Leitlinienprogramm Onkologie

Evidenztabellen der S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms

Version 1.0– September 2016

AWMF-Registernummer: 032/038OL

Evidenztabellen

DKG Krebsgesellschaft · Deutsche Krebshilfe Helfen. Forschen. Informieren. · AWMF

Inhaltsverzeichnis

Anmerkung: Schlüsselfragen, die mit „ keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche“ markiert sind, wurden durch Expertenkonsens oder eine externe De-Novo-Recherche beantwortet. Deshalb wurden für diese Schlüsselfragen keine Evidenztabellen erstellt.

1. Informationen zum Dokument

Dieser Dokument mit den Evidenztabellen dient der methodischen Ergänzung der S3-Leitlinie zur Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms, Version 1.0 (AWMF-Registrierungsnummer 032/038OL).

1.1. Autoren

Dr. Philipp Maisch, Heidrun Rexer, Thomas Langer, Anne Steeg, Mandy Strogiehs, Prof. Dr. Margitta Retz

1.2. Herausgeber

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

1.3. Federführende Fachgesellschaft

Deutsche Gesellschaft für Urologie e.V. (DGU)

Interdisziplinäre Arbeitsgruppe BlasenCarcinom der DKG e.V. (IABC)

1.4. Finanzierung der Leitlinie

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

1.5. Kontakt

Office Leitlinienprogramm Onkologie
c/o Deutsche Krebsgesellschaft e.V.
Kuno-Fischer-Straße 8
14057 Berlin

leitlinienprogramm@krebsgesellschaft.de
www.leitlinienprogramm-onkologie.de

1.6. Zitierweise

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Evidenztabellen zur S3-Leitlinie zur Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms, 2016, AWMF-Registrierungsnummer 032/038OL, http://leitlinienprogramm-onkologie.de/Blasenkarzinom.92.0.html (Stand: TT.MM.JJJJ)

1.7. Weitere Dokumente zur Leitlinie

Erstellt wurde diese Leitlinie von 2013-2016.

Die Langversion sowie alle zusätzlichen Dokumente zur „S3-Leitlinie zur Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms“, sind über die folgenden Internetadressen zu beziehen:

- Leitlinienprogramm Onkologie

  http://leitlinienprogramm-onkologie.de/Harnblasenkarzinom.92.0.html

- AWMF

  http://www.awmf.org/leitlinien/aktuelle-leitlinien.html

Neben Lang- und Kurzversion und dem Leitlinienreport gibt es die folgenden ergänzenden Dokumente zur Leitlinie:

- Leitlinienreport
- Patientenleitlinie "S3-Leitlinie zur Früherkennung, Diagnose und Therapie des Harnblasenkarzinoms" (Erstellung folgt nach Publikation der ärztlichen Leitlinie)
- Evidenzbericht des Departments für Evidenzbasierte Medizin und Klinische Epidemiologie, Donauuniversität Krems, Österreich: Subgruppeneffekte der Wirksamkeit und Sicherheit von organerhaltenden, adjuvanten und neoadjuvanten Therapien des muskelinvasiven Urothelkarzinoms der Harnblas - Systematische Übersichtsarbeit und Subgruppenanalyse (http://www.donau-uni.ac.at/imperia/md/content/department/evidenzbasierte_medizin/projekte/berichte/s3-ll_blasen-ca_systematic_review_duk_krems_final.pdf) von Dr. Peter Mahlknecht, Barbara Nußbaumer, Bakk., BSc, MSc, Mag.ª Isolde Sommer, PhD, MPH, Univ.-Prof. Dr. Gerald Gartlehner, MPH

1.8. Hinweise zur methodischen Bewertung der Studien

Für die Evidenzgraduierung wurde in der S3-Leitlinie zur Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms das System des Scottisch Intercollegiate Guidelines Network (SIGN) angewendet.

Tabelle 1: Schema der Evidenzgraduierung nach SIGN

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z.B. Fallberichte, Fallserien
4	Expertenmeinun

2. AG 1: Epidemiologie, Risikofaktoren, SDFVPrävention, Früherkennung

2.1. AG 1 Schlüsselfrage 1 - keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

2.2. AG 1 Schlüsselfrage 2 - keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

2.3. AG 1 Schlüsselfrage 3 - keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

2.4. AG 1 Schlüsselfrage 4 - keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

2.5. AG 1 Schlüsselfrage 5 (Präventionsmaßnahmen)

„Gibt es validierte Maßnahmen (z.B. Ernährung, Sport, Medikamente), um dem Auftreten eines Harnblasenkarzinoms in der Primärprävention bzw. der Tertiärprävention vorzubeugen?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Boehm 2010	Meta analyses 2++	Fifty-one studies with more than 1.6 million participants were included. 1 RCT, 23 prospective cohort studies, 27 retrospective case-control studies. The studies were published between 1985 and 2008.	Twenty-seven studies tried to establish an association between green tea consumption and cancer of the digestive tract, mainly of the upper gastrointestinal tract, five with breast cancer, five with prostate cancer, three with lung cancer, two with ovarian cancer, two with urinary bladder cancer, one with oral cancer, three further studies included patients with various cancer diagnoses.		The aims of this review were to examine the possible association between green tea consumption and the risk of cancer incidence and mortality. The review includes data from 50 observational studies and one RCT. We included all prospective, controlled interventional studies and observational studies, which either assessed the associations between green	Of the 23 cohort studies, 18 measured cancer incidence, 4 cancer mortality and one measured both, cancer incidence and mortality. All of the 27 case-control studies assessed any associations between green tea consumption and cancer risk. The only included RCT measured, amongst other outcomes, cancer incidence and QoL. Results of the RCT: Cancer incidence only reported for prostate cancer (high-risk population for developing prostate cancer) treatment group (incidence 3%) control group (incidence 30%). Cancer mortality: not reported. Results of the Review: There is insufficient and conflicting evidence to give any firm recommendations regarding green tea consumption for cancer prevention.	Prospective studies, controlled interventional studies, and observational studies were included. The methodological quality was measured with the Newcastle-Ottawa scale (NOS). The 9 nested case-control studies within prospective cohorts were of high methodological quality, 13 of medium, and 1 of low. One retrospective case-control study was of high methodological quality and 21 of medium and 5 of

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					tea consumption and risk of cancer incidence or that reported on cancer mortality and QoL. The primary outcome measures were the number of participants developing cancers (incidence), · the number of participants dying from cancers (mortality). Secondary outcomes were Safety data and data on quality of life (QoL).	The results of this review, including its trends of associations, need to be interpreted with caution and their generalisability is questionable, as the majority of included studies were carried out in Asia (n = 47) where the tea drinking culture is pronounced. Desirable green tea intake is 3 to 5 cups per day (up to 1200 ml/day), providing a minimum of 250 mg/day catechins. If not exceeding the daily recommended allowance, those who enjoy a cup of green tea should continue its consumption. Drinking green tea appears to be safe at moderate, regular and habitual use. Results for Urinary bladder cancer: There was limited to moderate evidence that the consumption of green tea reduced the risk of urinary bladder cancer. One cohort study (Chyou 1993), one case-control study (Wakai 2004). One cohort study (Chyou 1993) investigating Japanese-American men residing in Hawaii reported that green tea consumption did not reduce the risk of bladder cancer.	low.

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						RR (95% CI) green tea consumption "almost never" = 1.00 RR (95% CI) green tea consumption "ever" = 1.34 (0.79 to 2.27) No p-values provided One hospital-based case-control study found that green tea consumption was associated with an increased risk in both, male and female participants (Wakai 2004). < 1 cup/day OR = 1.00 1 to 4 cups/day OR = 1.40 (95% CI, 0.74 to 2.62) 5 to 9 cups/day OR = 2.67 (95% CI, 1.44 to 4.94) p< 0.01 ≥ 10 cups/day OR = 1.18 (95% CI, 0.49 to 2.84) p = 0.024 Breast cancer Inoue 2008, Key 1999, Suzuki 2004, Wu 2003, Zhang 2007 Colorectal cancer Kato 1990a, Sun 2007 Colon and rectal cancer Suzuki 2005, Yang 2007 Digestive tract cancer Inoue 1998	

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						Esophageal cancer Gao 1994, Ishikawa 2006, Wang 2007 Esophageal, cardiac and gastric cancer Wang 1999 Gastric cancer Fujino 2002, Galanis 1998, Hoshiyama 2002, Huang 1999, Inoue 1994, Ji 1996, Kato 1990b, Koisumi 2003, Kono 1988, Sasazuki 2004, Setiawan 2001, Tajima 1985, Tsubono 2001, Ye 1998, Yu 1995 Gastric, liver, esophageal cancer Mu 2003 Lung cancer Bonner 2005, Li 2008, Zhong 2001 Oral cancer Ide 2007 Ovarian cancer Song 2008, Zhang 2002 Pancreatic cancer Goto 1990, Lin 2008, Luo 2007, Mizuno 1992 Pancreatic and colorectal cancer Ji 1997	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Prostate cancer Bettuzzi 2006, Jian 2007, Kikuchi 2006, Kurahashi 2007, Sonoda 2004 Urinary bladder cancer Chyou 1993, Wakai 2004 Various cancer types Kuriyama 2006, Nagano 2001, Nakachi 2000	
Wang 2010	Meta analyses 2++	20 articles were included, 5 were conducted in the United States/ Canada, 9 in Europe, 4 in Japan, 2 in Uruguay	For inclusion the study needed to fulfill all the following criteria: (a) Case-control or cohort study published as an original article; (b) Papers reported in English between 1980 and 2010 October; (c) Papers providing odds ratio (OR) or relative risk (RR) with corresponding 95% confidence intervals (95% CI) adjusted for at least age, sex, and smoking, or sufficient information allowing		We performed a meta-analysis of evidence for relationships of meat consumption with risk of bladder cancer. Literature searches were conducted to identify peer-reviewed manuscripts published up to October 2010. Twenty publications from 10 cohort studies and 11 case-control	In the present metaanalysis of the published literature involving almost 8,500 cases, no statistically significant association was observed between meat intake overall and bladder cancer. In subgroup analyses, studies conduced in Unites States/Canada exhibited a positive relationship between high meat intake and bladder cancer risk, and studies using self-administered questionnaires for exposure assessment also showed a significant increased relative risk for high meat consumers. Overall meat - Not associated with bladder cancer risk (RR= 1.04, 95% CI 0.80-1.27) - Heterogeneity among studies was detected P < 0.1 - No evidence of heterogeneity in cohort studies	Epidemiological studies, case-control or cohort study First, as a meta-analysis of observational data, our results are prone to recall and selection bias inherent in the original studies. Second, although all studies included in our meta-analysis provided RR estimates adjusted for a common set of variables (age, sex, and smoking) that are known to be

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			us to compute them.		studies were included in the analyses. We quantified associations with bladder cancer using metaanalysis of relative risk (RR) associated with the highest versus the lowest category of meat intake using random effect model.	- Some evidence in case-control studies - No publication bias was found among all studies P = 0.79 Red meat - The summary RR of bladder cancer was 1.17, 95% CI 1.02–1.34) for subjects in the highest category of red meat consumption compared with those in the lowest category. - No evidence of heterogeneity among cohort studies - Some evidence among case-control studies and all studies - No publication bias was detected P = 0.29 Beef - Intake was not associated with bladder cancer risk (RR = 1.19, 95% CI 0.92–1.46). - No evidence of heterogeneity - No publication bias was detected P = 0.12 Pork - Intake was not associated with bladder cancer risk (RR = 0.82, 95% CI 0.43–1.20). - No evidence of heterogeneity - No publication bias was detected	related to bladder cancer, confounding by other dietary factors or lifestyle characteristics may introduce bias in an unpredictable direction. Third, the consumption levels in the lowest and highest categories and the range of consumption varied across studies. These differences may have contributed to the heterogeneity among studies in the analysis of the highest versus the lowest intake categories. Publication bias was assessed with the tests of Egger and Begg. Finally, because our

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						P = 0.64 Poultry - Intake was not associated with bladder cancer risk (RR = 0.77, 95% CI 0.48–1.06). - No evidence of heterogeneity - No publication bias was detected P = 0.11 Processed meat - We found a marginal elevated risk of bladder cancer with high processed meat intake. - The summary RR suggested a statistically significant 10% higher risk (95% CI 1.00–1.21) for the highest versus lowest category of processed meat. - No evidence of heterogeneity - No publication bias was detected P = 0.16 Jemal 2009, Murta-Nascimento 2007, Larsson 2006, Norat 2002, Sandhu 2001, Steinmaus 2000, Claude 1986, Steineck 1990, La Vecchia 1989, Riboli 1991, Chyou 1993, Mills 1991, Steineck 1988, Brinkman 2008, Wilkens 1996, Augustson 1999, Nagano 2000, Tavani 2000, Wakai 2000, Balbi 2001, Radosavljevic 2004, Wakai 2004, Sakauchi 2005, Baena 2006, Michaud	meta-analysis was based on published studies, and we only collected articles in English, possible publication bias is of concern, even though no significant evidence of publication bias was observed. However, because of borderline significance and small number of publications in individual analyses, more studies, particularly well-designed prospective studies, are needed to confirm these findings.

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						2006, Garcia-Closas 2007, Cross 2007, Lumbreras 2008, Hu 2008, Larsson 2009, Ferrucci 2010, Aune 2009, DerSimonian 1986, Higgins 2003, Egger 1997, Begg 1994, Ferguson 2002, Hughes 2001, Tricker 1991, IARC 1978, Faramawi 2007, Larsson 2006, Bandera 2007, Cross 2010	
Amaral 2010	Meta analyses 2+	3 case-control studies, 3 nested case-control studies, and 1 case-cohort study that examined the association between selenium status and bladder cancer risk were identified and used in the present analysis. The total number of cases and controls/cohort members in the identified studies was 1,910 and 17,339, respectively. Four studies were done in the United States and three in	Inclusion criteria: Epidemiological studies reporting measures of association between selenium and bladder cancer risk measurements of selenium in any of the following biological samples: blood/serum, nails, hair, saliva. Exclusion criteria: Not written in English, Spanish or Portuguese reviews not epidemiological studies insufficient data/other topic.			In the present meta-analysis, we observed a significant 39% decreased risk of bladder cancer associated with high levels of selenium by combining results from seven epidemiologic studies, conducted in different populations, which applied individual levels of selenium measured in serum or toenails. This meta-analysis supports an inverse association between selenium concentration and bladder cancer risk. To further elucidate this relationship, efforts to quantify selenium and other trace metals in biological sample specimens at the individual level in large observational studies or randomized trials are needed. The two oldest and smallest studies of the seven reported nonsignificant inverse associations.	Epidemiological studies, case–control or cohort study The trials in that meta-analysis were not specific for the effects of selenium on bladder cancer risk. 2 of the 4 trials that provided sex-specific data used a mix of compounds rather than selenium alone. The effects of selenium on cancer incidence and mortality were based on levels of supplementation

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		Northern Europe.				Three other studies reported the same tendency. Only two showed a significant decrease in the risk of bladder cancer among individuals with higher selenium levels. In two case-control studies, toenail selenium concentrations were inversely associated with bladder cancer risk only among women, moderate smokers, and p53-positive cancers. Using a random effects model, the overall OR of bladder cancer risk for the highest compared with the lowest selenium status was 0.61 (95% CI, 0.42-0.87). A comparable result was found when using a fixed effects model (OR = 0.70; 95% CI, 0.58-0.84). Among the pooled studies, a moderate level of heterogeneity was detected ($\chi 2$ = 15.32; degrees of freedom = 6; P = 0.018; I2 = 60.8%). In the analysis stratified by gender, only women yielded significant decreased risk associated with selenium (OR = 0.55; 95% CI, 0.32-0.95) with a nonsignificant I2 of 23.7%.	instead of internal levels of selenium.

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						The sample specimen in which selenium was determined (serum or toenails) was found to be a source of heterogeneity. Although selenium in toenails and in serum provided significant results, serum levels of selenium showed a stronger protective effect (OR = 0.33; 95% CI, 0.21-0.51). Stratifying the analysis according to smoking status decreased the heterogeneity found in the overall analysis, and results became similar between never and ever smokers. As for the type of study, the stratified results were consistent with the pooled overall estimate. Moreover, heterogeneity increased in the stratum of case-control studies ($\chi 2$ = 13.13; degrees of freedom = 2; P = 0.001; I2 = 84.8%). Publication bias was not detected in the meta-analysis (coefficient = - 1.84, P = 0.357), even when stratifying by the several study determinants. As expected, the most influential studies in the analysis were found to be the	

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						largest ones. Silverman 2006, Garcia-Closas, 2005, Murta-Nascimento 2007, Valko 2006, Navarro 2007, Bardia 2008, Bjelakovic 2008, Zhuo 2004, Etminan 2005, Meyer 2005, Duffield-Lillico 2003, Lippman 2009, Flores-Mateo 2006, Higgins 2002, Knekt 1991, Nomura 1987, Helzlsouer 1989, Kellen 2006, Michaud 2005, Michaud 2002, Zeegers 2002, Wallace 2009, Clark 1996, Longnecker 1991, Satia 2006, Thomson 2004, Murawaki 2008, Jackson 2008, Fowler 2004, Schrauzer 2000, Smith 2004, Fischer 2006, Slotnick 2006, Arnaud 2006, Longnecker 1996, Garland 1993, Sanchez 2010, Swanson 1990, Rodriguez 1995, Patterson 2001	
Liu 2013	Meta analyses 2+	Five cohort and five case-control studies were included. Five of these studies were conducted in the United States, five in Europe.	Inclusion criteria: (1) Case-control or cohort study published as an original article (2) papers reported in English between 1979 and 2011 October (3) Findings expressed as odds ratio (OR) or relative risk (RR) and its 95% confidence intervals (95% CI), or sufficient		This meta-analysis of cohort and case-control studies was undertaken to evaluate the relationship between cruciferous vegetables intake and risk of bladder cancer.	Three cohort studies and two case-control studies reported no significant association between cruciferous vegetables intake and bladder cancer incidence, whereas two cohort studies and three case-control studies found a significant decreased risk. Statistically significant protective effect of cruciferous vegetables intake on bladder cancer was observed in case-control studies (RR = 0.78, 95% CI 0.67-0.89), but not in cohort studies (RR = 0.86, 95% CI 0.61-1.11).	Case-control study and cohort study. This is the first meta-analysis evaluating the relationship between cruciferous vegetables intake and bladder cancer risk. Because of the limited number of

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			information allowing us to compute them.			No statistically significant heterogeneity was noted across the studies. When all these studies were analyzed together, we observed cruciferous vegetables intake was significantly associated with decreased risk of bladder cancer (RR = 0.80, 95% CI 0.69–0.92), with no significant heterogeneity between studies. There was no evidence of significant publication bias either with the Egger's test (P = 0.514) or with Begg's funnel plot (P = 0.721). The summary RR of 5 studies in USA did not markedly changed the summary RR of all studies and showed that cruciferous vegetables intake was significantly associated with decreased risk of bladder cancer (RR = 0.73, 95% CI 0.57–0.89). The summary RR of 5 studies in Europe showed that cruciferous vegetables intake had no association with the risk of bladder cancer (RR = 0.88, 95% CI 0.75–1.02). When separately analyzed by exposure assessment, we found no apparent	studies, further well-designed prospective studies are needed to explore the protective effect of cruciferous vegetables on bladder cancer. There are several important limitations: (1) Only published studies in English, limited resources prevented us from including articles published in other languages. (2) Search was restricted to studies published in indexed journals. (3) No search for unpublished studies or original data. (4) The small number of

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						difference between studies using a self-administered questionnaire (RR = 0.82, 95% CI 0.67–0.97) and studies using an interview (RR = 077, 95% CI 0.60–0.95). The results of this quantitative metaanalysis provided limited evidence for a protective association of high cruciferous vegetables intake with bladder cancer risk. Although the meta-analysis from the case–control studies suggested a moderate reduction in risk, the results from the cohort studies were null. There was statistically significant heterogeneity among 5 cohort studies (P = 0.005). However, no evidence of heterogeneity was noted across all studies (P = 0.055) and 5 case–control studies (P = 0.768). In conclusion, in this meta-analysis of 5 cohorts and 5 case–control studies, we find that high intake of cruciferous vegetables was associated with the reduced risk of bladder cancer. Siegel 2011, Murta-Nascimento 2007, Busby 2006, Vainio 2006, Kim 2009, Mettlin 1979, Michaud 1999, Zeegers	published studies severely limited the ability to detect publication bias although our results seem to suggest that there was no evidence of publication bias, the results of funnel plot and the Egger test still should be interpreted cautiously. (5) Most studies collected information through self-administered questionnaires. (6) People consume large amounts of cruciferous vegetables in Asia. (7) We did not search a study from Asia in this meta-analysis. (8) We assessed total cruciferous

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						2001, Michaud 2002, Castelao 2004, Holick 2005, Sacerdote 2007, Garcia-Closas 2007, Larsson 2008, Tang 2008, Lin 2009, Mantel 1959, DerSimonian 1986, Higgins 2003, Egger 1997, Begg 1994, Liu 2004, Tang 2004, Tang 2010, Tang 2006, Tang 2005, Tang 2004, Tang 2006, Zhang 2006, Munday 2008, Bhattacharya 2010, Ding 2010	vegetables consumption because of the relatively large number of studies on the topic. (9) Only 2 exposure levels (highest and lowest cruciferous vegetables) were examined.
Myung 2009	Meta analyses 1++	The final analysis included 161 045 total subjects, 88 610 in antioxidant supplement groups and 72 435 in placebo or nointervention groups, from 22 randomized controlled trials reported in 31 articles. In the studies in which the age and sex were reported, the mean (median) age was 58.4 years (age range 15–91 years), and 74.7% of	We included randomized controlled trials that reported the preventive effects of antioxidant supplements (beta-carotene; vitamins A, C, and E; and selenium) on cancer risk and compared the results of these trials with those in which placebo or no-intervention groups were used. We excluded studies that were conducted to investigate the treatment effect, not	Among the 22 trials, 20 had a placebo group as the control and two had a no-intervention group as the control	This meta-analysis investigate the quantitative preventive effects of the consumption of antioxidant supplements such as vitamins A, C, and E; betacarotene; and selenium on cancer risks determined via randomized controlled trials by type of prevention (primary or secondary), type	Effect of antioxidant supplements on prevention of cancer in all 22 trials: - No significant influence on the incidence of cancer compared with placebo administration or no intervention (RR 0.99; 95% CI 0.96–1.03) - Heterogeneity was not found (I^2 = 46.6%). - No evidence of publication bias (P = 0.98) Subgroup analyses by type of prevention - In the 12 studies on primary prevention trials, no significant effect on cancer prevention (RR 1.00; 95% CI 0.97–1.04) - In the 9 studies on secondary prevention trials, no significant	Randomized controlled trials Subgroup analyses by methodological quality 12 studies of the 22 having a high methodological quality. 10 studies had one or more inadequate components. No significant preventive effects were found in studies of either high (RR 1.00; 95%

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		the subjects were male. The selected articles were published from 1985 through 2007, spanning 22 years. Besides the countries belonging to the European Union (n = 1), the countries in which the studies were conducted were as follows: United States (n = 13), Finland (n = 7), China (n = 4), Canada (n = 3), UK (n = 1), France (n = 1), Italy (n = 1), and India (n = 1).	the preventive effect, of antioxidant supplements..		of antioxidant, and type of cancer. The main outcome measure was cancer incidence.	effect was observed (RR 0.97; 95% CI 0.83–1.13) Subgroup analyses by type of antioxidant administered singly: - No significant influence on cancer prevention - Beta-carotene (RR 1.01; 95% CI 0.96–1.07; n = 5), - Vitamin A (RR 0.98; 95% CI 0.90–1.08; n = 4), - Vitamin E (RR 1.02; 95% CI 0.90–1.16; n = 4), - Selenium (RR 0.62; 95% CI 0.36–1.08; n = 5). Subgroup analyses by type of cancer: - No preventive effect on 11 of the 13 types of cancers - The use of antioxidant supplements significantly increased the risk of bladder cancer (RR 1.52; 95% CI 1.06–2.17; n = 4). Conclusion: We found that there was no overall association between the consumption of antioxidant supplements and cancer risk.	CI 0.96–1.03) or low (RR 0.92; 95% CI 0.70–1.20) methodological quality. Methodological quality of the studies without additional information, only three studies having a high methodological quality. No significant effects were found in studies of either high (OR 0.99; 95% CI 0.92–1.07; n = 3) or low (OR 0.99; 95% CI 0.93–1.06; n = 19) methodological quality. Study included only synthetic antioxidants. Therefore, our findings are not

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						Further, subgroup analyses according to the type of prevention, type of antioxidant, and methodological quality of the studies also showed no preventive effect of antioxidant supplements on cancer. Our findings were consistent with those of previously published meta-analyses. No effects on either primary or secondary prevention of cancer, i.e. There was no specific difference in the effects of antioxidants between them. Tomita 1987, Glatthaar 1986, Sandhu 2000, Wright 2002, Hercberg 1998, Huang 2006, Bjelakovic 2007, Bjelakovic 2004, Bardia 2008, World Cancer Research Fund/American Institute for Cancer Research 2007, Kjaergard 2001, Munoz 1985, Greenberg 1990, Yu 1991, Li 1993, The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994, Clark 1996, Jyothirmayi 1996, Omenn 1996, Levine 1997, Moon 1997, Clark 1998, Heinonen 1998, Lee 1999, Rautalahti 1999, albanes 2000, Frieling 2000, Cook 2000, van Zandwijk 2000, Virtamo 2000, Mayne 2001, MRC/BHF Heart Protection Study 2002, Duffield-Lillico 2002, Malila 2002, Toma 2003, Virtamo 2003, Bairati 2005, Lee 2005,	applicable to the effects of fruits and vegetables.

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						Lonn 2005, Meyer 2005, Wright 2007, Dreno 2007, Blot 1993, Moon 1997, Kirsh 2006, Goodman 1993, Omenn 1994, Christen 2000, Costello 2001, Dawsey 1994, Mark 1994, Albanes 1995, Blot 1995, Albanes 1996, Hennekens 1996, Combs 1997, Yu 1997, Cook 1999, Reid 2002, Duffield-Lillico 2003, Hercberg 2006, Kamangar 2006, Omenn 1996, de Vet 1991, Correa 2000, Benner 1994, Benner 1994, Bolla 1994, Costa 1995, Ansari 2003, Perry 2005, Khuri 2006, Blot 1994, Blumberg 1994, Buiatti 1994, Taylor 1994, Wang 1994, Brawer 1995, Bolla 1996, Brawley 1996, Blot 1997, Biasco 1999, Del Mar 2000, Bollschweiler 2002, Holick 2002, Malila 2002, Michaud 2002, Akbaraly 2005, Cullen 2005, Buring 2006, Zhang 2006, Bairati 1996, Combs 1997, de Klerk 1998, Hartman 1998, Takagi 2003, Goodman 2004, Galan 2005, Stranges 2006, Caraballoso 2003, De Flora 1999, Cui 2007, Mayne 1996, Key 2002, Giovannucci 1993	
Wu 2013	Meta analyses 2+	A total of 24 studies were included. Studies were classified into 3 groups: Overall tea group, green tea group,	Inclusion criteria: 1) Original cohort or Case-control study design; 2) Overall, green tea, and black tea consumption; 3) Bladder cancer as			No significant association between overall tea consumption and bladder cancer were found in 15 studies on overall tea intake. Overall tea group - Based on 15 studies: No significant association between overall tea consumption (high in contrast	Cohort and case-control studies Several important limitations: Different units Subgroups Loss of follow up

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		black tea group. 15 studies based on overall tea, 5 studies on green tea and 6 studies on black tea. 8 were in Asia, 10 in the Americas, 5 in Europe, 1 in Oceania.	the outcome (or bladder cancer accounting for the majority); 4) The risks estimate RR or OR with their corresponding 95% CI.			to low intake) and bladder cancer risk (RR = 1.09, 95% CI: 0.85-1.40, *p* for heterogeneity: <0.01) Heterogeneity: subgroups of study design (sex, geographical region, smoking, adjustments, publication years (before or after 2000). No significant association by study design cohort: RR = 0.64, 95% CI: 0.40-1.04, case-control: RR = 1.22, 95% CI: 0.95-1.57 According to sex, both male (RR = 1.34, 95% CI: 0.62-2.88) and female (RR = 0.93, 95% CI: 0.56-1.53) showed no significant association by region, non-association was noted in the Americas (RR = 1.19, 95% CI: 0.86-1.64), Europe (RR = 0.91, 95% CI: 0.75-1.11) and other continents (China and Netherland) (RR = 1.26, 95% CI: 0.21-7.49). No publication bias was found among all studies either with Egger's (*p*=0.88) or Begg's test (*p*=0.11). Green tea group - Based on 5 studies: Green tea intake was not associated with bladder cancer risk (RR = 1.03, 95% CI: 0.82-1.31)	Recall bias Publication bias. Further studies are needed to confirm the findings.

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						No evidence of heterogeneity and publication bias (p=0.49 by Egger's test and p=0.81 by Begg's test) Black tea group - Based on 6 studies: A risk decrease in females subgroup were found The summary RR and 95% CI of bladder cancer risk were 0.84 and 0.70-1.01 A positive relationship between black tea consumption and bladder cancer risk was observed in women (RR = 0.6, 95% CI: 0.38-0.98), but not in men (RR = 0.91, 95% CI: 0.71-1.18). No evidence of heterogeneity among all studies and subgroup (sex) studies No publication bias was detected (p=1.00 by Egger's test and p=0.89 by Begg's test) Hussain 2003, Hu 2010, Herr 2008, Whitmore 1983, Zhang 2012, Busby 2006, Li 2011, Johansson 1997, Ross 1996, Sing 2011, Bushman 1998, Kuroda 1999, Tang 2009, Yang 2009, Chung 2003, Zeegers 2001, Li 2011, Zheng 2011, Higgins 2003, Sterne 2000, Wilkens 1996, Zeegers 2001, Zheng 1996, Kunze 1992, Nomura 1991, Woolcutt 2002, Slattery 1988, Bruemmer 1997, De Stefanie 2007, Lu 1999, Jensen 1986, La Vecchia 1992, D'Avanzo 1992, Ros 2011, Bates 2007, Jiang 2008,	

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						Bianchi 2000, Nagano 2000, Kurahashi 2009, Ohno 1985, Demirel 2008, Hemelt 2010, Wakai 2004, Slattery 1988, Ahmad 1999, Yang 1993, Gardner 2007, Nagle 2010, Lee 2002, Heilbrun 1986	
Zhou 2012	Meta analyses 2++	20 case-control studies with relative risks (RRs) adjusted for Smoking including 6,581 cases of bladder cancer and 11,985 controls. 5 cohort studies with relative risks (RRs) adjusted for smoking including 700 cases of bladder cancer and 229,099 participants. Published between Jan. 1971 and Dec. 2011. There were 28 outcomes for case-control studies and 6 outcomes for cohort studies.	Inclusion criteria: (1) Case-control or Cohort study; (2) The exposure of interest was the frequency of coffee Consumption; (3) The outcome of interest was bladder cancer; and (4) Adjusted risk estimate with their 95% CI for 3 or more quantitative categories of coffee consumption.		The purpose of the present study was to update and quantitatively assess the association between coffee consumption and bladder cancer risk by summarizing the separate results of published case-control studies and cohort studies, respectively.	In summary, although data from case-control studies suggest that coffee is a risk factor for bladder cancer, there is no conclusive evidence on this association because of inconsistencies between case-control and cohort studies. High vs. Low analysis in case-control studies. The pooled RRs (95%CI) for smoking: Highest category 1.45 (1.29-1.63) Second highest category 1.21 (1.12-1.31) Third highest category 1.08 (1.01-1.16) The pooled RRs (95%CI) among non-smokers: Highest category 1.74(1.12-2.71), Second highest category 1.36(1.05-1.76), Third highest category 1.24 (0.98-1.56) The effect was apparently stronger in	Cohort and case-control studies The significant association between coffee consumption and increased bladder cancer risk was observed in case-control studies, but the association was not found in cohort studies. These observational studies can be considered as the best available Epidemiological evidence, because no human experimental studies have been conducted. The potential bias of case-control

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		Among the 20 case-control studies, 8 studies reported 2 separate outcomes (men and women). Among the 5 Cohort studies, 1 study reported 2 separate outcomes (men and women).				nonsmokers than in smokers. High vs. Low analysis in cohort studies The RRs (95%CI) of bladder cancer were: Second highest category 1.22 (0.89–1.69) Third highest category 1.07 (0.86–1.33) The RRs for the highest category cannot be estimated for lacking data from the original studies Because only 5 cohort studies were available, we did not conduct subgroup analysis further. The pooled RRs (95%CI) among non-smokers from 2 cohort studies were 2.25 (1.07–4.73) for >1 cup/day, 1.53(0.69–3.41) for <1 cup/day. Dose-response meta-analysis for case-control studies. With RRs adjusted for smoking showed an increased bladder cancer risk of 1.10(95% CI, 1.07–1.15) for each 2 cups/day increase. Compared with non-drinkers, the summary RRs (95% CI) of bladder cancer were 1.07(1.02–1.13) for 1 cup/day	studies, such as selection bias and recall bias, might contribute to the discrepancy between case-control and cohort studies. The possibility that other factors such as cigarette smoking, age, other fluid intake, chlorinated tap water consumption and occupational factors may account for the observed association could not be ruled out.

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						1.15(1.05–1.26) for 2 cups/day 1.22(1.08–1.38) for 3 cups/day 1.29(1.12–1.48) for 4 cups/day. For the non-smokers, the pooled RRs (95% CI) were 1.20(1.01–1.42) for 1 cup/day 1.42(1.03–1.97) for 2 cups/day 1.62(1.07–2.45) for 3 cups/day 1.77(1.13–2.77) for 4 cups/day. Dose–response meta-analysis for cohort studies Showed an increased bladder cancer risk of 1.01(0.87–1.17) for each 2 cups/day increase. Compared with non-drinkers, The summary RRs (95%CI) of bladder cancer were: 1.09(0.89–1.34) for 1 cup/day 1.13(0.82–1.55) for 2 cups/day 1.09(0.77–1.56) for 3 cups/day 1.01(0.69–1.48) for 4 cups/day. No significant influence and publication bias were observed. Ames 1997, Anderson 1996, Asaad 2000, Bagnardi 2004, Bruemmer 1997, Cavin 1998, Chyou 1993, Ciccone 1988, Clavel 1991, Cole 1971, Cortez 2003,	

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						Covolo 2008, D'Avanzo 1995, De Stefanie 2007, Desquilbet 2010, Donato 1997, Egger 1997, Escolar 1993, Geoffroy-Perez 2001, Greenland 1992, Han 2011, Higgins 2002, Higgins 2003, Higgins 2008, Huber 2005, Jensen 1986, Jiang 2008, Joerges 2003, Kabat 1986, Kantor 1988, Kunze 1992, Kurahashi 2009, Michaud 1999, Mills 1991, Mohr 1993, Nagano 2000, Nomura 1991, Orsini 2006, Patsopoulos 2008, Pavanello 2010, Pelucchi 2009, Pohlabeln 1999, Porta 2003, Pozniak 1985, Risch 1988, Saiki 2011, Schreiber 1988, Slattery 1988, Spiller 1998, Stroup 2000, Tobias 1999, Ugnat 2004, van Dam 2005, Vena 1993, Villanueva 2004, Villanueva 2009, Wakai 2004, Wang 2004, Wells 2000, White 2009, Woolcott 2002, Yang 1998, Zeegers 2001, Zevin 1999	
Lotan 2012	RCT 1+	Included 34,887 men (eligible, evaluable SELECT participants) from a total of 427 participating sites in the United States, Canada and Puerto Rico. Included a large number of older	Randomly assigned to 4 groups (selenium, vitamin E, selenium plus vitamin E and placebo) double-blind fashion.	Placebo Group	We determined whether selenium and/or vitamin E would prevent bladder cancer. The primary endpoint was bladder cancer incidence, as determined by	The secondary analysis of SELECT showed no benefit from selenium or vitamin E independently or combined to decrease the bladder cancer incidence. This study showed no benefit to nutritional supplements, including vitamin E, for decreasing bladder cancer recurrence. Since selenium was not measured, there may possibly be a relationship between	Multiple sites, randomized, placebo controlled, double-blind. Further studies are needed to assess the effect in women, and at different doses and formulations.

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		men, and former (48%) and current (8%) smokers. Age 50 years or greater for black men age 55 years or greater for all other men. Only patients with pathology reports that confirmed a bladder cancer diagnosis were included.			routine clinical management. Secondary endpoints are not reported.	selenium and the bladder cancer incidence.	Various limitations: We did not analyze baseline plasma or toenail selenium or vitamin E in men with and without bladder cancer. This was a secondary analysis of a trial that did not focus on men at high risk for bladder cancer. The study was limited to men. There was no way to control for all risk factors for bladder cancer, such as smoking duration and extent, or environmental or occupational exposure. It is also unclear whether the 1 year off supplements had an impact on the study outcome.

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Michaud 2004	Nested Case Control Study 2+	The final sample size was 280 Cases. The ATBC Study was initiated between 1985 and 1988 when 29,133 male smokers, aged 50–69 years and living in Southwestern Finland. Baseline characteristics: smoking dose, smoking cessation, educational level, urban residence, beverage intake. In addition, data on health status, smoking, height, weight, and other characteristics were obtained at the time of entry into the trial.	Data for 280 incident bladder cancer cases were available for analysis. All participants provided toenail clippings (from all 10 toes).	The final sample size was 293 controls. One control was matched to every bladder cancer case on the basis of age, date of toenail collection, intervention group, smoking duration.	The authors examined the relation between toenail arsenic levels and bladder cancer risk among participants in the ATBC Prevention Study. Both intact toenails and pulverized toenails were used for this analysis.	The authors observed no association between inorganic arsenic concentration and bladder cancer risk (odds ratio = 1.13, 95% confidence interval: 0.70, 1.81 for the highest vs. Lowest quartile). The median arsenic concentration among controls was 0.105 µg/g (or ppm), and the concentration ranged from 0.02 µg/g to 2.11 µg/g. The present study suggests that arsenic exposure is unlikely to explain a substantial excess of bladder cancer in Finland or in countries with low arsenic exposure. No statistically significant effect modification was observed for smoking dose, number of years of smoking, place of residence, or beverage intake. Given our small sample size in the top percentiles, we cannot exclude the possibility that exposure levels of about 100 µg/liter may be associated with bladder cancer risk. Similarly, we cannot exclude the possibility that subgroups who are highly susceptible (genetic or environmental) may be at higher risk at lower arsenic levels given the potential	Randomized, doubleblinded, placebo-controlled study. This study is the first known to examine the association between internal inorganic arsenic exposure and bladder cancer risk using a biomarker. There are many limitations to using data from Taiwan, including differences in the environment, diet, and genetic susceptibility. The ATBC Study consists of male smokers. Therefore, our findings may not be generalizable to women or to nonsmokers.

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						for increasing misclassification of exposure over time, and with the knowledge that the latency period for bladder cancer is in excess of 20 years and may be as long as 50 years for arsenic exposure, we cannot rule out an association between low-dose arsenic exposure and bladder cancer among smokers.	Other, similar studies are needed to confirm these findings, especially for women.
Talaska 2006	RCT 1+	90 heavy smokers were recruited and randomly assigned to three groups conducted in Torino, Italy. Only healthy male heavy smokers of at least 15 cigarettes/day for the last 10 years, with average dietary habits, were admitted	3 groups and 3 different diets: The first diet was based on flavonoid-rich foods, particularly cruciferous vegetables, but not based on supplementation; The second was a normal isocaloric diet (with an adequate administration of fruits and vegetables); The third was based on supplementation of flavonoids in the form of green tea and soy products.	Subjects in the control group smoked more than those in the experimental groups	We have conducted a randomized trial which investigated the ability of dietary changes (in particular diets rich in cruciferous vegetables and flavonoids), to increase urinary antimutagenicity and inhibit DNA damage in smokers. The main objectives were an increase in urinary antimutagenicity and a reduction	The only statistically significant association was found in a regression model that adjusted for smoking, in which the increase in flavonoid intake was associated with a decrease in adducts after 1 year (P = 0.02). These data suggest that adherence to a diet rich in cruciferous vegetables and flavonoids might reduce genotoxicity in the human urinary bladder of smokers, but they should be interpreted with caution owing to small numbers and the uneven distribution of smoking habits in the experimental groups. The sample size for the present study was estimated on the basis of the following assumptions: An average expected concentration of DNA adducts was assumed to be ~ 40% lower in subjects with higher consumption of flavonoids.	Blind randomized controlled trial During the experiment 3 drop-outs occurred, corresponding to subjects who were not able to comply with the 'supplement' diet. Adducts could not be measured for technical problems (limited amount of DNA) in 17 of the remaining 87 subjects. The interpretation of our study is limited by the lack of correlation

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					in DNA adducts in exfoliated bladder cells. We tested multiple regression models with urinary antimutagenicity as the dependent variable, and dietary habits (fruit and vegetable intake) and level of urinary phenolics as independent variables.	Some differences can be noted among the 3 groups, none is statistically significant. We have found that dietary modifications using special recipes and instructions by a chef during an intensive course can affect the consumption of flavonoids and isoflavonoids. The intervention was focused on increasing the flavonoid/isoflavonoid intake, and it was successful in that respect. The intake of flavonoids was considerably different between the first and the other two groups, with a dose–response relationship that was statistically significant. We have now found that diets rich in flavonoids might modify the levels of DNA adducts in exfoliated bladder cells, but the evidence is equivocal. Our study suggests that an increased intake of plant foods can modify the adduct levels, whether or not this is due specifically to flavonoids. Given the complexity of dietary patterns,	between changes in flavonoid intake and levels of urinary phenolics.

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						and the equivocal nature of some of our findings, this is still a hypothesis that needs confirmation. At the present stage of knowledge it is totally unlikely that certain dietary habits can seriously counteract the effects of tobacco smoking.	
Virtamo 2000	RCT 1+	A total of 29,133 male smokers aged 50-69 years from southwestern Finland. Five or more cigarettes per day at entry. Urothelial cancer 169 incident cases, 47 were in the alpha-tocopherol-alone group, 42 in the alpha-tocopherol plus beta-carotene group, 43 in the beta-carotene-alone group, and 37 in the placebo group.	Exclusion: Subjects with prior cancer, or serious disease limiting long-term participation, or who used vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses. 4 groups: Alpha-tocopherol-group, Alpha-tocopherol plus beta-carotene group, Beta-carotene-group Placebo group		We studied the effect of alpha-tocopherol and beta-carotene supplementation on urinary tract cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.	Urothelial Cancer (Analyses were also repeated for bladder cancer separately, with similar results as for the urothelial cancers combined; thus their results are not presented) 169 incident cases of urothelial cancer The differences in incidences between the four groups were not statistically significant (p = 0.87). There was no interaction between alpha-tocopherol and beta-carotene supplementation effects (likelihood ratio test, p = 0.39). The cumulative incidence of urothelial cancer was similar among men receiving and not receiving alpha-tocopherol, relative risk 1.1 (95% CI 0.8-1.5) Similarly, beta-carotene supplementation had no effect on the incidence of urothelial cancer, relative risk 1.0 (95%	The study population was large, the intervention groups were balanced in all relevant characteristics, and the case ascertainment was essentially complete. Bias is an unlikely explanation for our lack of effect of alpha-tocopherol and beta-carotene supplementation on the incidence of urinary tract cancers. We found no evidence that high dietary intake or

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						CI 0.7-1.3). Neither was the effect of beta-carotene modified by the number of cigarettes smoked daily, or average daily alcohol consumption. The majority of urothelial cancers were of stage 0a (54%) when diagnosed, 5% were of stage 0is, 14% of stage I, 12% of stage II, 5% of stage III, and 8% of stage IV 2% could not be staged due to only cytologic specimen (n = 3). The distribution of stages was similar among recipients and nonrecipients of alpha-tocopherol (v2 test, p = 0.17), and beta-carotene (v2 test, p =0.47), respectively. Neither alpha-tocopherol nor beta-caro-tene affected significantly the risk of subgroups of urothelial cancer: relative risks of 0.9 (95% CI 0.6-1.5) and 0.8 (95% CI 0.5-1.2) for low and moderate grade superficial papillary tumors, respectively, and 1.2 (95% CI 0.8-1.9) and 1.2 (95% CI 0.8-1.9) for other bladder cancers (potentially invasive or invasion already present), respectively.	serum level of alpha-tocopherol or beta-carotene was protective against urothelial cancer, but rather a suggestion of increased risk with increasing intake of beta-carotene; however, we have no plausible explanation for this. We cannot, however, exclude the possible effect of residual confounding, since we had no data on lifetime occupations, which have been shown to account for up to one-fifth of bladder cancer risk.

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						The corresponding mortality rates did not differ (p = 0.91). Long-term supplementation with alpha-tocopherol and beta-carotene has no preventive effect on urinary tract cancers in middle-aged male smokers. We found no effect of alpha-tocopherol or beta-carotene supplementation on the incidence of urothelial (bladder, ureter, and renal pelvis) or renal cell cancer.	
Mondul 2012	Nested Case Control Study 2+	369 cases of bladder cancer were matched 1:1 with controls based on age (+/- 5 years), race, sex, and date of blood collection (+/- 30 days). Male participants	Models were conditioned on the matching factors. Multivariable models were further adjusted for smoking status, pack-years of smoking, dairy consumption, and use of aspirin or ibuprofen. Subgroup analyses were conducted stratifying by age, sex, race, smoking, season, study center, and DBP.	Controls were sampled with replacement from PLCO Study participants who were alive and cancer free at the time the case was diagnosed and were matched 1:1 to cases on age, race, sex, and date of blood collection.	We conducted an analysis of serum 25(OH)D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study, and examined whether serum vitamin D binding protein (DBP) concentration confounded or modified the association.	We did not observe a strong association between serum 25(OH)D and bladder cancer. An inverted U-shaped association was suggested, particularly when 25(OH)D was categorized as season-specific quartiles. This was attenuated with multivariable adjustment and was not statistically significant. Adjustment for serum DBP did not alter the findings, nor was DBP or the molar ratio of 25(OH) D:DBP associated with risk. We observed no interaction between 25(OH)D and any of the following:	Our study was sufficiently powered to detect an OR of 1.7 comparing the lowest to highest vitamin D quartile, we did not have power to detect a weaker association, particularly in subgroups. Future studies should plan to examine differences in the association by gender and smoking status. Additional studies in

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					We undertook an analysis of serum 25(OH)D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study, and examined whether serum DBP concentration confounded or modified the vitamin D association.	Age (p=0.48), Smoking (p=0.58), Sex (p=0.51), Race (p=0.56), DBP (p=0.64), or Study center UVB exposure (p=0.28). Restricting our analysis to current or former male smokers, an inverse association was suggested vs. Q4; Q1:OR=1.26, 95% CI=0.67-2.36; Q2:OR=1.64, 95% CI=0.92-2.92; Q3:OR=1.42, 95% CI=0.80-2.53; P trend = 0.34). We found no strong or statistically significant association between serum 25(OH)D and bladder cancer risk (Q1 vs. Q4: OR=0.84 95% CI=0.52–1.36; p-trend = 0.56). Further adjustment for serum DBP did not alter the findings, nor was there a main effect association between DBP and risk. In contrast to the one previous study of this hypothesis, we observed no association between vitamin D status and risk of bladder cancer; this difference could be due to the inclusion of women and non-smokers in the current study population, or to	populations with a range of vitamin D distributions may help clarify the inconsistent findings from the two studies.

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						differences in the distribution of vitamin D concentrations between the two study populations. Our study was sufficiently powered to detect an OR of 1.7 comparing the lowest to highest vitamin D quartile, we did not have power to detect a weaker association, particularly in subgroups. Importantly, the vitamin D distribution differs between the two cohorts; many PLCO participants were "replete" (25(OH)D 50-75 nmol/L; 41%) and few with 25(OH)D <25 nmol/L (5%). By contrast, given the population's geographic location, the majority of the ATBC Study participants had 25(OH)D levels <50 nmol/L (64%), and many (45%) had levels <25 nmol/L.	
Brinkman2011	Case-Control-Study 2+	200 bladder cancer cases and 386 healthy controls in the Belgian province of Limburg. Individuals 50 years of age and older according to municipality and social economic status.	Incident cases histologically confirmed with transitional cell carcinoma (TCC) of the bladder between 1999 and 2004. <1st or >99th percentiles, were excluded from analyses.	386 controls Individuals were eligible for inclusion as controls in the study if they belonged to the Caucasian race (to minimise differences due to genetic	A case-control study was designed to study possible risk factors for increased bladder cancer risk. The aim of our present study was to extend	We observed evidence for a protective effect by olive oil and a possible increased risk of bladder cancer associated with a high intake of cheese. Our results require further investigation and confirmation by other studies. Frequency distributions of sex, age, smoking characteristics and occupational exposures: - There were more men than	Population based case-control study To our knowledge this is the first epidemiological study on bladder cancer that has specifically investigated the effect of olive oil consumption.

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		Dietary data from a total of 198 cases and 377 controls were included in the analyses of this study. Adjustments were made for the following potential confounders: Age, sex, smoking (status, history and number of cigarettes smoked), occupational exposure (never versus ever: polycyclic aromatic hydrocarbons (pahs), aromatic amines) and calorie intake.		polymorphisms), were fluent in the Dutch language (spoken and written) and had no previous diagnosis of bladder cancer or any mental impairment which prevented their participation. The control subjects were a fair representation of the general population above 50 years from the province of Limburg in terms of established risk factors for bladder cancer: Age, sex and smoking characteristics.	investigations into this Belgian study population and examine the association between the consumption of major dietary fats and bladder cancer risk. We investigated the effects of consumption of animal products, olive oil and major dietary fats and observed a statistically significant inverse association between olive oil intake and the risk of bladder cancer consistent with a linear dose–response relationship. Whilst olive oil,	women in both the case and the control groups: 86% and 60% - On average cases were older than controls (67.6 ± 9.9 and 64.2 ± 9.6; p < 0.001 - A greater percentage of cases were current smokers, had smoked for a longer period and smoked more cigarettes per day than controls. - There were no other significant differences between cases and controls. Effects of daily intake level of food sources of dietary fat on bladder cancer risk: adjusted odds ratios (ors) and 95% confidence intervals (cis). - No statistically significant associations, either positive or negative, were observed between total meat consumption or any of the specific meat categories and bladder cancer - We did not detect an association either for consumption of chicken, fish or eggs - Borderline statistically significant increased odds of bladder cancer were observed for the highest versus the lowest tertile of cheese intake (OR: 1.53; 95% CI:	We did not detect any statistically significant associations Between bladder cancer and the other dietary sources of fat: margarine and deep frying oil. Consumption of butter and vegetable oil also contributed to total dietary fat intake but were consumed in quantities too small to be included into the logistic regression model. A comparison of the average intake for both these foods indicated that there were no statistically significant differences between the two groups of participants. Apart from the

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					the predominant fat in the Mediterranean diet, has been associated with many health benefits its role in bladder cancer aetiology is still unknown. Therefore, we investigated the effect of intake of animal products, olive oil and other major dietary fats on bladder cancer risk. Total intakes of meat, chicken, fish, eggs, milk, cheese and other dietary sources of fat, in particular olive oil, margarine and deep frying fat, were assessed in g/d.	0.95–2.46; p-trend = 0.08). - There was a statistically significant inverse association between olive oil intake and bladder cancer risk, with OR = 0.62 (95% CI: 0.39–0.99) for middle versus lowest tertile and OR = 0.47 (95% CI: 0.28–0.78) for the highest versus the lowest tertile of intake (p-trend = 0.002). Effects of intake level of major dietary fats on bladder cancer risk: adjusted odds ratios (ors) and 95% confidence Intervals (cis). - Consumption of major dietary fats: total fat and its subtypes, saturated fat, monounsaturated fat, polyunsaturated fat and linoleic acid and cholesterol - No association was observed between bladder cancer risk and any of these categories of dietary fats. We did not detect any associations between bladder cancer risk and any level of meat, chicken, fish, eggs, milk, margarine, deep frying fat, total fat, saturated fat, monounsaturated fat, polyunsaturated fat or linoleic acid	relatively small number of subjects, this study design is potential for selection bias due to the low response rate. Our results need to be confirmed by other studies and further investigation is required to elucidate the biological mechanisms and optimal levels of olive oil and cheese intake.

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					Assessments intake of total fat and subgroups of fat including saturated fat, monounsaturated fat, polyunsaturated fat and linoleic acid were calculated, also in g/d.	intake. There were no statistically significant differences between cases and controls for major dietary factors, calorie intake and total fat, suggesting that any potential recall error did not differ between the two groups. We observed a potentially protective effect from a high intake of olive oil and a suggestive increased risk associated with high cheese consumption.	
Brinkman2010	Case-Control-Study 2+	472 potentially eligible cases were contacted. As data were unavailable for 150 cases and 455 controls; a total of 322 cases and 239 controls were included in the dietary analyses of this study.	Inclusion criteria: New Hampshire residents, aged between 25 and 74, have a listed phone number, speak English.	Controls were shared with another study on non-melanoma cancer. Controls less than 65 years of age were selected from lists obtained from the New Hampshire Department of Transpor-tation. Controls 65 years of age and older were	The aim of our study was to investigate the association between major dietary minerals and vitamins and the risk of bladder cancer in a US population from a region with a high incidence rate. We investigated an extensive range of micronutrients in relation to the	Bladder cancer cases consisted of approximately three times more men (74%) than women. We detected no statistically significant differences between cases and controls for calorie, total fat, alcohol, or coffee intake. Fat-soluble vitamines Borderline statistically significant inverse association between total intake of vitamin E and bladder cancer (highest vs. Lowest quartile, OR: 0.66; 95% CI: 0.36–1.20; p trend = 0.09). No association between risk of bladder cancer overall and the intake of carotenoids either as individual	Population-based case–control study Possible confounding variables including sex, age, cigarette smoking status (current/noncurrent smoker), pack years of cigarette smoking. Limitations: Potential for recall bias is a consideration in dietary estimation. The effects of

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				chosen from data files provided by the Centers for Medicare & Medicaid Services (CMS) of New Hampshire. Controls were randomly assigned a comparable reference date to case group dates of diagnoses. We examined the charac-teristics of controls younger than 65 years and over 65 years and found them to be comparable with respect to sex, smoking, and medical access	risk of bladder cancer. We also performed additional analyses to assess the effects of minerals and vitamins from both dietary and supplemental sources separately. Minerals and vitamins that met the criteria were investigated for interactions with smoking characteristics and age.	carotenoids or collectively as total carotenoid intake. No statistically significant >ORs were observed when comparing the highest quartile of intake with the lowest quartile for carotenoids or for any of the individual carotenoids. Vitamin D also did not reach statistical significance (OR: 0.58; 95% CI: 0.31–1.06; p trend = 0.22). Water-soluble vitamins The OR for niacin and bladder cancer was of borderline statistical significance (highest vs. Lowest quartile OR: 0.56; 95% CI: 0.31–1.02). No other associations were observed between bladder cancer and any other B-group or water-soluble vitamins. No associations were observed between bladder cancer and total intake for any of the minerals sodium, potassium, magnesium, calcium, phosphorus, and iron. No detectable differences in the effects of any of the minerals and vitamins between invasive and non-invasive bladder cancer.	vitamin E, carotenoids, vitamin D, thiamin, and niacin in relation to the risk of developing bladder cancer may warrant further investigation. Future studies should focus on optimal doses and combinations of these micro-nutrients particularly for high risk groups such as heavy smokers and older individuals.

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				variables. Older subjects had less than a college education (40% under 65 years and 50% 65 years and older).		The OR for heavy cigarette smokers in the highest group for total intake of vitamin E 0.58 (95%: 0.34–0.99; p interaction 0.03). Inverse associations of borderline statistical significance were also observed among heavy smokers for the highest intake of total carotenoids (OR: 0.62; 95% CI: 0.36–1.09; p interaction 0.08) and niacin (OR: 0.66; 95% CI: 0.39–1.14; p interaction 0.08). Interaction between thiamin intake and the number of cigarettes smoked per day was also of borderline statistical significance. Possible reductions in risk of bladder cancer for older participants were also associated with higher intakes of total carotenoids (OR: 0.59; 95% CI: 0.35–0.99), vitamin D, thiamin, and niacin (p interaction: 0.04, 0.02, and 0.03, respectively). Reduced odds of bladder cancer among the older age group for the highest intake of vitamin E (OR: 0.61; 95% CI: 0.37–1.02) and interactions between vitamin C and ever-smoking (p = 0.08) and vitamin C and age (p = 0.08) were	

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						borderline. Possible inverse associations of borderline statistical significance were observed between bladder cancer and total intake of vitamin E and dietary phosphorus.	
Brinkman_2 2011	Case-control study Conducted in the Belgian province of Limburg 2+	200 bladder cancer cases 50 years of age and older. All cases were incident cases identified with histologically confirmed transitional cell carcinoma (TCC) of the bladder between 1999 and 2004. Cases were derived from the Limburg Cancer Registry (LIKAR). A total of 586 participants (200 cases and 386 controls) were included.	Odds ratios (ors) and 95% confidence intervals (cis) were calculated for age, sex, smoking characteristics, occupational exposures, and energy intake.	386 control subjects Control subjects were selected through the Belgian Authority. 50 years of age and older.	The aim of our study was to evaluate the effect of dietary intake of minerals and vitamins that have a biological association with bladder cancer risk, in terms of both main and potential interaction effects. Adjustment for potential confounders: Age, sex, smoking characteristics, occupational exposure to (pahs) and aromatic	We found a positive association between calcium intake and bladder cancer. There was some evidence of an interaction between intakes of magnesium and both phosphorus and calcium and phosphorus and vitamin D intake. Sub-optimal levels and balances between the related micronutrients calcium, phosphorus, magnesium and vitamin D may influence bladder cancer risk. Individuals most affected by these micronutrient imbalances: - Older participants, - Males, - Heavy smokers. Positive association between calcium intake and bladder cancer (OR: 1.77; 95% CI: 1.00–3.15; p-trend = 0.049). No associations between any of the	Our results need to be confirmed by other studies, and further investigation is clearly required to determine optimal intakes and balances between these and other interrelated nutrients.

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		Data from 11 participants (2 cases and 9 controls) reporting extreme energy intake and were excluded from analyses. Therefore, dietary data from a total of 198 cases and 377 controls were included. Greater percentage of males in both groups, and this percentage was higher in cases than controls (86 and 60%). Cases were older than controls (p = 0.001). Cases were more often current smokers, smoked more cigarettes per day, and had smoked for a longer			amines, and energy intake (kcal/day). Analyses were repeated for alcohol, water, coffee, and tea consumption, which might modulate the action of minerals and water-soluble vitamins.	other minerals or vitamins and the risk of bladder cancer. Increased risk of bladder cancer associated with a higher intake of calcium among older participants compared with the younger age group OR: 1.90; 95% CI: 1.08–3.36. Male and older age group also appeared to increase the risk of bladder cancer with a higher intake of phosphorus OR: 1.93; 95% CI: 1.08–3.44 and OR: 2.02; 95% CI: 1.05–3.92.	

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		period than controls. No statistically significant differences between cases and controls for the average daily intake of the micronutrients under investigation. Exposure to occupational carcinogens and intake of major dietary factors: Energy (kcal), fat, water, alcohol, and tea and coffee were not statistically significantly different between cases and controls.					
Catsburg 2013	Population-based case-control study Conducted in Los Angeles County, California.	Eligibility criteria: histologically confirmed first urothelial carcinoma diagnosis between 1987 and 1996 among non-Asian individuals between the ages of 25 and	Of 2,098 eligible cases, 1,671 (80%) were enrolled in this study. 11 cases were later determined not to be transitional cell carcinoma and so	1,586 controls (1,237 men and 349 Women). The mean age was 54.4 years. For each enrolled case, a	We investigated the role of dietary sources of nocs as potential bladder cancer risk factors. We investigated	In summary, in our study we found that intake of liver and of salami, pastrami or corned beef to be associated with increased risk of bladder cancer, particularly among nonsmokers. In particular, we observed that the effects of consuming these meats might be greater in the context of diets with	As far as we know, this study is the only one that has considered the role of processed meat in bladder cancer risk while taking into account potential modifying

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	2+	64 years. 1,660 cases (1,307 men and 353 women). The mean age was 54.4 years Characteristics: Non-Hispanic-White, Hispanic, African American Level of education differed between cases and controls (p< 0.001), controls have a higher level of education. Cases were more likely to have a history of diabetes (p = 0.016). More cases were ever smokers and among ever smokers. Mean duration and	were excluded. Additional Charakteristics: Age, Gender, BMI, Education, History of diabetes, Cigarette use, Tumor stage cases, Tumor grade cases.	control individual was recruited. Controls were matched by age, gender and race/ ethnicity. If a matched control was not found, the race criterion was dropped. A race/ ethnicity matched control could not be found for 86 cases. If a control could not be found under relaxed criterion, no control was included. A matched control was found for 1,586	associations between intakes of food items containing high amounts of exogenous nocs or NOC precursors and risk of bladder cancer, also taking into account dietary factors that can prevent or stimulate endogenous formation of nocs. We considered processed meats as direct sources of exogenous nocs, but also examined possible sources of precursors for endogenous formation of nocs, such as liver and processed meats, which are	overall high nitrate intake. Our findings support a role for endogenous nitrosation as a potential risk factor for bladder cancer, particularly among nonsmokers. Salami/pastrami/corned beef intake: - Positive associations p trend = 0.008 - The two highest categories compared with the lowest category associated with a 30% increased risk - Strongest association among never smokers p trend = 0.006 Liver intake: - Statistically significant association (highest compared with lowest category): o OR = 1.26; 95% CI = 1.00–1.60 o P trend = 0.039 - Strongest association among never smokers: o OR = 1.76; 95% CI = 1.09–2.85 o P trend = 0.016 A test of heterogeneity of trends between never and ever smokers was not statistically significant, p = 0.118.	effects of other sources of nitrosamine precursors, such as nitrate, nitrite and heme intake. As in all case-control studies, recall bias may be present, given that at the time this study was conducted. There was no widespread knowledge of the role of processed meats and bladder cancer, any such recall bias is likely nondifferential, and thus likely to bias results towards the null.

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		intensity of cigarette smoking were significantly higher in cases than in controls (p< 0.001).		(95%) of cases. Controls reported: Greater numbers of daily servings of fruit and vegetables (p < 0.001), Higher vitamin A and C intake (p < 0.001), Higher total carotenoid intake (p = 0.004) More servings of all food combined (p = 0.001).	abundant sources of amines, nitrate, nitrite and heme, as well as fruits and vegetables, which are sources of nitrate. We observed evidence of a synergistic effect between high nitrate intake and consumption of large amounts of processed meats and liver.	Total dietary intake of nitrate, nitrite, nitrosamines and heme: - No associations with bladder cancer risk - Among never smokers, high intake heme was associated with almost twice the risk, OR = 1.97; 95% CI = 1.16–3.33; P trend = 0.010 Nitrate intake appeared to modify the associations between bladder cancer risk and Intake of liver (p = 0.010), Intake of hot dogs/ Polish sausage (p = 0.005) and Heme (p = 0.010). We found no evidence that intake of nitrite, nitrosamines, nor various antioxidants and/or dietary factors known to inhibit endogenous nitrosation, modified the effects of the various sources of amines considered. We found no evidence that Vitamin A modified the association between total nitrosamines, nitrate or nitrite and bladder cancer risk. Fruits and vegetables are main contributors to total nitrate intake. Our findings suggest that fruits and vegetables are protective factors against	

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						bladder cancer. Vegetables, especially green leafy vegetables such as spinach, lettuce and parsley, also have a very high content of nitrate. We saw no evidence of an association with preformed nocs and bladder cancer risk in this study.	
Feki-Tounsi 2012	Case-control study 2 ++	344 male from central and southern regions of Tunisia. Women were excluded because of the very small number and in order to exclude gender-related hormonal risk factors. 124 patients were consulting in the Urology Department for bladder cancer symptoms such as hematuria or urination problems. A total of 108 (87 %) agreed to participate in this	Information regarding sex, age, residence, lifestyle habits and occupational exposure may contribute to variations in arsenic concentration. Also included were data on health status, medication, occupational covariates, place of residence, and utilization of individual protective equipment. The two population samples (affected and non-affected) can be taken as comparable in health, lifestyle,	A total of 214 (97 %) of the eligible Control patients were sequentially recruited. 196 (89 %) controls supplied an adequate volume of blood for testing. All controls did not have any cancerous history. Age distribution was comparable to that of cases.	We examined the possible association between exposure to Arsenic (As) and the risk of bladder cancer among Tunisian men. Tap and rain waters are the major sources of drinking water in the studied population. The proportion of people who use well water is very weak.	Cases and controls presented significant differences in the cigarette smoking parameters, Seafood meals per month, sources of drinking water, exposure to residential and/or occupational pollution or pollution caused by smoking habits, exposure to vehicle fumes. As levels in the blood samples of cases were significantly higher than those of the controls, they were more than twice higher. No significant associations between either vehicle fumes exposure or water consumption and Blood-As levels. Blood-As variations with the tumor stage and grade were not significant. Evaluation of potential confounders did not demonstrate any evidence of confounding by environmental or occupational exposure to pollution or	Our study is a pioneer investigation which provides much needed information regarding human exposure to As in Tunisia. Limitations to the current study: Use of atomic absorption spectrometric technique which affords a measure of total arsenic (Future investigations should use techniques that allow the distinction of the different As

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		study and get a confirmed Bladder cancer diagnosis. Cases were slightly older (mean age = 66.3 years) than the controls (mean age = 61.3 years). About 46.3 % of cases in the cancer group and 51.6 % in the control group were drawn from urban areas from the region of Sfax and the other regions from the center and the south of Tunisia.	and living conditions. The diagnosis of bladder cancer was confirmed after cystoscopy, and the identification of the hystological stage was obtained after the analysis of biopsies resected from bladder mucosa. We compared the As blood levels of the cases from different histological tumor stages and grades.			water consumption. The results indicate that B-As above 0.7 µg/L might relate to bladder cancer even if other important risk factors were taken into account. The lack of significant association between B-As level and tumor classification is probably due to the limited number of bladder cancer cases. Exposure assessment studies encompassing a wider population and differentiating between the arsenical species are needed to confirm the findings of this preliminary study. More information is needed about the sources and pathways of exposure to arsenic and other environmental toxicants in this population.	species). Blood measurements as a biomarker for As exposure, other studies have typically involved the measurement in urine, hair, and/or toenails. The findings were based on small numbers of cases and controls and we did not get significant association with the grade or the stage of the tumor. The designed questionnaire did not allow us to cover all the potential sources of exposure to arsenic. Future studies should focus on dietary sources as well as proximity

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							from waste sites. Environmental monitoring of As could help us find solutions to control exposure.
Mondul_2 2012	Case-control study 2+	369 Bladder cancer cases with pre-diagnosis serum available occurred during 13 years of follow-up. Caucasian male smokers from southwestern Finland were recruited between 1985 and 1988. 250 bladder cancer cases were randomly sampled by month of blood collection.	Vitamin D binding protein (DBP) was measured by ELISA (R&D kits). Models were conditioned on the matching factors. Multivariable models were further adjusted for smoking status and use of aspirin or ibuprofen (yes/no). Subgroup analyses were conducted stratifying by age, sex, race, smoking, season, study center and DBP. Characteristics of cases and controls: Age Male	Controls were sampled with replacement from PLCO-Study participants, who were alive and cancer free at the time the case was diagnosed and were matched 1:1 to cases on age, race, sex, and date of blood collection. Controls were matched 1:1 to cases on age at randomization and date of blood collection.	Analysis of serum 25(OH)D and risk of bladder cancer in the Prostate, Lung, colorectal, and Ovarian (PLCO) Cancer Screening Study. Examination, whether serum DBP concentration confounded or modified the vitamin D association.	We did not observe a strong association between serum 25(OH)D and bladder cancer. An inverted U-shaped association was suggested, particularly when 25(OH)D was categorized as season-specific quartiles. This was attenuated with multivariable adjustment and was not statistically significant. Adjustment for serum DBP did not alter the findings, nor was DBP or the molar ratio of 25(OH)D:DBP associated with risk. We found no evidence of an association between vitamin D and risk of bladder cancer. These results differ from those of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study of male smokers which found a protective association	Future studies should plan to examine differences in the association by gender and smoking status. Additional studies in populations with a range of vitamin D distributions may help clarify the inconsistent findings from the two studies.

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			Caucasian Height Weight BMI Education Smoking status Hours spent in vigorous activity None Family history of bladder cancer Personal history of diabetes Regular aspirin use Regular ibuprofen use Dietary and supplement intake (per day) Total energy (kcal) Vitamin D (µg) Calcium (mg) Dairy food Red meat (g) Supplemental vitamin D (µg) Supplemental calcium (mg) Supplemental vitamin E (mg) Serum 25(OH)D (nmol/L) Serum DBP (µg/ml).			between vitamin D and bladder cancer risk. This difference may be explained by the inclusion of women and Non-smokers in the current analysis. Although our study was sufficiently powered to detect an OR of 1.7 comparing the lowest to highest vitamin D quartile, we did not have power to detect a weaker association, particularly in subgroups.	
Mucci 2003	Case-control	The sample size was	Survey questionnaires	The sample size	We reanalysed a	Weekly intake of French fries and potato	The relation of risk

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	study, 2	cases with cancer of the large bowel (591), Bladder (263), Kidney (133). Incident cases were identified in the Stockholm Area. Participation rates were between 68 and 74%. Reasons for nonparticipation: death, illness, refusal, loss of questionnaire.	were mailed to 692 controls, and 875, 391, 186 cases of cancer of the large bowel, bladder, and kidney. 15 controls and 25 cases had missing dietary data on > 10% of items and were dropped from the analysis. A measure of acrylamide dose was determined by the following food: Potato crisps, French fries, fried potatoes, fried pancakes, pizza, meatballs, breaded fish, cereals, crisp and soft bread, and biscuits. The foodstuffs were ranked according to the median acrylamide content: Rank of 0 Without appreciable	was 538 controls. Randomly selected and frequency matched by age and gender. Participation rates were 80%.	population-based Swedish case–control study, assessing dietary acrylamide by linking extensive food frequency data with acrylamide levels in certain food items. We have analysed data to investigate whether higher intake of certain food items with higher acrylamide content increases the risk of cancers of the large bowel, bladder, or kidney. Potential confounders: Smoking, body mass index, alcohol intake,	crisps by both cases and controls was low, while intake of pan-fried potatoes was more common. Controlling for potential confounders, there is little evidence of an association between any specific baked or fried potato product and cancer risk. While the data suggest a higher risk of bladder cancer for those with daily intake (OR 1.6 (95% CI 0.7–3.5)), wide CIs preclude definitive assessment. There is no evidence of a positive association between crisp breads and cancer risk. The relative risk between dietary acrylamide dose and cancers of the bladder and kidney was essentially null, and was similar for smokers and nonsmokers. This study found no association between dietary exposure to acrylamide in amounts typically ingested by Swedish adults and risk of cancers of the large bowel, bladder, or kidney.	to the acrylamide content of all foods could not be studied. The classification of acrylamide by IARC as a probable human carcinogen (IARC, 1994) was based mainly on in vitro and animal models. The human data were less clear and limited to occupational settings. It was large and population-based with reasonably high response rates, thus reducing the possibility of selection bias while the data on demographic, lifestyle, and dietary, covariates would have reduced the opportunity for

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			acrylamide Rank of 1 With a median acrylamide content less than 100 $\mu g kg^{-1}$ Rank of 2 With a median acrylamide dose 100–200 $\mu g kg^{-1}$ Rank of 4 With a median acrylamide dose 200–600 $\mu g kg^{-1}$ Rank of 8 With a median acrylamide dose greater than 600 $\mu g kg^{-1}$ Variables that were statistically significant at $\alpha = 0.20$, or which confounded the relation between acrylamide and cancer, were included in the final model.		fruit and vegetable intake, saturated fat density, red meat density, and total energy.		confounding in the analysis. This first study of dietary acrylamide in relation to three major human cancers is reassuring. Additional epidemiological evidence is required, notably for other cancer sites as well as for neurological and other disorders. While the null hypothesis of no effect can never be scientifically proven, it would be useful to determine cooking methods that avoid acrylamide formation during food preparation. Residual confounding is a possible explanation

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							for some of our findings.
Kellen 2006	Populations-based case-control study 2 ++	200 caucasian in the Belgium province of Limburg. Diagnosed with histologically confirmed transitional cell carcinoma of the bladder, between 1999 and 2004. Included women 14%. Mean age: 67.67 Year, SD 9.82 The smoking prevalence was higher than in controls. Our cases are somewhat younger than the bladder cases in the Limburg Cancer Registry.	788 food items, based on 3 existing food tables (NEVO table of the Netherlands, Nubel table of Flanders, IPL table of Francophone Belgians). Frequencies of consumption and average daily quantities of foods, energy and nutrients are calculated by an adapted version of nutrition analysis of food frequency questionnaire (NAF). Biological samples were also collected, blood samples and buccal swabs, preference to blood samples, buccal swabs were collected in < 5%. DNA was	385 caucasian Represented the general population of the province, older than 50, although fewer women are included (41%) than in the general population (42.38%), (p = 0.00). Mean age: 64.26 year, SD 9.73. The smoking prevalence was lower than in cases. In our study, cases and controls were selected independently	Our study investigated the possible interaction between the protective effect of fruit intake, cigarette smoking and several genetic polymorphisms (GSTM1, GSTT1, NAT2 and SULT1A1) on bladder cancer risk. We adjusted for age, sex, smoking and occupational exposures to pahs or aromatic amines in the logistic model as these are, by far, the most important confounders for bladder cancer.	Findings suggest that the effect of cigarette smoking on bladder cancer risk is reduced by fruit consumption.	Our study had several methodological strengths. One was the detailed dietary questionnaire. We decided not to match cases and controls on age and gender. Matching on factors that are affected by exposure or disease can irreparably bias the study data. The loss of patients (because of high age or to the seriousness of disease) might introduce selection bias. However our study concerns bladder

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			resuspended in Tris-EDTA (TE) buffer and stored at -20°C for future use. Total fruit and total vegetable intake was calculated as the sum of the relevant food items.	of exposure and the controls were sampled randomly from a defined study base (the population of the Limburg province) from which also the cases arose.			cancer risk and not progression, the presence of relevantly biased study results is unlikely. We were only able to compare the sex and age distribution of the controls with those of the general population. A major limitation of case-control studies is the possibility of recall bias among cases and controls. This may be especially relevant in the case of dietary recall. We felt that the association between bladder cancer and diet or even smoking is not well known among the general population.

