed by immunohistochemistry or MSI-H as assessed by polymerase chain reaction or next-generation sequencing performed in a certified local laboratory. The protocol was amended on May 10, 2019, to use only the results of the immunohistochemistry MMR test for classifying patients. **Exclusion criteria:** Patients with no measurable disease at baseline, Patients with	Part 2B enrolled patients into 4 expansion cohorts based on tumor type and mutation status (cohort A1, dMMR EC; cohort A2, proficient MMR EC; cohort E, non–small cell lung cancer; and cohort F, MSI-H/dMMR nonendometrial solid tumors) to assess the antitumor activity and safety of dostarlimab. Here, we report a prespecified analysis of one of the expansion cohorts with patients with recurrent or advanced dMMR EC (cohort A1) that has progressed after treatment with a platinum-containing chemotherapy regimen. All patients with dMMR EC were treated with a 30-minute infusion of intravenous dostarlimab, 500mg, once every 3 weeks for 4 doses, then 1000 mg once every 6 weeks until disease progression, treatment discontinuation due to toxic effects, or patient withdrawal

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020			
			of consent. **Comparison:** Single-group trial
Notes:	**Oxford CEBM Level of Evidence: EL 3 Non-randomized trial** Article submitted by hand search. -Preliminary data are presented here, trial is ongoing -Single-group trial, no comparison group **Author's conclusion:** In this nonrandomized trial, dostarlimab was associated with clinically meaningful and durable antitumor activity with an acceptable safety profile for patients with deficient mismatch mutation repair endometrial cancers after prior platinum-based chemotherapy.		
Outcome Measures/results	**Primary** The primary objective of this analysis was to evaluate the antitumor activity of dostarlimab in patients with recurrent or advanced dMMR EC, with the assessment of the objective response rate (ORR), defined as the proportion of patients with confirmed complete or partial response by	**Results:** Preliminary data are presented here, trial is ongoing. As of the data cutoff, 104 women (median age, 64.0 years [range, 38-80 years]) with deficient mismatch mutation repair endometrial cancers were enrolled and treated with dostarlimab. Of these, 71 had measurable disease at baseline and at 6 months or more of follow-up and were included in the analysis. **Objective response rate**	

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020

	blinded independent central review (BICR) using RECIST v1.1, and duration of response (DOR), defined as the time from first documented evidence of complete or partial response until the first documented sign of disease progression or death from any cause, whichever occurred first. Radiographic evaluationswere conducted atweek 12 after the first dose of dostarlimab, then every 6 weeks (±10 days) or as clinically indicated until month 12, and then every 12 weeks thereafter. **Secondary** Secondary end points included the disease control rate, defined as the proportion of patients with an objective response or stable disease lasting 12 weeks or longer based on BICR using RECIST v1.1; immune-related ORR (irORR) and immune-related DOR (irDOR) based on investigator assessment using immune-relatedRECIST (irRECIST); progression-free survival (PFS), defined as the time from the first dose of study medication to the first documented	There was a confirmed response in 30 patients (objective response rate, 42.3%; 95% CI, 30.6%-54.6%); 9 patients (12.7%) had a confirmed complete response, and 21 patients (29.6%) had a confirmed partial response. Responses were durable; the median duration of response was not reached (median follow-up was 11.2 months). **Duration of response** At the July 8, 2019, data cutoff, the median DOR was not reached, with a median follow-up of 11.2 months. The estimated likelihood of maintaining a response was 96.4% at 6 months and 76.8% at 12 months. **Disease control rate** The disease control rate was 57.7% (95% CI, 45.4%- 69.4%). **Progression free survival** The median PFS was 8.1 months (95% CI, 3.0- 18.0months) . **Overall survival** Themedian OS was also not reached, with a Kaplan-Meier estimation of 72.7% survival at 12 months after treatment initiation **Adverse events** Among the 104 patients included in the safety analysis, most treatment-related AEs (TRAEs) were grade 1 or 2. Anemia (3 of 104 [2.9%]), colitis (2 of 104 [1.9%]), and diarrhea (2 of 104 [1.9%]) were the most common grade 3 or higher treatment-related adverse events.

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020		
	disease progression based on BICR using RECIST v1.1; immune-related PFS (irPFS) based on investigator assessment using irRECIST; and OS, defined as the time from the date of the first dose of study medication to the date of death from any cause. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities, version 20.016 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.	

2.41. Schlüsselfrage 46: Welchen Stellenwert haben gynäkologische Untersuchung, zytologischer Abstrich, vaginale Sonographie und Bestimmung von Tumormarkern, MRT, CT und PET-CT, PET-MRT in der Nachsorge der symptomatischen Patientin im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bollineni, V. R. 2016	4	SR and META (21 studies, 13 for MA)
Høeg, B. L. 2019	1	SR and META (53 trials)
Nomura, H. 2019	2	follow-up analysis of a phase III randomized trial
Oaknin, A. 2020	3	Nonrandomized Phase 1 Clinical Trial (GARNET trial (NCT02715284))
Yalamanchi, P. 2018	4	Retrospective single-institution review.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 4 **Study type:** SR and META (21 studies, 13 for MA) **Databases:** Pubmed **Search period:** inception to August 17, 2015. **Inclusion Criteria:** - Studies that reported the diagnostic performance of 18F-FDG PET/CT in detecting LNM preoperatively or disease recurrence in endometrial cancer patients after primary surgery; - clinical studies that included at least 10 patients; - studies that applied 18F-FDG as a tracer on a dedicated device and were published after peer review.	**Population:** 861 endometrial cancer patients were included for MA. **Intervention:** Diagnostic incidence of 18F-FDG PET/CT for preoperative prediction of pelvic lymph node metastases (PLN). **Comparison:** n.a.	**Primary:** preoperative prediction of PLN, Disease recurrence. **Secondary:** - **Results: Preoperative prediction PLN:** The pooled sensitivity and specificity values were 0.72 (95% CI, 0.63–0.80) and 0.94 (95% CI, 0.93–0.96) respectively. The pooled PLR was 10.9 (95% CI, 7.9–15.1), the pooled NLR was 0.36 (95% CI, 0.27–0.48), and the DOR was 39.7 (95% CI, 21.4–73.6). The SROC representing a global summary score for the test performance yielded an AUC of 0.94 and a Q* value of 0.88 (Fig. 3C), indicating a relatively high level of overall accuracy. Detection of ECR: 8 studies comprising 378 patients have been included. The pooled sensitivity was 0.95 (95% CI, 0.91–0.98), and the pooled specificity was 0.91 (95% CI,0.86–	see publication	

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016				
Exclusion Criteria: Studies on animals or in vitro studies, studies not available in full text or not written in English, and non original articles (e.g., reviews, editorials, letters, legal cases, interviews, case reports).		0.94). The pooled PLR was 8.8 (95% CI, 6.0– 12.7), NLR was 0.08 (95% CI, 0.05–0.15), and DOR was 171.7 (95% CI, 67.9–434.3). The SROC curve for the 18F-FDG PET/CT in the detection of ECR yielded an AUC and Q* values of 0.97 and 0.93, respectively, suggesting that the level of overall accuracy was high. **Author's Conclusion:** Overall, 18F-FDG PET/CT demonstrated a high diagnostic performance in identifying LNM preoperatively and in detecting recurrence after endometrial carcinoma surgery with curative intent. Larger prospective studies are needed to validate this high diagnostic performance of 18F-FDG PET/CT in endometrial cancer and further assess patient subgroups with particular clinical benefit from applying this advanced imaging procedure.		
Methodical Notes				
Funding Sources: The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This study was supported by funding from the Norwegian Cancer Society. No other potential conflict of interest relevant to this article was reported. **COI:** See funding.				

Bollineni, V. R. et al. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med. 57. 879-85. 2016

Study Quality: n.a.

Heterogeneity: The I-square index was used to test for heterogeneity between studies.

Publication Bias: Evaluated publication bias in our meta-analysis using funnel plot asymmetry, finding the funnel plots to be symmetric for both sensitivity and specificity pooling, implying no large bias in our study.

Notes:
OXford CEBM Level of evidence 2011: EL 3 diagnostic retrospective nonconsectutive studies or studies without consistently applied reference standards. (systematic review, downgraded one Level due to methodological flaws -see notes).

Notes:
- only one database searched
- no quality analysis of the included studies
-

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** SR and META (53	**Population:** Adult cancer survivors from the following cancer sites: breast, colon, colorectal, endometrial, ovarian,	**Primary:** OS and time to detection of recurrence.	Two studies with endometrial

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019			
trials) **Databases:** Cochrane CENTRAL, MEDLINE, Embase, PsycINFO Ovid, CINAHL EBSCO; www.clinicaltrials.com and www.who.int/ **Search period:** until 11 December 2018 **Inclusion Criteria:** Randomised trials comparing different follow-up strategies for adult cancer survivors following completion of curatively intended primary cancer treatment, which included at least one of the outcomes listed. **Exclusion Criteria:** We excluded studies testing only psychosocial or rehabilitation components or studies investigating diagnostic components that were not integrated as part of clinical cancer follow-up.	cervical, melanoma and oesophageal. **Intervention:** 1) nonspecialist-led follow-up (i.e. general practitioner(GP)-led, nurse-led, patient-initiated or shared care) versus specialist-led follow-up; 2) less intensive versus more intensive follow-up (based on clinical visits, examinations and diagnostic procedures) and 3) follow-up integrating additional care components relevant for detection of recurrence (e.g.patient symptom education or monitoring or survivorship care plans) versus usual care. **Comparison:** See intervention.	**Secondary:** · Health-related quality of life · Anxiety (including fear of recurrence) · Depression · Cost **Results:** 20.832 participants in 15 countries. Seventeen studies compared non-specialist-led followup with specialist-led follow-up, 24 studies compared intensity of follow-up and 12 studies compared patient symptom education or monitoring, or survivorship care plans with usual care. Only two studies were included with endometrial cancer. Non-specialist-led vs. specialist-led follow-up: <u>Time to detection of recurrence - endometrial cancer:</u> One study (Beaver 2017; 259 participants), investigated follow-up after endometrial cancer and reported median time to recurrence in the nurse led arm (307 days; range 48 to 662) versus the hospital arm (172 days; range 99 to 436) but did not carry out any statistical analysis. We judged	cancer patients: Beaver 2017 and Jeppesen 2018.

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019				
		the certainty of evidence to be very low and downgraded by three levels for serious concerns regarding inconsistency, indirectness and imprecision due to few studies, reporting of results by different estimates that could not be pooled and high variance of the result estimates. EORTC-C30: Beaver 2017 reported little or no effect of nurse-led telephone follow-up after endometrial cancer on all six subscales at time points ranging from 3 to 12 months after baseline data collection. For the overall results: there are no significant differences between non-speccialist-led vs. specialist-led follow-up regarding OS, time to detection or the secondary outomes. For details see publication. Comparing less intensive follow-up vs. more intensive follow-up theres is little or no difference to OS and probably an slight increase in time to detection of recurrence (HR 0.85, 95% CI 0.79 to 0.92; 12 studies; 11,276 participants; moderate-		

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019				
		certainty evidence). **Author's Conclusion:** Evidence regarding the effectiveness of the different follow-up strategies varies substantially. Less intensive follow-up may make little or no difference to overall survival but probably delays detection of recurrence. However, as we did not analyse the two outcomes together, we cannot make direct conclusions about the effect of interventions on survival after detection of recurrence. The effects of nonspecialist-led follow-up on survival and detection of recurrence, and how intensity of follow-up affects health-related quality of life, anxiety and depression, are uncertain. There was little evidence for the effects of follow-up integrating additional patient symptom education/ monitoring and survivorship care plans.		
Methodical Notes				

Høeg, B. L. et al. Follow?up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019

Funding Sources: Danish Cancer Society Research Foundation, Denmark (intern).

COI: Klaus Kaae Andersen (KKA), afer completing the work on the review and near to its final publication, KKA started working at Astra Zeneca. The other authors stated "none known".

Study Quality: Certainty of evidence was assessed by GRADE approach and risk of bias using the criteria described in Chapter 8 of Cochrane Handbook for Systematic Reviews of Intervention.
Risk of bias was generally low or unclear in most of the studies, with a higher risk of bias in the smaller trials.

Heterogeneity: We used the Chi2 test and the I2 statistic, to measure statistical heterogeneity among the trials in the analysis for each outcome.

Publication Bias: Where applicable, visuell inspection of funel plot revealed no evidence for publication bias.

Notes:
Oxford CEBM Level of evidence 2011: EL 1 (systematic review)

Notes:
- endometrial cancer was evaluated in two of the 53 trials. Thus the overall impact of the study results is not clear.

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

Nomura, H. et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 155. 413-419. 2019			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 **Study type:** follow-up analysis of a phase III randomized trial **Number of Patient:** 788 patients were registered in the JGOG2043 study and in 196 of those, relapse occurred. 3 were excluded because they didn't received chemotherapy. The other 193 were analyzed here. **Recruitung Phase:** n.s. **Inclusion Criteria:** Patients with histopathological confirmation of endometrial cancer who were considered to have a high risk of progression following surgery; patients who had undergone total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and maximal residual tumor of ≤ 2cm, as well as no prior anticancer therapy; age ≥20 years to < 75 years at registration, ECOG performance status (PS) of 0-2, adequate of vital organ function, no serious	**Intervention:** AP-Therapy: doxorubicin + cisplatin(263 patients) DP-therapy: docetaxel + cisplatin (263 patients) TC-therapy: paclitaxel + carboplatin (262 patients). 6 cycles of treatment **Comparison:** see intervention	**Primary:** Site of relapse, method of detecting relapse, CA125 prior to relapse, disease-free interval (DFI), and treatment following relapse. Overall survival (OS) **Secondary:** see primary. **Results:** <u>Pattern of relapse:</u> - local relapse: 50% of the patients (96/193) - distant relapse: 63% (121/193) - both types: 12% (24/193). Local relapse involved regional lymph nodes in 30% and distant relapse the abdominal cavity in 42%. Median DFI was 11.5 months (0-86.3 months): 9.7 months with AP, 9.5 with DP and 18.8 months with TC therapy. Thus, treatment with paclitaxel and carboplatin showed a significant correlation with DFI > 12 months (p=0.04). Factors showing a significant correlation with DFI ≤ 12 months were: - residual tumor at surgery (p<0.01), - Grade 3 histology (p< 0.01)	

Nomura, H. et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 155. 413-419. 2019			
complications. **Exclusion Criteria:** Patients without chemotherapy and lost to follow-up.		- lymph node metastasis (p= 0.03). Median post-relapse OS was 23.9 months. In multivariate analysis, CA125 ≥ 100 U/ml prior to relapse ((p **Author's Conclusion:** Relapse frequently occurred at 1 year after treatment in patients receiving adjuvant chemotherapy, and distant metastasis was less frequent, while local relapse was more frequent than reported previously after adjuvant chemotherapy. DFI >12 months was correlated with no residual tumor at surgery and with use of TC therapy, while the factors correlated with better RS were performing para-aortic lyphadenectomy and DFI >12 months.	
Methodical Notes			
Funding Sources: yes, see publication. **COI:** yes, see publication. **Randomization:** Random allocation 1:1:1 **Blinding:** No.			

Nomura, H. et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 155. 413-419. 2019

Dropout Rate/ITT-Analysis: Patients lost to follow-up were censored on the last day when survival was confirmed.

Notes:
Oxford CEBM Level of evidence 2011: EL 2 (randomized trial)

Limits:
- follow-up analysis
- it was not specified if the analyzing persons were blinded
- "Patients lost to follow-up were censored on the last day when survival was confirmed".

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Nonrandomized Phase 1 Clinical Trial (GARNET trial (NCT02715284))	**Funding sources:** This study was funded by GlaxoSmithKline. **Conflict of Interests:** Disclosures are provided in the article. **Randomization:** Non-randomized single-group trial.	**Total no. patients:** 104 patients with dMMR EC **Recruiting Phase:** Trial started March 7, 2016 and is still ongoing. Date of this preliminary analysis: July 8, 2019. **Inclusion criteria:** Eligible patients	**Interventions:** Part 1 was a dose-escalation study to evaluate weightbased doses of dostarlimab monotherapy. Part 2A was an extension of part 1 to evaluate the safety of non-weight-based fixed doses of dostarlimab.

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020			
	Blinding: Open-label trial, outcome assessors were blinded **Dropout rates:** /	were aged 18 years or older with histologically or cytologically proven recurrent or advanced EC with measurable lesion(s) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Patients could be screened on the basis of local MSI and/or MMR testing results, including dMMR as assessed by immunohistochemistry or MSI-H as assessed by polymerase chain reaction or next-generation sequencing performed in a certified local laboratory. The protocol was amended on May 10, 2019, to use only the results of the immunohistochemistry MMR test for classifying patients. **Exclusion criteria:** Patients with no measurable disease at baseline, Patients with	Part 2B enrolled patients into 4 expansion cohorts based on tumor type and mutation status (cohort A1, dMMR EC; cohort A2, proficient MMR EC; cohort E, non–small cell lung cancer; and cohort F, MSI-H/dMMR nonendometrial solid tumors) to assess the antitumor activity and safety of dostarlimab. Here, we report a prespecified analysis of one of the expansion cohorts with patients with recurrent or advanced dMMR EC (cohort A1) that has progressed after treatment with a platinum-containing chemotherapy regimen. All patients with dMMR EC were treated with a 30-minute infusion of intravenous dostarlimab, 500mg, once every 3 weeks for 4 doses, then 1000 mg once every 6 weeks until disease progression, treatment discontinuation due to toxic effects, or patient withdrawal

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020			
			of consent. **Comparison:** Single-group trial
Notes:	**Oxford CEBM Level of Evidence: EL 3 Non-randomized trial** Article submitted by hand search. -Preliminary data are presented here, trial is ongoing -Single-group trial, no comparison group **Author's conclusion:** In this nonrandomized trial, dostarlimab was associated with clinically meaningful and durable antitumor activity with an acceptable safety profile for patients with deficient mismatch mutation repair endometrial cancers after prior platinum-based chemotherapy.		
Outcome Measures/results	**Primary** The primary objective of this analysis was to evaluate the antitumor activity of dostarlimab in patients with recurrent or advanced dMMR EC, with the assessment of the objective response rate (ORR), defined as the proportion of patients with confirmed complete or partial response by	**Results:** Preliminary data are presented here, trial is ongoing. As of the data cutoff, 104 women (median age, 64.0 years [range, 38-80 years]) with deficient mismatch mutation repair endometrial cancers were enrolled and treated with dostarlimab. Of these, 71 had measurable disease at baseline and at 6 months or more of follow-up and were included in the analysis. **Objective response rate**	

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020

	blinded independent central review (BICR) using RECIST v1.1, and duration of response (DOR), defined as the time from first documented evidence of complete or partial response until the first documented sign of disease progression or death from any cause, whichever occurred first. Radiographic evaluationswere conducted atweek 12 after the first dose of dostarlimab, then every 6 weeks (±10 days) or as clinically indicated until month 12, and then every 12 weeks thereafter. **Secondary** Secondary end points included the disease control rate, defined as the proportion of patients with an objective response or stable disease lasting 12 weeks or longer based on BICR using RECIST v1.1; immune-related ORR (irORR) and immune-related DOR (irDOR) based on investigator assessment using immune-relatedRECIST (irRECIST); progression-free survival (PFS), defined as the time from the first dose of study medication to the first documented	There was a confirmed response in 30 patients (objective response rate, 42.3%; 95% CI, 30.6%-54.6%); 9 patients (12.7%) had a confirmed complete response, and 21 patients (29.6%) had a confirmed partial response. Responses were durable; the median duration of response was not reached (median follow-up was 11.2 months). **Duration of response** At the July 8, 2019, data cutoff, the median DOR was not reached, with a median follow-up of 11.2 months. The estimated likelihood of maintaining a response was 96.4% at 6 months and 76.8% at 12 months. **Disease control rate** The disease control rate was 57.7% (95% CI, 45.4%- 69.4%). **Progression free survival** The median PFS was 8.1 months (95% CI, 3.0- 18.0months) . **Overall survival** Themedian OS was also not reached, with a Kaplan-Meier estimation of 72.7% survival at 12 months after treatment initiation **Adverse events** Among the 104 patients included in the safety analysis, most treatment-related AEs (TRAEs) were grade 1 or 2. Anemia (3 of 104 [2.9%]), colitis (2 of 104 [1.9%]), and diarrhea (2 of 104 [1.9%]) were the most common grade 3 or higher treatment-related adverse events.

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020			
	disease progression based on BICR using RECIST v1.1; immune-related PFS (irPFS) based on investigator assessment using irRECIST; and OS, defined as the time from the date of the first dose of study medication to the date of death from any cause. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities, version 20.016 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.		
Yalamanchi, P. et al. Use of Aggressive Surveillance for Locoregional Endometrial Cancer After Local Therapy. Int J Gynecol Cancer. 28. 1264-1270. 2018			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective single-institution review.	**Funding sources:** Research for this work was supported by National Center for Advancing Translational Sciences of the National Institutes of Health under award number KL2TR001879.	**Total no. patients:** 149 of 184 patients had recurrent disease. **Recruiting Phase:** Cancer Registries and multidisciplinary tumor registries at the Hospital of Pennsylvania were searched	**Interventions:** surveillance method to detect asymptomatic (recurrences asymptomatic recurrences detected by routine surveillance vs. recurrences with symptoms).

Yalamanchi, P. et al. Use of Aggressive Surveillance for Locoregional Endometrial Cancer After Local Therapy. Int J Gynecol Cancer. 28. 1264-1270. 2018			
	Conflict of Interests: None **Randomization:** No **Blinding:** No **Dropout rates:** No	between 1990-2014. **Inclusion criteria:** Patients with locoregional endometrial cancer treated with total hysterectomy with bilateral salpingo-oophorectomy with or without adjuvant therapy who subseqenetly developed recurrent disease. Eligible patients had to underwent comprehensive surgical staging at the time of initial diagnosis. **Exclusion criteria:** -	**Comparison:** see intervention.
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective cohort study) Notes: - retrospective design - no blinding - heterogenous population - small groups. The results of the study should be interpreted with cation due to the low methodological quality of the study. **Author's conclusion:** Patients who develop asymptomatic recurrences of their endometrial carcinoma do not seem to have a		

Yalamanchi, P. et al. Use of Aggressive Surveillance for Locoregional Endometrial Cancer After Local Therapy. Int J Gynecol Cancer. 28. 1264-1270. 2018		
	better prognosis than those who present with symptomatic recurrences. Thus, these results do not support routine imaging surveillance for patients treated for locoregional endometrial carcinoma. Further prospective evaluation is needed.	
Outcome Measures/results	**Primary** Overall survival, progression free survival. **Secondary** -	**Results:** Median age of patients at diagnosis was 68.4 years, with most patients diagnosed at age older than 60. Recurrence detection: - distant (64.4%) - vaginal (20.8%), - pelvic (14.8%). 86 patients (57.7%) developed asymptomatic recurrences, 63 patients (42.3%) developed symptomatic recurrences. Of those detected asymptomatically, 80.2% were detected by imaging. The average time to detection of recurrence was 2.27 years (interquartile range 1.54-2.99 years) and there was no significant difference between recurrences detected as symptomatic vs. asymptomatic (p=0.66). Comparing symptomatic vs. asymptomatic recurrences, there was no difference in overall survival (HR 1.24; 95% CI, 0.84-1.83, p=0.29) or progression free survival (HR 1.14; 95% CI, 077-1.70, p=0.52).

2.42. Schlüsselfrage 47: Welchen Stellenwert haben die operative Therapie, die Chemotherapie, die endokrine Therapie, die zielgerichtete Therapie und die Strahlentherapie in der Behandlung von Rezidiv und Metastasen beim Endometriumkarzinom im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *7 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Ethier J.-L. 2017	3	Systematic Review and Meta-Analysis of observational studies and clinical trials (39 studies, 1837 patients)
Fader, A. N. 2020	2	Randomized phase II trial
Makker, V. 2020	3	Ongoing, multinational, open-label, single arm study (KEYNOTE-146/Study 111).
Marabelle, A. 2020	3	Nonrandomized, open-label, multisite phase II study.
Oaknin, A. 2020	3	Nonrandomized Phase 1 Clinical Trial (GARNET trial (NCT02715284))
Roncolato, F. 2019	1	SR and META (2 studies)
Yalamanchi, P. 2018	4	Retrospective single-institution review.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Ethier J.-L. et al. Is hormonal therapy effective in advanced emdometrial cancer. Gynecol Oncol. 147. 158-166. 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of observational studies and clinical trials (39 studies, 1837 patients) **Databases:** Medline, Embase, Cochrane Database of Systematic Reviews **Search period:** 1946 to July 1st 2016 **Inclusion Criteria:** 1) Studies of adult women with advanced or recurrent EC; 2) examining the use of progestins, AIs, SERMs, fulvestrant or gonadotropin-releasing hormone (GnRH) agonists alone or in combination; 3) reporting median ORR, clinical benefit rate (CBR), complete response (CR), partial response (PR), stable disease (SD), progression free survival (PFS) and or overall survival	**Population:** Women with advanced or recurrent endometrial cancer **Intervention:** Hormonal therapy: progestins, AIs, SERMs, fulvestrant or gonadotropin-releasing hormone (GnRH) agonists alone or in combination **Comparison:**	**Primary:** Median ORR, clinical benefit rate (CBR), complete response (CR), partial response (PR), stable disease (SD), progression free survival (PFS) and or overall survival (OS) **Secondary:** **Results:** 39 studies were included with seven providing subgroup data based on HR status. First-line HT was associated with a mean ORR of 21,6% and clinical benefit rate of 36,7%. Median PFS and OS were 2.8 and 10.2 months respectively. ORR was 20,4% in clinical trials and 25,3% in observational studies. Magnitude of ORR was lower in older age, adenosquamous histology and high grade. ORR was higher in ER+ (26,5%) and PgR+	First line: Anderson 1965, Benraad 1980, De Vriese 1992, Emons 2013, Fiorica 2004, Karagol 2006, Kelley 1961, Kline 1987, Kneale 1969, Lentz 1996, Lindemann 2014, Malkasian 1971, McCarty 1979, Morrison 1972, Pandya 2001, Piver 1980, Podratz 1985, Quinn 1985, Rendina 1984, Thigpen 1999, Thigpen 2001, Wait 1973, Whitney 2004 Second line: Bonte 1981, McMeekin 2003, Quinn 1989, Swenerton 1979 Mixed: Asbury 2002, Covens 1997, Covens 2011, Edmonson 1986, Gallagher 1991, Hald 1983, Jeyarajah

Ethier J.-L. et al. Is hormonal therapy effective in advanced emdometrial cancer. Gynecol Oncol. 147. 158-166. 2017			
(OS); 4) available as full-text publication; 5) clinical trials or cohort or case-control studies; and 6) English language publication ORR was defined as the percentage of patients with CR or PR , whereas CBR included those who achieved CR, PR or SD. **Exclusion Criteria:** Studies of combination HT were included, while those examining HT combined with chemotherapy or other targeted therapies were excluded. Case reports, conference abstracts and letters to the editor were excluded.		(35,5%) disease, and lower in ER- (9,2%) and PgR- (12,2%) tumors. Second-line ORR was 18,5%. CBR was 35,8%, but was significantly associated with timing of stable disease assessments in first- and second line therapy. Meta-regression performed in mixed and second-line studies showed an association between previous HT and greater ORR (beta 0.561; p = 0.024), suggesting potential confounding by indication (re-treatment of good responders to first-line HT). **Author's Conclusion:** HT is associated with modest ORR in the first- and second-line treatment of advanced EC, and benefits are greatest in ER and/or PgR positive tumors. Response rates in second-line are likely dependent on response to previous HT. Future studies are needed to explore the role of HT in the adjuvant setting, or in combination with newer targeted agents, and should incorporate	1996, Lhomme 1999, Ma 2004, Maenpaa 1992, Rose 2000, Slavik 1984

Ethier J.-L. et al. Is hormonal therapy effective in advanced emdometrial cancer. Gynecol Oncol. 147. 158-166. 2017				
		standardized methods for HR testing.		
Methodical Notes				
Funding Sources: None. **COI:** None, declared by the authors. **Study Quality:** Study quality was not investigated. **Heterogeneity:** Not investigated, although several meta-regressions were performed **Publication Bias:** Publication bias was not investigated. **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review and Meta-Analysis of Observational studies and clinical trials Article submitted by hand search **Downgraded to EL 3 due to methodical weakness:** <u>Limits:</u> -No quality assessment of the included studies was performed -No investigation of publication bias was performed -Heterogeneity was not analyzed although several meta-regressions were performed				

Roncolato, F. et al. PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer. Cochrane Database of Systematic Reviews. . . 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** SR and META (2 studies) **Databases:** Cochrane Central Register of Controlled Trials, MEDLINE and Embase. WHO ICTRP and ClinicalTrials.gov (in July 2018). **Search period:** From inception until 16 January 2019. **Inclusion Criteria:** RCTs comparing a regimen with a PI3K/AKT/mTOR inhibitor (either alone orin combination with other treatments, such as chemotherapy or hormonal therapy) versus a comparator regimen without a PI3K/AKT/mTOR inhibitor. There were no restrictions on which comparator(s) were included. **Exclusion Criteria:** -	**Population:** Women with locally-advanced (FIGO Stage III) or metastatic (FIGO Stage IV) endometrial cancer (EC), either newly diagnosed or recurrent disease of any stage. **Intervention:** mTOR inhibitor with or without chemotherapy **Comparison:** chemotherapy or hormone therapy	**Primary:** Progression-free survival and toxicity (grade 3/4 where available). **Secondary:** Overall survival, objective tumour response rate, quality of life and treatment-related death. **Results:** In total the two studies included 361 women. Study 1: mTOR inhibitor temsirolimus, in combination with carboplatin/paclitaxel versus carboplatin/paclitaxel and bevacizumab in treatment-naïve women with advanced or recurrent endometrial cancer. Study 2: mTOR inhibitor ridaforolimus alone versus progestin or investigator choice of chemotherapy in women who had received prior treatment for metastatic or recurrent endometrial cancer. For **first-line therapy,** an mTORinhibitor-containing regimen may worsen	Aghajanian 2018 Oza 2015 5 ongoing studies were also identified.

Roncolato, F. et al. PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer. Cochrane Database of Systematic Reviews. . . 2019				
		progression-free survival(HR1.43, 95% CI 1.06 to 1.93; 1 study, 231 participants; low-certainty evidence), while for **second/third-line therapy**, an mTOR inhibitor probably improves progression-free survival compared to chemotherapy or endocrine therapy (HR 0.53, 95% CI 0.31 to 0.91; 1 study, 95 participants; moderate-certainty evidence). **Toxicity:** administering an mTOR inhibitor regimen may increase the risk of grade 3/4 mucositis (RR 10.42, 95% CI 1.34 to 80.74; 2 studies, 357 participants; low-certainty evidence), but may result in little to no difference in risk of anaemia or interstitial pneumonitis (low-certainty evidence for both toxicities). Overall, event rates were low. For first-line therapy, an mTOR inhibitor containing regimen may result in little to no difference in **overall survival** compared to chemotherapy (HR 1.32, 95% CI 0.98 to 1.781 study, 231 participants; low-certainty evidence). The finding was similar for second/third-line therapy (HR 1.06, 95% CI 0.70 to 1.61; 1 study, 130 participants;		

Roncolato, F. et al. PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer. Cochrane Database of Systematic Reviews. . . 2019				
		low-certainty evidence). Administering mTOR inhibitor-containing regimens may result in little to no difference in tumour response compared to chemotherapy or hormonal therapy in first-line or second/third-line therapy (first line: RR 0.93, 95% CI 0.75 to 1.17; 1 study, 231 participants; second/third line: RR 0.22, 95% CI 0.01 to 4.40; 1 study, 61 participants; low-certainty evidence). QoL-Data not reported. **Author's Conclusion:** Two RCTs have been reported to date, with low certainty of evidence. In a recurrent disease setting, mTOR inhibitors may result in improved progression-free survival, but we found no clear benefit in overall survival or tumour response rate. We await the publication of at least five ongoing studies investigating the role of PI3K/AKT/mTOR inhibitors in advanced or recurrent endometrial cancer before any conclusions can be drawn on their use.		
Methodical Notes				

Roncolato, F. et al. PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer. Cochrane Database of Systematic Reviews. . . 2019

Funding Sources: This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.

COI: None known.

Study Quality: Risk of bias was assessed in accordance with Cochrane Handbook for Systematic Reviews of Interventions. Certainty of the evidence by using the GRADE approach. Both studies had high risk of performance bias (blinding). The other domains were at low risk in the majority.

Heterogeneity: Was assessed by 1) visual inspection of forest plots, 2) by estimation of the percentage of heterogeneity (I2 measurement), 3) by a formal statistical
test ofthe significance ofthe heterogeneity (Chi2) and 4) by subgroup analyses.

Publication Bias: Could not be assessed (only 2 studies included)

Notes:
Oxford CEBM Level of evidence 2011: EL1 (systematic review).