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							To investigate potential bias by dietary recall, we analyzed the most recently diagnosed cases separately and found similar results compared to when all cases were included in the analyses. This may indicate that recall bias may not have biased our results. Furthermore, recall bias does not necessary apply when studying statistical interaction between genotype and environmental exposure.
Ward 2003	Case-control study 2+	808 bladder cancer cases. 622 men 186 women	Age 40–85 residents of Iowa, newly diagnosed with bladder cancer in 1986–1989. We included cases of	1259 controls We included only those who used public supplies with nitrate data for	We conducted a population-based case-control study of bladder cancer in Iowa originally to	After adjustment for confounders, we found no increased risk of bladder cancer with increasing average nitrate levels in drinking water; the highest quartile odds ratio for women was 0.8 (95% CI = 0.4–0.8), and for men 0.5 (95% CI = 0.4–0.8).	Our study could not evaluate risk at nitrate levels above the maximum contaminant level because of the lack of exposure data for

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			in situ and invasive bladder cancer and only those who used public supplies with nitrate data for 70% or more of their person-years since 1960. Characteristics: Demographic factors, smoking, occupations and lifetime residences and drinking-water sources. Water nitrate intake was computed using total intake and residential nitrate levels. We computed person years by type of water source: - Iowa private wells, - Iowa public supplies - bottled water From the year of birth to the year of Diagnosis for cases (1986–1989).	70% or more of their person-years since 1960. Controls were frequency-matched to the case distribution at a different ratio in two study periods (1986–1987; 1988–1989). For controls we computed person-years to the year of interview or 1989, whichever date was earlier.	evaluate disinfection by products and risk of several cancers. We evaluated the association of drinking water nitrate levels and bladder cancer risk stratified by dietary vitamin C intake and smoking status, which are factors known to affect endogenous nitrosation. We computed person years by type of water source from the year of birth to the year of diagnosis for cases (1986–1989). We evaluated	Our data suggest that long-term exposure to nitrate in drinking water at levels in this study (90th percentile 5.5 mg/liter nitrate-nitrogen) is not associated with risk of bladder cancer. In summary, although it is biologically plausible that drinking-water nitrate intake is a risk factor for bladder cancer, we found no evidence that nitrate levels below about 5 mg/liter were associated with risk.	private wells and the infrequent exposure above this level among public water-supply users. Further, the large majority of the population using public water supplies had average nitrate levels that were half the maximum contaminant level. Lack of information about other factors of water quality likely resulted in substantial misclassification of nitrate exposure in our analysis of private well duration. Our study had limited power to evaluate higher exposure levels. Studies in

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			Excluded from the analyses were those with more than 30% of their person-years from 1960 in the following categories: 1) residing outside of Iowa; 2) residing in Iowa but using private wells; 3) residing in Iowa towns with unknown nitrate levels in the public supplies; and 4) having an unknown water source history. Any combination that summed to more than 30% of their person-years from 1960 resulted in exclusion from the analyses. Restricting the analysis to those who had 80% and 90% of their person-years with an estimated nitrate level did not change our results.		the duration of private well use in Iowa overall and duration of use of wells less than 50 feet deep. We stratified the analysis by ever having a bladder or kidney infection to evaluate a possible interaction between this bladder cancer risk factor and drinking water nitrate exposure. The detailed information on drinking water sources, tap water intake and diet allowed us to evaluate nitrate as a risk factor for bladder cancer.		populations with higher exposure levels are warranted. Strengths of our analysis include: - The high response rates among cases and controls, - The large sample size, - A lifetime watersource history, - The availability of historical nitrate levels for Iowa public water supplies and - Our ability to evaluate effect modification by vitamin C intake, smoking and bladder infections.

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			We computed an average public water-supply nitrate level from 1960. We also computed the number of years that an individual had an Iowa public water supply with nitrate levels ≥ 10 mg/liter nitrate-N; all years ≥ 10 mg/liter were after 1960. We evaluated the duration of private well use in Iowa overall and duration of use of wells less than 50 feet deep. Nitrate levels in shallow private wells in Iowa (less than 50 feet deep) can be substantially higher than deeper wells. We computed maximum likelihood estimates of the ORs				

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			to estimate the association between the exposure metrics and bladder cancer. We adjusted the ORs for known or suspected risk factors for bladder cancer including age, cigarette smoking, years of education and duration of chlorinated surface water use. Cases and controls included in the PWS nitrate analyses had used Iowa public water supplies for an average of 50 years, compared with 20 and 18 years for excluded cases and controls.				
Hotaling 2011	Cohort-Study 2+	Study participants are members of the VITAL cohort of 77,719 men and women. 50 to 76 years old.	Characteristics: Dietary supplement use, diet, medical history, personal characteristics and cancer risk factors.		We used the prospective VITAL cohort to examine the association of all commonly taken vitamin and	Participants in whom incident UC developed were significantly more likely to be male, and recency and pack-years of smoking were positively associated with UC risk. Fruit and vegetable intake did not show	Prospective study Advantages of our study include its prospective design, the focus on supplements and

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		Living in a 13-county area of western Washington State. We excluded 665 participants who reported a diagnosis of bladder cancer before entering the study or had missing data on prior bladder cancer. 4 Participants with incident nonurothelial bladder cancer (pure squamous cell carcinoma or pure adenocarcinoma) were also excluded from analysis, leaving 77,050 eligible participants.	We analyzed multivitamins, betacarotene, retinol, folic acid, vitamin B1, B3, B6, B12, C, D and E, as well as the minerals calcium, iron, magnesium, zinc and selenium. For each vitamin and mineral we ascertained intake from single supplements and multivitamins, including the frequency and duration of use of each supplement in the 10 years before baseline, and the average dose per day. Multivitamin use and vitamin supplement use were examined for an association with UC. For each subject the end of followup was the earliest of date of		mineral supplements as well as 6 common anti-inflammatory supplements with incident UC in a United States population. VITAL was specifically designed to assess the associations of supplement use with cancer risk.	a statistically significant association with risk of UC. None of the vitamin supplements had a statistically significant association with UC in the age adjusted or multivariate models. We also found no association between 5 commonly used mineral supplements (calcium, iron, magnesium, zinc or selenium) and UC: - HR for Ca 319 mg or greater daily vs nonuse 1.00 CI 0.71, 1.40, p trend = 0.66; - HR for Se 20 mcg or greater daily vs nonuse 0.97 CI 0.72, 1.31; p trend = 0.740. Similarly 6 commonly used anti-inflammatory supplements (glucosamine, chondroitin, saw palmetto, ginkgo biloba, garlic and fish oil) failed to show any statistically significant reduction in incident UC in the multivariate model: There was no evidence for effect modification by smoking status for the relationship between any of the supplements and UC risk.	cancer risk including recruitment of a high proportion of supplement users, and the large sample size. In addition, our assessment instrument for ascertaining supplement use included more types of supplements and more detail on their use than prior studies, and our study of the measurement properties of this questionnaire found it to have good reliability and validity. Nonetheless, nondifferential measurement error due to inaccuracies of self-report would have attenuated our results and we do

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			UC (0.43%), date withdrew from the study (0.03%), date moved out of the 13 counties of western Washington covered by SEER (5.44%), date died (5.69%) or date of last cohort followup (December 31, 2007; 88.42%).				not know how long participants continued supplement use. Other potential limitations of the study include the relatively low rate of use of some of the less common vitamin, mineral and anti-inflammatory supplements, and the modest number of UC cases (330) limiting power. Another significant limitation is that while we have DNA on approximately 54,000 individuals, we have yet to examine genetic polymorphisms in carcinogenesis and metabolic pathways that may modify our results. Recent work has suggested that

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							stratification by genetic polymorphisms of enzymes in the metabolic and carcinogenesis pathways is necessary to identify populations in which supplements could attenuate UC risk. Potentially these could allow us to identify a subgroup of patients who might benefit significantly from supplement use.
Jacobs 2002	Cohort study 2+	Subjects for this analysis were drawn from the 1,184,622 participants (508,334 men and 676,288 women) in the Cancer Prevention Study II (CPS-II). Participants were enrolled in 1982 in all 50 US states, the	All analyses excluded participants who reported a history of cancer other than non-melanoma skin cancer (*n* = 82,345) or for whom data on vitamin supplement use (*n* = 56,354) or on cigarette smoking (*n* = 54,401) were incomplete or uninterpretable.		We examined the association between use of vitamin C and vitamin E supplements and bladder cancer mortality in a large cohort of US men and women.	Among participants in this analysis, approximately 12 % were regular users of vitamin C and 9 % were regular users of vitamin E supplements. Compared with participants who did not use either vitamin C or vitamin E, regular users of vitamin C or vitamin E supplements were less likely to be current cigarette smokers and more likely to be White, to be college educated, and to report frequent consumption of vegetables and citrus	We had no updated information on vitamin supplement use during the 18 years of follow-up. Additional data will be needed to determine whether potential effects of long-duration vitamin E supplement use on

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		District of Columbia, and Puerto Rico.	A total of 991,522 participants (446,227 men and 545,295 women) remained for analysis. Questionnaire included information on: demographic characteristics and various behavioral, environmental, occupational, and dietary factors.			fruits/juices. There was considerable overlap between use of vitamin C and vitamin E supplements. When adjusted for age and sex only the rate ratio for regular long-duration vitamin C use was RR = 0.95 95 % CI: 0.72, 1.24, and the rate ratio for regular long-duration vitamin E use was RR = 0.66 95 % CI: 0.44, 0.99. The reduced risk associated with regular long-duration vitamin E use (≥10 years at enrollment) was more apparent among current cigarette smokers at enrolment RR = 0.31, 95 % CI: 0.10, 0.89, than among former cigarette smokers RR = 0.69, 95 % CI: 0.35, 1.36, or never cigarette smokers RR = 0.84, 95 % CI: 0.36, 1.93, although this difference could have been due to chance (p = 0.52 for heterogeneity of the rate ratios by smoking status). We found no evidence that the associations of vitamin C and vitamin E supplement use with bladder cancer mortality differed by citrus or vegetable intake. In this large cohort of US men and	bladder cancer differ by smoking status. Regardless of whether vitamin E supplement use reduces bladder cancer risk for cigarette smokers, our results do not suggest that cigarette smokers can meaningfully reduce their overall disease risk by using vitamin E supplements. The few epidemiologic studies of bladder cancer and vitamin C use have produced mixed results. As in any observational study, the effects of potential confounding factors need to be

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						women, regular long-duration use of vitamin E supplements was associated with a reduced risk of bladder cancer mortality. Shorter-duration vitamin E supplement use as well as vitamin C supplement use were not associated with bladder cancer mortality. The differences in rate ratios by smoking status that we observed could easily have been due to chance. Quitting smoking is by far the best way for smokers to prevent both bladder cancer and many other serious diseases. If high doses of supplemental vitamin E do inhibit bladder carcinogenesis, there could be potential implications for bladder cancer treatment as well as for primary prevention. Such vitamin supplementation is not used in the treatment of bladder cancer patients, possibly because of concerns about the toxicity of high doses of vitamin A. Our results, together with those from the Health Professionals Follow-up Study cohort, suggest that vitamin E, which has	considered, which is particularly true in analyses of vitamin supplement use because regular vitamin users are generally more likely to practice “health-conscious” behaviors. Although we were able to adjust (or determine that adjustment was unnecessary) for several potential confounding factors, we cannot rule out residual confounding. In this cohort, regular vitamin C and vitamin E users were very similar with respect to measured health-related behaviors and characteristics such as smoking, education, and vegetable

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						low toxicity, could have contributed to the reduction in tumor recurrence observed in the randomized trial. We found no association between bladder cancer mortality and vitamin C use, even regular long-duration use. In summary, our results, together with those from the Health Professionals Follow-up Study cohort, provide some support for the hypothesis that long-duration vitamin E supplementation may reduce bladder cancer risk.	consumption. We examined mortality from bladder cancer rather than incidence of bladder cancer. Further confirmation is needed.
Zeegers 2001	Cohort study 2+	58 279 men and 62 573 women. Aged 55–69 years. The study population originated from 204 municipal population registries throughout the country. More than 80% of the cases were male, whereas in the sub-cohort approximately 50%	After excluding prevalent cases with cancer other than skin cancer a total of 3346 subcohort members (1630 men and 1716 women) and 619 incident cases (532 men and 87 women) with microscopically confirmed, incident carcinomas of the urinary bladder, ureters, renal pelvis or urethra were identified. Of these cases, 584		There are many candidate agents in fruits and vegetables that influence bladder cancer risk. In the present prospective study, we were able to explore the influence of the intake of different vitamins (i.e. Retinol, vitamin C, vitamin E, and folate), and the	The results of the prospective Netherlands Cohort Study showed that, in general, the intake of retinol, vitamin C, vitamin E, folate, carotenoids, and the use of vitamin supplements are not associated with bladder cancer risk. Only ß-cryptoxanthin intake appeared to be inversely associated with bladder cancer risk, especially among heavy cigarette smokers. The protective effect of ß-cryptoxanthin intake was observed in each stratum of tumour invasiveness or morphology of male transitional cell carcinomas of the bladder, although the association was less pronounced for non-invasive papillary tumours.	Prospective study The prospective nature of a cohort study together with completeness of follow-up, as has been achieved in this study, reduced the potential for selection bias to a minimum. Nondifferential misclassification of exposure, may have resulted in underestimation of the strength of the

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		were male.	(94.3%) were diagnosed with bladder cancer of which 559 (95.7%) were transitional cell carcinomas. Because the overwhelming majority of tumours occurred in the urinary bladder and the ureters, renal pelvis, and urethra are covered by the same urothelium as the urinary bladder, the term bladder cancer is used as a synonym for these neoplasms. In this study, variables of principle interest were retinol, vitamins C and E, folate, several carotenoids and the use of vitamin-containing supplements. For calculating the		use of vitamin-containing supplements on bladder cancer risk with substantially more cases than in previous studies..	The intake of ß-cryptoxanthin appeared to be inversely associated with bladder cancer risk (p-trend < 0.01) with corresponding age- and sex adjusted RRs per increasing quintiles of intake of 1.00 (reference), 0.63 (CI: 0.48–0.83), 0.54 (CI: 0.40–0.72), 0.59 (CI: 0.44–0.80) and 0.71 (CI: 0.53–0.95). After adjustment for ß-cryptoxanthin intake, the inverse association for vitamin C intake disappeared. The RRs for ß-cryptoxanthin intake did not change essentially after adjustment for vitamin C intake. We found a statistically significant interaction effect with smoking amount (P < 0.01) but not with smoking duration (P = 0.10). The inverse association between ß-cryptoxanthin and bladder cancer risk was not found. The risks of bladder cancer for consumers of vitamin supplements containing vitamin A, vitamin C or Vitamin E were similar to the risk for non-consumers.	association. However, the results of the validation study showed that the questionnaire was able to rank subjects adequately according to their intake of most nutrients. Information bias is also largely avoided because dietary habits were reported before bladder cancer was diagnosed. A potentially more realistic problem in evaluating the observed inverse associations is residual confounding by cigarette smoking. We were not able to explain our results on the basis of confounding of

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			intake of specific carotenoids an additional food composition table has been constructed. We were able to evaluate six of the most important types of carotenoids: A-carotene, ß-carotene, Lutein, Zeaxanthin, ß-cryptoxanthin and Lycopene. Subjects were categorized in users or non-users of supplements containing vitamin A, C or E. Subjects with incomplete or inconsistent dietary data were excluded leaving 569 cases (491 men and 78 women) with bladder cancer and 3123 subcohort members (1525 men and 1598				other factors in addition to cigarette smoking, since our results were essentially unchanged after incorporating into the analyses many known or suspected risk factors for bladder cancer, including total consumption of alcohol, coffee, tea, and water, high risk occupation, and family history of bladder cancer.

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			women) for the analyses. Of the potential confounders, the distribution of age, total water, alcohol, coffee, tea, total vegetable, and total fruit consumption was similar for cases and sub-cohort members.				
Ros 2012	Cohort study 2++ EPIC is a cohort study comprising more than one-half million people recruited between 1992 and 2000 in 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy,	468,656 participants After 8.9 years of follow-up, 947 UCC were diagnosed among 468,656 EPIC participants. Of these, 421 could be classified as aggressive UCC and 433 as non-aggressive UCC cases. 93 UCC cases could not be classified as aggressive or non-aggressive UCC	Inclusion: Only urothelial cell 'papillomas' and carcinomas (morphology codes 812–813) were included in the analysis. Exclusion: We excluded all prevalent cancer cases at recruitment (n = 23,633), participants with missing follow-up data (n = 3448), missing questionnaires (n = 16,037).		We examined the relation between fruit and vegetable consumption and the risk of aggressive and non-aggressive UCC in the European Prospective Investigation into Cancer and Nutrition (EPIC). All analyses were stratified by age at recruitment (in one-year	Participants who developed UCC were somewhat older, more likely to be men, heavier in weight and longer in stature, more likely to be current smokers, to be exposed to arcinogens at the job, more frequently of a lower educational level and reported lower consumption of fruits and vegetables, higher intakes of alcohol and red and processed meats compared to the total cohort at baseline. We found no association between total fruit and/or vegetable consumption and the risk of non-aggressive or aggressive UCC. No association was found between fruit consumption and aggressive UCC (hazard ratio (HR) highest versus lowest tertile 1.01; 95% CI 0.76–1.35) nor for	EPIC is a large cohort study, well suited to examine the role of fruit and vegetable consumption in relation to different pathological features of UCC. Case–control studies have mainly observed inverse associations between fruit and vegetable consumption and bladder cancer risk. However, these

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	Netherlands, Norway, Spain, Sweden, and the United Kingdom). Aged between 25 and 70 years.	because information on stage and grade was lacking.	Participants with a ratio of energy intake versus energy expenditure in the top and bottom 1% of the distribution were also excluded to reduce the effect of implausible dietary values (n = 9674). After these exclusions, the study cohort comprised 468,656 participants. Participants were followed from study entry until a diagnosis of first primary UCC (code C67, ICD-Oncology third edition). All analyses were controlled for: smoking status, duration of smoking, lifetime intensity of smoking and energy intake from fat and non-fat sources.		categories) to control for length of follow-up, by sex, and by centre to control for country effects, as follow-up procedures and questionnaire design may slightly differ between countries.	non-aggressive UCC (HR highest versus lowest tertile 0.88; 95% CI 0.66–1.18). We observed no significant association between vegetable consumption and aggressive UCC (HR highest versus lowest tertile 0.91; 95% CI 0.68–1.23) nor for nonaggressive UCC (HR highest versus lowest tertile 0.83; 95% CI 0.61–1.12). For specific types of fruits and vegetables, the present study suggests an inverse association between the consumption of root vegetables, leafy vegetables, and grapes and the risk of UCC. Our joint analyses show an inverse association between fruit or vegetables and UCC risk, in particular non-aggressive UCC, among non-smokers. No effect was observed among current smokers with a high or a low consumption of fruit and vegetables. We observed a decreased risk of an increment of grapes with 25 g/day on non-aggressive UCC (HR 0.68; 95% CI 0.47–1.00) and in the analysis of the categorical intake variable (HR highest versus lowest tertile 0.67; 95% CI 0.48–	studies may have suffered from recall bias by disease-related changes in (the reporting of) dietary habits. This problem is overcome in prospective cohort studies. An international panel of experts concluded that the evidence for an association between fruit and vegetable consumption and bladder cancer is limited. The weak protective or null associations in epidemiological studies may be explained by the fact that most studies had a relatively short follow-up period, included relatively few participants and

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			Not included, as each factor did not noticeably affect risk estimates: Height, weight, consumption of red and processed meat, alcohol, physical activity, educational level.			0.94; P-trend = 0.04). We did find a decreased risk with increments of 25 g/day of root vegetables for aggressive UCC (observed HR 0.87; 95% CI 0.77–0.98, calibrated HR 0.70; 95% CI 0.50–0.97). Higher consumption of leafy vegetables was inversely associated with non-aggressive UCC (observed HR for 25 g/day increase in intake 0.88; 95% CI 0.78–1.00, calibrated HR 0.58; 95% CI 0.38–0.88). In summary, our study did not confirm a protective effect of total fruit and/or vegetable consumption on aggressive or non-aggressive UCC. High consumption of certain subtypes of vegetables and fruits may reduce the risk of aggressive or non-aggressive UCC, although chance findings cannot be excluded.	thereby lacked power to detect real associations. Inconsistencies between studies may also arise because the relation with fruit and vegetables was not stratified by bladder tumor aggressiveness. It has been recognized that bladder tumours vary in natural history and stratification into different UCC subgroups according to stage and grade may help in identifying risk factors involved in different UCC pathways. As far as we know, there are no previous studies that evaluated the

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							effect of subgroups of fruit and vegetable consumption separately for aggressive and non-aggressive bladder cancer. Even though results suggest inverse associations, this should be interpreted with caution because we conducted multiple comparisons and residual confounding cannot be excluded. As smoking is the predominant risk factor for the development of UCC, these findings should further reinforce recommendations for smoking prevention and cessation.

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							Despite the large cohort size, there is limited power to evaluate joint effects of smoking status and subgroups of fruits and vegetables. The strengths of our study include its large-scale and multi-centre prospective study design and the possibility to distinguish non-aggressive from aggressive urothelial bladder cancers. A limitation of our study was that the food frequency questionnaire was only used during enrolment and was not repeated during follow-up. The hazard ratio estimates may be

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							biased toward the null value and the calibrated HR estimates should be interpreted with caution. Future analyses of diet and UCC risk should preferably include data on specific genetic polymorphisms and biomarkers of diet such as concentrations of antioxidant levels in blood. It is of interest to identify dietary patterns that are associated with UCC risk. Analyses to this respect are planned within EPIC.
Ros_2 2012	Cohort study 2+ EPIC is a cohort	The current study included 856 pairs of first primary UCC cases and their matched controls.	Plasma carotenoids were measured by using reverse-phase HPLC, and plasma vitamin C was	856 cohort members Controls were randomly	We examined the association between prediagnostic plasma	No significant associations were observed between concentrations of individual carotenoids, vitamin C, and risk of total UCC.	Prospective design To our knowledge, only 2 previous studies evaluated

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	study comprising more than one-half million people recruited between 1992 and 2000 in 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and the United Kingdom). Aged between 25 and 70 years.	856 patients with newly diagnosed UCC were matched with 856 cohort members by sex, age at baseline, study center, date and time of blood collection, and fasting status. 405 cases were classified as aggressive. 384 cases were identified as nonaggressive. 67 UCC cases could not be classified because information on stage and grade was not available. Each case was matched to one control subject by incidence density sampling from all cohort members alive and free of	measured by using a colorimetric assay. Blood samples were collected (serum, plasma, red cells, and buffy coat for DNA extraction). Participants were followed from study entry until a first primary bladder cancer diagnosis (code C67, ICD-Oncology), death, emigration, or end of the follow-up period. Only urothelial cell papillomas and carcinomas (morphology codes 8120 and 8130) were included in the analyses. Matching criteria were sex, age at time of enrolment, study center, date of blood collection, time of day of blood collection,	selected from the population at risk at the time of the index case occurrence. A selected control could have served as a control for another case and may have become a case at a later time in follow-up.	carotenoids and vitamin C concentrations and risk of prognostic subgroups of UCC in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC).	The sum of carotenoids, showed an inverse association with total UCC (IRR for highest compared with lowest quartile: 0.64; 95% CI: 0.44, 0.93; P-trend = 0.04). For the sum of carotenoids, inverse associations were quite similar for aggressive and nonaggressive UCC risk, but the reduction in risk of aggressive UCC was only significant for subjects in the highest quartile (IRR for highest compared with lowest quartile: 0.53; 95% CI: 0.30, 0.94; P-trend = 0.05). Plasma ß-carotene was inversely associated with aggressive UCC (IRR for highest compared with lowest quartile: 0.51; 95% CI: 0.30, 0.88; P-trend = 0.02) but not with nonaggressive UCC. For nonaggressive UCC, inverse associations were observed for plasma lutein (IRR highest compared with lowest quartile: 0.56; 95% CI: 0.32, 0.98; P-trend = 0.05). For dietary ß-carotene, an inverse association was observed with total UCC risk (IRR for highest compared with lowest quartile: 0.70; 95% CI: 0.50, 0.97; P-trend = 0.04).	the effect of carotenoids stratified by bladder tumor aggressiveness, the Alpha-Tocopherol Beta-Carotene Prevention trial and the Netherlands Cohort Study. The inverse associations observed should be interpreted with caution because we conducted multiple comparisons, and residual confounding by smoking could not be excluded. Our results showed that the inverse associations remained unchanged when the results were adjusted for several lifestyle factors. Limitations in this

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		cancer at the time of diagnosis of cases (except for nonmelanoma skin cancer).	and fasting status at the time of blood collection. Matched controls were unavailable for 11 cases, and these individuals were excluded from analyses. All analyses were controlled for smoking status, duration of smoking, and lifetime intensity of smoking. Energy intake, consumption of processed or red meat, alcohol intake, physical activity, BMI, occupational history, and educational level were not included in the final analyses because none of these factors noticeably affected the ß-estimates of plasma variables.			A higher intake of dietary ß-carotene was borderline significantly inversely associated with nonaggressive UCC risk (IRR for higher compared with lowest quartile: 0.61; 95% CI: 0.37, 0.99; P trend = 0.09) but not with aggressive UCC risk. For plasma ß-carotene, an inverse association was shown for aggressive UCC but not for nonaggressive UCC. A graded decrease in UCC risk with increasing plasma concentrations of vitamin C was shown in current smokers (IRR for highest compared with lowest plasma vitamin C concentrations: 0.63; 95% CI: 0.41, 0.97; P-interaction = 0.007). The sum of plasma carotenoids was inversely associated with UCC risk. Inverse associations were also observed for ß-carotene and risk of aggressive UCC and between plasma lutein and risk of nonaggressive UCC. No association was observed between plasma vitamin C concentrations and UCC risk. Risk of UCC was reduced with increasing	study: Carotenoids are transported in blood as part of lipoprotein complexes, and plasma concentrations may depend on the type and amount of fat consumed. Optimally, plasma concentrations of carotenoids should be adjusted for blood lipids. The use of supplements such as ß-carotene or vitamin C could also affect plasma concentrations. Information about the type of supplement and frequency of use was not available in our study. Our analyses were

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			For all analyses, 2-sided P = 0.05 was considered statistically significant.			plasma concentrations of vitamin C in current smokers. In our study, dietary ß-carotene was borderline significantly inversely associated with UCC risk, whereas dietary vitamin C was not associated with UCC risk. After separation of prognostic risk groups, our findings suggest an inverse association between plasma b-carotene and risk of aggressive UCC. For nonaggressive UCC, inverse associations were observed for plasma lutein. Plasma vitamin C or carotenoid concentrations in combination with smoking status suggest that there is a graded decrease in UCC risk in current smokers with a high concentration of plasma vitamin C or carotenoids. If an effect of plasma vitamin C or carotenoids exists, our study suggests that it is more prominent in current smokers. High plasma concentrations of carotenoids may just be a marker of a healthy lifestyle.	based on single measurements of plasma carotenoids and vitamin C concentrations. Residual confounding by smoking or other factors cannot entirely be excluded, and confirmation of our results in other prospective settings is warranted. Results may have been biased by changes in blood concentrations after diagnosis.

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						Higher concentrations of carotenoids may also be a marker of a concerted effect of multiple bioactive compounds in fruit and vegetables. The correlation between plasma markers and the variety of fruit and vegetable consumption was rather weak, which makes interpretation difficult. Our results suggest that plasma ß-carotene may be protective for aggressive UCC, whereas plasma lutein may be protective for nonaggressive UCC.	

2.6. AG 1 Schlüsselfrage 6 (Diagnostische Marker für die Früherkennung)

„Welche diagnostischen Marker sind für die Früherkennung und Screening-Untersuchungen von Risikogruppen bzw. der Gesamtpopulation geeignet?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Turco 2009	Study of Diagnostic Accuracy 3	2,594 cytology specimens were eligible for analysis	We included all subjects meeting these criteria: (1) being resident in the districts of Florence and Prato; (2) submitting a urinary specimen for cytology-cal examination to an ISPO laboratory from general or urological practices, or from any hospital within the district (3) having no previous history and/or RTT registration of bladder or other types of urothelial carcinoma.		We evaluated the accuracy of urinary cytology for primary bladder cancer using population data linkage to provide valid estimates The aim of the present study was to assess the accuracy of urinary cytology on a population basis, using data linkage of cytology results in a consecutive well-defined series to a regional population cancer registry, ensuring complete ascertainment of outcomes in all	Overall, 130 bladder cancers matched with the cytology database, of which 97 occurred within 12 months of cytology and were included in assessing accuracy. Urine cytology is highly specific but has intermediate sensitivity, indicating that it has a role in adjunct diagnosis, but not in screening for primary bladder cancer. Sensitivity (C3–C5 considered positive) ranged between 40.2 and 42.3% C3 – C5 positive (Cx excluded) 42.3 % (39/92) C3 – C5 positive (Cx included) 40.2 % (39/97) If C3 results are counted as negative, sensitivity estimates reduced to 24.7–26.0% C4 – C5 positive (C3 counted as negative) (Cx excluded) 26.0 % (24/92) C4 – C5 positive (C3 counted as negative) (Cx included) 24.7 % (24/97) High Tumor Grade = significantly higher sensitivity compared to low and intermediate grades combined (p = 0.02)	Single Site Retrospective C3 results should considered ‘posit and further investigated, and positive results should prompt further interventi The most signific aspect - we have used better methodology tha previous studies, through populati data linkage and complete ascertainment of outcomes, hence our estimates are valid and do not

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			And who had urine cytology performed from January 2000 to December 2004. Cases with incident urothelial cancer other than bladder (i.e. kidney, urether, uretra) were excluded from the study.		subjects.	G1 = 42.8 % G2 = 20.6 % G3 = 51.2 % Gx (grade not known) = 33.3 % Specificity (C3-C5 considered positive) ranged between 93.7-94.1% C3 - C5 positive (Cx excluded) 93.7 % (2,173/2,319) C3 - C5 positive (Cx included) 94.1 % (2,318/2,464) C4 - C5 positive (C3 counted as negative) (Cx excluded) 98.5 % (2,286/2,319) C4 - C5 positive (C3 counted as negative) (Cx included) 98.6 % (2,431/2,464) PPV C3 = 11.7 % C4 = 39.2 % C5 = 66.6 % LR+ C3 - C5 positive (Cx excluded) - 0.46 C3 - C5 positive (Cx included) - 0.43 C4 - C5 positive (C3 counted as negative) (Cx excluded) - 0.26 C4 - C5 positive (C3 counted as negative) (Cx included) - 0.25	overestimate accuracy. The lower sensiti we have reported relative to others work is a reflecti of our approach ascertaining negative results.

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						LR- C3 – C5 positive (Cx excluded) – 0.44 C3 – C5 positive (Cx included) – 0.42 C4 – C5 positive (C3 counted as negative) (Cx excluded) – 0.25 C4 – C5 positive (C3 counted as negative) (Cx included) – 0.24	
Lotan 2009	Study of Diagnostic Accuracy 3	1328 patients were included, 56 patients were excluded due to lack of cytology (44) and race (12) data Leaving 1272 patients in the analysis Two subgroups One subgroup of 670 (52.7%) patients from four centres was used to develop the nomograms. The new BC	76 (6.0%) had bladder cancer 217 (17.1%) were NMP22-positive 17 (1.3%) had malignant cells on urinary cytology Most were men (723, 56.8%) and white (1050, 82.5%) Smoking was reported by 461 (36.2%) patients Microscopic haematuria was present in 960 (75.5%), vs gross in		To determine whether the nuclear matrix protein-22 (NMP22) assay can improve the accuracy of discriminating between highrisk patients with and without bladder cancer. Statistical Methods: Development of a multivariable (MVA) NMP22-based BC nomogram Development of a MVA urinary	The ability of the NMP22 test to predict bladder cancer in high-risk patients significantly exceeds that of urinary cytology. The NMP22-based nomogram can help to identify individuals at risk of bladder cancer. The NMP22 results were positive in 217 (17.1%) patients and urine cytology in 17 (1.3%) Sensitivity NMP22 = 55.7 % Specificity NMP22 = 85.7 % PPV Men % (n/N), 95% CI All 23.8 (34/143), 17.1–31.6 < 65 years 22.8 (13/57), 12.7–35.8 ≥ 65 years 24.4 (21/86), 15.8–34.9 Smokers 34.8 (16/46), 21.4–50.2 Non-smokers 18.6 (18/97), 11.4–27.7	Single Site Retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		nomograms were externally validated in 602 (47.3%) patients from nine other centres	206 (16.2%), 76 (6.0%) had bladder cancer The NMP22 results were positive in 217 (17.1%) patients and urine cytology in 17 (1.3%).		cytologybased BC nomogram Development of a Combined MVA nomogram that relies on both NMP22 and urinary cytology results All nomograms were externally validated and their accuracy compared directly	No haematuria 0 (0/9), 0.0–33.6 With microhaematuria 14.9 (14/94), 8.4–23.7 Non-smokers with microhaematuria 13.0 (9/69), 6.1–23.3 Smokers with microhaematuria 20.0 (5/25), 6.8–40.7 With gross haematuria 50.0 (20/40), 33.8–66.2 Non-smokers with gross haematuria 37.5 (9/24), 18.8–59.4 Smokers with gross haematuria 68.8 (11/16), 41.3–89.0 PPV Women % (n/N), 95% CI All 12.1 (9/74), 5.7–21.8 < 65 years 8.5 (4/47), 2.4–20.4 ≥ 65 years 18.5 (5/27), 6.3–38.1 Smokers 6.7 (2/30), 0.8–22.1 Non-smokers 15.9 (7/44), 6.6–30.1 Without haematuria 0 (0/5), 0.0–52.2 With microhaematuria 0.6 (3/48), 1.3–17.2 Non-smokers with microhaematuria 7.1 (2/28), 0.9–23.5 Smokers with microhaematuria 5.0 (1/20), 1.2–24.9	

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						With gross haematuria 28.6 (6/21), 11.3–52.2 Non-smokers with gross haematuria 33.3 (5/15), 11.8–61.6 Smokers with gross haematuria 16.7 (1/6), 0.4–64.1 NPV Men % (n/N), 95% CI All 95.9 (556/580), 93.9–97.3 < 65 years 97.0 (322/332), 94.5–98.5 ≥ 65 years 94.4 (234/248), 90.7–96.9 Smokers 93.9 (217/231), 90.0–96.6 Non-smokers 97.1 (339/349), 94.8–98.6 No haematuria 94.9 (56/59), 85.8–98.9 With microhaematuria 97.6 (409/419), 95.7–98.8 Non-smokers with microhaematuria 96.9 (253/258), 92.9–99.0 Smokers with microhaematuria 96.9 (156/161), 92.9–99.0 With gross haematuria 88.3 (91/103), 80.5–93.8 Non-smokers with gross haematuria 94.2 (65/69), 85.8–98.4 Smokers with gross haematuria 76.5 (26/34), 58.8–89.3 NPV Women % (n/N), 95% CI	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						All 98.1 (466/475), 96.4–99.1 < 65 years 100.0 (357/357), 99.0–100 ≥ 65 years 92.4 (109/118), 86.0–96.4 Smokers 97.4 (150/154), 93.5–99.3 Non-smokers 98.4 (316/321), 96.4–99.5 Without haematuria 87.2 (34/39), 72.6–95.7 With microhaematuria 98.1 (390/399), 95.7–99.4 Non-smokers with microhaematuria 98.1 (263/268), 95.7–99.4 Smokers with microhaematuria 96.9 (127/131), 92.4–99.2 With gross haematuria 66.7 (42/63), 53.6–78.0 Non-smokers with gross haematuria 68.7 (33/48), 53.7–81.3 Smokers with gross haematuria 100.0 (9/9), 0.66–100.0 LR+ NMP22 = - 0.66 LR- NMP22 = - 0.64	
Kapila 2008	Study of Diagnostic Accuracy	46 patients (38 men, 8 women)	-	-	The study was undertaken to evaluate nuclear	Combining NMP22 with malignant or suspicious cytological result improved sensitivity for the detection of bladder cancer	Single Site Retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
	Single site Kuweit 3	46 patients (38 men, 8 women) Age ranged from 30 to 78 years (median of 62.5 years) Patients suspected to have bladder cancer and those on follow up or who were suspected to have a recurrence were included in this study The patients were clinically categorized into newly diagnosed cases of transitional cell carcinoma (TCC), recurrent TCC, TCC in remission and			matrix protein (NMP22) compared to urine cytology in the detection of bladder cancer and also to determine whether indexing suspicious cytology to NMP22 could enhance the clinical utility of cytology Cytological findings of voided urine collected prior to a cystoscopic biopsy were correlated with urine NMP22 assay in 46 patients attending the urology clinic in Mubarak Al-Kabeer Hospital NMP22 Bladder Check Test Cytospin Millipore preparations stained by	but with a major decrease in specificity, suggesting a potential role in screening rather than diagnosis. There were three false positive cases on cytology and 13 false positive cases on NMP22 assay. There were three false negative cytology and five false negative NMP22 cases but only one was false negative for both, resulting in a high sensitivity (96%) but low specificity (30%) if either positive NMP22 or malignant or suspicious cytology was taken as a positive result. Our study showed a significant increase in sensitivity when suspicious were combined with malignant cases with a relatively slight drop in specificity. In summary, cystoscopy and bladder biopsy are the accepted gold standard methods for diagnosis of bladder cancer, but the possibility of an occult tumor elsewhere in the urinary tract cannot be excluded. Sensitivity Urine cytology lacks sensitivity while cystoscopy lacks specificity	There are conflic reports in the literature regardi its role as a screening test as recent studies ha shown that the value of NMP22 assay is limited b its low specificity and high false positive rates. 13 our study also th were 13 false positive cases or NMP22 assay as compared to thre false positive and three false suspicious cases cytology. this is a small stu we found that association of NMP22 with a malignant or

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		controls. Histological diagnosis as the gold standard The controls comprised of patients with urolithiasis or schistosomiasis. In the control group there was one false positive case on cytology that was also positive for NMP22. This patient was a case of schistosomiasis on follow up.			Papanicolaou stain were studied for cytological examination The biopsy was processed routinely and Hematoxylin and Eosin stained section examined for the presence or absence of TCC The Exact Binomial Method for confidence intervals (CI) Z-test for difference in proportions was used to generate the P-value for differences in sensitivity, specificity, PPV and NPV Using histological	Estimate [95 % C.I.] p* Cytology Malignant only 30 [13-53] - Malignant or suspicious 87 [66-97] 0.004 NMP22 NMP22+ only 78 [56-93] 0.02 Combinations NMP22+ and malignant cytology 22 [7-43] 0.73 NMP22+ and malignant or suspicious cytology 70 [47-87] 0.08 NMP22+ or malignant cytology 87 [66-97] 0.004 NMP22+ or malignant or suspicious cytology 96 [78-100] 0.0002 Specificity	suspicious cytological result improves significantly the sensitivity of the urinary detection bladder cancer b decreases drastic the specificity. Hence, this association could better preferred f bladder screenin than bladder diagnosis.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					diagnosis as the gold standard, Urine cytology has been the reference standard for noninvasive testing for bladder cancers.	Urine cytology lacks sensitivity while cystoscopy lacks specificity Estimate [95 % C.I.] p* Cytology Malignant only 87 [66–97] – Malignant or suspicious 74 [52–90] 0.31 NMP22 NMP22+ only 43 [23–66] 0.01 Combinations NMP22+ and malignant cytology 96 [78–100] 0.31 NMP22+ and malignant or suspicious cytology 87 [66–97] 1.0 NMP22+ or malignant cytology 35 [16–57] 0.005 NMP22+ or malignant or suspicious cytology	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						30 [13–53] 0.004 PPV Estimate [95 % C.I.] p* Cytology Malignant only 70 [35–93] – Malignant or suspicious 77 [56–91] 0.72 NMP22 NMP22+ only 58 [39–75] 0.58 Combinations NMP22+ and malignant cytology 83 [36–100] 0.59 NMP22+ and malignant or suspicious cytology 84 [60–97] 0.83 NMP22+ or malignant cytology 57 [39–74] 0.55 NMP22+ or malignant or suspicious cytology 58 [40–74] 0.56 NPV	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Estimate [95 % C.I.] p* Cytology Malignant only 56 [38–72] – Malignant or suspicious 85 [62–97] 0.05 NMP22 NMP22+ only 67 [38–88] 0.56 Combinations NMP22+ and malignant cytology 55 [38–71] 0.97 NMP22+ and malignant or suspicious cytology 74 [54–89] 0.22 NMP22+ or malignant cytology 73 [39–94] 0.40 NMP22+ or malignant or suspicious cytology 88 [47–100] 0.13 LR+ Cytology Malignant only - 0.35	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Malignant or suspicious - 1.19 NMP22 NMP22+ only - 1.86 Combinations NMP22+ and malignant cytology - 0.23 NMP22+ and malignant or suspicious cytology - 0.81 NMP22+ or malignant cytology - 2.56 NMP22+ or malignant or suspicious cytology - 3.31 LR- Cytology Malignant only - 0.33 Malignant or suspicious - 1.16 NMP22 NMP22+ only - 1.79 Combinations NMP22+ and malignant cytology - 0.22 NMP22+ and malignant or suspicious cytology - 0.79	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						NMP22+ or malignant cytology - 2.46 NMP22+ or malignant or suspicious cytology - 3.17	
Huber 2012	Study of Diagnostic Accuracy 3b	A total of 1772 chemical workers exposed to carcinogenic aromatic amines between September 2003 and June 2010 were enrolled in the study The study was based on a high-risk population of chemical workers who had been exposed to aromatic amines and who underwent annual occupational health checks for haematuria and urine cytology.	7091 urine examinations of 1609 participants were carried out The mean (range) age of the participants was 62 (27 – 90) years 27.7% of the participants were non-smokers.		The aim of the study is to evaluate the value of nuclear matrix protein-22 (NMP22) in bladder cancer (BC) screening, and its effect on variables in a prospective study in a high-risk population. Sensitivity, specificity, PPV, NPV. We investigated NMP22 with regard to factors that may influence its results, e.g inflammation, haematuria, urine creatinine concentration and	In all, 7091 screening check-ups in 1609 subjects were performed. Histopathological analysis found three papillary urothelial neoplasms of low malignant potential, five recurrent BCs and 13 primary BCs. Three tumours were at a muscle-invasive stage (pT2, pT3a or pT3b). We found higher NMP22 concentrations (> 10 U/mL) in 224 patients, which correctly predicted BC in six cases - sensitivity 97.29%, - specificity 28.57%; - NPV 99.04%, - PPV 12.24% Gross haematuria affected NMP22 results (odd ratio [OR] 3.49, 95% confidence interval [CI] 1.81 – 6.73). Infection also affected NMP22 results (OR 4.13, 95% CI 2.31 – 7.35).	Single Site prospective longitudinal stud It is the largest prospective validation study conducted over t longest period o time.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					concomitant systemic disease. Urine analysis using Combur 10 test ® dipsticks (Roche Diagnostics, Mannheim, Germany). Standard urine cytology of urine sediments according to Papanicolaou' s method. A quantitative assessment of NMP22, using the NMP22 ® - Elisa (Matritech Inc, Newton, MA, USA) and the UroVysion ® BC kit (Abbott Laboratories, Abbott Park, IL, USA). NMP22 in the	NMP22 was more frequently positive in urine with creatinine concentration > 2.5 g/L (OR 1.61, 95% CI 0.91 – 2.86). NMP22 outcomes are affected by haematuria, infection and concentrated urine. NMP22 alone cannot be recommended for primary screening in a high-risk population nor as an alternative to cystoscopy during follow-up. A NMP22 test might be a useful adjunct to urine cytology. The study results led us to conclude that, based on the currently available data, NMP22 should not be regarded as an alternative to endoscopy, and we could not make a general recommendation for screening or follow-up.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					supernatant was verified with an immunometric assay (Immulite NMP22; DPC Biermann GmbH, Bad Nauheim, Germany). Creatinine in the urine was measured using the enzymatic test CREA plus ® (Roche Diagnostics).		

3. AG 2: Tumorklassifikation

3.1. AG 2 Schlüsselfrage 1 – Literaturauswahl nicht abgeschlossen

3.2. AG 2 Schlüsselfrage 2 (Immunhistochemische Marker)

„Welche klinische Bedeutung haben immunohistochemische Marker?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Wang, 2011	study of diagnostic accuracy 3	patients age from 31 to 86 years (mean age 63 years). 11 male 6 female N = 43 patients 1 patients underwent radical cystectomy, whereas 5 were treated with transurethral resection. 1 patient was diagnosed by cystoscopic biopsy (different hospital for treatment)	Formalin-fixed, paraffin-embedded tissues from: 17 primary adenocarcinomas of the urinary bladder, 16 colorectal adenocarcinomas involving the bladder, 10 conventional urothelial (transitional) carcinomas for		Comparison of Immunohistochemical Features (β-catenin , expression of CK7, CK20, and TM) between: Primary Adenocarcinoma, Secondary Colorectal Adenocarcinoma, Urothelial Carcinoma of the Urinary Bladder	nuclear localization of β-catenin, an indicator of abnormal β-catenin regulation, was seen only in adenocarcinomas of the colorectal origin Positive nuclear immunostaining for β-catenin was observed in 13 of 16 (81%) colorectal adenocarcinomas secondarily involving the bladder but in none of the primary adenocarcinomas of the bladder (0 of 17) or the urothelial carcinomas (0 of 10). positive membranous (and some cytoplasmic) staining for β-catenin was evident in 15 of 17 (88%) primary adenocarcinomas of the bladder and all urothelial carcinomas	single site retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		None of the cases was associated with exstrophy or *Schisosoma haematobium* infestation. Microscopic evaluation of the hematoxylin and eosin slides revealed the coexistence of cystitis glandularis in three cases. Clinical follow-up information was available for nine patients	comparison			immunohistochemical expression of CK7, CK20, and TM: specifically, CK7 and TM were positive in all urothelial carcinomas, variably expressed in primary adenocarcinomas, and negative in all secondary colorectal adenocarcinomas. CK20 was frequently expressed in secondary colorectal cancers (94%) but was much less frequently expressed in primary adenocarcinomas (53%) and urothelial carcinomas (40%). our data demonstrate: positive CK7 and CK20 immunostaining in more than one half of the primary bladder adenocarcinomas (65% for CK7 and 53% for CK20). A CK7-negative and CK20-positive profile, typical for colorectal adenocarcinoma, is present in 5 of 17 (29%) primary bladder adenocarcinomas in our series	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						immunostaining for TM alone may aid the distinction between primary bladder adenocarcinoma and colorectal adeno-carcinoma secondarily involving the bladder when it is positive but is not useful when it is negative.	
Compèrat, 2006	case-control-studie 2+	The population concerned 41 females and 117 males, mean age 68.5 years (extremes 38–94), who underwent either trans-urethral resection of non-invasive bladder tumors by transurethral resection or cystectomy for invasive bladder cancer between 2001 and 2004 in our establishments We excluded from our study papillomas and		The control group composed of 12 cases of nontumoral bladder specimen from spinal cord-injuries patients were explored.	The aims were to explore the expression of p63 in bladder carcinomas and to compare this expression to p53 and MIB-1, as well as to stage and grade. Tissue microarrays were performed on 158 urothelial carcinomas (56 pTa, 45 pT1 and 57≥pT2). Immunohistochemical studies were performed with p63, p53 and MIB-1 antibodies.	In our study we observed that p63 immuno-staining is present in all cell layers in papillary urothelial neoplasm of low malignant potential (PUNLMP), but partially lost in non-invasive papillary urothelial carcinoma low grade (NILGC) and in pT1/≥pT2 bladder cancers. NILGC no immunostaining in 00/26 (0%) weak staining in 03/26 (12%) strong staining in 23/26 (88%) pT1 no immunostaining in 06/45 (13%) weak staining in 15/45 (34%) strong staining in 24/45 (53%) ≥pT2 no immunostaining in 13/57 (23%)	single site retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		carcinoma in situ as well as reactive atypia and dysplasia, because it is difficult to interpret these lesions with the TMA technique. The nuclear grading and the pT stage were adjusted according to the World Health Organization guide-lines 2004 into the following groups: pTa, (distinguishing PUNLMP, NILGC, NIHGC), pT1 and ≥pT2. The group ≥pT2 concerned pT2 to pT4 bladder cancers. Metastatic progression was not distinguished. Stage pTa was present in 56 cases (36%) with 2/56(39%) PUNLMP, 26/56 (47%) NILGC and 8/56 (14%) NIHGC. Forty-five cases (28%) were				weak staining in 26/57 (46%) strong staining in 18/57 (31%) P53 and MIB-1 displayed lower expression in PUNLMP/ NILGC vs non-invasive papillary urothelial carcinoma high grade (NIHGC)/pT1, but there was no correlation between the expression of p63, p53 and MIB-1. Our study demonstrates that p63 expression distinguishes between PUNLMP/NILGC and NIHGC/pT1 (p=4.105). A statistical difference disserving pTa and pT1/≥pT2 with a statistical significance (p<10−6) could also be observed. P63 should be considered as an additional biomarker that might help pathologists to classify their patients. p53 Statistical significant difference was seen between pTa, pT1 and =pT2 (p=2.10−5), with a stronger expression	

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		pT1, and 57 (36%) cases were ≥pT2.				in the pT1 and pT2 groups. No statistical significant difference could be observed between PUNLMP to NILGC/NIHGC (p=0, 25). Comparison between PUNLMP/NILGC vs NIHGC/pT1 showed statistical significant difference with 17/48 (35%) cases positive in the first group and 43/53 (83%) cases positive in the second group (p=10−6). MIB-1 By comparing pTa, pT1 and ≥pT2, statistical significance could be observed (p<10−4) with a stronger expression in pT1 and ≤pT2 groups. No statistical significant difference could be observed between PUNLMP to NILGC/NIHGC (p=0, 44). A statistical significant difference could be observed between PUNLMP/NILGC vs NIHGC/pT1, with a stronger expression in the second group (p=10−8). p63 Statistical significant difference was	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						found between PUNLMP/NILGC and NIHGC/pT1 groups (p=4.10−5). Between pTa, pT1 and >pT2, statistical significant difference was also observed. p63 expression in pTa showed more often score 2 than pT1 and pT2 cases together (p<10−6), while p63 expression was more often score 1 in pT2 group vs pTa and pT1 (p=2.10−5). According to the grade, no significant difference could be observed (p=1). Our study shows that there exists a relation-ship between MIB-1 expression and stage. The expression of MIB-1 between the different stages pTa, pT1 and ≥pT2 showed significant differences. pT1 disease displayed MIB-1 expression in 71% of cases and in 79% of ≥pT2 patients, while only 8% of pTa showed increased MIB-1 expression (p<0,0001). No correlation could be observed between p63, p53 and MIB-1 staining. Our study compares p63 expression in pTa (PUNLMP, NILGC, NIHGC), pT1 and	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						≥pT2. We clearly show for the first time that p63 immunostaining is present in all cell layers in PUNLMP and NILGC, but already partially lost in NIHGC and pT1 bladder cancers. Further studies have to investigate the role of p63 in bladder carcinogenesis and its prognostic value especially by focussing on NIHGC.	
Esheba, 2009	study of diagnostic accuracy 3	The study group consisted of: 25 Brenner tumors, 19 Walthard nests, 2 proliferating Brenner tumors, 1 malignant Brenner tumor, 1 mature teratoma with a benign-associated urothelial proliferation, 12 TCC			we evaluated the expression of S100P and GATA3, 2 proteins that we previously found to be strongly expressed Each lesion was also evaluated for p63 expression by immunohistochemistry S100P stained 78% of the bladder carcinomas GATA3 stained 67% of	the specificity and sensitivity are sufficiently high that the expression of these proteins, particularly in combination, serves as convincing evidence of urothelial differentiation in the appropriate clinical setting In that study, we demonstrated the utility of 2 monoclonal antibodies directed against S100P and GATA3 for distinguishing urothelial carcinoma from other genitourinary neoplasms As with most antibodies in current diagnostic use, neither of these markers shows perfect specificity for	single site retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					the bladder carcinomas S100P expression: Benign Brenner Tumors 22/25, 88% Proliferating Brenner T. 1/2 cases, 50% weak staining 1/2 cases, 50% negative staining Malignant Brenner Tumor 1 case, 100% weak staining tubal Walthard Nests 17/17 cases, 100% not observed Walthard Nests in the ovarian hilus 1/2 cases, 50% weak staining 1/2 cases, 50% strong	urothelial cells 88% of Brenner tumors were positive for S100P, whereas 96% and 100% were positive for GATA3 and p63, respectively. 1 of 2 proliferating Brenner tumors was positive for S100P, whereas both cases were positive for GATA3 and p63; the malignant Brenner tumor was positive for S100P and p63, but negative for GATA3. Only 17% of TCC were positive for S100p, whereas 33% and 50% of TCC were positive for GATA3 and p63, respectively. Tubal Walthard cell nests were either completely negative or showed only scattered positive staining for S100P; in contrast, 89.5% and 100% of Walthard nests, including the 2 ovarian cases were positive for GATA3 and p63. The teratoma-associated benign urothelial proliferation was also negative for	

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					staining Teratoma-associated Transitional Proliferation 1 case, 100% negative Transitional Cell Carcinomas 2/12 cases (17%) weak staining GATA3 expression: Benign Brenner Tumors 24/25, 96% Proliferating Brenner T. 1/2 cases, 50% weak staining 1/2 cases, 50% focal weak staining Malignant Brenner Tumor 100% negative staining	S100P, but positive for GATA3 and p63. Although proliferating and malignant Brenner tumors may exhibit a more intermediate immunoprofile, expression of S100P, GATA3, and p63 by a majority of ovarian Brenner tumors underscores the similarity between these neoplasms and urothelial proliferations of bladder origin. The indeterminate phenotype seen in Walthard nests and ovarian TCC suggests that these proliferations may represent an incomplete or alternate form of differentiation.	

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					tubal Walthard Nests 11/15 cases, 73% weak staining 4/15 cases, 27% strong staining Walthard Nests in the ovarian hilus 2/2 cases, 100% weak staining Teratoma-associated Transitional Proliferation 100 % positive Transitional Cell Carcinomas 4/12 cases, 33% focal positive staining, the intensity ranged from weak to strong p63 expression: Benign Brenner Tumors 25/25, 100%		

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					Proliferating Brenner T. 2/2 cases, 100% strong staining Malignant Brenner Tumor 100% strong staining tubal Walthard Nests 17/17, 100% positive staining Walthard Nests in the ovarian hilus 1/2 cases, 50% weak staining 1/2 cases, 50% strong staining Teratoma-associated Transitional Proliferation positive Transitional Cell Carcinomas 6/12 cases, 50% focal		

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					nuclear staining		
Gulman, 2013	study of diagnostic accuracy 3	50 cases of primary urothelial tract carcinomas, which included: 12 pure squamous cell carcinomas, 15 pure urothelial carcinomas, 23 urothelial carcinomas with squamous differentiation Urothelial carcinoma: male 10 – female 05 Squamous cell carcinoma: male 06 – female 06 Urothelial carcinoma with squamous differentiation: male 15 – female 08			GATA3 - Staining Uroplakin III - Staining S100P - Staining CK14 - Staining Desmoglein – Staining Urothelial neoplasms with squamous morphology raise the differential diagnosis between pure primary squamous cell carcinoma, urothelial carcinoma with squamous differentiation and secondary involvement by squamous cell carcinoma, for example, from uterine cervix. Accurate identification between these entities is critical due to differing prognosis and	the first study to compare urothelial neoplasms with varying degrees of squamous differentiation with a selective panel of contemporary antibodies to provide more objective support for squamous and urothelial differentiation. Of note, none of the individual antibodies showed complete sensitivity and specificity. We evaluated the utility of an: immunohistochemical panel of 3 urothelial-associated antibodies (uroplakin III, S100P, and GATA3) and two squamous-associated antibodies (CK14 and desmoglein-3) Squamous differentiation was defined by intercellular bridges or evidence of keratinization. Pure squamous cell carcinomas were positive for CK14 (100%) and desmoglein-3 (75%), negative for GATA3 and uroplakin III; one case was	single site retrospective

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					therapeutic strategies.	S100P positive (9%). Pure urothelial carcinomas had an opposite pattern and were positive for S100P (93%), GATA3 (93%), and uroplakin III (67%) and were negative for desmoglein-3; CK 14 was positive in 27% of cases; 74% of urothelial carcinomas with squamous differentiation had expression of urothelial and squamous associated markers (S100P, 83%; GATA3, 35%; uroplakin III, 13%; CK14, 87%; and desmoglein-3, 70%), although reactivity for individual markers within some tumors did not always correspond with morphologic differentiation. Of the remaining 26%, 4 showed an overall “squamous” immunoprofile, whereas 2 cases showed a “urothelial” immunoprofile. Our study showed that a panel of five antibodies identifies squamous and urothelial differentiation in most instances suggesting potential diagnostic utility.	

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Higgins, 2007	study of diagnostic accuracy 3	Urothelial carcinoma samples were obtained from: 3 fresh nephrectomy specimens, 1 cystectomy specimen, 1 pelvic lymph node. Renal cell carcinomas were isolated from 5 fresh nephrectomy specimens We studied over 1100 tissues including: 321 urothelial carcinomas, 267 prostate carcinomas, 150 renal cell carcinomas, including 125 clear cell, 9 papillary, 12 chromophobe, 2 collecting duct, and 2 that showed sarcomatoid dedifferentiation.			To search for urothelial carcinoma markers, we analyzed several urothelial neoplasms using cDNA arrays and compared these with prostate and renal carcinoma profiles We undertook to study expression of S100P and GATA3 using tissue microarrays (TMAs)	We analyzed expression patterns in prostate and bladder cancer tissues using complementary DNA microarrays Together with our prior studies on renal neoplasms and normal kidney, these studies suggested that the gene for placental S100 (S100P) is specifically expressed in benign and malignant urothelial cells. Using tissue microarrays, a polyclonal antiserum against S100P protein stained 86% of 295 urothelial carcinomas while only 3% of 260 prostatic adenocarcinomas and 1% of 133 renal cell carcinomas stained. A commercially available monoclonal antibody against S100P stained 78% of 300 urothelial carcinomas while only 2% of 256 prostatic adenocarcinomas and none of 137 renal cell carcinomas stained. A second gene, GATA3, also showed high level expression in urothelial tumors by cDNA array.	single site retrospective

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		Smaller numbers of carcinomas from other sites were also studied. These include: colorectal, squamous, ovarian, lung, endometrial, gastric, thyroid, liver, pancreas, adrenal cortex, and breast Renal cell carcinomas were isolated from 5 fresh nephrectomy specimens.				A commercially available monoclonal antibody against GATA3 stained 67% of 308 urothelial carcinomas, but none of the prostate or renal carcinomas. For comparison, staining was also performed for p63 and cytokeratin 5/6. p63 stained 87% of urothelial carcinomas whereas CK5/6 stained 54%. Importantly, when S100P and p63 were combined 95% of urothelial carcinomas were labeled by one or both markers. The monoclonal S100P antibody showed slightly reduced sensitivity to the S0084 antiserum, the sensitivity of GATA3 for urothelial carcinoma was lower than that of S100P By immunohistochemistry, S100P shows a comparable sensitivity and specificity for urothelial neoplasms as the best markers in current clinical use	

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						and stains additional cases of urothelial carcinoma not marked by either of them By immunohistochemistry, GATA3 showed slightly lower sensitivity than S100P for urothelial carcinoma, but very high specificity The monoclonal S100P antibody showed increased specificity relative to the S0084 antiserum, the specificity of GATA3 was very high We conclude that the detection of S100P and GATA3 protein expression may help distinguish urothelial carcinomas from other genitourinary neoplasms that enter into the differential diagnosis.	
Jiang, 2001	study of diagnostic accuracy 3	26 lymph node–positive patients who underwent radical cystectomy with bilateral lymphadenectomy between 1989 and 1998			All histologic slides of the radical cystectomy and lymphadenectomy specimens were reviewed	Positive immunoreactivity for CK20 was found in 12 (46%) of the primary tumors (range of positive tumor cells, 5% to 95%; mean, 72%). All of the corresponding lymph node	single site retrospective

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		at Indiana University Hospital, Indianapolis age from 36 to 86 years (median 62 years). The male-female ratio was 3:1.			CK7 and CK20 was performed on formalin-fixed paraffin-embedded tissues containing primary cancers and lymph node metastases The 1997 TNM-System was used for pathologic staging Grading was performed according to the 1998 WHO/International Society of Urologic Pathology classification	metastases also showed CK20 reactivity (range, 5% to 100%; mean, 70%). Positive immunostaining for CK7 was observed in from 80% to 95% of the tumor cells in both the primary and metastatic tumors in all of the cases Fourteen cases (54%) showed no CK20 staining in both the primary and metastatic tumors. Abnormal expression of cytokeratin has been found in various forms of neoplasia and other diseases. Cytokeratin 20 (CK20) is specifically expressed in the superficial and in some of the intermediate cells of the normal urothelium. Cytokeratin 20 is detected in some urothelial carcinomas and is associated with recurrence in the bladder. Cytokeratin 7 (CK7) is found in urothelial neoplasia of the urinary	

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						bladder. Immunohistochemical staining of CK7 and CK20 has been shown to be a helpful diagnostic aid in differentiating the origin of carcinomas, including urothelial carcinoma of urinary bladder. It is anticipated that the pattern of CK7 and CK20 expression in metastatic urothelial carcinoma is similar to its primary counterpart. As a result, immunohistochemical staining of metastatic tumor of the lymph node may help in determining the origin of the primary tumor. However, limited information is available about the pattern of CK7 and CK20 expression in lymph node metastases of urothelial carcinoma. In the present study, we sought to determine the expression of these 2 cytokeratins in primary bladder carcinomas and their co-existing lymph	

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						node metastases from 26 patients who underwent radical cystectomy and bilateral lymphadenectomy for urothelial carcinoma.	
Kaufmann, 2001	study of diagnostic accuracy 3	248 Study cases with squamous cell carcinoma of the lungs, head/neck, esophagus, cervix uteri, or anal canal, 73; non-squamous cell carcinomas of various primary sites, 141; urothelial carcinoma, 20 14 malignant mesotheliomas (13 primary tumors, 1 metastasis) of the pleura (10 cases), the pericardium (1 case), and the peritoneum (3 cases).			To facilitate the differential diagnosis of poorly differentiated metastatic carcinomas of unknown primary site, we evaluated p63 and cytokeratin (CK) 5/6 as immunohisto-chemical markers for squamous cell carcinomas. We tested whether the immunohisto-chemical detection of p63 alone and in combination with CK5/6 could be used to identify poorly differentiated and undifferentiated metastatic carcinomas of primary sites that are typical for	Immunoreactivity for p63: squamous cell carcinomas, 59 (81%); urothelial carcinoma, 14 (70%), most often with diffuse staining patterns; non-squamous cell carcinomas, 20 (14.2%), resulting in a specificity of 0.86 of p63 for squamous cell carcinomas. Coexpression of p63 and CK5/6: sensitivity of 0.77 and a specificity of 0.96 for squamous cell carcinomas. Increasing the minimal criterion of positive immunostaining for both markers to more than 50% of immunoreactive tumor cells resulted in a specificity of 0.99, although the sensitivity diminished to 0.66. All malignant mesotheliomas were negative for p63. Our data suggest that positive immunostaining for both p63	single site retrospective

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					squamous cell carcinomas and to distinguish them from poorly differentiated and undifferentiated carcinomas of other primary sites. We evaluated the potential significance of p63 as an immunohistochemical marker for poorly differentiated metastatic squamous cell carcinomas. We used the commercially available paraffin-reactive monoclonal antibody 4A4 against p63 and compared the results with immunostaining for CK5/6 using monoclonal antibody D5/16B4.	and CK5/6 in poorly differentiated metastatic carcinomas is highly predictive of a primary tumor of squamous epithelial origin. based on the study hypothesis that p63 and CK5/6 are expressed in all squamous cell carcinomas but not in non-squamous cell carcinomas Immunoreactivity for p63 = 0.81 Immunoreactivity for CK5/6 = 0.84 Coexpression of p63 and CK5/6 = 0.77	
Kaufmann_2	study of	385 study cases:			Uroplakins are specific	Uroplakin III was detected in:	

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, 2000	diagnostic accuracy 3	35 primary tumors (urinary bladder (31), ureter (1), renal pelvis (3) included 11 moderately differentiated (grade 2) and 24 poorly differentiated (grade 3) carcinomas 14 women, mean age 72.8 years; range 56-97 years), 21 men, mean age 68.6 years; (range 55-85 years). stage pT2 with muscle infiltration, including 26 pT2 tumors, 6 pT3 tumors, 3 pT4 tumors according TNM and UICC 32 metastases comprised 10 grade 2 tumors and 22 grade 3 tumors 9 women, mean age 65.9			differentiation products of terminally differentiated superficial urothelial cells We tested the value of a new commercially available monoclonal antibody against uroplakin III (clone AU 1) as a paraffin-reactive immuno-histochemical marker for primary and metastatic urothelial carcinomas	21 (60%) of the primary urothelial carcinomas 17 (53%) of the metastases resulting in an overall sensitivity of 0.57 Brenner tumors also were immunoreactive for uroplakin III all other studied carcinomas were consistently uroplakin III–negative (specificity 1.00) We found the new monoclonal antibody AU 1 against uroplakin III to be a highly specific paraffin-reactive immunohistochemical marker for urothelial tumors with a moderate sensitivity for the identification of primary and metastatic urothelial carcinomas. Sensitivity UP III in 21 (60%) of 35 primary urothelial carcinomas and in 17 (53%) of 32 metastases = overall sensitivity of	

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		years; range 48-73 years 23 men, mean age 67.4 years; range 54-85 years 318 nonurothelial carcinomas grade 2 or grade 3 tumors Mucinous adenocarcinomas were not included 5 benign Brenner tumors 2 transitional cell carcinomas of the ovaries				0.57 Specificity All nonurothelial carcinomas were consistently negative for UP III, specificity of 1.00	
Langner, 2003	study of diagnostic accuracy 3	241 cases of p63 immuno-reactivity in upper urinary tract 53 transitional-cell carcinoma 188 renal-cell carcinoma			Formalin-fixed and paraffin-embedded material was selected to investigate the expression of p63 and to assess the value of p63 for differential diagnosis in poorly differentiated and undifferentiated renal malignancies using a	P63 is essential for the differentiation of normal urothelium and is also expressed in transitional cell carcinoma (TCC) of the bladder. P63 expression was detected in 51/53 (96.2%) TCCs, showing decreased expression in high-stage (pT1 and pT2 100%; pT3 90.9%) and poorly differentiated (G1 and G2 100%;	single site retrospective

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					tissue microarray technique. Two specimens of nonneoplastic renal tissue were analyzed for comparison	G3 92%) tumors. All RCCs were negative for p63. P63 proved to be a helpful tool, even in poorly differentiated and undifferentiated renal malignancies, to distinguish TCC from RCC.	
Mallofre, 2003	study of diagnostic accuracy 3	120 patients 3 groups of patients were evaluated: 40 nonneoplastic urothelial samples 50 cases with histologically incontrovertible CIS 30 samples with nonconclusive atypical changes (atypia of unknown significance)			The objective was to establish the immuno-histochemical pattern of CK20, p53, and Ki-67 (MIB-1) in urothelial dysplasia and CIS. Three groups of patients were evaluated: 50 cases with histologically incontro-vertible urothelial CIS Samples from both ureter and urinary bladder were included	Monoclonal antibodies (MoAb) against CK20, p53, and Ki-67 (MIB-1) were used on paraffin-embedded samples First group: Nonneoplastic urothelium showed no reactivity to CK20 except for umbrella cells; p53 and Ki-67 were negative or weakly positive in <10% of basal cells. In the CIS group, 42% showed positivity for all three MoAb; 44%, for two; and 14%, only for one.	single site retrospective

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					40 cases of non-neoplastic urothelium, including: samples of urinary bladder from necropsies sections of ureter from nephrectomy specimens 30 samples with cellular atypia that was suspicious but nonconclusive for dysplasia (atypia of unknown significance);	CK20 was positive through the full thickness of the urothelium in 72% of cases, p53 was positive in 80% of cases, and Ki-67, in 94% of cases. In the third group, the suspected dysplastic cells showed strong positivity in scattered cells through the epithelium in 75% of cases. Aberrant CK20 expression in urothelial cells plus overexpression of p53 and Ki-67 are indicators of dysplastic change in urothelial mucosa. Thus, immunohistochemistry is a useful tool to confirm the diagnosis of CIS and could be helpful to distinguish dysplastic changes from reactive atypia. PPV CIS group	

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						42% showed positivity for all three MoAb; 44%, for two; and 14%, only for one CK20 positive in 72% of cases, p53 positive in 80% of cases, and Ki-67, in 94% of case third group: the suspected dysplastic cells showed strong positivity in scattered cells through the epithelium in 75% of cases NPV Nonneoplastic urothelium showed no reactivity to CK20 except for umbrella cells p53 and Ki-67 were negative or weakly positive in <10% of basal cells	
McKenney, 2001	study of diagnostic accuracy	46 cases 21 cases of CIS			Analysis of Cytokeratin 20, p53, and CD44 Antigens	The immunoprofile of 21 cases of CIS and 25 non-neoplastic urothelia was determined using antibodies against cytokeratin 20 (CK20), p53, and CD44	single site retrospective

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	3	25 non-neoplastic urothelia thereof 15 urothelial biopsies with reactive atypia from patients without a history of bladder cancer 10 normal ureter sections from nephrectomies performed for renal cell carcinoma only cases that were unequivocally diagnosted as CIS or as reactive atypia by light microscopy were included			morphology served as the gold standard against which immuno-histochemical findings could be compared	(standard isoform). In the normal urothelium CK20 showed patchy cytoplasmic immunoreactivity in only the superficial umbrella cell layer and CD44 stained only the basal cells. Nuclear immunoreactivity to p53 varied from negative to weak and patchy. Reactive urothelium also showed CK20 immunoreactivity in only the umbrella cell layer in all 15 cases, p53 nuclear staining was predominantly negative with occasional weak positivity in the basal and parabasal intermediate cells. CD44 was overexpressed in the entire reactive urothelium in 9 cases (60%) or focally positive in intermediate cells in 6 cases (40%). In contrast, CIS showed intense CK20 and p53 positivity (81% and 57%, respectively) in the majority (>50%) of	

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						malignant cells. CD44 staining revealed residual basal cells with membranous reactivity in 44% of the cases of CIS; however, the neoplastic cells were immunonegative in all cases. At least one positive immunomarker (CK20 or p53) was abnormally expressed in all cases of CIS. Abnormal expression of CK20 (increased), p53 (increased), and CD44 (decreased) in urothelial CIS, and increased expression of CD44 in reactive atypia allows more confident distinction of urothelial CIS from non-neoplastic urothelial atypias. From a differential diagnosis perspective, use of a panel of all three antibodies with morphologic correlation would be essential.	
Mhawech, 2002	study of diagnostic accuracy	40 consecutive cases of transurethral resection of prostate tumors with the		For UP and TM, reactivity of normal	evaluate the use of a panel of antibodies to distinguish the poorly	We evaluated a series of 40 PAC cases (Gleason's grade ≥ 8) and 45 (G3) UC cases obtained from transurethral	single site retrospective

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	3	diagnosis of high-grade PAC (Gleason's grade ≥8) 45 cases of endoscopic resection of bladder tumor with highgrade (G3) UC		urothelium and blood vessels were used as positive internal controls, respectively To evaluate the specificity of the antibodies, known positive and negative tissues were used as controls.	differentiated forms of poorly differentiated prostate adenocarcinoma (PAC) involving the bladder and high-grade urothelial bladder cancer (UC) with prostate extension The panel of antibodies consisted of: prostate specific antigen (PSA), prostate acid phosphatase (PAP), uroplakin III (UP), thrombomodulin (TM), CK7 and CK20.	endoscopic resection material PAC expressed PSA and PAP in 34 and 38 cases, respectively. sensitivity and specificity of expressing at least 1 marker (PSA+ or PAP+) is 95% and 100%, respectively. All UC cases were negative for both markers. UC expressed UP and TM in 27 and 22 cases, respectively. 36 of 45 cases stained positively for at least 1 marker (UP+ or TM+) with specificity and sensitivity of 80% and 100%, respectively. All cases of PAC were negative for both markers. 28 UC cases were CK7+/CK20+, and 4 PAC cases stained positively for both markers. 29 PAC cases and 4 UC cases were CK7-/CK20-.	

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						We concluded that PSA, PAP, UP, and TM are very useful markers in differentiating poorly differentiated UC from PAC. Finally, when all 4 markers (PAP, PSA, UP, and TM) were negative, CK7 and CK20 appeared of no major use in making the differential diagnosis. Sensitivity Immunohistochemical Markers in High-Grade PAC PSA 85% PAP 95% PAP+ or PSA+ 95% Immunohistochemical Markers in High-Grade UC of the Urinary Bladder CK 7 86.7% CK 66.7% CK7 + or CK20+ 91.1% UP 60.0% TM 48.9% UP+ or TM+ 80.0% Specificity	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Immunohistochemical Markers in High-Grade PAC PSA 100% PAP 100% PAP+ or PSA+ 100% Immunohistochemical Markers in High-Grade UC of the Urinary Bladder CK 7 72.5% CK 90.0% CK7 + or CK20+ 72.5% UP 100.0% TM 100.0% UP+ or TM+ 100.0% LR+ PSA - 0,9 PAP - 1 PAP+ or PSA+ - 1 CK 7 - 1,2 CK - 0,7 CK7 + or CK20+ - 1,3 UP - 0,6 TM - 0,5 UP+ or TM+ - 0,8	

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						LR- PSA - 0,8 PAP - 0,9 PAP+ or PSA+ - 0,9 CK 7 - 1,2 CK - 0,7 CK7 + or CK20+ - 1,2 UP - 0,6 TM - 0,5 UP+ or TM+ - 0,8	
Miettinen, 2014	study of diagnostic accuracy 3	2040 epithelial neoplasms 460 mesenchymal and neuroectodermal tumors In addition a spectrum of normal human adult, fetal, and embryonic tissues from surgical specimens. Lymphomas and related tumors were excluded			we examined normal developing and adult tissues and 2040 epithelial and 460 mesenchymal or neuroectodermal neoplasms for GATA3 expression to explore its diagnostic value in surgical pathology, using monoclonal antibody (clone L50-823) and Leica Bond auto-mated immunohisto-chemistry.	hier nur Ergebnisse bzgl. BCA dargestellt GATA3 was expressed in trophoblast, fetal and adult epidermis, adult mammary and some salivary gland and sweat gland ductal epithelia, urothelia, distal nephron in developing and adult tissues, some prostatic basal cells, and subsets of T lymphocytes. In epithelial neoplasms, GATA3 was expressed in >90% of primary and urothelial carcinomas GATA3 is a useful marker in the characterization of not only mammary	single site retrospective

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						and urothelial but also renal and germ cell tumors, mesotheliomas, and paragangliomas. The multiple specificities of GATA3 should be taken into account when using this marker to detect metastatic mammary or urothelial carcinomas. In terms of sensitivity, the findings are similar to a previous study (>80%)	
Miyamoto, 2010	study of diagnostic accuracy 3	34 transurethral resection cases where outside pathologists questioned the presence of MP invasion			expert review were diagnosable as T1 (muscularis mucosae invasion, 18 cases) T2 (muscularis propria invasion, 16 cases)	studies on diagnostically difficult (transurethral resection) specimens have not been performed Upon expert review of the H&E slides, there was no MP invasion in 18 cases Smoothelin in MM was: negative in 8/18 (44%), weakly positive (1+) in 5/18 (28%), moderately positive (2+) in 4/18 (22%), and moderately/strongly (2-3+) positive in 1/18 (6%). Smoothelin in uninvolved MP present in	single site retrospective

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						8 cases was: 2+ in 2/8 (25%) and 3+ in 6/8 (75%). Smoothelin expression in MM was weaker than in MP in 7/8 (88%) cases where both were present. Of 16 tumors with MP invasion, smoothelin in involved MP was: 1+ in 1/16 (6%), 2+ in 3/16 (19%), 2 to 3+ in 9/16 (56%), and 3+ in 3/16 (19%). Smoothelin expression in concurrent uninvolved MP was similar. Our data confirm the relatively distinct staining pattern of smoothelin between MM and MP. However, due to the overlap of intensity between MM and MP, caution should be maintained while using smoothelin immunohistochemistry as a diagnostic tool for MP invasion	
Paner, 2009	study of	44 patients			we compare the	In contrast to SMA, smoothelin	single site

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	diagnostic accuracy 3	nontumoral cystectomy sections of 42 nontrigonal bladder wall (from 34 patients) , 5 trigonal bladder wall, 6 bladder wall at the ureteric insertion, 10 TURBT sections with invasive urothelial carcinoma (from 10 patients). cystectomy sections: 34 of 42 showed at least the focal presence of hyper-plastic MM (>4 muscle fibers thick)			immuno-histochemical expression of smoothelin and SMA in the bladder wall to explore their potential use as a discriminatory stain between MM and MP muscle in cystectomy specimens and in a representative group of TURBT specimens We recently described topographical variations of the bladder MP (ie, trigone and ureteric insertion in bladder wall), we evaluate smoothelin immunohistochemistry in this muscle to further characterize these MP variations.	displayed striking differential immunoreactivity between MM and MP muscle. With smoothelin, the MM muscle (including hyperplastic forms) typically showed absent (19/42, 45%) or weak and focal (18/42, 43%) staining MP muscle typically showed strong and diffuse staining (36/42, 86%). Smoothelin accentuated individual muscle fibers within groups of MP bundles only, a feature which was evident in both MM and MP stained by SMA. When only strong and diffuse immunoreactivity in muscle was set as a threshold for positivity, 100% specificity and positive predictive value of smoothelin for MP (vs. MM) was achieved in our study. Smoothelin staining confirmed the	retrospective

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					immunohistochemical staining for smoothelin and SMA in bladder MM with and without hyper-plastic MM and MP muscle The interpretation of immunoreactivity was performed in a semiquantitative manner by analyzing the extent of the staining positivity of the muscle cells We performed immuno-histochemical staining in the bladder for smoothelin to: evaluate its expression in MM and MP muscle in cystectomy specimens and by comparing the staining pattern with smooth	morphologic variations in MP muscle in the bladder wall of the trigone and at the ureteric insertion. In addition to the well-defined muscle layers of MM and MP, SMA staining revealed a continuous band of ill-defined haphazardly oriented compact spindle cells that were immediately subjacent to the urothelium in all cases. These spindle cells blended with the morphologically recognizable thin slender fascicles of the MM muscle. We designate this hitherto uncharacterized thin layer of SMA-positive and smoothelin-negative cells as suburothelial band of myofibroblasts. In all 10 transurethral resection of bladder tumor sections, smoothelin staining was in agreement with the routine light microscopic presence and absence of MP muscle.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					muscle actin (SMA), study MP variations in the bladder trigone and at the ureteric insertion in the bladder wall, and assess the staining pattern of MM and MP in a representative group of transurethral resection of bladder tumor specimens.	In conclusion, the relatively distinct immunohistochemical staining pattern of smoothelin between MP and MM (including its hyperplastic forms) makes it a robust and attractive marker to be incorporated in the contemporary diagnostic armamentarium for the sometimes difficult area of staging bladder urothelial carcinoma. Sensitivity of Smoothelin Staining of Bladder Muscularis Propria (MP) % Weak or strong and +1 to +3 → 100 % Weak or strong and +2 to +3 → 100 % Strong and +3 → 86 % Specificity of Smoothelin Staining of Bladder Muscularis Propria (MP) % Weak or strong and +1 to +3 → 50 % Weak or strong and +2 to +3 → 63 % Strong and +3 → 100 % PPV of Smoothelin Staining of Bladder	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Muscularis Propria (MP) % Weak or strong and +1 to +3 → 71 % Weak or strong and +2 to +3 → 89 % Strong and +3 → 100 % NPV of Smoothelin Staining of Bladder Muscularis Propria (MP) % Weak or strong and +1 to +3 → 100 % Weak or strong and +2 to +3 → 100 % Strong and +3 → 85 % Smoothelin Staining of Bladder Muscularis Propria (MP) % LR+ Weak or strong and +1 to +3 → - 2 Weak or strong and +2 to +3 → - 1,6 Strong and +3 → - 0,9 LR- Weak or strong and +1 to +3 → - 1,9 Weak or strong and +2 to +3 →	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- 1,6 Strong and +3 → - 0,9	
Smith, 2014	study of diagnostic accuracy 3	archival tissues was assembled for testing in three diagnostically challenging settings. (n = 150) 1) whole sections of high-grade UC and high-grade prostatic adenocarcinomas (PCa) involving the bladder neck (n = 35). 2) a tissue microarray cohort, previously assembled and reported to comprise aggressive (>pT3) high-grade carcinomas of the upper tract (n = 70), plus whole tissue sections of upper tract UC (n = 10) and			we tested UP2 and UP3 antibodies 'head-to-head' in diagnostically challenging settings: high-grade carcinomas involving the bladder neck, high-grade carcinomas of the upper urothelial tract metastatic UC. immunohistochemistry (IHC) was performed on a Benchmark Ultra auto-stainer IHC used integrated heat-induced epitope retrieval in high pH CC1 buffer, with visualization using the	in each of the diagnostic settings we tested, the result is the same: UP2 outperforms UP3 in terms of sensitivity, while both are highly specific. While it bears consideration that neither are as sensitive as more established markers, our experience is that, other than uroplakins, no markers have a degree of specificity sufficient to confirm the diagnosis. The increased diagnostic performance of UP2 over UP3 may prove to be of great help to surgical pathologists in these diagnostically challenging settings and in the setting of limited tissue samples, where performance of extended immunohistochemical panels is not feasible. The UP2 antibody outperforms the UP3 antibody, including in diagnostically challenging settings, and is a useful	single site retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		collecting duct carcinomas (CDC) (n = 5). 3) whole sections of metastatic deposits of UC (n = 30) Finally, additional descriptive studies were performed on whole sections of rare variants of: UC (n = 30) tissue microarray (TMA) of representative examples of neoplasms of varying histologies (n = 88) including adenocarcinomas (n = 25), neuroendocrine tumours (n = 15), squamous cell			Ultraview DAB detection system (Ventana) and Mayer's haematoxylin counterstain. Preliminary comparisons using primary urothelial carcinomas and other cancers suggest that UP2 has greater sensitivity than UP3, with preserved specificity;10 these observations have not been tested in relevant diagnostic settings where identification of UC, as opposed to other lesions in the differential, may result in fundamental therapeutic differences.	addition to the armamentarium of biomarkers for UC. Sensitivity high-grade carcinomas involving the bladderneck UP2 staining showed significantly greater intensity (P = 0.003) and proportion (P = 0.03) than UP3 UP2 outperformed UP3, with a sensitivity of 63% versus 19% high-grade carcinomas of the upper tract In UC cases, UP2 showed significantly greater intensity and proportion positive (both P < 0.001), consistent with increased sensitivity of 68% versus 23% metastatic urothelial carcinoma As before, UP2 staining showed greater intensity and proportion than UP3 (both P < 0.001), consistent with higher sensitivity (73% versus 37%, respectively, P = 0.001)	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		carcinomas (n = 10), renal and germ cell tumours (n = 6), salivary gland and thyroid tumours (n = 5), other carcinomas (n = 4), paragangliomas (n = 3), urothelial carcinomas (n = 2) other (n = 7). These cases were selected across a wide anatomical distribution, including: respiratory (n = 15), gastrointestinal (n = 25), genitourinary and gynaecological (n = 36) endocrine (n = 12) organs				UC. variants of urothelial carcinoma we also stained a total of 27 rare variants of UC from the lower tract, finding a significantly greater intensity and proportion positive (both P < 0.001) across cases for UP2 versus UP3, with significantly greater sensitivity (70% versus 19%, respectively, P = 0.001). Specificity high-grade carcinomas involving the bladderneck UP2 outperformed UP3, with a specificity of 95% versus 100% (P = 0.02). high-grade carcinomas of the upper tract In UC cases, UP2 showed significantly greater intensity and proportion positive (both P < 0.001), consistent with equal specificity of 100% (P = 0.006)	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Yildiz, 2009	study of diagnostic accuracy 3	64 bladder biopsies were retrieved from our surgical pathology files 38 benign/reactive, 10 dysplasia, 9 CIS, 7 invasive carcinoma (IC) (6 papillary, 1 flat) cases			Our objective is to describe the use of double immunohistochemistry (DIHC) for p53+CK20 as a tool for diagnosing neoplasia in bladder biopsies. CK20 was evaluated according to distribution extent and degree of intensity whereas percentage of positive cells together with staining intensity was taken into account in the evaluation of p53.	92% of reactive cases were either CK20(-) or (+) only in the upper 1/3 urothelium. In dysplastic cases CK20 staining distribution was as follows: 60% in 2/3 of the urothelium, 30% full thickness, 10% in the upper 1/3 urothelium. Among CIS cases, 89% had full thickness CK20 positivity, of which 62% were p53(+). 71% of IC cases exhibited strong and full thickness dual staining. This is the first study in the literature to use DIHC of p53+CK20 in distinction of non-neoplastic and neoplastic bladder lesions. Dual staining by p53+CK20 cocktail allows for histologic correlation and diminishes the risk of losing the area of interest in limited biopsy specimens.	single site retrospective

3.3. AG 2 Schlüsselfrage 3 (Aufarbeitung von Zystektomie- und LA-Präparaten)

„Wie werden das Zystektomiepräparat und das Lymphadenektomiepräparat nach histomorphologischen Kriterien aufgearbeitet?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Bertz , 2010	retrospective, single site, observational study 3	N = 309 patients (237 male, 72 female) Initial pT1 urothelial bladder cancer	-	-	Evaluate several parameters in one of the largest series of initial pT1 bladder cancers. Progression, recurrence and survival (overall and cancer-specific almost identical).	- According to WHO: 220 tumours were G3, 89 were G2 and none was G1 - Substaging by HPF revealed G2 and G3 tumours as distinct prognostic groups with regard to recurrence and progression - No significance was found for substaging pT1a/pT1b - An infiltrative growth pattern was significantly correlated with progression and survival in univariate analysis. → Large prospective studies are needed to detect other histomorphological or immunohistochemical features supporting the detection of high-risk tumours and correlate them with new molecular risk markers such as gene expression profiles or FGFR3 mutations. Results of the multivariate analysis (Cox regression) . Grading according to WHO 1973 (G2 vs. G3) Significant relationship with CSS but not	Retrospective Re-evaluated Single site Blinding of reviewers unclear No adjustment despite repeated tests (multiple testing) Note of prognostic relevance of the infiltration depth.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						with RFS and PFS. Infiltration depth (<1 vs. HPF.> 1 HPF) Significant correlation with RFS and PFS but not with CSS (p = 0.062). No significant correlations for age, gender, multifocality, tumor size, CIS, growth pattern, subclassification pT1a/pT1b.	
Zarei, 2012	Retrospective, single site, observational study 3	N = 354, 148 patients with pT2N0 and 206 patients with pT3N0 148 patients with pT2 - 76 with pT2a - 72 with pT2b 206 patients with pT3 - 144 with pT3a - 62 with pT3b	-	-	Compared the prognostic ability of the current American Joint Committee on Cancer (AJCC) staging system to direct measurement of the depth of tumor invasion into the muscularis propria and perivesical fat → CSS	- Significant difference in CSS between patients with pT2 vs pT3 tumors (5 year CSS 65% vs 48%, p <0.002). - Prognostic significance of pathological substaging: 5-year CSS for patients with pT2a and pT2b was almost identical at 65% and 66%, respectively (p=0.94) - No cutoff point in the depth of tumor invasion in mm could be found that identified a CSS difference between patients with pT2a and pT2b. - No significant difference between pT3a vs. pT3b (5 year CSS 42% vs 32%) - No significant difference in cancer specific survival between the substages. - Patients with measured invasion less than 4.5 mm into perivesical fat had significantly improved cancer specific	First study of invasion depth into the muscularis propria and perivesical fat by direct measurement with correlation with patient outcome following radical cystectomy Single site Retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						survival compared to that in patients with invasion 4.5 mm or greater (5-year cancer specific survival 53% vs 40%, p=0.02). - In regard to lymph node involvement at radical cystectomy there was no statistically significant difference. →pT2a and pT2b substages of bladder cancer should be consolidated into a single pT2 classification, while the separation of pT3 should be based on direct measurement of the depth of perivesical fat invasion.	
Varinot, 2009	Retrospective, single site, observational study 3	N = 125 patients (RCP) Age ranged from 39–85 years	-	-	Determine the most reliable protocol of RCP sampling Protocol: examination of the whole prostatic urethra (PU) is possible, without using whole mount sections	- 101 RCP between 2000-2007 and 25 between 2008 and June 2009 - 2008-2009 vs 2000-2007 → Bladder cancer 36% vs 21% → Cis in the PU 28% vs 14% → Prostate cancer 44% vs 13% → This study clearly demonstrates the importance of studying the whole PU. → It prevents underestimation of its involvement and makes correct staging possible. → The protocol better detects prostate involvement by bladder cancer, therefore providing a better final stage of the patients.	Retrospective Single site All specimens examined before 2004 were reclassified according to the WHO classification 2004

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						→ This protocol is easy to use, and is not more time-consuming than other macroscopic protocols.	
Gakis, 2010	Retrospective, single site, observational study 3	N = 218 patients (170 male, 48 female)	FSA	FFPE	Evaluate the accuracy of frozen section analysis (FSA) for detecting and eliminating malignant Ureteral margins at radical cystectomy (RC) and to determine the impact of Wnal margin status obtained by a sequential resectioning strategy on the risk of upper urinary tract recurrence (UUT-R)	- Malignant ureteral margins were detected in 17 of 425 (4.0%) ureteral specimens (15 of the 218 patients, or 6.9%). - At definitive histological examination, true-positive distal ureteral malignancy was present in 23 of these 425 specimens (5.4%; 20 of the 218 patients, or 9.2%. - FSA results were false-positive in 1 of 402 ureteral specimens - FSA's sensitivity was 73.9%, - Specificity was 99.8% - Positive (negative) predictive value 94.4% (98.5%) - Univariate analysis: a significant correlation was found between true distal ureteric malignancy and positive frozen section margins ($p < 0.0001$). - Multivariate anaysis (95%-conWdence interval): positive frozen section margins ($p < 0.0001$) and tumor multifocality ($p = 0.04$) were independent predictors of true distal ureteral malignancy at RC. →Patients with positive final ureteral margins are at increased risk of UUT-R. →With regard to the high accuracy of	Retrospective re-examination Single site

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						98.3% for the detection of malignant ureteral margins at RC, the results of this study stress the importance of performing ureteral FSA at RC—especially in patients with tumor multifocality.	
Idrees, 2012	Retrospective, single site, observational study 3	N = 133 patients (122 male, 11 female) 48 pediatric, 85 adult	-	-	To document the common morphologic changes and neoplasms found in a large series of adult and pediatric vesical diverticula	- Of the 85 nonneoplastic cases, prominent morphologic findings included significant chronic inflammation, granulomatous inflammation including foreign body giant cell reaction, acute inflammation, squamous metaplasia, cystitis glandularis, and nephrogenic metaplasia. - Pediatric cases showed no malignancy - Thirty-three of the 48 neoplastic cases had high-grade urothelial carcinoma, 4 had carcinoma in situ, 7 had low-grade papillary urothelial carcinoma, 2 had primary squamous cell carcinoma, 1 had primary melanoma, and 1 had urothelial dysplasia. - Nine of the neoplastic cases had variant morphology. - Diverticula from 31 cases were involved by primary tumors, of which 6	Retrospective Single site

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						had coexisting intravesical neoplasia (3 had carcinoma in situ with invasion elsewhere). - In 19 of 33 high-grade urothelial carcinomas, infiltration into adjacent fat was noted. - Seven of these cases arose within diverticula. → Stage pT2 should be omitted, and stage pT3 should follow pT1	

3.4. AG 2 Schlüsselfrage 4 (Minimalanforderungen für Biobanking)

„Welche histopathologischen Minimalanforderungen sind für ein Biobanking erforderlich?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Litlekalsoy 2006	Cross-Sectional Study 3	Archival, paraffin wax-embedded autopsy/ biopsy tissue material collected from 144 patients with invasive bladder cancer (grade II and III). The mean age was ≈ 65–70 years. 144 tumours of WHO grade II and III with muscle infiltration, and some with metastases to local lymph nodes at the time of operation, were assessed.	Immunohistochemical staining with the biological markers p53 protein, p16 protein, epidermal growth factor receptor (EGFR), cytokeratin 7 and high molecular weight 34βE12 cytokeratin. All the cases were re-diagnosed by a consultant pathologist (O.D.L.) on the basis of new, haematoxylin and eosin-stained slides, and typed according to the last WHO classification from	Control immunohistochemistry was done on available normal tissue (i.e. connective and fatty tissue, heart, lungs and normal urinary bladder epithelium) obtained from the autopsies. As control to the biopsy tissue, four additional biopsies from 1932–48 and five from 1950–59 were selected. As a control of the state of the autopsy tissue, we also included 27 biopsies from the	The aims of this study were to examine whether archival bladder cancer material from 1932–2004 could be used for immunohistochemical analyses; whether the tissue was preserved sufficiently for comparative biological analyses even on autopsy material; to establish whether the chosen markers were expressed in the same way over the time span; and presuming that the population was genetically stable	The morphology was well preserved in all cases, although some degree of autolysis was present. Autolysis after death or long storage periods did not compromise good quality in the histochemical analyses of the autopsy tissue. The immunohistochemical detection of nuclear and cytoplasmic markers (EGFR, p53, p16, cytokeratin 7 and HMW-cytokeratin) was as good in old as in new paraffin-embedded material There was no correlation between the delay and the percentage of positive immunohistochemical reactions. Cytokeratin 7 positivity increased by 13% in the 70 years, but cross-tabulation analyses showed no significant trend across time (years in groups) for this cytokeratin ($P = 0.32$).	The present tested material gave optimum histological sections and immunohistochemical staining. It cannot be excluded that the relevant epitopes are degraded or chemically modified in the negative tumour specimens. The possibility that p53 protein becomes more degraded with time in archival

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Selected from the periods 1932–48, 1950–59, 1960–70 and 1990–2004. In addition, 13 cases with biopsies from surgically removed bladder carcinomas were selected from 1992–96 as a reference, representing optimally fixed, new material.	1999. Patient data were selected from records, including age, gender, metastasis, time from diagnosis until death, and time from death until autopsy. Several modifications were used to unmask the epitopes for EGFR, p53, p16 protein and the two cytokeratins, including proteinase K and citrate buffer with microwave treatment. The staining	same groups of patients as the 42 autopsies in the group from 1990–2004.	could identical 'molecular fingerprints' be identified during the period, or whether there were different patterns. Markers: p53, p16, Epidermal growth factor and its receptor (EGFR), cytokeratin 7, HMW-cytokeratin	The p16-positive tumours showed no significant variation, with the highest frequency of positive scores in recent years. For p53 there was a higher fraction of positive scores (borderline significant) with time. The odds of a positive HMW-cytokeratin score in a tumour decreased significantly with time (odds ratio 0.352; $P < 0.01$). The mean percentage of EGFR-positive cases was 74% over all four periods ($P = 0.21$). Retrospective biological diagnostics can serve as a valuable tool for retrieving rare types of tumours and for monitoring malignant disorders over long periods, back to times with an environment totally different from the present. We conclude that with proper handling and modern improved methods, paraffin waxembedded autopsy material stained	tissue, and is thus rarer in the oldest material, cannot be excluded. We conclude that with proper handling and modern improved methods, paraffin waxembedded autopsy material stained with immunohistochemical markers can be compared over 70 years. Differences in smoking habits

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			procedures were done on the Tech Mate 500 slide-processing equipment using ChemMate Detection Kit (DAKO). The results were evaluated statistically using the chi-square test, regression analyses and in a multivariate analysis.			with immunohistochemical markers can be compared over 70 years.	can therefore not explain the present differences in biological markers as shown by immunohistochemistry.

3.5. AG 2 Schlüsselfrage 5 (Diagnosesicherheit Schnellschnitt Urethra/Ureter)

„Welche Diagnosesicherheit bietet die Schnellschnittdiagnostik der Absetzungsränder von Urethra und Ureter im Vergleich zur Paraffinhistologie des Zystektomiepräparates?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Akkad 2006	Case serie 3	Between 1992 and 2004, 85 women with a mean age of 64.5 years (range 34 to 82) with clinically localized TCC of the bladder who had undergone radical cystectomy were included. Orthotopic bladder substitution was performed in 46 females, while 39 underwent nonorthotopic urinary diversion. Of the entire	Urinary diversion following radical cystectomy. Preoperative assessment included bimanual examination, laboratory tests and imaging with abdominal ultrasound, excretory urography, bone scintigraphy, and CT of the abdomen and chest. In all patients intraoperative frozen sections were obtained from the urethra		We analyzed the risk factors and incidence of secondary TCC of the remnant urothelium in women following radical cystectomy for TCC of the bladder.	Intraoperative frozen sections obtained from the urethra and distal ureters were negative for TCC and CIS in all patients. None of the patients had a positive urethral margin on permanent section analyses. Four women (4.7%) had TCC in the remnant urothelium a mean of 56 months postoperatively (range 36 to 76). These patients had a history of multifocal or recurrent disease (4 of 22 or 18%). No secondary TCC was seen in the 63 patients with solitary invasive or nonrecurrent bladder cancer ($p < 0.05$). In the orthotopic group 1 patient (2.1%) had an upper urinary tract	Single site, case series Because only a few contemporary studies include female patients, no conclusive data concerning the incidence of secondary UUTT in women are yet available. However, it can be assumed that the incidence of UUTT in women undergoing orthotopic bladder substitution is not different from that reported in men. To our knowledge no case of upper urinary tract recurrence has been reported in females following orthotopic

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		cohort 22 (26%) patients underwent cystectomy for multifocal or recurrent TCC. Follow-up: 6-month intervals mean 49,8 months. No patient had received neoadjuvant chemotherapy before cystectomy. Patients were selected for orthotopic substitution according to general performance status,	and distal ureters. Orthotopic bladder substitution was performed in 46 females, whereas in 39 nonorthotopic urinary diversion was done, including an ileal conduit in 30 and ureterosigmoidostomy in 9. Staging and grading were performed according to 1997 UICC guidelines and the 1974 WHO histopathological grading classification.			tumor 76 months after surgery, while in the nonorthotopic group 1 (2.5%) was found to have an upper urinary tract tumor 48 months postoperatively. None of the 62 patients undergoing cystectomy for solitary invasive bladder cancer had secondary TCC. This finding was statistically significant ($p < 0.05$). The presence/absence of CIS or positive lymph nodes did not result in a statistically significant difference concerning the urothelial recurrence rate ($p > 0.05$). In patients with upper urinary tract recurrence there was no statistically significant difference in terms of the type of urinary diversion ($p > 0.05$). Urethral recurrence was found in 2	bladder substitution to date. In the current study we report an overall recurrence rate of 4.7% in the remnant urothelium of women undergoing radical cystectomy for bladder cancer. Univariate analysis of our data showed that recurrent and/or multifocal bladder cancer is a possible risk factor for urothelial recurrence. Secondary TCC of the remnant urothelium following radical cystectomy for bladder cancer is a rare occurrence in women with long-term followup. The current study

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		motivation and urethral competence.				patients (4.3%) with an ileal neobladder at a mean follow-up of 50.5 months. In 1 patient multifocal muscle invasive bladder cancer (pT2) was found in the cystectomy specimen and she was diagnosed with urethral recurrence 65 months after cystectomy. In the other patient, who had recurrent CIS refractive to intravesical immunotherapy, urethral recurrence was seen 36 months after cystectomy. Recurrent or multifocal TCC may represent a risk factor for secondary TCC of the remnant urothelium after cystectomy. In our series all recurrent tumors were late recurrences (more than 36 months postoperatively). Because the rate of urethral	provides additional data that orthotopic bladder substitution in females undergoing urethra sparing cystectomy does not result in a higher urethral recurrence rate than in men. Multifocal and/or recurrent TCC of the bladder seems to be a risk factor for urothelial recurrence. In this risk group physicians should be alert to the possibility of late tumor recurrence in the remnant urothelium.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						recurrence in the current series corresponds to that reported in men (2% to 6%), urethra sparing cystectomy with orthotopic bladder replacement does not appear to compromise the oncological outcome in women.	
Cho 2009	Case serie 3	A study population of 294 patients was identified with a median age of 61 years (27–89) and a median follow-up duration of 54 months. Selected from 412 consecutive patients. All female patients were excluded; other exclusion criteria included non-	Radical cystectomy and urinary diversion for transitional cell carcinoma of the bladder between 1986 and 2004. Follow-up: abdomen-pelvis computed tomography, a whole-body bone scan, and a chest Xray. These tests were performed at 3-month intervals for the initial 2 years, at 6-month	No controls, case serie	We investigated the impact of various clinical and pathological features on urethral recurrence by univariate and multivariate analysis. We investigated tumor location (bladder neck, trigone, and prostatic urethra), tumor multiplicity, tumor size, T stage, tumor grade,	Urethral recurrence developed in 13 patients (4.4%) and the 5-year urethral recurrence-free probability was 94.9%. On univariate analysis, positive urethral margin, prostatic stromal invasion, and prostatic urethral involvement had a significant influence on urethral recurrence ($p < 0.05$). The other clinical and pathological features were not significantly associated with urethral recurrence ($p > 0.05$). A multivariate Cox proportional hazard model revealed that a positive urethral margin (hazards	Retrospective, single site, case series A positive urethral margin is considered an absolute indication for prophylactic urethrectomy. In addition, more careful patient selection is necessary for orthotopic urinary diversion in patients with prostatic urethral involvement and prostatic stromal invasion. Our study revealed an approximately 5%

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		TCC histology and the presence of a distant metastasis at diagnosis. Patients who were treated with urethrectomy or orthotopic urinary diversion were also excluded. Several forms of cutaneous urinary diversion were elected as follows: ileal conduit in 249 patients, ureterocutaneostomy in 20 patients, continent cutaneous	intervals for the subsequent 3 years, and annually thereafter.		concomitant carcinoma in situ, prostatic stromal invasion, urethral margin status, and N stage, among other factors.	ratio (HR) = 18.33, p < 0.001), prostatic urethral involvement (HR = 7.95, p < 0.001), and prostatic stromal invasion (HR = 5.80, p = 0.018) were independent risk factors for urethral recurrence. Five-year disease-specific survival rates were 52.1% in patients with urethral recurrence, and 71.7% in those without (p = 0.062). On univariate analysis, positive urethral margin (p < 0.001), prostatic stromal invasion (p < 0.001), and prostatic urethral involvement (p < 0.001) had a significant influence on time to urethral recurrence. The urethral recurrence-free probability was higher in superficial tumors (< pT2) than in invasive tumors ≥ pT2), with borderline significance (p = 0.071). Age, bladder neck involvement,	chance of urethral recurrence at 5 years in 294 males who underwent radical cystectomy and cutaneous diversion. This value is relatively lower than previously reported. Positive urethral margin, prostatic stromal invasion, and prostatic urethral involvement were independent risk factors for urethral recurrence. We have performed orthotopic urinary diversion but our experience is still limited.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		diversion in 13 patients, and colon conduit in 12 patients.				trigone involvement, tumor multiplicity, tumor size, tumor grade, and concomitant carcinoma in situ were not significantly associated with urethral recurrence ($p > 0.05$). We do not advocate using random TUR biopsies to evaluate prostatic stromal involvement in all patients, but if there is any suspicion of prostatic involvement in endoscopic or imaging studies, TUR biopsies are recommended to confirm the pathology of the prostate prior to cystectomy and urinary diversion.	
Donat 2001	Study of Diagnostic Accuracy 3	246 evaluable patients out of 416 patients (61%) with prostatic urethral biopsy before radical cystectomy between 1989 and 1997.	Transurethral lateromontanal loop biopsies. At the 10-year followup 129 patients (52.4%) were dead, 85 (32%) had no evidence of	Post-cystectomy review of the pathological findings.	The predictive value and sensitivity of transurethral biopsy, patterns of recurrence, survival and clinical impact were assessed with 10 years of	The sensitivity of transurethral biopsy for prostatic stromal invasion was 53%, specificity was 77%, positive predictive value was 45% and negative predictive value was 82%. Transurethral biopsy did not accurately determine prostatic involvement.	Single site, Retrospective The accuracy of transurethral loop biopsy for detecting prostatic involvement, which may later predict the risk of urethral recurrence, mirrors experience with the

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		6 patients were excluded from study. Mean patient age was 63.4 years (range 32 to 87). Pathologically organ confined, stage T3a or less disease was present in 110 cases (44.7%), while 136 involved pathologically non organ confined, stage T3b or greater disease. Patients were followed until death.	disease, 16 (6.5%) had disease and 16 (6.5%) were lost to followup. Delayed urethrectomy was performed in 15 of 235 cases (6.4%) at a mean of 15.2 months. Prostatic transurethral urethral loop biopsies were obtained at the 4 and 8 o'clock positions from the bladder neck to the verumontanum and were performed at the discretion of the attending surgeon.		followup.	In fact, each recurrence in patients with continent urethral diversion developed distal to the anastomosis and was managed by transurethral resection. Univariate analysis of the preoperative and postoperative variables indicated that superficial or stromal prostate involvement by bladder cancer on transurethral biopsy increased the risk of urethral recurrence. However, the only significant variables after cystectomy were a positive ure- thral, soft tissue or ureteral cystectomy margin and superficial prostatic involvement. A positive urethral margin only and prostatic stromal invasion at cystectomy did not result in an increased risk of urethral recurrence.	accuracy of frozen sections in the ureter for later predicting upper tract recurrence. Better methods of assessing the prostatic urethra are needed. The positive predictive value of transurethral biopsy for final prostate pathology at cystectomy in terms of the degree of prostate involvement was poor. This finding is important because it often factors into the decision of whether to offer a patient continent urethral diversion.

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			Patients with other types of prostatic biopsy, no identifiable method of biopsy or no biopsy were not included in the study. Mean followup in the cohort was 41.8 months (range 0.39 to 134.6, median 35.7). Mean followup in the patients still at risk for urethral recurrence was 61.7 months (range 0.56 to 134.64, median 56.8). Survival			Multivariate analysis was not possible due to the small number of urethral recurrences. Overall survival was 59.85 months (range 0.56 to 134.64, median 55.65). Disease specific survival was 48.95 months (range 0.39 to 134.64, median 44.58). The average disease free interval was 36.67 months (range 0.39 to 134.64, median 28). Overall metastasis developed in 83 of the 246 patients (33.7%), including 65% at multiple sites and 35% at a solitary site. Pelvic recurrence developed in 36 of the 246 patients (14.6%) at a mean of 20.93 months (range 2 to 56, median 16.26) and the pelvis was the only site of disease in 11 (31%). 10 of the 15 patients with urethral recurrence simultaneously	

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			distribution was calculated using the Kaplan-Meier model. Multivariate analysis using the Cox proportional hazards model. A commercially available computer statistical package was used for data analysis.			presented with pelvic recurrence or multiple sites of distant disease. Distant metastatic disease distribution in the cohort was similar to previous patterns of disease spread with the predominant metastatic sites being bone, lymph nodes, liver and lung. Intraoperative frozen section of the prostatic apical urethra has been proposed as an alternative to pre-cystectomy prostatic urethral biopsy for determining whether a patient is a candidate for orthotopic urethral diversion or complete urethrectomy. In our series 13 of 15 urethral recurrences (87%) were in patients with negative urethral margins, whereas only 2 of the 13 (15.4%) with positive urethral margins had urethral recurrence. Of the 246 patients 99 had prostatic disease	

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						at transurethral biopsy and/or cystectomy, including 11 (11%) with urethral recurrence. No patient required continent diversion takedown or died of urethral recurrence. Therefore, in this series the urethral margin did not accurately reflect which patient would have recurrence (p = 0.621). Prostatic involvement by tumor continues to be the most predictive factor for the risk of superficial and stromal urethral recurrence when detected preoperatively by transurethral biopsy (p = 0.004 and 0.013), and for superficial urethral recurrence when detected after cystectomy (p = 0.008). In this series the urethral recurrence rate was about 4-fold greater in patients with documented prostatic involvement	

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						than in those with no prostatic involvement (11% versus 2.7%). Prostatic involvement at biopsy or cystectomy translated into a higher risk of urethral recurrence. It did not have significant clinical impact or affect survival and should not be an absolute contraindication to urethral diversion.	
Gakis 2010	Study of Diagnostic Accuracy 3	218 patients who underwent RC from 1999 to 2009 for invasive or superficial urothelial carcinoma in which endoscopic control had failed. Patients with a history of urothelial carcinoma of the upper urinary	425 ureteral margins obtained from 218 patients were initially examined by FSA. When positive, additional resections were performed. Subsequently, all specimens were re-examined.	Definitive histological sectioning of the same distal ureteral segments. By formalin-fixed, paraffin-embedded (FFPE) sections.	1. Accuracy of intraoperative ureteral FSA for detecting and eliminating malignant ureteral margins. 2. To evaluate possible clinicopathological risk factors of distal ureteral malignancy at RC. 3. To determine the role of final margin status	Of 425 specimens, malignant ureteral margins were found on initial FSA in 17, on FFPE in 23 (sensitivity: 73.9%). FSA results were false-positive in 1/402 margins (specificity: 99.8%) resulting in an overall accuracy of 98.3%. On multivariate analysis (95%-CI), correlations were found between distal ureteral malignancy and FSA ($p < 0.0001$) and tumor multifocality ($p = 0.04$). In 10/17 positive initial margins it	Single site To exclude a possible bias, FSA results from subsequent resectioning performed in case of positive initial ureteral margins were precluded from analysis of error. Other clinical and pathologic parameters were documented to evaluate risk factors of true distal ureteral malignancy at RC: age, gender, ipsilateral

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		tract prior to cystectomy were excluded from analysis.			obtained by a sequential resectioning strategy on UUT-R (upper tract recurrence).	was not possible to obtain a negative final margin despite multiple reresections, of which one resulted in a UUT recurrence, which was more frequent than in patients with a negative margin (4/208, p = 0.03). All patients had multifocal disease at RC. FSA has a high accuracy for detecting malignant ureteral margins. Patients with positive final margins are at increased risk of UUT-R. With sequential resection, however, positive margins cannot reliably be converted to negative ones. No significant associations were found for the other parameters. Patients with positive final ureteral	hydronephrosis, prior BCG-therapy, organ-confined/extravesical disease, tumor multifocality (¸ 2 tumor lesions) and grade, tumor stage, lymph node involvement, lymphovascular invasion, non-transitional cell carcinoma pathology, tumor size, carcinoma in situ of the bladder, and concomitant urethral malignancy. Some limitations of our study have to be kept in mind. The data were prospectively acquired, but the sample size is moderate and, thus, significance levels should be interpreted carefully.

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						margins are at increased risk of UUT-R. With regard to the high accuracy of 98.3% for the detection of malignant ureteral margins at RC, the results of this study stress the importance of performing ureteral FSA at RC-especially in patients with tumor multifocality. With a sequential resection technique, however, initial positive ureteral margins cannot reliably be converted to negative final ones.	
Kassouf 2008	Study of Diagnostic Accuracy 3	From 1990 to 2004, 272 patients underwent radical cystectomy and orthotopic neobladder reconstruction. Of these, 252 patients were	Preoperative transurethral prostatic urethral biopsy.	Intraoperative frozen section of the urethra and final distal urethral margin status at radical cystectomy.	Here we sought to determine the value of preoperative transurethral prostatic urethral biopsy in predicting final distal urethral margin status at radical cystectomy and to correlate	Median patient age was 61 years (range 53 to 80 years) and median follow-up time was 48 months (range 4 to 161 months). Most patients had cT2 or greater (63%) lesions. A total of 78 patients (31%) received adjuvant chemotherapy for pT3 or greater and/or pN+ disease. Pathological stages were 26 pT0, 23 pTis, 17 pTa, 31 pT1, 81 pT2,	Single site, Retrospective, Male patients We perform TUR biopsy of the prostatic urethra via transurethral resection at the 5 and 7 o'clock positions from the bladder neck to the verumontanum.

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		males and form the basis of this report. Patients with cT4b disease despite chemotherapy or with distant metastasis were excluded from the study.			this with findings on intraoperative frozen section of the urethra. Collected variables included age, clinical stage, lymphovascular invasion, type of urinary diversion, pathological findings of prostatic urethral biopsies, final pathological findings of the prostate, frozen section of the distal urethra, final urethral margins, pathological stage, recurrence, site of recurrence and survival data.	46 pT3 and 28 pT4a. The 5-year disease specific survival rate was 71.6%. <u>Urethral Margin, Frozen Section and TUR Findings</u> A total of 127 patients had TUR of the prostatic urethra alone, 68 had urethral frozen section alone, 50 had both and 7 had neither, thus a total of 177 patients (70%) had preoperative TUR of the prostatic urethra at 5 and 7 o'clock, and 118 (47%) had urethral frozen sections. The positive predictive value of TUR biopsy of the prostatic urethral was 12.5%. The negative predictive values of TUR and urethral frozen section with respect to final margins were 99.4% and 100%, respectively. The optimal negative predictive value is obtained with urethral frozen sections.	

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						We found that while the absence of tumor on TUR biopsy of the prostatic urethra confers a high likelihood of a negative urethral margin on final pathological evaluation, a positive TUR biopsy correlates poorly with final margin status. Our data suggest that a negative TUR biopsy of the prostatic urethra can be used to counsel those patients as they have a high likelihood (99.4%) of a negative final urethral margin. The converse is not true, and a positive TUR biopsy of the prostatic urethra does not reliably predict a positive final urethral margin. A positive TUR prostatic urethral biopsy does not correlate with final margin and should not exclude patients from consideration for an orthotopic diversion.	

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						Preoperative TUR biopsy of the prostatic urethra appears to have limited utility in the selection of patients for orthotopic neobladder.	
Osman 2006	Study of Diagnostic Accuracy 3	100 consecutive patients (85 men and 15 women, mean age 59.1 years, SD 8.6, range 31–76) with non-metastatic muscle-invasive TCC or superficial TCC and failure of endoscopic control. All patients had a standard radical cystectomy with bilateral iliac lymphadenectomy.	FSA (frozen-section analysis) during cystectomy.	Definitive pathology with stepsectioning of the lower ureters , paraffin-wax embedded sections.	Sensitivity Specificity Accuracy Positive and negative predictive values Correlation with histo-pathological variables	There were 193 ureteric specimens examined; 16 ureters (8.3%) in 14 patients showed evidence of malignancy by FSA. True distal ureteric malignancy was diagnosed in 29 ureteric specimens (15%) in 24 patients. The sensitivity and specificity of the FSA were 45% and 98%, respectively, while the positive and negative predictive values were 81% and 91%, respectively. Overall accuracy: 90%. There was no significant correlation between distal ureteric malignancy and: patient age, tumour site or morphology, clinical or pathological staging, ipsilateral hydronephrosis, suspicious intraoperative ureter, biopsy or	Prospective study, Single site To our knowledge, the role and accuracy of routine ureteric FSA at the time of cystectomy have not been reported in a prospective study. In the present study the incidence was 15% using a more assiduous approach. To our knowledge, this is the only study investigating the true incidence of lower ureteric malignancy after using a universally accepted consensus for

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		Of the 100 patients who had a radical cystectomy and urinary diversion, 58 had orthotopic ileal neobladders, 38 an ileal loop conduit and 4 a continent cutaneous diversion. Patients with other than TCC were excluded.				tumour grade, associated carcinoma in situ or nodal involvement. Male gender and positive intraoperative FSA were the only predictors significantly associated with distal ureteric malignancy by univariate analysis (P = 0.01and < 0.01). Both predictors remained significant on multivariate analysis. A positive ureteric FSA during cystectomy has a high predictive value in the diagnosis of distal ureteric malignancy, and is justified as an independent predictor in male patients with bladder TCC. We showed that the sensitivity of FSA is low (45%) when compared with step-sectioning, but this low sensitivity is insufficient to negate the ability of FSA to diagnose	classifying urothelial neoplasia to overcome the problem of pathological overlap. We excluded patients with other than TCC to achieve an accurate incidence for the target population. The present study provides practising urologists with evidence based on logistic regression that positive intraoperative ureteric FSA has an independent high predictive value in diagnosing distal ureteric malignancy, justifying its need as a routine procedure. The pathological diagnosis followed the WHO/ International Society of Urologic

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						distal ureteric malignancy in patients with bladder cancer. The PPV was 81% and the NPV 91%. No significant association between true distal ureter malignancy and: patient age, tumour site or morphology, clinical or pathological staging, biopsy or tumour grade, ipsilateral hydronephrosis, suspicious intraoperative ureter, associated CIS or nodal involvement. Male gender and a positive FSA were the only predictors significantly associated with true distal ureteric malignancy by univariate analysis (P = 0.01 and < 0.01, respectively). By multivariate analysis, both variables remained significant as independent predictors.	Pathology (ISUP) consensus classification of urothelial neoplasms. The staging system was stratified according to the 1997 TNM system.
Raj	Study of Diagnostic	1330 bladder cancer patients	Ureteral frozen sections.	Pathologic findings on permanent	Sensitivity and specificity	Of 2579 ureteral margins evaluated in 1330 patients,	Retrospective, single site

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2006	Accuracy 3	from 1990 to 2004 with pathologic evaluation of their ureters. Patients with transitional cell carcinoma who had pathologic documentation of distinct specimens submitted for ureteral margin evaluation. Exclusion criteria were RC for nontransitional cell tumors and RC for nonmalignant conditions.	All ureters demonstrating evidence of distal ureteral involvement on frozen sections had additional tissue resected.	section as the reference standard.	Accurracy Ureteral involvement and margin status were examined as risk factors for upper tract and anastomotic recurrence and overall survival.	ureteral involvement was noted in 9% of ureters (13% of patients). Recurrent upper tract tumors were most frequently located in the renal pelvis (68%) followed by the ureterointestinal anastomosis (16%) and the ureters (16%). The sensitivity and specificity of frozen section analyses were approximately 75% and 99%, respectively. The 5-year probability of anastomotic and upper tract recurrences was low: 2% and 13%, respectively. Evidence of involvement of the ureter or at the ureteral anastomotic margin was associated with higher likelihood of upper tract recurrence but not anastomotic recurrence or overall survival. Sequential resection of ureters to	The discrepancy between our data and those published previously may be attributed to different pathologic criteria to define ureteral involvement; our criteria for ureteral involvement include findings described as marked or high-grade dysplasia; severe, marked, or high-grade atypia; suspected CIS; CIS; noninvasive carcinoma; and invasive carcinoma. Due to the retrospective nature of this database, we were unable to determine whether CIS was focal or diffuse, and if the extent of CIS is associated with an altered risk of ureteral involvement, upper tract

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						reach a negative anastomotic ureteral margin did not eliminate the risk of anastomotic or upper tract recurrence. Patients with involved ureters and/or ureteral anastomotic margins have a higher risk of upper tract recurrence. The data do not support routine intraoperative frozen sections to assess ureteral involvement. In a multivariable logistic regression model including age, pathologic stage, pathologic grade, and the presence of CIS within the bladder of the RC specimen, only CIS was found to be a significant predictor of ureteral involvement on permanent section (odds ratio, 3.99; 95% confidence interval [95% CI], 1.87–8.51 [P < .0005]). Patients with ureteral involvement	recurrence, or survival outcomes. Our analyses are limited by the retrospective nature, the small numbers of patients, and potential selection biases due to surgeon selection of the ureters chosen for frozen section analyses and whether a separate ureteral segment was sent for analyses. Given the low incidence of ureteral involvement and anastomotic and upper tract recurrences, the protracted time course to the development of radiographically documented upper tract recurrences, and the limited survival of

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						on permanent section were more likely to develop upper tract recurrence than those without ureteral involvement (hazards ratio [HR], 1.8; 95% CI, 1.1–3.1 [P =.048]). Similarly, a positive ureteral anastomotic margin on permanent section was found to be highly associated with upper tract recurrence (HR, 2.8; 95% CI, 1.5–5.3 [P <.001]), after adjustment for age, stage, grade, and presence of CIS. Similar data were noted at the time of evaluation of ureteral involvement or anastomotic margins on frozen sections. Our data indicate a reasonable specificity and sensitivity of intraoperative frozen sections in the detection of ureteral involvement.	bladder cancer patients after RC, only limited analysis of our data can be performed. Only the combined experience from multiple institutions can better define the utility of intraoperative ureteral evaluation. Only the first (most distal) section for each ureter was selected for comparison.

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						The data regarding the location of ureteral involvement precludes potential conclusions regarding the proximal limit of ureteral resection. Finally, given the low incidence of upper tract recurrence, and the weak association between upper tract recurrence and survival, our data do not support routine intraoperative frozen sections to assess ureteral involvement.	
Schumacher 2006	Study of Diagnostic Accuracy 3	805 consecutive patients between January 1984 and January 2005 with TCC of the bladder who underwent standardized pelvic lymph node dissection and cystectomy. Patients who underwent	We prospectively performed FSE (frozen section examination) of the ureters in 805 patients. The histopathological results in patients with CIS of the ureter were correlated to the possible presence	Corresponding permanent sections.	We hypothesized that resection of the ureters at the level where they cross over the common iliac arteries should increase the probability of a tumor-free ureterointestinal anastomosis. The	Transitional cell carcinoma or carcinoma in situ was found on frozen section examination of the distal ureter in 39 of 805 patients (4.8%) and on permanent sections in 29 (3.6%). In 755 patients the false-negative rate of frozen section examination of the ureters was 0.8%. In patients with positive ureteral FSE for TCC or CIS, the corresponding permanent section	Retrospective, single siteRisk factors for upper tract recurrence following radical cystectomy are documented in this study as a history of diffuse CIS, multifocal tumor, intramural tunnel or juxtavesical ureteral involvement with CIS, or a prior ureteral tumor. The initial impetus for

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		preoperative radiation therapy were excluded.	of concomitant CIS of the bladder.		histopathological findings of the ureteral segments were then correlated for upper urinary tract recurrence and overall survival. We analyzed the incidence of positive ureteral margins in a consecutive series of patients undergoing radical cystectomy for TCC of the bladder. We evaluated the incidence of pathological findings of the ureter at cystectomy for transitional cell	was only positive in 75%. This result may be due to a shedding of CIS cells during ureteral manipulations, nonexistence of CIS in the remaining ureter not sent for FSE or a false-positive diagnosis. However, when FSE is normal the false-negative rate is low, less than 1% in our series. Of the patients with carcinoma in situ diagnosed on the first frozen section examination 80% also had carcinoma in situ in the bladder. Transitional cell carcinoma or carcinoma in situ in the most proximally resected ureteral segments was found in 1.2% of patients. After radical cystectomy there was tumor recurrence in the upper urinary tract in 3% of patients with negative ureteral frozen section examination and in 17% with carcinoma in situ on frozen section	frozen section analysis was to ensure a cancer-free anastomosis, which theoretically would translate into reduced upper tract recurrence rates and longer cancer-free survival. This study confirms the rate of upper tract recurrence is higher in those with risk factors (17% vs 3%) and routine division of the ureters at the mid common iliac artery would decrease the risk of a positive ureteral margin in patients with risk factors for upper tract recurrence. Ngative ureteral margins did not result in a decrease in upper tract recurrence rate or

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					carcinoma of the bladder and assessed the usefulness of intraoperative frozen section examination of the ureter.	examination. In 9 of 805 patients (1.1%) TCC was found on frozen section. In 30 of 805 patients (3.7%) CIS was diagnosed on FSE. In 11 of 805 patients (1.4%) severe atypia was diagnosed on FSE. In 755 of 805 (94%) patients FSE was diagnosed as normal. Upper urinary tract recurrence was diagnosed in 31 of 805 patients (3.9%) after a median of 30 months (range 2 to 96). Median cancer specific survival was 42 months (range 1 to 142). Of these 31 patients 20 (65%) have died of metastatic disease. In this study FSE showed TCC, CIS or severe atypia of the first resected ureteral margins close to the bladder in 6.2% of our patients. Our results show that patients with negative histology in the distal ureteral segments are at a 3% risk	improve survival. Te study does not show how frozen section analysis at the level of the mid common iliac ureter would add anything to the simple division of the ureter at this level in all patients given the low incidence of anastomotic recurrence. The data confirm the risk factors for upper tract recurrence and lower ureteral involvement up to the level of the common iliac artery, and should be considered when selecting patients for minimally invasive extracorporeal diversions in which a greater ureteral length is

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						of upper urinary tract recurrence, whereas patients with CIS on FSE are at a 17% risk. Nevertheless, it must be kept in mind that the majority of these patients ultimately die of systemic disease. TCC and CIS are found in the most distal ureter in 4.8% and at the iliac cross in 1.2% of our patients, respectively. Most patients with CIS in the ureter have CIS in the bladder (80%). If ureteral CIS is diagnosed then there is a 5-fold risk of upper urinary tract recurrence after radical cystectomy for TCC of the bladder. Except for patients with CIS in the bladder, FSE of the ureters is not necessary if the ureters are resected at the level where they cross the common iliac vessels. Conclusion:Routine frozen section examination of the ureters at	needed. Final pathology was reported according to the TNM classification of 1997.

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						radical cystectomy is only recommended for patients with carcinoma in situ of the bladder, provided the ureters are resected where they cross the common iliac arteries.	
Tollefson 2010	Case series 3	We identified 1,430 patients, of whom 33 were excluded from study due to metastasis at cystectomy, leaving 1,397 available for analysis. 8 patients (0.57%) were lost to follow-up.	Frozen section analysis of the distal ureteral specimen. When positive, sequential resection was performed. Pathological staging was performed using the 1997 TNM staging system.	No control (case series)	Overall cancer specific and upper tract recurrence-free survival.	At last followup 432 patients (31%) had died of urothelial carcinoma a median of 1.8 years after cystectomy. Median followup in the 315 patients alive at last evaluation was 14.0 years. A total of 178 patients (12.7%) had a positive initial ureteral margin and only 31 (2.2%) had a positive final resection margin. Associations of margin status with overall and cancer specific survival were not statistically significant. Of 1,397 patients 69 (4.9%) experienced upper tract recurrence at a median of 3.1 years.	Retrospective, single site, moderate number of patients. Some limitations of data are apparent: Data were obtained from a single institutional registry and there may be a selection bias for patients undergoing surgery at our institution. UC is particularly difficult to study in this fashion, given the low incidence of ureteral involvement, the protracted time course

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						Positive initial margin status and final margin status were associated with upper tract recurrence (p < 0.001). With a serial sectioning strategy most positive initial margins can be converted to negative final margins. Patients who undergo conversion to a negative final margin with serial sectioning are at decreased risk for upper tract disease. Conversion from a positive to a negative ureteral margin decreased but did not eliminate the increased risk (HR 4.39, 95% CI 2.59–7.43, p < 0.001). Patients who underwent anastomosis with a positive margin were at even higher risk (HR 7.37, 95% CI 4.30–16.44, p < 0.001. This distinction was statistically	to radiographically detected upper tract recurrence and the high mortality of muscle invasive UC. At our institution the use of frozen section analysis has been aggressive, and with readily available genitourinary pathologists frozen section may be done more expeditiously and accurately than in the community setting. Further study in multi-institutional, randomized fashion may be needed to ultimately determine the role of frozen section at radical cystectomy.

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						significant (p = 0.04).	
Touma 2010	Study of Diagnostic Accuracy 3	We reviewed the records of 301 patients who underwent a radical cystectomy between March 2000 and January 2007. Patients undergoing prior pelvic radiotherapy were excluded.	Frozen section analysis (FS)	Permanent hematoxyllin and eosin (H&E) sections	Accuracy of FS and the associated costs. Associations with the pathological stage of the primary bladder tumour and regional lymph nodes, the presence of urothelial carcinoma in situ of the bladder (CIS) and survival outcomes with the FS.	We identified 602 ureters for this study. There were a total of 362 ureters analyzed by FS. The incidence of any abnormality on FS is 9.9%. The incidence of CIS or solid urothelial carcinoma in the ureter is even lower at 2.8%. The sensitivity was 71.9%, specificity 96.1%, positive predictive value 63.9% and negative predictive value 97.2%. The presence of CIS of the bladder and prostatic urethra was significantly associated with a positive FS (p = 0.02). The FS were not associated with survival outcomes. The cost to pick up 1 patient with any abnormality on FS was $2080. The cost to pick up 1 patient with CIS or solid urothelial carcinoma of	Single site, Retrospective The potential shortfalls were its retrospective study design, the fact that a significant number of ureters were not examined and the lack of uniformity in the management of positive frozen sections. These factors would lead to selection bias. The strengths are that this is one of the larger series examining FS at the time of radical cystectomy, one of the only studies to examine the sensitivity and specificity of FS of the ureters and the first to examine both the direct

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						the ureter on FS was $6471. Pathologic stage of the primary bladder tumour did not predict for a positive FS. The status of the regional lymph nodes did not predict for a positive FS. The presence of CIS of the bladder or prostatic urethra was significantly associated with a positive FS, p < 0.02. Results of the FS were not associated with survival outcomes. Frozen section analysis has the tendency to overestimate disease at the ureteral margin. Conclusion: FS should be performed in select patients undergoing radical cystectomy in the following circumstances: where CIS is present in the bladder, intramural ureter or prostate;	and indirect costs related to FS. Final pathology was reported according to the TNM classification of 1997.

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						where there is multifocal tumour, prior ureteral tumour and prostatic stromal; or where there is urethral involvement of UC.	
Volkmer 2009	Case series 3	Between January 1986 and October 2008 a total of 1,420 radical cystectomies with pelvic lymphadenectomy for bladder cancer were performed at our institution. Included were 1,138 males and 282 females, a ratio of 4:1. Median age at cystectomy was 63.9 ± 9.9 years (range 23 to 91).	Radical cystectomies with pelvic lymphadenectomy for bladder cancer. A complete follow-up was obtained until death or until October 2008. Mean followup was 58 months.	No control (case series)	The probability of upper tract recurrence. Factors predicting higher rates of UUTR (upper urinary tract recurrence).	Until October 2008 UUTR developed in 25 of 1,420 patients (1.8%) with a median interval from cystectomy to UUTR of 39 months (range 5 to 142). The overall probability of UUTR was 2.4% at 5, 3.9% at 10 and 4.9% at 15 years after cystectomy. Of the patients 3 had superficial tumors of the renal pelvis and 22 had invasive upper tract transitional cell carcinoma. The disease specific survival rate after diagnosis of upper tract recurrence was 60.8%, 44.2%, 27.6% and 27.6% at 1, 2, 5 and 10 years, respectively. Upper urinary tract recurrence did not develop in any patients with	Single site, Retrospective Small number of events (n=25).

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		The pathology report revealed transitional cell carcinoma in 93.5% of cases while adenocarcinoma (1.0%), squamous cell carcinoma (3.9%), small cell/oat cell/neuroendocrine carcinoma (1.2%) or signet ring cell carcinoma (0.5%) were observed less frequently.				nontransitional cell carcinoma. Four factors could be identified that were associated with an increased risk ratio for UUTR, including history of carcinoma in situ (RR 2.3), history of recurrent bladder cancer (RR 2.6), cystectomy for noninvasive bladder cancer (RR 3.8) and tumor involvement of the distal ureter in the cystectomy specimen (RR 2.7). Tumor grading did not influence the risk of UUTR. Patients with transitional cell carcinoma who had none of these risk factors had an upper urinary tract recurrence rate of only 0.8% at 15 years. This rate increased with the number of positive risk factors, i.e 8.4% in patients with 1 to 2 risk factors and 13.5% in those with 3 to 4 risk factors.	

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						If there is upper tract recurrence it is usually fatal (22 of 25 patients with upper tract recurrence had invasive disease and a dismal survival rate). Conclusions: Patients who underwent cystectomy for transitional cell carcinoma and with at least 1 risk factor for upper urinary tract recurrence should have closer follow-up regimens than those with nontransitional cell carcinoma or without any of these risk factors. Regular follow-up examinations with radiation exposure have a poor detection rate in patients without any risk factors for UUTR (0.8% in 15 years). Despite undergoing urine cytology and renal ultrasound every 3 months, CT every 6 months, and bone scan and IVP yearly, upper tract recurrence is rarely detected	

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						at a curable stage. In these patients urinalysis, urine cytology and ultrasound examinations might be sufficient to guarantee a safe followup regimen.	

4. AG 3: Diagnostik und Stadieneinteilung

4.1. AG 3 Schlüsselfrage 1 (Marker bei V. a. Harnblasenkarzinom)

„Welche diagnostischen Marker inklusive Urinzytologie sind für die Primär- und Rezidivdiagnostik (Lokalrezidiv und Metastasierung) geeignet?“

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Abogunrin 2012	Case-control study, prospective, multi site 3	Patients presenting with hematuria with planned cystoscopym were recruited between November 2006 and October 2008. The patients recruited were White Caucasians except for 1 of Black African origin. 2 patient cohorts: - 80 had pathologically proven urothelial cancer, either recurrent (n = 34) (43%) or newly diagnosed (n = 46) (58%). - Sixty-nine of 77 controls and 76 of 80 urothelial cancers presented with a	Twenty-two biomarkers in urine and carcinoembryonic antigen (CEA) in serum were evaluated using enzyme-linked immunosorbent assays (ELISAs) and biochip array technology.		To determine whether single biomarkers and/or multivariate algorithms could significantly improve on the predictive power of an algorithm based on demographics, for the prediction of urothelial cancer in patients presenting with hematuria.	- Sufficient cells were present for cytological assessment in 65 of 77 (84%) controls and 74 of 80 (93%) urothelial cancers. <u>Univariate Analyses</u> - Nine biomarkers were significantly higher in urothelial cancers compared with controls (BTA, CEA, d-Dimer, FAS, HA, IL-1, IL-6, IL-8, VEGF)) . <u>Multivariate Algorithms Enhanced Prediction of Urothelial Cancers</u> - Age and smoking years contributed to the prior predicted probability (PPP)-algorithm (AUC 0.76.). - The study identified 2 algorithms with enhanced AUCs in comparison to PPP: 1) PPP + NMP22 + epidermal growth factor (EGF) (AUC to 0.90, Sensitivity:	Prospective Multi site Used Forward Wald binary logistic regression analyses to create algorithms based on demographic variables designated prior predicted probability (PPP) and multivariate algorithms, which included PPP as a single variable.

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		history of macrohematuria.				91 %, specificity: 80 %, 71%) 2) PPP + BTA + CEA +thrombomodulin (TM) (AUC to 0.86., Sensitivity: 91%, specificity: 71%) - BPH was a significant confounding pathology for algorithms. - Median predicted probability scores for recurrences and newly diagnosed were similar. Conclusion: → Addition of biomarkers representing diverse carcinogenic pathways can significantly impact on the ROC statistic based on demographics. → Benign prostate hyperplasia was a significant confounding pathology and identification of nonmuscle invasive urothelial cancer remains a challenge.	Areas under the curve (AUC) were determined after receiver-operator characteristic (ROC) analysis for single biomarkers and algorithms. Scientists, blinded to patient data, completed analyses of biomarkers at Randox Laboratories Ltd.
Al-Maghrebi 2012	Validation study, prospective, single site 3	N=105 25 healthy controls and 80 patients diagnosed with transitional cell carcinoma (TCC) of the bladder. The healthy controls' and patients' ages (mean age +- SD) were 55 +- 15 (range: 20-70 years) and 53 +- 19	Urinary survivin mRNA expression. Urinary Nuclear Matrix Protein 22 BladderChek (NMP22BC) test. Urine cytology (UC)	Cystoscopy and bladder biopsy as the reference standard.	1) Sensitivity 2) Specificity 3) Correlate with tumour grade and Stage	1) Survivin mRNA expression showed the highest sensitivity (87.5%) followed by the NMP22BC test (61.3%) while UC exhibited the lowest sensitivity (40%). 2) All three urine markers had a similar specificity of 96% (95% CI 80.5–99.3%). 3) Survivin mRNA expression was the only urine marker that showed a significant difference in relation to tumour histological grade (χ^2 8.5, p = 0.015). None of the three urine markers	Prospective Single site Cohort with high pre-test probability. Therefore limited external validity - results may overestimate accuracy in cohorts with

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		(range: 16-77 years), respectively. There were 65 male and 15 female patients with TCC of the bladder while in the control arm there were 16 males and 9 females.				was significantly related to tumour pathological stages. Conclusion: The diagnostic sensitivity of urinary survivin mRNA expression was superior to that of UC and the NMP22BC test and correlates with tumour pathological grade but not stage.	lower prevalence of bladder cancer.
Banek 2013	Validation study, prospective, multi site 3	7,091 urine samples from 1,609 subjects between 2007 and 2010. Mean age of BC cases was 66 years (range 38–76 years) at diagnosis.	Fluorescence-in-situ-hybridization (FISH) test.	Urinary cytology	1) Sensitivity and positive predictive value. 2) Specificity and negative predictive value.	- Histopathology revealed 16 incidental bladder cancers (BCs) and 5 recurrent tumors in 20 study participants. - FISH was positive in 9 BC cases of which 7 were high grade. - Cytology detected 8 tumors. - FISH overlapped with cytology in 7 cases. 1) Sensitivity was 45.0% and PPV (positive predictive value) was 16.4% in all and 53.85% and 13.21% in high-grade tumors. 2) Specificity and negative predictive value (NPV) were 96.97% and 99.26% in all bladder tumors. - BC detected during UroScreen was associated with an odds ratio (OR) of 6.88 (95% CI 1.72–27.44) for positive FISH and with an OR of 8.81 (95% CI 1.41–54.96) for gross hematuria.	Prospective Multi site Cystoscopy was recommended in case of positive or suspicious findings. Logistic regression models were applied to estimate the influence of potential test confounders like urinary creatinine and hematuria on detecting BC.