OXFORD (2011) Appraisal Sheet: RCT: *3 Bewertung(en)*

Fader, A. N. et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Compared with Carboplatin-Paclitaxel-Trastuzumab in Advanced (Stage III-IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis. Clin Cancer Res. 26. 3928-3935. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Randomized phase II trial **Number of Patient:** 61 patients included. **Recruitung Phase:** August 2011 til March 2017. **Inclusion Criteria:** All patients were 18 years of age or older and had FIGO 2009 stage III to IV or recurrent (any previous stage) Her2/Neu-positive USC as defined by an IHC score of 3þ or 2þ with gene amplification confirmed by FISH. **Exclusion Criteria:** -	**Intervention:** Patients recieved intravenous carboplatin AUC 5 and paclitaxel 175 mg/m2 over 3 hours every 21 days with or without trastuzumab at 8 mg/kg for the first dose and 6 mg/kg in subsequent cycles until disease progression or prohibitive toxicity. **Comparison:** See intervention.	**Primary:** PFS (length of time from randomization to disease recurrence, disease progression, or death for any reason, whichever occurred first). **Secondary:** Objective response, OS, and safety of trastuzumab in study subjects. **Results:** The current updated analysis was performed at the time of 43 progressions and 38 deaths. CP Treatment outcome (28 patients): Alive and progression free: 5 Alive after progression: 2 Dead after progression: 20 Dead without progressing: 1 CP+T Treatment outcome (32 patients): Alive and progression free: 9 Alive after progression: 4 Dead after progression: 17 Dead without progressing: 0

Fader, A. N. et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Compared with Carboplatin-Paclitaxel-Trastuzumab in Advanced (Stage III-IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis. Clin Cancer Res. 26. 3928-3935. 2020

		PFS: Among all patients, the updated analysis continued to favor the trastuzumab arm, with median PFS of 8.0 months in patients who received carboplatin/paclitaxel alone and 12.9 months in patients who received chemotherapy plus trastuzumab (HR = 0.46; 90% CI, 0.28–0.76; P=0.005). Subgroup analysis: PFS was 9.3 in the control arm vs 17.7 months in the T-arm among 41 stage III to IV patients undergoing primary treatment (HR = 0.44; 90% CI, 0.23–0.83; P = 0.015), and 7.0 months versus 9.2 months among 17 patients with recurrent disease (HR = 0.12; 90% CI, 0.03– 0.48; P = 0.004). **OS:** OS was significantly higher in the trastuzumab arm compared with the control arm, with medians of 29.6 months versus 24.4 months, respectively (HR = 0.58; 90% CI, 0.34–0.99; P= 0.046). This benefit was particularly striking in the stage III to IV patients, in whom median OS was not reached in the trastuzumab arm versus 25.4 months in the control arm (HR =0.49; 90% CI, 0.25–0.97; P = 0.041). No significant OS benefit from trastuzumab was observed in those with recurrent disease . Of the 38 deaths thus far, 37 were preceded by disease progression. Toxicity was not different between arms.

Fader, A. N. et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Compared with Carboplatin-Paclitaxel-Trastuzumab in Advanced (Stage III-IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis. Clin Cancer Res. 26. 3928-3935. 2020

		Author's Conclusion: The identification of novel and improved treatment strategies for USC is imperative. The addition of trastuzumab to carboplatin and paclitaxel chemotherapy in this randomized phase II study may represent a new standard treatment for USC tumors that overexpress HER2/neu, particularly in women with advanced, primary disease. Future studies are needed to determine if the addition of other antiHER2/neu antibodies or targeted agents to trastuzumab have the potential to augment survival further.

Methodical Notes

Funding Sources: The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

COI: See publication.

Randomization: In 11 participating academic institutions within the United States, patients were randomized 1:1 by the lead study institution using minimization to balance the treatment arms for study site, disease status (advanced vs. recurrent USC), and residual tumor after debulking within the advanced-disease group.

Blinding: Not specified.

Dropout Rate/ITT-Analysis: 1 Subject withdrew consent.

Fader, A. N. et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Compared with Carboplatin-Paclitaxel-Trastuzumab in Advanced (Stage III-IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis. Clin Cancer Res. 26. 3928-3935. 2020		
Notes: Oxford CEBM Level of evidence: EL 2 (randomized controlled trials). Notes: - relative large number of U.S. centers included - small number of participants - control arm had significantly older participants enrolled (impact on outcome?) Preliminary results of this trial were published before in another publication.		
Makker, V. et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol. 38. 2981-2992. 2020		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Ongoing, multinational, open-label, single arm study (KEYNOTE-146/Study 111). **Number of Patient:** 125 patients with endometrial cancer. **Recruitung Phase:** September 10, 2015 to Juli 1, 2018.	**Intervention:** Lenvatinib 20 mg once daily orally and pembrolizumab 200 mg intravenously once every 3 weeks in 3-week cycles (maximum of 35 pembrolizumab treatments). **Comparison:** one arm rial.	**Primary:** ORR at week 24 **Secondary:** ORR, duration of response (DOR), PFS, overall survival (OS), disease control rate (DCR), and clinical benefit rate (CBR). **Results:** The median follow-up for these patients was 18.7 months (95% CI, 13.1 to 20.3 months), and 29 (26.9%) patients were receiving ongoing study treatment with at least 1 study drug at data

Makker, V. et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol. 38. 2981-2992. 2020			
Inclusion Criteria: Eligibility criteria for the endometrial cohort have been published elsewhere. (eligible patients were aged 18 years or older and had metastatic endometrial cancer (unselected for microsatellite instability or PD-L1), had an Eastern Cooperative Oncology Group performance status of 0 or 1, had received no more than two previous systemic therapies, had measurable disease according to the immune-related Response Evaluation Criteria In Solid Tumors (irRECIST), and had a life expectancy of 12 weeks or longer). **Exclusion Criteria:** -		cutoff. - 49.1% of the patients were PD-L1 positive - 94 (87.0%) and 11 (10.2%) patients were MSS or MMR proficient (pMMR) and MSI-H or dMMR, respectively. **ORR_{WK24}** : 38.0% (41/108 patients; 95% CI, 28.8% to 47.8%). In 102 patients the sum of diameters of target lesions decreased (any size) from baseline in 86 (84.3%) patients. **Secondary endpoints:** the ORR of patients previously treated for endometrial carcinoma was 38.9% (42/108, 95% CI, 29.7% to 48.7%; CR, 8/108, 7.4%, 95% CI, 3.3% to 14.1%; PR, 34/108, 31.5%, 95% CI, 22.9% to 41.1%) and the median DOR was 21.2 months (95% CI, 7.6 months to not estimable [NE]). Among responders: - DOR ≥$ 6 months was 87% (95% CI, 72% to 95%), - DOR ≥ 12 months was 63% (95% CI, 45% to 77%). - Median PFS was 7.4 months (95% CI, 5.3 to 8.7 months; median follow-up: 11.9 months; 95% CI, 9.9 to 18.4 months) and - median OS was 16.7 months (95% CI, 15.0 months to NE). Responses, % of patients):	

Makker, V. et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol. 38. 2981-2992. 2020			
		-PD-L1 +: 35.8% (19/53; 95% CI, 23.1% to 50.2%) and PD-L1 -: 39.5% (17/43; 95% CI, 25.0% to 55.6%) - MSS/pMMR tumor, ORR: 37.2% (35/94; 95% CI, 27.5% to 47.8%) - MSI-H/dMMR tumors, ORR was 63.6% (7/11; 95% CI, 30.8% to 89.1%). **Adverse events:** Any-grade treatment-related AEs occurred in 120 (96.8%) patients. Grade 3 or 4 treatment related AEs occurred in 83 (66.9%) patients. **Author's Conclusion:** Lenvatinib plus pembrolizumab showed promising antitumor activity in patients with advanced endometrial carcinoma who have experienced disease progression after prior systemic therapy, regardless of tumor MSI status. The combination therapy had a manageable toxicity profile.	
Methodical Notes			
Funding Sources: Supported by Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. **COI:** See publication.			

Makker, V. et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol. 38. 2981-2992. 2020

Randomization: None.

Blinding: n.s.

Dropout Rate/ITT-Analysis: (key efficacy analysis, n = 108; overall population, n = 124)

Notes:
Oxford CEBM Level of evidence 2011: EL 3 (non-randomized trial-one arm)
Article submitted by hand search.
The publication represents the final primary efficacy analysis results of the endometrial cohort of patients from KEYNOTE-146/Study 111.

Marabelle, A. et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 38. 1-10. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type:** Nonrandomized, open-label, multisite phase II study. **Number of Patient:** 233 patients **Recruitung Phase:** Between February 1, 2016, and May 8, 2018.	**Intervention:** Pembrolizumab **Comparison:** single arm study, no comparison.	**Primary:** The primary end point was objective response rate (ORR), defined as the proportion of patients with confirmed complete/partial response per RECIST version 1.1 by independent central radiologic review. **Secondary:** Secondary end points included duration of response, defined as the time from first documented evidence of complete/partial response until the first documented sign of disease progression

Marabelle, A. et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 38. 1-10. 2020

Inclusion Criteria: Eligible patients were age 18 years or older with a histologically/ cytologically confirmed advanced—unresectable and/or metastatic—incurable noncolorectal solid tumor with disease progression on or intolerance to prior standard therapy. In addition, patients had measurable disease per RECIST version 1.1, as assessed by independent central radiologic review; an Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate organ function as determined by laboratory assessments. **Exclusion Criteria:** Prior anticancer monoclonal antibody or investigational agent 4 weeks or less, or chemotherapy, targeted small-molecule therapy, or radiation therapy 2 weeks or less before initiating study treatment; immunodeficiency or systemic steroids 7 days or less before study treatment; active autoimmune disease requiring systemic treatment 2 years or less before study treatment, with the exception of replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal/pituitary insufficiency); active CNS metastases (previously treated brain metastases were permitted if stable) or carcinomatous meningitis (excluded regardless of clinical stability); active noninfectious pneumonitis or active infection requiring systemic therapy; prior anti–PD-1, –PD-L1, or		or death from any cause, whichever occurred first; progression-free survival, defined as the time from first dose of study medication to the first documented disease progression per RECIST version 1.1 by independent central radiologic review or death from any cause, whichever occurred first; overall survival, defined as the time from the date of first dose of study medication to the date of death from any cause; and safety and tolerability. **Results:** Among 233 enrolled patients, 27 tumor types were represented, with endometrial, gastric, cholangiocarcinoma, and pancreatic cancers being the most common. Median follow up was 13.4 months. Objective response rate was 34.3% (95% CI, 28.3% to 40.8%). Median progression-free survival was 4.1 months (95% CI, 2.4 to 4.9 months) and median overall survival was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%). Thirty-four patients (14.6%) had grade 3 to 5 treatment-related adverse events. Grade 5 pneumonia occurred in one patient; there were no other treatmentrelated fatal adverse events. **Author's Conclusion:** Our study demonstrates the clinical benefit of anti–programmed death-1 therapy

Marabelle, A. et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 38. 1-10. 2020			
–PD-L2 therapy; history of HIV; active hepatitis B or C infection; and live vaccine 30 days or less before study treatment.		with pembrolizumab among patients with previously treated unresectable or metastatic MSI-H/dMMR noncolorectal cancer. Toxicity was consistent with previous experience of pembrolizumab monotherapy	
Methodical Notes			
Funding Sources: Funded byMerck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. **COI:** declared. **Randomization:** non-randomized study **Blinding:** Open-label. **Dropout Rate/ITT-Analysis:** 163 / 233 patients discontinued treatment. Of the 163 discontinuations 119 are due to progressive disease, 29 due to adverse events, 8 due to patient withdrawal, 3 due to complete response, 2 due to physician decision, 1 each due to excluded medication or loss of follow-up. **Notes:** Oxford level of evidence: 3 Non-randomized controlled cohort / follow-up study. Objective assesment, but phase 2 study design (single group). Article submitted by hand search.			

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Nonrandomized Phase 1 Clinical Trial (GARNET trial (NCT02715284))	**Funding sources:** This study was funded by GlaxoSmithKline. **Conflict of Interests:** Disclosures are provided in the article. **Randomization:** Non-randomized single-group trial. **Blinding:** Open-label trial, outcome assessors were blinded **Dropout rates:** /	**Total no. patients:** 104 patients with dMMR EC **Recruiting Phase:** Trial started March 7, 2016 and is still ongoing. Date of this preliminary analysis: July 8, 2019. **Inclusion criteria:** Eligible patients were aged 18 years or older with histologically or cytologically proven recurrent or advanced EC with measurable lesion(s) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Patients could be screened on the basis of local MSI and/or MMR testing results, including dMMR as assessed by immunohistochemistry or MSI-H as assessed by polymerase chain reaction or next-generation sequencing performed in a certified local laboratory. The protocol was amended on May 10, 2019, to use only the results of the immunohistochemistry	**Interventions:** Part 1 was a dose-escalation study to evaluate weightbased doses of dostarlimab monotherapy. Part 2A was an extension of part 1 to evaluate the safety of non–weight-based fixed doses of dostarlimab. Part 2B enrolled patients into 4 expansion cohorts based on tumor type and mutation status (cohort A1, dMMR EC; cohort A2, proficient MMR EC; cohort E, non–small cell lung cancer; and cohort F, MSI-H/dMMR nonendometrial solid tumors) to assess the antitumor activity and safety of dostarlimab. Here, we report a prespecified analysis of one of the expansion cohorts with patients with recurrent or advanced dMMR EC (cohort A1) that has progressed

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020			
		MMR test for classifying patients. **Exclusion criteria:** Patients with no measurable disease at baseline, Patients with	after treatment with a platinum-containing chemotherapy regimen. All patients with dMMR EC were treated with a 30-minute infusion of intravenous dostarlimab, 500mg, once every 3 weeks for 4 doses, then 1000 mg once every 6 weeks until disease progression, treatment discontinuation due to toxic effects, or patient withdrawal of consent. **Comparison:** Single-group trial
Notes:	**Oxford CEBM Level of Evidence: EL 3 Non-randomized trial** Article submitted by hand search. -Preliminary data are presented here, trial is ongoing -Single-group trial, no comparison group **Author's conclusion:** In this nonrandomized trial, dostarlimab was associated with clinically meaningful and durable		

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020		
	antitumor activity with an acceptable safety profile for patients with deficient mismatch mutation repair endometrial cancers after prior platinum-based chemotherapy.	
Outcome Measures/results	**Primary** The primary objective of this analysis was to evaluate the antitumor activity of dostarlimab in patients with recurrent or advanced dMMR EC, with the assessment of the objective response rate (ORR), defined as the proportion of patients with confirmed complete or partial response by blinded independent central review (BICR) using RECIST v1.1, and duration of response (DOR), defined as the time from first documented evidence of complete or partial response until the first documented sign of disease progression or death from any cause, whichever occurred first. Radiographic evaluationswere conducted atweek 12 after the first dose of dostarlimab, then every 6 weeks (±10 days) or as clinically indicated until month 12, and then every 12 weeks thereafter. **Secondary** Secondary end points included the disease control rate,	**Results:** Preliminary data are presented here, trial is ongoing. As of the data cutoff, 104 women (median age, 64.0 years [range, 38-80 years]) with deficient mismatch mutation repair endometrial cancers were enrolled and treated with dostarlimab. Of these, 71 had measurable disease at baseline and at 6 months or more of follow-up and were included in the analysis. **Objective response rate** There was a confirmed response in 30 patients (objective response rate, 42.3%; 95% CI, 30.6%-54.6%); 9 patients (12.7%) had a confirmed complete response, and 21 patients (29.6%) had a confirmed partial response. Responses were durable; the median duration of response was not reached (median follow-up was 11.2 months). **Duration of response** At the July 8, 2019, data cutoff, the median DOR was not reached, with a median follow-up of 11.2 months. The estimated likelihood of maintaining a response was 96.4% at 6 months and 76.8% at 12 months. **Disease control rate** The disease control rate was 57.7% (95% CI, 45.4%- 69.4%). **Progression free survival** The median PFS was 8.1 months (95% CI, 3.0- 18.0months) .

Oaknin, A. et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 6. 1766-1772. 2020		
	defined as the proportion of patients with an objective response or stable disease lasting 12 weeks or longer based on BICR using RECIST v1.1; immune-related ORR (irORR) and immune-related DOR (irDOR) based on investigator assessment using immune-relatedRECIST (irRECIST); progression-free survival (PFS), defined as the time from the first dose of study medication to the first documented disease progression based on BICR using RECIST v1.1; immune-related PFS (irPFS) based on investigator assessment using irRECIST; and OS, defined as the time from the date of the first dose of study medication to the date of death from any cause. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities, version 20.016 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.	**Overall survival** Themedian OS was also not reached, with a Kaplan-Meier estimation of 72.7% survival at 12 months after treatment initiation **Adverse events** Among the 104 patients included in the safety analysis, most treatment-related AEs (TRAEs) were grade 1 or 2. Anemia (3 of 104 [2.9%]), colitis (2 of 104 [1.9%]), and diarrhea (2 of 104 [1.9%]) were the most common grade 3 or higher treatment-related adverse events.

Yalamanchi, P. et al. Use of Aggressive Surveillance for Locoregional Endometrial Cancer After Local Therapy. Int J Gynecol Cancer. 28. 1264-1270. 2018			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective single-institution review.	**Funding sources:** Research for this work was supported by National Center for Advancing Translational Sciences of the National Institutes of Health under award number KL2TR001879. **Conflict of Interests:** None **Randomization:** No **Blinding:** No **Dropout rates:** No	**Total no. patients:** 149 of 184 patients had recurrent disease. **Recruiting Phase:** Cancer Registries and multidisciplinary tumor registries at the Hospital of Pennsylvania were searched between 1990-2014. **Inclusion criteria:** Patients with locoregional endometrial cancer treated with total hysterectomy with bilateral salpingo-oophorectomy with or without adjuvant therapy who subseqenetly developed recurrent disease. Eligible patients had to underwent comprehensive surgical staging at the time of initial diagnosis. **Exclusion criteria:** -	**Interventions:** surveillance method to detect asymptomatic (recurrences asymptomatic recurrences detected by routine surveillance vs. recurrences with symptoms). **Comparison:** see intervention.
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective cohort study) Notes: - retrospective design - no blinding		

Yalamanchi, P. et al. Use of Aggressive Surveillance for Locoregional Endometrial Cancer After Local Therapy. Int J Gynecol Cancer. 28. 1264-1270. 2018		
	- heterogenous population - small groups. The results of the study should be interpreted with cation due to the low methodological quality of the study. **Author's conclusion:** Patients who develop asymptomatic recurrences of their endometrial carcinoma do not seem to have a better prognosis than those who present with symptomatic recurrences. Thus, these results do not support routine imaging surveillance for patients treated for locoregional endometrial carcinoma. Further prospective evaluation is needed.	
Outcome Measures/results	**Primary** Overall survival, progression free survival. **Secondary** -	**Results:** Median age of patients at diagnosis was 68.4 years, with most patients diagnosed at age older than 60. Recurrence detection: - distant (64.4%) - vaginal (20.8%), - pelvic (14.8%). 86 patients (57.7%) developed asymptomatic recurrences, 63 patients (42.3%) developed symptomatic recurrences. Of those detected asymptomatically, 80.2% were detected by imaging. The average time to detection of recurrence was 2.27 years (interquartile range 1.54-2.99 years) and there was no significant difference between recurrences detected as symptomatic vs. asymptomatic (p=0.66). Comparing symptomatic vs. asymptomatic recurrences, there was no difference in overall survival (HR 1.24; 95% CI, 0.84-1.83, p=0.29) or progression free survival (HR 1.14; 95% CI, 077-1.70, p=0.52).

2.43. Schlüsselfrage 48: Wie ist der Stellenwert der supportiven Mitbehandlung und Betreuung in Bezug auf Kurzzeit-/ Langzeitmorbidität, krankheitsspezifisches Gesamt-Überleben, Lebensqualität und weiteres Rezidiv?

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Lawrie, T. A. 2018	1	Systematic review and meta-analysis (90 studies) To determine which prophylactic interventions reduce the incidence, severity or both of adverse gastrointestinal effects among adults receiving radiotherapy to treat primary pelvic cancers.
Shisler, R. 2018	4	SR (27 studies)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *2 Bewertung(en)*

Lawrie, T. A. et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews. . . 2018				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 **Study type:** Systematic review and meta-analysis (90 studies) To determine which prophylactic interventions reduce the incidence, severity or both of adverse gastrointestinal effects among adults receiving radiotherapy to treat primary pelvic cancers. **Databases:** CENTRAL, MEDLINE, and Embase, trial registries. **Search period:** Last version - 11/2017 **Inclusion Criteria:** We included randomised controlled trials (RCTs) of interventions to prevent adverse gastrointestinal effects of pelvic radiotherapy among adults receiving	**Population:** Adults aged 18 years and older undergoing primary, adjuvant or neoadjuvant radiotherapy as part of anti-cancer treatment for primary pelvic cancers, including urological, gynaecological and gastrointestinal (GI) cancers. **Intervention:** · Radiotherapy techniques (e.g. 3DCRT, IMRT, BT) · Interventions related to radiotherapy delivery, including radiotherapy timing (e.g. evening radiotherapy schedules), patient positioning and positioning devices (e.g. belly boards), and other interventions (e.g. endorectal balloons); · Pharmacological interventions (e.g. sucralfate, 5- aminosalicylates, antioxidants, statins, ACE inhibitors); · Non-pharmacological interventions, including dietary modification of	**Primary:** 1. Gastrointestinal symptom score 2. Moderate or severe GI symptoms 3. Quality of life (QoL) score **Secondary:** 1. GI toxicity grade 1+; 2. Toxicity-related discontinuation; 3. Medication use for GI symptom control; 4. Patient satisfaction (as measured by investigators); 5. Total mean bowel dose (Gy) (for studies evaluating radiotherapy techniques, patient positioning or positioning devices). **Results: Study overview:** We included 92 RCTs involving more than 10,000 men and women undergoing pelvic radiotherapy. Trials involved 44 different interventions, including radiotherapy techniques (11 trials, 4 interventions/comparisons), other	90 studies included. See article for list.	

Lawrie, T. A. et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews. . . 2018				
radiotherapy to treat primary pelvic cancers, including radiotherapy techniques, other aspects of radiotherapy delivery, pharmacological interventions and non-pharmacological interventions. Studies needed a sample size of 20 or more participants and needed to evaluate gastrointestinal toxicity outcomes. We excluded studies that evaluated dosimetric parameters only. **Exclusion Criteria:** Participants receiving palliative radiotherapy or radiotherapy for recurrent cancer, and studies of participants with stomas. studies in which fewer than 80% of participants were eligible. Included studies needed to include at least 20 participants. Studies that evaluated dosimetric parameters only. Trials of interventions to treat acute gastrointestinal symptoms, trials of altered fractionation and dose escalation schedules, and trials of pre- versus postoperative	macronutrients (carbohydrate, fats, protein, with or without micronutrients) and/or non-starch polysaccharides (dietary fibre), probiotics, and other interventions. **Comparison:** Comparators for radiotherapy techniques or timing are other radiotherapy techniques or timing, whereas comparators for other types of interventions are placebos, no intervention, or alternative interventions.	aspects of radiotherapy delivery (14 trials, 10 interventions), pharmacological interventions (38 trials, 16 interventions), and non-pharmacological interventions (29 trials, 13 interventions). **Results: Radiotherapy techniques:** Intensity-modulated radiotherapy (IMRT) versus 3D conformal RT (3DCRT) may reduce acute (risk ratio (RR) 0.48, 95% confidence interval (CI) 0.26 to 0.88; participants = 444; studies = 4; I2 = 77%; low-certainty evidence) and late gastrointestinal (GI) toxicity grade 2+ (RR 0.37, 95% CI 0.21 to 0.65; participants = 332; studies = 2; I2 = 0%; low-certainty evidence). Conformal RT (3DCRT or IMRT) versus conventional RT reduces acute GI toxicity grade 2+ (RR 0.57, 95% CI 0.40 to 0.82; participants = 307; studies = 2; I2 = 0%; high-certainty evidence) and probably leads to less late GI toxicity grade 2+ (RR 0.49, 95% CI 0.22 to 1.09; participants = 517; studies = 3; I2 = 44%; moderatecertainty evidence). When brachytherapy (BT) is used instead of external beam radiotherapy (EBRT) in early endometrial cancer, evidence indicates that		

Lawrie, T. A. et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews. . . 2018				
radiotherapy regimens, to restrict the vast scope of the review.		it reduces acute GI toxicity (grade 2+) (RR 0.02, 95% CI 0.00 to 0.18; participants = 423; studies = 1; high-certainty evidence). **Other aspects of radiotherapy delivery:** There is probably little or no difference in acute GI toxicity grade 2+ with reduced radiation dose volume (RR 1.21, 95% CI 0.81 to 1.81; participants = 211; studies = 1; moderate-certainty evidence) and maybe no difference in late GI toxicity grade 2+ (RR 1.02, 95% CI 0.15 to 6.97; participants = 107; studies = 1; low-certainty evidence). Evening delivery of RT may reduce acute GI toxicity (diarrhoea) grade 2+ during RT compared with morning delivery of RT (RR 0.51, 95% CI 0.34 to 0.76; participants = 294; studies = 2; I2 = 0%; low-certainty evidence). There may be no difference in acute (RR 2.22, 95% CI 0.62 to 7.93, participants = 110; studies = 1) and late GI toxicity grade 2+ (RR 0.44, 95% CI 0.12 to 1.65; participants = 81; studies = 1) between a bladder volume preparation of 1080 mls and that of 540 mls (low-certainty evidence). Low-certainty evidence on balloon and hydrogel spacers suggests that these interventions for prostate cancer		

Lawrie, T. A. et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews. . . 2018				
		RT may make little or no difference to GI outcomes. **Pharmacological interventions:** Evidence for any beneficial effects of aminosalicylates, sucralfate, amifostine, corticosteroid enemas, bile acid sequestrants, famotidine and selenium is of a low or very low certainty. However, evidence on certain aminosalicylates (mesalazine, olsalazine), misoprostol suppositories, oral magnesium oxide and octreotide injections suggests that these agents may worsen GI symptoms, such as diarrhoea or rectal bleeding. **Non-pharmacological interventions:** Low-certainty evidence suggests that protein supplements (RR 0.23, 95% CI 0.07 to 0.74; participants = 74; studies = 1), dietary counselling (RR 0.04, 95% CI 0.00 to 0.60; participants = 74; studies = 1) and probiotics (RR 0.43, 95% CI 0.22 to 0.82; participants = 923; studies = 5; I2 = 91%) may reduce acute RT-related diarrhoea (grade 2+). Dietary counselling may also reduce diarrhoeal symptoms in the long term (at five years, RR 0.05, 95% CI 0.00 to 0.78; participants = 61; studies = 1). Low-		

Lawrie, T. A. et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews. . . 2018				
		certainty evidence from one study (108 participants) suggests that a high-fibre diet may have a beneficial effect on GI symptoms (MD) 6.10, 95% CI 1.71 to 10.49) and quality of life (MD 20.50, 95% CI 9.97 to 31.03) at one year. High-certainty evidence indicates that glutamine supplements do not prevent RT-induced diarrhoea. Evidence on various other non-pharmacological interventions, such as green tea tablets, is lacking. Quality of life was rarely and inconsistently reported across included studies, and the available data were seldom adequate for metaanalysis. **Author's Conclusion:** "Conformal radiotherapy techniques are an improvement on older radiotherapy techniques. IMRT may be better than 3DCRT in terms of GI toxicity, but the evidence to support this is uncertain. There is no high-quality evidence to support the use of any other prophylactic intervention evaluated. However, evidence on some potential interventions shows that they probably have no role to play in reducing		

Lawrie, T. A. et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews. . . 2018				
		RTrelated GI toxicity. More RCTs are needed for interventions with limited evidence suggesting potential benefits."		
Methodical Notes				
Funding Sources: Internal sources · No sources of support supplied External sources · National Institute for Health Research HTA Programme (project number 16/60/01), UK. **COI:** Declared, non present. **Study Quality:** Two review authors applied the 'Risk of bias' tool independently and resolved di*erences by discussion or by appeal to a third review author. Most studies (79/92) had design limitations. Thirteen studies had a low risk of bias, 50 studies had an unclear risk of bias and 29 studies had a high risk of bias. Overall quality of evidence was provided for each endpoint using GRADE methodology. **Heterogeneity:** We assessed heterogeneity between studies in each meta-analysis by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, where possible, by subgroup analyses. If there was evidence of substantial heterogeneity (I2>60%), we investigated and reported the possible reasons for this. Heterogeneity was considered in the GRADE methodology for each endpoint. **Publication Bias:** "We had planned to investigate reporting biases if there were 10 or more studies in meta-analyses using funnel plots, but all				

Lawrie, T. A. et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews. . . 2018			
metaanalyses included fewer than 10 studies. Our approach would have been to assess funnel plots visually for asymmetry and if we found asymmetry, we would have performed exploratory analyses to investigate it." **Notes:** Oxford level of evidence: 1 Systematic review and meta-analysis Risk of bias was unclear (50/92) or high (29/90) in most studies. Not all included studies investigate endometrial carcinoma.			
Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** SR (27 studies) **Databases:** Medline, Embase, Scopus, CINAHL. **Search period:** not specified. **Inclusion Criteria:** Observational studies (i.e. no drug intervention) reporting patient-related outcomes (PRO) among EC survivors; original data collection, use of validated scales.	**Population:** Women diagnosed with EC **Intervention:** Questionnaires used to assess PROs: for example the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) used in 9 of the 27 observational studies. **Comparison:** Two studies included non-cancer control groups	**Primary:** Association between - BMI and/or physical activity and PROs - Treatment and PROs - predictors of sexual function - catch-all "other" category. 19 studies assessed the PROs at some point in time after EC diagnosis; whereas 8 studies prospectively evaluated changes in PROs over time with the use of multiple assessements.	see publication.

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018				
Exclusion Criteria: Studies with outcomes other than PRO, studies that did not include EC survivors, pilot studies and clinical trials assessing drug effects, studies of gynecological cancer survivors that did not report estimates separately for EC patients.		**Secondary:** - **Results:** Sample size range between 38 and 666 women. **BMI and/or physical activity and PROs** (8 studies): QoL: 6 studies: lower overall QoL among obese EC survivors relative to their normal counterparts. 5 Studies reported that physical functioning was lower in obese patients relative to non-obese patients. **Treatment and PROs:** Treatment type affected several outcomes. Laparoscopy generally resulted in better QoL outcomes than laparotomy. Vaginal brachytherapy was associated with better outcomes compared to external beam radiation. **Predictors of sexual function:** Sexual function outcomes were dependent on age, time since diagnosis and having consulted a physician before engaging in sexual activities. In addition, a physical		

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018				
		activity intervention was associated with improved sexual interest but not sexual function. **Catch-all "other" category** (five studies): one study evaluating psychosocial factors and mortality found a significant association between active coping (which consists of putting effort into improving one's situation) with lower all-cause mortality. **Author's Conclusion:** Our review provides insights into the experiences of EC survivors from patient perspective. Factors that contribute to QoL such as pain, fatigue, emotional and social functioning should be monitored following an EG diagnosis.		
Methodical Notes				

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018

Funding Sources: n.s.

COI: None.

Study Quality: Quality assessment is mentioned in the title of a paragraph, but no further details are mentioned. Thus the assumption is, that a quality assessment of the included studies is missing.

Heterogeneity: not assessed.

Publication Bias: not assessed.

Notes:
Oxfrod Level of evidence 2011: EL 3 Systematic review of cross-sectional and retrospective cohort studies
(downgraded from EL 3 one level EL 4 due to methodological flaws).
- the search range is not specified
- no methodological quality of the included studies was performed
- no analysis regarding heterogeneity, bias assessment ... was performed.

2.44. Schlüsselfrage 50: Wie ist der Stellenwert der psychoonkologischen Mitbehandlung und Betreuung in Bezug auf Kurzzeit-/ Langzeitmorbidität, krankheitsspezifisches Gesamt-Überleben, Lebensqualität und weiteres Rezidiv?

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
de Rooij, B. H. 2019	2	Cluster RCT
White, I. D. 2016	1	SR (6 studies)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** SR (6 studies) **Databases:** Embase (1990–2015), MEDLINE (1990–2015), PsycINFO (1990–2015), CINAHL (1990–2015), BNI (1990–2015), AMED (1990–2015) using Ovid. **Search period:** See databases. **Inclusion Criteria:** Full text articles, published in the English language, report on the development and/or validation of an instrument measuring sexual (dys)function within an identifiable sample of women treated for either cervical or endometrial cancer. **Exclusion Criteria:** Quality of Life (QoL) or treatment toxicity studies that did not have a significant focus on sexual	**Population:** Female individuals with sexual (dys)function. **Intervention:** questionnaire, outcome measure or assessement instrument; evaluation of the instrument's measurement properties using the COSMIN checklist. **Comparison:** -	**Primary:** Clinical utility of instruments for female sexual dysfunction (FSD) **Secondary:** - **Results:** Six Instruments werde found and analyzed: - Female Sexual Function Index (FSFI) - Sexual Adjustment and Body Image Scale-Gynecologic Cancer (SABIS-G) - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module (EORTC QLQ CX-24) - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ EN-24) - Sexual function-vaginal changes questionnaire (SVQ) - Gynaecologic Leiden Questionnaire (GLQ)	- R.E. Baser, 2012, Cancer. - S.E. Ferguson, 2012, Cancer. - E.R. Greimel, 2006, Cancer. - E. Greimel, 2011, Eur. J. Cancer. - P.T. Jensen, 2004, Psycho-Oncology. - Q.D. Pieterse,

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016

dysfunction and papers with a primary focus on sexual history taking or professional/patient communication about sexual impact of illness or treatment or body image. Instruments were also excluded if they measured sexual dysfunction in diseases or treatment effects unrelated to cervical or endometrial cancer, or where results from a cervical or endometrial cancer sub-sample of women was not identifiable.		**Clinical utility:** - **conceptual scope**: only the SVQ and SABIS-G included pre-treatment sexual function comparisons - Four of the six instruments included commonly encountered **mediating treatment or illness effects** such as vaginal changes, menopause and altered body image or femininity. None of the instruments included items regarding the effect of therapeutic aids. - Although **partner and relationship items** were absent from both QOL instruments, this important contributory factor to women's sexual recovery was included in the content of the four sexual morbidity instruments reviewed. - The ideal clinical instrument should be brief and easy to complete and score to minimise burden for the patient and health professional, while still generating meaningful data. None of the instruments reviewed exceeded 24 items, but only two out of six papers reported completion time and participant feedback on ease of use. - Five of the six instrument scoring	2008, Psycho-Oncology.

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016				
		templates were complex or time-consuming for self or clinical interpretation and the absence of a clinical cut-off score for all but one instrument (FSFI) limits diagnostic and clinical management utility. **Author's Conclusion:** Findings suggest that the Female Sexual Function Index (FSFI) remains the most robust sexual morbidity outcome measure, for research or clinical use, in sexually active women treated for cervical or endometrial cancer. Development of an instrument that measures sexual dysfunction in women who are infrequently/not sexually active due to treatment consequences is still required to identify women in need of sexual rehabilitation.		
Methodical Notes				
Funding Sources: None. **COI:** None.				

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016

Study Quality: The COSMIN checklist evaluates the methodological rigour of each instrument paper across nine measurement properties.

Heterogeneity: Not assessed.

Publication Bias: Not assessed.

Notes:
Oxford CEBM Level of evidence 2011: EL 1 (systematic review)

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

de Rooij, B. H. et al. Patients' information coping styles influence the benefit of a survivorship care plan in the ROGY Care Trial: New insights for tailored delivery. Cancer. 125. 788-797. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Cluster RCT **Number of Patient:** 221 patients with endometrial cancer and 174 with ovarian cancer. **Recruitung Phase:** 12 hospitals in the Netherlands recruited woman with endometrial cancer between April 2011 and October 2012 and ovarian cancer (April 2011 and March 2014). **Inclusion Criteria:** Patients with a new diagnosis of endometrial or ovarian cancer **Exclusion Criteria:** Patients with borderline ovarian tumors, those who were receiving palliative care,	**Intervention:** Questionnaires were sent to the patients after treatment (6, 12 and 24 months). = SCP care (survivorship care plans). **Comparison:** Usual Care (in accordance with Dutch oncology guidelines).	**Primary:** Monitoring Coping style, Blunting Coping style. **Secondary:** Overall effect on patient satisfaction (25-item European Organization for Research and Treatment Quality-of-Life Group Information Questionnaire (EORTC-QLQINFO25)). **Results:** There was no significant interaction between cancer type and information coping style for any of the outcome scales. Patients with a **monitoring coping style** (N = 123): those in the SCP care arm reported higher satisfaction with information provision (mean score: 73.9 vs 63.9, respectively; P = .04) and care (mean score: 74.5 vs 69.2, respectively; P = .03) compared with those in the usual care arm. Patients who had a **blunting coping style** (N = 102): those in the SCP care arm reported a higher impact of the disease on life (mean score: 5.0 vs 4.5, respectively; P = .02) and a higher emotional impact of the disease (mean score: 5.4 vs 4.2, respectively; P = .01) compared with those in the usual care arm.

de Rooij, B. H. et al. Patients' information coping styles influence the benefit of a survivorship care plan in the ROGY Care Trial: New insights for tailored delivery. Cancer. 125. 788-797. 2019			
and those who were unable to complete a Dutch questionnaire were excluded from participation.		**Author's Conclusion:** Although SCPs may not be helpful for all cancer survivors,7,8 they appear to be valuable for some survivor subgroups. The current study demonstrates that SCPs may be beneficial for patients who desire detailed information about their cancer, whereas they may be less beneficial and perhaps even harmful for patients who prefer to avoid medical information. Our results emphasize the need to individualize the delivery of SCPs according to patients' information needs.	
Methodical Notes			
Funding Sources: The Registration System Oncological Gynecology (ROGY) Care Trial is supported by grant UVT 2010-4743 from the Dutch Cancer Society. Nicole P. M. Ezendam was supported by a Fellowship grant from the Dutch Cancer Society (UVT-2014-6632). **COI:** None. **Randomization:** Randomization was performed, using a table of random numbers, by an independent researcher who was blinded to the identity of the hospitals. Twelve hospitals in the Netherlands were randomized to deliver either SCP care or usual care. **Blinding:** Patients, but not oncology providers or researchers who assessed the outcomes, were blinded to trial assignment. **Dropout Rate/ITT-Analysis:** The current analysis included 131 patients (59%) with endometrial cancer and 95 patients (55%) with ovarian cancer who completed the questionnaires at 12 months after treatment. **Notes:**			

de Rooij, B. H. et al. Patients' information coping styles influence the benefit of a survivorship care plan in the ROGY Care Trial: New insights for tailored delivery. Cancer. 125. 788-797. 2019	
Oxford CEBM Level of evidence 2011: EL 2 Limits: - the number of patients in the current study was too small to conduct stratified analyses separately for those with endometrial cancer and ovarian cancer. - high loss to follow-up - SCPs provided in our trial were extensive documents (ie, up to 25 pages), this may be advantageous for monitors but disadvantageous for blunters.	

2.45. Schlüsselfrage 51: Wie ist der Stellenwert der psychosozialen Mitbehandlung und Betreuung und Rehabilitation in Bezug auf Kurzzeit-/Langzeitmorbidität, krankheitsspezifisches Gesamt-Überleben, Lebensqualität und weiteres Rezidiv?

Inhalt: *5 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Do, J. H. 2017	2	randomzied controlled trial (pilot study).
Haggerty, A. F. 2017	2	Multicenter randomized controlled trial (three clinical sites in USA)
Kitson, S. 2018	1	SR and META (3 studies included)
Shisler, R. 2018	4	SR (27 studies)
White, I. D. 2016	3	SR (6 studies)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *3 Bewertung(en)*

Kitson, S. et al. Interventions for weight reduction in obesity to improve survival in women with endometrial cancer. Cochrane Database of Systematic Reviews. . . 2018				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 **Study type:** SR and META (3 studies included) **Databases:** · Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, 2017, Issue 12, Appendix 1); · MEDLINE Ovid SP (1946 to January week 2 2018, Appendix 2); · Embase Ovid SP (1980 to 2018 week 4, Appendix 3). Unpublished and grey literature was searched, as well as handsearch was performed. **Search period:** From inception to January 2018.	**Population:** Women of all ages, who were either overweight (BMI more than or equal to 25 kg/m2) or obese (BMI more than or equal to 30 kg/m2), and who were currently undergoing, or had been previously treated for endometrial cancer, of any grade, stage, or histological subtype. **Intervention:** Interventions designed to promote weight loss as one of their primary stated goals, in any healthcare setting, including community-based studies. These could include: - lifestyle interventions - behavioral strategies to improve adherence to treatment - pharmacological interventions - surgical interventions. **Comparison:** Any of these interventions	**Primary:** - Overall survival; determined as the time from randomisation until death from any cause - Frequency of adverse events, of any nature **Secondary:** · Recurrence-free survival; length of time from randomisation to recurrence of the disease or death · Cancer-specific survival; length of time from randomisation to death from endometrial cancer · Weight loss; amount of weight lost between randomisation and end of study · Cardiovascular and metabolic event frequency; specifically the number of strokes, myocardial infarctions, and hospitalisations for heart failure · Quality of Life as measured on any validated scale.	Allison, 2016, TREC Scientific Grantee's Meeting, National Cancer Institute. Mc Carroll, 2014, Gynecologic Oncology. Von Gruenigen, 2009, Gyencologic Oncology.	

Kitson, S. et al. Interventions for weight reduction in obesity to improve survival in women with endometrial cancer. Cochrane Database of Systematic Reviews. . . 2018				
Inclusion Criteria: RCTs, Trials were included regardless of primary treatment modality, i.e. surgery, radiotherapy, hormonal treatment, or a combination, all languages. **Exclusion Criteria:** Studies of participants with mixed BMI were identified but subgroup data were not provided, or authors unable or unwilling to provide these data, the study was not included in the meta-analysis.	were compared with any other intervention, usual care, or placebo.	**Results:** In total 161 overweight and obese women with endometrial cancer were included in the analysis. <u>Overall survival:</u> Combined behaviour and lifestyle interventions were not associated with improved overall survival (RR mortality), 0.23 95% CI 0.01 to 4.55, P = 0.34, one RCT, 37 participants; very low-certainty evidence) compared with usual care at 24 months. There was no evidence that such interventions were associated with improvements in **cancer-specific survival** or **cardiovascular event frequency** as no cancer-related deaths, myocardial infarctions or strokes were reported in the included studies. None of the included RCTs reported data for the outcome of recurrence-free survival. Combined behaviour and lifestyle interventions were not associated with significant weight loss at either six months (MD -1.88 kg, 95% CI -5.98 to 2.21 kg, P = 0.37, three RCTs, 131 participants,I2= 0%; low-certainty		

Kitson, S. et al. Interventions for weight reduction in obesity to improve survival in women with endometrial cancer. Cochrane Database of Systematic Reviews. . . 2018				
		evidence)or 12 months (MD -8.98 kg, 95% CI -19.88 to 1.92 kg, P = 0.11, two RCTs, 91 participants, I2= 0%; very low certainty evidence) when compared with usual care. Combined behaviour and lifestyle interventions were not associated with increased quality of life, when measured using either the SF-12 Physical Health questionnaire or FACT-G at six months (FACT-G MD 2.51, 95% CI -5.61 to 10.64, P = 0.54, two RCTs, 95 participants, I2= 83%; very low-certainty evidence), or by FACT-G alone at 12 months (MD 2.77, 95% CI -0.65 to 6.20, P = 0.11, two RCTs, 89 participants, I2= 0%; very low-certainty evidence) when compared with usual care. **No serious adverse events**, for example hospitalisation or deaths, were reported in included trials. Lifestyle and behavioural interventions were associated with a higher risk of musculoskeletal symptoms (RR 19.03, 95% CI 1.17, 310.52, P = 0.04, two RCTs, 91 participants; low-certainty evidence). **Author's Conclusion:** There is currently insufficient high-quality evidence to		

Kitson, S. et al. Interventions for weight reduction in obesity to improve survival in women with endometrial cancer. Cochrane Database of Systematic Reviews. . . 2018

		determine the effect of combined lifestyle and behavioural interventions on survival, quality of life, or significant weight loss in women with a history of endometrial cancer compared to those receiving usual care. The limited evidence suggests that there is little or no serious or life-threatening adverse effects due to these interventions, although musculoskeletal problems were increased, presumably due to increased activity levels. Our conclusion is based on low- and very low-quality evidence from a small number of trials and very few patients. We therefore have very little confidence in the evidence: the true effect of weight-loss interventions in obese women with endometrial cancer is currently not known. Further methodologically-rigorous, adequately-powered RCTs are required with follow-up of 5 to 10 years duration. These should focus on the effects of varying dietary modification regimens, pharmacological treatments associated with weight loss and bariatric surgery on survival, quality of life, weight loss and adverse events.		

Kitson, S. et al. Interventions for weight reduction in obesity to improve survival in women with endometrial cancer. Cochrane Database of Systematic Reviews. . . 2018

Methodical Notes

Funding Sources: Dr Emma Crosbie was awarded funding via the Cochrane Review Support Programme to expedite the completion of this review which is a priority topic area. This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer.

COI: Nothing to declare.

Study Quality: We assessed and reported on the methodological risk of bias of included studies in accordance with the Cochrane Handbook of Systematic Reviews of Interventions. We assessed and reported the quality of the evidence for each outcome, using the GRADE approach.
The included RCTs were of low or very low quality, due to high risk of bias by failing to blind participants, personnel and outcome assessors, and significant loss to follow-up (attrition rate up to 29%).

Heterogeneity: By visual inspecting forest plots, by estimating the percentage of heterogneity (I2 statistic), by formally testing the significance of the heterogeneity (Chi2 statistics) and if possible, by conducting subgroup analyses.

Publication Bias: There were insufficient studies investigating each outcome to construct a funnel plot to assess for publication bias.

Notes:
Oxford CEBM Level of evidence 2011: EL 1 (systematic review).

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 4 **Study type:** SR (27 studies) **Databases:** Medline, Embase, Scopus, CINAHL. **Search period:** not specified. **Inclusion Criteria:** Observational studies (i.e. no drug intervention) reporting patient-related outcomes (PRO) among EC survivors; original data collection, use of validated scales. **Exclusion Criteria:** Studies with outcomes other than PRO, studies that did not include EC survivors, pilot studies and clinical trials assessing drug effects, studies of gynecological cancer survivors that did not report estimates separately for EC patients.	**Population:** Women diagnosed with EC **Intervention:** Questionnaires used to assess PROs: for example the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) used in 9 of the 27 observational studies. **Comparison:** Two studies included non-cancer control groups	**Primary:** Association between - BMI and/or physical activity and PROs - Treatment and PROs - predictors of sexual function - catch-all "other" category. 19 studies assessed the PROs at some point in time after EC diagnosis; whereas 8 studies prospectively evaluated changes in PROs over time with the use of multiple assessements. **Secondary:** - **Results:** Sample size range between 38 and 666 women. **BMI and/or physical activity and PROs** (8 studies): QoL: 6 studies: lower overall QoL among obese EC survivors relative to their normal counterparts. 5 Studies reported that physical functioning was	see publication.

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018				
		lower in obese patients relative to non-obese patients. **Treatment and PROs:** Treatment type affected several outcomes. Laparoscopy generally resulted in better QoL outcomes than laparotomy. Vaginal brachytherapy was associated with better outcomes compared to external beam radiation. **Predictors of sexual function:** Sexual function outcomes were dependent on age, time since diagnosis and having consulted a physician before engaging in sexual activities. In addition, a physical activity intervention was associated with improved sexual interest but not sexual function. **Catch-all "other" category** (five studies): one study evaluating psychosocial factors and mortality found a significant association between active coping (which consists of putting effort into improving one's situation)		

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018				
		with lower all-cause mortality. **Author's Conclusion:** Our review provides insights into the experiences of EC survivors from patient perspective. Factors that contribute to QoL such as pain, fatigue, emotional and social functioning should be monitored following an EG diagnosis.		
Methodical Notes				
Funding Sources: n.s. **COI:** None. **Study Quality:** Quality assessment is mentioned in the title of a paragraph, but no further details are mentioned. Thus the assumption is, that a quality assessment of the included studies is missing. **Heterogeneity:** not assessed. **Publication Bias:** not assessed.				

Shisler, R. et al. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 148. 403-413. 2018			
Notes: Oxfrod Level of evidence 2011: EL 3 Systematic review of cross-sectional and retrospective cohort studies (downgraded from EL 3 one level EL 4 due to methodological flaws). - the search range is not specified - no methodological quality of the included studies was performed - no analysis regarding heterogeneity, bias assessment ... was performed.			

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** SR (6 studies) **Databases:** Embase (1990–2015), MEDLINE (1990–2015), PsycINFO (1990–2015), CINAHL (1990–2015), BNI (1990–2015), AMED (1990–2015) using Ovid. **Search period:** See databases. **Inclusion Criteria:** Full text articles, published in the English language, report on the development and/or validation of	**Population:** Female individuals with sexual (dys)function. **Intervention:** questionnaire, outcome measure or assessement instrument; evaluation of the instrument's measurement properties using the COSMIN checklist. **Comparison:** -	**Primary:** Clinical utility of instruments for female sexual dysfunction (FSD) **Secondary:** - **Results:** Six Instruments werde found and analyzed: - Female Sexual Function Index (FSFI) - Sexual Adjustment and Body Image Scale-Gynecologic Cancer (SABIS-G) - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module	- R.E. Baser, 2012, Cancer. - S.E. Ferguson, 2012, Cancer. - E.R. Greimel, 2006, Cancer. - E. Greimel, 2011, Eur. J.

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016

an instrument measuring sexual (dys)function within an identifiable sample of women treated for either cervical or endometrial cancer. **Exclusion Criteria:** Quality of Life (QoL) or treatment toxicity studies that did not have a significant focus on sexual dysfunction and papers with a primary focus on sexual history taking or professional/patient communication about sexual impact of illness or treatment or body image. Instruments were also excluded if they measured sexual dysfunction in diseases or treatment effects unrelated to cervical or endometrial cancer, or where results from a cervical or endometrial cancer sub-sample of women was not identifiable.		(EORTC QLQ CX-24) - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ EN-24) - Sexual function-vaginal changes questionnaire (SVQ) - Gynaecologic Leiden Questionnaire (GLQ) **Clinical utility:** - **conceptual scope**: only the SVQ and SABIS-G included pre-treatment sexual function comparisons - Four of the six instruments included commonly encountered **mediating treatment or illness effects** such as vaginal changes, menopause and altered body image or femininity. None of the instruments included items regarding the effect of therapeutic aids. - Although **partner and relationship items** were absent from both QOL instruments, this important contributory factor to women's sexual recovery was included in the content of the four sexual morbidity instruments reviewed. - The ideal clinical instrument should be	Cancer. - P.T. Jensen, 2004, Psycho-Oncology. - Q.D. Pieterse, 2008, Psycho-Oncology.

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016

		brief and easy to complete and score to minimise burden for the patient and health professional, while still generating meaningful data. None of the instruments reviewed exceeded 24 items, but only two out of six papers reported completion time and participant feedback on ease of use. - Five of the six instrument scoring templates were complex or time-consuming for self or clinical interpretation and the absence of a clinical cut-off score for all but one instrument (FSFI) limits diagnostic and clinical management utility. **Author's Conclusion:** Findings suggest that the Female Sexual Function Index (FSFI) remains the most robust sexual morbidity outcome measure, for research or clinical use, in sexually active women treated for cervical or endometrial cancer. Development of an instrument that measures sexual dysfunction in women who are infrequently/not sexually active due to treatment consequences is still required to identify women in need of sexual rehabilitation.		

White, I. D. et al. Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. Gynecol Oncol. 143. 664-673. 2016

Methodical Notes

Funding Sources: None.

COI: None.

Study Quality: The COSMIN checklist evaluates the methodological rigour of each instrument paper across nine measurement properties.

Heterogeneity: Not assessed.

Publication Bias: Not assessed.

Notes:
Oxford CEBM Level of evidence 2011: EL 3 (systematic review) of retrospective cohort studies

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Do, J. H. et al. Effects of a complex rehabilitation program on edema status, physical function, and quality of life in lower-limb lymphedema after gynecological cancer surgery. Gynecol Oncol. 147. 450-455. 2017		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** randomzied controlled trial (pilot study). **Number of Patient:** 44 patients at the Department of Rehabilitation Medicine of Asan Medical Center in Seoul, South Korea. **Recruitung Phase:** December 2015 and August 2016. **Inclusion Criteria:** Patients with secondary unilateral lymphedema, after gynecologic surgery with pelvic lymph node dissection for cervical, endometrial, or ovarian cancer. **Exclusion Criteria:** Cancer recurrence and presence of other diseases (arterial insufficiency, heart or kidney diseas, ...),	**Intervention:** Intervention group: CR combined with CDT (CRCDT), n= 22 complex rehabilitation (CR) program, complex decongestive therapy (CDT) **Comparison:** control group: CDT alone, n= 22.	**Primary:** - Limb volumen - Bioimpedance - Lymphedema questionnaire (GCLQ-K) - Muscular strength (of the knee extensor) - 30-s chair stand test - QoL (EORTC QLQ-C30) **Secondary:** see primary **Results:** At baseline evaluation, there were no differences between the CRCDT and CDT group. At posttreatment evalutaion, - the physical function scores, - fatigue (EORTC QLQ-C30), - muscular strength of the knee extensor, and - 30-s chair stand test were significantly higher in the intervention group after treatment (p Improvement after treatment was significant in both groups for the following parameters: - fatigue, - pain, - GCLQ-K, - bioimpedance and

Do, J. H. et al. Effects of a complex rehabilitation program on edema status, physical function, and quality of life in lower-limb lymphedema after gynecological cancer surgery. Gynecol Oncol. 147. 450-455. 2017			
patients with skin problems (scarring, inflammation, infection).		- leg volume (p **Author's Conclusion:** The present study is the first randomized pilot study to examine the effect of CR program on edema status, physical function, and quality of life of patients with LLL after gynecological cancer surgery. The CR program showed beneficial effects on muscular strength, physical function, and fatigue without exacerbating LLL. This study provides evidence supporting the recommendation that patients with higher than stage 2 LLL can safely perform daily exercise at moderate intensity.	
Methodical Notes			
Funding Sources: n.s. **COI:** None. **Randomization:** Patients were randomly assigned to either the intervention group or the control group. **Blinding:** No. **Dropout Rate/ITT-Analysis:** Required sample size was 18 in each group for a repeated.measure analysis of variance. 4 patients were unable to complete the final evaluation, therefore , only 40 patients completed the study. **Notes:**			

Do, J. H. et al. Effects of a complex rehabilitation program on edema status, physical function, and quality of life in lower-limb lymphedema after gynecological cancer surgery. Gynecol Oncol. 147. 450-455. 2017		
Oxford CEBL Level of evidence 2011: EL 2 (randomized trial) Limits: - small sample size (20 patients per arm) - short period of rehabilitation program - no blinding (for evaluators) - No subgroup analysis was performed for EC patients (patient population consist of patients after gynecologic surgery in general). Thus the relevance of the results is unclear and has to be interpreted with caution.		
Haggerty, A. F. et al. A Randomized, Controlled, Multicenter Study of Technology-Based Weight Loss Interventions among Endometrial Cancer Survivors. Obesity (Silver Spring). 25 Suppl 2. S102-s108. 2017		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** Multicenter randomized controlled trial (three clinical sites in USA) **Number of Patient:** A total of 196 women (Wash U = 99, Penn = 90, Harvard = 7) completed the ECQ. Of those, 41 were eligible (Wash U = 31, Penn = 10), agreed to participate in the intervention, and	**Intervention:** Part I: Endometrial Cancer Questionnaire survey study (ECQ). Aim: assess the participants' perception of their weight status, physical activity, and whether they had access to internet and/or a smartphone with texting capabilities. Part II: Technology-based intervention: 1) Telemedicine weight management	**Primary:** Assessment of weight loss **Secondary:** Psychosocial analysis to measure quality of life metrics (mood, QoL, physical activity, sexual and relationship functioning, and general and cancer-specific body image). **Results:** 196 women completing the ECQ: mean age was 62.2 (SD = 8.7) years old; mean BMI of 39.1 kg/m2(range: 30–67 kg/m2).

Haggerty, A. F. et al. A Randomized, Controlled, Multicenter Study of Technology-Based Weight Loss Interventions among Endometrial Cancer Survivors. Obesity (Silver Spring). 25 Suppl 2. S102-s108. 2017		
were randomized 1:1:1 to one of the three arms for the 6-month weight loss intervention; 32 women completed the 6-month final assessment. **Recruitung Phase:** n.s. **Inclusion Criteria:** Women with a history of EC scheduled for follow-up visits in the gynecologic oncology clinic; English-speaking women 18 years of age or older with biopsy-proven EC and a BMI ≥ 30 kg/m2; no concurrent cytotoxic chemotherapy, radiation therapy, or further planned treatment; no evidence of active EC as determined by physician evaluation prior to randomization; Eastern Cooperative Oncology Group performance status 0–1; life expectancy of at least 1 year; and access to either wireless internet or a smartphone. **Exclusion Criteria:** Current or recent participation in a weight loss program or use of weight loss medications (history of bariatric surgery was not specifically excluded); uncontrolled serious medical or psychiatric condition(s) that would affect the patient's	plus Wi-Fi scale (telemedicine group). 2) Text messaging (texting) group. 3) Enhanced usual care group. **Comparison:** see intervention	41 women randomized to the intervention, mean age was 59.7 (SD = 8.7) years, weight at baseline was 109.5 (SD = 21.9) kg, mean height was 164.3 (SD = 7.1) cm, and mean BMI was 40.6 (SD = 7.5) kg/m2. ECQ outcomes: Of the 196 survey participants, 60.8% identified as having obesity, 36.6% identified as having overweight, 1.0% identified as having average weight, and 1.6% identified as having underweight. When asked whether obesity impacted risk of EC, 63% reported that obesity increased risk, 32% did not know, and the remainder believed it did not impact or reduced risk. Weight and adiposity intervention outcomes: Participants in all three arms lost weight (−4.4 [SD = 6.5] kg; −4% weight change) and reduced their waist circumference (−6.1 [SD = 15.5] cm), with no significant differences between the intervention and the EUC groups. Psychosocial assessments: Psychosocial functioning generally improved in all three groups. Telemedicine showed improvements in physical health and cancer-related body image (Ps = 0.04) compared to texting and in sexual functioning compared to EUC (P = 0.03). Total physical activity was increased in EUC compared with telemedicine (P =

Haggerty, A. F. et al. A Randomized, Controlled, Multicenter Study of Technology-Based Weight Loss Interventions among Endometrial Cancer Survivors. Obesity (Silver Spring). 25 Suppl 2. S102-s108. 2017

ability to participate in the interventional study; invasive malignancy other than EC or nonmelanoma skin cancer that required active treatment currently or within the last 5 years; or current pregnancy.		0.01), and vigorous physical activity was increased in EUC compared with both interventions (P = 0.01–0.03); walking significantly increased in texting compared with telemedicine (P = 0.02). **Author's Conclusion:** Weight loss was feasible in an older population of EC survivors using technology-based weight loss interventions. Unexpectedly, modest weight loss also occurred in the control group with only the attention of the study coupled with written information, perhaps due to increased motivation for lifestyle change during a teachable moment, such as recovery from cancer. However, knowledge of the link between excess weight and EC was still low for a population of survivors. Future larger-scale studies should focus on this knowledge gap and develop implementation strategies to ensure that all eligible patients are reached, with tailored approaches realistic for a busy gynecologic oncology clinic. This also speaks to a larger systematic need for funding, reimbursement of counseling time, and policies that stress the importance of weight management in cancer care. As EC incidence continues rising, mostly related to increasing rates of obesity, we should find more ways to remove barriers to effective behavioral interventions.

Haggerty, A. F. et al. A Randomized, Controlled, Multicenter Study of Technology-Based Weight Loss Interventions among Endometrial Cancer Survivors. Obesity (Silver Spring). 25 Suppl 2. S102-s108. 2017

Methodical Notes

Funding Sources: Funding for this study was provided by the Transdisciplinary Research on Energetics and Cancer (TREC) initiative through the following grants: NCI U54-CA155850, University of Pennsylvania; U54 CA155626, Harvard University; U54 CA155496CC, Washington University; U01 CA116850, Fred Hutchinson Cancer Research Center.

COI: The authors declared no conflict of interest.

Randomization: Survey participants who met eligibility for and desired to participate in the intervention trial were randomized 1:1:1 in clinic by random envelope selection by a trained research assistant into on of the three arms.

Blinding: n.a.

Dropout Rate/ITT-Analysis: 9 of the eligible women didn't complete 6 months final assessment.

Notes:
Oxford CEBM Level of evidence 2011: EL 2 (randomized, controlled trial)

Limits:
-small sample size
- self reported physical activity
- short intervention and follow-up period.

Due to the small study population the results have to be interpreted with caution.

2.46. Schlüsselfrage 53: Kann bei an Endometriumkarzinom erkrankten Patientinnen mit Trockenheit der Vagina, die durch inerte Cremes oder Gleitgele nicht befriedigend behandelbar ist, eine lokale Östrogenbehandlung durchgeführt werden, so dass sich die Lebensqualität verbessert in Bezug auf sexuelle Funktionsstörungen und vaginale Beschwerden?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Cerentini, T. M. 2019	2	RCT
Edey, K. A. 2018	1	SR and META (1 Trial)
Hanlon, A. 2018	2	pilot randomized trial (RCT)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Edey, K. A. et al. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 5. Cd008830. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** SR and META (1 Trial) **Databases:** Cochrane Register of Controlled Trials (CENTRAL 2017, Issue 5), MEDLINE (1946 to April, week 4, 2017) and Embase (1980 to 2017, week 18). **Search period:** see Databases. **Inclusion Criteria:** RCTs, all languages, efficacy of symptom relief and the safety of using HRT in women treated for endometrial cancer. **Exclusion Criteria:** -	**Population:** Women previously treated for endometrial cancer. **Intervention:** Oestrogen replacement therapy, - **alone vs placebo** - in combination with another agent (e.g. progestogens) vs oestrogen alone - in combination with another agent (e.g. progestogens) vs placebo - comparisons of different formulations. **Comparison:** see Intervention.	**Primary:** Rate of tumor recurrence, Rate of appearance of a new malignancy, rate of survival (overall survival, progression free survival). **Secondary:** Adverse effects. **Results:** 1236 participants were included in the study. **Tumour recurrence** in 2.3% of women in the oestrogen arm versus 1.9% of women receiving placebo (RR 1.17, 95% CI 0.54 to 2.50; very low-certainty evidence). New malignancies: one woman in the HRT arm (0.16%) and three women in the placebo arm (0.49%) who developed breast cancer during follow-up (RR 0.80, 95%CI 0.32 to 2.01; very low-certainty evidence). Not reported: - symptom relief, - overall survival - progression-free survival for HRT versus placebo - time to recurrence.	Barakat 2006.

Edey, K. A. et al. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 5. Cd008830. 2018				
		Women alive (at the end of 36-months follow up, with no evidence of disease): 94.3% in the HRT group and 95.6% in the placebo group; and the percentage of women alive irrespective of disease progression (95.8% in the HRT group and 96.9% in the placebo group). **Author's Conclusion:** Currently, there is insufficient high-quality evidence to inform women considering HRT after treatment for endometrial cancer. The available evidence (both the single RCT and non-randomised evidence) does not suggest significant harm, if HRT is used after surgical treatment for early-stage endometrial cancer. There is no information available regarding use of HRT in higher-stage endometrial cancer (FIGO stage II and above). The use of HRT after endometrial cancer treatment should be individualised, taking account of the woman's symptoms and preferences, and the uncertainty of evidence for and against HRT use.		
Methodical Notes				
Funding Sources: Barakat: This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.				

Edey, K. A. et al. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 5. Cd008830. 2018

For the cochrane review: None.

COI: Nothing to declare.

Study Quality: High risk of incomplete outcome bias, selective reporting bias and other bias. Unclear risk of Random sequence generation and allocation concealment. Low risk of bias for blinding of participants, personnel and outcome assessement.

Methodological quality see results.

Heterogeneity: no meta-analysis performed.

Publication Bias: one study included, assessment not possible.

Notes:
Oxford CEBM Level of evidence: EL 1 (SR)

!!It should be noted that this trial was closed before reaching its accrual goal of 2018 participants due to publication of the Women's Health Initiative (WHI) study. The results of the WHI trial, suggesting that risks of exogenous hormone therapy outweighed benefits,
resulted in a continually decreasing recruitment rate, such that the investigators felt that the goal of 2018 participants would not be reached in a reasonable time.

Only one study was included in this review. And the included study was published in 2008, which is not within the publication range of the literature review. Thus the study might already be included in an earlier version of the guideline.
The impact of the study is unclear, due to the at least moderate risk of bias, limited datas (early closing of the study, and low methodological quality).

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Cerentini, T. M. et al. Clinical and Psychological Outcomes of the Use of Vaginal Dilators After Gynaecological Brachytherapy: a Randomized Clinical Trial. Adv Ther. 36. 1936-1949. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT **Number of Patient:** 88 women with cervical cancer and assigned to radiotherapy. **Recruitung Phase:** January 2017 to May 2018. **Inclusion Criteria:** The dimensions of the vaginal canal at the initial pre-brachytherapy evaluation should be considered normal (mean vaginal length of 9.6 cm with a wide range varying from 6.5 to 12.5 cm) and the patient must not have undergone previous brachytherapy, been diagnosed with cervical cancer, be free of hysterectomy and aged over 18 years old. **Exclusion Criteria:** Patients with complications that impeded the protocol, such as severe bleeding, or those who did not complete the	**Intervention:** Brachytherapy followed by VD (vaginal dilatation) and all necessary guidelines for its use. **Comparison:** Brachytherapy (received only the usual guidance from the nursing team and participated in all the evaluations foreseen in the study).	**Primary:** Vaginal canal dimensions, QoL, Signs and symptoms and KFD-PF. **Secondary:** - **Results:** The frequency of conization was higher in the CG when compared to the IG. Adherence to the protocol declined with follow-up and there was a high rate of loss throughout the study but this behaviour was similar between the groups (X2 = 0.146, p = 0.702). **Vaginal canal size:** In the multivariate analysis no intervention effect was observed for any of the vaginal canal size variables on the ITT population (length: F = 2.545, p = 0.111; width: F = 0.490, p = 0.484; area: F = 0.107, p = 0.743). However, when we analysed the clinical occurrences only in the women who completed all the evaluations foreseen in the protocol, we identified that in the IG there was a significant reduction in constipation and vaginal dryness at the end of follow-up.