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						- The adjusted area under the curve was 0.77 (95% CI 0.62– 0.92) for all and for high-grade lesions (0.85; 95% CI 0.69 – 1.00). Conclusion: → FISH showed a performance in detecting bladder cancer comparable to cytology but a larger number or false-positive results. → It remains to be investigated if chromosomal instability can be detected earlier than morphologic changes of exfoliated bladder cancer cells. → Cystoscopy as diagnostic standard procedure cannot be replaced yet. → FISH alone cannot be recommended for BC screening in a healthy population or as a reliable alternative to cystoscopy. → FISH is helpful in distinguishing between tumor cells and reactive alterations in case of doubtful urine cytology.	Receiver operating characteristic (ROC) curves for FISH were adjusted for test confounders. Cancer-predictive values were calculated from test results in the last sample before diagnosis.
Barlandas-Rendón 2002	Validation study, single site (Austria) 3	N=115 Suspected bladder cancer. The male:female ratio was 2.40:1.	Flow cytometry of urine samples. Cells isolated from urine samples were analyzed by	Cytology of urine samples.	Sensitivity	- All positive cases were confirmed by histology (21/115), 18 were diagnosed by flow cytometry and 16 by cytology, with a sensitivity of 85.7% and 76.1%, respectively. - Two cases were found to be positive by flow cytometry, which were not	Single center

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		The average age was 68±12.7 years (±SD). Median age of 70 years (range 32–93 years).	cytometry for the expression of cytokeratin and CD 45 and for DNA measurements such as: DNA index, synthesis phase fraction and proliferative index (SPF + G2/M phase).			confirmed by histology, while no false positives were detected by cytology. - Both techniques gave almost identical results for the diagnosis of bladder cancer, although there were differences in non-malignant samples. Conclusion: - Flow cytometry is slightly more sensitive than cytology but the combination of the two techniques improves the diagnosis	
Bubendorf 2001	Validation study, prospective, multi site (Basel) 3	N=117 Group 1, 74 voided urine specimens and 52 bladder washings that were collected immediately before therapeutic transurethral resection of 80 bladder tumors from 68 patients. Group 2, 10 voided urine specimens and 7 bladder washings from 11 patients with a history of bladder cancer but no visible tumor at the time of follow-up cystoscopy.	Multitarget, multicolor FISH assay (UroVysion, Vysis, Downers Grove, IL), which is composed of 3 chromosome enumeration probes (CEP17, CEP3, and CEP7) and the single locus-specific indicator probe 9p21.	Cytology	Diagnostic usefulness	- FISH was positive in 1 of 27 control specimens and in 33 (73%) of 45 pTa, 12 (100%) of 12 pT1, and 13 (100%) of 13 pT2-4 tumors. - The results were similar in a series of 68 bladder washings. - In addition, FISH of voided urine specimens was positive in 5 of 10 patients with negative follow-up cystoscopy results. - Subsequent recurrence was found in 4 of these patients but in none of 5 patients with FISH-negative results. Conclusion: → Multiprobe FISH markedly improves the sensitivity and specificity of cytology for the detection of bladder cancer in urine specimens. → This results show that this multicolor	Prospective Multi site Cytologic grading was done by one cytopathologist (P.D.) in a blinded fashion. Cytologic grading was not possible because of poor fixation or inflammatory changes in 11 cases, including 6 voided urine specimens from

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		Group 3, 33 voided urine specimens and 16 bladder washings obtained before transurethral resection of the prostate for benign prostatic hyperplasia (BPH) from 38 patients without a history or clinical evidence of bladder cancer.				FISH probe is a rapid, simple, and powerful tool for an improved identification of bladder cancer in bladder washings and in voided urine specimens.	6 patients with BPH and 4 voided urine specimens and 1 bladder washing from 5 patients with tumor. For the analysis of sensitivity, specificity, and positive and negative predictive values of multiprobe FISH, only the cases were included in which cytologic grade also was available for comparison.
Coskuner 2012	Cross-sectional study on diagnostic accuracy, prospective, multi site (Turkey) 3	N= 95 Non-muscle-invasive (NMI) transitional cell carcinomas (TCC). Men/Female: 78/17. Mean age 60.7 years, range, 27–88.	Nuclear matrix protein-22 (NMP-22) (BladderChek®) test.	Cystoscopy	Sensitivity and specificity	Cystoscopy and NMP-22 results of the patients included in the study revealed the sensitivity (44.4%) of the test was very low and the specificity (98.4%) was quite high ($p < 0.001$). - Among the 10 cystoscopies where NMP-22 was negative, but cystoscopy was positive for tumor, 8 had low grade (LG) and 2 had high grade (HG)	Prospective Multi site TNM 2002 system was used for tumor staging. Tumor grading

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						TCC. - NMP-22 was never positive in low-grade tumors, in other words, all of the NMP-22-positive 8 tumors were high grade. - On the other hand, in 20% (2/10) of the cases, NMP-22 can be negative although the tumor was high grade. - Two (2.1%) HG upper urinary tract (UUT)-TCC were detected in 95 patients. - These 2 patients were within the 125 cystoscopies (75 patients) where both NMP-22 and cystoscopy were negative for tumor. Conclusion: → Nuclear matrix protein-22 cannot detect LG TCC. → However, it detects overwhelming majority of HG TCC. → For this reason, positive NMP-22 test largely indicates HG TCC. → NMP-22 is also not reliable in UUT-TCC, even in HG tumors.	was assigned as low grade and high grade.
Curry 2002	Cross-sectional study, single site (Illinois) 3	N=100 Patients who were diagnosed between 1996 and 1999. 78 male patients and	Previous WHO surgical diagnoses. Current WHO/ISUP surgical	Urine cytology	The Effects of the Current World Health Organization/International Society of Urologic Pathologists Bladder Neoplasm Classification System on Urine	- According to the original WHO classification system, there were 26 patients with Grade 1 transitional cell carcinoma (TCC), 61 patients with Grade 2 TCC, and 13 patients with Grade 3 TCC. - The corresponding cytology was	Single site The histologic specimens were reviewed blindly and were reclassified by

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		22 female patients. Median age of 72.0 years (average, 69.7 years).	diagnoses.		Cytology Results.	positive in 11 of 26 Grade 1 tumors, 28 of 61 Grade 2 tumors, and 12 of 13 Grade 3 tumors. - After the reclassification, there was 1 papilloma, 12 PUNLMP lesions, 50 low-grade urothelial carcinomas, and 37 high-grade carcinomas. - The cytology was positive in 0 of 1 papillomas, 5 of 7 PUNLMP lesions, 18 of 50 low-grade carcinomas, and 28 of 37 high-grade carcinomas. - In addition, morphologic uniformity and cytoplasmic homogeneity (50.0% and 45.0%, respectively) were seen more commonly in lowgrade bladder tumors. Conclusion: → The diagnostic accuracy of urine cytology for high-grade lesions decreased, as expected; however, cytologic detection of low-grade urothelial carcinomas was remarkably lower than expected. → In addition, no outstanding cytologic features could be identified to make a definitive diagnosis.	one pathologist using the criteria established by the 1998 WHO/ISUP Consensus Committee. All biopsies had corresponding urine specimens that had been diagnosed previously by a different cytopathologists.
Hosseini 2012	Cross-sectional study on diagnostic accuracy,	N=144 All patients with history of superficial transitional cell	Urinary nuclear matrix protein 22 (NMP22). Urine cytology.	Cystoscopy	1) Sensitivity 2) Specificity	1) -The sensitivities of the NMP22 test and cytology for detection of recurrence were 78.8% and 44.2%, respectively (P = .001)	Multi site (seven academic centers) From July 2007

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	multi site 3	carcinoma (TCC). 125 men and 19 women. Mean age was 61.8 years (range, 26 to 86 years).				- The NMP22 test showed significantly higher sensitivity than cytology in detecting recurrences in low-risk and intermediate-risk groups 2) The specificities of the NMP22 test and cytology for detection of recurrence were 69.6% and 83.7%, respectively (P = 0.019). Conclusion: The NMP22 assay could be used for detection of superficial bladder cancer, especially in low- and intermediate-risk groups; however, the value of the test is limited by its low specificity.	to February 2009. In each center, one cytopathologist performed cytologic examination, who was unaware of the cystoscopy and NMP22 results. All the NMP22 test results were interpreted by a single observer at each center, who was blind to the cystoscopy and cytology results.
Huber 2012	Cross-sectional study on diagnostic accuracy, prospective, multi site 3	N=1772 A high-risk population of chemical workers who had been exposed to aromatic amines and who underwent annual occupational health checks for haematuria	Nuclear matrix protein-22 (NMP22)	Cystoscopy and subsequent transurethral resection were performed where there were	To evaluate the value of nuclear matrix protein-22 (NMP22) in bladder cancer (BC) screening, and its effect on variables.	- Histopathological analysis found three papillary urothelial neoplasms of low malignant potential, five recurrent BCs and 13 primary BCs. Three tumours were at a muscle-invasive stage (pT2, pT3a or pT3b). - Higher NMP22 concentrations (> 10 U/mL) in 224 patients, which correctly predicted BC in six cases (sensitivity	Prospective Multi site In all, 7091 screening check-ups in 1609 subjects were performed.

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		and urine cytology. Mean age 62 years. 27.7% of the participants were non-smokers.		suspicious findings.		97.29%, specificity 28.57%; negative predictive value 99.04%, positive predictive value 12.24%). - Gross haematuria affected NMP22 results (odd ratio [OR] 3.49, 95% confidence interval [CI] 1.81 – 6.73). Infection also affected NMP22 results (OR 4.13, 95% CI 2.31 – 7.35). - NMP22 was more frequently positive in urine with creatinine concentration > 2.5 g/L (OR 1.61, 95% CI 0.91 – 2.86). Conclusion: → NMP22 outcomes are affected by haematuria, infection and concentrated urine. → NMP22 alone cannot be recommended for primary screening in a high-risk population nor as an alternative to cystoscopy during follow-up. → A NMP22 test might be a useful adjunct to urine cytology.	Urine samples were collected for a quantitative NMP22 immunoassay, urine analysis and creatinine concentration assessment.
Jeong 2012	Validation study, single site (Republic of Korea) 3	N=250 The subjects were classified into five groups: bladder cancer (n=54), healthy subjects (n=47), patients with hematuria (n=59), urinary	Compared the diagnostic utilities of CYFRA 21-1, nuclear matrix protein-22 (NMP22), urinary bladder cancer antigen (UBC), and	Diagnose of bladder cancer.		- Urinary levels of all 4 markers were higher in the bladder cancer group than the control group. - The areas under the receiver operating characteristic curves (ROC-AUCs) of CYFRA 21-1, NMP22, UBC and FDP, corrected with urine creatinine concentrations, were 0.90, 0.89, 0.80 and 0.77, respectively, for	Single site The median interval between sample collection and diagnosis of bladder cancers was 7.0 days (n=53, 1st to 3rd

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		inflammation/infection (n=22) and benign prostate hyperplasia (BPH) (n=68). The proportion of male patients was higher in the bladder cancer group than in the total control group (87.0% vs. 57.1%, P=0.0001) The median ages of the subjects in the bladder cancer and total control groups were 67.0 and 57.0 years, respectively.	fibrin/fibrinogen degradation products (FDP) for detecting urinary bladder cancer.			discriminating bladder cancer from controls. - The ROC-AUCs for the combinations of the markers were not significantly higher than those with CYFRA 21-1 or NMP22. NMP22 was the only independent variable for predicting bladder cancer among the four markers in the multivariate analysis. Conclusion: → All 4 tumor biomarkers exhibited diagnostic utility for predicting bladder cancer. → Among them, CYFRA 21-1 and NMP22 were the most effective at predicting bladder cancer.	quartiles=3.0 to 14.3).
Johnen 2012	Validation study, prospective, multi site (Germany) 3	N=1540 Chemical workers previously exposed to aromatic amines. Age in 2010 (years): Median (range) → 62 (27–90). Smoking status at baseline: Never → 424 Ever → 1116.	Survivin	Histopathological finding.	Sensitivity specificity, positive predictive value (PPV), negative predictive value (NPV).	- During the study, 19 bladder tumors were detected. - Multivariate generalized estimation equation (GEE) models showed that b-actin, representing RNA yield and quality, had the strongest influence on survivin positivity. - Inflammation, hematuria and smoking did not confound the results. - Survivin had a sensitivity of 21.1% for all and 36.4% for high-grade tumors. Specificity was 97.5%, the positive predictive value (PPV) 9.5%, and the negative predictive value (NPV) 99.0%.	Prospective Multi site The workers participated in a surveillance program with yearly examinations between 2003 and 2010. RNA was

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						Conclusion: → In this prospective and so far largest study on survivin, the marker showed a good NPV and specificity but a low PPV and sensitivity. → This was partly due to the low number of cases, which limits the validity of the results. → Compliance, urine quality, problems with the assay, and mRNA stability influenced the performance of survivin. → However, most issues could be addressed with a more reliable assay in the future. → One important finding is that survivin was not influenced by confounders like inflammation and exhibited a relatively low number of false-positives. → Therefore, despite the low sensitivity, survivin may still be considered as a component of a multimarker panel.	extracted from urinary cells and survivin was determined by Real-Time PCR.
Kamat 2011	Validation study, prospective, single site (The University of Texas MD Anderson	N=200 Patients with a history of bladder cancer. Median age, years (range): 66.9 (20–94)	A) cystoscopy and NMP22; B) cystoscopy and FISH (UroVysion®); C) cystoscopy and cytology; D) cystoscopy and	Cystoscopy alone	1) Detection of cancer 2) Costs	1) Cancer was detected in 13 patients at study entry. Detection rates for the five surveillance strategies were: (i) 52%, (ii) 56%, (iii) 72%, (iv) 60%, and (v) 56%. 2) The costs per tumour detected (at the time of initial marker analysis) were	Prospective Single site Consecutive patients

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	Cancer Center) 3	Gender (%): - Female 55 (27.5) - Male 145 (72.5) Stage prior to study entry (%): - Ta: 142 (71.0) - T1: 42 (21.0) - Cis: 15 (7.5) - Unknown: 1 (0.5) Grade prior to study entry (%): - Low: 116 (58.0) - High: 62 (31.0) - Unknown: 22 (11.0)	positive NMP22 confirmed by positive FISH (UroVysion®).			(i) $7692; (ii) $12 000; (iii) $26 462; (iv) $11 846; and (v) $10 292. - When early detection of biomarkers was factored in, the CPTD became: (i) $7692; (ii) $11 143; (iii) $19 111; (iv) $10 267; and (v) $9557. - There were 12 new cancers detected at first follow-up (median time, 4.1 months). - None of the tumours detected by biomarkers but not by cystoscopy were invasive. Conclusion: → Cystoscopy alone remains the most cost-effective strategy to detect recurrence of bladder cancer not invading the muscle. → The addition of urinary markers adds to cost, without improved detection of invasive disease.	
Karnes 2012	Cross sectional study on diagnostic accuracy (Validation study), prospective, multi site	Patients with hematuria Derivation population (n=288) Validation population (n=748)	FGFR3 and quantified matrix metalloproteinase 2 and the hypermethylation of TWIST1 and NID2		To test whether a noninvasive urine-based multianalyte diagnostic readout assay that uses protein and DNA biomarkers can risk stratify patients with hematuria into those who are or are not likely to have	- Cystoscopy/biopsy diagnosed 690 of 748 patients as negative and 58 as positive for bladder cancer. - Of 21 patients identified by FGFR3 as highly likely to have cancer, 20 were also positive by cystoscopy/biopsy, resulting in a PPV of 95.2% (20 of 21), with specificity of 99.9% (689 of 690). - The 4-marker combination identified 395 patients as having a low likelihood	Prospective Multi site Urine samples were analyzed for the presence of mutant FGFR3 and quantified matrix

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	3				bladder cancer and those who should receive standard care.	of cancer. - Of these, 56.2% (388 of 690) also had negative biopsy/cystoscopy findings, resulting in an NPV of 98.2% (388 of 395). - In total, 416 of the 748 patients with hematuria (55.6%) were identified with extremely high NPV and PPV to have or not have bladder cancer. Conclusion: → This multianalyte assay accurately stratified patients with high confidence into those who likely do or do not have bladder cancer. This test was developed to enhance and not to eliminate referrals for urologic evaluation.	metalloproteinase 2 and the hypermethylation of TWIST1 and NID2. A patient's chance of having (positive predictive value [PPV]) or not having (negative predictive value [NPV]) cancer was determined by FGFR3 alone or by all 4 biomarkers, respectively.
Kelly 2012	Validation study, prospective, multi site 3	N=1677 Consecutive patients Male/female: 1040/637	Mcm5 alone Mcm5 in combination with Nuclear Matrix Protein 22 (NMP22)	Pathological confirmation following transurethral resection.	To evaluate the diagnostic accuracy of Mcm5, a novel cell cycle biomarker of aberrant growth, alone and in combination with NMP22.	- Genito-urinary tract cancers were identified in 210/1564 (13%) patients with an Mcm5 result and in 195/1396 (14%) patients with an NMP22 result. - At the assay cut-point where sensitivity and specificity were equal, the Mcm5 test detected primary and recurrent bladder cancers with 69% sensitivity (95% confidence interval = 62–75%) and 93% negative predictive value (95% CI = 92–95%). - The area under the receiver operating characteristic curve for Mcm5 was 0.75	Prospective Multi site Blinded All patients underwent ultrasound, intravenous urography, cystoscopy, urine culture and

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						(95% CI = 0.71–0.79) and 0.72 (95% CI = 0.67–0.77) for NMP22. - Importantly, Mcm5 combined with NMP22 identified 95% (79/83; 95% CI = 88–99%) of potentially life threatening diagnoses (i.e. grade 3 or carcinoma in situ or stage >= pT1) with high specificity (72%, 95% CI = 69–74%). Conclusion: → The Mcm5 immunoassay is a non-invasive test for identifying patients with urothelial cancers with similar accuracy to the FDA-approved NMP22 ELISA Test Kit. → The combination of Mcm5 plus NMP22 improves the detection of urothelial cell carcinoma (UCC) and identifies 95% of clinically significant disease. → Trials of a commercially developed Mcm5 assay suitable for an end-user laboratory alongside NMP22 are required to assess their potential clinical utility in improving diagnostic and surveillance care pathways.	cytologic analysis. An immunofluorometric assay was used to measure Mcm5 levels in urine cell sediments. NMP22 urinary levels were determined with the FDA-approved NMP22H Test Kit.
Kundal 2010	Cross sectional study, prospective Single center	N=115 The number of males were 89 (77.4%) and females were 26 (22%).	Nuclear matrix protein NMP22 Bladder Chek Test Urine cytology	Cystoscopic findings and biopsy findings	1) Sensitivity and specificity	- Mean age of the patients was 57.2 years for males and 55.3 years for females. - A total of 59 cases of Bladder Cancer (TCC) were diagnosed among which NMP22 test was positive in 48 cases	Authors describe study as ‚randomized, double-blind' which is not specified and not

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	(Kaschmir) 3	72 patients (62.6%) were in age group of 40-60yrs and 7(6.1%) patients were below 40yrs of age and 36 patients (31.3%) were more than 60yrs of age.				and cytology in 26 cases. 1) The sensitivity and specificities of NMP22 Test in recurrent bladder cases was 81.3% and 92% which was significantly greater than that of cytology 44% and 96.1% respectively. - In non-invasive lesions of Bladder Cancer (TCC), NMP22 Test and Cytology was positive in 71.8% and 42.8% of cases respectively. - In muscleinvasive lesions, NMP22 Test was positive in 82.2% and 44.4% cases were positive for cytology. Conclusion: → The NMP22 Bladder Check is a new point of care diagnostic test for urinary bladder cancer. → The results have shown that the NMP22 can be used as a substitute for urine cytology as we detected high sensitivity and specificity of NMP22 in recurrent bladder cases.	believable. Patient with urinary tract infections, indwelling urinary catheters, foreign bodies in urinary bladder were excluded from the study. Patient having undergone bowel interposition surgery and Prostate and renal malignancy were also excluded from the study. Therefore study is of limited external validity.
Lotan 2009	Cohort study, prospective, single site (Texas) 3	N=1502 Subjects at high risk for bladder cancer based on age and smoking or occupational status	NMP22® BladderChek® testing was performed on voided urine samples.	-	To evaluate the use of a point of care urine based tumor marker (BladderChek) for screening.	- Based on 10-year or greater smoking history 1,298 participants were enrolled while 513 were enrolled based on a greater than 15-year high risk occupation for bladder cancer. - Positive BladderChek testing was	Prospective Single site Those with positive test

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		were solicited from 2 well patient clinics from March 2006 to November 2007. 1,175 men and 327 women. Subjects older than 50 years. Subjects had a 10-year or greater smoking history (any number of cigarettes) or a significant (15 or more years) high risk occupation such as working in the dye industry, petroleum industry or chemical industry. Mean participant age was 62.5 years (range 46 to 92).				observed in 85 (5.7%) participants and 69 agreed to undergo cystoscopy. - Three types of lesions were diagnosed including multifocal, high grade Ta (1); Ta, low grade tumor (1) and marked atypia (1). - Follow-up was available in 1,309 subjects. - Mean follow-up was 12 months (range 0.9 to 25.5) and 2 of 1,309 participants had low grade non-invasive bladder cancer. - Evaluation of patient records revealed that 73.4% of participants had urinalysis within 3 years before screening. Conclusion: → NMP22 BladderChek for screening an asymptomatic, high risk population can detect non-invasive cancers but the low prevalence of bladder cancer in this population did not permit assessment of intervention efficacy. → Frequent use of urinalyses in high risk persons may attenuate future efforts to study the effects of bladder cancer screening tests.	results underwent office cystoscopy and cytology testing. Participants were contacted for follow-up at 12 months after study enrollment to evaluate for unrecognized bladder cancer.
Lotan 2009	Cross-sectional study , multi site	N=1272 Most were men (723, 56.8%) and	Nuclear matrix protein-22 (NMP22).		To determine whether the nuclear matrix protein-22 (NMP22) assay can improve the	- Of 1272 patients, 76 (6.0%) had bladder cancer, 217 (17.1%) were NMP22-positive and 17 (1.3%) had malignant cells on urinary cytology.	Multi site The data of 670 from four study

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	3	white (1050, 82.5%). Smoking was reported by 461 (36.2%) patients. Microscopic haematuria was present in 960 (75.5%), vs gross in 206 (16.2%). 76 (6.0%) had bladder cancer.			accuracy of discriminating between high risk patients with and without bladder cancer.	- NMP22 and urinary cytology results were independent predictors of bladder cancer (P=0.005 and 0.007, respectively). - In external validation, the area under the curve (AUC) for NMP22 was 76.0% vs 56.2% for cytology. - External validation of the multivariable NMP22-based bladder cancer nomogram gave an AUC of 82.4% vs 74.7% for the multivariable cytology-based nomogram (gain 7.7%; P=0.006) vs 82.6% for the multivariable nomogram combining NMP22 and cytology results (gain 0.2%; P=0.1). Conclusion: → The ability of the NMP22 test to predict bladder cancer in high-risk patients significantly exceeds that of urinary cytology. → The NMP22-based nomogram can help to identify individuals at risk of bladder cancer.	sites were used to develop a logistic regression model-based nomogram to predict the presence of bladder cancer. The remaining data from 602 patients from nine study sites were used to externally validate the nomogram. A separate nomogram was developed for urinary cytology, and for the combination of NMP22 and urinary cytology findings. All tests were two-sided with a significance level

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
							set at 0.05.
Maffezzini 2010	Validation study, single site (Italy) 3	N=126 Consecutive patients. Patients with a history of non-muscle-invasive bladder cancer (NMIBC).	Fluorescent in situ hybridization (FISH) – UroVysion. Three FISH patterns were defined: negative; low-risk positive, i.e. positive staining for 9p21 and/or Ch3 abnormalities; and high-risk positive, i.e. positive staining for Ch7 and/or 17.	Followed-up with urinary cytology and cystoscopy.	To evaluate the potential contribution of a fluorescent in situ hybridization (FISH) as prognostic indicator of the risk of recurrence or progression in patients undergoing follow-up for non-muscle-invasive bladder cancer (NMIBC).	- Overall 73 out of 126 patients (57.9%) had a positive urinary FISH test. - After a median time of 14 months, 46 FISH-positive patients underwent recurrence (36.5%) and in 15 patients there was progression of disease (11.9%). - Among positive patients, the low-risk category was found in 34, and the high-risk in 39. - Low-risk FISH-positive patients had a higher rate of recurrence as compared to FISH-negative patients, with a hazard ratio (HR) of 1.6. - The recurrence rate was even greater in patients with a high-risk positive test, with an HR of 1.9. Conclusion: → The urinary FISH test can be used as an aid in predicting the risk of recurrence during follow-up of patients with history of NMIBC.	Single site The limitation of the study was that the impact of intravesical treatment was not assessed.
Mengual 2014	Validation study, single site (Barcelona)	A total of 239 consecutive urine samples from UCC patients and controls were collected between	Test for bladder cancer based on urine gene expression patterns.	Confirmed diagnose of bladder cancer.	Accuracy	- 12+2 gene expression signature has an overall sensitivity of 80% with 86% specificity (AUC 0.914) in discriminating between bladder cancer and control samples and 75% sensitivity	Single site Gene expression patterns of the previously

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	3	February 2009 and January 2010.	Tested: 12 + 2 gene expression signature.			and 75% specificity (AUC 0.83) in predicting tumor aggressiveness in the validation set of urines. three new signatures (containing 2, 5, and 10 genes) for diagnosis and one (containing 6 genes) for prognosis were designed. - Diagnostic performance for the 2, 5, 10, and 12 gene signatures was maintained or improved in the enlarged set of samples (AUC 0.913, 0.941, 0.949, 0.944, respectively). - The performance for aggressiveness prediction was also improved in the 14 and six gene signatures (AUC 0.855 and 0.906, respectively). Conclusion: → This validation study confirms the accuracy of the 12+2 gene signature as a non-invasive tool in the assessment of bladder cancer. → Improved models with a lower number of genes are presented that need to be validated in future studies.	reported 48 genes (including the 12+2 genes of the signature) were analyzed by TaqMan Arrays in an independent set of 207 urine samples.
Messing 2005	Validation study, multi site (US) 3	N=341 Patients with a history of bladder cancer undergoing monitoring.	Cytology and/or ImmunoCyt®	Biopsy	Sensitivity, specificity, positive predictive value, negative predictive value.	- The overall sensitivity of cytology alone, ImmunoCyt® alone and the 2 methods combined was 23%, 81% and 81%, respectively. - The specificity of cytology alone,	Multi site

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						ImmunoCyt® alone and of the 2 methods combined was 93%, 75% and 73%, respectively. - The immunocytochemical test was more sensitive than cytology for detecting grades 1 and 2, and stages Ta, T1, and T2 urothelial carcinoma, and it was equally sensitive for detecting grade 3 cancers and carcinoma in situ (CIS). - The sensitivity of the combined tests for grades 1 to 3/CIS was 79%, 90% and 82%, while for stages Ta, T1, T2+ and CIS it was 83%, 75%, 100% and 100%, respectively. - The overall positive and negative predictive values of the combined tests were 37% and 95%, respectively. - Importantly the immunocytochemical test could detect 71% of small (less than 1 cm) tumors. Conclusions: → ImmunoCyt® is a sensitive test for detecting bladder cancer. → Because of its high sensitivity for detecting small tumors, even those of low histological grade, and its high negative predictive value, this test may have a role in decreasing the frequency of cystoscopic examinations for monitoring patients with low risk	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						bladder cancer.	
Priolo 2001	Cross-sectional study on diagnostic accuracy, multi site 3	194 high risk patients undergoing a diagnostic cystoscopy (25 females and 169 males, mean age 66.0 years; group 1). 279 patients with previous history of transitional cell carcinoma awaiting a follow-up cystoscopy (42 females and 237 males, mean age 68.2; group 2). 45 healthy controls (11 females and 34 males, mean age 58.7 years).	Quantitative bladder tumor antigen (BTA) TRAKE immunoassay. Exfoliative urine cytology.	Biopsy	To compared the sensitivity, the specificity and the diagnostic accuracy of the BTA TRAK test and that of voided urine cytology (VUC) in the detection of primary or recurrent transitional cell carcinoma (TCC) of the bladder.	- BTA TRAK values resulted significantly higher in tumor positive cases than in absence of bladder tumor for both groups of patients. - Non neoplastic urothelial diseases as well as the absence of mucosal abnormalities were associated with a marked increase in BTA TRAK levels with respect to the control group. - Overall sensitivity and specificity was 63 and 63% for BTA TRAK (cut-off 34 U/ml), and 68.3 and 73.4% for urine cytology, respectively. - The diagnostic advantage of urine cytology was maintained when patients were stratified by tumor grade. Conclusion: → The clinical performance of the BTA TRAK in the detection of primary or recurrent bladder cancer is acceptable and reproducible as shown by similar results with previous reports, although urine cytology performed on three samples showed the highest sensitivity and specificity.	Multi site Urine cytology was performed by a skilled cytopathologist on three consecutive samples. (unaware of the results of BTA TRAK) A level of P < 0.01 was accepted as statistically significant.
Puerta-Gil 2012	Diagnostic study, prospective, multi site	A first set included tumors with available matching urinary samples (n = 37).			To define roles of miRNAs expression profiles on disease stratification and	miRNA Expression Profiles in Pairs of - Results showed a significant correlation in quantitative levels of	Prospective Exploratory research

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	3	Demographic information indicated 31 males and 6 females (median age, 66 years; range, 51 to 86 years). A second set included tumors (n = 164) for which tissue arrays were constructed. High-quality RNA was obtained from 113 tumors. Demographic information indicated 101 males and 12 females (median age, 73 years; range, 35 to 94 years).			outcome prognosis.	expression between the urinary samples and matching tumors for miR-452 (P = 0.005) and miR-222 (P = 0.008), but not for miR-143. - miR-143 staining was positive in urothelial hyperplasia, whereas little to no expression was detected in tumor cells of a high-grade T1 tumor. - Strong signals were observed for both miR-222 and miR-452 in the same highgrade T1 tumor. - Interestingly, little to no expression was observed for miR-452 and miR-222 in normal urothelium and surrounding stroma. - - miR-222 expression was significantly correlated with increasing tumor grade (P = 0.017), tumor size (P = 0.005), presence of carcinoma in situ (P = 0.035), and clinical outcome end points (recurrence, P = 0.006; progression, P = 0.003; disease specific, P = 0.034; and overall survival, P = 0.023). -143 expression significantly correlated with recurrence, P = 0.011; and progression, P = 0.039. <u>Diagnostic Properties of miRNAs in Urinary Specimens</u> - The miRNA profiles by RT-qPCR were	Multi site

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						measured in an independent series of urinary specimens belonging to patients with bladder cancer (n = 37) and controls (n = 57). - The receiver operating characteristic curve analyses indicated that urinary miR-452 alone (AUC = 0.772), and miR-452 (AUC = 0.848) or miR-222 (AUC = 0.718) normalized by miR-16 expression, provided significant accuracies for bladder cancer diagnosis. → In conclusion, urinary miRNAs were clinically useful for noninvasive bladder cancer diagnostics (miR-452 and miR-222) and tumor stratification and outcome assessment using tumor samples (miR-222 and miR-143). → urinary miRNA measurement could mirror the miRNA expression in bladder tumors and be potentially used for noninvasive bladder cancer diagnostics. →Protein expression profiles of targets (ERBB3 and ERBB4) potentially regulated by these miRNAs correlated with their expression, clinicopathologic correlates of tumor progression, and clinical outcome. →Our study suggests that, in the near future, novel miRNA-based panels might be explored for bladder cancer diagnostics.	

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Saeb-Parsy 2011	Cross-sectional study on diagnostic accuracy, multi site (UK). 3	N=497 The majority presenting with gross haematuria (GH) or undergoing cystoscopic surveillance (CS) following previous bladder cancer. Initial study of 313 patients, followed by a validation study of 184 patients.	Immunocytochemical staining for MCM-2.	Cystoscopy and biopsy.	Tested the accuracy of immunocytochemistry (ICC) for minichromosome maintenance protein-2 (MCM-2) in diagnosing bladder cancer, using cells retrieved from urine.	- In the initial study, receiver operator characteristic analysis showed an area under the curve of 0.820 (P<0.0005) for the gross haematuria (GH) group and 0.821 (P<0.01) for the cystoscopic surveillance (CS) group. - Optimal sensitivity/specificity were provided by threshold values of 50þ MCM-2-positive cells in GH samples and 200þ cells in CS samples, based on a minimum total cell number of 5000. - Applying these thresholds to the validation data set gave 81.3% sensitivity, 76.0% specificity and 92.7% negative predictive value (NPV) in GH and 63.2% sensitivity, 89.9% specificity and 89.9% NPV in CS. - Minichromosome maintenance protein-2 ICC provided clinically relevant improvements over urine cytology, with greater sensitivity in GH and greater specificity in CS (P=0.05). Conclusion: → Minichromosome maintenance protein-2 ICC is a reproducible and accurate test that is suitable for both GH and CS patient groups.	Multi site In all cases, presence/absence of bladder cancer was established by cystoscopy/biopsy. In all cases, the relevant tissue diagnosis was made by a member of the team of consultant urological histopathologists at the participating centre.
Shariat 2011	Cross-sectional study on diagnostic	N=2222 Patients with a history of non-muscle-invasive	Voided NMP22 and cystoscopy		To use decision analysis to determine whether NMP22 improves medical	- After cystoscopy, 581 (26%) patients were found to have cancer. - NMP22 level was significantly associated with bladder cancer	Multi site The study was limited by its

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
	accuracy, multi site 3	bladder cancer and current negative cytology			decision-making. Measurements: Clinical net benefit was calculated by summing the benefits (true positives) and subtracting the harms (false positives) and weighting these by the threshold probability at which a patient or clinician would opt for cytoscopy.	recurrence and progression (p<0.001 for both). - Using NMP22 in a model with age and gender was associated with better patient outcomes than performing cystoscopy on everyone for threshold probabilities above 8% for recurrence and above 3% for progression. - Only offering cystoscopy to those with a 15% or greater risk would reduce the number of cystoscopies by 229, while missing only 25 cancer recurrences per 1000 men with a negative cytology. Conclusion: → For clinicians who would perform a cystoscopy at a threshold of 5% for recurrence or 1% for progression, NMP22 will not aid clinical decision-making. → For less risk averse clinicians who would only perform a cystoscopy at a threshold probability >8% for recurrence or >3% for progression, NMP22 can help determine which patients require cystoscopy and which can be spared this procedure.	multicenter and cross-sectional design. No longitudinal measurement of patient related outcomes.
Smrkolj 2011	Cross-sectional study on diagnostic accuracy,	N=108 Bladder tumors. Between May 2006 and	Nuclear matrix protein 22 (NMP22) tumor marker test, BladderChek	Cystoscopic findings and histopathological examination	Sensitivity, specificity.	- For the prediction of malignant histopathological result, sensitivity and specificity were 45.2% and 75.0%, respectively, for NMP22 at a cut-off of 7.5 kU/L, 17.7% and 100% for the	Prospective Single site NMP22 was

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	prospective, single site (Slovenia) 3	January 2009. Mean age, years +- SD: 68.3 +- 9.9. Male/female: 74/34	point-of-care test and voided urinary cytology.	results after transurethral resection of the bladder lesion.		BladderChek_ test and 37.0% and 100% for voided urine cytology. - For the prediction of suspicious or positive cystoscopic finding, sensitivity and specificity were 40.4% and 72.1%, respectively, for NMP22 at a cut-off of 7.5 kU/L, 14.8% and 93.8% for the BladderChek test and 26.8% and 98.1% for voided urine cytology. Conclusion: → The NMP22 quantitative test showed higher sensitivity and lower specificity compared with voided urine cytology, whereas the sensitivity of the BladderChek test was low. → We could not recommend any of the three noninvasive tests as a replacement for cystoscopy for the diagnosis or follow-up of urinary bladder tumors.	measured using an ELISA assay in stabilized voided urine and using the BladderChek_ test. Voided urinary cytology was performed on urine samples. Results were compared to cystoscopic findings and histopathological examination results after transurethral resection of the bladder lesion.
Soyuer 2009	Validation study, single site (Turkey) 3	N=126 90 patients of which 54 with bladder cancer with primary/recurrent diagnosis (low grade urothelial carcinoma (LGUC) = 23/8 patients, high grade urothelial carcinoma (HGUC) =	Cytology ImmunoCyt/uCyt + (UCyt+™) test Cytokeratin 20 (CK20) Cytology+ UCyt+™	Cystoscopy	Sensitivity, specificity.	- The overall sensitivity detected for each tumor marker was as follows: for urine cytology was 75.9% and UCyt+™ was 83.3%, for CK20 70.4%, while the specificity was 66.7% for urine cytology and 86.1% for UCyt+™ and 83.3% for CK20. - The sensitivity of cytology and UCyt+™ combination was higher (88.9%) than the sensitivity cytology and CK20	Single site

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		18/5 patients), and 36 patients as control. Mean age: 66, range 46–80 years Control group: mean age: 49, range 30–78 years.	Cytology+ CK20 UCyt+™+ CK20 Cytology+ UCyt+™ + CK20			combination (77.8%). - The simultaneous use of the three markers, sensitivity was reaching 92.5%. Conclusion: → The UCyt+™ test and CK20 expression are valid tools for the performance of adjunctive analyses with conventional cytologic examination. → Combined use of UCyt+™ and cytology can improve the sensitivity and specificity over the CK20 and cytology combination for the detection of bladder cancer in urine. → Further new studies with larger patient populations should be done in order to assess the effectiveness of these tests to replace conventional cystoscopy in the primary diagnosis.	
Terrell 2011	Diagnostic study, rospective, multi site 3	N=434 Consecutive subjects.	Cytology	negative NMP22® BladderChek® test and negative cystoscopy.	To evaluate whether cytology provides additional diagnostic information in patients with a negative NMP22® BladderChek® test and negative cystoscopy.	First multi-center database: - In the detection database (n = 1331), 1065 patients had a negative cystoscopy and BladderChek. - There were 3 cancers (stages Ta, Tis and T1) and cytology was atypical in one and reactive in two. Second multi-center database: - In the surveillance cohort (n = 668) patients, 437 patients had negative	Prospective Multi site Consecutive subjects Subset analyses of 2 large prospective multi-center

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						cystoscopy and BladderChek. Cancer was found in 2 patients (stages Tis and Ta). - The patient with Tis has dysplastic cytology and Ta tumor had reactive cytology. Validation: - In the cohort of 434 patients, 288 patients had negative cystoscopy and BladderChek. - One cancer was missed, a Ta ureteral urothelial carcinoma with a reactive cytology. Conclusion: → In patients with negative cystoscopy and BladderChek, very few cancers are missed and cytology was not effective in detection. → Use of a point-of-care test in conjunction with cystoscopy in lieu of cytology could decrease cost, provide immediate results, improve negative predictive value and reduce the uncertainty that results from inconclusive cytologic results.	databases evaluating the BladderChek test.
Vinci 2011	Validation study, prospective, multi site	108 consecutive patients with non-muscle-invasive (NMI) urothelial carcinoma of the bladder (UCB) and	Methylation analysis of BCL2, hTERT, and DAPK promoters.	Diagnosis of bladder Cancer	Early detection of NMI UCB	- In tumor tissue, at least 1 gene was hypermethylated in 91% patients (BCL2 in 62%, hTERT in 53%, DAPK in 48%). - Methylation of hTERT was significantly correlated with tumor grade (P =	Prospective Multi site The frequency

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	3	105 controls with no genitourinary malignancies.				0.026). - In urine sediment sensitivity and specificity were 76% and 98%, respectively, using BCL2 and hTERT. - The number of methylated genes was highly correlated with tumor grade (P = 0.005). - Methylated BCL2 and hTERT in urine sediment were highly correlated with those of the corresponding bladder tumor qualitatively (P > 0.001), and only BCL2 also quantitatively (P = 0.005). - Methylation levels of BCL2 and hTERT were variably associated with tumor grade and stage, but were significantly correlated with patient age (P = 0.004 and P = 0.027, respectively). Conclusion: → These findings suggest that quantitative methylation analysis of BCL2 and hTERT, but not DAPK, in urine sediment may be a useful tool in the diagnosis of NMI UCB, deserving future applicability studies. → Further prospective, multi-institutional studies are required to validate these markers and their general applicability in the management of patients with UCB, both in the screening and the surveillance setting.	and levels of methylated BCL2, hTERT, and DAPK promoters were evaluated with quantitative methylation-specific real-time polymerase chain reaction in DNA extracted from tumor tissue and paired normal bladder mucosa retrieved at the time of TUR in patients, and from urine in patients and controls.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Vriesema2001	Validation study, multi site (Netherlands) 3	N=104 (18 patients excluded because of low cellularity (ie, insufficient assessable urothelial cells) → 86 patients. Patients in follow-up for superficial urothelial cell carcinoma (UCC) of the bladder. 71 men and 15 women Mean age of 68.5 years (range 39.0 to 86.7).	ImmunoCyt test/cytology	Urethrocystoscopy (and additional histologic examination in the case of suspicious cystoscopic findings).	Sensitivity, specificity, positive predictive value, negative predictive value.	- Tumor recurrence was found in 22 of 86 patients (17 pTa, 3 pT1, 1 carcinoma in situ, 1 pT2 or higher). - The test had a sensitivity of 50%, specificity of 73%, positive predictive value of 39%, and negative predictive value of 81%. - The diagnostic odds ratio was 2.8 (95% confidence interval 1.0 to 7.5). - The area under the curve for the different observers varied between 0.54 and 0.60. - The kappa values were low (0.05 to 0.45), representing high interobserver variability. Conclusion: → The promising results from other studies could not be confirmed in this specific group of patients in follow-up for superficial UCC of the bladder. → The validity of ImmunoCyt was insufficient to justify the omission of cystoscopy in patients in follow-up for superficial UCC.	Multi site ImmunoCyt slides were scored under a fluorescence microscope by 3 observers. ImmunoCyt test was considered positive if one or more observers scored the test positive.
Yafi 2013	Cross-sectional study on diagnostic accuracy, retrospective, single site	1,114 consecutive patients corresponding to 3251 specimens (2979 cytologic and 272 histologic specimens).	Urine cytology	Histologic specimens.	Sensitivity and specificity.	- On cytologic examination, 71% of specimens were benign, 23% atypical, and 6% suspicious or positive for urothelial carcinoma. - Reason for collection was surveillance in 61% and new symptoms in 28%. - Depending on the tumor grade,	Retrospective Single site Subsequent cytologic and surgical

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	(Canada) 3	Between January 2006 and July 2006. The median age of the population was 73 years (range, 33–98 years). 81.7% of the patients were male.				sensitivity results ranged from 10% for low-grade to 51% for high-grade tumors. - Importantly, specificity of urine cytology ranged from 83% to 88% (depending on the type of urine collection and type of clinical presentation). - Anticipatory positive rate was 44% after a median time of 15 months. - Specificity of other reported urinary markers ranges from 40% to 90%. Conclusion: → This experience with regard to specificity of urine cytology is lower than reported historically. → Whether this is a consequence of heterogeneous study designs and parameters is open to debate. → As the anticipatory positive rate was high, close surveillance remains recommended in patients with positive urine cytology and negative workup. → Other institutions are encouraged to evaluate whether there remains a significant advantage for urine cytology over other urinary marker assays within their own clinical setting.	specimen reports were examined with a minimum 2-year follow-up period. Collected parameters included the date of collection, reason for urinary evaluation, type of specimen, and tumor grade. Atypical diagnosis was considered negative.

4.2. AG 3 Schlüsselfrage 2 – Literaturauswahl nicht abgeschlossen

4.3. AG 3 Schlüsselfrage 3 (Vergleich photodynamische mit Weißlicht-Diagnostik)

„Besteht ein Vorteil der photo-dynamischen Diagnostik sowie anderer Verfahren im Vergleich zur konventionellen Zystoskopie mit Weißlicht bei Verdacht auf ein Harnblasenkarzinom?“

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Kausch 2010	Systemic review and meta-analysis, retrospect-tive design in all studies 2++	Seventeen trials were identified. Twelve diagnostic trials used WLC and PDD with the same patients. Seven reported results for the subgroup of patients with carcinoma in situ (CIS). Five randomised trials studied therapeutic outcome. The results were combined in random effects meta-analyses if end points, designs, and populations were comparable.	Photodynamic diagnosis (PDD)	White-light cystoscopy (WLC)	- To assess the effect of PDD in addition to WLC on (1) the diagnosis and (2) the therapeutic outcome of primary or recurrent non- muscle-invasive bladder cancer investigated by cystoscopy or transurethral resection. - Detection rate.	Twenty percent (95 % confidence interval [CI], 8–35) more tumour-positive patients were detected with PDD in all patients with non-muscle invasive tumours and 39 % (CI, 23–57) more when only CIS was analysed. Heterogeneity was present among diagnostic studies even when the subgroup of patients with CIS was investigated. Residual tumour was significantly less often found after PDD (odds ratio: 0.28; 95% CI, 0.15–0.52; p < 0.0001). RFS (recurrence-free survival) was 15.8–27,0 % higher at 12 mo and 12–15,0 % higher at 24 mo in the PDD groups than in the WLC-only groups. The three p-values (0.008, 0.004, 0.02) of log-rank tests of RFS gave a combined p value of 0.00002.	Database search of Medline, Embase, the Cochrane Library, and CancerLit. Hand searching of relevant congress abstracts and urologic journals. Two reviewers (IK and MS) performed the database searches and application of the selection criteria independently

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						(statistically significant) → PDD detects more bladder tumour–positive patients, especially more with CIS, than WLC. → More patients have a complete resection and a longer RFS when diagnosed with PDD.	Data were extracted by two reviewers (IK and RV) in consensus.
Isfoss 2011	Systemic review and meta-analysis 2-	Data from 16 original studies comprising 1503 patients were pooled.	Fluorescent-light cystoscopy (FLC) (alternative term: photodynamic diagnosis: PDD)	Total number of CIS detected by cystoscopy (WLC and FLC)	- To examine evidence on the sensitivity of fluorescentlight cystoscopy (FLC) for urothelial carcinoma in situ (CIS) of the bladder.	- The claimed sensitivity of FLC for detecting patients with CIS using the most commonly reported intravesical agents 5-aminolevulinic acid or hexaminolevulinic acid was 92.4 %, while that of white-light cystoscopy (WLC) was 60.5 %. The two agents did not differ significantly for sensitivity. - It must be pointed out that a ‘ gold standard ’ is lacking in FLC studies. - The occurrence of CIS of the bladder can only be established by the pathological examination of whole bladders. The true sensitivities of various modes of cystoscopy for detecting CIS can be revealed if patients scheduled for cystectomy are first examined with WLC, FLC, and optionally random biopsies. → Sensitivity of FLC for the detection of CIS in the bladder is unknown. → Further studies are needed, and must include WLC and FLC, and	Literature searches only in the PubMed Database. Use of only one observer performing the search and extracting the data.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						optionally random biopsies, on patients scheduled for cystectomy.	
Li 2013	Systemic review and meta-analysis, retrospect-tive design in all studies 2+	Seven studies including 1040 cases were included in the final analysis. → Two randomized studies. → Seven prospectively collected data studies. All studies: → N=1040 → Age,mean (range): 64 years (25 - 90 years) → Sex (male/female): 744/296 → NMIBC (non-muscle-invasive bladder cancer) patients: 611 → Gold standard: Biopsy	Narrow-band imaging White-light imaging	Biopsy	Evaluate the diagnostic accuracy	Patient- and tumor-level analysis: - An additional 17,0 % of patients (95 % confidence interval, 10–25 %) and an additional 24 % of tumors (95% confidence interval, 17–31 %) were detected by narrow-band imaging, respectively. - Significantly higher detection rates using narrow-band imaging (rate difference 11 %; 95 % confidence interval 5–17 %; $P < 0.001$; and rate difference 19 %; 95 % confidence interval 12–26 %; $P < 0.001$, respectively) rather than white-light imaging were found. On the tumor level: - An additional 28% of carcinoma *in situ* was detected (95% confidence interval 14–45%) by narrow-band imaging, and a significantly higher detection rate (rate difference 11%; 95% confidence interval 1–21%; $P = 0.03$) was found. - The false-positive detection rate of tumor level did not differ significantly between the two techniques. → Cystoscopy assisted by narrow-band imaging detects more patients and tumors of non-muscle-invasive	Primary sources were the PubMed, Embase, Cochrane Library, Ovid and Web of Science databases. Two authors (Li and Fan) independently extracted the following parameters from each study: first author, year of publication, study type, total population characteristics, numbers of patients (or tumors) detected and numbers of lesions obtained. Any disagreement was resolved by

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						bladder cancer than white-light imaging, and it might be an additional or alternative diagnostic technique for non-muscle-invasive bladder cancer.	the adjudicating senior authors (Huang and Lin). The quality of selected studies was assessed by modified questionnaires based on the CONSORT and the STARD.
Zheng 2012	Systemic review and meta-analysis, six studies are prospective 2++	8 studies were available for the meta-analysis, published between 2008 and 2012 and including 1022 patients. Mean age (range): 65 (26-90); N/A; N/A; 63,2 (27-80); 70,6 (38-90); 70,6 (38,1-90,2); 53,6 (25-87); 68 (33-75) Male/female: 316/111, N/A, N/A, 41/23, 88/16, 70/25, 88/55, 62/16	Narrow band imaging (NBI)	White light imaging (WLI)	To assess the test performance and clinical effectiveness of narrow band imaging (NBI) cystoscopy.	- On a per-person analysis, the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio of NBI and WLI were respectively 0.943 (95 % CI 0.914 - 0.964) and 0.848 (95 % CI 0.803 - 0.885), 0.847 (95 % CI 0.812 - 0.878) and 0.870 (95 % CI 0.831 - 0.903), 7.038 (95 % CI 3.357 - 14.754) and 6.938 (95 % CI 2.052 - 23.465), 0.054 (95 % CI 0.012 - 0.237) and 0.181 (95 % CI 0.091 - 0.361), and 185.32 (95 % CI 45.714 - 751.26) and 42.931 (95 % CI 8.088 - 227.88). - The area under the curve and Q * of NBI and WLI were respectively 0.9781 and 0.8944, and 0.9337 and 0.8253. - For the characterization of carcinoma in situ , the pooled sensitivity,	Database search of PubMed, EMBASE, Cochrane Library, MEDLINE and CNKI. Hand searching of relevant congress abstracts and journals. Two of the authors (C.J.Z. and Y.L.L.) independently searched the

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		No. of patients: 427, 50, 61, 64, 104, 95, 143, 78				specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio of NBI were 0.927 (95% CI 0.878 - 0.960), 0.768 (95% CI 0.730 - 0.802), 4.545 (95% CI 2.820 - 7.325), 0.125 (95% CI 0.051 - 0.304) and 48.884 (95% CI 15.642 - 152.77) on a per-person analysis. - The area under the curve and Q * were 0.9391 and 0.8763. → NBI is an effective method for the identification of abnormal lesions including carcinoma in situ and can provide higher diagnostic precision of bladder cancer than WLI. → Multicentre randomized studies are recommended to determine whether the visual advantages of NBI can translate into real therapeutic benefit for individual patients.	databases and reviews. Quality assessment of included studies using QUADAS questionnaire.
Geavlete 2012	Cross-sectional study on diagnostic accuracy, prospective, single site	95 NMIBC-suspected consecutive cases. Inclusion criteria were hematuria, positive urinary cytology or ultrasound suspicion of bladder Tumors. 71 men and 24	Narrow-band imaging (NBI) cystoscopy	White light cystoscopy (WLC)	To assess the impact of narrow-band imaging (NBI) cystoscopy. Primary endpoint of the study was to determine significant differences in detection rates between the two methods and the resulting postoperative	- Overall detection rates of NMIBC and carcinoma in situ (CIS) were significantly improved for NBI (96.2 % versus 87.2 % and 100% versus 66.7 % respectively). - NBI cystoscopy showed significantly superior detection for CIS, pTa and overall tumors (95.2 % versus 61.9 %, 93.9 % versus 85.2 % and 94.8 % versus 83.9 % respectively). - Additional tumors were diagnosed by	Prospective Single site Consecutive recruitment

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		Women. Mean age 68.4 years (range 32–81 years).			treatment changes.	NBI in a significant proportion of patients with CIS, pTa, pT1 and NMIBC (55.5 % versus 11.1 %, 26.5 % versus 10.2 %, 30,0 % versus 10,0 % and 30.8 % versus 10.3 %). - Postoperative instillation treatment was improved due to NBI cystoscopy in a significantly larger number of NMIBC cases (16.7 % versus 5.1 %). → NBI cystoscopy represents a valuable diagnostic alternative in patients with NMIBC, with significant improvement in tumor visual accuracy as well as detection. →This approach provides a substantial improvement to bladder cancer therapeutic management.	
Mostafid 2009	RCT (phase III), prospective, multiple site (28 European and USA centres) 1-	779 patients	Arm A: white-light cystoscopy (WLC) followed by hexaminolaevulinate fluorescence cystoscopy (HAL FC) or no further treatment	Arm B: white-light cystoscopy (WLC)	Initial detection of NMIBC. Subsequent recurrence rate at 9 months after transurethral resection of bladder tumour (TURBT).	- Of the 278 with Ta/T1 randomized to HAL FC, 47 (16.9 %) had at least one additional Ta/T1 tumour (*P* <0.001). - In all, 41 patients had CIS; 37 (90 %) were detected by HAL FC and 13 (32 %) were missed by initial WLC. - The false-positive biopsy rate of HAL FC was similar to WLC (12 % and 11 %, respectively) and lower than previous reports. - At 9 months 72/200 patients (36 %) who had HAL FC had a recurrence, compared with 92/202 patients (46 %) who had WLC alone (*P* =0.029), a	Prospective Multiple site Second intraoperative randomization was to ensure that in the HAL arm the urologists performed a thorough WLC (as they did not

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						relative reduction of 21%. → There are important clinical differences between 5-ALA and HAL FC, and this should be borne in mind when interpreting study results. → Although 5-ALA and HAL both improve initial tumour detection rates, only HAL shows an improvement in recurrence-free survival.	know if the patient would subsequently have FC) and thus avoid potential bias in favour of HAL FC.

4.4. AG 3 Schlüsselfragen 4-6 (Diagnostik mittels PET-CT vor kurativer Therapie, des metastasierten BCA und des NMBIC)

Schlüsselfragen

3. „Welchen Stellenwert hat die Bildgebung des oberen Harntrakts zur Detektion eines Zweittumors bzw. in der Rezidivsituation für unterschiedliche Subgruppen beim nicht-muskelinvasiven Blasenkarzinom (NMIBC)?“

4. „Welche diagnostischen Methoden (inkl. Mapping/Biopsie Harnröhre und Bildgebung mit CT/MRT/Szintigraphie/ PET-CT) sollen beim Blasenkarzinom vor geplanter kurativer Therapie durchgeführt werden?“

5. „Welche Bildgebung (CT/MRT/Szintigraphie/PET-CT) und welche zusätzlichen diagnostischen Maßnahmen inkl. Tumormarker sollen beim metastasierten Urothelkarzinom standardmäßig durchgeführt werden?“

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Lu 2011	Systemic review and meta-analysis, retrospective design in three studies 2-	Six selected studies N=236 (55, 17, 35, 43, 29, 57) Sex (M/F) = 157/50 (47/8, 15/2, 25/10, 32/11, not specified, 38/19) Age mean: 63.7 - 76	FDG PET or PET/CT	Pathology from biopsy or surgery	Evaluate the diagnostic accuracy of FDG PET or PET/CT in urinary bladder cancer	- Pooled sensitivity and specificity of PET/CT for primary lesion detection of bladder cancer were 0.90 (95% CI: 0.70–0.99) and 1.00 (95% CI: 0.74–1.00), respectively - Pooled sensitivity and specificity of FDG PET or PET/CT for staging or restaging (metastatic lesions) of bladder cancer were 0.82 (95% CI: 0.72–0.89) and 0.89 (95% CI: 0.81–0.95), respectively → Diagnostic accuracy of FDG PET or PET/CT is good in metastatic lesions of urinary bladder cancer → Due to the small number of patients and limited number of studies analyzed, the diagnostic capability of FDG PET or PET/CT in detection of primary bladder wall lesions could not be assessed. → The use of FDG PET/CT along with novel interventions will overcome the problem of urinary excretion in detection of urinary bladder cancer → They suppose that only a few studies that used FDG PET or PET/CT in detection of urinary bladder cancer can be found, which means that their meta-analysis is still valuable → Prospective randomized, controlled	Only 6 selected studies were analyzed The presence of clinical heterogeneity in the patient population, imaging techniques, study design, and quality in these selected studies affects the generalizability of the results. The retrospective design in three studies, as well as the interpretation of FDG PET with other available clinical information, further decreased the methodological quality.

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						studies with larger case numbers are needed to confirm the value of FDG PET (PET/CT) in detection of primary urinary bladder cancer	Verification bias in four studies Only two studies about detection of primary tumor of bladder cancer, and therefore the SROCs for detecting bladder cancer could not be calculated
Bachor 1999	Retrospektiv, monozentrisch, Cross-sectional study on diagnostic accuracy 3	64 Patienten 12 Frauen, 52 Männer Alter: zwischen 22 und 82 Jahren (Durchschnittsalter: 62,4 Jahre)	Präoperativ PET des Beckens nach i. v.-Injektion von Fluor-Deoxy-Glukose (FDG)	Histologischer Befund des Operations-präparates nach klassischem operativen Lymphknoten-staging	PET beim Lymphknotenstaging des Harnblasenkarzinoms	- Beim Lymphknotenstaging wurden bei 14 Patienten positive Lymphknoten richtig erkannt - Falsch-negatives Ergebnis trat bei 7 Patienten auf - Bei 37 Patienten wurden die Lymphknoten als richtig-negativ bewertet - 6 mal war ein falsch-positives Ergebnis erzielt worden → Sensitivität von 67 % → Spezifität von 86% → Treffsicherheit von 80 % → PET-Ergebnisse sind ermutigend und scheinen besser zu sein als die klassischen Stagingverfahren, wie CT	Retrospektiv Monozentrisch Visuelle Auswertung der PET-Bilder erfolgte durch zwei erfahrene Nuklearmedizine r, denen das histologische Untersuchungs-ergebnis nicht bekannt war

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						und MRT → Zum jetzigen Zeitpunkt ist es aber sicherlich verfrüht, eine Operationsindikation vom PET-Ergebnis abhängig zu machen → Es sollte der Stellenwert der PET in der Diagnostik von Lymphknotenmetastasen des Blasenkarzinoms in mehreren Studien weiter festgelegt werden → Auf der zweiten interdisziplinären Konsensuskonferenz „PET bei onkologischen Fragestellungen“ wurde die Bestimmung des Lymphknoten-Status beim Blasenkarzinom als eine IIa-Indikation (hilfreich) eingestuft → In der Zukunft werden Fusionsbilder zwischen PET und CT erstellt sowie Doppeltracer-Techniken eingesetzt werden, um die PET-Diagnostik weiter zu verbessern	Small number of cases
Gofrit 2006	Prospective, single site, study of feasibility 3	18 patients with 19 advanced transitional cell carcinomas (17 bladder tumors and 2 upper tract transitional cell carcinomas) 13 men, 5 women	PET/CT	results of surgery	Examines the contribution of 11C-choline positron emission tomography/computerized tomography to preoperative staging of transitional cell carcinoma	- 11C-choline uptake was found in all primary transitional cell carcinomas (maximum standardized uptake value of 7.3 +- 3.2 (mean +- SD)) - Series included 3 patients with refractory bladder carcinoma in situ, which was visualized in all 3, with a standardized uptake value of 6.9 +-5.6 - In 6 patients uptake of 11C-choline in lymph nodes as small as 5 mm	Prospective Single site All patients underwent CT of the chest, abdomen and pelvis

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		Mean age 74 years				was visualized (standardized uptake value 3.8 +- 1.4) - Of these patients 4 underwent surgery and histopathology confirmed malignancy in 3 of 4 - No additional patients with positive lymph nodes were found on histopathology - Metastases were visualized in bones with normal architecture on computerized tomography in 4 patients (standardized uptake value 5.2 +- 1.1) and were confirmed by followup computerized tomography → In this small series 11C-choline positron emission tomography/computerized tomography was highly sensitive for primary and metastatic transitional cell carcinoma → Carcinoma in situ, lymph node metastases and early bony metastases were visualized → 11C-choline positron emission tomography/computerized tomography is a promising tool for preoperative staging of advanced transitional cell carcinoma → Larger series are needed to verify these results	Diagnostic CT was interpreted by a uroradiologist Very small number of cases

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Golan 2010	Prospective, single site, Cross-sectional study on diagnostic accuracy 3	20 patients with histologically proven urothelial carcinoma Age: median 61.5, mean (range) 65.27 (50-84) 7 female, 11 male Before definitive treatment 15, after cystectomy 3 Ta: 1, T1: 3, T2: 11, T3: 2, T4: 1 High grade: 17, low grade: 1	11C-choline PET/CT	18F-FDG PET/CT	Compared the value of using 11C-choline with the well investigated 18F-FDG tracer Diagnostic potential Local and distant spread of urothelial carcinoma	- A total of 51 lesions showed abnormal tracer activity - Positive predictive value for all detected lesions was 84.7% for 11C-choline positron emission tomography/ computerized tomography and 90.7% for 18F-FDG positron emission tomography/ computerized tomography - The corresponding positive predictive values for extravesical lesions were 79.4% and 88.2%, respectively - Discrepant findings between the tracers were noted at 11 sites - 18F-FDG positron emission tomography/computerized tomography correctly identified 4 extravesical metastases missed by choline positron emission tomography/computerized tomography in the absence of a contrary observation - Mean maximum standardized uptake and lesion-to-background ratio at extravesical sites were significantly higher for FDG → The diagnostic performance of PET/CT in the detection of metastatic urothelial carcinoma was not improved when 11C-choline was used as the tracer instead of 18F-FDG → For extravesical disease, 18F-FDG	Prospective Single site Two patients have insufficient histopathological or clinical followup data and were excluded from the analysis Very small number of cases

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						PET/CT may have even better diagnostic potential than 11C-choline PET/CT → More data on the use of 18F-FDG and other novel tracers are needed for the diagnosis and staging of urothelial carcinoma	
Lodde 2010	Prospective, single site, Cross-sectional study on diagnostic accuracy 3	N= 70 - 44 patients with muscleinvasive urothelial bladder cancer (UBC) before radical cystectomy (RC) - 19 under follow-up after RC - 7 after systemic chemotherapy 57 male, 13 female Age mean 67 (range 49-89)	FDG-PET CT	For those who had RC, histopathology was used as the reference standard.	To investigate the role of 18Ffluorodeoxyglusose positron-emission tomography (FDG-PET), combined with computed tomography (CT) and forced diuresis, in the staging and follow-up of urothelial carcinoma (UC).	- For the detection of primary UBC, FDG-PET/CT was slightly more sensitive than CT (85% vs 77%) but less specific (25% vs 50%) - For the detection of pelvic node metastasis FDGPET/CT was more sensitive than CT (57% vs 33%) with a specificity of 100% for both imaging techniques - In 20 patients, extrapelvic FDG-PET/CT images showed suspected disease at the first evaluation - UC progressed in nine of the 10 patients who had synchronous multiple PET-positive retroperitoneal or mediastinal lymph nodes, and in only two of the nine with unique hyperactive lesions in the lung - FDG-PET/CT also detected a pT1G3 UC of the renal pelvis and all bone metastases detected by bone scintigraphy → FDG-PET/CT could replace standard CT and bone scintigraphy in the	Prospective Single site CT, FDG-PET/CT and bone scintigraphy images were analysed independently by the diagnostic radiologists and/or by one of two experienced nuclear medicine Physicians Small number of cases

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						presurgical staging and monitoring of patients with UC after surgery or chemotherapy	
Swinnen 2010	Retrospective, single site, Cross-sectional study on diagnostic accuracy 3	N = 51 patients 43 male, 8 female Mean age: 66 years (range: 48 – 82) Invasive transitional cell carcinoma (TCC; T2 or higher) or recurrent high-risk superficial TCC (T1G3 with or without Tis) Stage: T1 → 12 T2 → 22 T3 → 13 T4 → 4 Grade: G2 → 13 G3 → 37 G4 → 1	Preoperative FDG-PET/CT	Definitive pathologic results	To determine whether the use of FDG-PET in combination with CT can increase the reliability of preoperative lymph node staging	Accuracy of FDG-PET/CT: 84,3 % Sensitivity FDG-PET/CT: 46,2 % Specificity FDG-PET/CT: 97,4 % PPV FDG-PET/CT: 85,7 % NPV FDG-PET/CT: 84,1 % Accuracy of CT alone: 80,4 % Sensitivity CT alone: 46,2 % Specificity CT alone: 92,1 % PPV of CT alone: 66,7 % NPV of CT alone: 83,3 % → cannot conclude that there is a real, statistically significant difference between the two staging methods → no advantage for combined FDG-PET/CT over CT alone for lymph node staging of invasive bladder cancer or recurrent high-risk superficial disease → no statistical evidence for a difference between FDG-PET/CT and CT alone based on this study → Further research is needed on the use of other PET tracers and/or the resolution of PET scanners for the lymph node staging of bladder cancer	Retrospective Single site Exlusion: Patients showing any distant metastasis on preoperative staging with bone scan, CT, and plain chest radiography One patient was excluded from the study because of neoadjuvant chemotherapy for a bulky T4 bladder carcinoma All patients underwent cystectomy and

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							an extended lymphadenectomy between April 2004 and December 2007 The PET/CT images were reviewed together by an experienced nuclear medicine physician and a radiologis Small number of cases
Jensen 2011	Retrospective, single site, Cross-sectional study on diagnostic accuracy 3	N = 18 patients 14 male, 4 female Avarage age: 65,4 (range 49 – 75) All patients with invasive BC, at least pT1 All patients received 18F-FDG PET/CT and	18F-FDG PET/CT and MRI staging	Histology	Investigation of 18F-FDG PET/CT and MRI for preoperative N staging of BC	Specificitiy for detection of lymph-node metastases for MRI: 80 % (12/15) Specificitiy for detection of lymph-node metastases for 18F-FDG PET/CT: 93,33 % (14/15) Sensitivity for detection of lymph-node metastases for MRI: 0 % (0/3) Sensitivity for detection of lymph-node metastases for 18F-FDG PET/CT: 33,33 % (1/3)	Retrospective Single site All PET/CT images, including sagittal, coronal and transverse sections, were visually interpreted by two nuclear

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		MRI All patients underwent radical cystoprostatectomy + removal of lymph nodes for histology				PPV of 18F-FDG PET/CT: 50 % (1/2) PPV of MRI: 0 % (0/3) Negative preventive value of MRI: 80 % (12/15) Negative preventive value of 18F-FDG PET/CT: 87,5 % (14/16) → Differences in specificity and NPV not statistically significant → No significant statistical difference between 18F-FDG PET/CT and MRI for preoperative N staging → Larger prospective studies are needed to elucidate the role of 18F-FDG PET/CT in N staging of bladder cancer	medicine physicians and a radiologist in consensus Very small number of cases
Jong 2002	Retrospective, single site, Cross-sectional study on diagnostic accuracy 3	18 patients with histologically proven bladder cancer 5 healthy volunteers	11C-choline PET	Histopatho-logical findings after cystectomy	Visualisation of bladder cancer with CHOL PET	- In the normal bladder wall, the uptake of CHOL was low, and the bladder margin was only outlined by minimal urinary radioactivity, if present - In ten patients the tumour was detected correctly by CHOL PET, with an standardised uptake value (SUV) of 4.7±3.6 (mean±SD) - One false positive CHOL PET scan was seen in a patient with an indwelling	Retrospective Single site PET images were analysed by two independent physicians who were blinded to the clinical data Computed

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						catheter for 2 weeks prior to the PET scan - In two patients, lymph node metastases were detected by CHOL PET - Micrometastasis <5 mm was not visualised with CHOL PET - In seven patients, no residual tumour was found after surgery - In six of seven patients CHOL PET imaging was negative - In situ carcinoma, dysplasia and a non-invasive urothelial tumour (pTa) remained undetected in three of these six patients - Minimal to no urinary tract radioactivity was seen in 22/23 subjects - Non-specific uptake of CHOL was observed in the small bowel, rectum and prostate gland - CHOL uptake in bladder cancer was avid, visualising the tumour in the virtual absence of urinary radioactivity - No uptake of CHOL was seen in pre-malignant lesionsor in small non-invasive tumours → CHOL uptake in bladder cancer was avid, visualising the tumour in the virtual absence of urinary radioactivity	tomography (CT) or a magnetic resonance imaging (MRI) scan of the abdomen was performed routinely to assess the presence of lymph node metastases and invasion beyond the bladder wall CT scan of the lungs was performed routinely to assess pulmonary Metastases To minimise post-biopsy effects, all CHOL PET studies were performed at least 2 weeks after the transurethral resection or

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						→ No uptake of CHOL was seen in premalignant lesions or in small non-invasive tumours → results warrant further research into the value of CHOL PET in the clinical management of patients with bladder cancer	biopsy Very small number of cases
Liu 2006	Retrospective, single site, Cross-sectional study on diagnostic accuracy 3	46 patients - 46 consecutive men with endoscopic and radiographic findings suspicious for localized and/or metastatic TCC - average patient age was 66.2 years (range 50–81 years)	FDG PET	computed tomography (CT) imaging (n = 47), magnetic resonance imaging (MRI) imaging (n = 7), or both (n = 4)	Determine the value of fluorodeoxyglucose (FDG) positron emission tomography (PET) in the evaluation of metastatic transitional cell carcinoma (TCC)	- Of 48 scans in patients who had no prior systemic chemotherapy, 10 had increased uptake in proven metastatic TCC lesions and 3 PET studies failed to reveal metastatic TCC (sensitivity 76.9%) - In patients free of metastatic disease, 33 revealed no abnormal uptake and 1 study revealed a suspicious area in a patient free of metastases (specificity = 97.1%) - In 10 patients imaged after receiving chemotherapy, the sensitivity fell to 50% for the detection of histologically confirmed residual/recurrent tumor by PET - Three cases showed extraurinary increased uptake found to be due to secondary malignancy (one lymphoma, one head and neck tumor, one recurrent colon cancer) and were excluded from the sensitivity and specificity calculations.	Retrospective Single site 58 FDG PET 2 patients underwent 3 PET studies, 8 patients underwent 2 PET studies, and 36 patients had a single PET study Thirty-five patients with primary bladder TCC and 5 with upper tract TCC underwent whole body PET to evaluate for metastatic disease prior to

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							surgical resection.
						→ FDG PET detects increased metabolic activity → After chemotherapy, viable cancer cells may still be present but with a diminished metabolic rate → PET imaging is often useful in the evaluation of untreated metastatic TCC metastasis but should be interpreted with caution in patients who have received prior chemotherapy → Further investigation is necessary to define the prognostic ability of PET	An additional 18 studies were performed to rule out metastasis in 8 patients who had undergone prior cystoprostatectomy for invasive tumors or 10 patients who had undergone systemic chemotherapy The 10 patients who received systemic chemotherapy prior to imaging were all treated with *cis*-platinum, methotrexate, and vinblastine The time between receipt of

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							chemotherapy and PET imaging ranged from 1 to 38 months (mean 12 months) Consecutive recruitment Small number of cases
Maurer 2012	Retrospective, single site, Cross-sectional study on diagnostic accuracy 3	44 patients 34/10 male/female Pathologic stage pT1/is pN0: 8 pT2 pN0: 11 pT3 pN0: 11 pT4 pN0: 2 pTx pN+: 12 Pathologic grade G1: 1 G2: 4 G3: 39 Age, yr → Median	PET/CT CT	Histology: LN metastasis	Evaluate the diagnostic efficacy of [11C]choline positron emission tomography in combination with computed tomography (PET/CT) for LN staging of patients with BCa scheduled for RC and compare that efficacy with the diagnostic efficacy of CT and the gold standard of histopathologic evaluation	- LN metastases were found in 12 of 44 patients (27%) - On patient-based analysis, sensitivity, specificity, PPV, NPV, and accuracy for [11C]choline PET/CT were calculated as 58%, 66%, 39%, 81%, and 64%, respectively; and for CT the calculated percentages were 75%, 56%, 39%, 86%, and 61%, respectively - Twenty-five of 471 dissected LN fields (5%) showed metastases - On field-based analysis, sensitivity, specificity, PPV, NPV, and accuracy for [11C]choline PET/CT were 28%, 95%, 21%, 96%, and 91%, respectively; for CT, the calculated percentages were 39%, 92%, 20%, 96%, and 90%, respectively → Limitations of this study are small	Retrospective Single site To minimize pathologic understaging and maximize histologic LN yield, tissue from each anatomic field was dissected separately by experienced uropathologists Two independent board-certified nuclear medicine

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		(range) 66.5 (44–84)				patient number and the fact that not all patients underwent extensive PLND → before recommending PET/CT staging in this patient cohort and for patients with BCa prior to RC, larger prospective studies with sufficient follow-up and survival data, including analysis of cost effectiveness, are needed	physicians analyzed [11C]choline PET/CT images Two independent board-certified radiologists analyzed CT Images Small number of cases
Picchio 2006	Retrospective, single site, Cross-sectional study on diagnostic accuracy 3	27 patients median age, 69.1 y	11C-Choline PET and Contrast-Enhanced CT	Results of histologic analysis of the specimens obtained from cystectomy and PLND	To compare the diagnostic accuracies of contrast-enhanced CT and PET with 11C-choline for the staging of urothelial bladder cancer	- The presence of residual bladder cancer (pTa–pT4) was correctly detected in 21 of 25 histologically tumor-positive patients (84%) by CT and in 24 of 25 patients (96%) by 11C-choline PET - Lymph node involvement was correctly detected in 4 of 8 patients (50%) by CT and in 5 of 8 patients (62%) by 11C-choline PET - The median size of the 3 nodes with false-negative PET results was 9 mm (range, 6–21 mm), and the median size of the metastatic lesions within the lymph nodes was 3 mm (range, 1–15 mm) - CT resulted in 6 (22%) false-positive lymph nodes, whereas none was demonstrated by 11C-choline PET; these data indicated a significantly	Retrospective Single site Imaging was performed 22.8 6 18.6 (mean 6 SD) d (range, 5–64 d) after the TURB procedure and 23.9 6 29.7 d before surgery (radical cystectomy and PLND) 99mTc-MDP scintigraphy, CT, and PET images