Cerentini, T. M. et al. Clinical and Psychological Outcomes of the Use of Vaginal Dilators After Gynaecological Brachytherapy: a Randomized Clinical Trial. Adv Ther. 36. 1936-1949. 2019			
treatment with gynaecological brachytherapy were dismissed.		**QoL:** The overall quality of life assessment score was similar between the groups throughout the follow-up (X2 = 0.007, p = 0.936). all domains improved at the end of follow-up (global domain: X2 = 5.995, p = 0.05; functional domain: X2 = 24,767, p = 0.001; symptoms domain: X2 = 17,077, p = 0.001). Women with hypoactive PF had a significant decrease in vaginal width (p = 0.042). **Author's Conclusion:** The use of VD did not alter the dimensions of the vaginal canal within the first 3 months after the end of radiotherapy treatment. However, there was a large sample loss during follow-up so studies with a larger sample number and longer follow-up time need to be conducted.	
Methodical Notes			
Funding Sources: None. **COI:** Salvatore Giovanni Vitale is a member of the journal's Editorial Board. Valentina Lucia La Rosa is a member of the journal's Editorial Board. Taı´s Marques Cerentini, Ju´lia Schlo¨ttgen, Patrı´cia Viana da Rosa, Pierluigi Giampaolino, Gaetano Valenti, Stefano Cianci and Fabrı´cio Edler Macagnan have			

Cerentini, T. M. et al. Clinical and Psychological Outcomes of the Use of Vaginal Dilators After Gynaecological Brachytherapy: a Randomized Clinical Trial. Adv Ther. 36. 1936-1949. 2019		
nothing to disclose. **Randomization:** yes, random assingment in a ration 1:2. **Blinding:** Given the nature of the procedure, neither the participants nor the clinicians were masked to group assignment. **Dropout Rate/ITT-Analysis:** Drop out rate: Control group: 23 lost to follow up (of 32); Intervention group: 32 lost to follow up (of 56). ITT: yes: At a significance level of 1% and power of the hypothesis test of 80%, the estimated sample size was 85 volunteers. **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 (randomized trial) High drop out rate (only 28% of the CG and 30% of the IC performed final evaluation). Thus the clinical impact of the results may be limited.		
Hanlon, A. et al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. Cancer Nurs. 41. 200-209. 2018		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** pilot randomized trial (RCT)	**Intervention:** Theoretically guided, nurse led, one-on-one enhanced educational program (EEP) for vaginal	**Primary:** To establish feasibility of recruiting patients into a trial of vaginal dilator use

Hanlon, A. et al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. Cancer Nurs. 41. 200-209. 2018

Number of Patient: 58 patients consented (16 lost due to withdrewal, lost to follow up and lost through the re-consent process) thus in total 42 patients were randomized. **Recruitung Phase:** The study opened to accrual June 15, 2010 and closed April 30, 2013, with a 12 month hold on accrual from August 2011 to August 2012 due to relocation of the PI. **Inclusion Criteria:** Eligibility included women who underwent a hysterectomy and oophorectomy with/without lymphadenectomy for treatment of stage I-IIIc endometroid endometrial cancer. In addition, participants were required to have post-operative VBT and no prior history of external beam pelvic RT or chemotherapy. **Exclusion Criteria:** -	dilator use with telephone follow-up. **Comparison:** Standard institutional instruction (SII) for the use of a vaginal dilator.	**Secondary:** The secondary aim was assess preliminary efficacy of an enhanced educational program to improve adherence with vaginal dilator use. A tertiary aim is to assess sexual function using the validated Female Sexual Function Index. **Results:** Of 24 patients in the standard group 21 (88%) could be analyzed. In the EEP group of 18 patients 8 (44%) could be analyzed at the end of follow up. There was no difference in adherence between arms. Overall, 20% and 8.3% were adherent to the prescribed 3 times per week use; and 64% and 16% were adherent to use at least once per week at 6 weeks and 6 months, respectively. Adherence was greater among those motivated by vaginal health and having lower body mass index. Non-adherence was significantly higher among college educated, EEP group, and with higher weight. **Author's Conclusion:** Feasibility of recruitment into a study of vaginal dilator use was high. Adherence was low and there was no difference between groups. Adherence to vaginal dilator use requires novel interventions to test.

Hanlon, A. et al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. Cancer Nurs. 41. 200-209. 2018

Methodical Notes

Funding Sources: This study was supported by a grant from the National Cancer Institute 1R21CA140766-01.

COI: Nothing to declare.

Randomization: Block randomization was used to generate an a priori randomization sequence using a computer algorithm and sequential assignments.

Blinding: Group assignment was blinded to evaluating physicians, but not to the nurses.

Dropout Rate/ITT-Analysis: Targeted sample size was 58 patients based on Hertzog's recommendations for feasibility aims which suggests a threshold of 25 participants per group for pilot studies involving direct estimation of a between-group effect size, with an additional 8 patients to account for 15% estimated attrition.

Notes:
Oxford CEBM Level of evidence 2011: EL 2 (randomized trial).

Limits:
- small sample size
- high drop-out rate
- the study had a 12 month hold on accrual from August 2011 to August 2012 due to relocation of the PI (might be one reason for the high drop-out rate).

Due to the limits the results of the study has to be assessed with care.

2.47. Schlüsselfrage 54: Kann bei an Endometriumkarzinom erkrankten Patientinnen, die behandelt wurden mittels Strahlentherapie, welche die Vaginalregion einbezogen hat, eine mechanische Dilatation mittels Vaginaldilatatoren oder Tampons mit inerten Cremes ab vier bis sechs Wochen postoperativ eine Vaginalstenose verhindern, so dass die Lebensqualität erhalten bleibt in Bezug auf sexuelle Funktionsstörungen und vaginale Beschwerden?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Cerentini, T. M. 2019	2	RCT
Edey, K. A. 2018	1	SR and META (1 Trial)
Hanlon, A. 2018	2	pilot randomized trial (RCT)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Edey, K. A. et al. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 5. Cd008830. 2018			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type:** SR and META (1 Trial) **Databases:** Cochrane Register of Controlled Trials (CENTRAL 2017, Issue 5), MEDLINE (1946 to April, week 4, 2017) and Embase (1980 to 2017, week 18). **Search period:** see Databases. **Inclusion Criteria:** RCTs, all languages, efficacy of symptom relief and the safety of using HRT in women treated for endometrial cancer. **Exclusion Criteria:** -	**Population:** Women previously treated for endometrial cancer. **Intervention:** Oestrogen replacement therapy, - **alone vs placebo** - in combination with another agent (e.g. progestogens) vs oestrogen alone - in combination with another agent (e.g. progestogens) vs placebo - comparisons of different formulations. **Comparison:** see Intervention.	**Primary:** Rate of tumor recurrence, Rate of appearance of a new malignancy, rate of survival (overall survival, progression free survival). **Secondary:** Adverse effects. **Results:** 1236 participants were included in the study. **Tumour recurrence** in 2.3% of women in the oestrogen arm versus 1.9% of women receiving placebo (RR 1.17, 95% CI 0.54 to 2.50; very low-certainty evidence). New malignancies: one woman in the HRT arm (0.16%) and three women in the placebo arm (0.49%) who developed breast cancer during follow-up (RR 0.80, 95%CI 0.32 to 2.01; very low-certainty evidence). Not reported: - symptom relief, - overall survival - progression-free survival for HRT versus placebo - time to recurrence.	Barakat 2006.

Edey, K. A. et al. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 5. Cd008830. 2018				
		Women alive (at the end of 36-months follow up, with no evidence of disease): 94.3% in the HRT group and 95.6% in the placebo group; and the percentage of women alive irrespective of disease progression (95.8% in the HRT group and 96.9% in the placebo group). **Author's Conclusion:** Currently, there is insufficient high-quality evidence to inform women considering HRT after treatment for endometrial cancer. The available evidence (both the single RCT and non-randomised evidence) does not suggest significant harm, if HRT is used after surgical treatment for early-stage endometrial cancer. There is no information available regarding use of HRT in higher-stage endometrial cancer (FIGO stage II and above). The use of HRT after endometrial cancer treatment should be individualised, taking account of the woman's symptoms and preferences, and the uncertainty of evidence for and against HRT use.		
Methodical Notes				
Funding Sources: Barakat: This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.				

Edey, K. A. et al. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 5. Cd008830. 2018

For the cochrane review: None.

COI: Nothing to declare.

Study Quality: High risk of incomplete outcome bias, selective reporting bias and other bias. Unclear risk of Random sequence generation and allocation concealment. Low risk of bias for blinding of participants, personnel and outcome assessement.

Methodological quality see results.

Heterogeneity: no meta-analysis performed.

Publication Bias: one study included, assessment not possible.

Notes:
Oxford CEBM Level of evidence: EL 1 (SR)

!!It should be noted that this trial was closed before reaching its accrual goal of 2018 participants due to publication of the Women's Health Initiative (WHI) study. The results of the WHI trial, suggesting that risks of exogenous hormone therapy outweighed benefits,
resulted in a continually decreasing recruitment rate, such that the investigators felt that the goal of 2018 participants would not be reached in a reasonable time.

Only one study was included in this review. And the included study was published in 2008, which is not within the publication range of the literature review. Thus the study might already be included in an earlier version of the guideline.
The impact of the study is unclear, due to the at least moderate risk of bias, limited datas (early closing of the study, and low methodological quality).

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Cerentini, T. M. et al. Clinical and Psychological Outcomes of the Use of Vaginal Dilators After Gynaecological Brachytherapy: a Randomized Clinical Trial. Adv Ther. 36. 1936-1949. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT **Number of Patient:** 88 women with cervical cancer and assigned to radiotherapy. **Recruitung Phase:** January 2017 to May 2018. **Inclusion Criteria:** The dimensions of the vaginal canal at the initial pre-brachytherapy evaluation should be considered normal (mean vaginal length of 9.6 cm with a wide range varying from 6.5 to 12.5 cm) and the patient must not have undergone previous brachytherapy, been diagnosed with cervical cancer, be free of hysterectomy and aged over 18 years old. **Exclusion Criteria:** Patients with complications that impeded the protocol, such as severe bleeding, or those who did not complete the	**Intervention:** Brachytherapy followed by VD (vaginal dilatation) and all necessary guidelines for its use. **Comparison:** Brachytherapy (received only the usual guidance from the nursing team and participated in all the evaluations foreseen in the study).	**Primary:** Vaginal canal dimensions, QoL, Signs and symptoms and KFD-PF. **Secondary:** - **Results:** The frequency of conization was higher in the CG when compared to the IG. Adherence to the protocol declined with follow-up and there was a high rate of loss throughout the study but this behaviour was similar between the groups (X2 = 0.146, p = 0.702). **Vaginal canal size:** In the multivariate analysis no intervention effect was observed for any of the vaginal canal size variables on the ITT population (length: F = 2.545, p = 0.111; width: F = 0.490, p = 0.484; area: F = 0.107, p = 0.743). However, when we analysed the clinical occurrences only in the women who completed all the evaluations foreseen in the protocol, we identified that in the IG there was a significant reduction in constipation and vaginal dryness at the end of follow-up.

Cerentini, T. M. et al. Clinical and Psychological Outcomes of the Use of Vaginal Dilators After Gynaecological Brachytherapy: a Randomized Clinical Trial. Adv Ther. 36. 1936-1949. 2019			
treatment with gynaecological brachytherapy were dismissed.		**QoL:** The overall quality of life assessment score was similar between the groups throughout the follow-up (X2 = 0.007, p = 0.936). all domains improved at the end of follow-up (global domain: X2 = 5.995, p = 0.05; functional domain: X2 = 24,767, p = 0.001; symptoms domain: X2 = 17,077, p = 0.001). Women with hypoactive PF had a significant decrease in vaginal width (p = 0.042). **Author's Conclusion:** The use of VD did not alter the dimensions of the vaginal canal within the first 3 months after the end of radiotherapy treatment. However, there was a large sample loss during follow-up so studies with a larger sample number and longer follow-up time need to be conducted.	
Methodical Notes			
Funding Sources: None. **COI:** Salvatore Giovanni Vitale is a member of the journal's Editorial Board. Valentina Lucia La Rosa is a member of the journal's Editorial Board. Taı´s Marques Cerentini, Ju´lia Schlo¨ttgen, Patrı´cia Viana da Rosa, Pierluigi Giampaolino, Gaetano Valenti, Stefano Cianci and Fabrı´cio Edler Macagnan have			

Cerentini, T. M. et al. Clinical and Psychological Outcomes of the Use of Vaginal Dilators After Gynaecological Brachytherapy: a Randomized Clinical Trial. Adv Ther. 36. 1936-1949. 2019		
nothing to disclose. **Randomization:** yes, random assingment in a ration 1:2. **Blinding:** Given the nature of the procedure, neither the participants nor the clinicians were masked to group assignment. **Dropout Rate/ITT-Analysis:** Drop out rate: Control group: 23 lost to follow up (of 32); Intervention group: 32 lost to follow up (of 56). ITT: yes: At a significance level of 1% and power of the hypothesis test of 80%, the estimated sample size was 85 volunteers. **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 (randomized trial) High drop out rate (only 28% of the CG and 30% of the IC performed final evaluation). Thus the clinical impact of the results may be limited.		
Hanlon, A. et al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. Cancer Nurs. 41. 200-209. 2018		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** pilot randomized trial (RCT)	**Intervention:** Theoretically guided, nurse led, one-on-one enhanced educational program (EEP) for vaginal	**Primary:** To establish feasibility of recruiting patients into a trial of vaginal dilator use

Hanlon, A. et al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. Cancer Nurs. 41. 200-209. 2018

Number of Patient: 58 patients consented (16 lost due to withdrewal, lost to follow up and lost through the re-consent process) thus in total 42 patients were randomized. **Recruitung Phase:** The study opened to accrual June 15, 2010 and closed April 30, 2013, with a 12 month hold on accrual from August 2011 to August 2012 due to relocation of the PI. **Inclusion Criteria:** Eligibility included women who underwent a hysterectomy and oophorectomy with/without lymphadenectomy for treatment of stage I-IIIc endometroid endometrial cancer. In addition, participants were required to have post-operative VBT and no prior history of external beam pelvic RT or chemotherapy. **Exclusion Criteria:** -	dilator use with telephone follow-up. **Comparison:** Standard institutional instruction (SII) for the use of a vaginal dilator.	**Secondary:** The secondary aim was assess preliminary efficacy of an enhanced educational program to improve adherence with vaginal dilator use. A tertiary aim is to assess sexual function using the validated Female Sexual Function Index. **Results:** Of 24 patients in the standard group 21 (88%) could be analyzed. In the EEP group of 18 patients 8 (44%) could be analyzed at the end of follow up. There was no difference in adherence between arms. Overall, 20% and 8.3% were adherent to the prescribed 3 times per week use; and 64% and 16% were adherent to use at least once per week at 6 weeks and 6 months, respectively. Adherence was greater among those motivated by vaginal health and having lower body mass index. Non-adherence was significantly higher among college educated, EEP group, and with higher weight. **Author's Conclusion:** Feasibility of recruitment into a study of vaginal dilator use was high. Adherence was low and there was no difference between groups. Adherence to vaginal dilator use requires novel interventions to test.

Hanlon, A. et al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. Cancer Nurs. 41. 200-209. 2018

Methodical Notes

Funding Sources: This study was supported by a grant from the National Cancer Institute 1R21CA140766-01.

COI: Nothing to declare.

Randomization: Block randomization was used to generate an a priori randomization sequence using a computer algorithm and sequential assignments.

Blinding: Group assignment was blinded to evaluating physicians, but not to the nurses.

Dropout Rate/ITT-Analysis: Targeted sample size was 58 patients based on Hertzog's recommendations for feasibility aims which suggests a threshold of 25 participants per group for pilot studies involving direct estimation of a between-group effect size, with an additional 8 patients to account for 15% estimated attrition.

Notes:
Oxford CEBM Level of evidence 2011: EL 2 (randomized trial).

Limits:
- small sample size
- high drop-out rate
- the study had a 12 month hold on accrual from August 2011 to August 2012 due to relocation of the PI (might be one reason for the high drop-out rate).

Due to the limits the results of the study has to be assessed with care.

2.48. Schlüsselfrage 56 (neue Schlüsselfrage): Ändert die präoperative Bestimmung des L1CAM-Status und der molekularen Klassifikation (ProMisE) das operative Prozedere/die Radikalität des operativen Eingriffes?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bosse, T. 2015	2	RCT (post-hoc analysis of histological samples of PORTEC-1 and -2 trials).
Raffone, A. 2019	3	SR and META (6 studies).
Van Gool, I. C. 2016	4	Retrospective prognostic study.
Wortman, B. G. 2018	2	RCT (multicentre randomised trial, PORTEC-2 trial)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *1 Bewertung(en)*

Raffone, A. et al. TCGA molecular groups of endometrial cancer: Pooled data about prognosis. Gynecol Oncol. 155. 374-383. 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** SR and META (6 studies). **Databases:** Web of Science, Scopus; MEDLINE, Google Scholar, Cochrane Library, EMBASE and Clinicaltrials.gov. **Search period:** Inception to April 2019. **Inclusion Criteria:** Peer-reviewed, prospective or retrospective studies reporting data about prognosis in each TCGA group of EC. **Exclusion Criteria:** Sample size < 2 years. Studies not	**Population:** Patiens diagnosed with EC. **Intervention:** TCGA group (p53mt, MSI or POLEmt) assessed by molecular sequencing or immunohistochemical surrogates according to the ProMisE. **Comparison:** TCGA copy-number low group assessed according to the ProMisE (p53wt).	**Primary:** OS (time to death, defined as time from surgery until death of any cause). **Secondary:** DSS (time to death from disease, defined as time from surgery due to endometrial cancer), PFS (time to progression, defined as time from surgery until there is evidence of recurrent or progressive disease or if they diesd of the disease prior to the censoring date). **Results:** 2818 patients with EC were included. - p53wt: 48.2% (assessed by immunhistochemistry) - p53mt: 13.2% (s.a.) - MSI: 31.6% (s.a.) - POLEmt: 6.9% (assessed by sequencing). Results: pooled HRs regarding OS were p53wt = reference - p53mt: 3.179 and 1.986 - MSI: 1.522 and 1.192 - POLEmt: 0.598 and 0.795 univariable and multivariable analysis resp.(6 studies incl.).	- Talhouk, 2015, Br. J. Cancer. - Talhouk, 2017, Cancer. - Stelloo, 2016, Clin Cancer Res. - Kommoss, 2018, Ann. Oncol. - Cosgrove, 2017, Gynecol. Oncol. - Bosse, 2018, J. Surg. Pathol.

Raffone, A. et al. TCGA molecular groups of endometrial cancer: Pooled data about prognosis. Gynecol Oncol. 155. 374-383. 2019				
assessing prognosis in even only one TCGA group.		Results: pooled HRs regarding DSS were - p53mt: 5.052 and 2.133 - MSI: 1.965 and 1.068 - POLEmt: 0.552 and 0.325 univariable and multivariable analysis resp.(4 studies included). Results: pooled HRs regarding PFS were - p53mt: 3.512 and 1.833 - MSI: 1.354 and 0.817 - POLEmt: 0.287 and 0.217 univariable and multivariable analysis resp.(5 studies included). **Author's Conclusion:** Prognosis of p53mt group is consistently the worst one and is further worsened by unfavorable clinicopathological factors. Prognosis of MSI group overlaps with p53wt group but is worsened by unfavorable clinicopathological factors. Prognosis of the POLEmt group is the best one and does not seem to be significantly affected by clinicopathological factors.		
Methodical Notes				
Funding Sources: Nothing to declare. **COI:** None				

Raffone, A. et al. TCGA molecular groups of endometrial cancer: Pooled data about prognosis. Gynecol Oncol. 155. 374-383. 2019

Study Quality: Within studies evaluated by Methodological Index for Non-Randomized Studies (MINORS). Low to moderate. See publication.

Heterogeneity: Statistical heterogeneity I2: Null (I2 =0%), Minimal (0 to 25%), low (25-50%), moderate (50-75%) and high (I2 > 75%).
High heterogeneity for OS and PFS with p53mt.
Moderate for OS and PFS with MSI and
Null or low for other comparisons.

Publication Bias: n.a.

Notes:
Oxford CEBM Level of evidence: EL 3 (systematic review of prospective and retrospective cohort studies).

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Bosse, T. et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 51. 1742-50. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (post-hoc analysis of histological samples of PORTEC-1 and -2 trials). **Number of Patient:** Patients and follow-up data of the PORTEC-1 and PORTEC-2 studies were used. PORTEC-1 included 714 patients. The PORTEC-2 study included 427 patients. Histological slides and/or tumour samples were available from 926 (81.2%) patients with endometrioid type tumours, of the in total 1141 randomised patients. **Recruitung Phase:** PORTEC-1: 1990-1997 PORTEC-2: 2002-2006 **Inclusion Criteria:** PORTEC-1: Patients with FIGO (1988) stage IB grade 2 or 3 and stage IC grade 1 or 2 EC. PORTEC-2: Patients who had stage I EC with	**Intervention:** PORTEC-1: external beam radiation therapy (EBRT) versus no additional treatment (NAT). PORTEC-2: EBRT versus vaginal brachytherapy (VBT). For this post-hoc analysis: Lymph-vascular space invasion (LVSI) defined as the presence of tumour cells in a space lined by endothelial cells outside the immediate invasive border. Here analyzed by a scoring system based on a semi-quantitative approach (two-, three- and four-tiered approach). **Comparison:** See intervention.	**Primary:** Pelvic regional recurrence, distant metastasis (DM) and overall survival(OS) **Secondary:** - **Results:** LVSI was found in 129 (13.9%) tumours. No additional prognostic value was found for the four tiered-approach compared to the three-tiered approach. Substantial LVSI (n = 44, 4.8%) using the 3-tiered approach had the strongest impact on the risk of distant metastasis (HR 4.5 CI 2.4–8.5). In multivariate analysis (including: age, depth of myometrial invasion, grade, treatment) substantial LVSI remained the strongest independent prognostic factor for pelvic regional recurrence (HR 6.2 CI 2.4–16), distant metastasis (HR 3.6 CI 1.9–6.8) and overall survival (HR 2.0 CI 1.3–3.1). Only EBRT (HR 0.3 CI 0.1–0.8) reduced the risk of pelvic regional recurrence. **Author's Conclusion:** In conclusion, substantial

Bosse, T. et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 51. 1742-50. 2015			
high-intermediate risk features (FIGO 1988 stage 1B grade 3, IC grade 1 or 2 or stage 2A). Since the PORTEC-2 trial include high-intermediate risk patients while the PORTEC-1 trial also included (low-)intermediate risk cases, patients in the VBT group were on average older and had more grade 3 tumours. Median follow-up for patients alive was 160 months for PORTEC-1 and 89 months for PORTEC-2. **Exclusion Criteria:** n.s.		LVSI using a three-tiered scoring system is the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival. Adjuvant EBRT should be considered for the small subgroup of stage I EC patients who have substantial LVSI, especially those with grade 3 tumours, and the role of systemic therapy should be determined.	
Methodical Notes			
Funding Sources: Both the PORTEC-1 trial (CKTO 1990-01) and the PORTEC-2 trial (CKTO 2001-04) were supported by a research grant of the Dutch Cancer Society. **COI:** None. **Randomization:** PORTEC-1 and PORTEC-2 were randomized trials. **Blinding:** Analysis were performed blinded by the researches. **Dropout Rate/ITT-Analysis:** Histological slides and/or tumour samples were available from 926 (81.2%) patients with endometrioid type tumours, of the in total 1141 randomised patients.			

Bosse, T. et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 51. 1742-50. 2015		
Notes: Oxford CEBM Level of Evidence: EL 2 (randomized trial) This study displays a post-hoc analysis of two RCTs.		
Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018		
Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (multicentre randomised trial, PORTEC-2 trial) **Number of Patient:** 427 women with HIR endometrial carcinoma (214 received EBRT and 213 recieved VBT). **Recruitung Phase:** Between May 2002 and September 2006. **Inclusion Criteria:** Woman diagnosed with	**Intervention:** Vaginal brachytherapy (VBT) **Comparison:** Pelvic radiotherapy (EBRT).	**Primary:** Vaginal recurrence (VR) **Secondary:** Pelvic recurrence (PR), distant recurrence (DR), overall survival (OS, date of randomisation to death from any cause, with censoring at date of last information for patients alive), endometrial cancer-related survival (CSS, from date of randomisation to date of death related to endometrial cancer), disease-free survival (DFS, date of randomisation to date of disease recurrence or to date of death from any cause,), and toxicity and quality of life. **Results:** Patient and tumour characteristics were equally distributed over the two treatment groups. The database was

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018		
endometrial carcinoma with high-intermediate risk factors (HIR), HIR was defined as either (1) FIGO 1988 stage 1C (≥50% myometrial invasion) with age greater than 60 and grade 1 or 2; or (2) FIGO 1988 stage 1B (**Exclusion Criteria:** Serous or clear cell carcinoma; staging lymphadenectomy; > 8 weeks interval between surgery and radiotherapy; history of previous malignancy; previous radiotherapy, hormonal or chemotherapy; Crohn's disease or ulcerative colitis.		frozen on May 1st 2016 and by then, the median follow-up was 116 months (range 18–163 months). The 10-year **vaginal recurrence rates** were 3.4% and 2.4% for VBT and EBRT, respectively (p = 0.55). **Pelvic recurrences** were 6.3% vs. 0.9% (p = 0.004); of these, 2.5% vs. 0.5% were isolated pelvic recurrences (p = 0.10). Ten-year rates of **distant metastases** were 10.4% vs. 8.9% for VBT vs EBRT (p = 0.45). In the <u>confirmed HIR-group</u> the 10-year vaginal recurrence rates were 2.7% vs. 3.1% (p = 0.78) and the pelvic recurrence rates 7.4% and 1.2% (p = 0.01) for VBT vs. EBRT,respectively. Ten-year **overall survival** was 69.5% vs. 67.6% (p = 0.72) and 10-year endometrial cancer-related survival 88.2% vs. 90.9% (p = 0.42) for VBT vs. EBRT groups, respectively. <u>Prognostic factors:</u> Women with tumours harbouring a POLE mutation, 10-year CSS was 100%, in contrast to 96.2% for no specific molecular profile, 84.8% for MSI and 62.3% for p53-mutant tumours (p < 0.001). Substantial LVSI (in confirmed HIR group) was found to be a very strong independent risk factor for pelvic and distant recurrence (HR 8.73 (p = 0.005) and 5.36 (p = 0.001), respectively) and for endometrial cancer-related survival (HR 7.16, p < 0.001). L1CAM expression (HR 4.18, p = 0.016) and p53-mutant expression (HR 3.35, p = 0.015) were significant prognostic

Wortman, B. G. et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 119. 1067-1074. 2018			
		factors for distant recurrence and CSS (HR 5.05, p = 0.006 and HR 3.30, p = 0.015). **Author's Conclusion:** In conclusion, long-term results of PORTEC-2 confirmed VBT as the adjuvant treatment of choice for women with high intermediate risk endometrial cancer. EBRT might provide better pelvic control in the small subgroup of women with unfavourable risk factors (substantial LVSI, L1CAM expression or p53-mutant expression).	
Methodical Notes			
Funding Sources: The PORTEC-2 study was supported by a grant from the Dutch Cancer Society (CKTO 2001-04). **COI:** None. **Randomization:** Yes **Blinding:** n.s. **Dropout Rate/ITT-Analysis:** ITT yes **Notes:** Oxford CEBM Level of Evidence 2011: EL 2 (randomized controlled trial) Long term analysis of the outcomes of PORTEC-2 trial.			

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Van Gool, I. C. et al. Prognostic significance of L1CAM expression and its association with mutant p53 expression in high-risk endometrial cancer. Mod Pathol. 29. 174-81. 2016		
Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective prognostic study. **Number of Patient:** 116 high risk endometrial cancer patients (samples from the TransPORTEC consortium). **Recruitung Phase:** n.s. **Inclusion Criteria:** Endometrioid endometrial cancer with one of the following postoperative FIGO 2009 stages and grade: stage IA grade 3 with myometrial invasion, stage IB grade 3 or higher stages, and serous or clear-cell histology with stage IA with myometrial invasion, or higher stages. **Exclusion Criteria:** -	**Intervention:** L1CAM expression via histochemistry (two groups L1CAM **Comparison:** -	**Primary:** Rates of distant recurrences, locoregional recurrences, recurrence free, and overall survival. **Secondary:** - **Results:** Fifty-one (44%) tumors were found to be L1CAM-positive (cutoff value 10%). L1CAM positivity was significantly associated with advanced age (68.7 vs 64.3 years, P = 0.033), non-endometrioid morphology (P< 0.001), and high tumor grade (P< 0.001). Subanalysis in endometrioid endometrial cancers: - significant association between L1CAM expression and high tumor grade (P =0.022) - no significant association between L1CAM expression and FIGO stage, depth of myometrial invasion, presence of lymphovascular space invasion. L1CAM-positive tumors did not have a significantly different **rate of distant recurrences** (P = 0.195). Median follow-up time was 28.6 months (range 0.3–120 months),

Van Gool, I. C. et al. Prognostic significance of L1CAM expression and its association with mutant p53 expression in high-risk endometrial cancer. Mod Pathol. 29. 174-81. 2016

		whereas subanalysis indidicated that the rate in case of >50% L1CAM expression was higher (p=0.018). Relationship between L1CAM and mutant p53 expression: A significant association was found with p53-mutant tumors often showing diffuse L1CAM expression (P = 0.001). **L1CAM (cutoff of 50%) and p53 expression,** univariate analysis for rate of distant recurrences suggests added prognostic value of L1CAM to p53 as the highest rate was seen in combined mutant p53 and >50% L1CAM expression (P = 0.031). Validation via TCGA endometrial cancer series: L1CAM positivity was associated with older age, advanced disease stage, non-endometrioid morphology, high tumor grade, and high-risk endometrial cancer (P<0.001). **Author's Conclusion:** In summary, our findings suggest that, although it has proven to be an independent prognostic factor in patients with low- and intermediate-risk features, L1CAM expression with a threshold of >10% may not be prognostically relevant in high-risk endometrial cancer. For this group, a higher threshold of >50% seems to be more appropriate. L1CAM expression and mutant p53 expression are strongly associated, but the two markers are not surrogates. The question remains

Van Gool, I. C. et al. Prognostic significance of L1CAM expression and its association with mutant p53 expression in high-risk endometrial cancer. Mod Pathol. 29. 174-81. 2016			
		whether L1CAM should be clinically implemented as an independent prognostic biomarker next to p53 and what threshold(s) should be used. In addition, because of the high frequency of L1CAM expression found in this study, its potential as a therapeutic target for high-risk endometrial cancer seems promising.	
Methodical Notes			
Funding Sources: This work was supported by the Dutch Cancer Society (KWF-UL2012-5719; to ICvG, ES, RAN, CLC, VTHBMS, and TB). DNC was funded by a Health Foundation/Academy of Medical Sciences Clinician Scientist Fellowship. **COI:** None. **Randomization:** - **Blinding:** Immunohistochemical evaluation was done blinded for patient characteristics and outcome by two independet investigators. **Dropout Rate/ITT-Analysis:** - **Notes:** Oxford CEBM Level of evidence: EL 3 (retrospective, cohort study - Prognosis) Limitations (stated by authors): - explorative study - modest group sizes - limited follow-up data			

Van Gool, I. C. et al. Prognostic significance of L1CAM expression and its association with mutant p53 expression in high-risk endometrial cancer. Mod Pathol. 29. 174-81. 2016	
- lack of central pathologogy review; so the results should be interpreted with care.	

2.49. Schlüsselfrage 57 (neue Schlüsselfrage): Ist beim frühen Endometriumkarzinom (Typ 1, G1, G2, pT1a) die Sentinel-Node-Entfernung prognostisch relevanter UND prädiktiver als der Verzicht auf ein solches chirurgisches Staging im Hinblick auf Lebensqualität, Kurzzeit-/Langzeitmorbidität, Rezidivhäufigkeit, krankheitsspezifisches und Gesamt-Überleben?

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Body, N. 2018	4	Retrospective Cohort Study
Cusimano, M. C. 2021	3	Prospective multicenter cohort study
Plante, M. 2017	3	Prospective cohort study.
Zheng, Y. 2019	4	Retrospective cohort study (SEER database)

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *2 Bewertung(en)*

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective Cohort Study	**Number of patients / samples:** 119 patients with endometrial cancer **Reference standard:** No reference standard **Validation:** Detection rate, sensitivity and negative predictive value (NPV) **Blinding:** Not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	**Results:** Sentinel lymph node mapping with Indocyanin green A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection (p = 0.01). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymphe node. **Author conclusions:** ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection (p = 0.01). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.		
Methodical Notes				

Body, N. et al. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol. 150. 267-273. 2018		
Funding Sources: Not stated. COI: None. Notes: Oxford CEBM Level of Evidence 2011: EL 4 Retrospective cohort study without blinding or reference standard Articles submitted by hand search.		
Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type:** Prospective multicenter cohort study	**Number of patients / samples:** 156 patients **Reference standard:** Lymphadenectomy as the reference standard **Validation:** Sensitivity of the SLNB algorithm in detecting metastatic disease, False negative rate and negative predictive value Additional measures of diagnostic accuracy, sentinel lymph node detection rates, and adverse events	**Results:** Performance characteristics of Sentinel Lymph Node Biopsy (SLNB) using indocyanine green (ICG) The study enrolled 156 patients (median age, 65.5 years; range, 40-86 years; median body mass index [calculated as weight in kilograms divided by height in meters squared], 27.5; range, 17.6-49.3), including 126 with high-grade EC. All patients underwent SLNB and PLND, and 101 patients (80%) with high-grade EC also underwent PALND. Sentinel lymph node detection rates were 97.4%per patient (95%CI, 93.6%-99.3%), 87.5%per hemipelvis (95%CI, 83.3%-91.0%), and 77.6%bilaterally (95%CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the SLNB algorithm, yielding a sensitivity of 96%(95%CI, 81%-100%), a false-negative rate of 4%(95%CI,

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021				
	Blinding: Blinding was not performed **Inclusion of clinical information:** Yes **Dealing with ambiguous clinical findings:** /	0%-19%), and a negative predictive value of 99%(95%CI, 96%-100%). Only 1 patient (0.6%) was misclassified by the SLNB algorithm. Seven of 27 patients with node-positive cancer (26%) were identified outside traditional PLND boundaries or required immunohistochemistry for diagnosis. **Author conclusions:** In this study, SLNB had acceptable diagnostic accuracy compared with lymphadenectomy for the detection of nodal metastatic disease in high-grade EC. On the basis of this study and the existing literature, SLNB appears to be a viable option for the surgical staging of both low- and high-grade EC.		
Methodical Notes				
Funding Sources: Dr Clarke reported receiving personal fees from AstraZeneca outside the submitted work. No other disclosures were reported. **COI:** This study was supported by the Princess Margaret Cancer Foundation of Princess Margaret Cancer Centre (Toronto, Ontario) and the McArthur Research Fund of the Department of Obstetrics and Gynecology at the University of Toronto (Toronto, Ontario). Dr Cusimano is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship and American College of Surgeons Resident Research Scholarship. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Prospective cohort study with consistently applied reference standard but without blinding** Article submitted by hand search.				

Cusimano, M. C. et al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. JAMA Surg. 156. 157-164. 2021			
Limitations: -Blinding was not performed			

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 Study type: Prospective cohort study.	Funding sources: None. Conflict of Interests: None. Randomization: - Blinding: - Dropout rates: n.s.	**Total no. patients:** 519 patients with early stage endometrial cancer **Recruiting Phase:** November 2010 to December 2015 **Inclusion criteria:** Histological diagnosis of endometrial carcinoma who underwent SLN mapping procedure followed by surgical staging at L`Hotel-Dieu de Quebec Hospital **Exclusion criteria:** -	**Interventions:** adjuvant treatment (chemotherapy and radiotherapy) **Comparison:** Brachytherapy
Notes:	Oxford CEBM Level of evidence: EL 3		

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017		
	Limitations/Notes: - small groups - one study group, results based on staging (not a cohort study in the original design) - no stratification **Author's conclusion:** Patients with endometrial cancer found to have SLN ITCs have an excellent outcome. The use of adjuvant treatment should be tailored to uterine factors and histology and not solely based on the presence of ITCs. Patients with ITCs and otherwise low risk uterine disease probably derive little benefit from receiving additional treatments. More studies are needed to confirm our data.	
Outcome Measures/results	**Primary** progression free survival (PFS), overall survival (OS) **Secondary** -	**Results:** Median age was 64 years. All patients were staged surgically (by laprotomy (47%), laparoscopy or laparoscopy assisted vaginal surgery (33%), robotic surgery (20%). Cancer type: 86% endometrial cancer, 6.9% serous cancer, 4.2% carcinosarcoma. Grade: 79% either grade 1 or 2, 21% grade 3. FIGO stage: 62.4% stage IA, 20.2% stage IB, 2.5% stage II, 3.2% IIIA, 0.4 IIIB, 6.9% IIIC1, 2.1% IIIC2, 2.1% stage IV. 85 patients (16.4%) had SLN metastases (43 (51%) macrometastasis, 11 (13%) micrometastasis, 31 (36%) ITC. ITC patients received significant less chemotherapy (p=0.0001) and WRT (p=0.007) compared to patients with macrometastasis. Median follow up was: 29 months (0-67): PFS for ITC patients was 95.5%, similar to node negative (87.6%) and micrometastasis patients (85.5%) at three years. And it was statistically better than patients with macrometastasis (58,5%) (p=0.0012). Only 1 of 31 patient with ITC

Plante, M. et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 146. 240-246. 2017			
		recurred despite adjuvant treatment. None of the ITC patients with endometrioid histology recurred and none of the ITC patients who did not received adjuvant treatment or VBT recurred.	

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study (SEER database)	**Funding sources:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. **Conflict of Interests:** see funding surces **Randomization:** - **Blinding:** -	**Total no. patients:** 103,103 patients with endometrial cancer identified from the SEER database of the National Cancer Institute (USA) were identified. Analysed were 11.603 patients. **Recruiting Phase:** 2004-2013 **Inclusion criteria:** Patients with endometrium as the primary site and endometrial cancer malignancy as the disease classification; grade 1 endometrial cancer; focused on early-stage endometrial cancer, in which total hysterectomy – with/without bilateral salpingo-oophorectomy – is the most common type of surgery.	**Interventions:** Lymphadenectomy (total hysterectomy – with/without bilateral salpingo-oophorectomy) **Comparison:** -

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019			
	Dropout rates: -	**Exclusion criteria:** Patients with more than one primary site, only a clinical diagnosis, other disease stages and survival times less than 3 months.	
Notes:	Oxford CEBM Level of evidence: EL 4 (retrospective, cohort study) Limitations: - The authors stated, that the lack of significance after matching may be due to the small number of patients after matching. - high loss rate (not specified by the authors) - some relevant medical information (depth of myometrial invasion, time to recurrence, and subsequent surgical and medical therapies) are noch available due to the retrospective approach - number of patients for lymph node biopsies ist very small - only one cohort (patient group)- not a cohort study in the original meaning. **Author's conclusion:** In conclusion, using SEER database, we found that for all stage IA patients, most patients died of cardiovascular disease (27%) and diabetes (8%); lymphadenectomy has no influence on survival and sentinel lymph node biopsies can reduce the number of lymph node removed but have no effect in survival. Given that practice patterns have shifted in the world to predominantly sentinel node biopsy, we think our manuscript applicable to current clinical practice		
Outcome Measures/results	**Primary** Survival **Secondary** cause of death spectrum, the effect of sentinel lymph node	**Results:** Mean age at diagnosis was 56.5 years old. 22.83% of the women analyzed died from endometrial cancer; other sources were: cardiovascular disease (27%), diabetes (8%) and respiratory diseases (3%). But as the differentiation of the cancer became worse, more women died from the cancer.	

Zheng, Y. et al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. Future Oncol. 15. 2251-2266. 2019		
	biopsy and adjuvant therapies.	Overall survival - multivariant analysis: - age and grade were crucial factors in terms of survival, and a younger age and lower grade were associated with a better prognosis ($p < 0.0001$). - Asian women had better survival times than white women and black women ($p < 0.0001$) - no significant influence can be found for geographic region or number of removed lymph nodes. - lymphadenectomy can increase survival in grade 3/4 stage I patients ($p = 0.013$). **Sentinel lymph nodes biopsies:** Sentinel lymph nodes biopsy could reduce the number of lymph node removed (12 vs 6, $p = 8.387e-10$ in Wilcox test), but had no effect on survival (n=102 patients). Propensity score Matching: no difference was observed in survival between the lymphadenectomy group & the nonlymphadenectomy group ($p = 0.93$ and 0.65 respectively).

2.50. Schlüsselfrage 58 (neue Schlüsselfrage): Welchen Stellenwert hat die molekular-pathologische Klassifikation ProMisE hinsichtlich der Indikationsstellung der Strahlentherapie?

Inhalt: *3 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
León-Castillo, A. 2020	2	RCT (phase-III-trial, molecular analysis)
Stelloo, E. 2016	3	Post-Hoc Analysis of two RCTs (PORTEC-1 and -2 trials)
Wortman, B. G. 2018	3	RCT (Multicenter-phase 3 trial; ongoing- results of pilot phase)

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (phase-III-trial, molecular analysis) **Number of Patient:** FFPE tissue samples of 423 patients of the PORTEC-3 trial! **Recruitung Phase:** n.a. **Inclusion Criteria:** Patients with high-risk EC (endometrioid EC [EEC] grade 3 stage IA with documented lymphovascular space invasion [LVSI]; EEC grade 3 stage IB; EEC stage II-III; and nonendometrioid invasive EC stages I, II, or III).	**Intervention:** Of the original PORTEC-trial: Abdominal or laparoscopic hysterectomy with bilateral salpingooophorectomy was performed on all patients. Combined adjuvant chemotherapy and EBRT (CTRT, (2 cycles of cisplatin followed by 4 cycles of carboplatin and paclitaxel)) versus EBRT alone. **In this follow-up analysis:** Immunohistochemical staining for p53 and MMR proteins (MLH1, PMS2, MSH2, and MSH6) was performed on all cases. If p53 immunohistochemistry was not evaluable, TP53 mutational status was used (n 5 9; 2.1% of the total 423 EC cases). If MMR immunohistochemistry was not evaluable, microsatellite instability (MSI) was assessed (n 5 8; 1.9%). Tumors with >1 classifying feature (multiple-classifier EC) were allocated in 1 of the 4 molecular subgroups. ECs with a pathogenic POLE EDM with p53 abnormal expression and/or MMR protein loss were classified as POLEmut EC, whereas ECs with loss of any MMR protein or MSI-high with a p53 mutant staining	**Primary:** RFS, defined as time from randomization to date of first relapse or death, whichever occurred first. **Secondary:** The secondary end point was overall survival (OS), defined as the time from randomization to date of death of any cause. **Results:** Molecular testing was successful for 410 tumors (=97%). Patient and tumor characteristics of these 410 ECs were comparable to the original trial population. Median follow-up was 6.1 years (range, 0.52-11.03 years). Tumors were classified: 1. 93 (22.7%) were p53abn 2. 51 (12.4%) were POLEmut 3. 137 (33.4%) were MMRd 4. 129 (31.5%) were NSMP ECs. The respective five-year RFS for patients was: - p53abn EC: 48%

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020			
Exclusion Criteria: n.s.	pattern were classified as MMRd EC. **Comparison:** See Intervention.	- POLEmut EC: 98% - MMRd EC: 72% and - NSMP EC: 74% (P <.001) The 5-year RFS with CTRT versus RT for p53abn EC was 59% versus 36% (P = .019); 100% versus 97% for patients with POLEmut EC (P = .637); 68% versus 76% (P = .428) for MMRd EC; and 80% versus 68% (P = .243) for NSMP EC. **Author's Conclusion:** In conclusion, our study shows the strong prognostic information the EC molecular classification carries, as well as its great potential to guide adjuvant treatment. It is essential to implement the molecular EC classification in clinical diagnostics and decision-making. Patients with p53abn EC may be considered for adjuvant treatment including chemotherapy, whereas adjuvant treatment de-escalation should be considered for those with POLEmut EC; additional studies are needed especially for MMRd and NSMP EC. Future clinical trials should include molecular subgroups in their design and study specific targeted adjuvant treatments.	
Methodical Notes			

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020

Funding Sources: Supported by the Dutch Cancer Society (KWF Kankerbestrijding; Grant No. 10418/2016-1 [T.B.]). E.J.C. is supported by National Institute for Health Research Manchester Biomedical Research Centre (Grant No. ISBRC-1215-20007).

COI: Declared online-

Randomization: Patient allocation in the original trial was performed randomly 1:1 to EBRT alone or CTRT.

Blinding: Sequencing and immunohistochemistry results were evaluated blinded for patient outcome.

Dropout Rate/ITT-Analysis: If ≥ 1 of the molecular features (p53, MMR, and/or POLE status) could not be determined (eg, not enough tumoral material or testing failed), and thus the molecular subgroup could not be determined, the case was classified as EC, not otherwise specified and excluded from the study (n = 13).
ITT was done, but data not shown.

Notes:
Oxford CEBM Level of Evidence (2011): EL 2 (randomized trial)

This study was not a standard RCT, but a follow up molecular analysis. Limiting factor may be the small study groups, discussed by the authors.

Wortman, B. G. et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 151. 69-75. 2018

Population	Intervention - Comparison	Outcomes/Results

Wortman, B. G. et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 151. 69-75. 2018

Evidence level: 3

Study type: RCT (Multicenter-phase 3 trial; ongoing- results of pilot phase)

Number of Patient: 50 (a total of 500 is planned).

Recruitung Phase: Started in June 2016. A total of 500 evaluable patients will be enrolled. The
first 50 patients who were randomized in the PORTEC-4a trial were included in the pilot phase of the study to evaluate patient acceptability and feasibility of logistics, where after recruitment continued for the main trial endpoints.

Inclusion Criteria: Women are eligible for the trial when diagnosed with high intermediate risk (HIR) endometrial cancer, defined as: endometrial cancer of either (1) FIGO stage IA (with invasion) and grade 3; (2) FIGO stage IB grade 1 or 2 with age ≥60 and/or LVSI; (3) FIGO stage IB grade 3 without LVSI; or (4) FIGO stage II (microscopic) and grade 1. Eligible patients

Intervention: Treatment in the experimental arm is based on the molecular integrated risk profile: women with a favorable profile are observed after surgery; those with an intermediate profile receive VBT; and those with an unfavorable risk profile receive EBRT (to a total dose of 45–48.6 Gy in 1.8–2 Gy daily fractions, 5 times a week, using CT-based IMRT or VMAT.

Comparison: Women in the standard arm and those with an intermediate profile in the experimental arm will receive VBT to the vaginal vault (target volume including the upper 3.5–4 cm of the proximal vagina) with a vaginal cylinder and a high-dose-rate (HDR) afterloader. The VBT dose is 21 Gy HDR in 3 fractions of 7 Gy, specified at 5 mm from the applicator surface and top, 5–7 days apart, with an overall treatment time of 2 weeks.

Primary: 5-year cumulative incidence of vaginal recurrence.

Secondary: Pelvic and distant recurrence rates, 5-year vaginal control rate including treatment for relapse, 5-year recurrence-free and overall survival, adverse events, patient-reported symptoms and quality of life, and endometrial cancer-related healthcare costs.

Results: Endpoints for the pilot phase are patient acceptability of the trial and feasibility of obtaining the molecular-integrated profile within two weeks after randomization.
The first 50 patients were included between June 10th 2016 and June 12th 2017, in 10 radiation oncology centers in The Netherlands.

In the first year, 145 eligible women were informed about the trial at 13 centers, of whom 50 (35%) provided informed consent. Patient accrual ranged from 0 to 57% per center. Most common reasons for not participating were: not willing to participate in any trial (43.2%) and not willing to risk

Wortman, B. G. et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 151. 69-75. 2018			
have had surgery using laparoscopic or abdominal hysterectomy and bilateral salpingo-oophorectomy (with or without pelvic lymphadenectomy) and a WHO-performance status of 0–2. **Exclusion Criteria:** Exclusion criteria are non-endometrioid type endometrial cancer, uterine sarcoma, a history of malignancy within 5 years, previous pelvic radiotherapy and an interval of N8 weeks between surgery and start of radiotherapy.		receiving no adjuvant treatment (32.6%). Analysis of the pathology database showed an average time between randomization and determination of the molecular-integrated risk profile of 10.2 days (1–23 days). In 5 of the 32 patients (15.6%), pathology review took N2 weeks. **Author's Conclusion:** In conclusion, the PORTEC-4a trial design has been proven feasible by assessment of the pilot phase and recruitment is ongoing. PORTEC4a is the first trial to assess the use of an integrated molecular profile to determine adjuvant treatment, and other studies using molecular based treatment are eagerly awaited.	
Methodical Notes			
Funding Sources: This study is supported by the Dutch Cancer Society (UL 2011-5336 amended version). **COI:** None. **Randomization:** Eligible woman were randomly allocated (1:2) to VBT or the experimental arm using a biased coin minimization procedure with stratification for participating center, tumor grade and type of surgery.			

Wortman, B. G. et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 151. 69-75. 2018

Blinding: No.

Dropout Rate/ITT-Analysis: For a total of 500 evaluable patients, with 334 in the experimental arm and 167 patients in the standard arm, the estimated power (based on 10.000 simulations) is 84.4% ($\alpha = 0.05$).

Notes:
Oxford CEBM Level of Evidence: EL 3 (description of pilot phase).

This is an ongoing trial and the current publication describes the results of the pilot phase, focusing on pro/con of patient recruiting and time management of the laboratory analyses. So the clinical impact is low at the moment.

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *1 Bewertung(en)*

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016			
Population	Intervention	Outcomes/Results	
Evidence level: 3 **Study type:** Post-Hoc Analysis of two RCTs (PORTEC-1 and -2 trials) **Number of Patient:** 947 available early-stage endometrioid endometrial carcinomas from the PORTEC-1 and -2 trials **Recruitung Phase:** PORTEC-1 (1990–1997), PORTEC-2 (2000–2006) **Inclusion Criteria:** PORTEC-1 included patients with stage I endometrial carcinoma, grade 1 or 2 with deep myometrial invasion, or grade 2 or 3 with superficial invasion PORTEC-2 included endometrial carcinoma patients with high-intermediate risk features: stage I, age	**Intervention:** Prognostic significance of the proposed molecular classification tool in early-stage endometrioid endometrial carcinomas. Analysis of MSI, hotspot mutations in 14 genes including POLE, protein expression of p53, ARID1a, b-catenin, L1CAM, PTEN, ER, and PR **Comparison:** /	**Primary:** Prognostic value **Secondary:** / **Results:** Molecular analyses were feasible in >96% of the patients and confirmed the four molecular subgroups: p53-mutant (9%), MSI (26%), POLE-mutant (6%), and NSMP (59%). Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Approximately 15% of highintermediate risk patients had unfavorable features (substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM), 50% favorable features (POLE-mutant, NSMP being microsatellite stable, and CTNNB1 wild-type), and 35% intermediate features (MSI or CTNNB1-mutant). **Author's Conclusion:** Integrating clinicopathologic and molecular factors improves the risk assessment of patients with early-stage endometrial carcinoma. Assessment of this	

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016			
>60 years, grade 1–2 with deep invasion, or grade 3 with superficial invasion and stage IIA disease (except grade 3 with deep invasion). Post-hoc analysis: All tumor samples with confirmed endometrioid histology were included in the current analysis. **Exclusion Criteria:** n.a.		integrated risk profile is feasible in daily practice, and holds promise to reduce both overtreatment and undertreatment.	
Methodical Notes			
Funding Sources: This study was supported by the Dutch Cancer Society (UL2012-5719). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact. Clinical Trial Tissue Samples: Translational research was performed on tissue samples from two randomized clinical trials (PORTEC-1 and PORTEC-2). PORTEC-2 trial register number is ISRCTN16228756 and PORTEC-1 was conducted before time of trial registries. Both trials were supported by grants from the Dutch Cancer Society (CKTO 90-01 and CKTO 2001-04). **COI:** None. **Randomization:** Yes. **Blinding:** Blinding was performed in this post-hoc analysis.			

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016

Dropout Rate/ITT-Analysis: n.a.

Notes: Oxford CEBM Level of Evidence 2011: EL 3 Post-Hoc analysis of two RCTs
Article submitted by hand search

2.51. Schlüsselfrage 59 (neue Schlüsselfrage): Welche zusätzlichen operativen Maßnahmen, z.B. Omentektomie, z.B. multipler peritoneale Biopsie, sind bei Typ-II-Karzinomen indiziert?

Inhalt: *1 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Versluis, M. A. C. 2018	3	Retrospective Cohort Study

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 3 **Study type:** Retrospective Cohort Study	Funding sources: n.s. Conflict of Interests: None Randomization: - Blinding: - Dropout rates: -	**Total no. patients:** 1.140 patients diagnosed with UCS undergoing primary surgery with a curative intent - from the Netherlands Cancer Registry (NCR) and PALGA (Nationwide Network and registry of histo- and cytopathology in the Netherlands. **Recruiting Phase:** January 1, 1993, and December 31, 2012. **Inclusion criteria:** Patients diagnosed with uterine carcinoma as identified by corresponding ICD-O-3 codes (C54; C55 combined with morphological code 8950, 8951, or 8980) **Exclusion criteria:** Patients who did not undergo primary surgery defined as TAH-BSO with or without LND.	**Interventions:** LND with or without RT and/or CT LND was defined as the removal of any number of nodes. **Comparison:** see intervention.

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018		
Notes:	Oxford CEBM Level of Evidence: EL 3 (Non-randomized cohort) Limitations: -Patients are noch equally distributed over the analyzed groups, this may influence the results. - only one cohort group (not a cohort study in the original design) **Author's conclusion:** Conclusion: LND is related to improved survival when more than 10 nodes are removed. Adjuvant therapy improves survival when LND is omitted, or when nodes are positive.	
Outcome Measures/results	**Primary** Overall survival (OS) was defined as the time until death, with a maximum of 5 years. Disease free survival (DFS) was defined as the time until recurrence or death, with a maximum of 5 years. **Secondary** -	**Results:** Median age at diagnosis was 70 years. The majority (64%) of the patients was diagnosed with early-stage disease (FIGO stage 1–2). The median number of nodes removed was 12 (IQR 3–18). LND was related to higher FIGO stage and age below 70 years ($p < 0.001$). 622 patients received adjuvant treatment (77.8% received RT, 16.7% received CT, and 5.5% received RCT). Survival analysis: Multivariant analysis (Corrected for adjuvant therapy, FIGO stage, age below/above 70 years, myometrial invasion, and distant metastasis) LND >10 was an independent predictor of OS (HR 0.65, 95% CI 0.48–0.87). LND ≤10 was not related to OS (HR 0.83, 95% CI 0.65–1.05). Adjuvant therapy was also related to improved OS. RT and CT had similar HRs of 0.64 (95% CI 0.54–0.75) and 0.65 (95% CI 0.48–0.88), respectively. RCT had an HR of 0.25 (95% CI 0.13–0.46). The results were similar for DFS, with LND > 10 and adjuvant treatment related to improved DFS. Stratified by lymph node status: Adjuvant treatment was not related to OS when the nodes were negative. Positive nodes: adjuvant treatment was related to improved OS, with an HR of 0.17 (95% CI 0.07–0.39) for RT, an HR of 0.40 (95% CI 0.19–

Versluis, M. A. C. et al. Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. Oncology. 95. 100-108. 2018		
		0.84) for CT, and an HR of 0.04 (95% CI 0.03–0.18) for RCT.

2.52. Schlüsselfrage Endometriumkarzinom Biomarker und Risikofaktoren

Inhalt: *17 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Aird, J. J. 2020	4	Retrospective analysis of biopsies and resections
Asano, H. 2020	4	Retrospective analysis
Bosse, T. 2018	4	Genetic association study (cohort of patients from 6 centers) To investigate whether molecular classification can be used to refine prognosis in grade 3 endometrioid endometrial carcinomas (EECs).
Carr, C. 2020	4	Retrospective cohort study
Coll-de la Rubia, E. 2020	3	Systematic Review and Meta-Analysis
Conlon, N. 2020	4	Retrospective analysis
Costigan, D. C. 2020	4	Retrospective analysis
Guo, M. 2021	3	Systematic Review and Meta-Analysis of retrospective cohort studies
He, Y. 2020	2	Systematic Review and Meta-Analysis of retrospective cohort studies (6 studies)

Literaturstelle	Evidenzlevel	Studientyp
Jones, N. L. 2020	4	Retrospective analysis
Kandoth, C. 2013	3	Cross-sectional, prognostic cohort study
Kir, G. 2020	4	Consecutive case study.
Kommoss, S. 2018	3	Retrospective prognostic cohort study.
León-Castillo, A. 2020	2	RCT (phase-III-trial, molecular analysis)
Raffone, A. 2020	2	Systematic review and meta-analysis (10 cohort studies, retrospective and prospective). Define 1) the diagnostic accuracy of MMR proteins immunohistochemistry as surrogate of MSI molecular assay in endometrial carcinoma and 2) whether a combination of only two MMR proteins may be used instead of all the four MMR proteins to reduce the costs, through a systematic-review and meta-analysis.
Raffone, A. 2020	2	systematic review and meta-analysis (3 cohort studies)
Stelloo, E. 2016	3	Prognostic cohort study of two RCTs (PORTEC 1 and PORTEC 2) to confirm and validate the prognostic significance of the proposed molecular classification tool in early-stage endometrioid endometrial carcinomas (EEC).

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *5 Bewertung(en)*

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis **Databases:** Medline **Search period:** 1991 to February 2020 **Inclusion Criteria:** (1) studies including endometrial cancer with an epithelial origin; (2) biomarker studies performed at protein level; (3) prognostic biomarker studies, i.e., studies that identify or validate biomarkers that are associated to EC risk factors, recurrence or survival; (4) studies performed on any biological human sample, but not on cultured cells or animal models; (5) studies based on the expression of biomarkers. **Exclusion Criteria:** (1) not written in English; (2) based on the characterization of one specific EC subtype; (3) based on response-to-	**Population:** Patients with endometrial cancer with an epithelial origin **Intervention:** All protein biomarkers associated with clinical prognostic factors of EC, recurrence and survival. **Comparison:**	**Primary:** Overall survival **Secondary:** **Results:** The majority of biomarkers identified in this systematic review were associated with histological grade, FIGO stage and OS, with more than 100 biomarkers described for each of these parameters. Other biomarkers were associated with lymph node status, histological type, myometrial invasion, LVSI, DFS, recurrence, DSS, PFS, risk, RFS, metastasis, cervical invasion and the TCGA subgroups. The vast majority of biomarkers are related to more than one of the above-mentioned parameters, indicating that they provide relevant prognostic information but are not specifically linked to one feature in particular. In fact, those that were associated with a specific parameter generally corresponded to those biomarkers that have been scarcely studied. List of proteins associated with each prognostic factor: See full text article Figure 6	398 studies were included.

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020				
treatment biomarkers; (4) articles performed using less than 10 samples in total; (5) reviews, meta-analyses, opinion articles or case report studies.		Results of the meta-analysis on OS of the five most studied proteins The number of investigations meeting our criteria for the estimation of HR was low, ranging from five to seven articles per protein. Substantial heterogeneity in the HRs across studies was observed for MUC16 and PGR, where the point estimates of the pooled HR and the 95% CI from the fixed and random effects model were wide. On the contrary, in ESR1, TP53, and WFDC2 the point estimates and the error margins were similar. Focusing on the data available, there is not enough evidence to affirm that MUC16 and PGR are useful EC prognostic biomarkers. However, articles studying ESR1, TP53 and WFDC2 point out these biomarkers as promising to be prognosticators of OS. Specifically, a pooled HR estimation of 3.51 [2.22; 5.57] for ESR1, 2.80 [2.00; 3.92] for TP53, and 4.56 [2.32; 9.00] for WFDC2 was obtained. Remarkably, WFDC2 has higher HR and 95% CI than ESR1 and TP53, making this protein a good and easy-to-assess biomarker, since it has been identified in serum samples (Figure 8A).		

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020

		Author's Conclusion: Here, we systematically reviewed the literature for EC prognostic biomarkers at the protein level and compiled a list of 255 proteins, although 79% of those proteins would require further validation. The only proteins that have been extensively studied are carbohydrate antigen 125 (CA125 or MUC16), human epididymis protein 4 (HE4 or WFDC2), estrogen receptor (ESR1) and progesterone receptor (PGR), mismatch repair proteins (MMR proteins: MSH2, MSH6, MHL1, PMS2), the tumor suppressors PTEN and TP53, the cell adhesion molecules E-cadherin (CDH1) and neural cell adhesion molecule L1 (L1CAM), the proliferation marker protein Ki-67 (KI67), and the Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2). On the basis of our meta-analysis, ESR1, TP53 and WFDC2 may be useful prognosticators for OS of EC. We also identified critical conceptual, methodological and analytical factors that need to be improved in further research. Consequently, we encourage the scientific community to follow these considerations in order to successfully identify clinically valuable EC prognostic biomarkers: (i) design studies whose primary aim is the identification of prognostic biomarkers. Thus, patient selection should be balanced		

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020				
		and controlled to achieve this objective, and the sample of the study source of biomarkers should be carefully chosen; (ii) include high-throughput technologies such as MS to have a broad analysis of biomarkers and to have the feasibility to develop biomarker panels; (iii) the statistical analysis in every step of the biomarker pipeline should be thoughtfully performed.		
Methodical Notes				
Funding Sources: This work was supported by CIBERONC (CB16/12/00328), the “Fondo Europeo de Desarrollo Regional” FEDER (RTC-2015-3821-1), the Asociación Española Contra el Cáncer (GCTRA1804MATI), Grups consolidats de la Generalitat de Catalunya (2017 SGR-1661) and the Instituto de Salud Carlos III (DTS17/00146, PI17/02071 and PI17/02155; and the IFI19/00029 to E.C.-d.l.R), and a PERIS grant funded EColas (SLT002/16/00315) from Generalitat de Catalunya. EM-G was supported by a grant from Télévie awarded to G.D. (F5/20/5-TLV/DD). **COI:** None. **Study Quality:** The guidelines from Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) were used to evaluate the quality of studies that were eligible. **Heterogeneity:** Pooled estimates of the HR (overall-eect model), and statistics I2 and tau-squared were computed following the guidelines of Doing Meta-Analysis in R. Substantial heterogeneity in the HRs across studies was observed for MUC16 and PGR, where the point estimates of the pooled HR and the 95% CI from the fixed and random effects model were wide				

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020			
Publication Bias: Publication bias was not investigated **Notes:** **Article included through handsearch** Oxford CEBM Level of Evidence 2011: EL 2 Systematic review and meta-analysis of observational studies **Downgrading to EL 3 due to methodical weakness:** -Only one database was searched -No search for grey literature or unpublished studies was conducted -Unclear, if screening and data extraction was performed by two authors -Publication bias was not investigated -No overview of the included studies. It is unclear which study design the studies have -Quality assessment was performed but the results were not provided. Therefore the quality of the included studies is unclear -Substantial heterogeneity was present in the meta-analysis, which was not further explored in subgroup or sensitivity analyses			
Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies **Databases:** PubMed, MEDLINE, EMBASE, and	Population: Women with endometrial cancer Intervention: L1CAM	**Primary:** OS and DFS **Secondary:** Clinicopathological characteristics **Results:** Overall, 17 studies encompassing 7146	17 studies included, see full text article.

Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021				
Web of Science **Search period:** Inception to June 2019 **Inclusion Criteria:** studies on women with endometrial cancer, confirmed by pathological examination; Studies on quantitative data of hazard ratios (HRs) for overall survival (OS) and disease-free survival (DFS), and odds ratios (ORs) for clinicopathological characteristics; and studies in which the detection techniques and cut-off values for L1CAM expression were provided. **Exclusion Criteria:** The exclusion criteria were as follows: case reports, reviews, letters, and other studies without sufficient data; non-English articles; and single-arm or multiple-arm studies.	Comparison:	patients were eligible for the meta-analysis. **Overall survival** Nine studies (5116 patients) reported the HRs for OS. The pooled results indicated high L1CAM expression to be associated with decreased OS in patients with endometrial cancer (HR 2.87, 95% CI 1.81–4.55, P **Disease free survival** Eight studies (3970 patients) reported the HRs for DFS. The pooled results indicated high L1CAM expression was associated with decreased DFS in patients with endometrial cancer (HR 3.32, 95% CI 1.99–5.55, P **Association between L1CAM expression and clinicopathological characteristics in women with endometrial cancer** Fifteen studies reported dichotomous data for clinicopathological characteristics. A high L1CAM expression was positively associated with disease grade (OR=3.57, 95% CI 2.05–5.14, P P 0.05, P<.001)		

Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021

		Author's Conclusion: This systematic review demonstrated that high L1CAM expression is correlated with poor survival outcomes and adverse clinicopathological parameters in patients with endometrial cancer.		

Methodical Notes

Funding Sources: Not described.

COI: None.

Study Quality: Not investigated

Heterogeneity: Heterogeneity across trials was measured by the X2-based Q test and I2 statistics When a P50% indicated statistically significant heterogeneity across the studies, the effect sizes were measured using a random-effect model; otherwise, a fixed-effect model was used. We conducted sensitivity analysis and subgroup analysis to validate stability of the pooled effect sizes and explore the possible origins of heterogeneity.

A subgroup analysis was conducted to investigate the origin of high heterogeneity for the outcome OS(I 2= 82.6%, P=.478). We observed a significant relationship between high L1CAM expression and decreased OS in the following subgroups: the detection method (immunohistochemistry vs others), cut-off value (10% vs others), and FIGO stage (I–III vs I– IV). However, in subgroup analysis based on study region and sample size, significant results were observed in European group (HR 2.43, 95% CI 1.97–2.99, P

Subgroup analysis was conducted to investigate the origins of high heterogeneity for the outcome DFS(I 2=83.5%,P=.545). We observed a significant relationship between high L1CAM expression and decreased DFS in the following subgroups: study region (European vs non-European), sample size (<

Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021

200 vs≥ 200), detection method (immunohistochemistry vs others), cut-off value (10% vs others), and FIGO stage (I–III vs I–IV).