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						higher accuracy of PET than of CT (P , 0.01) - Both modalities missed a small peritoneal metastasis verified by histologic evaluation - No positive results were obtained from bone scintigraphy → These preliminary data suggest that 11C-choline PET is comparable to CT for detecting residual bladder cancer after TURB but appears to be superior to CT for the evaluation of potential additional lymph node metastases → 11C-choline imaging may allow for the selection of patients for possible neoadjuvant treatment before radical bladder resection → 11C-choline PET should be further evaluated for staging in patients who have bladder cancer and who are scheduled for radical cystectomy	were interpreted by consensus by 2 experienced radiologists and 2 nuclear medicine physicians unaware of the results of the other investigations Very small number of cases
Kosuda 1997	Retrospective, single site, study of feasibility 3	12 patients (7 male, 5 female) Ages ranged from 39 to 83 years, with a mean of 63.5 years	FDG-PET	CT and/or MRI findings	To assess the feasibility of imaging of bladder cancer with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scanning	- FDG-PET scanning was true-positive (presence of focal FDG uptake relative to surrounding tissue uptake) in eight of the patients (66.7%), but false-negative in four (33.3%) - Of 20 organs with tumor mass lesions confirmed pathologically or clinically, 16 (80%) were detected by FDG-PET scanning - FDG-PET scanning detected all of 17	Retrospective Single site On average the therapies had been performed 2.7 months before FDG-PET study

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						distant metastatic lesions and two of three proven regional lymph node metastases - FDG-PET was also capable of differentiating viable recurrent bladder cancer from radiation-induced alterations in two patients → These preliminary data indicate the feasibility of FDG-PET imaging in patients with bladder cancer, although a major remaining pitfall is intense FDG accumulation in the urine → Further prospective detailed studies of the FDG-PET method in patients with bladder tumors appear warranted, possibly including methods to reduce the urinary activity of FDG	All dynamic and static PET images were taken and interpreted by two nuclear medicine specialists Very small number of cases
Ahlström 1996	Retrospective, single site, study of feasibility 3	23 patients 17 male, 6 female Aged 48-82, mean 69 years	Positron emission tomography (PET) using 18F-2-fluoro-2-deoxy-D-glucose (18FDG) and L-methyl-11C-methionine	CT or MR findings and TNM classification before and after treatment	Evaluation of positron emission tomography (PET) using 18F-2-fluoro-2-deoxy-D-glucose (18FDG) and L-methyl-11C-methionine in the diagnosis and staging of urinary bladder carcinoma	- The urinary excretion of 18FDG prevented distinction of the primary tumour from the surrounding tracer - With 11C-methionine it was possible to detect 18/23 primary tumours - A trend was seen, suggesting that the highter the uptake values of 11C-methionine un the tumour, the greater the tumour stage → It is possible to visualize urinary bladder tumours larger than 1 cm in	Retrospective Single site Small study of feasibility Very small number of cases

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						diameter with PET using 11C-methionine, but the value of the method in the staging of the lesions is not superior to conventional methods	

4.5. AG 3 Schlüsselfrage 5 (Diagnostik vor kurativer Therapie)

„Welche diagnostischen Methoden (inkl. Mapping/Biopsie Harnröhre und Bildgebung mit CT/MRT/Szintigraphie/PET-CT) sollen beim Blasenkarzinom vor geplanter kurativer Therapie durchgeführt werden?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Hara 2009	Cross-sectional study on diagnostic accuracy, retro-spective, single site, Japan 3	N=173 Primary bladder cancer Male/female: 145/28 Age: median/Mean (range): 71/69.6 (36–90) Bladder cancer cases (low-risk	Biopsy results	Pre-operative/ patho-logical features	To identify the risk of concomitant CIS and the candidates for bladder biopsy	- Positive cytology was statistically associated with the presence of concomitant CIS in multivariate analysis ($P < 0.01$). - Abnormal cystoscopic appearance outside the tumor almost achieved statistical significance in multivariate analysis among preoperative factors ($P = 0.06$). - In this series, one (12.5%) of eight low-risk, 18 (24.7%) of 73 intermediate-risk and 41 (59.4%) of 69 high-risk cases	Retrospective Single site All procedures (biopsy) were performed by one member of the experienced urological staff and one urological

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		group/intermediate-risk group/high-risk group): 8/81/84				had CIS in normal-looking sites, respectively. - In cases with a single papillary tumor and negative cytology, one of 16 (6.3%) had concomitant CIS in their biopsy specimens at the normal-looking sites. → All non-muscle-invasive bladder cancer patients with positive cytology are candidates for additional random biopsies. → Targeted biopsies should be performed for all suspicious areas in the bladder mucosa. → Random biopsies should be considered in cases with the macroscopic types of cancer for predicting intermediate- and high-risk cancer.	resident. All biopsy specimens were examined by two histopathologists (M.T.,T.G.). Histo-pathological extensions were re-classified according to the Tumor-Node-Metastasis classification (2002) and the histo-pathological grading according to the World Health Organization/ International Society of Urological Pathology classification system (1998).
Kibel 2009	Pilot study, prospective, single site, St.	N=43 Sex(male/female):	Positron emission tomography/	Pathologic and/or biopsy findings.	Recurrence-free survival (RFS), disease-specific survival (DSS), overall	- Median follow-up was 14.9 months (range, 0.4 to 46.1 months). - One patient who did not undergo	Prospective Single site

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
	Louis 3	32/11 Race (white/black/other): 41/1/1 Age, years Median 70 Mean 68 Range 32-87 Clinical stage cT2: 40 cT3: 3 Clinical grade 1: 0 2: 2 3: 41 Pathologic stage pT2Nx: 21 pT3Nx: 16 pT4Nx: 3 pTxNxM1: 2 pTxN + M0†: 8 Pathologic grade 1: 0 2: 1 3: 40	computed tomography (PET/CT) with [18F]fluoro-deoxyglucose (FDG).		survival (OS), sensitivity, specificity.	lymphadenectomy was excluded from the pathology data analysis (n =42), whereas another patient who failed to return for follow-up was excluded from survival analysis (n =42). - FDG-PET/CT demonstrated a positive predictive value of 78% (seven of nine), a negative predictive value of 91% (30 of 33), sensitivity of 70% (seven of 10), and specificity of 94% (30 of 32). - RFS rates at 6 and 24 months for PET-positive patients were 50% (95% CI, 16% to 79%) and 0% (95% CI, not applicable), respectively, compared with 89% (95% CI, 69% to 96%) and 55% (95% CI,27% to 76%) for PET-negative patients (*P*= .0001). - DSS rates at 6 and 24 onths for PET-positive patients were 63% (95% CI, 23% to 86%) and 23% (95% CI, 1% to 62%), respectively, compared with 100% (95% CI, not applicable) and 62% (95% CI, 32% to 82%) for PET negative patients (*P*=0003). - OS rates at 6 and 24 months for PET-positive patients were 63% (95% CI, 23% to 86%) and 23% (95% CI, 1% to 62%), respectively, compared with 93% (95% CI, 76% to 98%) and 58% (95% CI, 31% to 78%) for PETnegative patients (*P*=.0062). - RFS, DSS, and OS were all significantly	PET/CT study was interpreted by one of two experienced nuclear radiologists and by a diagnostic radiologist specializing in genitourinary radiology Small sample size Small number of patients with metastatic disease.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						poorer in the patients with positive FDG-PET/CT than in those with negative FDG-PET/CT. → FDG-PET/CT detected occult metastatic disease in seven of 42 patients with negative conventional preoperative evaluations. → PET findings were strongly correlated with survival. → FDG-PET/CT may help in making treatment decisions before radical cystectomy.	
Schöder 2011	Pilot study, prospective, single site 3	N=17 (male) Age (range): 42-70 At the time of initial presentation, one, four, and 12 patients were clinical stage TisN0M0, T1N0M0, and T2N0M0, respectively. Six patients had previously received intravesical Bacillus Calmette-Guerin (BCG) therapy, on average 8 months prior to RC and PLND (range 5-28 months).	11C-acetate positron emission tomography/ computed tomography (PET/CT)	Histo-pathology	To investigate the utility of 11C-acetate positron emission tomography/ computed tomography (PET/CT) for staging of bladder cancer and response assessment after neoadjuvant chemotherapy.	- Eight of 10 residual tumors showed abnormal 11C-acetate uptake - Two cases of residual TiS were false negative, three cases were false positive, and three true negative. - Three patients showed true positive uptake in LN. - False positive uptake occurred in 14 LN regions secondary to granulomatous disease after prior intravesical Bacillus Calmette-Guerin (BCG) therapy. Sensitivity: - For detecting residual bladder cancer is 8/10 (80%, 95% CI 55-100%) - For correctly identifying metastatic nodal regions is 3/3 (100%) Specifity:	Prospective Single site All PET studies were interpreted by two investigators (HS, SO) who were unaware of other imaging findings, clinical data (other than the diagnosis of bladder cancer), or patient outcome. Histo-pathologic

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Preoperative neoadjuvant cisplatin based chemotherapy was completed by 10 of the cT2N0M0 patients.				- For detecting residual bladder cancer is 3/6 (50%, 95% CI 10–90%) - For correctly identifying metastatic nodal regions is 92/106 (87%; 95% CI 80–93%) → 11C-acetate has good sensitivity for bladder cancer and LN metastases → False positive uptake due to inflammation or granulomatous infection can occur, limiting the staging utility of 11C-acetate after prior intravesical BCG therapy. → Further studies are warranted in larger patient cohorts to prove the true clinical utility of 11C-acetate PET/CT in the staging and management of patients with bladder cancer.	analysis was performed by a genitourinary pathologist. Small number of patients Treatment histories varied

4.6. AG 3 Schlüsselfrage 6 (Diagnostik des metastasierten BCA)

„Welche Bildgebung (CT/MRT/Szintigraphie/ PET-CT) und welche zusätzlichen diagnostischen Maßnahmen inkl. Tumormarker sollen beim metastasierten Urothelkarzinom standardmäßig durchgeführt werden?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Gunes, 2012	Prospective, single site, case-control 2-	Patients: 60 patients (32 men and 28 women) with median age of 53 (39 - 63) years and bladder cancer Healthy Persons: 58 age- and sexmatched healthy volunteers (32 men and 26 women), with a median age of 51 (39 - 60) years	-	-	To investigate the plasma HNPs 1 - 3 levels in patients with bladder cancer. Comparison of the levels of the secreted proteins from patients with bladder cancer with clinicopathologi-cal variables.	Compared to the healthy controls, the plasma concentrations of HNPs 1–3 were significantly higher in the patients with bladder cancer ($p < 0.0001$) The levels of HNPs increased with increasing tumor grade. This difference was statistically significant ($p < 0.001$). Additionally, the serum levels of HNPs were significantly higher in patients with bladder cancer with metastatic disease and in the setting of lymphovascular involvement and lymph node metastasis; in addition, the serum levels of HNPs increased with increasing tumor burden ($p < 0.001$).	The pathologic stage was assigned according to the 2002 American Joint Committee on Cancer TNM staging system. The pathologic grade was classified according to the 1998 WHO/International Society of Urological Pathology classification system. Sample size probably too small. First paper reporting increased plasma HNPs 1 - 3 levels in patients with bladder cancer. Further studies with larger

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
							populations are needed to explore this relationship.
Hogue, 2008	Retrospective single site 3	175 patients with bladder cancer The study population was predominantly male (73%), with a median age of 67 years (interquartile range 29 - 90 years)	-	-	Evaluation of the 9 methylation markers in urine to determine a valid tumour marker	Among the 9 methylation markers in urine, only TIMP3 and ARF methylation state correlated significantly with patient survival (HR 1.99, 95% CI 1.22 - 3.27, P = 0.01 and HR 1.66, 95% CI 1.00 - 2.76, p = 0.05 respectively) These findings remained statistically significant in multivariate analysis for TIMP3 after adjusting for the stage (Table 2B, Figure 1B, 1C; HR 1.83, 95% CI 1.11 - 3.01, p = 0.02) In a multivariable model, TIMP3 methylation was associated with an almost two and a half fold increase in risk of death even after adjusting for the presence of metastasis (odd ratio = 2.45, 95% CI 1.14 - 5.26)	Bladder cancer cases were finally confirmed by standard pathology. Out of 175 total cases, 149 were available for follow up. Sample size and Follow-up-duration might be too small. Explorative study design incl. multiple testing. First publication on the subject. Value angepasst?

5. AG 4: NMIBC

5.1. AG 4 Schlüsselfrage 1 (Vorgehensweise bei TUR-B)

„Welche standardisierte Vorgehensweise in Bezug auf Technik und Qualitätskriterien ist bei der transurethralen Resektion des Blasentumors erforderlich?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Del Rosso 2013	RCT, single site From January 2007 to December 2009 1+	N=132 Male/female: 107/25 Tumor stage: → pTa: 96 → pT1: 36 Tumor grade: → Low: 110 → High: 22 Tumors: → Single: 110 → Multifocal: 22	Transurethral resection of the bladder with bipolar plasmakinetic energy transurethral resection of the bladder.	Conventional monopolar transurethral resection.	To compare the safety and the efficacy 1) Operative time 2) Changes in hemoglobin and serum electrolytes 3) Catheterization time 4) Duration of hospital stay 5) Tumor recurrence 6) Overall recurrence-free survival rate	<u>1) Operative time</u> - No significant differences: The mean operative time was 27 min for bipolar plasmakinetic energy transurethral resection of the bladder and 31 min for monopolar transurethral resection of the bladder. <u>2) Changes in hemoglobin and serum electrolytes</u> - No significant differences in the mean change of hemoglobin and serum sodium level were observed. <u>3) Catheterization time</u> - Mean catheterization time was 1.3 days and 2.3 days for bipolar plasmakinetic energy transurethral resection of the bladder and monopolar transurethral resection of the bladder, respectively. ($p < 0.05$) <u>4) Duration of hospital stay</u> - The mean hospital stay was significantly shorter in the bipolar	Single site Details of blinding not reported. The size (147 patients) was computed using a power of 80%, with a confidential level of 95%. Not declared if study was designed to test superiority oder noninferiority. Therefore nonsignificant results are not a proof of

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						plasmakinetic energy transurethral resection of the bladder (2.2 vs 3.5 days). - Bladder perforation was reported in two cases for the monopolar transurethral resection of the bladder group and obturator nerve reflex occurred in a single case for both procedures. - None of the patients experienced transurethral resection syndrome. <u>5) Tumor recurrence</u> - The median time of bladder tumor recurrence: 12.4 months (bipolar) vs. 11.9 months (monopolar) <u>6) Overall recurrence-free survival rate</u> - No significant differences in the overall recurrence-free survival rate were observed comparing the two procedures. Conclusions: → Plasmakinetic bipolar transurethral resection represents a safe and effective procedure in the management of non-muscle invasive bladder cancer.	noninferiority or equivalence.
Gupta 2010	Case series, prospective 3	N=108 Male/female: 100/8	Bipolar energy for transurethral resection of bladder tumours	No control group.	To evaluate the efficacy and safety of using bipolar energy at low-power setting for	- Out of the ten patients who were operated at the recommended default settings of 160 W cutting and 80 W coagulation, three patients had	Prospective Small sample size.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Superficial bladder carcinoma Age (years): → Mean ± SD: 56.34 ± 13.51 → Range: 25–88 Smoking, n (%): 56 (57) Comorbidities, n: → Coronary artery disease: 18 → Pacemaker: 6 → NSTEMI: 2 → Dilated cardiomyopathy: 1 → Hypertension: 14 → Diabetes mellitus: 11 → COPD: 22 Duration of symptoms (months): → Mean ± SD: 20.11 ± 25.3 → Range: 6–120 Tumour number,n: → Single: 36 → Multiple: 62 Location,n: → Lateral wall: 68	at low-power settings (50 W cutting and 40 W coagulation).		transurethral resection (TUR) of bladder tumours.	obturator jerks leading to two-bladder perforation. - The results of 98 patients operated on at the low-power settings of 50 W cutting and 40 W coagulation are reported. - Mean ± SD age was 56.34 ± 13.51 years. - Tumours were multiple in 62 (63%) patients and single in 36 (37%) patients, with 68 (69%) in the lateral wall and six (6%) involving the ureteric orifice. - Mean ± SD tumour size was 2.5 ± 0.81 cm with a mean ± SD resection time of 36.64 ± 16.5 min. - The mean drop in haemoglobin was 0.94 ± 0.71 (0.20–4.0), with a mean ± SD (range) drop in haematocrit of 1.33 ± 1.29 (1–7). Five (5%) patients required blood transfusion as a result of preoperative low haemoglobin. - Mean ± SD drop in sodium was 2.06 ± 0.66 mEq/L, with no patient developing TUR syndrome. None of the 98 patients developed obturator jerks and perforation at low-power settings. - Complete resection was achieved in 94 (96%) patients. - Mean postoperative hospital stay was 3 days.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		→ Base: 14 → Dome: 7 → Bladder neck: 4 → Anterior wall: 6 → Involving ureteric orifice: 6				Conclusions: → TURBT using bipolar energy is safe and effective in the treatment of bladder tumours at power settings lower than the conventionally recommended settings. → Lower power settings reduce the number of obturator jerks and perforations.	
Langbein 2006	Cohort study Retrospective 2+	N=163 Patients with primary and recurrent superfi cial bladder cancer treated with video-guided transurethral resection between 1993 and 2000. 134 male and 29 female. All patients underwent a routine second resection within 6–10 weeks.	Differentiated resection technique (with separate deep resection of tumour base and tumour surroundings), n=66	Regular resection (with complete resection of all visible tumours), n=97	Recurrence and progression rates.	minimum follow-up period was 48 months, Kaplan-meier plot goes up to 100 months - Patients with differentiated resections of bladder tumours did not have higher tumour recurrence and progression rates:recurrence: (21% (differentiated) vs. 22% (regular) after 24 months, (27% (differentiated) vs. 29% (regular) after 48 months. - Also, these patients had a significantly higher percentage of tumour-free second resections (33% (differentiated) vs. 42% (regular)(p = 0.03). Conclusion: → The differentiated resection technique for excising superficial bladder cancer has no negative influence on recurrence and progression rates, but it leads to a reduced tumour persistence.	Senior urologists determined the method of resection and treated their respective patients with their preferred technique. All first tumour resections were carried out by urologists in training, supervised by senior urologists, while the routine second resections were performed by senior urologists. Baseline

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
							characteristica were stated only for tumor stages and grades. Notable more G3 tumors in non differentiated Group (22 % vs. 8 %). Results can not be interpreted as proof of noninferiority.
Mariappan 2011	Case series 3	N=566 Patients with new non-muscle-invasive bladder cancer (NMIBC). Patients, who had undergone complete first resections. WGH, NMIBC cohort 1978 – 84 (%): → Male/female: 224 (72.7)/ 84 (27.3) → Tumour size, n: - Small or ≤ 30 mm: 222 (72.1) - Large or > 30 mm: 86	White-light transurethral resection of bladder tumours (GQ-WLTURBT)		To evaluate Presence/absence of detrusor muscle (DM) in the specimen and surgeon experience as independent predictors of the quality of transurethral resection of bladder tumour (TURBT)	- From a total of 566 patients evaluated from both cohorts, 473 NMIBC specimens were suitable for analysis. - Logistic regression multivariate analysis revealed that the absence of DM was associated with a higher recurrence rate at the first follow-up cystoscopy (RRFFC) (odds ratio [OR] = 3.6, 95% CI = 1.7 – 7.5, P < 0.001). - Senior surgeons were more likely to resect DM (OR = 4.9, 95% CI = 2.3 – 10.7, P < 0.001) - Senior surgeons were independently associated with a lower RRFFC (OR = 5.3, 95% CI = 2.1 – 12.9, P < 0.001). Conclusions: - Detrusor muscle status at the first,	Multi site Surgeons were stratified into a senior group (consultant and trainees in year five or six) and a junior group (trainees below year five). (RRFFC), was was defined as finding pathologically confirmed tumour at early

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		(27.9). ARI, contemporary cohort 2005/6 (%): → Male/female: not requested → Tumour size, n: not requested.				apparently complete, TURBT and surgeon ' s experience independently predict the quality of TURBT. - Documented complete resection by experienced surgeons with DM presence (good quality white-light TURBT) should be considered a benchmark for white-light TURBT in NMIBC.	re-TURBT or the first check cystoscopy. Study comprised no associations with patient-related outcomes
Matsushima 2010	Case-control study, single site (Tokyo) 2+	N=293 Patients with non-muscle invasive bladder cancer. Treated with transurethral resection of bladder tumor (TUR-BT) between 1998 and 2005. Mean age: 68.7 ± 0.57 (25-92) 349 men and 75 women Median follow-up period was 3.6 ± 0.1 years	Case: Biopsies from suspicious-appearing urothelium (N = 59).	Control: Biopsies from normal-appearing urothelium (N = 234).	The study evaluated: 1) tumor up-staging and up-grading of these biopsies, 2) the relationship between urinary cytology and biopsy results, 3) its impact on further treatment decision-making, and 4) whether or not additional bladder biopsies promote the intravesical recurrence of bladder carcinoma.	- Bladder cancer was observed in 23 cases (39.0%) who underwent a biopsy of suspicious-appearing urothelium. - Among these 23 cases, 9 cases with visible tumor resection had carcinoma in situ (CIS) only in the biopsies from suspicious-appearing urothelium. - Urinary cytology was negative in 3 of the 9 cases. - Bladder cancer was observed in 26 cases (11.1%) who underwent a biopsy of normal-appearing urothelium. - Of them, 5 cases with visible tumors had CIS only in the multiple biopsies from normal-appearing urothelium. - Urinary cytology was positive in all of the 5 cases. - No upstaging or upgrading cases were found in these patients by the addition of these two types of biopsy. - Furthermore, therapy was not altered in these patients. - With or without bladder biopsy was not a significant factor for tumor	Single site no direct comparison of biopsy strategies. Study comprised no associations with patient-related outcomes.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						recurrence in either the univariate or multivariate analysis. Conclusions: → Based on the results, it is concluded the multiple biopsies from normal-appearing urothelium are not necessary in patients with negative cytology results because of the low detection rate and lack of influence on therapeutic decisions. → Meanwhile, biopsy of suspicious-appearing urothelium is needed in patients with negative cytology results in order to detect CIS due to staging properties.	
Richterstetter 2012	Case series, retrospective, single site 3	N=221 Consecutive patients pTa → 145 (47.5) pT1 → 76 (24.9) pT2 → 70 (23.0) pT3/4 → 8 (2.6) Positive Bm, n (%): → pTa: 19 (13.1) → pT1: 22 (28.9) → pT2: 14 (17.5)	Standardised extended TURBT protocol, with the objective of obtaining a higher certainty in evaluating the extent of tumour infiltration by taking additional specimens from endoscopically 'normal'-appearing areas from the bottom and the margin	No control group.	To assess the feasibility of our extended TURBT technique and to analyse its impact on the determination of clinically relevant parameters, e.g. residual tumour status (R) and recurrence rate in the primary resection area.	- Across all tumour stages, residual tumour (pR1) was found in 38% of the additionally taken specimens. - There was a significant association of pR1 status with tumour stage, grade, and size. - Also in the group of non-muscle invading tumours, the rate of R1 resection was rather high at 22%. - There was no association with focality and the training status of the surgeon. - At follow-up, of all the patients with a unifocal primary tumour there was recurrence in the same area as the primary in 5.1%.	Retrospective Single site Consecutive patients. All the TURBTs were extended by taking additional deep and marginal specimens, according to a standardised protocol.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		→ pT3/4: 0 Positive Bg, n (%) or n/N: → pTa: 0 → pT1: 3 (4.0) → pT2: 18 (22.6) → pT3/4: 3/8 Positive Bm and Bg, n (%) or n/N: → pTa: 1 (0.7) → pT1: 2 (2.6) → pT2: 25 (31.3) → pT3/4: 5/8 Total, n (%) or n/N: → pTa: 20 (13.8) → pT1: 27 (35.5) → pT2: 57 (71.4) → pT3/4: 8/8	of the tumours.			Conclusion: → Extended TURBT provides detailed information about the horizontal and vertical extent of the bladder tumour. → The implementation of standardised TURBT procedures, such as our protocol of an extended TURBT, is greatly needed to improve local tumour control. → Whether a diagnostic re-TUR may be restricted to those cases with positive margins or ground specimens remains to be studied.	Clinical and histopathological data were retrieved from the patients ' records.
Rouprét 2012	Case series, retrospective, single site 3	N=340 Patients diagnosed with pT1 bladder tumors. 68 (21%) patients were female and 254 (79%) male. The median patient age was 69 years (range 33	Transurethral resection of bladder tumor(TURBTs)	No control group.	To assess the quality of transurethral resection of bladder tumors (TURBTs) performed by "senior" and "junior" urologists for pT1 tumors in terms of detrusor muscle (DM) presence and recurrence rate at 3 month first cystoscopy	- Of the 340 TURBTs for pT1 tumors, "senior" and "junior" surgeons performed 237 (69.7%) and 103 (30.3%), respectively. - Overall, 238 (70%) TURBTs had DM in the specimen, including 175 (73.8%) and 63 (61.3%) for the "senior" and "junior" operators, respectively (p = 0.02). - The overall RR-FC was 37.4% (n = 127) and was significantly different for DM	Retrospective Single site The operative surgeon specified tumor size "junior" surgeons were young

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		to 98).			(RR-FC).	presence and DM absence (30.7% versus 52.9%; p = 0.01). - On multivariate analysis, tumor recurrence was associated with "junior" operator experience independent of the presence or absence of DM (OR = 2.33 [1.45-3.74]) p = 0.01). Conclusions: → The presence of DM in a primary TURBT for pT1 NMIBC is directly associated with operator experience, with an associated increased 3 month recurrence rate for "junior" resectionists.	certified urologists (with an autonomous position with no senior supervision) but in a training program and the "senior" surgeons were certified urologists.
Zhong 2010	Cohort study retrospective, single site (China) 2-	N=97 Non-muscle invasive bladder tumor. 2 micron: Age (year): 68.30 ± 13.97 (27–87) Tumor maximum diameter (cm): 2.23 ± 0.76* (1.0–3.0) Tumor multiplicity: 1.53 ± 0.57 (1–2) Preoperative hemoglobin (g/dl): 13.12 ± 1.08 (11.3–15.6).	2 micron continuous wave laser resection of non-muscle invasive bladder tumor (NMIBT).	Holmium laser resection of bladder tumor (HoLRBT) Standard transurethral resection of bladder tumor (TURBT).	Efficacy and safety.	Follow-up: up to 24 months. - There were no differences with the preoperative characteristics among the three groups, except the diameter of the tumors. - The maximum diameter of the tumors in 2 micron laser group was larger than the other two groups (P<0.05). - Two micron laser group was associated with less hemoglobin decrease compared with TURBT group (P<0.05). All of the patients were followed and the recurrence rate of the three groups indicated no statistical significance (P>0.05). Conclusions:	Retrospective Single site Small sample size. because of sample size and nonrandomized groups, results can not be interpreted as proof of noninferiority.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		HoLRBT: Age (year): 65.76 ± 12.46 (33–86) Tumor maximum diameter (cm): 1.38 ± 0.58** (0.5–2.0) Tumor multiplicity: 1.40 ± 0.50 (1–2) Preoperative hemoglobin (g/dl): 13.24 ± 1.12 (11.2–15.7). TURBT: Age (year): 66.26 ± 11.01 (46–84) Tumor maximum diameter (cm): 1.54 ± 0.66** (0.5–2.5) Tumor multiplicity: 1.45 ± 0.50 (1–2) Preoperative hemoglobin (g/dl): 12.87 ± 1.05 (11.4–15.2.				→ In conclusion, 2 micron continuous wave laser resection of non-muscle-invasive bladder tumor is a safe and reliable treatment. → With the distinguished hemostasis, it is an available optional treatment.	
Zhu 2008	Cohort study single site 2	N=212 Consecutive patients Primary nonmuscle-invasive bladder cancer	Holmium laser resection for primary, clinically nonmuscleinvasive, bladder cancer (HoLRBT) (n = 101).	Standard transurethral resection of bladder tumor (TURBT) (n = 111).	Intraoperative complications Postoperative catheterization time Recurrence-free survival.	- The patient demographics and tumor characteristics in the 2 groups were comparable. - HoLRBT was superior to TURBT in terms of intraoperative complications and postoperative catheterization time (P < .001). - Recurrence-free survival after HoLRBT	Single site Consecutive patients. The patients in each group were stratified into 3

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						was similar to that after TURBT (P = .283). Conclusion: →This results have indicated that HoLRBT is a feasible, safe, and effective alternative for the management of primary, clinically nonmuscle-invasive, bladder cancer compared with TURBT, with similar recurrence-free survival and fewer perioperative complications. → It also can provide sufficient material for the pathologic evaluation.	risk subgroups (low, intermediate, and high risk) according to the prognostic factors for recurrence using the European Association of Urology guidelines. HoLRBT and TURBT were performed by 3 surgeons. Groups not randomized, Not stated if planed to test superiority or noninferiority. Therefore results can not be interpreted as proof of noninferiority.

5.2. AG 4 Schlüsselfrage 2 (Flouresezenzassistierte vs. Weisslicht-TUR-B)

„Welchen Einfluss hat die fluoreszenzassistierte TUR-BT mit Hexylaminolaevulinat gegenüber einer konventionellen Weisslicht-TUR-BT auf die Rezidiv- und Progressionsrate?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
O'Brian 2013 England	Prospective randomized trial 1-	N=185 patients with newly presenting suspected NMIBC (249 were randomized) Patients with a history of bladder cancer were excluded. The suspicion of NMIBC was based on the appearance of the bladder at a diagnostic flexiblecystoscopy performed under local anaesthetic. Patients with suspected carcinoma invading the bladder muscle or a history of bladder cancer were excluded, as well as patients with porphyria, pregnancy and sensitivity to 5-	Hexylaminolevulinate (HAL) PPD-TURBT + White-light-TURBT + single-shot intravesical mitomycin C n=97	White-light-TURBT + single-shot intravesical mitomycin C n=88	- Recurrence at 3 months and 12 months (primary) - Detection rate	Single shot intravesical mitomycin C was administered to 61/97 patients (63%) in the HAL-PDD arm compared with 68/88 patients (77%) in the white-light arm (P=0.04). Histological analysis of resected tumour: - Secondary CIS identified in the HAL-PDD arm vs. in the white-light arm: 25/97 (26%) vs. 12/88 (14%) (P=0,04). - High-grade tumors identified in the HAL-PDD arm vs. in the white-light arm: 48/97 (49%) vs. 38/88 (43%) (P=0,46). Recurrence within 3 months in the HAL-PDD arm vs. in the white-light arm: 17/86 (20%) and 14/82 (17%) (P =0,7). Recurrence within 12 months in the HAL-PDD arm vs. in the white-light arm:10/63 (16%) and 15/67 (22%) (P =0,38). No adverse reactions to HAL were seen Authors conclusion:	Small sample size. Single-center-study In all patients white-light cystoscopy was carried out initially to map the bladder. In the HAL-PDD arm, the bladder was then re-mapped under blue-light and the presence of any. This may be a bias in detection. No intention to treat (ITT) analysis (32 and 34 patients were

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		aminolevulinate-acid based intravesical photosensitizers.				Despite HAL-PDD offering a more accurate diagnostic assessment of a bladder tumour, in this trial we did not show that this led to lower recurrence rates of newly presenting NMIBC compared with the best current standard of care.	excluded because no cancer was detected or cancer proved to ≥ T2. Study was possibly underpowered to detect a small difference. Trials published since the start of the study have shown at best a 10% difference between HAL-PDD and white-light arms. A higher percentage of patients in the white-light arm received mitomycin C than in the HAL-PDD arm (HAL-PDD 63% vs white light 77%.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
							Different mortality rates (1 Death vs. 7 Deaths in the HAL PDD) were not discussed by the authors. First author is speaker for GE Healthcare and Photocure. (markets HAL PDD)

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Kausch 2009 Meta-analysis	s. Evidenztabelle AG 3-SF 2					
Mowatt 2011 Meta-analysis	Two reviewers independently assessed the quality of the included studies with the QUADAS	Included studies: RCTs, nonrandomized comparative studies, diagnostic cross-sectional	WLC vs. PDD for patients with supected bladder cancer or patients with previous diagnosed bladder	1. Test/diagnostic performance of PDD 2. Clinical effectivness of PDD	31 studies included, with n=2.949 patients; n=2.807 for analysis. 27 studies for diagnostic accuracy; 4 studies for clinical effectiveness.	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	tool. 2++	studies that assessed tes performance and effectiveness of photodynamic diagnosis (PPD) vs. white light cystoscopy (WLC). For clinical effectivness only RCTs were considered. 15 databases and websides were searched (not named).	cancer.		1. Diagnostic performance Patient level analysis [evidence from 5 studies]: - Overall sensitivity of PDD vs. WLC: 92% (95% CI 80-100) vs. 71% (95% CI 49-93). - Overall specificity of PDD vs. WLC: 57% (95% CI 36-79) vs. 72% (95% CI 47-96). - Sensitivity of PDD vs. WLC for high risk tumors: 89% (95% CI 6-100) vs. 56% (95% CI 0-100) [evidence from 6 studies]. - Sensitivity of PDD vs. WLC for low risk tumors: 92% (95% CI 20-95) vs. 95% (95% CI 8-100) [evidence from 3 studies]. - Sensitivity of PDD vs. WLC for CIS: 83% (95% CI 41-100) vs. 32% (95% CI 0-83) [evidence from 6 studies]. Biopsy level analysis [evidence from 14 studies]: - Overall sensitivity of PDD vs. WLC: 93% (95% CI 90-96) vs. 65% (95% CI 55-74). - Overall specificity of PDD vs. WLC: 60% (95% CI 49-71) vs. 81% (95% CI 73-90). - Sensitivity of PDD vs. WLC for high risk tumors: 99% (95% CI 54-100) vs. 67% (95% CI	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					0-100) [evidence from 13 studies]. - Sensitivity of PDD vs. WLC for low risk tumors: 96% (95% CI 88-100) vs. 88% (95% CI 74-100) [evidence from 7 studies]. - Sensitivity of PDD vs. WLC for CIS: 86% (95% CI 54-100) vs. 50% (95% CI 0-86) [evidence from 13 studies]. 2. Clinical effectivness 4 RCTs (n=544 patients) reportet clinical effectivness (10-14 days to 10-15 weeks after TURBT). - Overall fewer residual tumors: RR 0,37; 95% CI 1,18-1,59. - pTa fewer residual tumors: RR0,32; 95% CI 0,15-0,70. - pT1 fewer residual tumors: RR0,26; 95% CI 0,12-0,57. Recurrence-free survival of PDD vs. WLC after 12 months: RR 1,40; 95% CI 0,96-2,03. Recurrence-free survival of PDD vs. WLC after 24 months: RR 1,37; 95% CI 1,18-1,59. [no p-values given] Authors conclusion: PDD detects more bladder tumors than WLC, including more high risk tumors. Based on 4 RCTs reporting clinical effectiveness, 5-	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					aminolaevulinic acid-mediated PDD at TURBT facilitates a more complete resection and proglongs recurrence-free survival.	
Yuan 2013 Meta-analysis	The quality of the literature was assessed seperately by two authors using the 6 items of Jaded scale score: all studies were of high quality. 1++	Only RCTs were included that assessed the clinical efficacy of FC and compared it with that of WLC.	Fluorescence cystoscopy (FC) guided TUR vs. white light cystoscopy.	1. Recurrence rate 2. Time to first recurrence 3. Recurrence-free survival rate 4. Progression rate	12 RCTs included with n=2258 patients. 1. Recurrence rate of FC vs. WLC: OR 0,5; 95% CI 0,4-0,62; p<0,00001 [evidence from 9 studies, n=1562]. 2. Delay of time to first recurrence of FC vs. WLC: 7,39 weeks; 95% CI 3,87-10,91; p<0,0001 [evidence from 3 studies, n=759]. 3. Recurrence-free survival rate of FC vs. WLC after 1 year: HR: 0,69; 95% 0,59-0,81; p<0,00001 [evidence from 9 studies, n=2027]. Recurrence-free survival rate of FC vs. WLC after 2 years: HR: 0,65; p<0,0004 [evidence from 3 studies, n=552]. 4. Progressin rate of FC vs. WLC: OR 0,85; 95% CI 0,6-1,22; p=0,39 [evidence from 9 studies, n=1973]. Authors conclusion: FC guided TUR was demonstrated to be an effective procedure for delaying recurrence of NMIBC. Unfortunately, FC guided TUR could	Riedl 2001 Kriegmair 2002 Filbeck 2002 Babjuk 2005 Schumacher 2010 Stenzl 2011 Stenzl 2010 Grossman 2012 Dragoescu 2011 Geavlete 2012 Hermann 2011 Karaolides 2012

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					not significantly decrease the rate of progression into muscle invasive bladder cancer.	

5.3. AG 4 Schlüsselfrage 3 (Nachresektion)

„Welchen Einfluss hat die TUR Blasentumor-(TUR-BT)-Nachresektion in den verschiedenen Subgruppen gegenüber einer einmaligen TUR-BT auf die Rezidiv- und Progressionsrate?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Lazica 2011	Diagnostik, retrospektiv, monozentrisch, Deutschland 3	N=167 Von Juli 2007 bis Februar 2012 wurden insgesamt 2172 TURB bei 1390 Patienten wegen Abklärung, Verdacht auf oder bestätigtem Blasentumor durchgeführt. Darunter waren 449	Nachresektion	-	- Inzidenz und Art von Rezidivtumoren. - Häufigkeit Upstaging. - Prädiktoren für Rezidivtumoren. (Wertigkeit)	- Die Inzidenz von T1 high grade-Tumoren war in unseren Patienten 22,8 % (N = 258). - Von 167 Patienten, die eine Nachresektion nach T1-Blasentumor erhielten, zeigte sich ein Rezidivtumoren in 58,1 % (97 Patienten). - Die Rezidivtumoren waren meist multifokal (61,9 %) und kleiner als 3 cm (69,1 %). - Die Histologie der Nachresektion zeigte Ta-Tumoren in 24,6 % (41 von	Retrospektiv Monozentrisch Prospektiv wurde die Indikation und der Tumorbefund mit Größe, Anzahl und Histologie dokumentiert.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Frauen (32,3 %) und 941 Männer (67,7 %). Das durchschnittliche Alter bei OP war 71 Jahre bei beiden Geschlechtern. Bei 167 von 258 Patienten mit einem T1-Blasentumor (64,7 %) wurde eine Nachresektion durchgeführt.				167 Patienten), Persistenz von T1 high grade in 19,8 % (33 von 167 Patienten) und ein Upstaging auf T2 und mehr in 6,6 % (11 von 167 Patienten). - Die Anzahl der Initialtumoren zeigt einen signifikanten Einfluss auf die Rezidivrate bei Nachresektion: Patienten mit multifokalen Tumoren hatte ein Rezidivrate von 69 %, im Gegensatz zu 46,3 % bei solitären Tumoren. - Ebenso zeigte sich ein tendenzieller Einfluss für die Tumorgröße und für das Vorhandensein von Detrusor im Präparat. → T1 high grade-Blasentumoren zeigten eine relevante Rate von Rezidivtumoren in der Nachresektion, was nach diesen Ergebnissen die leitliniengerechte obligate Nachresektion rechtfertigt. → Einen signifikanten Einfluss zugunsten einer tumorfreien Nachresektion zeigt sich in den Daten für solitäre Tumoren. → Ein tendenzieller Einfluss konnte für Detrusor im Präparat gezeigt werden. → Es scheint somit die Tiefe der Initialresektion von Bedeutung zu sein. → Für das optimale Zeitintervall zur Nachresektion gibt es derzeit noch	Histologische Aufarbeitung erfolgte in dem hiesigen Institut für Pathologie, einem Referenz-Zentrum für Uropathologie. Tumoren wurden gemäß der WHO-Klassifikation von 2004 eingeteilt.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						keine Daten.	
Divrik 2010	RCT, single site, Turkey 1+	N=210 Patients with newly diagnosed pT1 tumours Mean age, yr (range): A → 62.7 (37–87), B → 61.5 (37–82) Male: A → 82 (88.2), B→ 89 (90.8) Female: A →11 (11.8), B → 9 (9.2) Single tumour: - <3 cm, no. (%): A → 20 (40.0), B → 16 (37.2) - >= 3 cm, no. (%): A → 30 (60.0), B → 27 (62.8) Multiple tumours: - <3 cm, no. (%): A → 15 (34.9), B → 20 (36.4) - >= 3 cm, no. (%): A → 28 (65.1), B → 35 (63.6)	A: Second TUR was performed within 2–6 wk after the initial resection for the patients of group 1 (N=105). If tumour was detected macroscopically and/or histologically during the second TUR, a third TUR was recommended.	B: Second TUR was not done in group 2 (N=105)	1) Recurrence 2) Progression rate 3) Overall survival rate 4) Disease-specific survival	- The mean follow-up period was 66.1 mo without a significant difference between the groups. - Residual tumour was detected histopathologically in 35 of 105 patients in group 1. - Of these patients, eight had upper-stage (pT2) disease. - Group 1: 12 patients were excluded - Group 2: 7 patients were excluded (4 patients were lost to follow-up within the first year after TURB, and 3 patients could not complete the 8-wk intravesical treatment because of skin reaction or severe irritative urinary symptoms). 1) Recurrence - Rate of RFS was 82%, 65%, and 59% in group 1 and 57%, 37%, and 32% in group 2 for the first, third, and fifth year, respectively (overall: 52 vs 21%; log-rank test result: 0.0001) - Observed in 37 of the 93 patients in group 1 and 70 of the 98 patients in group 2. - Nineteen of the 37 patients in group 1 and 51 of the 70 patients in group 2 recurred within 12 mo - Median recurrence-free survival was	Single site Blinding not reported Randomization was not specifically described. All patients (groups 1 and 2) received the first instillation of intravesical chemotherapy within 24 h after the initial resection. Urine cytology and follow-up cystoscopy were performed at 3-mo intervals for the first year, biannually for the second year, and annually thereafter.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Multiple tumour or _3 cm, no. (%): A → 73 (78.5), B → 82 (83.6) Grade, no. (%): - Low: A → 48 (51.6), B → 54 (55.1) - High: A → 45 (48.4), B → 44 (44.9)				47 mo for group 1 compared with 12 mo for group 2. 2) Progression - Rate of PFS was 96%, 93%, and 93% in group 1and 94%, 83%, and 79% in group 2 for the first, third, and fifth year, respectively (overall: 93% vs. 76%; log-rank test result: 0.0001) - Was observed in 6.5% of patients for group 1 compared to 23.5% of patients for group 2 (p = 0.001). - Median progress-free survival was 73 mo for group 1 compared to 53.5 mo for group 2. 3) Overall survival rate (not significant) - 67.7% and 64.3% in groups 1 and 2, respectively (logrank test result: 0.363). 4) Disease-specific survival - Only 5 of the 30 patients in group 1 died of cancer compared to 11 of the 35 patients in group 2 (p = 0.038). Conclusion: → Second TUR, which is performed only after complete first TUR, has significantly decreased the recurrence and progression rates in patients with newly diagnosed T1 disease compared to patients with T1 disease but with no	All patients were followed until death or a minimum of 54 mo.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						second TUR. → This study once more underscores the effect of TUR, which is usually underappreciated.	
Ali 2010	Cohort study, prospective, single site, Egypt 2+	N=91 Patients with stage T1 and Ta bladder cancer. Diagnosis of non-muscle-invasive bladder cancer (NMIBC) in the initial transurethral resection of bladder tumor (TURBT). Mean age: 59 years Male/Female: 65/26	Second-look transurethral resection (TUR) within 2 to 6 weeks after the initial resection.	Initial resection	1) Staging errors 2) Possibility of changing treatment strategy 3) Risk factors	1) Specimens obtained during the second TURBT showed no tumor in 38 (41.7%) patients; 22 (24.2%) patients had residual cancer of the same stage, 9 (14.8%) patients of PT1 had a lower stage, and 22 (24.2%) had a higher stage. 2) Upstaging had changed treatment strategy in 22 (24.2%) cases. 3) Appearance, size, grade, and stage of the tumor at the initial resection are all considered independent risk factors for upstaging detected at second-look TURBT. Conclusion: → Second TURBT is a valuable procedure for accurate staging of nonmuscle-invasive bladder cancer. → It changed the treatment strategy of a significant proportion of patients. → Second TURBT is indicated in T1, high grade, large size (>3 cm), and nodular tumors because of the significant risk of detecting muscle-invasive disease.	Prospective Single site At the initial TURBT, the procedure was performed by both senior staff and residents in the department, without any special assignment. All visible tumors were completely resected, with a deep muscular sample taken from the tumor base as well as the tumor margins.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Guevara 2010	Prognostic cohort study, retrospective, France 2-	N=151 Mean age of 68.6 years (range 32 to 86). Patients with primary high grade, non-muscle invasive (Ta, T1 or CIS) bladder cancer.	Repeat transurethral bladder tumor resection before bacillus Calmette-Guerin (tumor-free).	-	Differences between tumor-free patients and patients with residual tumor according to: 1) Progression 2) Time to recurrence	- A total of 70 tumor-free patients and 47 with residual tumor received bacillus Calmette-Guerin induction and maintenance therapy after repeat transurethral bladder tumor resection, of whom 84 (71.8%) were disease-free during follow up. - In the tumor-free group 11.4% of tumors recurred compared with 27.7% in the residual tumor group ($p < 0.05$). 1) Progression was noted in 5.7% of tumorfree cases vs 17.0% of residual tumor cases ($p < 0.05$). 2) Time to recurrence was significantly less in the residual tumor group than in the tumor-free group (17.8 vs 23.9 months, $p < 0.001$). Conclusion: → Tumor-free status at repeat transurethral bladder tumor resection improves the bacillus Calmette-Guerin response rate and delays tumor recurrence. → During follow-up recurrence in residual tumor-free patients develop more likely as low grade lesions than in patients with residual tumor at repeat transurethral bladder tumor resection.	Retrospective Consecutive patients
Takaoka	Prognostic	N=73	Second	Initial TUR	1) Recurrence-free	- The pathological findings for second	Retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
2013	cohort study, retrospective, multi site, Japan 2-	Patients with newly diagnosed high-grade T1 bladder cancer. Mean age, years: 70.3 Male/Female: 56/17	transurethral resection (TUR)		survival 2) Progression-free survival 3) Risk factors → Related to the presence of residual tumors or recurrence-free survival.	transurethral resection were pT0 36 (49%), pTis/a 21 (29%), pT1 13 (18%) and pT2 3 (4%), respectively. <u>1) and 2):</u> The bladder was preserved in all 57 patients with pT0/is/a tumors on second transurethral resection, and 43 patients (75%) received intravesical BCG therapy. Of these patients, 3-year recurrence-free survival and 3-year progression-free survival rates were 81 and 96%, respectively. In addition, the presence of pTis/a residual tumors on second transurethral resection had a significant impact on the recurrence. Five of the 13 patients with pT1 on second transurethral resection were immediately treated by radical cystectomy or radiation therapy combined with chemotherapy, and two (25%) of the eight who were treated by intravesical BCG therapy had progression including distant metastasis. <u>3):</u> The risk factor for residual tumors at second transurethral resection was the presence of concomitant carcinoma in situ at the initial transurethral resection ($P < 0.01$).	Multi site All of the second TURs were performed by experienced urologists at one of the three university hospitals. Selection biases between the two groups due to a small sample size and retrospective study design.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Conclusion: → High recurrence-free survival and progression-free survival were achieved by a second transurethral resection and intravesical BCG therapy in the patients with pT0/is/a on the second transurethral resection. → In this group, the residual tumors at second transurethral resection are risk factors for intravesical recurrence.	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Vianello, 2011 Systematic review and meta-analysis	Six were retrospective studies, two prospective, and study design was not specified in nine. The entire process selection (ie, searches, selection, and study exclusion)	From 1980 to June 2010 PubMed, MEDLINE, ISI Web of Knowledge, EBSCO, EMBASE, and Biomed Central databases were searched for reports in English No restrictions due	Repeated white light transurethral resection of the bladder (TURB)	1) Prevalence 2) Upstaging	- There were 2327 original articles and 562 reviews retrieved. - Data from 15 studies were pooled and analyzed. <u>1) and 2)</u> - Prevalence of T1 was reported in all and of Ta in 8. - Persistence rate prevalence at repeated TURB was 0.39 (95% confidence interval [CI] = 0.26 to 0.54) for Ta and 0.47 (95% CI = 0.41 to 0.53) for T1. -Persistence was 19.4% to 56% and 15.2% to	Bouchot 2001, Eur Urol Brauers 2001, J Urol Divrik 2006, J Urol

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	was performed by two reviewer. One reviewer extracted data, after discussion to solve eventual discrepancies and reach consensus with other two reviewer. Random-effects models were preferred to fixed-effects models. Heterogeneity test (Cochrane Q test and I2 statistics) was highly significant (I2 > 80%, P < 0.0001) in both analyses . Beggs and Egger tests did not show significant	to study design Inclusion criteria: White-light repeated TURB performed to assess persistence of primary urothelial bladder cancer shortly after white-light TURB. Exclusion criteria: Incomplete TURB (as defined by authors), endocavitary adjuvant therapy after TURB because it could influence pathologic assessment at repeated TURB, resections with sources other than white light and different endoscopic techniques (eg,			55%, and upstaging occurred in 0% to 14.3% of Ta and 0% to 24.4% of T1 at repeated TURB, respectively. Conclusion: → High percentages of persistence and upstaging confirm a repeated TURB is needed in patients with high-risk non-muscle-invasive bladder cancer. → Further investigation is encouraged taking risk stratification into consideration to evaluate the role of repeated TURB in low- and mid- risk diseases.	Engelhardt 1998, J Endourol Geavlete 2002, Eur Urol Giulianelli 2007, J Endourol Grimm 2003, J Urol Han 2008, J Endourol Herr 2006, BJU Int Herr 2007, J Urol Mersdorf 1998, J

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	publication bias. Sensitivity analysis. No methodological quality assessment stated. 1-	fluorescence followed by white light) for TURB, and repeated TURB because white-light TURB is the gold standard and because fluorescence, although improving endoscopic detection of bladder cancers, does not indicate stage adequately.				Urol Sanseverino 2008, J Urol Schips 2002, Urology Schwaibold 2006, BJU Int Zurkirchen 2003, Urol Int

5.4. AG 4 Schlüsselfrage 4 (Postoperative Chemotherapie-Frühinstillation)

„Welchen Einfluss hat eine postoperative Chemotherapie-Frühinstillation im Vergleich zur alleinigen TUR-BT auf die Rezidiv- und Progressionsrate?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Saika 2010	RCT, multi site (25 institutions) Details of blinding not reported. No information why 8 patients dropped out of the follow-up schedule. 1-	A total of 303 patients were enrolled in this trial with 257 determined as eligible (83 patients in Group A, 90 in Group B and 84 in Group C). Male/female: 221/36 Primary/recurrent: A (50/33), B (51/39), C (50/34) Single/multiple: A (38/45), B (38/52), C (36/48) Primary single: A (28), B (28), C (24) Primary multiple: A (22), B (23), C (26) Recurrent single: A (10), B (10). C (12) Recurrent multiple: A (23), B (29), C (22) Maximum tumor, diameter (<1 cm) (%): A	Group A: patients were treated with two intravesical infusions of epirubicin (EPI) 20 mg/40 ml saline immediately after transurethral resection (TUR) and within 24 h. Group B: patients were treated with EPI 50 mg/100 ml on the same schedule as group A.	Group C: patients were treated by TUR alone.	Duration to the first recurrence To evaluate the efficacy, dose effectiveness and safety of early short-duration intravesical instillation therapy using epirubicin (EPI) administered immediately after TUR and on the next day following TUR. Disease progression Recurrence-free survival	- Of the 303 patients, 79 in Group A, 84 in Group B, and 77 in Group C could be evaluated for recurrence. - Median follow-up was 44 months. - Median recurrence-free survival durations for Groups A, B, and C were 24, 38, and 13 months, respectively. - The difference between Groups B and C was statistically significant ($p = 0.04$). - Adverse reactions related to instillation were observed in about 30% of the patients. - These reactions included micturition pain and frequency. - These toxicities were mild and transient. Disease progression: was defined as the appearance of muscle-invasive disease, metastatic disease, or both and included only one patient in Group B. Recurrence-free survival: analysis included patients with tumor at 1 month after TUR as recurrence and patients without cystoscopy at 1 month after TUR revealed a clearer difference between Groups B and C with a stronger statistical significance ($n = 270$) ($p = 0.004$ in generalized Wilcoxon test, 0.010 in log-rank test).	Multi site Random allocation to the treatment groups was done by the central enrollment method. Patients were assigned into three groups in a ratio of 1:1:1 using a dynamic randomization method that took into consideration recurrence status (primary or recurrent), multiplicity (single or multiple), and institution.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		(49), B (56), C (48) Tumor grade (G1/G2/G3): A (21/49/12), B (30/42/18), C (26/44/14) Stage (Ta/T1): A (45/36), B (54/36), C (54/30)				→ Intravesical instillation of EPI 50 mg twice within 24 h after TUR was effective as prophylactic therapy for non-muscle-invasive bladder cancer with tolerable toxicity problems.	
Serretta 2010	RCT Details of blinding not reported 1-	N=577 (95 patients were excluded after early treatment due to pathology report not meeting inclusion criteria). Arm A: 294 (237) Arm B: 283 (245) Patients with primary or recurrent, single or multiple, non-muscle-invasive bladder cancer (NMI-BC) at intermediate risk of recurrence Median (range) age, years: A (68 (37–97)), B (69 (35–88))	Five more weekly instillations (total of six instillations, Arm A)	Five more weekly instillations followed by monthly instillations for 10 months (total of 16 instillations, Arm B).	Toxicity recurrence-free survival (RFS) To evaluate the efficacy of 1-year maintenance after a 6-week cycle of early intravesical chemotherapy, as the role of maintenance in intravesical chemotherapy is debated.	- The tumours' characteristics were equally distributed between the two arms. - In all, treatment interruption for toxicity was required in 39 patients. - One death due to toxicity of early instillation occurred. - The median follow-up was 48 months. - In all, ten patients (2.5%) progressed and 117 patients (29.6%) recurred. - No statistically significant difference in the recurrence-free rate (RFS) was detected between the two arms (*P*=0.43). - An advantage in favour of the maintenance arm was evident only at 18 months after TUR (*P*=0.03). - A trend for a higher benefit from maintenance in primary and multiple tumours was detected.	Randomization was obtained before TUR to avoid any selection bias. Randomization ratio, 1:1 The patients were centrally randomized at the GSTU Foundation immediately before TUR and each centre informed by Fax. The lack of central pathology

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Sex: Male: A (199), B (218); Female: A (38), B (27) History: Primary: A (138), B (152) Recurrent Multiplicity: A (99), B (93) Single: A (80), B (84) Multiple: A (157), B (161) T/G: TaG1–2: A (83), B (91) T1G1: A (49), B (59) T1G2: A (105), B (95) Mean (SD) diameter, cm: A (1.4), B (1.5)				→ In patients with intermediate risk NMI-BC treated by TUR and early adjuvant chemotherapy, adding a maintenance regimen with monthly instillations for 1 year is of limited efficacy in preventing recurrence.	introducing a bias in patients' selection. Reduced statistical power when analysing the patient subgroups.

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Abern 2013	Random effects model	Randomized clinical trials (RCTs)	A single immediate postoperative dose of intravesical	Recurrence rates To analyze	- A total of 3103 patients were randomized in the 18 RCTs that met inclusion criteria. - The recurrence rate in patients receiving	Burnand, 1976

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Systematic review and meta-analysis	Data abstraction by two independent reviewers. No methodological quality assessment stated. Overall I^2 measure of between-study inconsistency was 75 %. Epirubicin and mitomycin were administered to most of the patients in the trials. Several plots, including the standard funnel plot, the Galbraith radial plot, the normal QQ plot and the	RCTs published between 1976 and 2011 Searched in Cochrane Controlled Trials Register (CENTRAL), ClinicalTrials.gov, PubMed, and Embase electronic databases. Reference lists of included studies were screened for missed studies. Selection criteria: - The study included RCTs that compared TUR alone with the combination of TUR and a single does of intravesical	chemotherapy (IVC) within 24 hours of transurethral resection (TUR).	whether this effect varies by drug or by basline patient risk factors.	perioperative IVC and TUR was 37% versus 50% in the TUR-alone group. - Using a random-effects model, the pooled relative risk (RR) of recurrence for IVC and TUR was 0.67 (95% CI, 0.56-0.79), corresponding to a 13% absolute reduction and a number needed to treat of 7.2 patients to avoid 1 recurrence. - The proportions of patients with tumor risk factors (T1, high-grade, multifocal, or recurrent) were not associated with IVC efficacy. - A single dose of IVC administered within 24 hours of TUR of non-muscle-invasive bladder cancer (NMIBC) was found to result in a reduction in tumor recurrence (RR, 0.67; 95% CI, 0.56-0.79). - Patients with higher-risk tumor features seem to benefit at a similar rate.	Malling and Sorensen, 1980 Zincke, 1983 Tolley, 1988 Ossterlinck, 1993 MRC, 1994 Ali-El-Dein Rajala, 1999 Solsona, 1999

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	Duval-Tweedie trim-fill funnel plot: the plots suggested the existence of publication bias and this was confirmed with Egger´s test. 1-	chemotherapy IVC (TUR + IVC) administered within 24 hours of surgery for the treatment of bladder cancer. → Included in Meta-analysis: n=18				Okamura, 2002 Barghi, 2006 El-Ghobashy, 2007 Berrum-Svennung, 2008 Cai, 2008 Jalon Monzon, 2008 Böhle, 2009 Gudjónsson, 2009 De Nunzio, 2011

5.5. AG 4 Schlüsselfrage 5 (Adjuvante intravesikale Chemotherapie)

„Wann ist eine adjuvante intravesikale Chemotherapie-Instillation bzw. adjuvante BCG-Instillation indiziert?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Sylvester 2010	European multicenter prospective randomized trial. 1+	N=957 patients with intermediate or high-risk Ta, T1 bladder cancer.	Epirubicin (Epi) (n=318)	BCG alone (n=320) BCG + Isoiazid (INH) (n=319)	Long-term efficacy. Endpoints: - time to recurrence (primary) - progression - distant metastases - overall survival - disease-specific survival	N=837 patients included in the analysis. Because there was no benefical or adverse effect of the addition of INH to BCG and the main interest centers on the comparison of epirubicin to BCG (with or without INH), the two BCG treatment groups were pooled together for comparison purposes. Median follow-up: 9,2 years. All results include high - and intermediate risk patients: Time to recurrence of BCG vs. Epi: HR 0,62; 95% CI 0,50 - 0,76; p <0,001. Progression of BCG vs. Epi: HR 0,84; 95% CI 0,51 - 1,39; p =0,55. Distant metastases of BCG vs. Epi: HR 0,55; 95% CI 0,32 – 0,94; p =0,046. Overall survival of BCG vs. Epi: HR 0,76; 95% CI 0,59 – 0,96; p =0,023.	Long time of follow-up. 12-13 % of randomized patients were excluded (inappropriate stage) because histology was available after randomization. Therefore no ITT-analysis, no relevant differences indicated. Analyses are exploratory and in some cases are based on small number of events. Allocation concealment and blinding not

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Disease-specific survival of BCG vs. Epi: HR 0,47; 95% CI 0,25 – 0,89; p =0,026. Authors conclusion: In patients with intermediate and high-risk stage Ta and T1 urothelial bladder cancer, intravesical BCG with or without INH is superior to intravesical epirubicin not only for time to first recurrecne but also for time to distant metastases, overall survival, and disease-specific survival. The benefit of BCG is not limited to just high-risk patients; intermediate risk patients also benefit from BCG.	reported (therefore unclear), no indication for relevant loss to follow-up. Multiple testing Toxicity not reportet: 19% BCG vs. 6%.

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Shang 2011 Cochrane Review	5 tirals of 1111 participants were included. 549 patients were treated with BCG; 562 with Epirubicin Trial eligibilty,	All randomised or quasi-randomised controlled trial (in which allocation was obtained by alternation) in patients with Ta or T1 bladder cancer that compared intravesical BCG	Intravesical treatment of BCG vs. Epi in Ta or T1 bladder cancer.	Frequency of tumor recurrence Progressive disease by stage Mortality Distant metastases	Frequency of tumour recurrence (relapse) of BCG vs. Epi: 35,5% vs. 51,4% (P<0,05; RR 0,69; 95% CI 0,60 – 0,79). Disease progression by stage (> T2) of BCG vs. Epi: 8,02% vs. 10,32% (P=0,19; RR 0,78; 95% CI 0,54 – 1,13). Overall mortality of BCG vs. Epi: RR 0,86; 95% CI 0,71-1,04; P=0,12	Cheng et al. 2005 Melekos et al. 1993 Melekos et al. 1996a

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	methodological quality and data extraction were assessed independently by two reviewers. Included studies were judged to have a high risk of bias and the overall methodological quality to be low. Nearly none of the included studies described clearly the method of sequence generation, allocation concealment and blinding. Only 2 trials (Cheng, Sylvester) of 769 patients had sufficient data to	with Epirubicin (Epi).		Local and systemic adverse effects Treatment delayed or stopped due to adverse effects	[reported by 2 studies with 769 patients (Cheng 2005, Sylvester 2010]. Disease-specific mortality: RR 0,94; 95% CI 0,23-0,80; P=0,93 [reported by 2 studies with 769 patients (Cheng 2005, Sylvester 2010]. Distant metasteses of BCG vs. Epi: 4,7% vs. 6,3% (P=0,29) [reported by 4 studies (Cheng 2005, Melekos 1996a, Melekos 1996b, Sylvester 2010)]. Local adverse effects of BCG vs. Epi (P<0,05): - Drug-induced cystitis of BCG vs. Epi: 54,1% vs. 31,7%. - Haematuria of BCG vs. Epi: 30,8% vs. 16,1%. [reported by 4 studies] Systemic adverse effects (fever, influenza-like syndrome, nausea, vomiting, anorexia, BCG lung infection, skin rush, general malaise) of BCG vs. Epi: 34,8% vs. 1,3% (P<0,05; RR 0,53; 95% CI 2,25 – 143,91). [reported by 3 studies (Melekos 1996a, Melekos 1996b, Sylvester 2010)]. Authors conclusion: The data from the present meta-analysis	Melekos et al. 1996b Sylvester et al. 2010

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	analyze both disease-specific and overall mortality. The group of BCG+ioniazid, which was analysed by Sylvester together with the BCG-alone-Group were not considered by the authors. These results in different outcome data according to mortality. 1-				indicate that intravesical BGG treatment is more efficacious than Epi in reducing tumor recurrrence for Ta and T1 bladder cancer. However, BCG appears to be associated with higher incidence of adverse effects, such as drug-inducecystitis, haematuria and systemic toxicity, than Epi. The overall quality of the evidence is rather low. Well-designed, high quality randomised controlled tirals with good allocation concealment are required.	

5.6. AG 4 Schlüsselfrage 6 (Adjuvante BCG-Instillations-Schemata)

„Welchen Einfluss haben die verschiedenen adjuvanten BCG-Instillations-Schemata auf die Rezidiv- und Progressionsrate?“

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Böhle 2003 Meta-analysis	Of the 11 studies 8 were randomized studies (good quality) Two independent reviewers (A. B. and P. B.) extracted and interpreted the data according to the analysis protocol. No methodological quality assessment stated No sensisivity analysis (Non-RCTs included without sensitivity analysis for study design) In case of a potential risk of	Of the 11 studies 9 were prospective clinical trials (8 randomized studies) and 2 were retrospective (observational) cohort studies with concurrent groups An electronic search of MEDLINE, EMBASE, Cancerlit, Current Contents and Cochrane Library data bases from 1985 to 2000 was performed. Hand searches were made from 1993 to 2000 of the annual meeting proceedings of American Urological Association, EAU, International	Mitomycin C / intravesically administered BCG	1. The frequency of tumor recurrence within the follow-up time period of the studies 2. The frequency of treatment associated toxicity	- In 11 eligible clinical trials 1,421 patients were treated with BCG and 1,328 were treated with mitomycin C. Zu 1. Within the overall median follow-up time of 26 months 38.6% of the patients in the BCG group and 46.4% of those in the mitomycin C group had tumor recurrence. - In 7 of 11 studies BCG was significantly superior to mitomycin C, in 3 studies no significant difference was found, while in 1 study mitomycin C was significantly superior to BCG. - An overall statistically significant superiority of BCG versus mitomycin C efficacy in reducing tumor recurrence was detected (OR 0.56, 95% CI 0.38 to 0.84, p = 0.005). - In the subgroup treated with BCG maintenance all 6 individual studies showed a significant superiority of BCG over mitomycin C (OR 0.43, 95% CI 0.35 to 0.53, p < 0.001). Zu 2. - In 4 of the 5 studies with reported data on toxicity BCG associated cystitis was significantly more frequent than in the mitomycin C group (53.8% versus 39.2%). - The combined cystitis OR was 1.81 (95% CI 1.48 to 2.23, p < 0.001). - The OR for cystitis in the BCG maintenance	Ayed, 1998, Prog Urol Debruyne, 1992, Urology Jauhiainen, 1990, New York: Churchill Livingstone Krege, 1996, J Urol Lamm, 1995, Urol Oncol Lundholm, 1996, J Urol Millán-Rodríguez,

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	bias in the overall results due to included studies that violated some of the eligibility criteria, a sensitivity analysis was performed by evaluating the results with and without the suspected studies. 1+	Society of Urology, American Society of Clinical Oncology, and the German, French and Italian urological associations. Unpublished data and additional information were requested from the individual authors by personal contact. Selection criteria: - Patients with histologically confirmed stage Ta or T1 of any grade bladder carcinoma Studydesign: Controlled clinical trial or a controlled observational cohort study, comparison of the			group did not significantly differ from that in the nonmaintenance therapy group. → The results suggest superiority of BCG over mitomycin C for prevention of tumor recurrences in the combined data and particularly in the BCG maintenance treatment subgroup, irrespective of the actual (intermediate or high) tumor risk status. → The toxicity with BCG is higher but does not differ between BCG maintenance and nonmaintenance groups.	2000, J Urol Nogueira, 2000, Eur Urol Pagano, 1987, Acta Urol Ital Vegt, 1995, J Urol Lee, 1992, Korean J Urol

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
		efficacy of intravesically administered BCG and mitomycin C, and the treatment doses and regimen as well as followup duration were reported - Carcinoma in situ was not considered in this meta-analysis				
Böhle 2004 Meta-analysis	Of the 9 studies 7 were randomized studies (good quality) No methodological quality assessment stated No sensisivity analysis (Non-RCTs included without sensitivity analysis for study	Comparative clinical trials and cohort studies - Patients with histologically confirmed Stage Ta or T1, any grade, bladder carcinoma Studydesign: Controlled clinical trial or a controlled observational cohort study; comparison of the	Mitomycin C / intravesically administered BCG	The frequency of tumor progression within the follow-up period of the studies	- In nine eligible clinical trials, 1277 patients were treated with BCG and 1133 with MMC. - Within the overall median follow-up of 26 months, 7.67% of the patients in the BCG group and 9.44% of the patients in the MMC group developed tumor progression. - In all nine individual studies and in the combined results, no statistically significant difference in the ORs for progression between the BCG and MMC-treated groups was found (combined OR = 0.77; 95% CI 0.57 to 1.03; *P* = 0.081). - In the subgroup with BCG maintenance, the combined result of the five individual studies showed a statistically significant superiority of BCG over MMC (OR = 0.66; 95% CI 0.47 to 0.94; *P* = 0.02). - In the four studies without BCG maintenance,	Ayed, 1998, Prog Urol Debruyne, 1992, Urology Jauhiainen, 1989, Churchill Livingstone Krege, 1996, J Urol Lamm, 1995, Urol Oncol Malmström, 1999, J Urol Millén-Rodríguez, 2000, J Urol

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	design) Two independent reviewers (A.B. and P.B.) extracted and interpreted the data according to the analysis protocol. Fixed model In the case of a potential risk of bias in the overall results owing to included studies that violated some of the eligibility criteria, a sensitivity analysis was performed by evaluating the results with and without the suspect studies. 1+	efficacy on tumor progression of intravesically administered BCG and MMC; and the treatment doses and regimen, as well as the follow-up duration, were reported Electronic search of Medline, Embase, Cancerlit, Current Contents, and the Cochrane Library databases from 1985 to 2001 Hand searches: in publications from 1993 to 2001 of the annual meeting proceedings of the American Urological Association, European Association of			the combined result indicated no statistically significant difference between the two treatments (OR = 1.16; 95% CI 0.65 to 2.07; *P* = 0.612). - Potential confounders, such as tumor risk status, duration of follow-up, BCG strain, BCG and MMC treatment regimen, and year of publication did not significantly influence these results. → The results demonstrated statistically significant superiority for BCG compared with MMC for the prevention of tumor progression only if BCG maintenance therapy was provided.	Nogueira, 2000, Eur Urol Vegt, 1995, J Urol

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
		Urology, International Society of Urology, American Society for Clinical Oncology, and the German, French, and Italian urologic associations				
Han 2006 Meta-analysis	Fixed effect model and random effect model were applied (only random was calculated) No methodological quality assessment stated). Two independent reviewers extracted and interpreted the data according to the analysis protocol	Randomized clinical trials Selected trials from 1997 to 2005 by electronic search of Medline, the OVID database, and the Cochrane Library database Hand searches of abstracts published in the Journal of Urology, the European Urology journal, and the British Journal of Urology were also	Intravesical bacillus Calmette-Guérin (BCG) and non BCG-therapy, chemotherapy and BCG plus chemotherapy/immunotherapy	Tumor recurrence after transurethral resection of superficial bladder cancer	- 176 trials - 151 of them were eliminated - Identified 25 trials with recurrence information on 4767 patients. - Of 2342 patients undergoing BCG therapy, 949 (40.5%) had tumor recurrence compared with 1205 (49.7%) of 2425 patients in the non-BCG group. - In the combined results, a statistically significant difference in the OR for tumor recurrence between the BCG and no BCG-treated groups was found (randomized combined effect OR 0.61, 95% CI 0.46 to 0.80, P < 0.0001). - Stratified by BCG maintenance and disease type, the combined results of the individual reports showed statistical significance for BCG maintenance (OR 0.47, 95% CI 0.28 to 0.78, P = 0.004) and treatment of papillary carcinoma (OR 0.50, 95% CI 0.33 to 0.75, P = 0.0008). - Chemotherapy and BCG plus	Jimenez-CruzJF, 1997 Ayed M, 1998 Wtjes JA, 1998 Witles, 1998 Malmstrom, 1999 Moyano CalvoJL, 1999 Altay B, 2000 Lamm DL, 2000 Sekine H, 2001 Tozawak, 2001 Van der Meijden,

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	1++	performed. SELECTION CRITERIA: - Patients with histologically confirmed Stage Ta or T1 of any grade or carcinoma in situ bladder carcinoma - Trials had to have compared intravesical bacille Calmette-Guérin (BCG) plus TUR to TUR alone, or TUR plus intravesical chemotherapy or TUR plus immunotherapy, or, alternatively, intravesical chemotherapy/ immunotherapy and BCG.			chemotherapy/immunotherapy were not better than BCG alone. → Adjuvant intravesical BCG with maintenance treatment is effective for the prophylaxis of tumor recurrence in superficial bladder cancer. → For patients with papillary carcinoma, adjuvant intravesical BCG with maintenance therapy should be offered as the treatment of choice.	2001 Chepurov AK, 2002 Kaassine E, 2002 Kolodziej A, 2002 Martinez-Pineiro, 2002 Hara I, 2003 Irie A, 2003 Kaasinen E, 2003 Librenjak, 2003 Shakin O, 2003 Tong M, 2003 Peyromaure M, 2004 Yumura Y, 2004 Reijke TM, 2005 Patard JJ, 2002

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Malmström2009 Meta-analysis	Quality assessments of included studies not reported Nothing to publication bias reported Meta-analysis of individual patient data 1++	Randomised trials comparing TUR plus MMC to TUR plus BCG in patients with NMIBC (stages Ta, T1, Tis) were included in the meta-analysis. Searched the National Library of Medicine (PubMed) and CancerLit These searches were supplemented by hand searching meeting abstracts and proceedings and also by discussion with relevant trial investigators and organisations.	Mitomycin C (MMC) / intravesically administered BCG	1. Time to recurrence 2. Progression, 3. Overall survival 4. Cancer-specific survival .	- Nine trials that included 2820 patients were identified, and individual patient data (IPD) were obtained from all of them. - Patient characteristics were 71% primary, 54% Ta, 43% T1, 25% G1, 58% G2, and 16% G3, and 7% had prior intravesical chemotherapy. - Based on a median follow-up of 4.4 yr, 43% recurred. Zu 1. Overall, there was no difference in the time to first recurrence (p = 0.09) between BCG and MMC. - In the trials with BCG maintenance, a 32% reduction in risk of recurrence on BCG compared to MMC was found (p < 0.0001), while there was a 28% risk increase (p = 0.006) for BCG in the trials without maintenance. - BCG with maintenance was more effective than MMC in both patients previously treated and those not previously treated with chemotherapy. Zu 2. 3, 4. In the subset of 1880 patients for whom data on progression, survival, and cause of death were available, 12% progressed and 24% died, and, of those, 30% of the deaths were due to bladder cancer. - No statistically significant differences were	Rintala, 1991, Eur Urol Witjes, 1998, Urology Witjes, 1996, Semin Urol Oncol Lamm, 1995, Urol Oncol Krege, 1996, J Urol Malmström, 1999, J Urol Ojea, 2007, Eur Urol Friedrich, 2007, Eur Urol Di Stasi, 2003, J Urol

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					found for these long-term end points. → For prophylaxis of recurrence, maintenance BCG is required to demonstrate superiority to MMC. → Prior intravesical chemotherapy was not a confounder. → There were no statistically significant differences regarding progression, overall survival, and cancer-specific survival between the two treatments.	
Shelley 2010 Systematic review	Data were extracted independently by two reviewers Four reviewers assessed trial quality (only randomisation and allocation concealment were considered) Cochrane Review 1++	Randomised or quasi-randomised trials searched the Cochrane Controlled Trials Register (March 2000), Medline (February, 2000), EMBASE (February, 2000), Cancerlit (February, 2000), Healthstar (February, 2000), Database of Abstracts of Reviews of Effectiveness (February, 2000)	Transurethral resection versus transurethral resection plus intravesical Bacillus Calmette-Guérin (BCG)	1. Incidence of tumour recurrence after the standard therapy of transurethral resection versus transurethral resection plus intravesical Bacillus Calmette-Guérin 2. Toxicities	- Six randomised trials were included involving 585 eligible patients. Zu 1. There were significantly fewer patients with disease recurrence at 12 months in the BCG plus TUR group compared to those that received TUR alone (odds ratio 0.30, CI 0.21 to 0.43). - The overall log hazard ratio for recurrence (-0.83, variance 0.02) indicated a significant benefit of BCG treatment in reducing tumour recurrence. Zu 2. Toxicities associated with BCG consisted mainly of cystitis (67%), haematuria (23%), fever (25%) and urinary frequency (71%). - No BCG-induced deaths were reported. → In patients with medium/high risk Ta or T1	Krege, 1996, Journal of Urology Lamm, 1985, Journal of Urology Melekos, 1990, Urology International Pagano, 1990, New York: Churchill Livingstone Pinsky, 1985, Cancer Treatment Reports Yamamoto, 1990, Japanese Journal of Urology

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
		and the Bath Information Data Service The Proceedings of the American Society Clinical Oncology was hand searched (1996 to 1999). Patients with Ta and T1 bladder cancer of medium or high risk of tumour recurrence			bladder cancer, immunotherapy with intravesical BCG following TUR appears to provide a significant advantage over TUR alone in delaying tumour recurrence.	
Sylvester, 2008 Systematic review	Randomized clinical trials Fixed effects model Quality assessments of included studies not reported Nothing to publication bias reported	Randomized clinical trials Before May 2007 MEDLINE, reference lists in trial publications and review articles, and annual meeting abstracts in the Journal of Urology and European Urology	Schedules or durations of intravesical chemotherapy after TUR	Recurrence rate	- 19 trials 1) TUR plus one immediate instillation versus TUR plus one immediate instillation plus maintenance: → 3 trials (MRC, 1985, 1994; Tolley, 1988, 1996; Selvaggi, 1990) → MRC, 1985, 1994: - No reduction in the percentage of patients who had recurrence, 41.9% versus 37.5% - Trial has been criticized because of the low drug concentration used, 30 mg/50 ml → Tolley, 1988, 1996: - A reduction in the percentage with recurrence from 48.3% to 36.3% overall (p =	MRC, 1985, Br J Urol MRC, 1994, Br J Urol Tolley, 1988, Br Med J Tolley, 1996, J Urol Selvaggi, 1990, Acta Urol Ital Bouffioux, 1995, J Urol Okamura, 1998, Eur

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	1+	- Patients with stage Ta–T1 bladder cancer - Trials that compared different schedules or durations of intravesical chemotherapy after TUR - Trials that compared intravesical instillations with respect to their number, frequency, timing, duration, dose, or dose intensity - Studies assessing device-assisted chemotherapy (electromotive drug administration [EMDA] or hyperthermia) and chemotherapy relative to or in			0.04) and from 70% to 50% in patients with multiple tumors (p = 0.09) - In both of these studies, patients who recurred at 3 mo prior to starting their additional instillations were already counted as having their first recurrence, potentially diluting the size of any treatment effect. - The benefit of additional instillations in patients still free of disease at 3 mo was not reported and may be underestimated by the overall results. → Selvaggi, 1990: - There was a small non-significant reduction in the percent of patients with recurrence, from 31.8% to 24.0% (p = 0.11) → There is thus a suggestion that additional instillations may reduce the recurrence rate, but no definitive conclusions can be drawn. → Approximately 70% of the patients had a single tumor and only one study provided separate results for single and multiple tumors. 2. TUR plus one immediate instillation followed by short-term versus long-term instillations during 12 mo: → 3 trials (Bouffioux, 1995; Okamura, 1998; Koga, 2004) → Bouffioux, 1995: - Comparing nine instillations of MMC or Adriamycin given during 6 mo to 15	Urol Koga, 2004, J Urol Ali-el-Dein, 1997, Br J Urol Liu, 2006, Cancer Invest Hendricksen, 2007, Eur Urol Suppl Iborra, 1992, Arch Esp de Urol Ueda, 1992, Cancer Chemother Pharmacol Nomata, 2002, Cancer Chemother Pharmacol Rubben, 1988, J Urol Kuroda, 2004, Eur Urol Flamm, 1989, Urologe A

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		combination with BCG were not included			instillations given during 12 mo, there was no difference in the percentage of patients with recurrence - No results were presented taking 6 mo as time zero → Okamura, 1998: - No difference was found when comparing six instillations of epirubicin during 1 mo to 17 instillations in 12 mo → Koga, 2004: - A third study comparing nine instillations of epirubicin given during 3 mo to 19 instillations in 12 mo found that fewer patients had recurrence with 12 mo of treatment, 13% versus 31.5% (p = 0.005) → Contradictory concerning whether 12 mo of treatment is more effective than a shorter duration of treatment after an immediate instillation 3. TUR plus one immediate instillation versus TUR plus delayed instillations to month 12: → 3 trials (Ali-el-Dein, 1997; Liu, 2006; Selvaggi, 1990) → Ali-el-Dein, 1997: - No differences were found in trials comparing one immediate instillation to either 8 weekly instillations starting 1–2 wk after TUR followed by monthly instillations to 1 yr (18 instillations) → Liu, 2006:	Flamm, 1990, Eur Urol Huland, 1990, J Urol Schwaibold, 1997, Eur Urol Friedrich, 2007, Eur Urol Mitsumori, 2004, BJU Au, 2001, J Natl Cancer Inst Akaza, 1987, Cancer Chemother Pharmacol Niijima, 1983, Cancer Chemother Pharmacol Ali-el-Dein, 1997, J Urol Koontz, 1981, J Urol

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					- No differences were found in trials comparing one immediate instillation to to weekly instillations for 6–8 wk followed by monthly instillations to 1 yr (16–18 instillations) → Selvaggi, 1990: - Comparing one immediate instillation to 4 weekly instillations starting 2 wk after TUR followed by monthly instillations to 1 yr (15 instillations), fewer patients had recurrences in the delayed multiple instillation group, 24.8% versus 30.2% (p = 0.05) → These results suggest that one immediate instillation of epirubicin might not be less effective than a delayed course of multiple epirubicin instillations in patients at low to intermediate risk. 4. TUR plus one immediate instillation plus additional instillations during 6 mo versus TUR plus delayed instillations during 6 mo: → 2 trials (Bouffioux, 1995; Hendricksen, 2007) → Bouffioux, 1995: - In the first trial in which patients were randomized to start immediately or start 1–2 wk after TUR (9 instillations of MMC or Adriamycin during 6 mo), fewer patients receiving immediate chemotherapy had recurrence, 43.8% versus 55.8%(p = 0.03).	