We conducted a sensitivity analysis by sequentially omitting each study from the analysis. Results showed that the study by Zeimet et al[20] led to the statistical heterogeneity in the primary outcomes (OS and DFS; Fig. 3). When this study was omitted, the pooled results showed high L1CAM expression to be associated
with decreased OS (HR 2.46, 95% CI 2.02–3.00, P
fixed model, resulting in I2=18.6% and P=.272 for OS and I2=0.0% and P=.954 for DFS.

Publication Bias: We also generated a Begg funnel plot and performed Egger test to investigate potential publication bias in the meta-analysis. Symmetry in the funnel plot was observed for both OS (P=.436 for Begg test and P=.400 for Egger test)
and DFS (P=.721 for Begg test and P=.214 for Egger test).

Notes:
Oxford CEBM Level of Evidence 2011: Systematic Review and Meta-Analysis of retrospective cohort studies

Downgrading to EL 3 due to methodical weakness:

-Quality of the included studies was not investigated
-Substantial heterogeneity was present for the main outcomes, which waa further explored in subgroup and senstivity analyses

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020

Evidence level: 2 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies (6 studies) **Databases:** PubMed,Web of Science, data of China National Knowledge Infrastructure, Wan fang Medical Network **Search period:** **Inclusion Criteria:** (1) Literatures including POLE-mutant EC patients who were tested by gene sequencing; (2) At least included 5 POLE-mutant EC cases; (3) Enough data such as Federation of International of Gynecologists and Obstetricians (FIGO) pathological staging group, differentiation degree, lymphatic vessel invasion group, histology type, depth of myometrial invasion, European Society for Medical Oncology (ESMO) risk stratification can be extracted from the included studies; (4) Sufficient data to calculate hazard ratio (HR), odds ratios (ORs), and 95% confidence interval (CIs) are available **Exclusion Criteria:** (1) Studies without enough data (the above-mentioned) for calculation; (2)	**Population:** POLE-mutant endometrial cancer patients who were tested by gene sequencing **Intervention:** **Comparison:** Patients without POLE-mutant endometrial cancer	**Primary:** Overall survival, progression-free survival, histological type, tumor grade, FIGO stage, LVSI, myometrial invasion, lymph node status, ESMO risk stratification **Secondary:** **Results:** Six cohort studies assessing 179 EC patients with POLE EDMs were included. **Overall survival** Six studies provided the data for OS among 371 POLE-mutant EC patients. The estimated HR for OS was 0.68 (95% CI=0.41–1.13), indicated a favorable OS was associated with POLE-mutant EC patients. **Progression free survival** Only 2 studies provided appropriate data for analysis of PFS. The overall result of HR was 0.32 (95% CI: 0.09–1.18), indicated a reduced PFS	6 retrospective cohort studies included: Cosgrove et al. 2018, Kommoss et al. 2018, Talhouk et al. 2017, Stelloo et al. 2016, Billingsley et al. 2016, Talhouk et al. 2015

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020				
Patients were not confirmed by EDM sequencing; (3) Duplicated publications or data; (4) Papers published in other languages other than English or Chinese. (5) Commentaries, single case reports, editorials, review articles, letters to the editor, and unrelated articles.		was associated with POLE-mutant EC patients. **FIGO stage in POLE-mutant EC** Four articles were selected for analyzing the association of FIGO stage with POLE mutations. The pooled OR was 0.34 [0.12–0.94] (P=.04), indicating that most of POLE mutations are FIGO I comparing to FIGO IIIV. No statistical significant differences were found for LVSI in POLE-mutant EC, Myometrial invasion in POLE-mutant EC, Lymph node status in POLE-mutant EC and for ESMO risk stratification in POLE-mutant EC, Histological type in POLE-mutant EC, Tumor grade in POLE-mutant **Author's Conclusion:** This meta-analysis has confirmed POLE EDMs may serve as a predictive biomarker of favorable prognosis. Further studies are needed to explore the		

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020

		appropriate clinical utility of POLE EDMs in EC.		

Methodical Notes

Funding Sources: This work was supported by the Scientific Research Funding of Tianjin Science and Technology Committee (17ZXMFSY00160).

COI: None.

Study Quality: The methodological quality of the included 6 studies was evaluated by Review manager 5.3, indicating the general quality was good as is shown in Figure 11.

Heterogeneity: Heterogeneity was assessed by I2 inconsistency test and chi-squared-based Cochran Q statistic test; I2>50% or Ph.1, the fixed effect model was used.
Significant heterogeneity was present for FIGO stage (I^2 = 58%), LVSI (I^2 = 94%), myometrial invasion (I^2 = 52%), lymph node status (I2 = 71%), ESMO risk stratification (I2 = 58%)

Publication Bias: Less than ten studies were included.

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review of retrospective cohort studies

Limits:
-Significant heterogeneity was present for FIGO stage (I^2 = 58%), LVSI (I^2 = 94%), myometrial invasion (I^2 = 52%), lymph node status (I2 = 71%), ESMO risk

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020			
stratification (I2 = 58%) -Small sample size			
Raffone, A. et al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. Pathol Oncol Res. 26. 1417-1427. 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (10 cohort studies, retrospective and prospective). Define 1) the diagnostic accuracy of MMR proteins immunohistochemistry as surrogate of MSI molecular assay in endometrial carcinoma and 2) whether a combination of only two MMR proteins may be used instead of all the four MMR proteins to reduce the costs, through a systematic-review and meta-analysis. **Databases:** Web of Sciences, Scopus, MEDLINE, Google Scholar,	**Population:** Endometrial carcinoma patients. **Intervention:** IHC for MMR proteins as surrogate marker for Microsatellite instability (MSI) **Comparison:** -	**Primary:** Diagnostic accuracy **Secondary:** - **Results:** Ten studies with 3097 patients were included. Out of these, 1110 were suitable for the meta-analysis. Immunohistochemistry for all the four MMR proteins showed sensitivity = 0.96, specificity = 0.95, LR + =17.7, LR- = 0.05, DOR = 429.77, and high diagnostic accuracy (AUC = 0.988). The combination of MLH1 and MSH2 showed sensitivity = 0.88, specificity = 0.96, LR + =22.36, LR- = 0.15, DOR = 200.69, and high diagnostic accuracy (AUC = 0.9838). The combination of MSH6 and PMS2 showed the same results as the complete panel of four MMR proteins.	10 studies included: Chao, Libera, Bruegl, Stelloo, McConechy, Goodfellow, Haraldsdottir, Peterson, Choi, Ollikainen

Raffone, A. et al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. Pathol Oncol Res. 26. 1417-1427. 2020				
EMBASE, ClinicalTrial.gov and Cochrane Library. **Search period:** Inception to September 2019. **Inclusion Criteria:** We included all peer-reviewed studies assessing the association between MMR proteins immunohistochemistry and MSI molecular assay in endometrial carcinoma. **Exclusion Criteria:** Exclusion criteria were: reviews; case reports; studies not allowing comparisons between immunohistochemistry and molecular analysis; sample size		**Author's Conclusion:** Immunohistochemistry for MMR proteins (MLH1, MSH2, MSH6, PMS2) is a very highly accurate surrogate of MSI molecular testing in endometrial carcinoma. A combination of MSH6 and PMS2 may allow reducing the costs without a decrease in diagnostic accuracy. These findings support the feasibility of the introduction of the TCGA classification into the common practice.		
Methodical Notes				
Funding Sources: None described. **COI:** The authors report no conflict of interest. **Study Quality:** The risk of bias within studies assessment was performed following the revised Quality Assessment of Diagnostic Accuracy Studies				

Raffone, A. et al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. Pathol Oncol Res. 26. 1417-1427. 2020

(QUADAS-2).
In the “patient selection” domain, three studies were judged at unclear risk of bias because they did not report if the patients were consecutive or randomly selected, while the remaining studies were considered at low risk. High concerns about applicability were raised for two studies (only patients with presumed Lynch syndrome were included). In the “index test” domain, two studies were considered at high risk of bias because results of MMR proteins immunohistochemistry were incompletely reported, while the remaining studies were considered at low risk. High concerns about applicability were raised for two studies (not all MMR proteins were assessed). In the “reference standard” domain, all studies were considered at low risk of bias, since results ofMSI testing and the microsatellite markers assessed were clearly reported. No concerns about applicability were raised. In the “flow and timing” domain, 3 studies were considered at unclear risk of bias, because it was unclear if all eligible patients were assessed with both index and reference standard; all the remaining studies were considered at low risk.

Heterogeneity: Statistical heterogeneity amongst the included studies was evaluated by using the Higgins I2 index, and judged as null for I2 = 0%, minimal for 0% < I2 ≤ 25%, low for 25 < I2 ≤ 50%, moderate for 50 < I2 ≤ 75% and high for I2 > 75%.
High heterogeneity for NLR was observed.

Publication Bias: Publication bias was not assessed.

Notes:
Oxford level of evidence: 2 Systematic review and meta-analysis of diagnostic cohort studies with consistently applied reference standard.
High heterogeneity for NLR was observed. Publication bias was not assessed.

Raffone, A. et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. Gynecol Oncol. 157. 252-259. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Raffone, A. et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. Gynecol Oncol. 157. 252-259. 2020				
Evidence level: 2 **Study type:** systematic review and meta-analysis (3 cohort studies) **Databases:** Web of Sciences, MEDLINE, Google Scholar Scopus, Cochrane Library, Clinicaltrials.gov and EMBASE **Search period:** Inception to May 2019. **Inclusion Criteria:** All peer-reviewed studies that allowed extraction of histopathological characteristics of each ProMisE group of EC were included in our study. **Exclusion Criteria:** Reviews and case reports were a priori defined as exclusion criteria. Studies with patient selection based on histopatholoigcal characteristics were also excluded from our analysis because they would affect overall prevalence of each histopathological characteristic in each ProMisE group.	**Population:** Women diagnosed with EC, overlapping patients were excluded. **Intervention:** ProMisE group of EC. **Comparison:** -	**Primary:** Prevalence of several histopathological characteristics in each ProMisE group of EC. These were histological grade 3 (G3), endometrioid histotype, present LVSI, deep myometrial invasion, lymph node involvement, ESMo 2013 low- and high-risk category. **Secondary:** - **Results:** Four studies with 1171 patients were included in the systematic review, out of which three studies with 912 patients were included in the meta-analysis. Pooled prevalence estimates were: - in the MMR-d group G3 = 47.4%, G1-2= 52.6% endometrioid = 85,5%, non-endometrioid = 14.2%, LVSI - present = 41.3%, - absent = 58.7%, deep myometrial invasion-present = 44.5%, - absent = 55.5%, lymph node involvement - present = 9.9%, absent - 90.1%, low-risk = 30.1%, intermediate risk = 19.9%, high risk = 50%. -in the POLE-mt group, G3 = 39,6%, G1-2= 60.4% endometrioid = 86,1%, non-endometrioid = 13.9%, LVSI - present = 32.7%, - absent = 67.3%, deep myometrial invasion-present = 27.3%, - absent = 72.7%, lymph node involvement - present = 0%, absent - 100%, low-risk = 44.1%, intermediate risk = 22.5%, high risk = 33.4%.	3 studies included: Talhouk 2015, Talhouk 2017, Kommoss 2018.	

Raffone, A. et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. Gynecol Oncol. 157. 252-259. 2020				
		Author's Conclusion: The histopathological characterization of the ProMisE groups suggests that many patients are currently undertreated or overtreated (especially in the POLE-mt and MMR-d groups).		
Methodical Notes				
Funding Sources: No financial support was received for this study. **COI:** The authors declare no conflict of interest. **Study Quality:** The methodological Index for Non-Randomized studies (MINORS) was followed to perform the risk of bias within studies assesment. All included studies were considered at low risk of bias in all domains, with the exception of "inlcusion of consecutive patients" domain. **Heterogeneity:** Statistical heterogeneity among studies was assessed by the inconsistency index I2 as previously described. Heterogeneity was categorized as well: null for I2 = 0%, minimal for I2 < 25%, low for I2 < 50%, moderate for I2 < 75% and high for I2 ≥ 75%. The random effect model of DerSimonian Laird was adopted for all analyses. The statistical heterogeneity among the included studies was high in many analysis. **Publication Bias:** Not investigated, but not feasible with three studies. **Notes:** Oxford level of evidence: 2 Systematic review of cohort studies The statistical heterogeneity among the included studies was high in many analysis, despite random effect model. No investigation of heterogeneity was performed. No study descriptives or results of individual quality assessments for each study.				

OXFORD (2011) Appraisal Sheet: RCT: *1 Bewertung(en)*

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** RCT (phase-III-trial, molecular analysis) **Number of Patient:** FFPE tissue samples of 423 patients of the PORTEC-3 trial! **Recruitung Phase:** n.a. **Inclusion Criteria:** Patients with high-risk EC (endometrioid EC [EEC] grade 3 stage IA with documented lymphovascular space invasion [LVSI]; EEC grade 3 stage IB; EEC stage II-III; and nonendometrioid invasive EC stages I, II, or III).	**Intervention:** Of the original PORTEC-trial: Abdominal or laparoscopic hysterectomy with bilateral salpingooophorectomy was performed on all patients. Combined adjuvant chemotherapy and EBRT (CTRT, (2 cycles of cisplatin followed by 4 cycles of carboplatin and paclitaxel)) versus EBRT alone. **In this follow-up analysis:** Immunohistochemical staining for p53 and MMR proteins (MLH1, PMS2, MSH2, and MSH6) was performed on all cases. If p53 immunohistochemistry was not evaluable, TP53 mutational status was used (n 5 9; 2.1% of the total 423 EC cases). If MMR immunohistochemistry was not evaluable, microsatellite instability (MSI) was assessed (n 5 8; 1.9%). Tumors with >1 classifying feature (multiple-classifier EC) were allocated in 1 of the 4 molecular subgroups. ECs with a pathogenic POLE EDM with p53 abnormal expression and/or MMR protein loss were classified as POLEmut EC, whereas ECs with loss of any MMR protein or MSI-high with a p53 mutant staining	**Primary:** RFS, defined as time from randomization to date of first relapse or death, whichever occurred first. **Secondary:** The secondary end point was overall survival (OS), defined as the time from randomization to date of death of any cause. **Results:** Molecular testing was successful for 410 tumors (=97%). Patient and tumor characteristics of these 410 ECs were comparable to the original trial population. Median follow-up was 6.1 years (range, 0.52-11.03 years). Tumors were classified: 1. 93 (22.7%) were p53abn 2. 51 (12.4%) were POLEmut 3. 137 (33.4%) were MMRd 4. 129 (31.5%) were NSMP ECs. The respective five-year RFS for patients was: - p53abn EC: 48%

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020			
Exclusion Criteria: n.s.	pattern were classified as MMRd EC. **Comparison:** See Intervention.	- POLEmut EC: 98% - MMRd EC: 72% and - NSMP EC: 74% (P <.001) The 5-year RFS with CTRT versus RT for p53abn EC was 59% versus 36% (P = .019); 100% versus 97% for patients with POLEmut EC (P = .637); 68% versus 76% (P = .428) for MMRd EC; and 80% versus 68% (P = .243) for NSMP EC. **Author's Conclusion:** In conclusion, our study shows the strong prognostic information the EC molecular classification carries, as well as its great potential to guide adjuvant treatment. It is essential to implement the molecular EC classification in clinical diagnostics and decision-making. Patients with p53abn EC may be considered for adjuvant treatment including chemotherapy, whereas adjuvant treatment de-escalation should be considered for those with POLEmut EC; additional studies are needed especially for MMRd and NSMP EC. Future clinical trials should include molecular subgroups in their design and study specific targeted adjuvant treatments.	
Methodical Notes			

León-Castillo, A. et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. . Jco2000549. 2020

Funding Sources: Supported by the Dutch Cancer Society (KWF Kankerbestrijding; Grant No. 10418/2016-1 [T.B.]). E.J.C. is supported by National Institute for Health Research Manchester Biomedical Research Centre (Grant No. ISBRC-1215-20007).

COI: Declared online-

Randomization: Patient allocation in the original trial was performed randomly 1:1 to EBRT alone or CTRT.

Blinding: Sequencing and immunohistochemistry results were evaluated blinded for patient outcome.

Dropout Rate/ITT-Analysis: If ≥ 1 of the molecular features (p53, MMR, and/or POLE status) could not be determined (eg, not enough tumoral material or testing failed), and thus the molecular subgroup could not be determined, the case was classified as EC, not otherwise specified and excluded from the study (n = 13).
ITT was done, but data not shown.

Notes:
Oxford CEBM Level of Evidence (2011): EL 2 (randomized trial)

This study was not a standard RCT, but a follow up molecular analysis. Limiting factor may be the small study groups, discussed by the authors.

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: *1 Bewertung(en)*

Aird, J. J. et al. Should you repeat mismatch repair testing in cases of tumour recurrence? An evaluation of repeat mismatch repair testing by the use of immunohistochemistry in recurrent tumours of the gastrointestinal and gynaecological tracts. Histopathology. 76. 521-530. 2020				
Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 4 **Study type:** Retrospective analysis of biopsies and resections	**Number of patients / samples:** Between 2001 and 2016, MMR IHC was performed on 4525 specimens. Local recurrence or distant metastasis were identified in 150 patients occuring at least 30 days after resection of primary tumor. **Reference standard:** N.a. **Validation:** Repeat MMR IHC was performed at the time of recurrence or had tissue available for testing. **Blinding:** Slides of the recurrences were reviewed by J.J.A. to confirm the diagnosis and to identify the best tissue block for testing. **Inclusion of clinical information:** Yes, pathological databases were screened. **Dealing with ambiguous clinical findings:** The three discordant cases all had a normal MMR profile in the primary tumour, and then loss of staining for at least	**Results:** Thirteen patients had primary tumours with dMMR, all of which showed dMMR on their recurrence. The remaining 137 primary tumours were MMR-proficient. Three of 137 (2%) initially showed a discordant staining pattern. **Author conclusions:** In conclusion, we have shown that the MMR IHC status of a primary tumour does not change in local recurrences or metastases, and we do not advocate repeating MMR IHC on recurrences when the primary tumour shows intact or normal MMR staining. Care should be taken when MMR stains are interpreted, to avoid common pitfalls – look for an internal positive control to avoid misinterpretation of poorly stained sections, be cautious in interpreting MMR IHC in postradiotherapy samples (particularly MSH6), and be mindful of subclonal loss of MLH1 in endometrial carcinomas. When repeat MMR IHC on a recurrence is requested, review of the MMR IHC in the primary tumour may be of more benefit. If equivocal		

Aird, J. J. et al. Should you repeat mismatch repair testing in cases of tumour recurrence? An evaluation of repeat mismatch repair testing by the use of immunohistochemistry in recurrent tumours of the gastrointestinal and gynaecological tracts. Histopathology. 76. 521-530. 2020				
	one marker in the recurrence. Two cases showed loss of MLH1 and PMS2 staining, and one case showed loss of MSH6 staining. After further evaluation, however, the discordances were not due to a genuine change in the MMR status, but to errors in the staining process or the interpretation of the stains.	staining patterns are identified, further testing for MSI should be strongly considered.		
Methodical Notes				
Funding Sources: n.s. **COI:** All authors declare no conflicts of interest. **Notes:** Oxford CEBM Level of evidence 2011: EL 4 (retrospective analysis of biopsies, study without reference standard)				

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *9 Bewertung(en)*

Asano, H. et al. L1CAM Predicts Adverse Outcomes in Patients with Endometrial Cancer Undergoing Full Lymphadenectomy and Adjuvant Chemotherapy. Ann Surg Oncol. 27. 2159-2168. 2020			
Population	Intervention	Outcomes/Results	
Evidence level: 4 **Study type:** Retrospective analysis **Number of Patient:** 161 patients were included in the analysis. **Recruitung Phase:** 2003 to 2015 **Inclusion Criteria:** Patients diagnosed with endometrial cancer, including endometrioid, non-endometrioid, and carcinosarcoma. **Exclusion Criteria:** Patients who did not undergo full LND; lesions were not enough to prepare FFPE-TMA; Neo-adjuvant chemotherapy; short follow-up periods (< 36 months)	**Intervention:** Immunohistochemical staining of L1CAM. **Comparison:** s.o.	**Primary:** OS (overall survival), PFS (progression free survival) **Secondary:** - **Results:** L1CAM Expression: Based on the H-score, 113 patients (70.2%) were evaluated as L1CAM negative and 48 patients (29.8%) as L1CAM-positive. Patient characteristics: Significant differences for: - median age was older in L1CAM-positive patients than L1CAM-negative patients (56 vs. 64.5 years; p Correlation between L1CAM expression and pathological risk factors: - prevalence of Grade 3 endometrioid and non-endometrioid subtype (G3/ Non-endo, 20.4% vs. 56.3%; p< 0.0001), - vascular invasion (6.2% vs. 18.8%, p = 0.0157), and - positive peritoneal washing cytology (PWC) [3.5% vs. 22.9%; p = 0.0001] was significantly more frequent in L1CAM-positive women than L1CAM-negative women. Failure pattern according to L1CAM expression:	

Asano, H. et al. L1CAM Predicts Adverse Outcomes in Patients with Endometrial Cancer Undergoing Full Lymphadenectomy and Adjuvant Chemotherapy. Ann Surg Oncol. 27. 2159-2168. 2020

		Ten of 113 cases (8.8%) in L1CAM-negative patients, and 14 of 48 cases (29.2%) in L1CAM-positive patients finally developed recurrent disease. Frequency of failure was significant higher in L1CAM positive than L1CAM negative patients (30% vs. 71.4%; p = 0.0420), and median time was significantly shorter in L1CAM positive patients (24 vs. 15 months; p = 0.0402). **Effects on survival:** - Early stage patients: no statistically significant differences for OS or PFS; - Advanced disease: positive vs, negative PFS (p = 0.0223) and OS (p = 0.0011); **Adding adjuvant chemotherapy:** - L1CAM-negative intermediate- or high-risk patients who received adjuvant chemotherapy (5-year OS: 100% vs. 98.6%, p = 0.1741; 5-year PFS: 95.1% vs. 90.3%, p = 0.2470), but were significantly worse in L1CAM-positive intermediate- or high-risk patients who received adjuvant chemotherapy (5-year OS: 100% vs. 82.1%, p<0.0001). Multivariate analysis revealed that LNM, including para-aortic LNM (PANM; p = 0.0256), deep MI (p = 0.0237), and L1CAM positivity (p = 0.0285) were independent predictors of poor PFS. PANM (p = 0.0150) and L1CAM positivity (p = 0.0107) were also independent predictors of poor OS.

Asano, H. et al. L1CAM Predicts Adverse Outcomes in Patients with Endometrial Cancer Undergoing Full Lymphadenectomy and Adjuvant Chemotherapy. Ann Surg Oncol. 27. 2159-2168. 2020

		Author's Conclusion: We conclude that L1CAM is an independent predictor of poor survival of patients with advanced-stage endometrial cancer undergoing full LND and adjuvant chemotherapy. Limitations of this study include that it was a retrospective study, and the number of samples was relatively small compared with previous large-scale studies. However, our findings clearly indicated that adjuvant chemotherapy did not effectively rescue L1CAM-positive patients undergoing extensive surgery. We should develop new treatment strategies using known targeting agents or new targeting drugs for L1CAM-positive endometrial cancer patients with poor survival.	
Methodical Notes			
Funding Sources: n.s. **COI:** The authors declared no relevant conflicts of interest or disclosures to declare. **Randomization:** no **Blinding:** no **Dropout Rate/ITT-Analysis:** -			

Asano, H. et al. L1CAM Predicts Adverse Outcomes in Patients with Endometrial Cancer Undergoing Full Lymphadenectomy and Adjuvant Chemotherapy. Ann Surg Oncol. 27. 2159-2168. 2020

Notes: Oxford CEBM Level of evidence 2011: EL 4 (Retrospective analysis (Cohort?)).

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Genetic association study (cohort of patients from 6 centers) To investigate whether molecular classification can be used to refine prognosis in grade 3 endometrioid endometrial carcinomas (EECs). **Number of Patient:** 381 **Recruitung Phase:** not described. **Inclusion Criteria:** Institutional approval for this study was obtained from each of the participating centers. FIGO grade 3 EECs with clinical follow-up data were collected from 6 institutions in Europe and North America (Table	**Intervention:** POLE sequencing for hotspots in the exonuclease domain (exons 9–14) was performed using either Sanger or next-generation approaches, as described previously. Either 2 (PMS2 and MSH6) or 4 (MLH1, PMS2, MSH2, MSH6) DNA mismatch repair IHC markers were performed on representative sections at the referring institution, as well as p53 IHC staining. Grade 3 EECs were classified into four subgroups: p53-abnormal, based on mutant-like immunostaining (p53abn); MMR-deficient, based on loss of mismatch repair protein expression (MMRd); presence of POLE exonuclease domain hotspot mutation (POLE); no specific molecular profile (NSMP), in which none of these aberrations were present.	**Primary:** Overall (OS), and recurrence-free survival (RFS) rates were compared using the Kaplan-Meier method (Log-Rank test) and univariable and multivariable Cox proportional hazard models. **Secondary:** - **Results: Study population:** 281 patients met the inclusion criteria. Median follow-up was 6.1 years (range 0.2–17.0). Median age was 66 years (range 33–96). The FIGO 2009 stage distribution was as follows: IA, 44.9%; IB, 31.5%; II, 6.3%; III, 13.1%; IV, 2.9%. Results: There were 49 (12.9%) POLE, 79 (20.7%) p53abn, 115 (30.2%) NSMP, and 138 (36.2%) MMRd tumors. Median follow-up of

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018			
1). Strict diagnostic criteria were applied, as follows: 1) tumors demonstrated endometrioid lineage evidenced by a component of low-grade endometrioid adenocarcinoma with low-intermediate nuclear grade and/or metaplasias typical of endometrioid differentiation. **Exclusion Criteria:** Exclusion of histological mimics (i.e. "confirmatory endometrioid features"); 2) tumors were characterized by predominantly solid architecture exclusive of squamous differentiation, or mixtures of glandular and solid architecture with diffusely distributed high-grade nuclei.	**Comparison:** -	patients was 6.1 years (range 0.2–17.0). Compared to patients with NSMP, patients with POLE mutant grade 3 EEC (OS: Hazard Ratio [HR] 0.36 [95%CI: 0.18–0.70], p=0.003; RFS: HR 0.17 [0.05–0.54], p=0.003) had a significantly better prognosis; patients with p53abn tumors had a significantly worse RFS (HR 1.73 [1.09–2.74], p0.021); patients with MMRd tumors showed a trend towards better RFS. Estimated 5-year OS rates were as follows: POLE 89%, MMRd 75%, NSMP 69%, p53abn 55% (Log Rank p=0.001). Five-year RFS rates were as follows: POLE 96%, MMRd 77%, NSMP 64%, p53abn 47% (p=0.000001), respectively. In a multivariable Cox model that included age and FIGO stage, POLE and MMRd status remained independent prognostic factors for better RFS; p53 status was an independent prognostic factor for worse RFS. Molecular classification of grade 3 EECs reveals that these tumors are a mixture of molecular subtypes of endometrial carcinoma, rather than a homogeneous group. **Author's Conclusion:** In summary, we have shown that the pathologic entity typically	

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018

		recognized as “FIGO grade 3 endometrioid carcinoma” is, in reality, a collection of at least four distinct disease types. In this era of increasingly individualized patient care, the elucidation and recognition of these subgroups will contribute significantly to prognostication and the selection of novel therapeutics.	

Methodical Notes

Funding Sources: Funding: This study was funded in part by the Dutch Cancer Society (KWF-UL2012-5719) (Dr. Bosse, Dr. Nout). This study was funded in part through the NIH/NCI Support Grant P30 CA008748 (Dr. Abu-Rustum, Dr. Levine, Dr. Soslow).

COI: The authors have no conflicts of interest to disclose.

Randomization: -

Blinding: -

Dropout Rate/ITT-Analysis: -

Notes: Oxford level of evidence: 3 Cohort study.
Downgrade to evidence level 4.
Lacking description of the cohort and participating centers. Lack of replication cohort.

Conlon, N. et al. Endometrial Carcinomas with a "Serous" Component in Young Women Are Enriched for DNA Mismatch Repair Deficiency, Lynch Syndrome, and POLE Exonuclease Domain Mutations. Am J Surg Pathol. 44. 641-648. 2020

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective analysis **Number of Patient:** 25 patients with ESC and 12 with mixed endometrioid/serous carcinoma **Recruitung Phase:** 2006-2012 **Inclusion Criteria:** Patients younger than 60 years with ESC or mixed endometrioid /serous carinoma. **Exclusion Criteria:** -	**Intervention:** IHC for p53, ARID1A, PTEN and the DNA mismatch repair proteins MSH2, MSH6, MLH1 and PMS2 was performed on all cases. POLE hotspot mutations analysis. **Comparison:** -	**Primary:** The association between morphologic features, and the presence of POLE-EDM and/or MMR-D and overall survival was analyzed, and survival curves were calculated. **Secondary:** - **Results:** Patient characteristics: At the time of diagnosis, - 51% (19/37) of patients had stage I (14 stage Ia, 5 stage Ib), - 3%(1/37) stage II, - 27% (10/37) stage III (3 stage IIIa, 7 stage IIIc) and - 19% (7/37) stage IV disease. <u>Immunohistochemical analysis:</u> Upon histologic re-review of the cases, tumors were subcategorized into those with exclusively serous morphology (n=16) and those with confirmatory endometrioid features in addition to serous morphology (n=21, 47%). - Sixteen percent showed mismatch repair deficiency (MMR-D); - 11% were diagnosed with Lynch syndrome; - 16% of cases tested harbored a hotspot POLE exonuclease domain

Conlon, N. et al. Endometrial Carcinomas with a "Serous" Component in Young Women Are Enriched for DNA Mismatch Repair Deficiency, Lynch Syndrome, and POLE Exonuclease Domain Mutations. Am J Surg Pathol. 44. 641-648. 2020			
		mutation (POLE-EDM); Based on histology review, patients were divided in three groups: - Group 1 cases with POLE-EDM or MMR-D - Group 2 cases with at least focal endometrioid morphology but without POLE-EDM or MMR-D. - Group 3 cases apparently archetypal ESC, with no clear endometrioid morphology, no POLE-EDM and no MMR-D. Clinically, the overall survival in patients with MMR-D and POLE-EDM was significantly better than that of patients without these abnormalities (p=0.0329). **Author's Conclusion:** In summary, ESC at our center in women aged less than 60 years are a heterogeneous group of tumors spanning the clinical, morphological, immunohistochemical, and molecular spectrum between endometrioid and serous carcinomas. A subset with superior outcomes showed POLE EDMs and DNA MMR-D as well as other features usually restricted to endometrioid-type tumors. This study further emphasizes the importance of the identification of underlying molecular abnormalities in high-grade ECs in young patients as these findings may result in a diagnosis of Lynch syndrome as well as a distinct prognosis and adjuvant therapy.	
Methodical Notes			

Conlon, N. et al. Endometrial Carcinomas with a "Serous" Component in Young Women Are Enriched for DNA Mismatch Repair Deficiency, Lynch Syndrome, and POLE Exonuclease Domain Mutations. Am J Surg Pathol. 44. 641-648. 2020

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COI: The authors have no conflicts of interest to declare.

Randomization: n.a.

Blinding: n.a.

Dropout Rate/ITT-Analysis: n.a.

Notes: Oxford CEBM Level of evidence 2011: EL 4 (Retrospective analysis)

Costigan, D. C. et al. Clinicopathologic and Immunohistochemical Correlates of CTNNB1 Mutated Endometrial Endometrioid Carcinoma. Int J Gynecol Pathol. 39. 119-127. 2020

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Retrospective analysis **Number of Patient:** 79 patients	**Intervention:** Endometrioid endometrial carcinomas with CTNNB1 mutations **Comparison:** CTNNB1 wild-type	**Primary:** Immunohistochemical (IHC) analysis of beta-Catenin clone 14 and Cyclin D1 clone SP14. IHC results were correlated with CTNNB1 mutation status and clinicopathological parameters. **Secondary:** -

Costigan, D. C. et al. Clinicopathologic and Immunohistochemical Correlates of CTNNB1 Mutated Endometrial Endometrioid Carcinoma. Int J Gynecol Pathol. 39. 119-127. 2020		
Recruitung Phase: **Inclusion Criteria:** Endometrioid endometrial carcinomas with or without CTNNB1 mutations **Exclusion Criteria:** -	(WT) endometrioid enodmetrial carcinomas	**Results:** Clinicopathological features: - predominantly low grade, low-stage disease (78% grade 1, 3% grade 1-2, 11% grade 2, 8% grade 3, and 87% were FIGO stage I-II). - patients with CTNNB1 mutated EEC were younger than those with CTNNB1 wt. Correlation of IHC with mutation status: - beta catenin expression was significantly associated with underlying CTNNB1 mutation (82%, 32/39) of all mutated tumors vs. 10% (4/40) of tumors in the wt-cohort (p - Analysis by separation based on exon 3 mutation status, the sensitivity of beta-catenin increased to 91% (31/34) within a similar specificity of 89% (40/45, PPV 86%, NPV 93%). - in non exon 3 CTNNB1 mutations this association was not evident, - Cyclin D1 IHC was specific (90%) but not sensitive (29%) for exon 3 underlying CTNNB1 mutation (p=0.07). Recurrence in Stage IA Tumors: - Recurrence rate of 30% (7/23 patients with follow-up available) stage IA tumor and exon 3 mutation CTNNB1, compared with no recurrence in the wt group (p=0.0025). - Mean time to recurrence was 79.85 mo (30 to 100 mo). Molecular context: 79% of exon 3 mutated tumors did not harbor TP53 mutations or POLE mutations and were microsatellite stable.

Costigan, D. C. et al. Clinicopathologic and Immunohistochemical Correlates of CTNNB1 Mutated Endometrial Endometrioid Carcinoma. Int J Gynecol Pathol. 39. 119-127. 2020

		Author's Conclusion: In conclusion, beta-catenin IHC (potentially with addition of Cyclin D1 IHC) represents a potential low-cost method of screening for this aggressive subset of low-grade low-stage EECs. However, further studies are required to definitively ascertain wether patients with low-grade low-stage EECs harboring CTNNB1 exon 3 mutations would be benefit from adjuvant therapy or, more likely, closer clinical follow-up.

Methodical Notes

Funding Sources: n.s.

COI: The authors declare no conflict of interest.

Randomization: n.a.

Blinding: n.s.

Dropout Rate/ITT-Analysis: n.a.

Notes: Oxford CEBM Level of evidence 2011: EL 4 (Retrospective analysis)

Jones, N. L. et al. Immune checkpoint expression, microsatellite instability, and mutational burden: Identifying immune biomarker phenotypes in uterine cancer. Gynecol Oncol. 156. 393-399. 2020

Population	Intervention	Outcomes/Results
Evidence level: 4 Study type: Retrospective analysis Number of Patient: 621 Recruitung Phase: 2012-2015 Inclusion Criteria: Not described Exclusion Criteria: Not described	Intervention: Comparison:	**Primary:** MSI, TMB, PD-L1, POLE mutations, Triple negative biomarker phenotype **Secondary:** **Results:** In total, 18% were G1 (113/621), 28% were G2 (172/621), 25% were G3 (156/621) and 29% were unknown (180/621). The median age was 62, ranging from 28 to 92. **MSI-H** Overall, MSI-H was found in 33% of EECs, most frequent in grade 3 (G3), followed by grade 2(G2) and grade 1(G1) tumors (G3: 37%, G2: 32%, G1: 22%, p = 0.007). **TMB-H** TMB-H was identified in 25% of EECs. TMB-H was most common in G3, followed by G2 and G1 tumors (G3: 34%, G2: 23%, G1: 13%, p = 0.006). **PD-L1 expression** Overall, PD-L1 expression was found in 5.5% of EECs. G3 EECs had the most frequent PD-L1 expression, followed by G2 and G1 tumors (G3: 12%, G2: 3%, G1: 0.9%, p **POLE** We identified POLE mutations in 4.5% (28/618). All POLE mutated tumors harbored TMB-H phenotypes but MSI-H and PD-L1 were only present in 10.7% and 14.8% of tumors respectively, suggesting upregulation of T-cell immune response in only a fraction of POLE mutated EECs.

Jones, N. L. et al. Immune checkpoint expression, microsatellite instability, and mutational burden: Identifying immune biomarker phenotypes in uterine cancer. Gynecol Oncol. 156. 393-399. 2020			
		TN Triple negative (TN) biomarker phenotype (ER-/PR-/Her2-) was evaluated as a potential surrogate marker of tumor immunogenicity. We identified TN phenotype in 4% of G1 EEC compared with 9% in G2 and 33% in G3, suggesting loss of hormone expression and possible greater immunogenicity with increasing tumor grade. **Author's Conclusion:** High grade tumors appear to be more immunogenic than low grade tumors and may preferentially benefit from IT.	
Methodical Notes			
Funding Sources: None. **COI:** Joanne Xiu is a Caris Life Sciences employee. The other authors have no disclosures. **Randomization:** / **Blinding:** Researchers were blinded from patient identifiers and analyses were performed on de-identified data **Dropout Rate/ITT-Analysis:** / **Notes: Oxford CEBM Level of Evidence 2011: EL 3 Retrospective analysis** <u>Limits:</u> -Retrospective analysis -Inclusion and exclusion criteria were not described			

Kandoth, C. et al. Integrated genomic characterization of endometrial carcinoma. Nature. 497. 67-73. 2013		
Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Cross-sectional, prognostic cohort study **Number of Patient:** 373 tumour patients (307, endometrioid and 66 serous (53) or mixed histology (13)) **Recruitung Phase:** not described. **Inclusion Criteria:** Not described. **Exclusion Criteria:** Not described.	**Intervention:** Exposure to genetic risk factors. Assesment using genomic, transcriptomic and proteomic characterization **Comparison:** Non-exposure	**Primary:** Endometrial carcinoma. **Secondary:** - **Results:** Uterine seroustumours and 25%of high-grade endometrioid tumours had extensive copy number alterations, few DNA methylation changes, low oestrogen receptor/progesterone receptor levels, and frequent TP53 mutations. Most endometrioidtumours had few copynumberalterations or TP53 mutations, but frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A and KRAS and novel mutations in the SWI/SNF chromatin remodelling complex gene ARID5B. A subset of endometrioid tumours that we identified had a markedly increased transversion mutation frequency and newly identified hotspot mutations in POLE. Our results classified endometrial cancers into four categories: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high. Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas. **Author's Conclusion:** We demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may affect post-surgical adjuvant treatment for women with aggressive tumours.
Methodical Notes		

Kandoth, C. et al. Integrated genomic characterization of endometrial carcinoma. Nature. 497. 67-73. 2013		
Funding Sources: The authors declare no competing financial interests. **COI:** The authors declare no competing financial interests. **Randomization:** - **Blinding:** - **Dropout Rate/ITT-Analysis:** Themedian follow-up of the cohort was 32months (range, 1–195months); 21%of the patients have recurred, and 11% have died. **Notes: Article included by hand search.** Oxford level of evidence: 3 Prognostic / cross-sectional study. No validation cohort was evaluated. No discription of inclusion criteria or cohort.		

Kir, G. et al. Correlation of PD-L1 expression with immunohistochemically determined molecular profile in endometrial carcinomas. Virchows Arch. 477. 845-856. 2020		
Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Consecutive case study. **Number of Patient:** 59	**Intervention:** IHC for MMR proteins, ARID1A, PTEN, and p53 and PD-L1 **Comparison:** -	**Primary:** Correlation of PD-L1 staining patterns with clinical and pathological parameters **Secondary:** - **Results:** Clinical and pathological details:

Kir, G. et al. Correlation of PD-L1 expression with immunohistochemically determined molecular profile in endometrial carcinomas. Virchows Arch. 477. 845-856. 2020		
consecutive patients **Recruitung Phase:** November 2018 to September 2019 **Inclusion Criteria:** Patients aged 42-89 who had undergone surgery for endometrial carcinoma. **Exclusion Criteria:** no or minimal residual tumor tissue for IHC		In terms of histological type, - 40 cases were low-grade endometrioid carcinoma (67.8%), - eight were high-grade endometrioid carcinoma (13.6%), - five were serous carcinoma (8.4%), and - two each were clear cell carcinoma, undifferentiated carcinoma, and carcinosarcoma (3.4%). Serous, clear cell, and undifferentiated carcinoma and carcinosarcoma were defined as non-endometrioid type (n = 11, 18.6%). FIGO stage - n = 34 were stage IA (57.7%), - 13 were IB (22%), and - 12 were ≥ II (20.3%). TC and IC PD-L1 positivity with a 1% cut-off value was observed in 10.2% and 67.8% of cases, respectively, and with a 5% cut-off value in 3.4% and 42.4% of cases, respectively. <u>Correlation of PD-L1 staining patterns with clinical and pathological parameters:</u> -**TC PD-L1** positivity with 1% and 5% cut-off values were significantly related to **ARID1A loss** (p = 0.001 and p = 0.046, respectively). -**IC PD-L1** positivity with 1% and 5% cut-off values and CS were significantly associated with **MMR protein deficiency** (p = 0.041, p = 0.031, and p = 0.028, respectively). - PTEN loss and mutation-type p53 expression did not show any correlation with PD-L1 positivity. - Lymphovascular space invasion was significantly related to IC PD-L1 positivity with a 5% cut-off value and CS (p = 0.029 and p = 0.008, respectively).

Kir, G. et al. Correlation of PD-L1 expression with immunohistochemically determined molecular profile in endometrial carcinomas. Virchows Arch. 477. 845-856. 2020

		Author's Conclusion: Our study is the first to demonstrate an association between ARID1A loss and PD-L1 expression in endometrial carcinomas. ARID1A loss represents a potential biomarker for immune checkpoint inhibitor response in endometrial carcinomas. We also show that MELF-type myometrial invasion pattern is more common in tumors with ARID1A loss. Future studies should investigate the cut-off values of PD-L1 expression on ICs and TCs which predict response to immunotherapy in clinical trials of endometrial carcinoma.

Methodical Notes

Funding Sources: This study was supported by Istanbul Medeniyet University Scientific Research Project fund.

COI: The authors declare that they have no conflict of interest.

Randomization: n.a.

Blinding: n.a.

Dropout Rate/ITT-Analysis: n.a.

Notes: Oxford CEBM Level of evidence 2011: EL 4 (Case control).

Kommoss, S. et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 29. 1180-1188. 2018

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Retrospective prognostic cohort study. **Number of Patient:** Women from the Tübingen University Women's Hospital treated for endometrial carcinom **Recruitung Phase:** Between 2003 and 2013. **Inclusion Criteria:** Clinical data was collected from patient charts and included age at diagnosis, body mass index (BMI), stage (updated according to FIGO 2009 classification), nodal involvement and adjuvant treatment. Surgical staging and adjuvant therapy had been performed according to national guidelines. Pathology data was taken from a specialized gynaecopathological case review, and clinicopathological parameters, e.g., histological subtype, grade, lymphovascular space invasion (LVSI) were recorded. For cases in which LVSI was controversial, immunohistochemical stains were applied to support the review diagnosis. All patients with a confirmed diagnosis of endometrial	**Intervention:** Predictors: Age, BMI, Stage, Grouped Stage, Grade, Grouped Grade, Histolological subtype, Simplified Histology, Grouped Histology, LVSI, Nodes, Myometrial invasion, adjuvant Treatment, Grouped Treatment, ESMO (ordinal),POLE (binary), p53 IHC (binary), MMR (binary). **Comparison:** -	**Primary:** Primary outcomes of overall, disease-specific, and progression-free survival were evaluated for clinical, pathological, and molecular features. **Secondary:** - **Results:** Complete clinical and molecular data were evaluable from 452 women. Patient age ranged from 29 to 93 (median 65) years, and 87.8% cases were endometrioid histotype. Grade distribution included 282 (62.4%) G1, 75 (16.6%) G2, and 95 (21.0%) G3 tumors. 276 (61.1%) patients had stage IA disease, with the remaining stage IB [89 (19.7%)], stage II [26 (5.8%)], and stage III/IV [61 (13.5%)]. ProMisE molecular classification yielded 127 (28.1%) MMR-D, 42 (9.3%) POLE, 55 (12.2%) p53abn, and 228 (50.4%) p53wt. ProMisE was a prognosticmarker for progression-free (P¼0.001) and disease-specific (P¼0.03) survival even after adjusting for known risk factors. Concordance between diagnostic and surgical specimens was highly favorable; accuracy 0.91, j 0.88.

Kommoss, S. et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 29. 1180-1188. 2018		
carcinoma, adequate FFPE material, and outcome data were eligible for study inclusion. Where both endometrial biopsy and hysterectomy specimens were available for a patient, the biopsy data was used unless the molecular features were un-interpretable, then the hysterectomy was used. **Exclusion Criteria:** Patients who had not had a hysterectomy or those who were treated with neoadjuvant chemotherapy were excluded from this study.		**Author's Conclusion:** We have developed, confirmed, and now validated a pragmatic molecular classification tool (ProMisE) that provides consistent categorization of tumors and identifies four distinct prognostic molecular subtypes. ProMisE can be applied to diagnostic samples and thus could be used to inform surgical procedure(s) and/or need for adjuvant therapy. Based on the IOM guidelines this classifier is now ready for clinical evaluation through prospective clinical trials.
Methodical Notes		
Funding Sources: Canadian Institutes of Health Research POP1 (grant # PP- 144251); British Columbia Conservation Foundation Clinician Scientist Award (JMc) (#10VRG013). **COI:** The authors have declared no conflicts of interest. **Randomization:** - **Blinding:** - **Dropout Rate/ITT-Analysis:** The median overall observation time was 5.1 years, and median follow-up was 5.3 years (reverse Kaplan Meier).		

Kommoss, S. et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 29. 1180-1188. 2018

Notes: Article included by handsearch.
Oxford level of evidence: 3 Retrospective prognostic cohort study.

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prognostic cohort study of two RCTs (PORTEC 1 and PORTEC 2) to confirm and validate the prognostic significance of the proposed molecular classification tool in early-stage endometrioid endometrial carcinomas (EEC). **Number of Patient:** 947 **Recruitung Phase:** - **Inclusion Criteria:** Early-stage	**Intervention:** Analysis of MSI, hotspot mutations in 14 genes including POLE, protein expression of p53, ARID1a, b-catenin, L1CAM, PTEN, ER, and PR was **Comparison:** -	**Primary:** AUCs of different risk stratification models were compared **Secondary:** - **Results:** Molecular analyses were feasible in >96% of the patients and confirmed the four molecular subgroups: p53-mutant (9%), MSI (26%), POLE-mutant (6%), and NSMP (59%). Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Approximately 15% of highintermediate risk patients had unfavorable features (substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM), 50% favorable features (POLE-mutant, NSMP being microsatellite stable, and CTNNB1 wild-type), and 35% intermediate features (MSI or CTNNB1-mutant).

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016			
endometrioid endometrial carcinomas from the PORTEC-1 and -2 trials, mostly high-intermediate risk (n = 614). Unclear inclusion criteria for original studies. **Exclusion Criteria:**		**Author's Conclusion:** In conclusion, integration of molecular risk factors with clinicopathologic factors in early-stage endometrial carcinoma leads to improved risk stratification with potential clinical utility. This molecular integrated risk prediction holds promise to reduce both overtreatment and undertreatment and should form the basis for future prospective clinical studies.	
Methodical Notes			
Funding Sources: The sponsor of the study (Dutch Cancer Society) had no role in study design, data collection, data analysis, data interpretation, or with writing the report. **COI:** No potential conflicts of interest were disclosed. **Randomization:** - **Blinding:** For immunohistochemical analyses, all slides were evaluated by two investigators and a gyneco-pathologist, blinded for patient characteristics and outcome. **Dropout Rate/ITT-Analysis:** not described. **Notes: Article by hand search.** Oxford level of evidence: 3 Cohort study or control arm of randomized trial.			

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Carr, C. et al. Clinicopathologic characteristics and outcomes of endometrial Cancer patients with mismatch repair deficiency in the era of universal Lynch syndrome screening. Gynecol Oncol. 159. 712-720. 2020

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 4 **Study type:** Retrospective cohort study	Funding sources: n.s. Conflict of Interests: No relevant conflicts of interests to disclose. Randomization: n.a. Blinding: n.a. Dropout rates: n.a.	**Total no. patients:** 1018 patients **Recruiting Phase:** August 2012-August 2016 **Inclusion criteria:** Patients who underwent hysterectomy for EC for primary or secondary surgical treatment. **Exclusion criteria:** Patients with incomplete follow-up or non-surgical primary treatment(chemotherapy, radiation therapy or hormonal therapy).	**Interventions:** MMR testing using immunohistochemistry for MMR proteins MLH1, MSH2, MSH6, PMS2. Tumors with lack of expression of PMS2 or MLH1 were submitted for reflex testing for MLH1 promotor methylation. **Comparison:** s.a.
Notes:	Oxford CEBM Level of evidence 2011: EL 4 (retrospective cohort study) **Author's conclusion:** MMR deficiency is associated with adverse prognostic factors and worse PFS among endometrioid tumors, particularly in early stage EC. MMR testing outside of LS screening has prognostic value, warranting considerations for inclusion as a biomarker in prospective clinical trials.		
Outcome Measures/results	**Primary** OS (overall survival) and PFS (progression free survival)	**Results:** Tumors were classified into three subgroups for comparison: MMR-I (intact expression of all MMR proteins), MMR-DM (MMR deficient due to MLH1 promotor methylation), and MMR-DU (MMR-Deficient, unmethylated).	

Carr, C. et al. Clinicopathologic characteristics and outcomes of endometrial Cancer patients with mismatch repair deficiency in the era of universal Lynch syndrome screening. Gynecol Oncol. 159. 712-720. 2020		
	Secondary -	Patient demographics: - MMR-I: 71.6% (N=729) - MMR-DM: 23.8% (N= 242) - MMR-DU: 4.6% (N= 47). MMR status was significantly associated with age, BMI, and menopausal status. There was no significant difference in PFS and OS between the three types. Three-year PFS for MMR-I, MMR-DM and MMR-DU patients was 77.3% (CI: 71.6, 82.9%), 70.8% (CI: 61.0, 80.6%) and 82.4% (CI: 67.7, 97.1%), respectively (p=0.13). Three-year OS for MMR-I, MMR-DM and MMR-DU patients was 83.5% (CI: 79.7, 87.4%), 84.9% (CI: 78.7, 91.2%) and 94.1% (CI: 86.0, 100.0%), respectively. When **stratified by stage**, PFS in stage I/II patients with MMR-DM approached significance (HR 1.72 (0.97-3.04), p=0.64), while there was no difference in PFS for stage III/IV patients with MMR-DM tumors vs. MMR-I (HR 1.24 (0.72-2.12), p=0.44). OS did not differ between MMR subgroups of stage I/II and stage III/IV patients. In patients with endometrioid EC, MMR-DM tumors were associated with lower PFS vs. MMR-I (HR: 2.51, CI: 1.54, 4.10, P

2.53. Handsuche zur Nachbewertung Molekulare Marker

Inhalt: *9 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Bosse, T. 2018	4	Genetic association study (cohort of patients from 6 centers) To investigate whether molecular classification can be used to refine prognosis in grade 3 endometrioid endometrial carcinomas (EECs).
Coll-de la Rubia, E. 2020	3	Systematic Review and Meta-Analysis
Guo, M. 2021	3	Systematic Review and Meta-Analysis of retrospective cohort studies
He, Y. 2020	2	Systematic Review and Meta-Analysis of retrospective cohort studies (6 studies)
Kandoth, C. 2013	3	Cross-sectional, prognostic cohort study
Kommoss, S. 2018	3	Retrospective prognostic cohort study.
Raffone, A. 2020	2	Systematic review and meta-analysis (10 cohort studies, retrospective and prospective). Define 1) the diagnostic accuracy of MMR proteins immunohistochemistry as surrogate of MSI molecular assay in endometrial carcinoma and 2) whether a combination of only two MMR proteins may be used instead of all the four MMR proteins to reduce the costs, through a systematic-review and meta-analysis.
Raffone, A. 2020	2	systematic review and meta-analysis (3 cohort studies)
Stelloo, E. 2016	3	Prognostic cohort study of two RCTs (PORTEC 1 and PORTEC 2) to confirm and validate the prognostic significance of the

Literaturstelle	Evidenzlevel	Studientyp
		proposed molecular classification tool in early-stage endometrioid endometrial carcinomas (EEC).

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *5 Bewertung(en)*

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis **Databases:** Medline **Search period:** 1991 to February 2020 **Inclusion Criteria:** (1) studies including endometrial cancer with an epithelial origin; (2) biomarker studies performed at protein level; (3) prognostic biomarker studies, i.e., studies that identify or validate biomarkers that are associated to EC risk factors, recurrence or survival; (4) studies performed on any biological human sample, but not on cultured cells or animal models; (5) studies based on the expression of biomarkers. **Exclusion Criteria:** (1) not written in English; (2) based on the characterization of one specific EC subtype; (3) based on response-to-	**Population:** Patients with endometrial cancer with an epithelial origin **Intervention:** All protein biomarkers associated with clinical prognostic factors of EC, recurrence and survival. **Comparison:**	**Primary:** Overall survival **Secondary:** **Results:** The majority of biomarkers identified in this systematic review were associated with histological grade, FIGO stage and OS, with more than 100 biomarkers described for each of these parameters. Other biomarkers were associated with lymph node status, histological type, myometrial invasion, LVSI, DFS, recurrence, DSS, PFS, risk, RFS, metastasis, cervical invasion and the TCGA subgroups. The vast majority of biomarkers are related to more than one of the above-mentioned parameters, indicating that they provide relevant prognostic information but are not specifically linked to one feature in particular. In fact, those that were associated with a specific parameter generally corresponded to those biomarkers that have been scarcely studied. List of proteins associated with each prognostic factor: See full text article Figure 6	398 studies were included.

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020				
treatment biomarkers; (4) articles performed using less than 10 samples in total; (5) reviews, meta-analyses, opinion articles or case report studies.		Results of the meta-analysis on OS of the five most studied proteins The number of investigations meeting our criteria for the estimation of HR was low, ranging from five to seven articles per protein. Substantial heterogeneity in the HRs across studies was observed for MUC16 and PGR, where the point estimates of the pooled HR and the 95% CI from the fixed and random effects model were wide. On the contrary, in ESR1, TP53, and WFDC2 the point estimates and the error margins were similar. Focusing on the data available, there is not enough evidence to affirm that MUC16 and PGR are useful EC prognostic biomarkers. However, articles studying ESR1, TP53 and WFDC2 point out these biomarkers as promising to be prognosticators of OS. Specifically, a pooled HR estimation of 3.51 [2.22; 5.57] for ESR1, 2.80 [2.00; 3.92] for TP53, and 4.56 [2.32; 9.00] for WFDC2 was obtained. Remarkably, WFDC2 has higher HR and 95% CI than ESR1 and TP53, making this protein a good and easy-to-assess biomarker, since it has been identified in serum samples (Figure 8A).		

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020

		Author's Conclusion: Here, we systematically reviewed the literature for EC prognostic biomarkers at the protein level and compiled a list of 255 proteins, although 79% of those proteins would require further validation. The only proteins that have been extensively studied are carbohydrate antigen 125 (CA125 or MUC16), human epididymis protein 4 (HE4 or WFDC2), estrogen receptor (ESR1) and progesterone receptor (PGR), mismatch repair proteins (MMR proteins: MSH2, MSH6, MHL1, PMS2), the tumor suppressors PTEN and TP53, the cell adhesion molecules E-cadherin (CDH1) and neural cell adhesion molecule L1 (L1CAM), the proliferation marker protein Ki-67 (KI67), and the Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2). On the basis of our meta-analysis, ESR1, TP53 and WFDC2 may be useful prognosticators for OS of EC. We also identified critical conceptual, methodological and analytical factors that need to be improved in further research. Consequently, we encourage the scientific community to follow these considerations in order to successfully identify clinically valuable EC prognostic biomarkers: (i) design studies whose primary aim is the identification of prognostic biomarkers. Thus, patient selection should be balanced		

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020				
		and controlled to achieve this objective, and the sample of the study source of biomarkers should be carefully chosen; (ii) include high-throughput technologies such as MS to have a broad analysis of biomarkers and to have the feasibility to develop biomarker panels; (iii) the statistical analysis in every step of the biomarker pipeline should be thoughtfully performed.		
Methodical Notes				
Funding Sources: This work was supported by CIBERONC (CB16/12/00328), the "Fondo Europeo de Desarrollo Regional" FEDER (RTC-2015-3821-1), the Asociación Española Contra el Cáncer (GCTRA1804MATI), Grups consolidats de la Generalitat de Catalunya (2017 SGR-1661) and the Instituto de Salud Carlos III (DTS17/00146, PI17/02071 and PI17/02155; and the IFI19/00029 to E.C.-d.l.R), and a PERIS grant funded EColas (SLT002/16/00315) from Generalitat de Catalunya. EM-G was supported by a grant from Télévie awarded to G.D. (F5/20/5-TLV/DD). **COI:** None. **Study Quality:** The guidelines from Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) were used to evaluate the quality of studies that were eligible. **Heterogeneity:** Pooled estimates of the HR (overall-eect model), and statistics I2 and tau-squared were computed following the guidelines of Doing Meta-Analysis in R. Substantial heterogeneity in the HRs across studies was observed for MUC16 and PGR, where the point estimates of the pooled HR and the 95% CI from the fixed and random effects model were wide				

Coll-de la Rubia, E. et al. Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 9. . 2020			
Publication Bias: Publication bias was not investigated **Notes:** **Article included through handsearch** Oxford CEBM Level of Evidence 2011: EL 2 Systematic review and meta-analysis of observational studies **Downgrading to EL 3 due to methodical weakness:** -Only one database was searched -No search for grey literature or unpublished studies was conducted -Unclear, if screening and data extraction was performed by two authors -Publication bias was not investigated -No overview of the included studies. It is unclear which study design the studies have -Quality assessment was performed but the results were not provided. Therefore the quality of the included studies is unclear -Substantial heterogeneity was present in the meta-analysis, which was not further explored in subgroup or sensitivity analyses			
Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies **Databases:** PubMed, MEDLINE, EMBASE, and	Population: Women with endometrial cancer Intervention: L1CAM	**Primary:** OS and DFS **Secondary:** Clinicopathological characteristics **Results:** Overall, 17 studies encompassing 7146	17 studies included, see full text article.

Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021				
Web of Science **Search period:** Inception to June 2019 **Inclusion Criteria:** studies on women with endometrial cancer, confirmed by pathological examination; Studies on quantitative data of hazard ratios (HRs) for overall survival (OS) and disease-free survival (DFS), and odds ratios (ORs) for clinicopathological characteristics; and studies in which the detection techniques and cut-off values for L1CAM expression were provided. **Exclusion Criteria:** The exclusion criteria were as follows: case reports, reviews, letters, and other studies without sufficient data; non-English articles; and single-arm or multiple-arm studies.	Comparison:	patients were eligible for the meta-analysis. **Overall survival** Nine studies (5116 patients) reported the HRs for OS. The pooled results indicated high L1CAM expression to be associated with decreased OS in patients with endometrial cancer (HR 2.87, 95% CI 1.81–4.55, P **Disease free survival** Eight studies (3970 patients) reported the HRs for DFS. The pooled results indicated high L1CAM expression was associated with decreased DFS in patients with endometrial cancer (HR 3.32, 95% CI 1.99–5.55, P **Association between L1CAM expression and clinicopathological characteristics in women with endometrial cancer** Fifteen studies reported dichotomous data for clinicopathological characteristics. A high L1CAM expression was positively associated with disease grade (OR=3.57, 95% CI 2.05–5.14, P P 0.05, P<.001)		

Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021

		Author's Conclusion: This systematic review demonstrated that high L1CAM expression is correlated with poor survival outcomes and adverse clinicopathological parameters in patients with endometrial cancer.		

Methodical Notes

Funding Sources: Not described.

COI: None.

Study Quality: Not investigated

Heterogeneity: Heterogeneity across trials was measured by the X2-based Q test and I2 statistics When a P50% indicated statistically significant heterogeneity across the studies, the effect sizes were measured using a random-effect model; otherwise, a fixed-effect model was used. We conducted sensitivity analysis and subgroup analysis to validate stability of the pooled effect sizes and explore the possible origins of heterogeneity.

A subgroup analysis was conducted to investigate the origin of high heterogeneity for the outcome OS(I 2= 82.6%, P=.478). We observed a significant relationship between high L1CAM expression and decreased OS in the following subgroups: the detection method (immunohistochemistry vs others), cut-off value (10% vs others), and FIGO stage (I–III vs I– IV). However, in subgroup analysis based on study region and sample size, significant results were observed in European group (HR 2.43, 95% CI 1.97–2.99, P

Subgroup analysis was conducted to investigate the origins of high heterogeneity for the outcome DFS(I 2=83.5%,P=.545). We observed a significant relationship between high L1CAM expression and decreased DFS in the following subgroups: study region (European vs non-European), sample size (<

Guo, M. et al. High L1CAM expression predicts poor prognosis of patients with endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 100. e25330. 2021

200 vs≥ 200), detection method (immunohistochemistry vs others), cut-off value (10% vs others), and FIGO stage (I–III vs I–IV).

We conducted a sensitivity analysis by sequentially omitting each study from the analysis. Results showed that the study by Zeimet et al[20] led to the statistical heterogeneity in the primary outcomes (OS and DFS; Fig. 3). When this study was omitted, the pooled results showed high L1CAM expression to be associated
with decreased OS (HR 2.46, 95% CI 2.02–3.00, P
fixed model, resulting in I2=18.6% and P=.272 for OS and I2=0.0% and P=.954 for DFS.

Publication Bias: We also generated a Begg funnel plot and performed Egger test to investigate potential publication bias in the meta-analysis. Symmetry in the funnel plot was observed for both OS (P=.436 for Begg test and P=.400 for Egger test)
and DFS (P=.721 for Begg test and P=.214 for Egger test).

Notes:
Oxford CEBM Level of Evidence 2011: Systematic Review and Meta-Analysis of retrospective cohort studies

Downgrading to EL 3 due to methodical weakness:

-Quality of the included studies was not investigated
-Substantial heterogeneity was present for the main outcomes, which waa further explored in subgroup and senstivity analyses

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020

Evidence level: 2 **Study type:** Systematic Review and Meta-Analysis of retrospective cohort studies (6 studies) **Databases:** PubMed,Web of Science, data of China National Knowledge Infrastructure, Wan fang Medical Network **Search period:** **Inclusion Criteria:** (1) Literatures including POLE-mutant EC patients who were tested by gene sequencing; (2) At least included 5 POLE-mutant EC cases; (3) Enough data such as Federation of International of Gynecologists and Obstetricians (FIGO) pathological staging group, differentiation degree, lymphatic vessel invasion group, histology type, depth of myometrial invasion, European Society for Medical Oncology (ESMO) risk stratification can be extracted from the included studies; (4) Sufficient data to calculate hazard ratio (HR), odds ratios (ORs), and 95% confidence interval (CIs) are available **Exclusion Criteria:** (1) Studies without enough data (the above-mentioned) for calculation; (2)	**Population:** POLE-mutant endometrial cancer patients who were tested by gene sequencing **Intervention:** **Comparison:** Patients without POLE-mutant endometrial cancer	**Primary:** Overall survival, progression-free survival, histological type, tumor grade, FIGO stage, LVSI, myometrial invasion, lymph node status, ESMO risk stratification **Secondary:** **Results:** Six cohort studies assessing 179 EC patients with POLE EDMs were included. **Overall survival** Six studies provided the data for OS among 371 POLE-mutant EC patients. The estimated HR for OS was 0.68 (95% CI=0.41–1.13), indicated a favorable OS was associated with POLE-mutant EC patients. **Progression free survival** Only 2 studies provided appropriate data for analysis of PFS. The overall result of HR was 0.32 (95% CI: 0.09–1.18), indicated a reduced PFS	6 retrospective cohort studies included: Cosgrove et al. 2018, Kommoss et al. 2018, Talhouk et al. 2017, Stelloo et al. 2016, Billingsley et al. 2016, Talhouk et al. 2015

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020				
Patients were not confirmed by EDM sequencing; (3) Duplicated publications or data; (4) Papers published in other languages other than English or Chinese. (5) Commentaries, single case reports, editorials, review articles, letters to the editor, and unrelated articles.		was associated with POLE-mutant EC patients. **FIGO stage in POLE-mutant EC** Four articles were selected for analyzing the association of FIGO stage with POLE mutations. The pooled OR was 0.34 [0.12–0.94] (P=.04), indicating that most of POLE mutations are FIGO I comparing to FIGO IIIV. No statistical significant differences were found for LVSI in POLE-mutant EC, Myometrial invasion in POLE-mutant EC, Lymph node status in POLE-mutant EC and for ESMO risk stratification in POLE-mutant EC, Histological type in POLE-mutant EC, Tumor grade in POLE-mutant **Author's Conclusion:** This meta-analysis has confirmed POLE EDMs may serve as a predictive biomarker of favorable prognosis. Further studies are needed to explore the		

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020

		appropriate clinical utility of POLE EDMs in EC.		

Methodical Notes

Funding Sources: This work was supported by the Scientific Research Funding of Tianjin Science and Technology Committee (17ZXMFSY00160).

COI: None.

Study Quality: The methodological quality of the included 6 studies was evaluated by Review manager 5.3, indicating the general quality was good as is shown in Figure 11.

Heterogeneity: Heterogeneity was assessed by I2 inconsistency test and chi-squared-based Cochran Q statistic test; I2>50% or Ph.1, the fixed effect model was used.
Significant heterogeneity was present for FIGO stage (I^2 = 58%), LVSI (I^2 = 94%), myometrial invasion (I^2 = 52%), lymph node status (I2 = 71%), ESMO risk stratification (I2 = 58%)

Publication Bias: Less than ten studies were included.