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					→ Hendricksen, 2007: - In the second trial in which patients received 4 weekly instillations of epirubicin followed by 5 monthly instillations (9 instillations in 6 mo) preceded or not by one ‘‘immediate’’ instillation within 48 h, no significant difference was found. - This study has been criticized because the first instillation was not given on the same day as the TUR - However, there was no difference according to whether or not the immediate instillation was given within 24 h. 5. TUR plus one immediate instillation plus additional instillations during 12 mo versus TUR plus delayed instillations during 12 mo: → 3 trials (Selvaggi, 1990; Bouffioux, 1995; Iborra, 1992) → Selvaggi, 1990; Bouffioux, 1995: - In these studies, the percentage with recurrence in the two treatment groups was similar → Iborra, 1992: - In these study, more patients had recurrences on the delayed treatment (p = 0.04); however, patients on delayed treatment tended to have a worse prognosis → Combining these three studies, the percentage with recurrence on the immediate	

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					and delayed arms was similar. → These results suggest that one immediate instillation may still be necessary if further chemotherapy is given during only 6 mo; however, it might not be necessary if chemotherapy is given during 12 mo. 6. TUR plus delayed short-term instillations versus TUR plus delayed long-term instillations: → 9 trials (Bouffioux, 1995; Hendricksen, 2007; Nomata, 2002; Rubben, 1988; Kuroda; 2004; Flamm, 1989; Flamm 1990; Huland, 1990; Schwaibold, 1997; Friedrich, 2007) → One year of chemotherapy (Bouffioux, 1995; Hendricksen, 2007; Nomata, 2002; Rubben, 1988; Kuroda; 2004) - Bouffioux, 1995: fewer patients had recurrence with 12 mo of MMC or Adriamycin (15 instillations) as compared to 6 mo of treatment (9 instillations), 41.2% versus 55.8% (p = 0.01) - Hendricksen, 2007: comparing 11 instillations of epirubicin during 12 mo to 9 instillations during 6 mo, no difference was found - Nomata, 2002: no difference was found in a study comparing 19 instillations of epirubicin during 12 mo to 12 instillations during 5 mo - In all three of these trials there is a possible dilution of the size of the treatment effect due	

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					to recurrences in the long-term treatment arm prior to starting the long-term instillations at 5 or 6 mo. - Rubben, 1988: comparing 12 instillations of Adriamycin during 6 wk to an additional 15 instillations to 1 yr, no difference was found - Kuroda; 2004: A further study comparing 4mo (40 mg/40 ml) to 7mo (30 mg/ 40 ml) to 12 mo (20 mg/40 ml) of epirubicin found a higher percentage of patients with recurrence on the 12-mo arm, but treatment duration is confounded with drug concentration so no conclusions can be drawn from this study concerning the optimal duration of treatment - Although some evidence suggests that 1 yr of chemotherapy may be better than shorter durations, the study results are inconsistent. → Two years of chemotherapy (Flamm, 1989; Flamm 1990) - Trials compared weekly instillations of Epodyl or Adriamycin during 6 wk to 6 weekly instillations followed by monthly instillations during 2 yr (30 instillations) - No difference in the percentage of patients who had recurrences in the two treatment groups in either study → Three years of chemotherapy (Huland, 1990; Schwaibold, 1997; Friedrich, 2007) - Huland, 1990; Schwaibold: Weekly	

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					instillations of MMC for 20 wk were compared to either weekly instillations for 8 wk followed by monthly instillations to 3 yr (42 instillations) or to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations). There was no difference in the percentage who had a recurrence on 20 wk or 3 yr of treatment; however, the comparisons are confounded by different treatment intensities during the initial 20 wk. - Friedrich, 2007: In a recent study comparing 6 weekly instillations of MMC to 6 weekly instillations followed by monthly instillations during 3 yr (42 instillations), there was a large decrease in the percentage of patients with recurrence in the group receiving 3 yr of MMC, 25.7% versus 10.5% (p = 0.0006). 7. Dose intensity and frequency of instillation: → 9 trials (Mitsumori, 2004; Au, 2001; Akaza, 1987; Niijima, 1987; Ali-el-Dein, 1997; Koontz, 1981; Huland, 1190; Schwaibold, 1997; Kuroda, 2004) → Total dose and dose concentration: - Mitsumori, 2004: Comparing 180 mg of epirubicin instilled within 6–11 wk (6 instillations) to 360 mg instilled within 10–12 wk (12 instillations), fewer patients had recurrences on the higher total dose, 31.8%	

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					versus 70.2% (p = 0.012) - Au, 2001: showed that the efficacy of MMC can be improved by increasing the drug's concentration in the bladder; a dose of 20 mg/20 ml was compared to an optimized dose with 40 mg/20 ml and pharmacokinetic manipulations to maintain a high drug concentration in the bladder, with fasting to decrease the urine volume and urine alkalinisation to stabilize the drug - Akaza, 1987; Niijima, 1987; Ali-el-Dein, 1997; Koontz, 1981: other studies did not, however, find a difference in efficacy between different drug concentrations - Akaza, 1987; Niijima, 1987: two concentrations of Adriamycin, 20 mg/ 40 ml and 30 mg/30 ml, were compared using two different treatment schedules: 8 instillations within 4 wk (160 mg vs. 240 mg) or 21 instillations within 2 yr (420 mg vs. 630 mg), no difference in efficacy was found between the two doses for either 4 wk or 2 yr of treatment - Ali-el-Dein, 1997: When 18 instillations of epirubicin were given within 1 yr, there was no difference between 50mg/50 ml (900 mg) and 80 mg/50 ml (1440mg) in the percentage who had recurrence, 25.0% versus 17.6%, respectively - Koontz, 1981: no difference in efficacy in a trial comparing 30 mg/30 ml to 60 mg/60 ml	

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					of thiotepa where instillations were given every 4 wk for a maximum of 2 yr - Once again the results of the different trials are inconsistent and no definitive conclusions can be drawn. → More intense or frequent short-term instillations compared to less intense long-term instillations - Huland, 1190; Schwaibold: weekly instillations of MMC 20mg/20 ml for 20 wk were compared to weekly instillations for 8 wk followed by monthly instillations to 3 yr (42 instillations) and to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations), no difference in efficacy between the frequent short-term instillations and either of the less intense long-term instillations - Kuroda, 2004: Comparing 20 mg/40 ml of epirubicin (17 instillations in 12 mo) to 30 mg/40 ml (12 instillations in 7 mo) to 40 mg/40 ml (9 instillations in 4 mo), the percentage of patients with recurrence decreased as the drug concentration increased despite the decrease in the duration of treatment - Huland, 1190; Schwaibold: weekly MMC instillations for 8 wk followed by monthly instillations to 3 yr were compared to	

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					instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations), a small non-significant decrease in the percentage of patients with recurrence in the group receiving 8 weekly instillations, 17.7% versus 24.4% - Thus, evidence indicates that frequent, dose intense, short-term instillations may provide results that are at least as good as less intense instillations given over a longer period of time - One immediate instillation after transurethral resection (TUR) is recommended in all patients. - In low-risk patients, no further treatment is recommended before recurrence. - In patients with multiple tumors, one immediate instillation is insufficient treatment. - Additional instillations may further reduce the recurrence rate; however, no recommendations can be made concerning their optimal duration. - A short intensive schedule of instillations within the first 3–4 mo after an immediate instillation may be as effective as longer-term treatment schedules (grade C). - Instillations during >= 1 yr in intermediate-risk patients seem advisable only when an	

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					immediate instillation has not been given (grade C). - Higher drug concentrations and optimization of the drug's concentration in the bladder may provide better results (grade C). → The optimal schedule and duration of intravesical chemotherapy after an immediate instillation remain unknown. → Future studies should focus on the eradication of residual disease after TUR and the prevention of late recurrences.	
Sylvester 2002 Meta-analysis	Randomized clinical trials Quality assessments of included studies not reported Nothing to publication bias reported 1+	Randomized clinical trials - All randomized trials in patients with superficial bladder cancer (stages Ta, T1 or carcinoma in situ) that compared transurethral resection plus intravesical BCG to either resection alone, resection plus intravesical chemotherapy or resection plus immunotherapy	Transurethral resection plus intravesical Bacillus Calmette-Guerin (BCG) /resection alone or resection plus intravesical chemotherapy or resection plus immunotherapy other than BCG	1. Risk of progression 2. Overall survival 3. Cancer-specific survival	Zu 1. - 24 trials with progression information on 4,863 patients Based on a median follow-up of 2.5 years and a maximum of 15 years, 260 of 2,658 patients on BCG (9.8%) had progression compared to 304 of 2,205 patients in the control groups (13.8%), a reduction of 27% in the odds of progression on BCG (OR 0.73, p = 0.001). - The percent of patients with progression was low (6.4% of 2,880 patients with papillary tumors and 13.9% of 403 patients with carcinoma in situ, reflecting the short follow-up and relatively low risk patients entered in many of the trials. - The size of the treatment effect was similar in patients with papillary tumors and in those with carcinoma in situ. - However, only patients receiving	Cookson, 1997, J Urol Pagano, 1991, J Urol Badalament, 1987, J Clin Oncol Lamm, 2000, J Urol Palou, 2001, J Urol Rintala, 1996, J Urol Rintala, 1995, J Urol Witjes, 1998, J Urol Lamm, 1995, Urol Oncol

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
		other than BCG were considered. - Trials published before January 2002 were identified by searching MEDLINE, the *US Physicians' Data Query*, *Cochrane Controlled Trials Register* and reference lists in trial publications and review articles. - Abstracts published in *The Journal of Urology* and *European Urology* were also reviewed.			maintenance BCG benefited. Zu 2. Und 3. - There was no statistically significant difference in treatment effect for either overall survival or death due to bladder cancer. → Intravesical BCG significantly reduces the risk of progression after transurethral resection in patients with superficial bladder cancer who receive maintenance treatment. → Thus, it is the agent of choice for patients with intermediate and high risk papillary tumors and those with carcinoma in situ.	Malmström, 1999, J urol Nogueira, 2001, Eur Urol Rintala, 1991, Eur Urol Vegt, 1995, J Urol Witjes, 1998, Urology Martínez-Pineiro, 1990, J Urol De Reijke, 2001, Eur Urol Melekos, 1993, Cancer Van der Meijden, 2001, J Urol Brosman, 1982, J Urol Witjes, 1999, Eur Urol Jimenez-Cruz, 1997,

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
						Urology Kalble, 1994, Urologe Kalble, 1991, Urologe Ibrahiem, 1988, J Urol
Sylvester 2005 Meta-analysis	Randomized clinical trials Quality assessments of included studies not reported Nothing to publication bias reported 1+	Randomized clinical trials - All randomized trials including patients with primary, secondary or concurrent CIS and that compared intravesical BCG to intravesical chemotherapy were considered. - Trials which also included some patients classified as having dysplasia were not excluded. - Trials published or accepted for publication before August 2004 were	Bacillus Calmette-Guerin (BCG)/ intravesical chemotherapy	1. Complete Response (based on negative cystoscopy, cytology and biopsies) 2. Evidence of Disease (overall disease free rate) 3. Progression rate	- Nine randomized trials including 700 patients with CIS compared BCG to either mitomycin C (MMC), epirubicin, adriamycin, or sequential MMC/adriamycin. Zu 1.Of 298 patients on BCG 203 (68.1%) had a complete response compared with 158 of 307 patients on chemotherapy (51.5%), a reduction of 47% in the odds of nonresponse on BCG (OR 0.53, p = 0.0002). Zu 2.Based on a median follow-up of 3.6 years, 161 of 345 patients on BCG (46.7%) had no evidence of disease compared with 93 of 355 patients on chemotherapy (26.2%), a reduction of 59% in the odds of treatment failure on BCG (OR 0.41, p < 0.0001). - Although the long-term benefit of BCG was smaller in trials with MMC, BCG was superior to MMC in trials with maintenance BCG (OR 0.57, p = 0.04). Zu 3. The reduction of 26% in the risk of progression on BCG (p = 0.20) is consistent	Lamm, 1995, Urol Oncol Vegt, 1995, J Urol Witjes, 1998, Urology Malmstrom, 1999, J Urol Dr. Stasi, 2003, J Urol Lamm, 1991, N Engl J Med Martínez-Pineiro, 1990, J Urol De Reijke, 2005, J Urol Sekine, 2001, Int J Urol

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		identified by searching MEDLINE, the United States Physicians' Data Query, the Cochrane Central Register of Controlled Trials, and reference lists in trial publications and review articles. - Abstracts published in the Journal of Urology and European Urology were also reviewed.			with the reduction of 27% (p = 0.001) previously reported in a larger superficial bladder cancer meta-analysis. → Intravesical BCG significantly reduces the risk of short and long-term treatment failure compared with intravesical chemotherapy. → Therefore, it is considered to be the intravesical agent of choice in the treatment of CIS.	
Zhu Meta-analysis	Begg's and Egger's tests: Publication bias existed in only 1 (BCG maintenance vs. induction for RFS in high-risk NMIBC group) of all comparisons Sensitivity-	21 randomized controlled trials (RCTs) and 9 retrospective comparative studies Electronic databases (PubMed, Embase, and the Cochrane Library)	Schedules or durations of Bacillus Calmette-Guérin (BCG)	1. Recurrence-free survivals (RFS) 2. Progression-free survival (PFS) 3. Adverse events	- 30 trials Zu 1. - Significantly better recurrence-free survivals (RFS) were observed respectively in patients who received BCG maintenance, standard-dose and BCG plus epirubicin therapy comparing to those received induction, low-dose and BCG alone. Zu 2. und 3. - BCG maintenance therapy was also	Badalament, 1987, J Clin Oncol Koga, 2010, Int J Urol Hinotsu, 2011, BJU Int Lamm, 2000, J Urol Palou, 2001, J Urol Hudson, 1987, J Urol

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	analyses i.e. according to study design Most RCTs were of low-quality, which was caused by obvious side-effects which made it difficult to address double-blind (Quality assessment for RCTs using Jadad (5-point)) 1+	Inclusion criteria: (1) The diagnosis of BCa had to be confirmed pathologically; (2) All patients should be confirmed as NMIBC; (3) Included studies had to provide comparative data; and (4) Only the most recent trials with the greatest number of patients was chosen when overlapped subjects were selected in more than one study.			associated with significantly better progression-free survival (PFS), but there were more incidences of adverse events. - Pooled results showed no remarkable advantage of BCG combined with Mitomycin C or with interferon α-2b in improving oncologic outcomes. Sensitivity-analyses: For sensitivity analysis, we only included RCT. Subgroup data showed that BCG maintenance was no longer significantly prevent patients from getting the chance of progression HR=0.781; 95% CI 0.598-1.019; P=0.068; However, the obvious trend favoring BCG maintenance could be found still. Sensitivity-analyses stratified by study-design and tumor stage led to very similar overall results and often to a decrease of the between-study heterogeneity. → All patients with superficial BCa should be encouraged to accept BCG maintenance therapy with standard-dose if well tolerated. → Patients can benefit from BCG combined with epirubicin but not from BCG combined with Mitomycin C or interferon α-2b.	Andius, 2004, BJU Int Okamura, 2011, Int J Clin Oncol Decobert, 2008, Cancer Ojea, 2007, Eur Urol Yalcinkaya, 1998, Int Urol Nephrol Kumar, 2002, J Urol Oddens, 2013, Eur Urol Takashi, 1995, Int Urol Nephrol Yoneyama, 2008, Urology Irie, 2003, Int J Urol Kaasinen, 2003, Eur Urol Stasi, 2006, Lancet

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						Oncol Oosterlinck, 2011, Eur Urol Gulpinar, 2012, Int Braz J Urol El Mohsen, 2010, Uro Today Int J Badalato, 2011, Can J Urol Rintala, 1996, J Urol Jarvinen, 2012, Scand J Urol Nephrol Witjes, 1998, J Urol Cai, 2008, J Urol Bilen, 2000, Int J Urol Tozawa, 2001, Urol Int Nepple, 2010, J Urol Bazarbashi, 2000, J

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						Surg Oncol

5.7. AG 4 Schlüsselfrage 7 (Unterstützende Maßnahme bei Instillationstherapie)

„Welche unterstützenden Maßnahmen (z.B. Dosismodifikationen, Antibiotika) sind geeignet, um die Nebenwirkungsrate einer Instillationstherapie zu reduzieren und eine Steigerung des Therapieeffektes zu erreichen?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Reduktion der Nebenwirkungen							
Al Khalifa 1999	Randomized prospective, double-blind, multicentre study. 1+	N=160 Male/female: 136/24 Mean age: 73 years Histologically documented superficial (pTa-T1, pTis, G1-3) urothelial cancer.	Treatment with 6 weekly instillations of BCG (81 mg). Administration concomitantly with a 3-day course of isoniazid (300 mg o.d.). N=80	Treatment with 6 weekly instillations of BCG (81 mg). Administration concomitantly with a 3-day course of placebo. N=80	Isoniazid prophylaxis for reduction of BCG-induced toxity. Impact of Isoniazid prophylaxis on BCG efficacy.	Patients treated with isoniazid vs. patients treated with placebo: - 19% vs. 16% remained free from side-effects (no p-value available). - 35% vs. 48% had local side-effects confined to the bladder (dysuria, increased micturation frequency and/or haematuria) ($p < 0,01$). - 30 % vs. 30% had local side-effects together with systemic adverse effects (fever, nausea, skin rash). - Follow-up period (about 2 years) no	Follow-up investigations including cystoscopy were performed every 3 month during the first year and thereafter every 6 month.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						differences in curative (pTis) and prophylactic (pTa-pT1) efficacy between the two groups. [Isoniazid can cause side-effects (liver toxicity, gastrointestinal complications, peripheral and central nervous system disturbances, fever).]	
Colombel 2006	Randomized prospective, double-blind, multicentre study (16 centers). 1-	N=115 Mean age: 65,6 (ofloxacin)/65.7 (placebo) years Primary or recurrent superficial bladder cancer (Ta/T1, Cis, G1-G3)	6 consecutive plus 3 consecutive instillations (with a drug-free period inbetween of 6 weeks) of BCG (81 mg) plus 2 x 200 mg ofloxacin. Administration of ofloxacin 6 hours after the first urination after BCG instillation and 10 to 12 hours after or in the early morning after capsule 1. N=57	6 consecutive plus 3 consecutive instillations (with a drug-free period inbetween of 6 weeks) of BCG (81 mg) plus 2 x placebo. N=58	Ofloxacin prophylaxis for reduction of BCG-induced toxity and the impact of ofloxacin on BCG-antitumor efficacy.	Follow-up was 369 (group 1) and 374 (group 2) days. Patients treated with ofloxacin vs. patients treated with placebo: - Treatment cessation: 11 (19,3%) vs. 20 (34,5%) (p-value not significant). -75,9% vs. 94,4% (p=0,013) of patients with at least 1 AE (class II to III) between instillation 4 and 6. - 61,1% vs. 83,3% (p=0,017) of patients with at least 1 AE class II between instillation 4 and 6. - 38,9% vs. 55,6% (p=0,123) of patients with at least 1 AE class III between instillation 4 and 6. - 54,4% vs. 75,9% (p=0,019) of patients with at least 1 AE class IV between instillation 1 and 9. - No significant difference of incidence of systemic symptoms between the two groups. - No significant difference of incidence	Adverse events were assessed using a detailed grid of classification for BCG. Short period of follow-up. Study was not powered for equivalence of BCG efficacy with or without ofloxacin. Study was powered for reduction of BCG-induced toxity. Baseline symptoms were recorded.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						of local symptoms between the two groups. - Recurrence rate: 12.7% vs. 17.2% (no p-value available) - Progression rate: 5.5% vs. 1.7% (no p-value available). [Classification of adverse events: - Category A: systemic - Category B: local - Class I: mild - Class II: moderate - Class IIII: severe - Class IV: complications]	No data given for total percentage of local and systemic symptoms.
Johnson 2013	Randomized prospective, double-blind, single-centre study 1-	N=50 Patients with Cis, Ta, T1	6 weekly BCG treatments with 10 mg oxybutynin daily. N=25	6 weekly BCG treatments with placebo daily. N=25	Reduce irritative urinary symptoms: - frequency - burning with urination - urinary urgency - bladder pain or spasm - hematuria caused by BCG therapy. Reduce 3 non-urinary symptoms: - fever - flu-like symptoms - joint ache.	- Completition of the entire 6-week course statistically equvialent in both groups. - Urinary frequency (p=0.004) and burning on urination (p=0,04) higher in oxybutynin the in placebo group. - No significant differences for other urinary symptoms. - Treatment group experienced increases in fever (p<0,00001), flu-like symptomx (p=0,0008), dry mouth (p=0,045), constipation (p=0,001).	Baseline symptoms were asked. Small sample size.
Vegt	Randomized	N=868	3 Arms:	3. Tice strain		-> No differences in local or systemic	Interim results.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
1997	prospective, multicentre study 1-	- Epirubicin n=289 - BCG n=290 - BCG + isoniazid n=289 Patients with pTa and pT1	1. Epirubicin 2. Tice strain BCG alone: 6 weeks consecutively followed by 3 weekly instillations at months 3, 6, 12, 18, 24, 30 and 36	BCG plus isoniazid 300 mg orally on the day before, 2 h before and the day after instillation.		adverse reactions. Toxity data available for n=436 patients (BCG n=224, BCG + isoniazid n=212) (no reason given for reduced number of patients): No data mentioned for epirubicin group. Local side effects BCG vs. BCG + Isoniazid: - Frequent micturation: 53% vs. 50% (p=051) - Chemical cystitis: 40% vs. 36% (p=0,53) - Bacterial cystitis: 23% vs. 21% (p=0,74) - Delay because of bacterial cystitis: 22 vs. 20 patients - Stop of therapy because of bacterial cystitis: 2 vs. 2 - Hematuria: 34% vs. 28% (p=0,29) - Granulomatous prostatitis, epididymoorchitis, ureteral obstruction: 27% vs. 28% (p=0,89) Systemic side effects BCG vs. BCG + isoniazid: - Fever more than 39°C: 11% vs 15% (p=0,34) - Influenca-like symptoms: 17% vs. 21% (p=0,35)	No follow-up data available since 1997. No blinding. No ITT. Baseline symptoms were recorded.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- Allergic reactions, skin rash: 2% vs. 3% Liver function for BCG vs. BCG + isoniazid: - Increase of aspartate aminotransaminase: 7% vs. 14% (p=0,05) - Increase of alanine aminotransaminase: 5% vs. 9% (p=0,12) -> BCG plus isoniazid: slightly increased liver toxicity. [Classification of adverse events: - local - systemic Severity: - none - not requiring a delay - requiring a delay - requiring cessation]	
Dosismodifikation							
Agrawal 2007	Prospective, randomized study 2++	N=128 N=40: 40 mg dose N=48: 80 mg dose N=40: 120 mg dose Age range: 45 to 84 years. Men/women: 92/36. Patients with Ta or T1.	BCG 40 mg vs. 80 mg vs. 120 mg dose weekly for 6 weeks. Followed by a monthly instillation for 1 year.		Toxity and efficacy of 3 different BCG doses. Efficacy is defined as: - Tumor recurrence - Progression rate.	Mean follow-up: 36 month (18 to 52 months). Recurrence rate of 40 mg vs. 80 mg vs. 120 mg dose: 20% vs. 25% vs. 20% (p>0,05). No progression in any group. Toxicity of 40 mg vs. 80 mg vs. 120 mg dose:	Randomisation through a systematic sampling technique. Small sample size. Study was powered to show

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		No Tis, no BCG treatment before.				Side effects: 30% vs. 41,7% vs. 70% (p<0,01) Local toxity: - Dysuria: 30% vs. 33,3% vs. 70% - Frequency: 20% vs. 33,3% vs. 60% - Hematuria: 0% vs. 8,3% vs. 30% (p<0,01) Systemic toxity: - Fever <39°C: 20% vs. 16,7% vs. 30% - Fever >39°C: 0% vs. 0% vs. 30% - Malaise: 10% vs. 16,7% vs. 30% (p<0,01)	(non-)inferiority of different BCG doses. Sufficient follow-up period.
Bazarbashi 2010	Single-center non-randomized, prospective study. 3	N=50 Median age: 60 (38-85) Men/women: 48/2 Tumor stage: Cis, Ta, T1 No previous intravesical therapy, systemic chemotherapy or iradiation	BCG 27 mg mixed with INFalpha-2B 10 million units for 6 consecutive weeks followed by 3-weekly booster instillations at 3 month (if there was no recurrence)		Evaluate the efficacy and toxicity of the combination of BCG and interferon alpha-2B in treating superficial bladder cancer.	All patients completed the 6 weekly doses, and 74% completed the maintenance booster doses. Median follow-up period of 55,8 (5,3-82,8) months Recurrence in 19 patients (38%), with 8 patients with progression. Disease-free remained 31 patients (61%). Toxity: no grade 4 toxity	No randomization. Due to study design (no control) and sample size, high risk of bias)
Herr 2005	Prospective single center cohort study. 2++	N=347 Median age: 68 years (36 to 93).	Single transurethral resection followed by 6 weekly	Restaging TUR (2 to 4 weeks after first TUR) followed by 6 weekly	Evaluation of whether restaging TUR of supperficial bladder cancer improves the early response to	Evaluation for recurrence/response (= presence or absence of tumor) at first follow-up cystoscopy or at follow-up examination 6 to 12 monsths after treatment.	No randomization. Only short term response is

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Male/female: 266/81 N=250 (72%) Ta high grade N=97 (28%) T1 high grade 74% of patients had associated Cis with multiple papillary tumors.	intravesical BCG treatments N=132	intravesical BCG treatments N=215	BCG. End points were recurrence and progression.	Evaluation of stage progression within 3 years of follow-up. Residual or recurrent tumor at first cystoscopy of single TUR vs. restaging TUR: 75 patients (of 132, 57%) vs. 62 patients (of 215, 29%) (p=0,001). Total of patients with residual or recurrent tumor at first cystoscopy: 75 + 62 patients = 137 patients (40%): - 40% with Ta - 37% with T1 Total of patients with residual or recurrent tumor at 6 to 12 months of follow-up: 129 patients (37%): - 37% with Ta - 37% with T1 Progression of tumor at first cystoscopy of single TUR vs. restaging TUR: 45 patients (of 132, 34%) vs. 16 patients (of 215, 7%) (p=0,001). Total of patients with progression to higher stage within 3 years of follow-up: 45 + 16 patients = 61 patients (18%): - Ta to T1: 17% - T1 to T2: 19%	measured (max. 3 years).

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Time to progression of the 137 patients with residual or recurrent tumor at first cystaoscopy vs. 210 patients with residual or recurrent tumor later than first cystoscopy: 85 patients (62%) recurrence within 12 months/49 patients (36%) recurrence within 3 years vs. 31 patients (15%) within 1months/12 patients (6%) within 3 years (p=0,001). Multivariate logistic regression: single TUR (p=0,005 [progression], p=0,001[recurrence]) and lack of BCG-response after first TUR (p=0,001 [progression], p=0,001[recurrence]) are independent factors associated with subsequent tumor recurrence and stage progression.	
Martinez-Pineiro 2002	Randomized multicenter prospective trial 1+	N=499 Patients with Ta, T1, Tis. Distribution of age, gender, number of tumors, disease status and size are similar in both arms.	Six weekly instillations of BCG 27 mg followed by six fortnightly instillations. N=247	Six weekly instillations of BCG 81 mg followed by six fortnightly instillations. N=252	Recurrence, progression and toxity of a three-hold reduced dose (27 mg) of BCG against the standard dose (81 mg) in patients with supperficial bladder cancer.	Median follow-up: 69 months. Mean number of instillations of BCG 27 mg vs. BCG 81 mg: 11,5 vs 11,14 instillations (p=0,417). 12 instillations of BCG 27 mg vs. BCG 81 mg: 209 patients vs. 222 patients (total: 431 patients (86,2%)). Recurrence:	18 spanish hospitals. No information about blinding is available.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Recurrence of tumor of BCG 27 mg vs. BCG 81 mg: 76 patients (30,7%) vs. 71 patients (28,1%) (total: 147 patients (29,4%)) (no p-value available). Time to recurrence: no significant differences in HR. 5 years mean percentage of recurrence-free patients of BCG 27 mg vs. BCG 81 mg: 70,4 vs. 70,5. Subgroup analysis by age, disease status, size, grade and T category: no differences. Effictiveness against recurrence of multifocal tumors: BCG 81 mg more effective (p=0,0151). Effictiveness against recurrence of G3 tumors: superiority of BCG 81 mg marginal (p=0,0060). Effictivness against recurrence of high risk tumors: superiority of BCG 81 mg marginal (p=0,0082). Progression: Progression of tumor of BCG 27 mg vs.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						BCG 81 mg: 33 patients (13,3%) vs. 29 patients (11.5%) (total: 62 patients (12,4%)). Progression to muscle invasive tumor only of BCG 27 mg vs. BCG 81 mg: 21 patients (8,5%) vs. 14 tumors (5.5%). Progression of distant metastases of BCG 27 mg vs. BCG 81 mg: 4 patients (1,6%) vs. 7 tumors (2.7%). Progression-free patients of BCG 27 mg vs. BCG 81 mg after 5 years: 86,9% vs. 88,8% (p=0,52). Effictiveness against progression of multifocal tumors: BCG 81 mg more effective (p=0,048). Subgroup analysis by age, status of tumor, size, G category and T category: no differences. Only patients with 3 or more tumors fared significantly better with the BCG 81 mg treatmant (p=0,043). Survival analysis: Surviving patients at 5 years of BCG 27 mg vs. BCG 81 mg: 80,57% vs. 84,25% (no p-value available).	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Toxity: No local toxity of BCG 27 mg vs. BCG 81 mg: 112 patients (45,3%) vs. 84 patients (33,3%). No systemic toxity of BCG 27 mg vs. BCG 81 mg: 209 patients (84,6) vs. 172 patients (68,3). Local toxity Grade 1-2 of BCG 27 mg vs. BCG 81 mg: 119 patients (48,2) vs. 124 patients (49,2) (no sig.). Local toxity Grade 3-4 of BCG 27 mg vs. BCG 81 mg: 16 patiens (6,5%) vs. 44 patients (17,5%) (p<0,001). Systemic toxity Grade 1-2 of BCG 27 mg vs. BCG 81 mg: 27 patients (10,9) vs. 71 patients (28,2%). Systemic toxity Grade 3-4 of BCG 27 mg vs. BCG 81 mg: 11 patients (4,4%) vs. 9 patients (3,6%) (no sig.). Withdrawn from study of BCG 27 mg vs. BCG 81 mg: 10 patients (4,0%) vs. 23 patients (9,1%). Instillations delayed of BCG 27 mg vs.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						BCG 81 mg: 22 patients (8,8%) vs. 37 patients (16,8%).	
Mohanty 2002	Prospective singel-center cohort study 3	N=230 N=130 with pTa N=100 with pT1 N=170 primary tumor. N=60 tumor recurrence.	BCG 60 mg + interferon alpha 2b 5 million IU weekly for 8 weeks. Followed by monthly instillation for 8 weeks. Followed by maintenance dose at 9, 12, 18, 24 months. Total of 18 instillations over 2 years.			Avarage follow-up period of 60 months (range 42-72 months). Complete response (= no progression) after 1st vs. 2nd vs. 3rd vs. 4th vs. 5th year: 84% vs. 70% vs. 58% vs. 44% vs. 36%. Partial response after 1st vs. 2nd vs. 3rd vs. 4th vs. 5th year: 16% vs. 25% vs. 34% vs. 40% vs. 44%. No response (= progression) after 1st vs. 2nd vs. 3rd vs. 4th vs. 5th year: 0% vs. 5% vs. 8% vs. 16% vs. 20%. Toxity: The incidence of adverse reactions at the end of follow-up was found to 19%.	Due to study design (no control) high risk of bias).
O'Donnell 2001	Cohort study 3	N=40 Men/women: 30/10 Age: 43-92 years BCG induction courses failed: N=19: 1 cours of BCG N=21: 2 courses of BCG N=39 patients (98%)	6 to 8 weekly instillations of BCG 27 mg + interferon alpha2b 50 million units (= induction cycle). Additional 3 week miniseries		Treatment efficacy of intravesical low-dose BCG + interferon alpha2b	Median follow-up: 30 months. Disease-free patients at 12 months vs. 24 months vs. 30 months: 63% vs. 53% vs 55%. Disease-free patients with only 1 induction cycle at 12 months vs. 24 months: 56% vs. 48%. 5 of 12 patients* (42%) with a second	Cave: Result information is not clear! Results vary between written text and table. Insufficient sample size and lack of strict comparison

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		with mulitfocal disease	of decreased BCG 1/10, 1/30, 1/100 dose titrated to symptoms + interferon alpha2b 50 million units were given at 5, 11 and 17 months. 12 patients* received a second induction course with BCG 1/10 dose + interferon alpha2b 100 million units.			induction course were long term responders. Patients who received all 3 maintenance cycles hat no recurrence.	groups do not permit meaningful statistical evaluations . High risk of bias.
O'Donnell 2004	Prospective, multicenter, controlled, phase II cohort study 2	N=490 BCG naive and BCG failure patients: N=259: BCG naive N=231: BCG failure Patients with Ta, T1 and Tis tumors.	Group 1: BCG naive group: 6 weekly induction treatments of BCG 81 mg + interferon alfa-2b 50 million units followed by 3 times 3-week maintenance		Efficacy and toxicity of BCG plus interferon .	Median follow-up: 24 months. Disease-free at 24 months for BCG naive: 57%. Disease-free at 24 months for BCG failure: 42%. Recurrence rate for BCG naive:40,1% Recurrence rate for BCG failure:51,5%. Progression to muscle invasive disease for BCG naive: 5%.	Interim results. 125 sites participating.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			cycles of BCG 1/3 or 1/10 dose + interferon alfa-2b 50 million units at 3, 9 and 15 months after induction. Group 2: BCG failure group (not BCG-intolerant, recurrent superficial bladder cancer): Same treatment except induction therapy started with BCG reduced dose (1/3). Group 3: BCG failure group (BCG-intolerant, no other characterisation given): Same treatment except induction therapy started			Progression to muscle invasive disease for BCG failure: 4,3%. Progression to metastatic disease for BCG naive: 2,3%. Progression to metastatic disease for BCG failure: 2,6%. SAEs in BCG naive vs. BCG failure: 2,6% vs. 5,5%	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			with BCG reduced dose (1/10) + interferon alfa-2b 100 million units. Group 3 amounted 9% of the "total" BCG failure group (= group 2 and 3). Due to similar responses they are grouped together as BCG failure group.				
Okamura 2008	Cohort study 2-	N=213 Age range: 36-84 years (average 67,0 years). Male/female ratio: 185/28. Patients with Ta-T1. Dosage of 40 mg vs. 60 mg vs. 80 mg: 40 patients (18,8%) vs. 26 patients (12,2%) vs. 147 patients (69,0%).	6-8 weekly instillations of BCG 40, 60 or 80 mg. In some cases 6-8 monthly instillations.		The role of BCG focusing on dose, age, high grade/stage and pretreatment episodes with other therapies.	Recurrence-free survival: - Overall recurrence in 213 patients: 31,9% (68 patients). - Overall recurrence-free rates for 3 vs. 5 vs. 10 years: 70,8% vs. 67,1% vs. 57,6%. - Recurrence-free rates according to age groups: younger cases demonstrated higher recurrence-free rates (P=0,2870). - Recurrence-free rates after 3 years of 40 mg vs. 60 mg vs. 80 mg: 67,5% vs. 63,4% vs. 72,4%.**	BCG dosage was decided by the attending doctor of after group discussion according to the condition and/or coexisting disease of each patient. High risk of bias. **Data presented is very

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
							inconsistent.
						- Recurrence-free rates in the BCG 80 mg group after 3 vs. 5 vs. 10 years: 72,4% vs. 69,1% vs. 59,3% (P=0,7325).** - Recurrence-free rates in the no previous treatment group after 3 vs. 5 vs. 10 years: 73,9% vs. 70,8% vs. 60,7%.** - Recurrence-free rates in the previous treatment group after 3 vs. 5 years: 26,8% vs. 17,9% vs. 60,7%.** - Recurrence-free rates according to the tumor grade: no significant difference (P=0,4706). - Recurrence-free rates of T1 vs. Ta: higher rates of T1 vs. Ta (P=0,0762). - No significant differences with reference to gender, initial or recurrent status, single or multiple tumor and tumor number. Progression-free survival: - Overall progression in 13 of 68 recurrent cases.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- Mean interval to progression 20,15 +/- 27,47 months (1-99 months). - Overall progression-free survival rates for 3 vs. 5 vs. 10 years: 94,5% vs. 93,6% vs. 90,6%. - Progression-free rates according to age groups: younger cases demonstrated higher Progression-free rates (P=0,2940). - Progression -free rates after 3 years of 40 mg vs. 60 mg vs. 80 mg: 91,6% vs. 95,8% vs. 94,6%.** - Progression -free rates after 5 years of 40 mg vs. 60 mg vs. 80 mg: 84,0% vs. [no data] vs. 94,5%.** - Progression -free rates in the BCG 80 mg group after 3 vs. 5 vs. 10 years: 94,6% vs. 94,6% vs. 94,5%. - Progression -free rates in the no previous treatment group after 3 vs. 5 years: 92,4% vs. 86,6% vs. 83,3%.** - Progression -free rates in the previous treatment group after 3 vs. 5 vs. 10 years: 88,4% vs. 88,4% vs. 85,1%.**	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- Progression-free rates of T1G3: lower rates than in others (P=0,0001). - No significant differences with reference to gender, initial or recurrent status, single or multiple tumor and tumor number. Significant results of univariate analysis influencing: a) Recurrence: - T stage (P=0,0488) - Previous treatment (P=0,0010) - T1G3 (P=0,0389) b) Progression: - Grade (P=0,0116) - T stage (P=0,0319) - T1G3 (P=0,0007)	

5.8. AG 4 Schlüsselfrage 8 (Diagnostik und Therapie beim Cis)

„Welche spez. Diagnostik und Therapiestrategien müssen beim CIS erfüllt sein?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Burger 2013	Meta-analysis, prospective studies 2+	2212 patients (1345 hexaminolevulinate (HAL) patients) 10 publications (9 studies) included in meta-analysis Consecutive patients Patients with known or suspected non-muscle-invasive bladder cancer (NMIBC)	Blue light (BL) hexaminol-evulinate (HAL) cystoscopy	White light (WL) cystoscopy	To evaluate the effect of HAL cystoscopy on the detection of papillary (Ta/T1) and flat (CIS) tumours, and the impact it may have on tumour recurrence	BL cystoscopy detected significantly more Ta tumours (14.7%; p < 0.001; odds ratio [OR]: 4.898; 95% CI, 1.937–12.390) and CIS lesions (40.8%; p < 0.001; OR: 12.372; 95% CI, 6.343–24.133) than WL. There were 24.9% patients with at least one additional Ta/T1 tumour seen with BL (p < 0.001), significant also in patients with primary (20.7%; p < 0.001) and recurrent cancer (27.7%; p < 0.001), and in patients at high risk (27.0%; p < 0.001) and intermediate risk (35.7%; p = 0.004). In 26.7% of patients, CIS was detected only by BL (p < 0.001) and was also significant in patients with primary (28.0%; p < 0.001) and recurrent cancer (25.0%; p < 0.001). Recurrence rates up to 12 mo were significantly lower overall with BL, 34.5% versus 45.4% (p = 0.006; RR: 0.761 [0.627–0.924]), and lower in patients with T1 or CIS (p = 0.052; RR: 0.696 [0.482–1.003]), Ta (p = 0.040; RR: 0.804 [0.653–0.991]), and in high-risk (p = 0.050) and low-risk (p = 0.029) subgroups.	Consecutive patients Some subgroups had too few patients to allow statistically meaningful analysis Heterogeneity was minimised by the statistical analysis method used Database search of PubMed and the Cochrane Library Completed but unpublished trials were sought through www.clinicaltrials.gov, www.clinicaltrialsregister.eu, and www.icmje.org/faq_clinical.html

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						→ This meta-analysis confirms that HAL BL cystoscopy significantly improves the detection of bladder tumours leading to a reduction of recurrence at 9–12 mo. → The benefit is independent of the level of risk and is evident in patients with Ta, T1, CIS, primary, and recurrent cancer.	Only included well-controlled studies to reduce bias.
Zheng 2012	Systematic review and meta-analysis, 2+	N=1022 Eight studies, six studies are prospective. Published between 2008 and 2012 People suspected of new or recurrent bladder cancer	Narrow band imaging (NBI) cystoscopy	White light imaging (WLI) cystoscopy	To assess the test performance and clinical effectiveness.	On a per-person analysis, the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio of NBI and WLI were respectively 0.943 (95% CI 0.914 − 0.964) and 0.848 (95% CI 0.803 − 0.885), 0.847 (95% CI 0.812 − 0.878) and 0.870 (95% CI 0.831 − 0.903), 7.038 (95% CI 3.357 − 14.754) and 6.938 (95% CI 2.052 − 23.465), 0.054 (95% CI 0.012 − 0.237) and 0.181 (95% CI 0.091 − 0.361), and 185.32 (95% CI 45.714 − 751.26) and 42.931 (95% CI 8.088 − 227.88). The area under the curve and *Q* * of NBI and WLI were respectively 0.9781 and 0.8944, and 0.9337 and 0.8253. For the characterization of carcinoma in situ , the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds	Literature was searched in PubMed, EMBASE, Cochrane Library, MEDLINE and CNKI, with hand searching of relevant congress abstracts and journals. Two of the authors (C.J.Z. and Y.L.L.) independently searched the databases and reviews. Data from included studies

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						ratio of NBI were 0.927 (95% CI 0.878 − 0.960), 0.768 (95% CI 0.730 − 0.802), 4.545 (95% CI 2.820 − 7.325), 0.125 (95% CI 0.051 − 0.304) and 48.884 (95% CI 15.642 − 152.77) on a per-person analysis. - The area under the curve and *Q* * were 0.9391 and 0.8763. → NBI is an effective method for the identification of abnormal lesions including carcinoma *in situ* and can provide higher diagnostic precision of bladder cancer than WLI. → Multicentre randomized studies are recommended to determine whether the visual advantages of NBI can translate into real therapeutic benefit for individual patients. → Prospective studies are recommended to determine whether the visual advantages of NBI can translate into real therapeutic benefit for individual patients. - As only a few studies with small study populations were available, we believe that more results with high quality trials should be provided to update this study.	were independently extracted by two reviewers (C.J.Z. and Y.L.L.). Included papers were assessed using the Quality Assessment of Diagnostic Studies (QUADAS). Quality assessment of studies was done by two reviewers independently (C.J.Z. and Y.L.L.) and differences of opinion were resolved by mutual agreement.
Bolenz 2013	Cross-sectional study on diagnostic	N=882 M/F: 612/270	Urinary cytology	Bladder biopsy or trans-urethral	To test the sensitivity of urinary cytology.	Urinary cytology detected 237 out of 503 UCB (overall sensitivity 47.1%).	Retrospective Single site

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
	accuracy, retro-spective, single site 3	Consecutive patients 8574 cytology specimens were evaluated		resection of bladder tumor for UCB (urothelial carcinoma of the bladder).	To assess the impact of pathologist experience on detection of urothelial carcinoma of the bladder (UCB).	Cytology after bladder washing resulted in higher sensitivity than in voided urine (50.4% vs. 36.2%; P = 0.008). Sensitivity rates significantly increased by UCB stage; 30.6% in pTa (n = 245), 60.5% in patients with any form of CIS (n = 119), 62.9% in pT1 (n = 89), and 69.6% in >= pT2 (n = 46; P < 0.001). Similarly, higher sensitivity was observed with increasing grade, ranging from 16.7% in low (n = 108) to 62.2% in high grade tumors (n = 283; P < 0.001). No statistically significant difference between more and less experienced investigators was observed. → Sensitivity rates of urinary cytology are not superior to those reported in the literature. → Cytology missed many high grade cancers, pointing to inherent methodological limitations of urinary cytology. → A higher experience level of the pathologist was not significantly associated with higher sensitivity rates. → Urinary cytology represents a flawed adjunct to cystoscopy with limited	Consecutive patients Cytology evaluation was performed blinded to clinical data 21 different pathologists evaluated urinary cytology specimens

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						potential of improvement even in the hands of experience pathologists. → Prospective studies are needed to determine whether the use of cytology can be omitted in favour of more sensitive and potentially equally specific novel urinary markers.	
Fritsche 2010	Cross-sectional study on diagnostic accuracy, pro-spective, single site 3	N=25 Consecutive unselected cohort Patients with a history of high-grade non-muscle-invasive urothelial carcinoma of the bladder (NMIBC). 210 follow-up events	Multicolor fluorescence in situ hybridization (FISH) (UroVysion)	Combined cystoscopy and cytology	To assess the diagnostic benefit of UroVysion (Vysis-Abbott Laboratories, Downers Grove, IL) in the follow-up. To evaluate the use of UroVysion.	- Sensitivity and specificity for standard combined cystoscopy and cytology were 78% and 83%, respectively. - UroVysion yielded a considerably higher detection rate with 94% and 93%, respectively. - In 89% of the follow-up events of patients with a history of previous carcinoma in situ (CIS) and negative cystoscopy but a positive UroVysion finding, CIS recurrence was noticed within 5 months. → UroVysion is a worthwhile approach in patients with previous CIS, a high risk for the development of CIS, or previous unequivocal cytology suggestive of CIS, especially during or shortly after instillation therapy. → Thus, tighter follow-up schemes or photodynamic assessment should be considered in positive UroVysion and	Prospective Single site Consecutive unselected cohort All cystoscopies were performed by 1 highly experienced urologist (E.B.) Transurethral resection was performed with photodynamic diagnosis (PDD) by experienced surgeons in 1 institution The resected specimens were processed

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						concomitant negative cystoscopy and cytology results in the surveillance of patients with a history of high-grade NMIBC. → The benefits of UroVysion must be balanced against its costs.	according to standard pathologic procedures and diagnosed by 2 experienced uropathologists (A.H. and S.S.) based on the current American Joint Committee on Cancer TNM classification Cytology and UroVysion analysis was performed by 2 experienced uropathologists (A.H. and S.S.) and UroVysion also by 1 experienced molecular biologist (W.D.), all blinded to other results. Small population Might result in a

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							biased selection
Gudjónsson 2011	Cross-sectional study on diagnostic accuracy, pro-spective, multi site 3	N=162 Consecutive patients Median age, years: 68 Gender: all male History of BCG treatment, *n* (%): 21 (13) Median (range) nodes removed: 28 (1 – 67) Nodal status, *n* (%): N0 113 (70) N1 24 (15) N 24 (15) N3 1 (1) Pathological T stage, *n* (%): T0 15 (9) Tis 14 (9) Ta 9 (6) T1 15 (9) T2 38 (23) T3 51 (31) T4 20 (12)	Bladder mapping (BMAP)	Cysto-prostat-ectomy specimen	To assess the value of bladder mapping and prostatic urethra biopsies for detection of urothelial carcinoma *in situ* (CIS).	- CIS was detected in 46% of the cystoprostatectomy specimens, and multiple (≥ 2) CIS lesions were found in 30%. - BMAP (cold-cup bladder biopsies + resection biopsies from the prostatic urethra) provided sensitivity of 51% for any CIS, and 55% for multiple CIS lesions. - The cold-cup biopsies for CIS in the bladder mucosa showed sensitivity and specificity of 46% and 89%, respectively. → Traditional cold-cup biopsies are unreliable for detecting CIS in bladder mucosa and negative findings must be interpreted with caution. → A study comparing the outcome of PDD-guided biopsies with the presence of CIS in cystectomy specimens is warranted.	Prospective Multi site Consecutive patients Each biopsy sent to an uropathologist for analysis All histological material was evaluated by experienced uropathologists (G.C. and H.O.). Blinding is not reported
Lerner 2012	Meta-analysis,	Pooled data from 3	Hexaminol-	White light	To understand the	- 174 patients had at least one CIS	All studies are

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	all studies are prospective 2-	phase III studies N=551	evulinate (HAL) fluorescence cystoscopy	cystoscopy (WL)	additional benefits of HAL. To explore relationships of urine cytology and CIS. To assess the cumulative difference in detection of CIS.	lesion detected by HAL, WL, or random biopsy. - The CIS detection rate of HAL was 0.87 vs. 0.75 for WL (P = 0.006). - By multivariate Poisson regression, female patients had fewer CIS lesion (P < 0.0001) while older patients (>=65) had a higher number of CIS lesions detected by HAL (P = 0.04). - HAL was less likely to detect CIS in patients previously treated with chemotherapy or BCG (P = 0.01 and 0.03, respectively), after adjusting for age. - CIS was unifocal in 44% and multifocal in 56%. - Mulifocal CIS was associated with positive cytology more frequently than unifocal (65% vs. 45%; P = 0.016) whereas a negative cytology was more frequently associated with unifocal CIS. - Patients with positive urine cytology had twice as many CIS lesions detected by HAL as patients with negative urine cytology (P =0.02).	prospective. Two data sets for white and blue light were reviewed by an independent urologist (similar in all three studies). Number of evaluable intent-to-treat Patients in the 3 studies were 209, 196 and 146.

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						→ HAL cystoscopy had a higher CIS detection rate than WL cystoscopy. → The average number of CIS lesions detected was associated with baseline clinical characteristics. → Cytology was positive more frequently in mulifocal CIS suggesting that HAL may be particularly useful in this setting to optimize detection of the exent of CIS. → Randomized trial data evaluating CIS would be required to determine whether this translates to improved long-term cancer control. → Both Hal and WL detected more CIS lesions in patients with prior BCG therapy and positive cytology.	
Sengiku 2013	RCT, pro-spective, multi site 1-	N=178 → 49 patients were excluded from study. → 66 and 63 patients who received the Tokyo and Connaught stains, respectively, completed 1 course of intravesical BCG therapy (6 to 8 doses) and were included in efficacy analysis. Nonmuscle invasive	Bacillus Calmette-Guérin (BCG) therapy with the Tokyo 172 strain. 80 mg Tokyo strain were suspended in 40 ml saline, transurethrally instilled in the bladder and maintained for 1 to 2 hours.	Bacillus Calmette-Guérin (BCG) therapy with the Connaught strain. 81 mg Connaught strain were suspended in 40 ml saline, transurethrall y instilled in	Complete response rate in patients with pTis and concomitant carcinoma in situ (pTa or pT1). Recurrence-free survival in patients with pTa, pT1 and carcinoma in situ who achieved a complete response after therapy. Frequency of adverse events.	- Administration of the Connaught strain ceased because its production was suspended in June 2012. - Therefore, analysis was performed using data gathered to date. - Overall, 66 and 63 patients who received the Tokyo and Connaught strains, respectively, were included in efficacy analysis. - Patient and tumor characteristics were well balanced between the 2 groups.	Prospective Multi site Open label Computer generated random number table. 1:1 randomization Randomization

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		bladder cancer (NMIBC). Patients with pTa/T1 and pTis, multiple tumors and a recurrence-free period of 3 months or less who required intravesical bacillus Calmette-Guérin therapy.	Instillation: weekly up to 8 times. Therapy was deemed complete after at least 6 doses.	the bladder and maintained for 1 to 2 hours. Instillation: weekly up to 8 times. Therapy was deemed complete after at least 6 doses.		- Median follow-up was 855 days. - Adverse events were similar in the groups. - The complete response rate was 90.3% and 85.0% in patients given the Tokyo and Connaught strains, respectively, which did not significantly differ (p = 0.896). - The 2-year recurrence-free survival rate was 73.2% and 68.8%, respectively. → Results suggest no significant differences between the Tokyo and Connaught strains in the complete response, recurrence-free survival or adverse event rate. → Larger clinical studies are warranted to confirm our results.	codes were centrally assigned at a coordination center after assessing the main study eligibility criteria. Observation period began at the start of BCG treatment and ended on the day of the last visit. Observation period too short to assess long-term outcomes. Short follow-up Study was terminated prematurely.
Chade 2010	Cohort study, retro-spective, single site 2-	N=476 221 with primary and 255 with secondary carcinoma in situ	Primary carcinoma in situ	Secondary carcinoma in situ	Time to progression to invasive disease (cT1 or higher) or radical cystectomy before progression.	- Patients with primary carcinoma in situ responded significantly more within 6 months of bacillus Calmette-Guerin than those with secondary carcinoma in situ (65% vs 39%, p =	Retrospective Single site Cox proportional hazards

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		High grade cTis After transurethral resection and intravesical bacillus Calmette-Guerin therapy. Consecutive cohort Median age: 66.7 years 389 (82%) were male 446 (94%) were white 341 (72%) were current or former smokers			Time to progression to muscle invasive disease (cT2 or higher) or radical cystectomy before progression. Clinical outcomes.	0.001). - In the primary vs secondary groups the 5-year cumulative incidence of progression to cT1 or higher was 43% (95% CI 36–51) vs 32% (95% CI 27–39) and for progression to cT2 or higher it was 17% (95% CI 12–23) vs 8% (95% CI 5–13). - 173 patients underwent RC, including 92 with primary and 81 with secondary CIS. - RC was done before progression in 67 patients with primary and in 66 with secondary CIS. - On multivariate analysis primary carcinoma in situ was significantly more likely to progress to cT1 or higher (HR 1.38, 95% CI 1.05–1.81, p = 0.020) and to cT2 or higher, or radical cystectomy (HR 1.72, 95% CI 1.27–2.33, p = 0.001). - No significance for age, gender or response to bacillus Calmette-Guerin as outcome predictors. - Median followup was 5.1 years. → Patients presenting with primary carcinoma in situ have a worse outcome than those with secondary carcinoma in situ, suggesting a need to differentiate these 2 entities in the treatment decision process.	regression Models. Large cohort Consecutive cohort Cohort covered 19 years, during which a trend occurred toward earlier RC.

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						→ Patients with primary CIS respond better to BCG therapy. → No association with progression. → RC before progression was recommended more often in the primary CIS group but this was not enough to decrease the progression rate close to that in the secondary CIS group.	
Meijer 2010	Case series, retro-spective, multi site 3	N=90 Mean age: 63.4 years (range 24–85 years) Predominantly men (91.1%)	-	-	To further clarify the risk profiles of three clinical types of carcinoma in situ (CIS) of the bladder. Primary (P-), concomitant (C-) or secondary (S-) CIS. Overall survival (is defined as the time to any cause of death: patients who were alive at the end of follow up were censored at that date). Progression rate (was defined as the development of muscle-invasive bladder cancer).	- Overall, 90 patients with CIS were identified with a mean age of 63.4 years, predominantly men (91.1%). Primary CIS (P-CIS) was found in 43 patients (47.8%), concomitant CIS (C-CIS) in 21 patients (23.3%) and secondary CIS (S-CIS) in 26 patients (28.9%). Mean follow up was 81.3 months (range 8–222 months). - Recurrence of disease was observed in 68.9% of patients, with significantly more recurrences in the SCIS group (88.5%). - Progression to muscle-invasive disease was seen in 17 patients (18.9%): eight patients (18.7%) with P-CIS, four (19.0%) with C-CIS and five (19.2%) with S-CIS. Overall, 29 patients underwent a cystectomy, equally distributed over the three groups. The duration of bladder preservation was worse in the C-CIS group but did not differ significantly between the groups.	Retrospective Multi site Population-based data from the Comprehensive Cancer Centre Middle Netherlands (CCCMN). Netherlands Cancer Registry is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological

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					Recurrence rate (was defined as first relapse of disease in the bladder).	- Overall survival at 5 years was 79.6% for the total group, with poorer results for the C-CIS group, although the difference was not significant. → Carcinoma *in situ* is clearly an entity that requires meticulous treatment and thorough follow up because of its high recurrence rate (68.9%) and high rate of progression to muscle-invasive bladder cancer (18.9%). → The C-CIS group appears to have a poorer prognosis with a shorter duration of bladder preservation and a worse overall survival.	archive. Quality of the data is high because of the thorough training of the data managers and computerized consistency checks at regional and national levels. Patients were divided into three groups according to their 'clinical type', being primary (P-), concomitant (C-) or secondary (S-) CIS. Small number of patients
Tilki 2010	Case series, retro- spective, multi site (8 centers in the	N=243 Male/female: 193/50	Clinical stage	Pathological stage	Describe the rate of up staging and the cancer specific outcomes of patients with carcinoma	- Of the 3,207 patients who underwent radical cystectomy 243 (7.6%) had clinical carcinoma in situ only disease before radical cystectomy.	Retrospective Multi site

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	United States, Canada and Europe) 3	Discrepancy between clinical - pathological stage: Down staged → 39 (16.0) Same stage (both CIS) → 117 (48.1) Up staged → 87 (35.8) Lymph node status: pN0 → 229 (94.2) pN1-2 → 14 (5.8) LVI (lymphovascular invasion): Neg → 221 (90.9) Pos → 22 (9.1)			in situ refractory to transurethral resection with intravesical therapy treated with radical cystectomy. Recurrence-free survival. Cancer specific survival.	- At radical cystectomy 117 patients (48.1%) had carcinoma in situ only, 20 (8.2%) had pT0 urothelial carcinoma of the bladder, 19 (7.8%) had pTa urothelial carcinoma of the bladder and 36% had disease up staged (32 [13.2%] pT1, 29 [11.9%] pT2, 12 [4.9%] pT3 and 14 [5.8%] pT4). - A total of 22 patients (9.1%) had lymphovascular invasion in the radical cystectomy specimen and 14 (5.8%) had metastasis to regional lymph nodes. - Overall 5-year recurrence-free and cancer specific survival estimates were 74% (95% CI 68–79) and 85% (95% CI 80–89), respectively. - On multivariable analysis adjusting for the effects of standard predictors, lymph node metastasis and lymphovascular invasion were associated with an increased risk of disease recurrence (p = 0.017 and p = 0.043, respectively) and cancer specific mortality (p = 0.019 and p = 0.001, respectively). - Female gender was an independent risk factor for cancer specific mortality (p = 0.029) but not for disease recurrence (p = 0.173). → Approximately a fourth of patients treated with radical cystectomy for	Before final analysis the database was frozen and the final data set was produced for the current analysis. To ensure validity of the pathological data extraction 2 investigators independently reviewed pathology from a subgroup of patients while blinded to patient clinical parameters and the finding of the other reviewer. The population in this study underwent surgery by multiple surgeons and had specimens evaluated by

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						clinical carcinoma in situ only had muscle invasive disease and 5.8% had metastasis to regional lymph nodes. → Identification of those patients with a potentially aggressive natural history of carcinoma in situ is of the utmost importance as they are likely to benefit from early radical cystectomy.	multiple pathologists. → This characteristic can be construed as a strength because it represents a real-world practice.
Huang 2009	Case series, single site (Depart-ment of Urology at the University of Southern California) 3	N=27 Mean and median age was 64.2 and 63, respectively (range 42–83). 26/27 patients were male	Radical cystectomy	-	Long-term oncological efficacy of radical cystectomy To characterize the likelihood of clinical understaging, and to characterize the pattern of recurrence. Overall survival Recurrence-free survival	- At time of cystectomy, 33% of patients were found to be clinically understaged. - Median follow-up was 94 months. - At time of last follow-up, 12 patients are alive, two patients died from recurrent disease, and 12 patients died from other causes. - Two patients experienced disease recurrence (one in urethra at 104 months, one in upper tract at 61 months), both subsequently died from metastatic disease. - Estimated 5- and 10-year overall survival was 87 and 56%, respectively. - Estimated 5- and 10-year recurrence-free survival was 100 and 83%, respectively. → Excellent long-term survival outcomes can be achieved with radical cystectomy. → Radical cystectomy should be strongly considered for patients who	Single site Follow-up: postoperatively at 4-month intervals during the first year, 6-month intervals during the second year, and annually thereafter (physical examination, routine serum chemistry Studies (including a biochemical liver profil and alkaline phosphatase))

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						have failed prior intravesical therapy. → Long-term surveillance of the retained urethra and of the upper tract is essential, as recurrence can occur years following cystectomy. → Patients who recur are at high risk of dying from disease.	Radiographic evaluation (urinary diversion, upper urinary tract, chest radiography) were performed 4 months postoperatively and annually thereafter unless otherwise clinically indicated. Bone scans and chest/ abdominal/ pelvic computed tomography were performed when clinically indicated Small sample size
Gofit 2009	Case series, pro-spective	N=104 Patients with bladder	-	-	To explore patterns of reccurence, muscle invasion, and disease	- The 5- and 10-year recurrence-free survival rates were 63% and 54%, respectively.	Prospective Follow-up:

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	3	carcinoma in situ. Mean age: 67 years Pure (38 patients) or concomitant (66 patients) CIS. Patients who responded to one (92 patients) or two (12 patients) induction courses of intravesical BCG instillation werde included in the study.			specific mortality.	- The 5- and 10-year muscle-invasive-free survival rates were 79% and 77%, respectively. - The 5- and 10-year disease-specific survival rates were 90.5% and 85.8%, respectively. - Median time to recurrence, muscle invasion, and disease-specific mortality was 18, 18, and 40 month, respectively. - Pure and concomitant CIS were associated with similar outcome. - The recurrence of nonmuscle-invasion tumor did not increase the risk for muscle invasion or mortality. → Pure and concomitant bladder CIS share similar biologic behaviour. → Muscle-invasive disease is expected in about 25% of the BCG responders followed for long time periods and disease-specific mortality in 15%. → Tumor recurrence, whether nonmuscle-invasive or muscle-invasive, follows a similar time table suggesting that these are not sequential but parallel and independent processes.	Urinary cytology and bladder biopsies every 3 month for 2 years, then every 6 month for an additional 3 years, and then annually with urinary cytology and cystoscopy without biopsie

5.9. AG 4 Schlüsselfrage 9 (Adjuvante Therapie mit Gemcitabin und andere Verfahren)

„Welchen Einfluss haben die verschiedenen adjuvanten Chemotherapie-Schemata (Gemcitabine, Apaziquone, Mitomycin C, Doxorubicin) und andere Verfahren (Hyperthermie, EMDA…) auf die Rezidiv- und Progressionsrate sowie die Lebensqualität?“

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Di Stasi 2003	RCT, multi site 1+	N=108 Median age: - A (electromotive mitomycin C (MMC) =64,5 - B (passive (MMC)) = 68,5 - C (bacillus Calmette-Guerin (BCG)) = 66,5 Men/women: 79/29 Median mos follow-up (IQR): BCG → 43 (23.5), Passive MMC → 42 (23), Elektromotive MMC → 45 (23.5) Patients with high risk superficial bladder cancer. The patient population	A: 40 mg electromotive MMC instillation with 20 mA electric current for 30 minutes (n=36) B: 40 mg passive MMC with a dwell time of 60 minutes (n=36)	C: 81 mg BCG with a dwell time of 120 minutes (n=36)	1) Complete response rate at 3 and 6 months 2) Time to recurrence 3) Side effects 4) Progression 5) Survival 6) MMC pharmacological	1) The complete response for electromotive vs passive MMC at 3 and 6 months was 53% versus 28% (p = 0.036) and 58% versus 31% (p = 0.012). For BCG the responses were 56% and 64%. 2) Median time to recurrence was 35 vs 19.5 months (p = 0.013) and for BCG it was 26 months. 3) Side effects: - Local side effects and systemic side effects were significantly more prominent in the BCG arm than in the 2 MMC arms. - There were no statistical differences between the 2 MMC arms, although there was a trend toward increasing numbers and side effect severity in the electromotive MMC group. - There were significant differences in modified treatment between the BCG and MMC arms.	Multi site Randomisation: - Using a central computer - Blocked randomization across 8 (2 x 2 X 2) strata resulting from 3 factors, namely Tis only vs Tis with concurrent T1 papillary tumors, grades III vs II concurrent T1 papillary tumors and multifocal vs unifocal concurrent T1 papillary tumors (→prognostic parity).