Notes:
Oxford CEBM Level of Evidence 2011: EL 2 Systematic Review of retrospective cohort studies

Limits:
-Significant heterogeneity was present for FIGO stage (I^2 = 58%), LVSI (I^2 = 94%), myometrial invasion (I^2 = 52%), lymph node status (I2 = 71%), ESMO risk

He, Y. et al. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). 99. e19281. 2020			
stratification (I2 = 58%) -Small sample size			
Raffone, A. et al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. Pathol Oncol Res. 26. 1417-1427. 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Systematic review and meta-analysis (10 cohort studies, retrospective and prospective). Define 1) the diagnostic accuracy of MMR proteins immunohistochemistry as surrogate of MSI molecular assay in endometrial carcinoma and 2) whether a combination of only two MMR proteins may be used instead of all the four MMR proteins to reduce the costs, through a systematic-review and meta-analysis. **Databases:** Web of Sciences, Scopus, MEDLINE, Google Scholar,	**Population:** Endometrial carcinoma patients. **Intervention:** IHC for MMR proteins as surrogate marker for Microsatellite instability (MSI) **Comparison:** -	**Primary:** Diagnostic accuracy **Secondary:** - **Results:** Ten studies with 3097 patients were included. Out of these, 1110 were suitable for the meta-analysis. Immunohistochemistry for all the four MMR proteins showed sensitivity = 0.96, specificity = 0.95, LR + =17.7, LR- = 0.05, DOR = 429.77, and high diagnostic accuracy (AUC = 0.988). The combination of MLH1 and MSH2 showed sensitivity = 0.88, specificity = 0.96, LR + =22.36, LR- = 0.15, DOR = 200.69, and high diagnostic accuracy (AUC = 0.9838). The combination of MSH6 and PMS2 showed the same results as the complete panel of four MMR proteins.	10 studies included: Chao, Libera, Bruegl, Stelloo, McConechy, Goodfellow, Haraldsdottir, Peterson, Choi, Ollikainen

Raffone, A. et al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. Pathol Oncol Res. 26. 1417-1427. 2020				
EMBASE, ClinicalTrial.gov and Cochrane Library. **Search period:** Inception to September 2019. **Inclusion Criteria:** We included all peer-reviewed studies assessing the association between MMR proteins immunohistochemistry and MSI molecular assay in endometrial carcinoma. **Exclusion Criteria:** Exclusion criteria were: reviews; case reports; studies not allowing comparisons between immunohistochemistry and molecular analysis; sample size		**Author's Conclusion:** Immunohistochemistry for MMR proteins (MLH1, MSH2, MSH6, PMS2) is a very highly accurate surrogate of MSI molecular testing in endometrial carcinoma. A combination of MSH6 and PMS2 may allow reducing the costs without a decrease in diagnostic accuracy. These findings support the feasibility of the introduction of the TCGA classification into the common practice.		
Methodical Notes				
Funding Sources: None described. **COI:** The authors report no conflict of interest. **Study Quality:** The risk of bias within studies assessment was performed following the revised Quality Assessment of Diagnostic Accuracy Studies				

Raffone, A. et al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. Pathol Oncol Res. 26. 1417-1427. 2020			
(QUADAS-2). In the “patient selection” domain, three studies were judged at unclear risk of bias because they did not report if the patients were consecutive or randomly selected, while the remaining studies were considered at low risk. High concerns about applicability were raised for two studies (only patients with presumed Lynch syndrome were included). In the “index test” domain, two studies were considered at high risk of bias because results of MMR proteins immunohistochemistry were incompletely reported, while the remaining studies were considered at low risk. High concerns about applicability were raised for two studies (not all MMR proteins were assessed). In the “reference standard” domain, all studies were considered at low risk of bias, since results ofMSI testing and the microsatellite markers assessed were clearly reported. No concerns about applicability were raised. In the “flow and timing” domain, 3 studies were considered at unclear risk of bias, because it was unclear if all eligible patients were assessed with both index and reference standard; all the remaining studies were considered at low risk. **Heterogeneity:** Statistical heterogeneity amongst the included studies was evaluated by using the Higgins I2 index, and judged as null for I2 = 0%, minimal for 0% < I2 ≤ 25%, low for 25 < I2 ≤ 50%, moderate for 50 < I2 ≤ 75% and high for I2 > 75%. High heterogeneity for NLR was observed. **Publication Bias:** Publication bias was not assessed. **Notes:** Oxford level of evidence: 2 Systematic review and meta-analysis of diagnostic cohort studies with consistently applied reference standard. High heterogeneity for NLR was observed. Publication bias was not assessed.			
Raffone, A. et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. Gynecol Oncol. 157. 252-259. 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Raffone, A. et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. Gynecol Oncol. 157. 252-259. 2020			
Evidence level: 2 **Study type:** systematic review and meta-analysis (3 cohort studies) **Databases:** Web of Sciences, MEDLINE, Google Scholar Scopus, Cochrane Library, Clinicaltrials.gov and EMBASE **Search period:** Inception to May 2019. **Inclusion Criteria:** All peer-reviewed studies that allowed extraction of histopathological characteristics of each ProMisE group of EC were included in our study. **Exclusion Criteria:** Reviews and case reports were a priori defined as exclusion criteria. Studies with patient selection based on histopatholoigcal characteristics were also excluded from our analysis because they would affect overall prevalence of each histopathological characteristic in each ProMisE group.	**Population:** Women diagnosed with EC, overlapping patients were excluded. **Intervention:** ProMisE group of EC. **Comparison:** -	**Primary:** Prevalence of several histopathological characteristics in each ProMisE group of EC. These were histological grade 3 (G3), endometrioid histotype, present LVSI, deep myometrial invasion, lymph node involvement, ESMo 2013 low- and high-risk category. **Secondary:** - **Results:** Four studies with 1171 patients were included in the systematic review, out of which three studies with 912 patients were included in the meta-analysis. Pooled prevalence estimates were: - in the MMR-d group G3 = 47.4%, G1-2= 52.6% endometrioid = 85,5%, non-endometrioid = 14.2%, LVSI - present = 41.3%, - absent = 58.7%, deep myometrial invasion-present = 44.5%, - absent = 55.5%, lymph node involvement - present = 9.9%, absent - 90.1%, low-risk = 30.1%, intermediate risk = 19.9%, high risk = 50%. -in the POLE-mt group, G3 = 39,6%, G1-2= 60.4% endometrioid = 86,1%, non-endometrioid = 13.9%, LVSI - present = 32.7%, - absent = 67.3%, deep myometrial invasion-present = 27.3%, - absent = 72.7%, lymph node involvement - present = 0%, absent - 100%, low-risk = 44.1%, intermediate risk = 22.5%, high risk = 33.4%.	3 studies included: Talhouk 2015, Talhouk 2017, Kommoss 2018.

Raffone, A. et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. Gynecol Oncol. 157. 252-259. 2020				
		Author's Conclusion: The histopathological characterization of the ProMisE groups suggests that many patients are currently undertreated or overtreated (especially in the POLE-mt and MMR-d groups).		
Methodical Notes				
Funding Sources: No financial support was received for this study. **COI:** The authors declare no conflict of interest. **Study Quality:** The methodological Index for Non-Randomized studies (MINORS) was followed to perform the risk of bias within studies assesment. All included studies were considered at low risk of bias in all domains, with the exception of "inlcusion of consecutive patients" domain. **Heterogeneity:** Statistical heterogeneity among studies was assessed by the inconsistency index I2 as previously described. Heterogeneity was categorized as well: null for I2 = 0%, minimal for I2 < 25%, low for I2 < 50%, moderate for I2 < 75% and high for I2 ≥ 75%. The random effect model of DerSimonian Laird was adopted for all analyses. The statistical heterogeneity among the included studies was high in many analysis. **Publication Bias:** Not investigated, but not feasible with three studies. **Notes:** Oxford level of evidence: 2 Systematic review of cohort studies The statistical heterogeneity among the included studies was high in many analysis, despite random effect model. No investigation of heterogeneity was performed. No study descriptives or results of individual quality assessments for each study.				

OXFORD (2011) Appraisal Sheet: Prognostic Studies: *4 Bewertung(en)*

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018

Population	Intervention	Outcomes/Results
Evidence level: 4 **Study type:** Genetic association study (cohort of patients from 6 centers) To investigate whether molecular classification can be used to refine prognosis in grade 3 endometrioid endometrial carcinomas (EECs). **Number of Patient:** 381 **Recruitung Phase:** not described. **Inclusion Criteria:** Institutional approval for this study was obtained from each of the participating centers. FIGO grade 3 EECs with clinical follow-up data were collected from 6 institutions in Europe and North America (Table 1). Strict diagnostic criteria were applied, as follows: 1) tumors demonstrated endometrioid lineage evidenced by a component of low-grade endometrioid adenocarcinoma with low-intermediate nuclear grade and/or metaplasias	**Intervention:** POLE sequencing for hotspots in the exonuclease domain (exons 9–14) was performed using either Sanger or next-generation approaches, as described previously. Either 2 (PMS2 and MSH6) or 4 (MLH1, PMS2, MSH2, MSH6) DNA mismatch repair IHC markers were performed on representative sections at the referring institution, as well as p53 IHC staining. Grade 3 EECs were classified into four subgroups: p53-abnormal, based on mutant-like immunostaining (p53abn); MMR-deficient, based on loss of mismatch repair protein expression (MMRd); presence of POLE exonuclease domain hotspot mutation (POLE); no specific molecular profile (NSMP), in which none of these aberrations were present. **Comparison:** -	**Primary:** Overall (OS), and recurrence-free survival (RFS) rates were compared using the Kaplan-Meier method (Log-Rank test) and univariable and multivariable Cox proportional hazard models. **Secondary:** - **Results: Study population:** 281 patients met the inclusion criteria. Median follow-up was 6.1 years (range 0.2–17.0). Median age was 66 years (range 33–96). The FIGO 2009 stage distribution was as follows: IA, 44.9%; IB, 31.5%; II, 6.3%; III, 13.1%; IV, 2.9%. Results: There were 49 (12.9%) POLE, 79 (20.7%) p53abn, 115 (30.2%) NSMP, and 138 (36.2%) MMRd tumors. Median follow-up of patients was 6.1 years (range 0.2–17.0). Compared to patients with NSMP, patients with POLE mutant grade 3 EEC (OS: Hazard Ratio [HR] 0.36 [95%CI: 0.18–0.70], p=0.003; RFS: HR 0.17 [0.05–0.54], p=0.003) had a

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018

typical of endometrioid differentiation. **Exclusion Criteria:** Exclusion of histological mimics (i.e. "confirmatory endometrioid features"); 2) tumors were characterized by predominantly solid architecture exclusive of squamous differentiation, or mixtures of glandular and solid architecture with diffusely distributed high-grade nuclei.		significantly better prognosis; patients with p53abn tumors had a significantly worse RFS (HR 1.73 [1.09–2.74], p0.021); patients with MMRd tumors showed a trend towards better RFS. Estimated 5-year OS rates were as follows: POLE 89%, MMRd 75%, NSMP 69%, p53abn 55% (Log Rank p=0.001). Five-year RFS rates were as follows: POLE 96%, MMRd 77%, NSMP 64%, p53abn 47% (p=0.000001), respectively. In a multivariable Cox model that included age and FIGO stage, POLE and MMRd status remained independent prognostic factors for better RFS; p53 status was an independent prognostic factor for worse RFS. Molecular classification of grade 3 EECs reveals that these tumors are a mixture of molecular subtypes of endometrial carcinoma, rather than a homogeneous group. **Author's Conclusion:** In summary, we have shown that the pathologic entity typically recognized as "FIGO grade 3 endometrioid carcinoma" is, in reality, a collection of at least four distinct disease types. In this era of increasingly individualized patient care, the elucidation and recognition of these

Bosse, T. et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 42. 561-568. 2018			
		subgroups will contribute significantly to prognostication and the selection of novel therapeutics.	
Methodical Notes			
Funding Sources: Funding: This study was funded in part by the Dutch Cancer Society (KWF-UL2012-5719) (Dr. Bosse, Dr. Nout). This study was funded in part through the NIH/NCI Support Grant P30 CA008748 (Dr. Abu-Rustum, Dr. Levine, Dr. Soslow). **COI:** The authors have no conflicts of interest to disclose. **Randomization:** - **Blinding:** - **Dropout Rate/ITT-Analysis:** - **Notes:** Oxford level of evidence: 3 Cohort study. **Downgrade to evidence level 4.** Lacking description of the cohort and participating centers. Lack of replication cohort.			
Kandoth, C. et al. Integrated genomic characterization of endometrial carcinoma. Nature. 497. 67-73. 2013			
Population	Intervention	Outcomes/Results	

Kandoth, C. et al. Integrated genomic characterization of endometrial carcinoma. Nature. 497. 67-73. 2013

Evidence level: 3

Study type: Cross-sectional, prognostic cohort study

Number of Patient: 373 tumour patients (307, endometrioid and 66 serous (53) or mixed histology (13))

Recruitung Phase: not described.

Inclusion Criteria: Not described.

Exclusion Criteria: Not described.

Intervention: Exposure to genetic risk factors. Assesment using genomic, transcriptomic and proteomic characterization

Comparison: Non-exposure

Primary: Endometrial carcinoma.

Secondary: -

Results: Uterine seroustumours and 25%of high-grade endometrioid tumours had extensive copy number alterations, few DNA methylation changes, low oestrogen receptor/progesterone receptor levels, and frequent TP53 mutations. Most endometrioidtumours had few copynumberalterations or TP53 mutations, but frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A and KRAS and novel mutations in the SWI/SNF chromatin remodelling complex gene ARID5B. A subset of endometrioid tumours that we identified had a markedly increased transversion mutation frequency and newly identified hotspot mutations in POLE. Our results classified endometrial cancers into four categories: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high. Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas.

Author's Conclusion: We demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may affect post-surgical adjuvant treatment for women with aggressive tumours.

Methodical Notes

Funding Sources: The authors declare no competing financial interests.

COI: The authors declare no competing financial interests.

Kandoth, C. et al. Integrated genomic characterization of endometrial carcinoma. Nature. 497. 67-73. 2013
Randomization: - **Blinding:** - **Dropout Rate/ITT-Analysis:** Themedian follow-up of the cohort was 32months (range, 1–195months); 21%of the patients have recurred, and 11% have died. **Notes: Article included by hand search.** Oxford level of evidence: 3 Prognostic / cross-sectional study. No validation cohort was evaluated. No discription of inclusion criteria or cohort.

Kommoss, S. et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 29. 1180-1188. 2018		
Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Retrospective prognostic cohort study. **Number of Patient:** Women from the Tübingen University Women's Hospital treated for endometrial carcinom **Recruitung Phase:** Between 2003 and 2013.	**Intervention:** Predictors: Age, BMI, Stage, Grouped Stage, Grade, Grouped Grade, Histolological subtype, Simplified Histology, Grouped Histology, LVSI, Nodes, Myometrial invasion, adjuvant Treatment, Grouped Treatment, ESMO (ordinal),POLE (binary), p53 IHC (binary), MMR (binary).	**Primary:** Primary outcomes of overall, disease-specific, and progression-free survival were evaluated for clinical, pathological, and molecular features. **Secondary:** - **Results:** Complete clinical and molecular data were evaluable from 452 women. Patient age ranged from 29 to 93 (median 65) years, and

Kommoss, S. et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 29. 1180-1188. 2018

Inclusion Criteria: Clinical data was collected from patient charts and included age at diagnosis, body mass index (BMI), stage (updated according to FIGO 2009 classification), nodal involvement and adjuvant treatment. Surgical staging and adjuvant therapy had been performed according to national guidelines. Pathology data was taken from a specialized gynaecopathological case review, and clinicopathological parameters, e.g., histological subtype, grade, lymphovascular space invasion (LVSI) were recorded. For cases in which LVSI was controversial, immunohistochemical stains were applied to support the review diagnosis. All patients with a confirmed diagnosis of endometrial carcinoma, adequate FFPE material, and outcome data were eligible for study inclusion. Where both endometrial biopsy and hysterectomy specimens were available for a patient, the biopsy data was used unless the molecular features were un-interpretable, then the hysterectomy was used. **Exclusion Criteria:** Patients who had not had a hysterectomy or those who were treated with neoadjuvant chemotherapy were excluded from this study.	**Comparison:** -	87.8% cases were endometrioid histotype. Grade distribution included 282 (62.4%) G1, 75 (16.6%) G2, and 95 (21.0%) G3 tumors. 276 (61.1%) patients had stage IA disease, with the remaining stage IB [89 (19.7%)], stage II [26 (5.8%)], and stage III/IV [61 (13.5%)]. ProMisE molecular classification yielded 127 (28.1%) MMR-D, 42 (9.3%) POLE, 55 (12.2%) p53abn, and 228 (50.4%) p53wt. ProMisE was a prognosticmarker for progression-free (P¼0.001) and disease-specific (P¼0.03) survival even after adjusting for known risk factors. Concordance between diagnostic and surgical specimens was highly favorable; accuracy 0.91, j 0.88. **Author's Conclusion:** We have developed, confirmed, and now validated a pragmatic molecular classification tool (ProMisE) that provides consistent categorization of tumors and identifies four distinct prognostic molecular subtypes. ProMisE can be applied to diagnostic samples and thus could be used to inform surgical procedure(s) and/or need for adjuvant therapy. Based on the IOM guidelines this classifier is now ready for clinical evaluation through prospective clinical trials.

Kommoss, S. et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 29. 1180-1188. 2018		
Methodical Notes		
Funding Sources: Canadian Institutes of Health Research POP1 (grant # PP- 144251); British Columbia Conservation Foundation Clinician Scientist Award (JMc) (#10VRG013). **COI:** The authors have declared no conflicts of interest. **Randomization:** - **Blinding:** - **Dropout Rate/ITT-Analysis:** The median overall observation time was 5.1 years, and median follow-up was 5.3 years (reverse Kaplan Meier). **Notes: Article included by handsearch.** Oxford level of evidence: 3 Retrospective prognostic cohort study.		
Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016		
Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** Prognostic cohort	**Intervention:** Analysis of MSI, hotspot mutations in 14 genes including POLE, protein expression of p53, ARID1a, b-	**Primary:** AUCs of different risk stratification models were compared

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016		
study of two RCTs (PORTEC 1 and PORTEC 2) to confirm and validate the prognostic significance of the proposed molecular classification tool in early-stage endometrioid endometrial carcinomas (EEC). **Number of Patient:** 947 **Recruitung Phase:** - **Inclusion Criteria:** Early-stage endometrioid endometrial carcinomas from the PORTEC-1 and -2 trials, mostly high-intermediate risk (n = 614). Unclear inclusion criteria for original studies. **Exclusion Criteria:**	catenin, L1CAM, PTEN, ER, and PR was **Comparison:** -	**Secondary:** - **Results:** Molecular analyses were feasible in >96% of the patients and confirmed the four molecular subgroups: p53-mutant (9%), MSI (26%), POLE-mutant (6%), and NSMP (59%). Integration of prognostic molecular alterations with established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Approximately 15% of highintermediate risk patients had unfavorable features (substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM), 50% favorable features (POLE-mutant, NSMP being microsatellite stable, and CTNNB1 wild-type), and 35% intermediate features (MSI or CTNNB1-mutant). **Author's Conclusion:** In conclusion, integration of molecular risk factors with clinicopathologic factors in early-stage endometrial carcinoma leads to improved risk stratification with potential clinical utility. This molecular integrated risk prediction holds promise to reduce both overtreatment and undertreatment and should form the basis for future prospective clinical studies.
Methodical Notes		
Funding Sources: The sponsor of the study (Dutch Cancer Society) had no role in study design, data collection, data analysis, data interpretation, or with writing the report.		

Stelloo, E. et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 22. 4215-24. 2016

COI: No potential conflicts of interest were disclosed.

Randomization: -

Blinding: For immunohistochemical analyses, all slides were evaluated by two investigators and a gyneco-pathologist, blinded for patient characteristics and outcome.

Dropout Rate/ITT-Analysis: not described.

Notes: Article by hand search.
Oxford level of evidence: 3 Cohort study or control arm of randomized trial.

2.54. Negativ bewertete Artikel

Inhalt: *20 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Burden, S. 2019	5	
Dogan, A. 2017	5	
Dork, T. 2020	5	
Emons, G. 2020	5	
Green, A. K. 2020	5	
How, J. A. 2018	1	
Ignatov, A. 2020	5	
Janda, M. 2017	1	
Jordan, S. J. 2017	5	To investigate the association between breastfeeding and endometrial cancer risk using pooled data from 17 studies participating in the Epidemiology of Endometrial Cancer Consortium.
Martin, F. E. 2020	1	
Mäenpää, M. M. 2016	5	

Literaturstelle	Evidenzlevel	Studientyp
Mørch, L. S. 2016	1	
Phelippeau, J. 2016	1	
Ryan, N. A. J. 2018	5	
Salehi, S. 2017	2	
Staley, A. 2017	1	
Stute, P. 2018	5	
Tzur, T. 2017	5	
Vermij, L. 2020	5	
Vitale, S. G. 2019	1	

OXFORD (2011) Appraisal Sheet: Systematic Reviews: *16 Bewertung(en)*

Burden, S. et al. Dietary interventions for adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:	
Methodical Notes			
Funding Sources: **COI:** **Study Quality:** **Heterogeneity:** **Publication Bias:**			

Burden, S. et al. Dietary interventions for adult cancer survivors. Cochrane Database of Systematic Reviews. . . 2019	
Notes: Excluded in SF 51 because of wrong population (no subgroup analysis for endometrial cancer) and the study of Kitson et al 2018 adresses a similar PICO question with a more adequate study population. Thus this study was preferred for analysis.	

Dork, T. et al. Genetic Susceptibility to Endometrial Cancer: Risk Factors and Clinical Management. Cancers (Basel). 12. . 2020				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: COI:				

Dork, T. et al. Genetic Susceptibility to Endometrial Cancer: Risk Factors and Clinical Management. Cancers (Basel). 12. . 2020	
Study Quality: Heterogeneity: Publication Bias: Notes: Nicht bewertet, da kein systematisches Review	

Emons, G. et al. Tamoxifen and Endometrial Cancer: A Janus-Headed Drug. Cancers (Basel). 12. . 2020				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		

Emons, G. et al. Tamoxifen and Endometrial Cancer: A Janus-Headed Drug. Cancers (Basel). 12. . 2020	
Methodical Notes	
Funding Sources: COI: Study Quality: Heterogeneity: Publication Bias: Notes: Nicht bewertet, da kein systematisches Review	

Green, A. K. et al. A Review of Immune Checkpoint Blockade Therapy in Endometrial Cancer. Am Soc Clin Oncol Educ Book. 40. 1-7. 2020				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period:	Intervention: Comparison:	Primary: Secondary: Results:		

Green, A. K. et al. A Review of Immune Checkpoint Blockade Therapy in Endometrial Cancer. Am Soc Clin Oncol Educ Book. 40. 1-7. 2020				
Inclusion Criteria: Exclusion Criteria:		Author's Conclusion:		
Methodical Notes				
Funding Sources: **COI:** **Study Quality:** **Heterogeneity:** **Publication Bias:** **Notes:** Kein systematisches Review, daher kann diese Arbeit nicht bewertet werden.				

How, J. A. et al. Sentinel lymph node mapping in endometrial cancer: a systematic review and meta-analysis. Minerva Ginecol. 70. 194-214. 2018				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	

How, J. A. et al. Sentinel lymph node mapping in endometrial cancer: a systematic review and meta-analysis. Minerva Ginecol. 70. 194-214. 2018				
Evidence level: 1 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: COI: Study Quality: Heterogeneity: Publication Bias: Notes: Ausgeschlossen, da kein Volltext verfügbar.				

Ignatov, A. et al. Endocrine Risk Factors of Endometrial Cancer: Polycystic Ovary Syndrome, Oral Contraceptives, Infertility, Tamoxifen. Cancers (Basel). 12. . 2020				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: COI: Study Quality: Heterogeneity: Publication Bias:				

Ignatov, A. et al. Endocrine Risk Factors of Endometrial Cancer: Polycystic Ovary Syndrome, Oral Contraceptives, Infertility, Tamoxifen. Cancers (Basel). 12. . 2020				
Notes: Nicht bewertet, da narratives review				
Jordan, S. J. et al. Breastfeeding and Endometrial Cancer Risk: An Analysis From the Epidemiology of Endometrial Cancer Consortium. Obstet Gynecol. 129. 1059-1067. 2017				
Evidence level/Study Types		P - I - C	Outcomes/Results	Literature References
Evidence level: 5 **Study type:** To investigate the association between breastfeeding and endometrial cancer risk using pooled data from 17 studies participating in the Epidemiology of Endometrial Cancer Consortium. **Databases:** **Search period:** **Inclusion Criteria:** **Exclusion Criteria:**		Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:	
Methodical Notes				

Jordan, S. J. et al. Breastfeeding and Endometrial Cancer Risk: An Analysis From the Epidemiology of Endometrial Cancer Consortium. Obstet Gynecol. 129. 1059-1067. 2017

Funding Sources:

COI:

Study Quality:

Heterogeneity:

Publication Bias:

Notes:
Oxford level of evidence: 1
Recommend exclusion of article.
This articles' included studies overlap to some degree with the analysis from Ma et al 2018. But since this article does not list the author's initials but Trial names, (such as WISE, EDGE, PECS etc.) the overlap can not be reliably quantified.
No description of a systematic review process. No evaluation of study quality.

Martin, F. E. et al. Functional recovery in older women undergoing surgery for gynaecological malignancies: A systematic review and narrative synthesis. J Geriatr Oncol. . . 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	

Martin, F. E. et al. Functional recovery in older women undergoing surgery for gynaecological malignancies: A systematic review and narrative synthesis. J Geriatr Oncol. . . 2020				
Evidence level: 1 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: COI: Study Quality: Heterogeneity: Publication Bias: Notes: Ausgeschlossen, da Volltext nicht verfügbar.				

Mäenpää, M. M. et al. Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. Am J Obstet Gynecol. 215. 588.e1-588.e7. 2016				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: **COI:** **Study Quality:** **Heterogeneity:** **Publication Bias:**				

Mäenpää, M. M. et al. Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. Am J Obstet Gynecol. 215. 588.e1-588.e7. 2016				
Notes: Study excluded in SF 36 because this study is included in the systematic review of Ind T., et al. 2017.				
Mørch, L. S. et al. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. Int J Cancer. 138. 1506-15. 2016				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: **COI:**				

Mørch, L. S. et al. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. Int J Cancer. 138. 1506-15. 2016	
Study Quality: **Heterogeneity:** **Publication Bias:** **Notes:** Study is already included in the Systematic review by Sjörgen et al 2016.	

Ryan, N. A. J. et al. The prevalence of Lynch syndrome in women with endometrial cancer: a systematic review protocol. Syst Rev. 7. 121. 2018				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				

Ryan, N. A. J. et al. The prevalence of Lynch syndrome in women with endometrial cancer: a systematic review protocol. Syst Rev. 7. 121. 2018

Funding Sources:

COI:

Study Quality:

Heterogeneity:

Publication Bias:

Notes:
Study protocol of a systematic review. Contains no actual data to evaluate.

Staley, A. et al. Sentinel Lymph Node Technique in Endometrial Cancer. Obstet Gynecol Surv. 72. 289-295. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Databases: Search period: Inclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:	

Staley, A. et al. Sentinel Lymph Node Technique in Endometrial Cancer. Obstet Gynecol Surv. 72. 289-295. 2017				
Exclusion Criteria:				
Methodical Notes				
Funding Sources: **COI:** **Study Quality:** **Heterogeneity:** **Publication Bias:** **Notes:** Exclusion of article Not a systematic review, but a narrative summary with database search. No evaluation is possible.				

Stute, P. et al. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 21. 111-122. 2018				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	

Stute, P. et al. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 21. 111-122. 2018				
Evidence level: 5 **Study type:** **Databases:** In May 2016, a systematic literature search was performed by an independent agency (gwd consult) using the databases Medline (Pubmed) and Embase. Only articles in English were included. There was no time restriction applied. **Search period:** **Inclusion Criteria:** **Exclusion Criteria:**	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: **COI:** **Study Quality:** **Heterogeneity:** **Publication Bias:** **Notes:** Oxford level of evidence: 1				

Stute, P. et al. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 21. 111-122. 2018
Downgrade to exclusion of article Unclear study aim. No search for grey literature or reference lists, unpublished articles. Unclear description of inclusion criteria. No evaluation of study quality.

Tzur, T. et al. Current strategies in the diagnosis of endometrial cancer. Arch Gynecol Obstet. 296. 5-14. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				
Funding Sources: **COI:**				

Tzur, T. et al. Current strategies in the diagnosis of endometrial cancer. Arch Gynecol Obstet. 296. 5-14. 2017	
Study Quality: **Heterogeneity:** **Publication Bias:** **Notes:** Article can not be graded or assesed for methodological quality, because of its nature as a narrative review.	

Vermij, L. et al. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 76. 52-63. 2020				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 5 Study type: Databases: Search period: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:		
Methodical Notes				

Vermij, L. et al. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 76. 52-63. 2020	
Funding Sources: COI: Study Quality: Heterogeneity: Publication Bias: Notes: Article from hand search. Quality of the article cannot be ascertained, as this a narrative review.	

Vitale, S. G. et al. Management of endometrial, ovarian and cervical cancer in the elderly: current approach to a challenging condition. Arch Gynecol Obstet. 299. 299-315. 2019				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 Study type: Databases: Search period:	Intervention: Comparison:	Primary: Secondary: Results:		

Vitale, S. G. et al. Management of endometrial, ovarian and cervical cancer in the elderly: current approach to a challenging condition. Arch Gynecol Obstet. 299. 299-315. 2019				
Inclusion Criteria: Exclusion Criteria:		Author's Conclusion:		
Methodical Notes				
Funding Sources: COI: Study Quality: Heterogeneity: Publication Bias: Notes: Ausgeschlossen, da narrativer Review.				

OXFORD (2011) Appraisal Sheet: RCT: *2 Bewertung(en)*

Janda, M. et al. Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer: A Randomized Clinical Trial. Jama. 317. 1224-1233. 2017			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 1 Study type: Number of Patient: Recruitung Phase: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:	
Methodical Notes			
Funding Sources: COI: Randomization: Blinding:			

Janda, M. et al. Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer: A Randomized Clinical Trial. Jama. 317. 1224-1233. 2017			
Dropout Rate/ITT-Analysis: Notes: Ausgeschlossen, da in Meta-Analyse in Sammlung 35 enthalten.			
Salehi, S. et al. Robot-assisted laparoscopy versus laparotomy for infrarenal paraaortic lymphadenectomy in women with high-risk endometrial cancer: A randomised controlled trial. Eur J Cancer. 79. 81-89. 2017			
Population	Intervention - Comparison	Outcomes/Results	
Evidence level: 2 Study type: Number of Patient: Recruitung Phase: Inclusion Criteria: Exclusion Criteria:	Intervention: Comparison:	Primary: Secondary: Results: Author's Conclusion:	
Methodical Notes			

Salehi, S. et al. Robot-assisted laparoscopy versus laparotomy for infrarenal paraaortic lymphadenectomy in women with high-risk endometrial cancer: A randomised controlled trial. Eur J Cancer. 79. 81-89. 2017

Funding Sources:

COI:

Randomization:

Blinding:

Dropout Rate/ITT-Analysis:

Notes:
The evidence table of this study can be found included in the study of Salehi et al 2018 (e.g. included in SF 36), because both publications are describing the same trial but different outcomes.

NEWCASTLE - OTTAWA Checklist: Cohort: *2 Bewertung(en)*

Dogan, A. et al. Synchronous Endometrial and Ovarian Cancer in Young Women: Case Report and Review of the Literature. Anticancer Res. 37. 969-978. 2017

Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 5 Study type:	Funding sources: Conflict of Interests:	Total no. patients: Recruiting Phase:	Interventions: Comparison:

Dogan, A. et al. Synchronous Endometrial and Ovarian Cancer in Young Women: Case Report and Review of the Literature. Anticancer Res. 37. 969-978. 2017			
	Randomization: Blinding: Dropout rates:	Inclusion criteria: Exclusion criteria:	
Notes:	Keine Bewertung möglich. Es handelt sich um einen Case report. **Author's conclusion:**		
Outcome Measures/results	Primary Secondary	Results:	
Phelippeau, J. et al. Impact of Radical Hysterectomy on Survival in Patients with Stage 2 Type1 Endometrial Carcinoma: A Matched Cohort Study. Ann Surg Oncol. 23. 4361-4367. 2016			
Evidence level	Methodical Notes	Patient characteristics	Interventions
Evidence level: 1 Study type:	Funding sources: Conflict of Interests: Randomization:	Total no. patients: Recruiting Phase: Inclusion criteria:	Interventions: Comparison:

Phelippeau, J. et al. Impact of Radical Hysterectomy on Survival in Patients with Stage 2 Type1 Endometrial Carcinoma: A Matched Cohort Study. Ann Surg Oncol. 23. 4361-4367. 2016			
	Blinding: Dropout rates:	Exclusion criteria:	
Notes:	Exclusion of article. Data is includede in the meta-analysis by Liu et al. 2019. **Author's conclusion:**		
Outcome Measures/results	Primary Secondary	Results:	

3. Tabellenverzeichnis

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