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		had histologically proven multifocal carcinoma in situ (Tis) of the bladder and most had concurrent pT1 papillary transitional cell carcinoma. Adequate bone marrow reserve, normal renal function, normal liver function and a Karnofsky performance score of 50 to 100.				- A total of 32 patients on BCG, 34 on passive MMC and 33 on electromotive MMC completed treatment. - Nine patients (8.3%) did not complete the first 6 weekly treatments due to severe toxicity, including 4 in the BCG arm due to prostatitis, persistent gross hematuria, drug induced cystitis and systemic side effects, 2 in the passive MMC arm and 3 in the electromotive MMC arm due to allergic reactions. - No haematological toxicity was observed, no patients had a contracted bladder and no life threatening adverse effects or treatment related deaths occurred. 4) Progression: - Five patients underwent cystectomy for persistent Tis at 9 to 12 months and 15 progressed to muscle invasive disease with subsequent cystectomy. - Ten of the 15 patients first showed progression at 24 to 39 months, while in 5 progression was detected at 12 to 24 months. - Progression (95% CI): BCG → 16.7 (6.4–32.8), Passive MMC → 22.2 (10.1–39.1), Electromotive MMC → 16.7 (6.4–32.8) 5) Survival:	All clinical analyses were performed on an intent to treat basis. Details of blinding not reported. Small sample size and short follow-up period.

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						- There was an overall mortality of 32 of 108 cases (29.6%), including 11 in the BCG, 12 in the passive MMC and 9 in the electromotive MMC groups. 6) Peak plasma MMC was significantly higher following electromotive MMC than after MMC ((43 vs 8 ng/ml), consistent with bladder content absorption. → Intravesical electromotive administration increases bladder uptake of MMC, resulting in an improved response rate in cases of high risk superficial bladder cancer	
Di Stasi 2006	RCT, multi site or single site not reported 1+	N=212 Patients with stage pT1 bladder cancer. Patients with high-risk superficial bladder cancer. Sex: - Men: B → 86 (81,9%), A → 87 (81,3%) - Women: B → 19 (18,1%), A → 20 (18,7%) Age (years):	A: 81 mg BCG infused over 120 min once a week for 2 weeks, followed by 40 mg electromotive mitomycin (intravesical electric current 20 mA for 30 min) once a week as one cycle for three cycles (n=107).	B: 81 mg BCG infused over 120 min once a week for 6 weeks (n=105).	1) Disease-free interval 2) Recurrence 3) Progression 4) Overall survival 5) Disease-specific survival 6) Side effects	Median follow-up was 88 months (IQR 63–110). 1) Patients assigned sequential BCG and electromotive mitomycin had higher disease-free interval than did those assigned BCG alone (69 months [95% CI 55–86] *vs* 21 months [15–54]; difference between groups 48 months [42–54], log-rank p=0,0012). 2) Patients assigned sequential BCG and electromotive mitomycin also had lower recurrence (41,9% [32,7–51,5] *vs* 57,9% [48,7–67,5]; difference between groups 16,0% [2,7–29,3], log-rank	Intention to treat All clinical assessors were adequately trained in the above procedures, and no methods were used to enhance the quality of measurements. Randomisation: - Use of a central

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		- Median (IQR): B → (67 (61–73)), A → (66 (56–73)) Follow-up (months): - Median (IQR): B → (84 (61–111)), A → (91 (65–108)) Previous intravesical treatment: - Epirubicin: B → 21 (20%), A → 25 (23,4%) - Mitomycin: B → 16 (15,2%), B → 14 (13,1%) - Interferon: B → 2 (1,9%), A → 2 (1,9%) - Gemcitabine: B → 4 (3,8%), A → 5 (4,7%) Disease characteristics: - pT1-G2 (all multifocal): B → 64 (61%), A → 65 (60,7%) -- Primary: B → 34 (32,4%), A → 33 (30,8%) -- Recurrent: B → 30 (28,6%), A → 32 (29,9%) -- Concomitant carcinoma in situ: B → 4 (3,8%), A → 4 (3,7%) - pT1-G3: B → 41 (39%),				p=0,0012) 3) Progression (9,3% [3,8–14,8] *vs* 21,9% [17,9–25,9]; difference between groups 12,6% [3,0–22,2], log-rank p=0,004) 4) Overall mortality (21,5% [13,5–29,5] *vs* 32,4% [23,4–41,4], difference between groups 10,9% [0,6–21,2], log-rank p=0,045). 5) Disease-specific mortality (5,6% [1,2–10,0] *vs* 16,2% [6,1–23,3], difference between groups 10,6% [2,5–18,7], log-rank p=0,01). 6) Side-effects were mainly localised to the bladder. → BCG-induced inflammation might increase the permeability of the bladder mucosa such that mitomycin can reach the target tissue more easily and exert its anticancer effect.	computer - stratified, blocked randomisation across 14 (ie, 24–2) strata as a result of four factors: primary versus recurrent tumours; multifocal versus unifocal tumours; grade 3 versus grade 2 tumours; and presence versus absence of carcinoma in situ. Open label (because of differences in treatment schedules and drug appearance).

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		A → 42 (39,3%) -- Primary: B → 28 (26,7%), A → 28 (26,2%) -- Recurrent: B → 13 (12,4%), A → 14 (13,1%) -- Unifocal: B → 20 (19%), A → 20 (18,7%) -- Multifocal: B → 21 (20%), A → 22 (20,6%) -- Concomitant carcinoma in situ: B → 24 (22,8%), A → 25 (23,4%).					
Di Stasi 2011	RCT, multi site (three centres in Italy) 1+	N=374 (A=126, B=124, C=124) Patients with primary urothelial non-muscle invasive bladder cancer. Number of women (%): C → 24 (21%), A → 27 (23%), B → 25 (21%). Number of men (%): C → 92 (79%), A → 92 (77%), B → 92 (79%). Median age, years (IQR): C → 66,5 (60,0–73,0), A → 67,0 (61,0–72,0), B → 67,0 (63,0–74,0).	A: Immediate post-TURBT (transurethral resection of bladder tumours) instillation of 40 mg PD mitomycin dissolved in 50 mL sterile water infused over 60 min. B: Immediate pre-TURBT instillation of 40 mg electromotive	C: TURBT alone	1) Recurrence rate 2) Disease-free interval 3) Side effects 4) Progression 5) Overall survival 6) Disease-specific survival	- 22 patients excluded from analyses because they did meet our eligibility criteria after TURBT - Median follow-up was 86 months (IQR 57–125). 1) Patients assigned to receive EMDA mitomycin before TURBT had a lower rate of recurrence (44 [38%] of 117) than those assigned to receive PD mitomycin after TURBT (70 [59%] of 119) and TURBT alone (74 [64%] of 116; log-rank p<0·0001). 2) Patients assigned to receive EMDA mitomycin before TURBT also had a higher disease-free interval (52 months, IQR 32–184) than those assigned to receive PD mitomycin after	Multi site Parallel-group Intention to treat Stratified blocked randomisation across six strata derived from two prognostic criteria: unifocal versus multifocal tumours, and grade 1 versus grade 2 versus grade 3 urothelial

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Median follow-up, months (IQR): C → 92,0 (61,0–126,0), A → 82,0 (50,0–125,0), B → 85,0 (57,0–126,0) Number with disease characteristics (%): - pTa/G1 unifocal: C →9 (8%), A → 10 (8%), B → 11 (9%) - pTa/G1 multifocal: C → 12 (10%), A → 13 (11%), B → 11 (9%) - pTa/G2 unifocal: C → 18 (16%), A → 17 (14%), B → 16 (14%) - pTa/G2 multifocal: C → 24 (21%), A → 24 (20%), B → 25 (21%) - pT1/G2 unifocal: C → 4 (3%), A → 3 (3%), B → 3 (3%) - pT1/G2 multifocal: C → 17 (15%), A → 20 (17%), B → 18 (15%) - pT1/G3 unifocal: C → 5 (4%), A → 5 (4%), B → 6 (5%) pT1/G3 multifocal: C → 27 (23%), A → 27 (23%),	drug administration (EMDA) mitomycin dissolved in 100 mL sterile water with intravesical 20 mA pulsed electric current for 30 min.			TURBT (16 months, 12–168) and TURBT alone (12 months, 12–37; log-rank p<0·0001). 3) We recorded persistent bladder symptoms after TURBT in 18 (16%) of 116 patients in the TURBT-alone group (duration 3–7 days), 37 (31%) of 119 in the PD mitomycin post-TURBT group (duration 20–30 days), and 24 (21%) of 117 in the EMDA mitomycin pre-TURBT group (duration 7–12 days); haematuria after TURBT in eight (7%) of 116 patients in the TURBT-alone group, 16 (13%) of 119 in the PD mitomycin post-TURBT group, and 11 (9%) of 117 in the EMDA mitomycin pre-TURBT group; and bladder perforation after TURBT in five (4%) of 116 patients in the TURBT-alone group, nine (8%) of 119 in the PD mitomycin post-TURBT group, and seven (6%) of 117 in the EMDA mitomycin pre-TURBT group. 4) 24 (21%) of 116 patients treated with TURBT alone, 23 (19%) of 119 treated with PD mitomycin after TURBT, and 19 (16%) of 117 treated with EMDA mitomycin before TURBT progressed to muscle-invasive disease (log-rank p=0,55). There was no disease progression in patients with	carcinoma (→ prognostic parity). Patients and physicians giving the interventions were aware of assignment, but it was masked from outcome assessors and data analysts.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		B → 27 (23%) Number in risk categories in accordance with EAU guidelines (%): - Low (all unifocal): C → 9 (8%), A → 10 (8%), B → 11 (9%) - Intermediate: C → 75 (65%), A → 77 (65%), B → 73 (62%) -- Unifocal: C → 22 (19%), A → 20 (17%), B → 19 (16%) --Multifocal: C → 53 (46%), A → 57 (48%), B → 54 (46%) -High: C → 32 (28%), A → 32 (27%), B → 33 (28%) --Unifocal: C → 5 (4%), A → 5 (4%), B → 6 (5%) -- Multifocal: C → 27 (23%), A → 27 (23%), B → 27 (23%)				low-risk disease, but 28 (12%) of 225 with intermediate-risk disease and 37 (38%) of 97 with high risk disease progressed (log-rank p=0,66). 5) No significant differences in overall survival (50 [43%] of 116 patients treated with TURBT alone, 58 [49%] of 119 treated with PD mitomycin after TURBT, and 54 [46%] of 117 treated with EMDA mitomycin before TURBT had died; log-rank p=0,66). 6) No significant differences in disease specific survival (15 [13%] of 116 treated with TURBT alone, 15 [13%] of 119 treated with PD mitomycin after TURBT, and 11 [9%] of 117 treated with EMDA mitomycin before TURBT had died of disease-specific causes; logrank p=0,62). → Intravesical EMDA mitomycin before TURBT is feasible and safe; moreover, it reduces recurrence rates and enhances the disease-free interval compared with intravesical PD mitomycin after TURBT and TURBT alone.	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Jones 2012 Systematic review	Titles and abstracts were screened by three authors independently. Data extraction was carried out by three reviewers. Bias in included studies (Cochrane Collaboration's method): - low risk of bias: 2 trials - low to intermediate risk of bias: 3 trials - intermediate risk of bias: 1 trial Nothing to publication bias reported Cochrane Review	Randomized studies From1947 to May 2011 Electronic search of MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, LILACS, SCOPUS, BNI, Biomed Central, Web of Science and BIOSIS. Handsearching of meeting proceedings, international guidelines and trial registries Selection criteria: randomised, controlled trials or quasi randomised clinical trials that included	Intravesical gemcitabine (compared with saline placebo/ intravesical mitomycin C/ intravesical bacille Calmette-Guérin (BCG)).	Rate of tumour recurrence Recurrence-free survival Progression Averse Events	Six relevant randomised trials were identified with the number of patients randomised in each trial varying from 30 to 341 (total 704). Gemcitabine vs. saline placebo One study compared a single post-operative instillation of intravesical gemcitabine with a saline placebo in 341 patients and found no significant difference in the rates of tumour recurrence (28% versus 39%, respectively) or recurrence-free survival (HR (hazard ratio) 0.95, 95% CI 0.64 to1.39, P = 0.77). The rate of progression to invasive disease was greater with gemcitabine (2.4% versus 0.8%). Gemcitabine vs. intravesical mitomycin C A further trial compared gemcitabine with intravesical mitomycin C and demonstrated that the rates of recurrence (28% versus 39%) and progression (11% versus 18%) were lower with gemcitabine but did not reach statistical significance. The global incidence of adverse events was significantly less with gemcitabine (38.8% versus 72.2%, P = 0.02). Gemcitabine vs. intravesical BCG Three trials (meta-analysis not possible due to clinical heterogeneity). In untreated patients	Bohle A European Urology 2009;56:495–503 Addeo R Journal of Clinical Oncology 2009;28:543–58 Bendary L Conference Proceedings American Urological Association. 2011; Vol. 185 (4 suppl 1):e664–5 Porena M Urologia Internationalis 2010;84:23–7 Lorenzo GD Cancer 2010; 116:1893-900 Gardmark T Urology 2005;66:527–30

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	1++	intravesical gemcitabine in at least one arm of a comparative study.			at intermediate risk of recurrence (primary Ta-T1 no CIS) one trial (Bendary, 2011) showed that gemcitabine and BCG were similar with respective recurrence rates of 25% and 30% (P = 0.92) and overall progression equal (P = 1.0). Dysuria (12.5% versus 45%, P < 0.05) and frequency (10% versus 45%, P < 0.001) were significantly less with gemcitabine. In a second trial (Porena, 2010) of high risk patients the recurrence rate was significantly greater with gemcitabine compared to BCG (53.1% and 28.1%, P = 0.04) and the time to recurrence significantly shorter with gemcitabine (25.5 versus 39.4 months, P = 0.042). Finally in a third trial (Lorenze, 2010) of high risk patients who had failed previous intravesical BCG therapy, gemcitabine was associated with significantly fewer recurrences (52.5% versus 87.5%, P = 0.002) and a longer time to recurrence (3.9 versus 3.1 months, P = 0.9) compared to BCG. Progression rates were similar in both groups (33% versus 37.5%, P = 0.12) with no significant differences in grade 2 or 3 toxicities. Greater response rates (marker lesion study) when intravesical gemcitabine (2 g) was given as three bi-weekly doses (36%) or six weekly doses (40%) compared to a single dose (9%). → A single dose immediately following	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					surgery is ineffective based on one study. → Gemcitabine may be more active than mitomycin C with a lower toxicity profile. → Compared to intravesical BCG therapy, gemcitabine had similar effects in intermediate risk patients, less effective in high risk patient and superior in BCG refractory patients. → However, each randomised trial identified represents a different clinical setting in non-muscle invasive bladder cancer (NMIBC) and therefore the evidence base is limited. → Consequently these data should be interpreted with caution until further corroborative evidence becomes available. → The aim of intravesical therapy in NMIBC is to prevent tumour recurrence and progression and to avoid the morbidity associated with cystectomy. → Intravesical gemcitabine is a promising drug that may add to the urologist's options in achieving this goal.	
Lammers 2011 Systematic review	Limited number of randomized trials. Two reviewers (RL and BI) independently performed database	Publication range between 1990 and 2011 Electronic search of the Medline, Embase, Cochrane Library, CancerLit, and	Chemohyperthermia (C-HT) (Deskription: Microwave-induced hyperthermia (HT) with intravesical chemotherapy typically mitomycin C	1) Time to recurrence 2) Time to progression 3) Bladder preservation rate	- A total of 22 studies met inclusion criteria and underwent data extraction. - When possible, data were combined using random effects meta-analytic techniques. 1) and 2) Recurrence was seen 59% less after C-HT than after MMC alone. Due to short follow-up, no conclusions can be drawn about time to recurrence and progression.	Colombo R J Clin Oncol 2003;21:4270–6. Nativ O J Urol 2009;182:1313–7. Halachmi S Urol Oncol. In press.

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	searches, assessed candidate manuscripts for inclusion criteria, and extracted primary data. Random effects meta-analysis. 15 original articles were eligible for analysis. Nothing to publication bias reported. No methodological quality assessment stated. 1-	ClinicalTrials.gov. Relevant conference abstracts and urology journals were also searched manually. No searching of study design.	(MMC))/Mitomycin C (MMC).	4) Adverse event (AE) rate	3) The overall bladder preservation rate after C-HT was 87.6%. This rate appeared higher than after MMC alone, but valid comparison studies were lacking. 4) AEs were higher with C-HT than with MMC alone, but this difference was not statistically significant. → Published data suggest a 59% relative reduction in NMIBC recurrence when C-HT is compared with MMC alone. → C-HT also appears to improve bladder preservation rate. → However, due to a limited number of randomized trials and to heterogeneity in study design, definitive conclusions cannot be drawn. → In the future, C-HT may become standard therapy for high-risk patients with recurrent tumors, for patients who are unsuitable for radical cystectomy, and in cases for which bacillus Calmette-Guérin treatment is contraindicated.	DOI:10.1016/j.urolonc.2009.02.012. Witjes JA World J Urol 2009;27:319-24. Moskovitz B Ann Oncol 2005;16:585-9. Van der Heijden AG Eur Urol 2004;46:65-72. Gofrit ON Urology 2004;63:466-71. Lamm DL, J Clin Oncol 2003;21:4259-60. Colombo R Eur Urol 2001;39:95-100. Colombo R J Urol 1998;159:783-7. Paroni R Clin Chem 1997;43:615-8. Colombo R J Urol 1996;155:1227-32.

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
						Colombo R J Urol 1995;153:959-63. Uchibayashi T Br J Urol 1993;72:65-7.

5.10. AG 4 Schlüsselfrage 10 (Zystektomie beim NMIBC)

„Wann ist die Zystektomie beim nicht-muskelinvasiven Blasenkarzinom indiziert?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Denzinger 2007 Germany	Retrospective cohort study 2-	N=105 patientes with recurrent pT1G3 or muscle-invasive bladder cancer after an initial bladder sparing approach	Early cystectomy n=54	Deferred cystectomy n=51	- Cancer specific survial rate - Disease progression - Prognostic factors	Upstaging in the deferred cystectomy specimen was found in 30% (n=32). 5-year cancer-specific survival rate in early vs. deferred cystectomy: 83% vs. 67% (p<0,01). 10-year cancer-specific survival rate in early vs. deferred cystectomy: 78% vs. 51% (p<0,01). Prognostic factors for cancer-specific	Risk factors considered (age, gender, multiple tumors, tumor size, CIS) were distributed evenly between the groups. Small sample size.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						survival (univariate analysis): - CIS: HR 3,05; 95% CI 1,04-15,24; p<0,001. CIS is related to a lower cancer-specific survival rate in deferred cystectomy only. - Deferred cystectomy: HR 5,11; 95% CI 2.14-18.66; p<0,01. Prognostic factors for cancer-specific survival (multivariate analysis): - Deferred cystectomy: HR 5,13: 95% CI 1,62-17.08; p<0,01. - CIS: HR 2,55; 95% CI 1,21-12,89; p=0,02). - Not significant: tumor size, multifocality, gender. Disease progression in early vs. deferred cystectomy: 8% vs. 24%. No risk factors are related to upstaging. No risk factors predict cancer-related death. Authors conclusion: Early as opposed to deferred cystectomy seems to prolong the cancer-specific survival rate in high-risk pT1G3 bladder cancer. Patients with CIS should be considered for early cystectomy owing to reduced cancer-	Early cystectomy were offered to all patients, deferred cystectomy was opted by patients. Single center study (Regensburg).

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						specific survival in case of deferred cystectomy.	
Fritsche 2009 Europe, USA, Canada	Retrospective case series 3	N=1136 patients with pT1G3 bladder cancer treated with radical cystectomy without neoadjuvant chemotherapy.	Radical cystectomy in patients with T1G3 bladder cancer.		Patients' characteristics and outcomes were evaluated.	Median follow-up: 48 month. Disease recurrence: - 22,5% within 2 years. - 7,3% died due to metastatic disease. - 8,0% overall mortality. Upstaging of patients to muscle-invasive disease: 49,7%. Downstaging of patients lower than T1G3: 21,4%. Predictors of upstaging: - Female gender: p=0,02. - Older age (>60 years): p<0,001. Predictors of not upstaging: - Age <60 years: p=0,03. Predictors of disease recurrence: Univariate analysis - Female gender: p=0,09 - Older age: p=0,01 - Pathologic stage: p<0,001 - Stage discrepancy: p<0,001 - Tumor grade: p<0,001 - Positive STSM status: p<0,001 - LVI: p<0,001 - Concomitant CIS: p=0,77 - Number LN removed: P=0,29 - Number positive LN: p<0,001	Short follow-up period.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- LN metastasis: p<0,001 Multivariate analysis - Older age: p=0,12 - Pathologic stage: p<0,001 - Tumor grade: p=0,56 - Positive STSM status: p=0,10 - Number positive LN: p<0,001 - LN metastasis: p<0,001 Predictors of cancer specific mortality: Univariate analysis - Female gender: p=0,025 - Older age: p<0,001 - Pathologic stage: p<0,001 - Tumor grade: p<0,001 - Positive STSM status: p<0,001 - LVI: p<0,001 - Concomitant CIS: p=0,55 - Number LN removed: p=0,18 - Number positive LN: p<0,001 - LN metastasis: p<0,001 Multivariate analysis - Female gender: p=0,23 - Older age: p<0,001 - Pathologic stage: p<0,001 - Tumor grade: p=0,36 - Positive STSM status: p=0,02 - LVI: p<0,001 - Number positive LN: p=0,04 - LN metastasis: p<0,001	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Predictors of overall mortality: Univariate analysis - Female gender: p=0,045 - Older age: p<0,001 - Pathologic stage: p<0,001 - Stage discrepancy: p<0,001 - Positive STSM status: p<0,001 - LVI: p<0,001 - Concomitant CIS: p=0,852 - Number LN removed: p=0,022 - Number positive LN: p<0,001 - LN metastasis: p<0,001 Multivariate analysis - Female gender: p=0,310 - Older age: p<0,001 - Pathologic stage: p<0,001 - Positive STSM status: p=0,234 - LVI: p=0,001 - Number positive LN: p=0,001 - LN metastasis: p<0,001 Authors conclusion: Approximately half of the patients treated with radical cystectomy without neoadjuvant chemotherapy for clinical T1G3 urothelial bladder cancer are upstaged to muscle-invasive UBC. These rates support the inadequacy of clinical decision making based on current treatment paradigms and staging	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						tools. Therefore, identification of patients with clinical T1G3 disease at high risk of disease progression is of the outmost importance, as these patients are likely to benefit from early RC.	
Palou 2011 Spain	Single-center case series 3	N=146 patients with primary T1G3 NMIBC.	TUR-B + biopsies than induction course of BCG without maintenance therapy.		Endpoints: - time to recurrence - time to progression - cancer-specific mortality	Median follow-up: 8,7 years. - Recurrence: n=65 (44,5%). - Progression: n=25% (17,1%). - Cancer-specific mortality: n=18 (12,3%). **Prognostic parameters for recurrence:** Univariate analysis - Female gender: HR 2,30; 95% CI 1,25-4,22; p=0,008. - CIS in prostatic urethra: HR 2,40; 95% CI 1,16-4,95; p=0,02. Multivariate analysis - CIS in prostatic urethra or female gender: HR 2,53; 95% CI 1,50-4,25; p=0,0003. **Prognostic parameters for progression:** Univariate analysis - Older age: HR 1,33; 95% CI 0,96-1,85; p=0,09.	Long period of follow-up.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- Female gender: HR 2,41; 95% CI 0,96-6,04; p=0,06 - CIS in prostatic urethra: HR 4,35; 95% CI 1,65-11,50; p=0,003. Multivariate analysis - CIS in prostatic urethra or female gender: HR 3,59; 95% CI 1,64-7,88; p=0,001. **Prognostic parameters for cancer-specific mortality:** Univariate analysis - CIS in prostatic urethra or female gender: HR 3,53; 95% CI 1,40-8,89; p=0,004. Multivariate analysis - CIS in prostatic urethra or female gender: HR 3,53; 95% CI 1,40-8,89; p=0,004. Authors conclusion: In primary T1G3 bladder tumours treated with induction BCG, female gender or having CIS in the prostatic urethra were the only prognostic factors for time to recurrence, progression, and disease-related mortality. It is very important to	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						perform a biopsy of the prostatic urethra in patients with primary high-grade NMIBC as a first step to obtain this prognostic information.	
Badalato 2012 USA	Retrospective cohort study 2-	N=349 patients with high grade cT1 bladder cancer	Immediate radical cystectomy (surgery within 90 day of diagnosis, no TURBT, no intravesical therapy) n=113	Bladder-sparing therapy: TURBT + intravesical therapy n=236	Endpoints: - Cancer-specific survival - Patient selection for therapy	Median follow-up time: 43 months in cystectomy group, 36 months in conservative group. Patient selection: 1990-1999: n=90 patients with high grade cT1; n=54 (60%) underwent cystectomy 2000-2010: n=259 patients with high grade cT1; n=59 (23%) underwent cystectomy. Cancer specific survival between decades 1990-1999 vs. 2000-2010: 77% vs. 80% (p=0,566). Risk factors for recurrence/progression for the decades (only significant factors ar e mentioned here): 1990-1990: precence of muscularis propria: p=0,001. 2000-2010: lymphovascular invasion: p<0,001. Authors conclusion: Conservative management strategies are viable treatment option within a well selected subset of patients with	Loss of follow-up rate of 34% (1990-1999) and 18% (2000-2010) (p=0,003). The sudy reports a management shift from IRC to conservative approaches due to better risk assessments. As patient populations für IRC and conservative approaches differ by time, direct comparisons between the groups is not appropriate (because of selection bias).

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						high grade cT1.	

6. AG 5: Muskelinvasives Blasenkarzinom

6.1. AG 5 Schlüsselfrage 1- keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

6.2. AG 5 Schlüsselfrage 2 - keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

6.3. AG 5 Schlüsselfrage 3 (Perioperatives Management bei Zystektomie)

„Welches perioperative Management inkl. Fasttrack-Regime soll bei Zystektomiepatienten durchgeführt werden?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Aslan 2013 Turkey	Prospective randomised multicenter study 1+	N=118 patients with radical cystectomy.	Limited bowel preparation only the day before surgery: - liberal use of liquid diet - sodium phosphate laxative - enemas	Standard 3-day bowel preparation: - diet restriction - oral antibiotics - oral laxatives - saline enemas	Investigate outcomes and complication rates of urinary diversion using mechanical bowel preparation. Endpoints: - anastomotic leakage - wound infection - wound dehiscence - intraperitoneal	N=112 patients available for assessment. No statistical difference in any of the variables assessed: - wound infection (limited: 3,5% vs. standard: 3,5%; P=0,54) - wound dehiscence (limited: 12,5% vs. standard: 14,2%; P=0,78) - ileus (limited: 8,9% vs. standard: 10,7%; P=0,75)	Sufficient randomisation. 9 centers. Small sample size. Power calculation not stated, results are no

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			n=59	n=59	abscess - peritonitis - sepsis - ileus - reoperation - mortality - bowel function recovery - time to first bowel movement - time to first oral intake - time to regular oral intake - length of hospital stay	- clinical anastomotic leaks with pritonitis (limited: 1 patient vs. standard: 1 patient; P=1) - mortality (limited: 1 patient vs. standard: 2 patient; P=0,55) - sepsis (limited: 0 patient vs. standard: 1 patient; P=0,31) - intraabdominal abscess - recover of bowel function - length of hospital stay (12 vs. 13 days; P=0,97) Limited bowel preparation arm: - lower complication rate - favorable of bowel function - favorable of time to discharge - earlier first bowel movement Autors conclusion: Regarding all endpoints, including septic and nonseptic complications, current clinical research offers no evidence to show any advantage of 3-day bowel preparation over limited bowel preparation.	proof of noninferiority or equivalence but indicate no dramatic negative consequences of the limited bowel preparation.
Adamakis 2011 Greece	Propective, randomised single center study 1-	N=43 patients with radical cystectomy.	Removal of nasogastric tube (NGT) 12 h after operation. n=22	Removal of NGT after the first flatus. n=21	Examination of beneficial effect of early nasogastric tube removal. Endpoints: - appearance of ileus	No significant differences in: - complications (P=0,69) - ileus of intervention vs. control group: 2 patients (9,09%) vs. 3 patients (14,3%). - time to hospital discharge (P=0,686).	No information given of randomisation. Small sample size.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					- patient ambulation - time to regular diet - time to hospital discharge - patient discomfort due to NGT	- 1st defecation (P=0,14). - 1st flatus (P=0,955) - 1st bowel sound (P=0,898). 100% of the patients wanted the NGT removed first of all drains. Authors conclusion: This is the first randomized, prospective study, to our knowledge, to assess early NGT removal after radical cystectomy. We advocate early removal, independently of the selected type of urinary diversion, since it is not correlated with ileus, and is advantageous in terms of patient comfort and earlier ambulation.	The only parameter which showed a statistically significant difference was the mean operative time (p = 0.026).

6.4. AG 5 Schlüsselfrage 4 (Lymphadenektomie bei Zystektomie)

„Welchen Einfluss hat die Lymphadenektomie im Rahmen der radikalen Zystektomie auf das progressionsfreie Überleben und das Gesamtüberleben?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Abdollah	Retrospective	N=11.183 patients with	Pelvic lymph	No pelvic	Endpoints:	Overall lymph node dissection omitted	Data of 17

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
2011 Canada	cohort study 2-	radical cystectomy.	node dissection (PLND) with radical cystectomy in elderly patients (n=8.394)	lymph node dissection (n=2.729)	- cancer specific mortality - overall mortality Subgroup analysed: Patients > 80 years vs. < 80 Years.	in 25% of patients. Lymph node dissection omitted in patients > 80 years: 30,8%. Lymph node dissection omitted in patients < 80 years: 24,2%. Patients with PLND n=8394: Lymph node count more than 10 in patients < 80 years vs. > 80 years: 45,0% vs. 35,0% (p<0,001). Lymph node count more than 10 vs. less than 10 in patients > 80 years: 22,7% vs. 26,5% (p=0,001). Lymph node count more than 10 vs. less than 10 in patients < 80 years: 28,0% vs. 24,6% (p=0,02). Caner specific mortality: - 5-year cancer specific mortality for pN0 vs. pNx vs. pN1-3 in all patients: 71,0% vs. 57,9% vs. 31,6% (p<0,001). - 5-year cancer specific mortality for pN0 vs. pNx vs. pN1-3 in patients > 80 years: 60,2% vs. 46,1% vs. 18,9% (p<0,001). - 5-year cancer specific mortality for pN0 vs. pNx vs. pN1-3 in patients < 80 years: 72,0% vs. 59,9% vs. 33,1%	Surveillance, Epidemiology and End Results registries = SEER database. High risk of bias due to selection bias: groups significantly differ according to age, gender, tumor grade, tumor stage and surgery year

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						(p<0,001). - 5-year cancer specific mortality of PLND vs. no PLND in all patients: 61,3% vs. 57,9% (p<0,01). - 5-year cancer specific mortality of PLND vs. no PLND in patients > 80 years: 50,0% vs. 46,1% (p=0,005). - 5-year cancer specific mortality of PLND vs. no PLND in patients < 80 years: 62,5% vs. 59,9% (p=0,01). Overall mortality: - 5-year overall mortality for pN0 vs. pNx vs. pN1-3 in all patients: 55,6% vs. 41,2% vs. 21,3% (p<0,001). - 5-year overall mortality for pN0 vs. pNx vs. pN1-3 in patients > 80 years: 34,2% vs. 24,7% vs. 10,4% (p<0,001). - 5-year overall mortality for pN0 vs. pNx vs. pN1-3 in patients < 80 years: 57,9% vs. 43,9% vs. 22,6% (p<0,001). - 5-year overall mortality of PLND vs. no PLND in all patients: 46,8% vs. 41,2% (p<0,01). - 5-year overall mortality of PLND vs. no PLND in patients > 80 years: 28,3% vs. 24,7% (p=0,01). - 5-year overall mortality of PLND vs. no PLND in patients < 80 years: 48,8% vs.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						43,9% (p<0,001). Multivariate analysis: - PLND associated with 1,3-fold higher cancer specific rate for patients > 80 years (p<0,001) and < 80 years (p<0,001). - PLND associated with 1,2-fold higher overall mortalitiy rate for patients > 80 years (p<0,005) and 1,3-fold higher for patients < 80 years (p<0,005).	
Abdollah 2012 Canada	Retrospective cohort study 2-	N=11183 patients with radical cystectomy.	Pelvic lymph node dissection (PLND) with radical cystectomy in elderly patients.	No pelvic lymph node dissection.	Assessment of stage-specific PLND. Endpoints: - cancer specific mortality - overall mortality	Overall lymph node dissection omitted in 25% of patients. Omitted PLND in patients with pTa/is vs. pT1 vs. pT2 vs. pT3 vs. pT4: 50,3% vs. 34,9% vs. 27,2% vs. 16,1% vs. 23,4% (p<0,001). Patients with PLND n=8394: Caner specific mortality: - 10-year cancer specific mortality of patients with pTa/is disease with PLND vs. no PLND: 80,0% vs. 71,9% (p=0,02). - 10-year cancer specific mortality of patients with pT1 disease with PLND vs. no PLND: 81,7% vs. 70,0% (p<0,001). - 10-year cancer specific mortality of patients with pT2 disease with PLND vs. no PLND: 71,5% vs. 56,1% (p=0,001). - 10-year cancer specific mortality of	Data of 17 Surveillance, Epidemiology and End Results registries = SEER database. Same patients in the study above. High risk of bias due to selection bias: groups significantly differ according to age, gender, tumor grade, tumor stage and surgery year.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						patients with pT3 disease with PLND vs. no PLND: 43,7% 38,8% (p=0,006). - 10-year cancer specific mortality of patients with pT4 disease with PLND vs. no PLND: 35,1% vs. 32,0% (p=0,1). Overall mortality: - 10-year overall mortality of patients with pTa/is disease with PLND vs. no PLND: 53,4% vs. 48,1% (p=0,07). - 10-year overall mortality of patients with pT1 disease with PLND vs. no PLND: 57,7% vs. 41,4% (p=0,001). - 10-year overall mortality of patients with pT2 disease with PLND vs. no PLND: 4,6% vs. 29,4% (p<0,001). - 10-year overall mortality of patients with pT3 disease with PLND vs. no PLND: 23,4% 18,5% (p=0,001). - 10-year overall mortality of patients with pT4 disease with PLND vs. no PLND: 17,5% vs. 11,8% (p<0,001). Multivariate analysis: - PLND omission was associated with a higher cancer specific mortality in patients with pTa/is, pT1 and pT2 disease (p<0,01), but has no predictor status for patients with pT3 or pT4 disease (p>0,05).	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- Omitted PLND predicted for higher overall mortality across all tumor stages (all p<0,03). - No PLND vs. PLND higher hazard ratio for cancer specific mortality (HR: 1,3; p<0,001) and higher hazard ratio for ovarall mortality (HR: 1,3; p<0,001). Autors conclusion: PLND was more frequently omitted in patients with organ-confined disease and showed more beneficial effect on cancer control outcomes in these patients than in patients with pT3 or pT4 disease.	
Gray 2013 USA	Retrospective case series 3	N=16953 patients with radical cystectomy. No distant metastases.	T-staging of lymph nodes at cystectomy.		Examination of the accuracy of clinical staging vs. pathologic stage and its effects on outcome in bladder cancer patients. Endpoints: - overall survival	T-staging at cystectomy: - 37,9% of patients were upstaged. - 6,5% of patients were downstaged. Clinically node negative at cystectomy: 93,3% → Upstaged to node-positiv: 19,3%. Node-positiv at cystectomy → 11,7% pathologically node-negativ. Survival analysis n=7270 patients: Overall survival: - 5-year overall survival of pT0 vs. pT1 vs. pT2 vs. pT3 vs. pT4: 70,8% vs. 75,8% vs. 63,7% vs. 41,5% vs. 24,7%.	National Cancer Data Base: sponsored by the American College of Surgeons and the American Cancer Society. Hospital-based registry. Analysis shows a low accuracy of clinical staging.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- 5-year survival rate for 0 lymph nodes examined vs. 1-9 lymph nodes examined vs. > 10 lmyph nodes examined: 45,5% vs. 47,3% vs. 55,4%. Multivariate analysis: - Upstaging was associated with increased 5-year mortality (hasard ratio: 1,8, p<0,001). - Downstaging was not associated with survival (hazard ratio: 0,88; p=0,0160). - More extensive lymphadenectomy associated with decreased 5-year mortality (hazard ratio: 0,76, p<0,001) (for > 10 lymph nodes examined).	
Herr 2004 USA	Retrospective case series 3	N=268 patients with cystectomy.	Cystectomy. with or without neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) and cystectomy. Expost analysis of an RCT-population		Endpoints: - post cystectomy survival - local recurrence	24 (9%) patients with node dissection 98 (37%) patients with limited node sampling 146 (54%) patients with standard bilateral PLND. - 5-year post cystectomy survival: 54% (for no node dissection: 33%, for limited dissection 46%, for standard dissection: 60%; for patients >10 nodes removed 61%, for patients <10 nodes removed 44% (p=0,0007). - Local recurrence: 15%. Multivariate model adjusted for	Cystectomies were performed by 106 surgeons in 109 institutions.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- MVAC: p=0,97 - age: p=0,03 - pathologic stage: p=0,0002 - node status: p=0,04 showed longer post cystectomy survival for - negative margins vs. positive (hazard ratio 0,37; p=0,0007) - >10 nodes removed vs. <10 nodes (hazard ratio 0,51, p=0,0001). No difference between treatment arms (p=0,21). Multivariate model for predictive factors for local recurrence adjusted for - MVAC: p=0,16 - pathologic stage: p=0,02 - node status: p=0,37 were - positive margins vs. negative (odds ratio: 11,2; p=0,0001) - <10 nodes removed vs. >10 nodes (odds ratio 5,1; p=0,002). Association between surgical factors: - Surgical margins were associated with fewer nodes removed: p=0,1. - 17 (68%) of the 25 patients with positive margins had less than 10 nodes removed.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Autors conclusion: Surgical factors influence bladder cancer outcomes after cystectomy, after adjustment for pathologic factors and neoadjuvant chemotherapy usage.	
Karadeniz 2011 Turkey	Single center etrospective cohort study 2-	N=74 patients with cystectomy. Only pT2 and pT3 included.	Cystectomy with removed lymph nodes > 13 (= group 1). n=36 13 was the median number of lymph nodes.	Cystectomy with removed lymph nodes < 13 (= group 2). n=38	5-year overall survival 5-year disease specific survival	Mean lymph nodes dissected in group 1 vs. group 2: 6,17 (range 1 to 12) vs. 21,6 (range 13 vs. 41). 5-year overall survival rate of group 1 vs. group 2: 24,5% vs. 60,5% (p=0,002). 5-year disease specific survival rate of group 1 vs. group 2: 43,7% vs. 74,4% (p=0,049). Autors conclusion: Although exact guidelines are not described, it seems that dissection of high number of LNs during radical cystectomy is crucial.	Small number of patients Interestingly, although the number of retrieved LNs was significantly different in two groups, the number of node-positive patients was not different. Patients with pT0, pT1, or pT4 were excluded (they might distort survival outcomes).
Leissner 2004	Multicenter prospective case series 3	N=290 patients with cystectomy.	Cystectomy with extended lymphadenectomies and microscopically		Conducting a comprehensive prospective analysis of lymph node metastases to obtain precise	Complete lymphadenectomy was accomplished in 211 of 290 patients. ean number of lymph nodes removed: 41,3.	No longer followup data for adverse events.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			examination of lymph nodes from 12 well-defined anatomical locations.		knowledge about the pattern of lymphatic tumor spread.	Nodal metastases present in: 27,9% of patients. A well-defined sentinel lymph node was not identified. During the immediate postoperative followup period none of the participating centers observed any significant adverse effects related to extended radical lymphadenectomy. Autors conclusion: We strongly recommend extended radical lymphadenectomy to all patients undergoing radical cystectomy for bladder cancer to remove all metastatic tumor deposits completely.	
May 2011 Germany	Retrospective multi center case series 3	N=1291 patients who underwent open RC due to LN-negative transitional-cell carcinoma of the urinary bladder between 1989 and 2008.	Radical cystectomy with extended PLND The extent of PLND was determined by the treating surgeon on the basis of clinical presentation and personal experience.		On the basis of multivariate Cox regression analyses the authors sought to determine a threshold number of removed LNs that exerted an independent influence on cancer-specific survival (CSS). Endpoint:	Follow-up: 45 months (mean 54 months, mean 2-240 months). 1052 had a lymph node count > 8. Univeriate analysis: Predictive for cancer-specific survival: - age - female sex - advanced pathologic stage - high tumor grade - no CIS	Multi-institutional database. Patients with invalid data regarding the extended PLND (n = 548) were excluded from analysis.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					- cancer-specific survival	- adjuvant chemotherapy - lymphovascular invasion Increased number of removed lymph nodes associated with improved cancer-specific survival. Each additional removed lymph node: hazard ratio: 0,97 (95% CI 0,95-0,99; p=0,008). Multivariate analysis: Predictive for cancer-specific survival: - age - sex - pathologic stage - lymphovascular invasion ! continuous number of LNs removed was not an independent significant predictor of CSS! Patients with removal of at least 16 LNs showed a decreased probability of cancer-specific mortality compared to patients with removal of ≤16 LNs (hazard ratio 0.74, 95% CI 0.56–0.99, P=0.046 5-year cancer specific survival of patients removed < 16 lymph nodes vs. > 16 lymph nodes: 72% vs. 83% (P=0,01) (hazard ratio: 0,74; 95% CI 0,56-0,99; p=0,046).	Comorbidities of patients have not been assessed therefore it is unknown whether patients with marked comorbidities underwent more limited PLND than healthier patients. Patients removed < 16 lymph nodes differ significantly in terms of year of surgery to patents with > 16 lymph nodes.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						5-year cancer-specific survival of all patients: 75%. 10-year cancer-specific survival of all patients: 67%. 5-year overall survival rate: 60%. 10-year overall survival rate: 45%. Autors conclusion: In patients undergoing radical cystectomy, removal of a higher LN count is associated wth an improved oncological outcome. [...] Several confounder for the association were mentioned by the others (e.g. example, in patients with marked comorbidities, limited PLND may be performed more often,	
Nishiyama 2003 Japan	Retrospective case series 3	N=1013 patients with cystectomy for invasive bladder cancer between January 1990 and December 2000	Radical cystectomy		Outcome of invasive bladder cancer treatment with radical cystectomy. Endpoint: - overall survival	Patients with lymph node metastases at cystectomy: 162 (16,0%). 5-year overall survival: 68%. 5-year overall survival with lymph node dissection vs. no lymph node dissection: 69,8% vs. 54,1% (p=0,001). Multivariate analysis: Predictive factors for survival: - gender - clinical stage	Data from 32 hospitals. Differences in survival according to LN dissection may due to selection bias. High risk of bias for this finding.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- pathological stage - lymph node involvment - lymph node dissection Autors conclusion: These clinical results demonstrate that radical cystectomy with lymph node dissection results in good survival for invasive bladder cancer, providing standard data with which other forms of therapy can be compared.	
Power 2012 Canada	Retrospective multicenter cohort study 2-	N=1180 patients from 1993 to 2008 with >pT3N0 or pT0-4N+ bladder cancer who underwent RC ± standard from 8 Canadian centres.	Radical cystectomy with standard lymph node dissection. n=643	Radical cystectomy with extended lymph node dissection. n=402 Extended LND (eLND) included a farther dissection proximally to include nodal tissue to the bifurcation of the aorta and laterally to the genitofemoral	Endpoints: - overall survival - disease-specific survival - recurrence-free survival	Standard vs. extended vs. no lymph node dissection: 55% (n=643) vs. 34% (402) vs. 11%. Median follow-up: 2,1 years Overall 30-day mortality: 3,2%. No significant differences in overall survival, disease-specific survival, recurrence-free survival between groups with standard lymph node dissection and extended lymph node dissection. **Overall survival:** 2-year overall survival for all patients: 60%. 5-year overall survival for all patients: 43%. Overall survival for nodal status:	Data from 8 Canadian Centers. Short follow-up. The extent and performance of a lymph node dissection (LND) was physician- and institution-dependent

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
				nerve.		2-year overall survival for high-risk node-negative disease: 67%. 5-year overall survival for high-risk node-negative disease: 52%. 2-year overall survival for node-positive disease:52% 5-year overall survival for node-positive disease: 32%. **Disease-specific survival:** 2-year disease-specific survival for all patients: 67%. 5-year disease-specific survival for all patients: 53%. Disease-specific survival for nodal status: 2-year disease-specific survival for high-risk node-negative disease: 73%. 5-year disease-specific survival for high-risk node-negative disease: 61%. 2-year disease-specific survival for node-positive disease:58% 5-year disease-specific survival for node-positive disease: 40%. Disease-specific survival for chemotherapy: 2-year disease-specific survival with adjuvant chemotherapy: 72%.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						5-year disease-specific survival with adjuvant chemotherapy: 57%. 2-year disease-specific survival without adjuvant chemotherapy: 64%. 5-year disease-specific survival with out adjuvant chemotherapy: 51%. **Recurrence-free survival:** 2-year recurrence-free survival for all patients: 50%. 5-year recurrence-free survival for all patients: 36%. Recurrence-free survival for nodal status: 2-year recurrence-free survival for high-risk node-negativedisease: 56%. 5-year recurrence-free survival for high-risk node-negativedisease: 43%. 2-year recurrence-free survival for node-positive disease:39% 5-year recurrence-free survival for node-positive disease: 25%. **Kaplan-Meier analysis:** Overall survival & disease-specific survival & recurrence-free survival for patients with pN0 vs. pN1: p<0,001 &	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						p<0,001 & p<0,001. Overall survival & disease-specific suvival & recurrence-free survival for adjuvant chemotherapy vs. no adjuvant chemotherapy: p=0,0039 & p=0,16 & p=0,34. Overall survival & disease-specific survival & recurrence-free survival for patients with pN0 (standard or extended LND) vs. pNX (no LND): p=0,0035 & p=0,0241 & 0,0383. Autors conclusion: This series suggests that bladder cancer outcomes in advanced disease have improved in the modern era. The need for improved staging investigations, use of neoadjuvant chemotherapy and performance of complete LND is emphasized.	
Rink 2012	Retrospective multicenter case series 3	N=4188 patients with cystectomy. N=3088 patients for analysis.	Radical cystectomy with pelvic lymphadenectomy without neoadjuvant chemotherapy.		Endpoints: - disease recurrence - cancer-specific mortality To determine whether the number of lymph nodes (LNs) examined is associated with outcomes in patients	N=3088 patients without lymph node metastasis. Median follow-up: 47 months. - n=764 (24,7%) with recurrence - n=1255 (40,6%) died - n=597 (19,3%) died from bladder cancer. Median nodal yield: 18 (range: 1-123).	Data from 12 international centers. High risk of bias due to selection bias. The extent of LN dissection was at

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
					without nodal metastasis after radical cystectomy (RC).	Patients with lymph node yield >9: 2591 (84%). Patients with lymph node yield >20: 1445 (47%). Median 3-, 5- and 10-year recurrence-free survival estimates were: 74%, 70% and 66%. Median 3-, 5- and 10-year cancer-specific survival estimates were: 80%, 76% and 69%. Univariate analysis: a) for disease recurrence: - all patients: all nodal yield stratifications associated with reduced recurrence (all p<0,049). - only muscle-invasive disease: none of the nodal yield stratifications associated with outcome. - only >9 lymph nodes removed: only those with >20 lymph nodes removed had significantly reduced recurrence (p=0,042). b) for cancer-specific mortality: - all patients: all nodal yield stratifications associated with reduced recurrence (all p<0,049). - only muscle-invasive disease: none of the nodal yield stratifications associated with outcome.	the surgeon's discretion, and extended LN dissection was not routinely performed.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- only >9 lymph nodes removed: only those with >20 lymph nodes removed had significantly reduced recurrence (p=0,046). Multivariate analysis: - Independet predictors for disease recurrence and cancer-specific mortality: - pathologic stage (p<0,001). - grade (p<0,001). - soft tissue margin (p<0,011). - lymphvascular invasion (p<0,001). - Higher lymph node yield associated with decreased risk of disease recurrence: hazard ratio 0,853; p=0,048; cutoff >20 lymph nodes: hazard ratio 0,851; p=0,032). None was associated with cancer-specific mortality. Autors conclusion: In this large multicenter cohort of patients with node-negative UCB, higher nodal yield improved recurrence-free survival when all patients were analyzed. Patients with a high LN yield (>20 LN removed or 3rd tertile) had the largest benefit. The lack of prognostic significance of LN yield in patients with muscle-invasive UCB or those stratified	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						by 9 LNs removed suggests that this effect is weak. Further prospective studies are needed to help identify preoperatively the optimal template for each patient.	
Simone 2013 Italy	Retrospective case series 3	N=933 patients with cystectomy.	Cystectomy with extended lymph node dissection.	Cystectomy with standard lymph node dissection.	Evaluate the impact of an extend vs. a standard pelvic lymph node dissection. Endpoints: - disease-free survival - cancer-specific survival	Median number nodes removed overall: n=25. Median number nodes removed overall in extended group: n=29. Median number nodes removed overall in standard group: n=18. **Univariate analysis:** - disease-free survival with extended LND: hazard ratio 1,96; p<0,001. - cancer-specific survival with extended LND: hazard ratio 1,76; p<0,001. - 1-year disease-free survival of extended vs. standard LND: 86,0% vs. 71,2%. - 3-year disease-free survival of extended vs. standard LND: 68,6% vs. 49,4%. - 5-year disease-free survival of extended vs. standard LND: 63,1% vs. 42,6%. (log-rank p<0,001) - 1-year cancer-specific survival of extended vs. standard LND: 93,5% vs. 87,7%.	Data from 2 prospectively-maintained institutional databases.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- 3-year cancer-specific survival of extended vs. standard LND: 78,5% vs. 62,0%. - 5-year cancer-specific survival of extended vs. standard LND: 68,8% vs. 50,9%. (log-rank p<0,001) **Multivariate analysis:** - disease-free survival with extended lymph node dissection: hazard ratio 1,95; p<0,001. - cancer-specific survival with extended lymph node dissection: hazard ratio 1,80; p<0,001. Kaplan-Mayer analysis: Benefit for extended LND significant (p<0,05) over all pT stages, exept pT2, and over all pN stages for disease-free survival and cancer-specific survival. (log-rank p=0,437 for disease-free survival, p=0,229 for cancer specific survival). Autors conclusion: The staging accuracy and the survival benefit provided by extended pelvic lymph node dissection suggests the adoption of this template as the standard template for patients with muscle-invasive urothelial carcinoma of	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						the bladder undergoing radical cystectomy.	
Yafi 2010 Canada	Retrospective case series 3	N=2287 patients with radical cystectomy	Radical cystectomy.		Endpoints: - mortality rates - recurrence-free survival - disease-specific survival - overall survival	Mean follow-up: 35 months. Patients with neoadjuvant chemotherapy: 1,3%. Patients with adjuvant chemotherapy: 19,4%. 30-, 60- and 90-day postoperative mortality rates were 1,3%, 2,6% and 3,2%. Entire population: 5-year overall-survival: 57%. 5-year recurrence-free survival: 48%. 5-year disease-specific survival: 67%. Patients with nodal metastasis (pTxN+): 5-year overall-survival: 32%. 5-year disease-free survival: 40%. Patients with organ-confined node negative disease (<pT2N0): 5-year overall-survival: 75%. 5-year disease-free survival:85%. Patients with non-organ-confined node negative disease (>pT2N0): 5-year overall-survival: 53%. 5-year disease-free survival:62%. Independent prognostic markers for	Data collected from 8 Canadian academic centers. Large number of patients. High risk of bias due to selection bias. Only 9% without PLND.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						overall survival: - younger age - no smoking - lower pathological stage - negative surgical margins - adjuvant chemotherapy. [not PLND] Independent prognostic markers for disease-free survival: - no smoking - lymphadenectomy Local recurrence rate: 6%. Autors conclusion: Radical cystectomy performed at academic centres provides excellent local control of disease and an acceptable clinical outcome with low perioperative mortality in patients who are treated within a universal healthcare system.	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Bi 2013 Meta-analysis	Definition of ePLND: include all lymph nodes between the aortic bifurcation and common iliac vessels (proximally), the genitofermoral nerve (laterally), the circumflex iliac vein and lymph nodes of Cloquet (distally), and the internal iliac vessels (posteriorly), including the obturator fossa and the presacral lymph nodes anterior to the sacral promotory. As the number of included studies was only six, there was apparent publication bias in most of the outcomes.	Searches in PubMed, Embase and Cochrane Library. Until Sept. 2012 Comparative studies were included assessing the extent of pelvic lymph node dissection and its influence on recurrence-free survival. Studies with a single treatment arm and no extractable survivial data were excluded.	Extended pelvic lymph node dissection (ePLND) vs. non-extended pelvic lymph node dissection (non-ePLND) in patients undergoing radical cystectomy.	Recurrence-free survival	- Duratin of follow-up: 23,5 to 96 months. - The majority of included patients had pT2-pT3 stage disease. - 6 studies with N=2824 patients were identified. - Overall analysis showed a significantly better recurrence-free survival of ePLND than of non-ePLND (Hazard ratio: 0,65; 95% CI 0,56-0,78; p<0,001). - Subgroup analysis of patients with positive lymph nodes of ePLND vs. non-ePLND: Hazard ratio: 0,58; p<0,001. - Subgroup analysis of patients with negative lymph nodes of ePLND vs. non-ePLND: Hazard ratio: 0,68; p=0,007. - Subgroup analysis of patients with pT3-T4 disease of ePLND vs. non-ePLND: Hazard ratio: 0,61; p<0,001. - Subgroup analysis of patients with pT2 disease of ePLND vs. non-ePLND: Hazard ratio: 0,95; p=0,81. Autors conclusion: The results of this meta-analysis indicate that ePLND provides a RFS benefit compared with non-ePLND. On subgroup analysis, ePLND provides better recurrence-free survival not only for patients who had positive lymph	Abol-Enin 2011 Dhar 2008 Holmer 2009 Jensen 2010 Poulsen 1998 Simone 2012

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	2- (high risk of bias due to study design of the included studies (5 retrospective studies with historical controls).				nodes and pT3-pT4 disease, but also for patients with negative lymph nodes.	

6.5. AG 5 Schlüsselfrage 5 (Indikation zur Urethrektomie)

„Welche Patientengruppe braucht zusätzlich eine Urethrektomie?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Ali-El-Dein 2004 Egypt	Case series 3	n=239 women Mean age 50 ± 8.5 years Orthotopic bladder substitution (n=145)	Radical cystectomy Orthotopic bladder substitution	No control group.	Incidence of oncological failure and tumor recurrence in the urethra.	n=1 Death - postoperatively massive pulmonary embolism. Follow-up 12 to 97 months (mean 36, median 55.8). Follow-up isolated urethral recurrence	Single-institutional Study Prospective Design (First prospective study of the incidence of local urethral recurrence after radical cystectomy and

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Another type of diversion (n=94) Between January 1995 and December 2001 Exclusion: Clinically evident pelvic lymphadenopathy, bladder neck involvement, vaginal wall involvement or positive intraoperative frozen urethral sections were considered contraindications. Pathological stage: P1 (n=12) P2 (n=29) P3a (n=56) P3b (n=44) P4a (n=4) Grade: G1 (n=61) G2 (n=62) G3 (n=22)				n=2 (1.4%) with one P3a N1 (positive iliac lymph nodes) M0, Grade 2 squamous cell carcinoma and one P3b N0M0 tumor associated with trigonal carcinoma in situ. Local pelvic recurrence n=18 Distant metastasis n=6 Both n=10 Oncological failure positively correlated with high stage, high grade and positive lymph nodes.	orthotopic bladder reconstruction in women with the possible exception of a single case report). Limitations: Small number of patient Short Follow-Up.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Lymph nodes: Positive (n=28) Negative (n=117) Histopathology: Carcinoma in situ (n=11) Squamous metaplasia (n=7)					
Ali-El-Dein 2008 Egypt	Case series 3	n=180 women Mean age 50.6 years Orthotopic neobladder reconstruction after radical cystectomy for muscle-invasive bladder cancer. Between Januar 1995 and June 2003 Inclusion: Tumor had to be organ confined without infiltrating the trigone, bladder neck and/or anterior vaginal wall.	Radical cystectomy Orthotopic bladder substitution	No control group	Pathological outcome after radical cystectomy and orthotopic bladder substitution. Possibility of genital sparing.	n=2 – death postoperatively from massive pulmonary embolism. Mean Follow Up 57 months. At Follow Up isolated urethral recurrence n=2 (1,1 %) one P3a N1 (positive iliac lymph nodes) M0, Grade 2 squamous cell carcinoma one P3b N0M0 tumor associated with trigonal carcinoma in situ. Local pelvic recurrence n=30. Distant Metastasis n=14. Both n=9.	Single-institutional Study Prospective Design Limitations: Small number of patient Short Follow-Up Probably a subpopulation of the study from Ali-El-Dein et al. 2004. Population comprised only organ confined tumors and mainly squamous cell carcinoma.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Exclusion: Clinically evident pelvic lymphadenopathy, bladder neck involvement, vaginal wall involvement and positive intraoperative frozen section taken from the retained urethra. Histopathological type: Squamous cell carcinoma (n=107) Transitional cell carcinoma (n=39) Adenocarcinoma (n=21) Mixed and other cancers (n=13). Pathological stage: P1 (n=18) P2 (n=41) P3a (n=72) P3b (n=45) P4 (n=4) Histopathological grade:				Uterine infiltration confirmed by histopathology n=2. Oncological failure: 5-year-disease-free survival 66%.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		G1 or G2 in the majority of cases. Lymph Nodes: Positive (n=33).					
Boorjian 2011 USA	Case series 3+	n=1506 Review of Mayo Clinic Cystectomy Registry. Between 1980 and 2000. Exclusion: Urethrectomy ≤90 d after RC (n = 95). Routine preoperative biopsy of the prostatic urethra was not performed. Frozen section biopsy of the urethral margin was routinely obtained during RC. Considered factors:	Radical Cystectomy (RC) without urethral disease at the time of RC,(patients with Urethrectomy ≤ 90 d after RC (n = 95) were excluded)	No control group	Incidence, risk factors, and outcomes of patients with urethral recurrence (UR).	Median follow-up after RC was 13.5 yr (interquartile range [IQR]: 10.5–18.4). UR was identified in n= 85 (5.6%) at a median of (IQR: 6.1–23.2) after RC, including n= 80 of 1243 (6.4%) cutaneous urinary diversion and n=5 of 242 (2.1%) orthotopic neobladder (p = 0.002). Prostate involvement with UC (hazard ratio [HR]: 4.89; p < 0.0001), bladder tumor multifocality (HR: 2.34; p = 0.001), and orthotopic diversion (HR: 0.34; p = 0.02) were significantly associated with the risk of UR. The 5-yr Cancer-Specific Survival after UR diagnosed by cytology was 80% versus 41% for patients who presented with symptoms (p < 0.0001). Patients with symptomatic UR have	Multi-institutional study. Retrospective Design. Largest series of UR afte RC. Limitations: Not randomized Absence of data regarding competing causes of mortality Tertiary referral nature of our practice Many patients received follow-up locally Surveillance was not standardized Population comprised mainly men.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Gender Male (n=1230) ECOG 0 (n=1133) 1 (n=272) ≥ 2 (n=89) Tobacco use (ever) yes (n=1221) no (n=276) Pathologic tumor stage ≤pT1 (n=451) pT2 (n=568) pT3/4 (n=486) CIS in RC specimen (n=671) Urothelial carcinoma in prostatic urethra at RC (n=124) -excluded Tumor multifocality at RC (n=712)				significantly higher stage disease at urethrectomy (p = 0.04) and an increased risk of death from UC (HR: 1.94; p = 0.08).	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Urinary diversion: Cutaneous (conduit) (n=1243) Orthotopic neobladder (n=242) Receipt of neoadjuvant/adjuvant chemotherapy (n=166).					
Cho 2009 Korea	Case series 3	n=294 Median age 61 years (27–89). Consecutive patients with radical cystectomy and urinary diversion for transitional cell carcinoma of the bladder. Between January 1986 and June 2004. Exclusion: Female patients Non-Transitional Cell Carcinoma histology Presence of distant	Radical Cystectomy.	No control group.	Incidence and risk factors for urethral recurrence following radical cystectomy and urinary diversion in transitional cell carcinoma.	Median follow-up duration of 54 months (range 6–227). Urethral recurrence (UR) n=13 (4.4%) and the 5-year urethral recurrence-free probability was 94.9 %. Independent risk factors for urethral recurrence: Positive urethral margin (hazards ratio (HR) = 18.33, p < 0.001) Prostatic urethral involvement (HR = 7.95, p < 0.001) Prostatic stromal invasion (HR = 5.80, p = 0.018)	Single-institutional Study. Retrospective Design. More careful patient selection is needed. Further study is needed to elucidate selection criteria for orthotopic diversion in patients with prostatic involvement. Women were excluded. Limitation of Orthotopic diversion:

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		metastasisat diagnosis Urethrectomy Orthotopic urinary diversion. Considered factors: Age Bladder neck involvement yes (=90) no (n=204) Trigone involvement yes (n=103) no (n=191) Prostatic urethral involvement yes (n=31) no (n=263) Multiplicity tumors <4 (n=179) ≥4 (n=115) Size					Confined to patients with cutaneous diversions.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		<3 (n=145) ≥3 (n=149) T stage pTis, a, 1 (n=98) pT2 (n=106) pT3 (n=75) pT4 (n=15) Tumor grade low (n=64) high (n=230) Carcinoma in situ yes (n=63) no (n=231) Prostatic stromal invasion yes (n=15) no (n=279) Urethral margin status positive (n=5) negative (n=289)					
Osman 2012	Study of Diagnostic Accuracy (cross	n=100 Between November 2004	Routine frozen section analysis (FSA) of	Different clinical and pathological	Diagnostic value (sens., spec., accuracy etc.).	Evidence of malignancy by FSA of the prostatic urethral margin (n=6, one patient was false positive).	Single-institutional Study.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Egypt	sectional) 3	and September 2005. Consecutive male patients. Mean age of 59.5 ± 7.5 years. Standard radical cystectomy with bilateral iliac lymphadenectomy and urinary diversion. Transitional cell carcinoma with tumor invasion into the muscularis propria, or Ta, T1, or carcinoma in situ refractory to transurethral resection with intravesical adjuvant therapy. Exclusion: Non-transitional cell carcinoma.	urethral margin.	predictors.		Prostatic ± urethral involvement by definitive histopathology (n=15) (15 %). Sensitivity of urethral margin frozen section (33.3%). Specificity of urethral margin frozen section (98.8%). Overall accuracy of (89%) Positive predictive value (83.3%) Negative predictive value (89.4%). No significant correlation between tumor site or morphology, clinical staging, clinically suspicious prostate, cystoscopic involvement of bladder neck, tumor grade, and associated carcinoma in situ or nodal involvement with prostatic malignant involvement. Positive intraoperative FSA was significantly associated with malignant urothelial involvement of the prostate. (high predictive diagnostic value).	Prospective Design. Limitations: Main limitation includes weak power to detect an infrequent event, that is urethral recurrence, as well as limited power to correlate tumor characteristics to the presence of urothelial carcinoma of the prostate.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Patients with false-negative results were followed for 5 years. None of the 10 patients with false negative results developed late urethral recurrence at 5 years.	
Shariat 2007 3 US academic centres Bladder Cancer Research Consortium (BCRC)	Case series 3	n=713 Consecutive patients with radical cystectomy and pelvic lymphadenectomy for bladder Transitional Cell Carcinoma (TCC). Median age 66.4 years (range: 33.1–89.2). Between March 11, 1984, and January 1, 2003 Exclusion: n=99 of 812 (12%) had CIS only at radical cystectomy Considered factors: Gender: Female (n=137)	Radical Cystectomy and pelvic lymphadenectomy.	No control group.	Inzidenz of concomitant CIS Association of concomitant CIS with cancer control.	n=330 of 713 (46.3%) patients had concomitant CIS at radical cystectomy. Patients with TCC involvement of the urethra were more likely to have concomitant CIS than not (61% vs. 40%, p = 0.018). Concomitant CIS was significantly more common in patients with lower cystectomy stages and higher tumour grades. In multivariate analyses that adjusted for the effects of standard postoperative features, concomitant CIS was not associated with either disease recurrence or bladder cancer-specific mortality when evaluated in all patients. In patients with non–muscle-invasive bladder tumour stage and patients with organ-confined tumour stage,	Multi-institutional Study Retrospective Design Limitations: Multiple internal and external reviews and exclusion of patients with incomplete information (selection bias) Absence of association between concomitant CI and bladder cancer-specific survival may have been due to limited sample size and follow-up duration. Treatment by multiple surgeons Specimens evaluated by multiple pathologists.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Year of surgery: 1984–1989 (n=36) 1990–1994 (n=120) 1995–2000 (n=300) 2001–2003 (n=257) Clinical stage: cta (n=11) ctis (n=39) cT1 (n=165) cT2 (n=381) cT3 (n=49) cT4 (n=37) Clinical grade: 1 (n=5) 2 (n=64) 3 (n=642) Pathologic stage: pT0 (no tumour) (n=59) pTa (n=25) pT1 (n=105) pT2 (n=188) pT3 (n=245) pT4 (n=91)				concomitant CIS was associated with a significantly higher probability of disease recurrence (p = 0.048 and 0.012, respectively) but not bladder cancer-specific mortality (p = 0.160 and 0.408, respectively). Follow Up Postoperatively at least every 34 mo the first year, semiannually for the second year, and annually thereafter.	Study reflects a real-world practice. Study period spans over 20 yr, the data may not represent current practice patterns.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Pathologic grade: 0 (no tumour) (n=59) 1 (n=8) 2 (n=58) 3 (n=588) Lymphovascular invasion: Present (n=287) Absent (n=406) Metastases to lymph nodes: Present (n=175) Absent (n=528) Discrepancy between clinical and pathologic stage: Pathologic downstaging (n=126) Same stage (n=233) Pathologic upstaging (n=323).					
Donath 2001	Study of Diagnostic Accuracy (cross	n=246 of 416 male Radical cystectomy	Transurethral lateromontanal loop biopsies	Final pathological stage,	Primary study end points: Correlation of	Sensitivity of transurethral biopsy for prostatic stromal invasion was 53%	Single-insitutional Study Retrospective Design

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
USA	sectional) 3	between 1989 and 1997. Mean age was 63.4 years (range 32 to 87). Exclusion: n=6 cold cup biopsies or unclear method of biopsy Considered factors: Pathologically organ confined, stage T3a or less disease (n=110) Pathologically nonorgan confined, stage T3b or greater disease (n=136) Preoperatively chemotherapy (n=26) Radiation (n=7) No therapy (n=213)		survival and clinical impact	transurethral biopsy results, urethral margin and final pathological condition with the risk of urethral recurrence and survival.	Specificity of transurethral biopsy for prostatic stromal invasion was 77% Positive predictive value was 45% Negative predictive value was 82% Long-term 10-year follow-up: Death n=129 (52.4%) No evidence of disease n=85 (32%) Disease n=16 (6.5%) Lost to follow-up n=16 (6.5%) Mean follow-up at risk for urethral recurrence was 61.7 months (range 0.56 to 134.1, median 56.8). Delayed urethrectomy in 15 of 235 cases (6.4%) at a mean of 15.2 months Of the 246 patients 99 had prostatic disease at transurethral biopsy and/or cystectomy, including 11 (11%) with urethral recurrence 4/147 (2,7 %) in patients with negative biopsy and negative cystectomy 0/19 in patients with negative biopsy	Limitations: Not reported

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Preoperatively. Continent diversion (n=108), including continent urethral diversion (n=86) and continent stomal diversion (n=22) Ileal conduit diversion (n=138)				and positive cystectomy 3/36 (8,3 %) in patients with positive biopsy and negative cystectomy 8/44 (18,3 %) in patients with positive biopsy and positive cystectomy. No patient required continent diversion takedown or died of urethral recurrence.	
Kassouf 2008 USA	Study of Diagnostic Accuracy (cross sectional) 3	n=252 men Patients with radical cystectomy and orthotopic neobladder reconstruction. Median age 61 years (range 53 to 80) Between 1990 and 2004 Exclusion: cT4b disease despite chemotherapy Distant metastasis Considered factors:	Preoperative transurethral prostatic urethral biopsy and/or frozen section of the urethra at the time of surgery.	Final distal urethral margin status at radical cystectomy. Survival	Value of in predicting final distal urethral margin status at radical cystectomy.	Data were available for 245 of 252 patients. Transurethral resection of the prostatic urethra (n=127). Urethral frozen section (n=68). Both (n=50) Incidence of positive distal urethral margin 1.1% (n=3 of 252). Urethral recurrence 0.7% (n=2 of 252). Correlation between transurethral resection findings and frozen section margins 68% n=16 positive transurethral resection findings had negative frozen section margins.	Single-institutional Study. Retrospective design Limitations: Surgeons would not proceed with a neobladder in the face o a positive frozen section our series is, by definition, biased toward the negative predictive value of frozen section examination of the urethra.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Clinical stage: cT1 or Less (n=88) cT2 (n=152) cT3 (n=12) Pathological T stage: T0 (n=26) Tis (n=23) Ta (n=17) T1 (n=31) T2 (n=81) T3 (n=46) T4a (n=28) Pathological N stage: N0 (n=210) N1 (n=32) N2 (n=10) Lymphovascular invasion (n=54) Preop chemotherapy (n=49)				Negative predictive value of transurethral resection biopsy 99.4% Negative predictive value of frozen section 100%. Median follow-up 48 months (range 4 to 161). 5-year disease specific survival rate 71.6%.	
Nelles 2008	Cross-sectional study	n=2401 men Radical			Identify clinical characteristics that predict	Only significant predictor of receiving urethrectomy was stage.	Single-institutional Study.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
USA The Urologic Diseases in America Project	3	cystoprostatectomy. Between 1991 and 2002 Identified in SEER-Medicare database. Considered factors: Age, Grade, Stage, Race. Divided in3 groups: Cystectomy only Urethrectomy within 6 weeks Urethrectomy after 6 weeks.			performance of urethrectomy. Additional independent survival benefit in performance of urethrectomy.	Significant independent predictors of survival: Age, race, number of comorbidities, tumor stage. Survival in men who underwent urethrectomy concurrently with cystoprostatectomy was higher than those who did not undergo urethrectomy (HR = 0.775, CI 0.592 – 1.014,) but not statistically significant (p = 0.0632). Median follow up of 29 months (range 0–143).	Retrospective Design. Limitations: Lack of data regarding adjuvant chemotherapy Data regarding prostatic urethral margin status a the time of cystectomy Selection bias Ascertainment bias Assessment for presenc of new metastatic disease impossible.
Nixon 2002 USA	Case series 3	n=192 consecutive men Orthotopic neobladder (n=108) Ileal conduit (n=79) Continent pouch urinary diversion (n=5) Between June 1995 and June 2000.	Radical cystoprostatectomy due to urothelial carcinoma of the bladder.	No control group.	Preoperative bladder tumor characteristics predictive of prostatic urethral involvement.	Prostatic urethral involvement was evident in 30 of the 192 patients (15.6%). Of n=80 carcinoma in situ in the bladder n=25 (31.3%) had concomitant prostatic urethral involvement with carcinoma. Only n=5 (4.5%) of the 112 with no evidence of carcinoma in situ had prostatic urethral involvement.	Single-institutional study. Retrospective design Further studies are warranted.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Mean age 66 years (range 41 to 88). Exclusion: No transitional cell carcinoma Previously radical prostatectomy.				Likewise n=25 of the 72 (34.7%) with multifocal tumors had concomitant prostatic urethral involvement with carcinoma. Only n=5 (4.2%) of the 120 with no evidence of multifocality had prostatic urethral involvement.	
Spies 2006 USA	Cross-sectional study 3	n=76 men Cystectomy for transitional cell carcinoma of the bladder and Urethrectomy in absence of established urethral recurrence Staged urethrectomy (n=19). Considered factors: Median age 67 years (range 41–81). Positive smoking history (n=47).	Concomitant cystoprostatectomy and urethrectomy (n=57).	Staged urethrectomy (n=19).	Comparison treatment-related outcomes of immediate and staged urethrectomy in patients at high risk of urethral recurrence.	The most common pathologic finding was prostatic duct involvement (31.6%) in the immediate urethrectomy group and Stage pT0 in the delayed urethrectomy group (73.7%). No statistically significant difference in disease-specific survival between immediate and staged groups (P = 0.14). No difference in postoperative complication rates or total operative blood loss (P = 0.77 and P = 0.64). Slight benefit for immediate urethrectomy in the total duration of hospitalization (P = 0.01). The presence of local or distant	Multi-institutional study. Retrospective design. Limitations: Small sample size. Clinical decisions affecting the choice of immediate or delayed urethrectomy. Very high risk of bias.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Positive employment/ environmental exposure (n=10). Clinical presentation: Gross hematuria (n=59) Lower urinary tract symptoms (n=14) Upper tract cancer history (n=3). Examination under anesthesia: Normal (n=61) Mobile mass (n=14) Fixed (n=1). Preoperative clinical stage: Tis (n=8) T1 (n=21) T2 (n=28) T3 (n=1) T4a (n=18) Upper tract status: Normal (n=72) Right hydronephrosis				recurrence was a predictor of disease-specific survival (P = 0.02 and P = 0.02).	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		(n=3) Left hydronephrosis (n=1) Bilateral hydronephrosis (n=0) Indication for urethrectomy: CIS in prostatic urethra (n=17) Prostatic duct Transitional Cell Carcinoma (TCC) (n=32) Prostatic stromal TCC (n=18) Positive urethral margin (n=9)					

6.6. AG 5 Schlüsselfrage 6 (Zeitintervall zwischen ED und Zystektomie)

„Welchen Einfluss hat das Zeitintervall zwischen der Erstdiagnose und der radikalen Zystektomie in Bezug auf die Progressions- und Überlebensrate?“

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Fahmy, 2006 Systematic review	2++	Studies published before January 2006. Searches in PubMed and Ovid gateway. Studies were included if they met the following criteria: (1) The article describes a delay in treatment of bladder cancer by radical cystectomy, and (2) the article includes information on the effect of delay on prognosis. For publications studying the delay in relation to	-	To determine if delay in cystectomy leads to worse prognosis. To determine if a possible cutoff point for delay exists, after which a worse outcome would be expected.	- A total of 13 papers published from 1965 to 2006 were included in this study. - Three (23%) papers did not find any correlation between pretreatment delays and survival. - Two (15%) papers reported a trend towards worse survival with delay. - Eight (62%) papers documented significant association between delay and worse prognosis. - Delay influenced survival as an independent variable in two (25%) of these eight papers. - In the remaining six (75%) manuscripts, delay was significantly associated with a higher pathologic stage. → Although studies on bladder cancer failed to show a linear relationship between delay and prognosis, the majority confirmed that delays are associated with worse outcome. → Studies suggested a window of opportunity of less than 12 weeks from diagnosis of invasive disease to radical cystectomy.	Liedberg, 2003, Scand J Urol Nephrol Chahal, 2003, Eur Urol Wallace, 2002, BJU Int Gulliford, 1991, BMJ Mommsen, 1983, Scand J Urol Nephrol Wallace, 1965, Lancet

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
		multiple management modalities, if shown, only data concerning radical cystectomy were included. Published abstracts and papers published in languages other than English were excluded. All papers that described only delay without any outcome correlations were excluded.				Mahmud, 2006, J Urol Liedberg, 2005, J Urol May, 2004, Scand J Urol Nephrol Sanchez-Ortiz, 2003, J Urol Chang, 2003, J Urol Hara, 2002, Jpn J Clin Oncol Hautmann , 1998, J Urol

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Lee 2006	Case series, retro-spective, single site 3	N=214 Consecutive patients Clinical T2 bladder cancer Radical cystectomy as primary therapy. Male/female: 162/52 Mean age: 65 years	Radical cystectomy	-	To evaluate the timing from T2 bladder cancer diagnosis to cystectomy, its impact on survival and potential causes of delay.	- Mean followup and time to cystectomy in the entire cohort was 40 months and 60 days, respectively. - A significant disease specific survival and OS advantage was observed in patients undergoing cystectomy by 93 days or less (3.1 months) compared to greater than 93 days (p=0.05 and 0.02, respectively). - Pathological staging was similar between the groups p=0.15). - A multivariate benefit in OS was observed in patients treated with timely cystectomy. - The most common factor contributing to cystectomy delay was scheduling delay, as seen in 46% of cases. → A cystectomy delay of 3.1 months undermines patient survival, likely through the development of micrometastases, since local stage progression is not apparent at this point. → Most delays are avoidable and should be minimized. → Despite the need for second opinions and the impact of busy surgical schedules clinicians must strive to schedule patients efficiently and complete surgical treatment within this time frame.	Retrospective Single site Consecutive patients

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Gore 2009	Case series 3	N=441 Subjects with AJCC/UICC stage II (T2, N0, M0: tumor extension into but not beyond the muscularis propria of the bladder wall [T2], no regional lymph node metastases [N0], no distant metastases [M0]). Transitional cell carcinoma (TCC) of the urinary bladder. Male/female: 301/140 Race/ethnicity: White → 386 African American → 23 Hispanic → 15 Other → 17	Radical cystectomy	-	To evaluate the relationship between the timing of radical cystectomy following a diagnosis of muscle-invasive bladder cancer and patient clinical outcome.	- Compared with immediate surgery (i.e., within 4–8 weeks of transurethral resection), longer time to cystectomy increased the risk of both disease-specific and overall mortality (HR 2.0, p<0.01 and HR 1.6, p<0.01, respectively, for those delayed 12-24 weeks; HR 2.0, p<0.01 for disease-specific and overall death among those delayed beyond 24 weeks 1 year following diagnosis). - Covariates associated with overall mortality included older age (HR 1.04, p<0.01) and comorbidity (HR 2.0 for Charlson ≥3 vs. Charlson 0-1, p<0.01) → Delay in definitive surgical treatment beyond 12 weeks conferred an increased risk of disease-specific and all-cause mortality among subjects with stage 2 bladder cancer.	Database integrating data from the Surveillance, Epidemiology, and End Results (SEER) national cancer registry and the Medicare claims database. Modeled survival time since diagnosis rather than time since cystectomy to minimize lead-time bias in the analysis.
Kulkarni 2009	Case series, retro-spective, multi site 3	N=2535	Cystectomy	-	To determine the impact of extended wait times on the survival of patients who underwent radical cystectomy for bladder cancer.	- Median wait time from transurethral bladder resection to cystectomy was 50 days. - Unadjusted and adjusted analyses demonstrated that prolonged wait times were significantly associated with a lower overall survival rate. - The relative hazard of death with	Retrospective Multi site Canadian Institute for Health Information

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						increasing wait times appeared greater for low stage vs high stage cancers. - The cubic splines regression analysis revealed that the risk of death began to increase after 40 days. → Treatment delay between transurethral bladder tumor resection and radical cystectomy resulted in worse overall survival. → The effect of wait time was greatest in lower stage lesions. The suggested maximum wait time from transurethral bladder tumor resection to cystectomy was 40 days. → Further studies assessing disease-free survival are required to corroborate these findings.	Discharge Abstract Database Confounders were extracted from OHIP billing data.
Nielsen 2007	Case series,re-trospective multi site 3	N=592 Consecutive patients Transitional cell carcinoma (TCC) of the bladder. Median (range) age: 66.4 (33.8–89.2) years	Radical cystectomy	-	To examine the association between the interval from the last transurethral resection (TUR) to radical cystectomy (RC) and bladder cancer-specific outcome.	- The mean (SD) actuarial cancer-specific survival was 70.5 (2.3)% and 60.7 (3.2)% at 3 and 7 years, respectively. - Overall, the median (range) time from TUR to RC was 1.8 (0.3–11.6) months. - The interval to RC analysed as a continuous or categorical variable was not associated with extravesical or nodal disease, lymph node metastases, disease recurrence, overall or cancer-specific survival. - The results were similar in the subgroup of 320 patients (54%) with	Retrospective Multi site Consecutive patients

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						clinically muscle-invasive disease. → These results suggest that a reasonable delay from the last TUR to RC is not independently associated with stage progression or with decreased recurrence-free or disease-specific survival. → These findings might have important implications for trial design in the ongoing evaluation of neoadjuvant regimens. → No reason to advocate anything less than the timely consideration of definitive treatment for patients with high-risk bladder cancer	
Tracey 2014	Case series 3	N=6880 5026 men and 1854 women	-	-	To investigate the associations of a range of personal and clinical variables with bladder cancer survival in men and women in NSW to see if we could explain why bladder cancer survival is consistently poorer in women than in men.	- A total of 16% of patients with bladder cancer underwent cystectomy (16% of men and 15% of women).Women who underwent cystectomy were 26% more likely to die than men (hazard ratio [HR] 1.26, 95% confidence interval [CI] 1.00–1.59) after adjustment for age, stage, time from diagnosis to cystectomy, distance from treatment facility and country of birth. - None of the above covariates had a material effect on the difference in hazard between women and men; however, when stratified by a history of cystitis, the adjusted hazard was 55% higher in women (HR 1.55, 95% CI	A total of 105 cases (1.5%) were identified only by death certificate or autopsy; these were excluded from the survival analysis but included in the descriptive and comparative analyses.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						1.15–2.10) than in men with a history of cystitis while, in the absence of this history, there was no difference in the hazard between men and women (HR 0.99, 95% CI 0.57–1.70). - This apparent modification of the effect of sex on bladder cancer outcome was not seen in patients treated only by resection: the adjusted HRs in women relative to men were 1.10 (95% CI 0.92–1.31) in those with a history of cystitis and 1.21 (95% CI 0.98–1.50) in those without. - A history of haematuria did not modify appreciably the association of sex with bladder cancer outcome. → Women's poorer survival from bladder cancer compared with that of men remains unexplained; however, the possibility that some factor associated with a history of cystitis may contribute to or explain the poorer outcome in women merits further investigation.	
Fahmy 2008	Case series, retro-spective 3	N=1633 Mean patient age: 66.4 (SD 10.1) years Median age was 69 years.	-	-	To characterize and measure the contribution of the different components of delay experienced by bladder cancer patients before radical cystectomy in Quebec.	- A total of 25 862 visits for 1633 patients - Median diagnostic delays from family physician (FP) to specialist, then to cystoscopy, then to TURBT and finally from TURBT to CT were 20, 11, 4 and 14 days, respectively, over the entire study period. - Median overall delay from FP visit to	Retrospective Database of physician fee-for-service claims (Régie de l'Assurance Maladie du

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Male to female ratio was 2.6:1.			To identify predictors of longer delays To determine the impact of the various components of delay on mortality.	radical cystectomy was 93 days. - In addition, median FP to radical cystectomy delay progressively increased from 1990 to 2000 from 58 to 120 days (p<0.01). - Multivariate analyses showed that patients with an overall delay of either <25 or >84 days had a 2.1 and 1.4 times increased risk of dying, respectively (p<=0.01). → Preoperative delays have been progressively increasing over time. → Overall, delays from FP to radical cystectomy of <25 and > 84 days may translate into worse outcomes. → Poor survival in cases with <25 days delay may be attributed to case selection, with more advanced cases being managed much quicker. → Poor survival in cases with delays of >84 days may be attributed to disease progression while awaiting completion of management.	Québec).
Santos 2014	Cohort study, retro-spective, multi site 2-	N=2778 Male/female: 2095/683 Age (less than 60 years-old, between 60-69 years-old, between 70-75 years-old, more than	Radical cystectomy	-	To characterize and measure different components of preoperative delays experienced by bladder cancer patients before radical cystectomy in the province of Quebec,	- Median urologist referral delay was 32 days. Median delays between first urologist visit and radical cystectomy and from TURBT to surgery were 90 days and 46 days, respectively. - Median overall delay was 116 days. - All components of delay progressively increased from the decade of 1990 to	Retrospective Multi site RAMQ database (data on medical services dispensed to

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		75 years-old): 638, 823, 573, 744.			Canada and to identify predictors of long wait times.	the 2000's. - Male sex was a protective factor for several components of delay, which suggests that gender-related variations may exist in the continuum of care for bladder cancer (OR=0.67, 95%CI: 0.50-0.89 for overall delay). - Patient's age and gender were associated with delayed urologist referral, delayed time to TURBT, and long overall wait time. - Factors related to the health system were associated with long cystoscopy delays. → Median preoperative delays among patients with bladder cancer have been increasing and remain unacceptably long. → Patient's age, gender, and type of hospital facility were associated with long wait times.	Quebec residents), and the ISQ database (demographic data on births and deaths).
Nuhn 2012	Cohort study, multi site 2-	N=2483 1738 patients with pT2-4a tumors and negative soft tissue margins (STSM) according to the selection criteria of the previous study (study group (SG))	Radical cystectomy	-	To perform the first external validation of a recently identified association between disease-free survival at two years (DFS2) or three years (DFS3) and overall survival at five years (OS5) in patients after radical cystectomy	- The overall agreement between DFS2 and OS5 was 86.5% (EPG: 88.7%) and 90.1% (EPG: 92.1%) between DFS3 and OS5. - The kappa values for comparison of DFS2 or DSF3 with OS5 were 0.73 (SE:0.016) and 0.80 (SE:0.014) respectively for the SG, and 0.67 (SE: 0.033) and 0.78 (SE: 0.027) for the EPD (all p-values < 0.001).	Multi site

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		→ Age, median: 66.6 → Gender, male: 1365 745 patients with positive STSM or other tumor stages (pT0-T1, pT4b) were excluded from the previous study (excluded patient group (EPG)). → Age, median: 65.0 → Gender, male: 611			(RC) for muscle-invasive urothelial carcinoma of the bladder (UCB).	→ Validated a correlation between DFS2 or DFS3 and OS5 for patients with pT2-4a UCB with negative STSM that underwent RC → Furthermore, this correlation was found in patiens with other tumor stages regardless of STSM status. → These findings indicate DFS2 and DFS3 as valid surrogate markers for survival outcome with RC.	

6.7. AG 5 Schlüsselfrage 7 (Offene vs. laparoskopische vs. roboterassistierte Zystektomie)

„Gibt es Unterschiede in der onkologischen Qualität (Anzahl der entnommenen Lymphknoten, Lymphadenektomiefelder, R1- und R2-Resektionsrate, Lokalrezidive, Morbiditäts- und Mortalitätsrisiko, progressionsfreies Überleben und Gesamtüberleben) zwischen der offenen radikalen Zystektomie und der laparoskopischen bzw. roboterassistierten Zystektomie?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Albisinni 2014 Belgium	Prospective cohort study 2-	N=108 patients	Laparoscopic radical cystectomy (LRC) n=54	Open radical cystectomy (ORC) n=54	- Operative time - Blood loss - Perioperative morbidity - Postoperative morbidity - Long-term oncologic results	- Median oncologic follow-up of LRC vs. ORC: 42 vs. 18 months. - Blood loss of LRC vs. ORC: 750 (500-1250) vs. 1500 (900-2700) ml (P<0,0001). - Operative time of of LRC vs. ORC: 360 (300-433) vs. 330 (255-360) min. (P=0,02). - Frequent postoperative ileus of LRC vs. ORC: less in LRC P=0,03. - Serious postoperative complications of LRC vs. ORC: no difference. - Median lymph node retrieval of LRC vs. ORC: 12 87-15) vs. 14 (9-20) (P=0,11). - Recurrence free survival of LRC vs. ORC: no difference (log rank p=0,677). - Postoperative surgical margins of LRC vs. ORC: 6 (11%) vs. 7 (13%). - Length of stay of LRC vs. ORC: 23 (18-26) vs. 22 (18-25) (p=0,28). Authors conclusion: We found that LRC is safe and associated with lower blood loss and decreased postoperative ileus compared with ORC. Moreover, on long-term oncologic follow-up, LRC appeared non-inferior to PRC with no significant diffenrence in recurrence-free survival. None-theless, these results must be confirmed by larger series and stronger	Matching 1:1 Small sample size. Short follow-up in ORC group (relevant for recurrence free survival) .

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						long-term follow-up data are needed.	
Lin 2014 China	Prospective randomized controlled clinical trial 1-	N=70	Laparoscopic radical cystectomy (LRC) n=35	Open radical cystectomy (ORC) n=35	- Lymph node yield (primary) - Operative time - Estimated blood loss - Analgesic requirement - Time to oral intake - Length of hospital stay - Complication rate - Positive surgical margin - 5-year recurrence-free survival - Overall survival	- Median follow-up of LRC vs. ORC: 26 vs. 32 months. - Mean number of lymph node yields of LRC vs. ORC: 12 (4-32) vs. 14 (5-25) (P=0,467). - Operative time of of LRC vs. ORC: 282±51 vs. 235±34 min. (P<0,001). - Estimated blood loss of LRC vs. ORC: 215 (55-810) vs. 510 (105-1700) ml (P<0,001). - Analgesic requirement of LRC vs. ORC: 12,6±5,2 vs. 19,3±6,3 (P<0,001). - Time to oral intake of LRC vs. ORC: 3,8±1,1 vs. 4,8±1,2 days (P<0,001). - Length of hospital stay of LRC vs. ORC: 15,8±5,5 vs. 16,4±6,1 (p=0,677). - Complication rate of LRC vs. ORC for grade II, IIIa and IIIb: no differences P=0,322; P=0,607; P=0,669. - 5-year recurrence-free survival of LRC vs. ORC: no difference p=0,773. - Overall survival of LRC vs. ORC: no difference p=0,551. Authors conclusion: Our study demonstrated that LRC is superior to ORC in perioperative outcomes, including EBL, blood transfusion rate, and analgesic requirement. We found no major difference in oncologic outcomes. The	Noninferiority single-centre study. The primary end point by which the sample size was determined was LN yield: Assuming the mean difference of LN yield between the two groups was 2 with a standard deviation of 4. Short follow-up. Small sample size. Therefore no differences in most of the endpoints may due to low event rates. Only six patients were stage pT3b, and five of them were in the open group. Therefore

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						number of patients is too small to allow for a final conclusion.	favourable results may due to selection bias. One surgeon performed all operation (LRC and ORC).
Parekh 2013 USA	Pilot prospective randomized trial 1-	N=47 patients; N=39 patients for analysis	Robotic assisted laparoscopic radical cystectomy (RARC) n=20	Open radical cystectomy (ORC) n=19	- Perioperative outcomes - Oncologic efficacy	Perioperative endpoints: - Median operative time of RARC vs. ORC: 300 (240-366) vs. 285,5 (240-321,3) min. (P=0,0329). - Estimated blood loss of RARC vs. ORC: 400 (300-762,5) vs. 800 (400—1125) ml (P=0,003). - Median units transfused of RARC vs. ORC: 0 (0-4) vs. 2 (0-4) (P=0,410). - Number of transfusions of RARC vs. ORC: 8/20 (40%) vs. 10/20 (50%) (P=0,0268). - Median days of length of stay of RARC vs. ORC: 6 (5-9,5) vs. 6 (5-9,3) (P=0,0288). - Rate of exessive length of stay of RARC vs. ORC: less in RARC P=0,11. - Length of stay of 5 days or less of RARC vs. ORC: less in RARC P=0,030. - Median days of diet of RARC vs. ORC: 4 (3-6,8) vs. 5,5 (3-7) (P=0,50). - Number of complications of Clavien 2 or greater of RARC vs. ORC: no differences P=0,50.	Small sample size. Pilot study to establish feasibility of randomization, no power calculation reported. Randomization and allocation of concealment reported. Therefore no differences in most of the endpoints may due to low event rates.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Oncologic endpoints: - Positive margins of RARC vs. ORC1/20 (5%) vs. 1/20 (5%) (P=0,50). - Number of lymph nodes removed of RARC vs. ORC: 11 (8,8-21,5) vs. 23 (15-28) P=0,135. Authors conclusion: […] Our results sugegst no significant differences in surrogates of oncologic efficacy. RARC demnostrates potential benefits of dereased estimated blood loss and decreased hospital stay compared to ORC. Our results need to be validated in a larger multicenter prospective randomized clinical trial.	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Aboumarzouk 2013 Meta-analysis	The systematic review was conducted in a line with both Cochrance and PRISMA guidelines. Searches in Medline, EMBASE,	Studies comparing Laparoscopic radical cystectomy (LRC) and open radical cystectomy (ORC). Non english articals were included if data	LRC vs. open ORC.	- Operative time - Blood loss - Transfusion rate - Time to oral intake - Length of hospital stay - Lymph node yield - Analgetic	- 8 studies with n=427 patients. - LRC vs. ORC: n=211 vs. n=216 patients. - Operative time of LRC vs. ORC: longer in LRC P<0,0001 (reported in 6 studies). - Blood loss of LRC vs. ORC: less in LRC P<0,00001 (reported in 6 studies). - Transfusion rate of LRC vs. ORC: less in LRC P<0,0001 (reported in 6 studies). - Time to oral intake of LRC vs. ORC: less in	Basillote 2004 Gregori 2007 Guillotreau 2009

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	CENTRAL, CINAHL, Clinicaltrials.gov, Google Scholar, individual journals. Risk of bias: - 3 studies with selection bias - no studies with performance bias - all studies with detection bias - all studies with attrition bias - all studies with reporting bias - all studies with other source of bias 2- (very high risk of bias)	were extractable. All included studies were cohort oberservational studies with no randomiziaton. 2 of them conducted in a retrospective manner.		requirement - Complications - Positive margins - Bladder cancer at least pT2N0 - Bladder cancer pT3N0 and above - Local recurrence - Distant metastases	LRC P<0,00001 (reported in 6 studies). - Length of hospital stay of LRC vs. ORC: less in LRC P<0,00001 (reported in 6 studies). - Lymph node yield of LRC vs. ORC: no differences P=0,58 (reported in 2 studies). - Analgetic requirement of LRC vs. ORC: less in LRC P<0,0009 (reported in 4 studies). - Minor complications of LRC vs. ORC: less in LRC P=0,02 (reported in 5 studies). - Major complications of LRC vs. ORC: no differences P=0,70 (reported in 5 studies). - Positive margins of LRC vs. ORC: more in LRC P=0,12 (reported in 5 studies). - Bladder cancer at least pT2N0 of LRC vs. ORC: more in ORC P=0,31 (reported in 8 studies). - Bladder cancer pT3N0 and above of LRC vs. ORC: less in LRC P=0,61 (reported in 8 studies). - Nodal positive of LRC vs. ORC: less in LRC P=0,02 (reported in 6 studies). - Local recurrence of LRC vs. ORC: no differences P=0,90 (reported in 2 studies). - Distant metastases no differences P=0,43 (reported in 3 studies). Authors conclusion: In experienced hands, LRC is a feasible and safe alternative to ORC with less blood loss, transfusion and analgesic requirement,	Ha 2010 Haber 2008 Hemal 2007 Porpiglia 2007 Wang 2010

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					shorter lengths of hospital stay, and less complications. LRC does, however, have longer operative times.	
Tang 2014 Meta-analysis	Searches in Medline, EMBASE, Cochrane Library. Level of Evidence (US Preventive Service Task Force System): all studies were rated 3b, just Nix et al. was rated 2b. The meta-analysis was performed according to the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines. Apparent similarities to the metaanalysis of	Studies comparing robot-assisted radical cystectomy (RACR) and open radial cystectomy (ORC).	RARC vs. ORC	- Operative time - Length of hospital stay - Blood loss - Transfusion rate - Time to oral intake - Lymph node yield - Positive lymph node - Surgical margins - Complications	- 13 studies with n=1011 patients. - 7 prospective (1 RCT), 5 retrospective studies. - RARC vs. ORC: n=418 vs. n=539 patients. - Operative time of RARC vs. ORC: longer in RARC P<0,001 (reported in 12 studies). - Estimated blood loss of RARC vs. ORC: less in RARC P<0,001 (reported in 6 studies). - Blood transfusion rate RARC vs. ORC: less in RARC P=0,002 (reported in 8 studies). - Transfusion need RARC vs. ORC: less in RARC P<0,001 (reported in 3studies). - Length of hospital stay of RARC vs. ORC: less in RARC P<0,001 (reported in 4 studies). - Time regular diet of RARC vs. ORC: less in RARC P=0,002 (reported in 4 studies). - Positive surgical margins of RARC vs. ORC: no differences [no P value given]. - Nodal positive of RARC vs. ORC: less in RARC P=0,02 (reported in 6 studies). - Lymph node yield of RARC vs. ORC: more in RARC P=0,03 (reported in 9 studies). - Complications RARC vs. ORC: less in RARC p<0,001 (reported in 10 studies). Very high heterogeneity (>80%) for Operative time	Galich 2006 Gondo 2012 Khan 2012 Knox 2012 Martin 2011 Nepple 2011 Ng 2010 Nix 2010 Rhee 2006 Richards 2012 Sterrett 2006 Styn 2012 Wang 2007

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	Li et al. 2- (very high risk of bias due to study designs)				- Length of hospital stay, Blood loss, Transfusion rate, Time to oral intake, Lymph node yield. Authors conclusion: In early experience, our data suggest that RARC appears to be a safe, feasible and minimally invasive alternative to its open counterpart when performed by experienced surgeons in selected patients.	
Li 2013 Meta-analysis	Searches in PubMed, Scopus Cochrane Library. The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and Meta-Analysis of Observational Studies in Epidemiology recommendations for study reporting.	Studies comparing robot-assisted radical cystectomy (RACR) and open radial cystectomy (ORC).	RARC vs. ORC	Primary outcomes: - Complications - Positive surgical margins - Lymph node yield Secondary outcomes: - Operative time - Blood loss - Length of stay	- 13 studies with n=962 patients. - 1 RCT, 8 prospective, 4 retrospective studies. - RARC vs. ORC: n=364 vs. n=598 patients. - Overall perioperative complications of RACR vs. ORC: less in RARC P=0,04 (reported in 5 studies). - Intra- and postoperative complications of RACR vs. ORC: no difference P=0,36 and P=0,15, respecively (reported in 2 and 3 studies, respectively). - Minor complications of RACR vs. ORC: no difference P=0,92 (reported in 3 studies). - Major complications of RACR vs. ORC: less in RARC P=0,057 (reported in 7 studies). - Positive surgical margins of RACR vs. ORC: no difference P=0,92 (reported in 3 studies). - Lymph node yield of RARC vs. ORC: more in RARC P=0,009 (reported in 9 studies).	Galich 2006 Sterrett 2006 Pruthi 2007 Wang 2008 Richards 2010 Martin 2010 Ng 2010 Nix 2010 Sung 2011 Abaza 2012 Styn 2012

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	Level of Evidence (Oxford): all studies were rated 3b, just Nix et al. was rated 2b. The RCT was assessed by the Cochrane risk of bias tool. Apparent similarities to the metaanalysis of Tang et al. 2- (very high risk of bias due to study designs)				- Operative time of RARC vs. ORC: longer in RARC P<0,001 (reported in 9 studies). - Estimated blood loss of RARC vs. ORC: less in RARC P<0,001 (reported in 9 studies). - Perioperative blood transfusion rate RARC vs. ORC: less in RARC P<0,001 (reported in 3 studies). - Length of hospital stay of RARC vs. ORC: less in RARC P<0,001 (reported in 9 studies). Authors conclusion: RARC is a mini-invasive alternative to ORC with less overall perioperative complications, more lymph node yields, less estimated blood loss, less need for a perioperative transfusion, and shorter length of stay.	Gondo 2012 Nepple 2011

6.8. AG 5 Schlüsselfrage 8 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

6.9. AG 5 Schlüsselfrage 9 (Qualitätsstandards für TUR-B vor RT/RCT)

„Gibt es technische Qualitätsstandards für die Durchführung einer TUR-B vor RT/RCT?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis Extrahierte Ergebnisse beziehen sich nur auf die Fragestellung nach Qualitätstandards für die Durchführung einer TUR-B vor RT/RCT.	Methodische Bemerkungen
Arias 2000 Spain	Prospective case series 3	N=50 T2 to T4 operable untreated bladder cancer.	1. Cytoreductive TUR. 2. Two cycles of M-VAC. 3. 45 Gy on pelvic coume and at same time 20 mg/m^2 cisplatin on days 1 and 5. 4. Cystoscopic evaluation. 5a. If complete response: radiotherapy completed up to 65 Gy. 5b. No complete			No information for quality standards of TUR-B before RT/RCT are given.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis Extrahierte Ergebnisse beziehen sich nur auf die Fragestellung nach Qualitätstandards für die Durchführung einer TUR-B vor RT/RCT.	Methodische Bemerkungen
			response: cystectomy.				
Coen 2012 USA	Retrospective case series 3	N=325 T2NXM0 to T4NXM0 bladder cancer.	1. TUR 2. Split-course of chemoradiaton. 3a. If complete response: completition of radiaon. 3b. No complete response: cystectomy.			No information for quality standards of TUR-B before RT/RCT are given.	
Given 1995 USA	Prospective case series 3	N=94 T2 to T4, NX, M0 bladder cancer.	1. TUR 2. Two or three cycles of methotrexate, vinblastine and cisplatin. 3. Non-responders or partial responders treated to the pelvis with fourfield box			No information for quality standards of TUR-B before RT/RCT are given.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis Extrahierte Ergebnisse beziehen sich nur auf die Fragestellung nach Qualitätstandards für die Durchführung einer TUR-B vor RT/RCT.	Methodische Bemerkungen
			technique of 6480 cGy				
Kaufman 2000 USA	Prospective case series 3	N=34 T2-T4a, NX MO bladder cancer.	1. TUR 2a. Cisplatin 15 mg/m² an 5-FU 400 mg/m² on day 1, 2, 3, 15, 16, 17 and 2b. Radiation using twice-a-day 3 Gy fraction cores to the pelvis for a total of dose of 24 Gy on day 1, 3, 15, 17. 3a. Complete response: consolidation therapy with same drugs and dose on day 1, 2, 3, 15, 16, 17 combined with twice-daily radiation therapy on the bladder of 2.5 Gy (total 20			No information for quality standards of TUR-B before RT/RCT are given.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis Extrahierte Ergebnisse beziehen sich nur auf die Fragestellung nach Qualitätstandards für die Durchführung einer TUR-B vor RT/RCT.	Methodische Bemerkungen
			Gy. 3b. No complete response: cystectomy.				
Oh 2008 USA	Prospective case series 3	N=23 cT2 bladder cancer.	1. TUR 2. Twice-weekly gemcitabine chemotherapy with a dose escalation design till the maximum tolerated dose for 6 weeks with concurrent radiotherapy of 2 Gy/day (total of 60 Gy) over 6 weeks. 3a. Complete response: follow-up. 3b. No complete response: cystectomy.			No information for quality standards of TUR-B before RT/RCT are given.	
Perdona 2007	Retrospective case series	N=121	1. TUR			No information for quality standards of TUR-B before RT/RCT are given.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis Extrahierte Ergebnisse beziehen sich nur auf die Fragestellung nach Qualitätstandards für die Durchführung einer TUR-B vor RT/RCT.	Methodische Bemerkungen
Italy		T2 to T4 bladder cancer.	2. Two cycles of neoadjuvant chemotherapy with methotrexate 30mg/m^2, cisplatin 70 mg/m^2 and vinblastine 3 mg/m^2. 3a. Radiotherapy (n=43). 3b. Radiochemotherapy (n=78). 4a. Complete response: follow-up. 4b. No complete response: recommendation of further treatment.				
Rödel 2002							Siehe AG 5-SF 11

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis Extrahierte Ergebnisse beziehen sich nur auf die Fragestellung nach Qualitätstandards für die Durchführung einer TUR-B vor RT/RCT.	Methodische Bemerkungen
Germany							

6.10. AG 5 Schlüsselfrage 10 (Radio- /Radiochemotherapie)

„Ist die simultane Radiochemotherapie gegenüber der alleinigen Radiotherapie bezüglich lokaler Kontrolle, Organerhalt und Gesamtüberleben überlegen?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Dunst 2005	Case series, retro-spective, single site (Germany) 3	N=68 Male/female: 64/4 Patients with urothelial bladder cancer. Median age: 68 years (range 42–82 years) T-category: T2 → 32 T3 → 20 T4 → 16	Concurrent cisplatin-based chemotherapy (25 mg/m2 on days 1–5 and 29–33).	Patients with impaired renal function were either treated with irradiation alone (n=7) or received paclitaxel as alternative to cisplatin in a phase II protocol or on an individual decision (n=27).	To investigate the outcome of patients with muscle-invasive bladder cancer treated at a single institution.	1. Complete remission (CR) A histologically confirmed complete remission (CR) on restaging cystoscopy was observed in 40/46 patients (87%) who underwent restaging cystoscopy. - CR rates were not significantly correlated to T-category (CR: 24/32 T2, 9/19 T3, and 9/16 T4 tumors) or clinical nodal status. - Patients with non-radical resection and macroscopic residual tumor (R2 resection) achieved a CR in only 39% (12/31); this figure was significantly lower as compared to patients with radical R0 TUR-BT (CR: 15/16, 94%, p = 0.013). - Furthermore, age and preexisting anemia had no impact on response. 2. Overall survival (OS) The overall survival of the whole group was 45% after 5 years, and survival according to clinical T-category was 62% for T2, 43% for T3, and 19% for T4 (p=0.015). In eleven patients, local disease progression or relapse was observed.	Retrospective Single site Median follow-up was 34 months (range 2–104 months). TUR was performed in all cases, and a complete TUR-BT was attempted, if possible. all patients: Radiotherapy was administered in conventional fractionation (five fractions of 1.8 Gy per week) up to 50.4 Gy to bladder, and regional nodes and the whole

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						- So far, only one salvage cystectomy has been performed, due to contraindications to surgery in the majority of patients. → The data obtained in this study confirm the high efficacy of TUR and radiochemotherapy for locally advanced bladder cancer.	bladder received a boost up to 54–59.4 Gy. Patient group was relatively small and heterogeneous with regard to prognostic factors.
Nowak-Sadzikow-ska 2013	Case series, single site (Poland) 3	N=35 Patients with histologically proven invasive carcinoma of the bladder (T2-4a, N0-1, M0) Fit for combined radiochemotherapy Refused radical surgery or were medically or surgically inoperable. Mean age: 63 years (range 46-76) Male/female: 29/6 Karnofsky status:	TURB + neoadjuvant chemotherapy with gemcitabine and cisplatin + combined irradiation with cisplatin (N=9). TURB + neoadjuvant chemotherapy with gemcitabine and cisplatin + irradiation alone (N=12). TURB + neoadjuvant chemotherapy	-	Clinical effectiveness Survival rate	- Twenty-five patients (25/35; 72%) received two cycles of neoadjuvant chemotherapy, and ten of them (10/35; 28%) only one, because of treatment-related toxicity. - In twenty-one patients (21/35; 60%) chemotherapy consisting of gemcitabine with cisplatin and in fourteen patients (14/35; 40%) gemcitabine with carboplatin were applied. - Only 13 patients (13/35; 37%) received combined irradiation with cisplatin. - All patients completed their planned course of radiation therapy. - Complete response (CR) occurred in 26/35 (74%) patients, partial response (PR) in 2/35(6%), and stable disease (SD) in 7/35 (20%). - The overall actuarial survival rates at 3	Single site

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		70 →18/35 80 → 13/35 ≥ 90 → 4/35 clinical stage: T2 → 8/35 T3 → 17/35 T4 → 10/35 7/35 with hydronephrosis and 28/35 without	with gemcitabine and carboplatin + combined irradiation with cisplatin (N=4). TURB + neoadjuvant chemotherapy with gemcitabine and carboplatin + irradiation alone (N=10).			and 5 years were 75% and 66%, respectively. - Disease-specific actuarial survival rates at 3 and 5 years were 81% and 71%, respectively. → Conservative treatment of patients with muscle-invasive bladder cancer by transurethral resection, neoadjuvant chemotherapy, and accelerated hyperfractionated radiotherapy with concomitant boost, with or without concurrent cisplatin, provides a high probability of local and distal response with acceptable toxicity in properly selected patients.	
Krause 2011	Case series, single site 3	N=473 Bladder cancer patients Consecutive patients 366 men and 107 women Mean age: 65.3 years (range: 28-91 years)	Transurethral resection (TUR) of a bladder tumor (TURBT) followed by radiochemo-therapy (RCT)	Trans-urethral resection (TUR) of a bladder tumor (TURBT) followed by radiation therapy (RT).	To evaluate 15-year experience. To describe the association of different parameters with clinical outcome.	- Complete remission (CR) was achieved in 70.4% of the patients. - The 5-, 10- and 15-year overall survival rates were 49%, 30% and 19%, respectively. - Long-term results were significantly affected by pT stage, lymphatic vessel invasion, residual tumor status, lymph node metastasis, kind of therapy (RCT vs. RT), and the response as confirmed by restaging TUR after RCT/RT. → Organ-preservation therapy in patients with bladder cancer is a valid option compared to radical cyst-ectomy	Single site Consecutive patients

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						in selected patients, ideally with early-stage bladder cancer, in whom a complete transurethral resection of the tumor can be accomplished and radiochemotherapy is superior to radiation for favorable long-term outcome.	
Lagrange 2011	Single arm, Phase II study, prospective, multi site 3	N=53 Two patients did not receive treatment after TUR and were excluded → 51 patients were evaluated. Median age: 68 years Male/female: 45/6	Pelvic irradiation delivered 45 Gy, followed by an 18 Gy boost. Concurrent chemotherapy with cisplatin and 5-fluorouracil by continuous infusion was performed atWeeks 1, 4, and 7 during radiotherapy. Patients initially suitable for surgery were evaluated with macroscopically complete transurethral resection after	-	To evaluate bladder preservation and functional quality 1. Overall survival (OS) 2. Quality of life (measured by QLQ-C30 and Late Effects in Normal Tissues–Subjective, Objective, Management, and Analytic (LENT-SOMA)	- Thirty-two percent of patients had T2a tumors, 46% T2b, 16% T3, and 6% T4. - Avisibly complete transurethral resection was possible in 66%. - Median follow-up was 8 years. - Bladder was preserved in 67% (95% confidence interval, 52–79%) of patients. 1. OS Overall survival was 36% (95% confidence interval, 23–49%) at 8 years for all patients, and 45% (28–61%) for the 36 patients suitable for surgery. 2. Quality of life - Satisfactory bladder function, according to LENT-SOMA, was reported for 100% of patients with preserved bladder and locally controlled disease 6–36 months after the beginning of treatment. - Satisfactory bladder function was reported for 35% of patients before treatment and for 43%, 57%, and 29%, respectively, at 6, 18, and 36 months.	Prospective Multi site European Organization for Research and Treatment of Cancer quality of life questionnaire QLQ-C30, specific items on bladder function, and the Late Effects in Normal Tissues–Subjective, Objective, Management, and Analytic (LENT-SOMA) symptoms scale were used to evaluate quality of life before

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			45 Gy, followed by radical cystectomy in case of incomplete response.			At the time of the study, a specific module for urinary symptoms of the QLQC-30 questionnaire was not available, and a specific questionnaire was built, based on other published studies. Using this tool, 70% of patients maintained a good score for bladder function 12 months after treatment. In the first year after treatment, symptoms such as frequency, pain, and control problems improved, probably owing to tumor disappearance. This good quality of bladder function was maintained up to 24 months, but thereafter deterioration was seen. The daily frequency was better at 6 and 12 months than before treatment, but at 36 months 5 of 7 patients had a urinary interval of 2 to 3 h. The same observation was made for nightly frequency of urination. The majority of patients with pain on urination before treatment usually experienced an improvement, but in 37.7% at 6 months there was deterioration, and 14% had frequent pain at 36 months. Urine leakage can have an important impact on social life. In the majority of the cases patients never had this symptom. → Concurrent chemoradiation therapy allowed bladder preservation with	treat-ment and 6, 12, 24, and 36 months after treatment.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						tumor control for 67% patients at 8 years. Quality of life and quality of bladder function were satisfactory for 67% of patients.	

6.11. AG 5 Schlüsselfrage 11 (Re-Staging nach RT/RCT)

„Mit welchen diagnostischen Methoden (Urin-Zytologie, Zystoskopie, Biopsie) und wann sollte das Re-Staging nach RT/RCT erfolgen?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Chung 2007 Canada	Single center retrospective case-series 3	N=340 N=298 for assessment T1 to T4 bladder cancer. N=264 men N=76 women Median age: 71 years. Assessment and Staging by:	1.) Radiotherapy alone n=247. 2.) Radiotherapy and concurrent chemotherapy n=36. 3. Radiotherapy (6-18 MV) with neoadjuvant chemotherapy (3-6 cycles,		Endpoints: - 10-year overall survival - cause-specific survival - local relapse-free rates	Patients with complete response (63,5%) were followed by regular cystoscopy. Median follow-up: 7,9 years (range 1,5 months to 16.8 years). Complete response rates: - All therapies: 55%. - Radiotherapy and concurrent chemotherapy: 79%. - Radiotherapy alone: 64%. - Radiotherapy with neoadjuvant	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		blood count (96% of patients), renal function tests (96%), urine cytology (87%), computed tomography (CT) of abdomen/pelvis (97%), chest x-ray (97%), and bone scan (85%). Staging by a radiation oncologist and urologist by cystoscopy and examination under anesthesia before radiotherapy in 90% of patients. The original diagnostic biopsy was reviewed to confirm the diagnosis, depth of muscle invasion, and presence of associated CIS. TNM-Classification by UICC 1997	methotrexate + vinblastine + doxorubicin + cisplatin or methotrexate + vinblastine + cisplatin) n=57.			chemotherapy: 53% For total study population (10-years): - overall survival: 19% - cause-specific survival: 35% - local relapse-free rates: 32% For total study population (5-years): - overall survival: 32% - cause-specific survival: 42% - local relapse-free rates: 34% For T2N0M0 (out of n=116 patients) (5-years): - overall survival: 58% - cause-specific survival: 44% - local relapse-free rates: 49% For T2N0M0 + no CIS vs. T2N0M0 + CIS (out of n=116 patients) (5-years): - overall survival: 58% vs. 29% (P<0,001) - cause-specific survival: 68% vs. 47% (P=0,003) - local relapse-free rates: 61% vs. 29% (P=0,02) Multivariable analysis for prognostic factors: Age: - overall survival: P<0,01 - cause-specific survival: P=0,02 - local relapse-free rates: P=0,41	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						T category: - overall survival: P<0,01 - cause-specific survival: P<0,01 - local relapse-free rates: P=0,01 CIS : - overall survival: P<0,01 - cause-specific survival: P<0,01 - local relapse-free rates: P<0,01 Chemotherapy cocurrent or neoadjuvant: no significant p-values. Autors conclusion: Combined treatment appeared to provide high response rates and can be offered as an alternative option to radical cystectomy in selected patients who refuse or are unsuitable for surgery.	
Danesi 2004 Italy	Single-center retrospective case-series 3	N=77 patients. pT2-pT4aN0M0 bladder cancer. N=67 men N=10 women	1. Complete TURB and bladder mapping n=77. 2a. Two cycles of induction chemotherapy followed by hyperfractionated radiotherapy		Endpoints: - complete/partial response - local response - toxicity - survival	Complete response: n=65 (90,3%): (5 patients died before restaging TURB.) Complete response induction chemotherapy vs. no induction chemotherapy: 33 (84,6%) vs. 32 (97,0%) patients (p-value not significant). The only significant factor for complete response is tumor stage T2 vs. T3-T4a	Small sample size. Remarkable differences between the different treatment arms (i.e. T3-T4 8% vs. 20%).

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			(9-12 MV) and cisplatin (4-6 mg(m^2 per day) plus 5-FU (180-220 mg/m^2 per day) n=42. 2b. Only hyperfractionated radiotherapy (9-12 MV) and cisplatin (4-6 mg(m^2 per day) plus 5-FU (180-220 mg/m^2 per day) n=35. 3. Six to 8 weeks after therapy response evaluation with: - CT scan - urine cytology - TURB.			(P=0,04). Partial response: n=7 (9,7%). (5 patients died before restaging TURB.) Partial response induction chemotherapy vs. no induction chemotherapy: 6 (15,4%) vs. 1 (3,0%) patients. Toxicity in patients with induction chemotherapy was higher than without (no p-value significant). Survival: (Median follow-up of 82,2 months.) All patients (n=77): 5 year overall survival rate: 58,5% 5 year bladder-intact survival rate: 46,6% 5 year tumor-specific survival rate: 75,0% 5 year disease-free survival rate: 53,5% 5 year cystectomy-free survival rate: 76,1% Patients with complete response (n=65): 5 year overall survival rate: 69,5% 5 year bladder-intact survival rate: 55,2%	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						5 year tumor-specific survival rate: 83,0% 5 year disease-free survival rate: n.a. 5 year cystectomy-free survival rate: n.a. No statistically significant differences between the two treatment arms in survival. Autors conclusion: Combined treatment appeared to provide high response rates and can be offered as an alternative option to radical cystectomy in selected patients who refuse or are unsuitable for surgery.	
Efstathiou 2012 USA	Single-center case series. 3	N=348 patients. cT2-T4aN0M0 bladder cancer.	1. Maximal TURBT. 2. Neoadjuvant chemotherapy in 2 of 7 studies. 3. Induction therapy: concurrent cisplatin-based chemotherapy and radiation therapy.		Endpoints: - disease-specific survival - overall survival	Median follow-up of surviving patients: 7,7 years. Complete response to induction therapy: - All patients: 72%. - T2 carcinoma: 78%. Disease-free survival at 5 vs. 10 vs. 15 years: - All patients: 64% vs. 59% vs. 57%. - T2 carcinoma: 74% vs. 67% vs. 63%. - T3-T4 carcinoma: 53% vs. 49% vs. 49%. Overall survival at 5 vs. 10 vs. 15 years.	Single-center but retrospective analysis of patients participated in 7 studies. Toxity not reported.

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			4a. No complete response: radical cystectomy. 4b. Complete response: consolidation therapy with adjuvant chemotherapy and radiation therapy. 5. Adjuvant chemotherapy in 4 of 7 studies (n=173). 6. Repeat biopsy was performed after 40 Gy.			- All patients: 52% vs. 35% vs. 22%. - T2 carcinoma: 61% vs. 43% vs. 28%. - T3-T4 carcinoma: 41% vs. 27% vs. 16%. Patients undergoing cystectomy after complete TURBT vs. incomplete TURBT: 22% vs. 42% (P<0,001). Multivariate analysis: - Only clinical T-stage and complete response were significant associated with disease-specific survival and overall survival. - Neoadjuvant chemotherapy had no positive effect on outcomes. Autors conclusion: Combined-modality therapy achieves a complete response and preserves the native bladder in > 70% of patients while offering long-term survival rates comparable to contermporary cystectomy series. These results support modern bladder-sparing therapy as a proven alternative for selected patients.	
Gamel El-Deen 2007 Egypt	Retrospective single center case series 3	N=55 patients. T2-T4NXMX bladder cancer.	1. Complete TUR . 2. Concurrent chemotherapy with cisplatin		Endpoints: - overall survival - complete response	Median follow-up: 48 months. 55 patients available for evaluation. Complete response: n=37 (67,3%).	Small number of patients for evaluation. Short follow-up period.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			and irradiation with 4500 cGy. 3. Urologic evaluation by cystoscopy, cytology, rebiopsy 2-3 weeks later. 4a. No complete response: cystectomy. 4b. Complete response: additional chemotherapy with cisplatin and radiotherapy up to 6480 cGy.			Overall survival at 5 years: 43,12%. Early tumor stage and complete response were the most important factors predicting bladder preservation and survival (P=0,001). Autors conclusion: Conservative combination treatment may be an acceptable alternative to immediate cystectomy in selected patients with bladder cancer.	
George 2004 France	Retrospective single center case series 3	N=60 patients. T2-T4N0M0 bladder cancer.	1. TUR. 2a. Neoadjuvant chemotherapy (methotrexate + cisplatin + vinblastin or methotrexate + adriamycin, cisplatin an 5-FU) followed by		Endpoints: - complete response - overall survival - disease-specific survival	Median follow-up: 48,5 months (range 10 to 126 months). Complete respone: n=45 (75%). Incomplete response n=14. Toxic death: n=1. 5 year overall survival: 36% 5 year disease-specific survival: 54% 5 year freedom from local/distant relapse: 42%.	Retrospective, single center, small sample size.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			concomitant chemoradiotherapy n=22. 2b. Concomitant chemoradiotherapy (45 Gy to the abdomen, 65 Gy to the bladder) alone n=38. 3. Follow-up evaluation with cystoscopy with biopsies 2 months after therapy.			No statistically significant differences were found in univariate analysis for whether patients received neoadjuvant chemotherapy before concomitant chemoradiotherapy (P=0,7). Autors conclusion: Transurethral resection of bladder tumor with this chemoradiotherapy combinatin achieved satisfactory results in this unfavorable population with invasive bladder cancer.	
Kaufman 2009 USA	Prospective multicenter case series 3	N=80 patients T2-T4aNXM0 bladder carcinoma.	1. TUR. 2. Induction therapy: radiation and chemotherapy with cisplatin and paclitaxel. 3. Follow-up with repeat biopsy. 4. If less than T1 in repeat biopsy: consolidation		Endpoints: - safety/toxity - protocol completition - response rate - survival of chemoradiotherapy	Median follow-up of 49,4 months. Survival: - 5-year overall survival rate: 56%. - 5 year disease-specific survival rate: 71%. Toxity: Grade 3-4 toxity: 26% of the patients. Protocol completition: Completed 4 cycles of adjuvant chemotherapy: 70% of the patients. Response rate:	

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			chemoradiotherapy (more than T1 cystectomy).			Post induction complete response rate: 81% of the patients. Autors conclusion: These favorable tumor response rates with possible increased bladder preservation rates suggest that this treatment regimen deserves further study.	
Lin 2009 Taiwan	Single center case series 3	N=30 patients. pT2-pT4aN0M0 bladder cancer.	1. TUR. 2a. Induction chemotherapy: 3 cycles cisplatin and 5-FU followed by concurrent chemoradiotherapy: 6 cycles of cisplatin chemotherapy and radiaton with 64,8 GY (n=17). or 2b. Induction chemotherpy: 3 cycles cisplation, 5-FU and paclitaxel		Endpoints: - complete response - protocol completition - overall survival - progression-free survival	Median follow-up: 47 months. Complete response: - Complete response after induction chemotherapy: n=23. - Complete response after completition of protocol: n=22 (73%). Completition of protocol (until disease progression): n=28 (93%). Survival: - 3 year overall survival rate: 77% of patients. - 3 year progression-free survival rate: 54% of patients. No significant differences in gender, age, Karnofsky Performance Status, T stage or protocol. Autors conclusion: Our protocols may be alternatives to	Very small number of patients.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			followed by concurrent chemoradiotherapy: 6 cycles of cisplation and paclitaxel chemohtherapy and radion with 64,8 Gy (n=13). 3. Cystoscopic reevaluation with biopsies and cytology after 6 weeks.			cystectomy for selected patients who wish to preserve the bladder.	
Maarouf 2011 Egypt	Single center case series 3	N=33 patients. T2-T3NxM0 bladder cancer.	1. Maximal TUR. 2. Three cycles of adjuvant chemotherapy with methotrexate, vinblastin, adriamycin, cisplatin followed by radiotherapy. 3. Four weeks later radiological and cystoscopial re-evaluation.		Endpoints: - complete response - completition of study - response rates	Completition of study protocol: n=28. Overall response after 3 cycles of chemotherapy: 64,3% - complete response: 28,6% - partial response: 35,7%. No response after 3 cycles of chemotherapy: 35,7%. Complete response after 12 months: 39,3%. Response rates for selected prognostic variables: - T2 lesion: 69,2%. - T3 lesion: 40,0%. - complete TURBT: 60,8%	Very small number of patients. Short follow-up period of 1 year.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- incomplete TURBT: 20,0%. Survival (follow-up 1 year): - 1 year disease-free survival: 39,3%. - 1 year overall survival: 64,3%. Autors conclusion: In the present study, bladder preservation protocol with MVAC and radical radiotherapy achieved suboptimal response rates at 1 year in patients with localized TCC invading bladder muscle. Patients with solitary T2 lesions that are amendable to completeTURBT achieved the best response rates. Longer follow-up is needed to verify these results. Patients with localized disease should be encouraged for radical cystectomy, which achieved better results.	
Mitin 2013 USA	Multicenter randomised phase II trial	N=97 T2-T4aNX/N0M0 bladder carcinoma.	1. TUR 2. Paclitaxel + cisplatin with twice daily radiation (40,3 Gy) n=46. 3. Cystoscopic and biopsy	1. TUR 2. Fluorouracil + cisplatin with twice daily radiation (40,3 Gy) n=45. 3.	Assessment of effectiveness, safety and tolerability of paclitaxel or fluorouracil. Endpoints: - overall survival - bladder-intact survival - completition of study	N=6 patients drop-outs. Median follow-up was 5 years. **5-year overall survival** 5-year overall survival of paclitaxel vs. fluorouracil group: 71 % (95% CI 57-84) vs. 75% (95% CI 62-88). 5-year overall survival of patients who completed induction + consolidation chemoradiotherapy + adjuvant	No blinding. 24 centers in the USA. Randomisation stratified by clinical T stage T2 vs. T3/T4. Only one p-value mentioned in the

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			assessment of response. 4a. If downstaging was achieved consolidation chemoradiotherapy with 64,3 Gy and same chemotherapy as above. 4b. If not: cystectomy was recommended.	Cystoscopic and biopsy assessment of response. 4a. If downstaging was achieved consolidation chemoradiotherapy with 64,3 Gy and same chemotherapy as above. 4b. If not: cystectomy was recommented.		chemotherapy vs. those who did not receive adjuvant chemotherapy: 44 patients/81% vs. 19 patients/49% (p=0,002). **5-year bladder-intact survival** 5-year bladder-intact survival of paclitaxel vs. fluorouracil group: 67% (95% 53-81) vs. 71% (95% CI 57-84). Completition of induction chemoradiotherapy of paclitaxel vs. fluorouracil group: 45 patients/98% (95% CI 89-100) vs. 45 patients/96% (95% CI 86-99). **Completition of study** Completition of induction and consolidation regimens of paclitaxel vs. fluorouracil group: 39 patients/85% (95% CI 71-94) vs. 39 patients/83% (95% CI 69-92).	study.
Turgeon 2014 Canada	Retrospective single center case series 3	N= 24 patients. Median age: 79 patients (range 72-88 years). T2-T4N0M0 bladder cancer.	1. Maximally feasible TURBT. 2. Hypofractionated intensity modulated radiation therapy (IMRT) (50 Gy in 20 fractions) and		Endpoints: - complete response - completiton of study - overall survival - cancer-specific survival - toxity	Median follow-up: 28 months (range 7-60 months). Complete response: 19 patients/83%. 3-year overall survival rate: 61%. 3-year cancer-specific survival rate: 71%. 75% of the surving patients have a	Inclusion criteria: age > 70 years. Short period of follow-up. Very small number of patients.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			concomitant chemotherapy with gemcitabine or cisplatin. 3. Evaluation 1 and 3 months after treatment.			disease-free and functioning bladder. Completition of hypofractionated IMRT: 100%. Completiton of Grade 3 gastrointestinal or genitourinary toxites: 4%. Grade 3/4 hematologic toxities, liver toxities: 17%. Autors conclusion: Hypofractionated IMRT with concurrent radiosensitizing chemotherapy appears to be an effective and well-tolerated curative treatmet strategy in the elderly population and should be considered for patients who are not candidates for cystectomy or who wish to avoid cystectomy.	
Zietman 2001 USA	Retrospective single center case series 3	N=190 patients. T2-T4 bladder cancer.	5 different protocols for selective bladder preservation: 1. Complete transurethral resection. 2a. Two cycles of neoadjuvant chemotherapy		Outcomes of patients with superficical relapse after trimodality treatment. Endpoints: - complete response - disease-specific survival rate - overall survival - recurrence	Median follow-up: 6,7 years (range: 1,3 to 12,1 years). Complete response: n=125 patients (64%). 5-year disease-specific survival rate of all patients vs. T2 vs. T3/4: 63% vs. 74% vs. 53%. Recurrence of invasive tumor vs. superficial tumor: 16 patients (13%) vs.	Retrospective single center, Population treated with 5 different protocols for selective bladder preservation

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			with methotrexate, cisplatin and vinblastine n=96. 2b. 40 Gy radiation therapy + chemotherapy for all patients. 3. Cystoscopic evaluation.			32 patients (26%). Median time to failure: 2,1 years. 32 patients with recurrence of superficial tumor: - 60% of superficial failures: CIS. - 67% with recurrence at original tumor site. - Tis in the original TURBT did not appear to predict a lower complete response rate to trimodality therapy. Comparison of 5-year overall survival of patients with no recurrence vs. patients with recurrence: 68% vs. 69%. Chance of 5-year survival with native bladder of patients with no recurrence vs. patients with recurrence: 69% vs. 52%. Comparison of 8-year overall survival of patients with no recurrence vs. patients with recurrence: 61% vs. 54% (not statistically significant). Chance of 8-year survival with native bladder of patients with no recurrence vs. patients with recurrence: 61% vs. 34% (P=0,07).	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Autors conclusion: A trimodality approach to transitional cell bladder cancer mandates lifelong cystoscopic surveillance. Although most completely responding patients retain their bladders free from invasive relapse, one quarter will develop superficial disease. This may be managed in the standard fashion with transurethral resection of the bladder tumor and intravesical therapies but carries an additional risk that late cystectomy will be required.	

6.12. AG 5 Schlüsselfrage 12 (Salvage-Zystektomie nach RT/RCT)

„Wann ist die Salvage-Zystektomie beim High-Risk T1 Urothelkarzinom und beim muskelinvasiven Urothelkarzinom nach erfolgter RT/RCT indiziert?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Rödel 2002 Germany	Single-center case-series 3	N=415 patients. n=89 T1 high risk n=326 T2-T4	Radiotherapy (RT) n=126. Radiochemothera		Evaluation of long-term experience with combined modality treatment and selective	Median follow-up: 60 months (range: 6-199 months) for all surving patients.	Intent-to-treat analysis for the impact of chemotherapy on

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		- Organ metastases n=0. - Pelvic lymph node metastases n=28 (unknown n=56). - Lymph vessel involvment n=157 (unknown n=53). - Multifocality of tumor n=127 (unknown n=37).	py (RCT) after TUR n=289. RT/RCT 4 to 8 weeks after initial TUR using 6- to 10-mV photons and a 4-field box technique with individually shaped portals and daily fractions of 1,8 to 2,0 Gy on 5 consecutive days. Median total dose of 54 Gy (range 45 to 69,4 Gy) was applied to the bladder. Median total dose of 45 Gy (range 40 to 59,4 Gy) was applied to the pelvis. Chemotherapy:		bladder preservation. Endpoints: 1. (complete) response 2. recurrence 3. freedom from distant metastasis 4. toxity 5. overall survival 6. cause-specific survival Identification of factors for prediciton of treatment response, risk of relapse and survival.	1. (Complete) Response: At restaging-TUR: - Complete response n=288 (72%). - Only superficial residual tumor n=20 (5%). - Muscle-invasive tumor n=90 (23%). Factors for prediction on complete treatment response and survival (univariate analysis): - Early tumor stage (p<0,0005) - Complete initial TUR (p<0,0005) - Pelvic lymph node status (p=0,03) - Treatment modality. RCT more effective than RT in therms of complete response and survival 2. Recurrence: Local control (n=288): - Continuously free of tumor after complete response without muscle-invasive relapse in n=186 (65%) patients at 10 years. - Relapse of non-invasive tumor (Ta/Tis) n=26 (9%) patients. - T1-recurrent tumor in n=15 (5%) patients. - Muscle-invasive relapse in n=32 (11%) patients. - Pelvic recurrence in n=10 (3%) patients.	the different end points. High number of patients. Long time period of follow-up.

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			- Cisplatin (n=145) (25 mg/m²/d) applied during the first and fifth week. - Carboplatin (n=95) (65 mg/m²/d) on five consecutive days. - Combination of cisplatin (20 mg/m²/d) and 5-fluorouracil (600 mg/m²/d) (n=49). Reevaluation of response after six weeks by restaging-TUR.			→ Multifocality of primary tumor is associated with higher risk for local relapse (P=0,08). 3. Freedom from distant metastasis Distant metastases: Distant metastases diagnosed in 98 (35%) patients at 10 years. Ten-year specific survival was 42% (80% of survivors preserved their bladder). Prognostic factors for the development of distant metastases (univariate analysis) (n=415): - R0 (p<0,0001) - T1 (p<0,0001) - cN0 (p=008) - L0 (p=0,001) → Concurrent systemic chemotherapy had no impact on the development of distant metastases. Salvage Treatment: Salvage cystectomy for local failure was associated with 45% survival at 10 years. 5. Overall survival Overall survival at 5 years was 51%, at 10 years 31%. Prognostic factors for overall survival	

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						after combined modality treatment (multivariat analysis): - Age < 67 years: p=0,003 - R0: p=0,003 - T1: p=0,02 - cN0: p=0,4 - L0: p=0,02 - RT alone: p=0,06 6. Cause-specific survival Cause-specific survival at 5 years was 56%, at 10 years 42%. Authors conclusion: TUR with RCT is a reasonable option for patients seeking an alternative to radical cystectomy. Ideal candidates are those with early-stage and unifocal tumors, in whom a complete TUR is accomplished.	
Weiss 2006 Germany	Single-centre case series 3	N=141 patients with primary or recurrent high-risk T1 bladder cancer. n=84 with T1G3 n=57 with T1G1/2	Initial TURBT. Radiotherapy (RT) n=28 (4 to 6 weeks after TURBT) using 6- to 10-MV photons and four-field box technique with individually shaped portals		Endpoints: - (complete) response - local control - recurrence - progression - disease-specific survival - overall survival - bladder preservation - toxity	Median follow-up: 62 months (range: 5,8 to 233,3 months). 65 patients have been observed for 5 years or more. 31 patients have been observed for 10 years or more. At restaging TURBT: - Complete response: n= 121 (88%) (of 137 patients, 4 patients without restaging TURBT). - Complete response for patients with	Patient collective seems to be partly the same as in the study of Rödel et al. 2002.

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			and daily fractions of 1.8 to 2 Gy on 5 consequtive days. Platinum-based radiochemotherapy (RCT) n=113: - n=43: Cisplatin (25 mg/m²/d) - n=16: Carboplatin (65 mg/m²/d) - n=54: Combination of cisplatin or carboplatin and 5-fluorouracil (600 mg/m²/d). N=8 received deep regional hyperthermia. 6 weeks after RT/RCT response was evaluated by restaging TURBT.			T1G3: n=84 (89%). - Noncomplete response n=16: n=5 with Ta n=3 with Tis n=7 with T1 n=1 with tumor progression (distant metastases). Complete responders (n=121): - n=72 (60%): no further relapse - n=36 (30%): further relapse (16 of 36 received salvage cystectomy; 9 of 16 no further relapse) - n=13 (10%): progression Noncomplete responders (n=16): - n=4: salvage cystectomy (3 of 4 no further relapse) - n=11: TURBT with or without intravesial therapy (4 of 11 no further relapse) - n=1: no further treatment (0 of 1no further relapse). Overall failure rates: - Overall failure rates (n=141) at 5 vs. 10 years: 49% vs. 64%. - Failure rates for T1G3 (n=84) at 5 vs. 10 years: 35% vs. 46%. - Overall failure rates (n=141) for patients after complete response at TURBT at 5 vs. 10 years: 44% vs. 61%.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Overall progression rates: - Overall tumor progression (n=141) at 5 vs. 10 years: 19% vs. 30%. - Tumor progression for T1G3 (n=84) at 5 vs.10 years: 13% vs 99%. - Overall progression rates (n=121) for patients after complete response at TURBT at 5 vs. 10 years: 15% vs. 28%. Disease-specific survival rates (n=141) at 5 vs. 10 years: 82% vs. 73%. Overall survival rates (n=141) at 5 vs. 10 years: 71% vs. 51%. More than 80% of survivors preserved their bladder. Factors for prediction on complete treatment response and survival (univariate analysis): - Completeness (R0) at initial TURBT (p<0,001). Authors conclusion: RT/RCT after TURBT with selective bladder preservation is a reasonable alternative to intravesical treatment or early cystectomy for high-risk T1 bladder cancer.	

7. G 6: Harnableitung

7.1. AG 6 Schlüsselfrage 2 (Komorbiditäten bei Zystektomie)

„Welche Komorbiditäten (Alter, Stadien etc.) und andere Kriterien beeinflussen die peri- und postoperative Morbiditätsrate bzw. das progessionsfreie- und tumorspezifische Überleben sowie Gesamtüberleben bei der radikalen Zystektomie mit Harnableitung?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Abdollah 2012 USA	Population-based report Prognostic cohort study to develop and validate predictive factors 3	N=12,274 diagnosed with bladder cancer and treated with Radical Cystectomy (RC) between 1998 and 2007. Average patient age was 68.5 years (median 70, range 40–95). Most patients were male (83.1%) and white (65.4%).	Development cohort consisted of 6188 (50.4%) patients, used to fit univariable and multivariable logistic regression models predicting POM after RC.	Validation cohort consisted of 6086 (49.6%) patients, used to assess the accuracy of the reference table in predicting POM.	Develop and externally validate a reference table that quantifies postoperative mortality (POM after RC. Analysis for prediction of POM adjusted for: age, sex, race, Charlson comorbidity index (CCI), urinary diversion type, year of surgery, annual hospital caseload,	POM occurred in 2.4% of patients. POM proportion increased with increasing age (≤ 59: 0.6% vs. 60–69: 1.6% vs. 70–79: 3.1% vs. ≥ 80: 4.6%, P < 0.001), and higher CCI (CCI 0: 1.7% vs. CCI 1: 3.0% vs. CCI 2: 4.2% vs. CCI 3: 4.3% vs. CCI ≥ 4: 12.1%, P < 0.001). (publication entails a Reference table for individual prediction of POM rate after RC using CCI and age category) In multivariable analyses, only age and CCI remained as independent predictors of POM, after stepwise variable removal. The discrimination accuracy of the reference table in predicting POM was 70%.	Retrospective The current study could be affected by surgical selection bias. The accuracy of the model is good (70%), and it is highly generalizable. Limitations: The use of in-hospital ICD-9 codes without accounting for preadmission

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		Most patients had no comorbidity according to Charlson comorbidity index (CCI) (68.1%). Urinary diversion consisted of ileal conduit in the majority of cases (76.4%). Most patients were operated in hospitals of low caseload (38.9%), in the South region (35.7%), and within urban-teaching hospitals (62.9%).			location/teaching status of hospital, region and bed size of hospital.		data. Retrospective data were abstracted by trained personnel (coding errors may have affected the findings). The current study could be affected by surgical selection bias.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Bastian 2008 USA	Prognostic cohort study [non-inception]) 3	n=381 Patients with pT2 and pT3 stages, treated with radical cystectomy and bilateral pelvic lymphade-nectomy for transitional cell carcinoma of the urinary bladder. 172 patients with pT2 (organ-confined muscle-invasive disease) 209 patients with pT3 (88 pT3a microscopic perivesical fat invasion and 121 pT3b macroscopic perivesical fat invasion.			To examine whether the presence of microscopic (pT3a) or macroscopic (pT3b) disease worsens the prognosis relative to pT2 disease at radical cystectomy. Bladder cancer-specific survival Bladder cancer recurrence-free survival Bladder cancer recurrence or death.	Patients were followed every 3 or 4 months for the first year, semi-annually for the second year and annually thereafter. Follow-up: median 2,9 years Microscopic perivesical fat extension (pT3a) was not associated with higher recurrence (*P*=0.3) or the mortality rate (*P*=0.06) vs pT2 disease. Deep perivesical fat extension (pT3b) was associated with 1.8 times the rate of recurrence (*P*=0.002) and with twice the rate of death (*P*=0.001) vs pT2 disease.	Retrospective Further validation of our data is required. Findings and suggestions need to be confirmed and validated in other series. Limitations: Patients with unifocal pT3a disease are classified in the same category as those with multifocal pT3a disease. Limitations, which might affect the classification of pathological stage, and the determination of

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Exclusion of patients with neoadjuvant or adjuvant therapy.					the outcomes of interest, i.e. recurrence and death. Limited Sample size
Bolenz 2010 Germany	Prognostic cohort study(inception cohort) 3	1099 lymph node-negative patients treated with RC at six German institutions. All patients underwent bilateral pelvic lymphadenectomy (LA), Radical Cystectmoy and urinary diversion between 1985 and 2008. Indications for RC included centre-based	Radical Cystectomy in lymphnode-negative patients.	No control	The aim was to validate the importance of lymphovascular invasion (LVI) as a prognostic marker (disease recurrence and cancer-specific survival (CSS) in a large multicentre cohort of lymph node-negative patients who underwent RC.	Lymphovascular invasion (LVI) was present in 295 (26.8%) patients; the presence of LVI correlated significantly with increasing tumour stage, i.e. pT1, 65 (29.4%); pT2, 88 (31.5%); pT3 110 (31.8%); and pT4 32 (38.1%) (*P*=0.002) and grade (*P*<0.001). In univariable analysis the presence of LVI was significantly associated with reduced recurrence-free survival (*P*=0.008) and reduced CSS (*P*=0.039). On multivariable Cox regression analysis tumour stage (*P*<0.001), age (> 75 vs ≥ 75 years; *P*=0.018) and LVI (*P*<0.001) were identified as independent predictors of CSS. Assessment of LVI might be useful as an	Retrospective, Multicentre Study Limitations: Various physicians and pathologists were involved. The study period exceeded two decades. The change in certain practice patterns might have created heterogeneity in the patient cohort. There was no re-evaluation of the pathological slides.

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		cystoscopic and biopsy findings, and recurrent multifocal non-muscle-invasive disease refractory to repeated TUR. Adjuvant chemotherapy was used in 64 patients (5.8%). Exclusion: Patients with pathologically confirmed lymph node-positive disease (n=549), distant metastases (n=21), RC for palliative reasons (n=39), benign disease of the urinary bladder				additional staging tool and could improve the selection of patients who are likely to benefit from adjuvant therapy after RC.	To reduce bias, only patients for whom the pathology reports contained explicit information on the presence or absence of tumour cells within a clear endothelial lining were included.

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		and/or metastatic invasion by other primaries (including non-UBC, 12), and invalid and/or incomplete pathological data (on the presence or absence of LVI, 50) or follow-up information (n=227). We also excluded patients who received neoadjuvant chemotherapy (n=14).					
Chromecki 2012 USA, Austria,	Multi-institutional,Case Series/prognostic cohort study	4,429 patients treated with Radical Cystectomy (RC) and	Multicenter validation of the prognostic value of patient age in patients treated	No control	The association of chronological age with pathologic and long-term oncologic	Higher age at RC was associated with advanced pathologic stage ($P < 0.001$), higher tumor grade ($P = 0.045$), presence of lymphovascular invasion ($P = 0.018$), and positive soft-tissue surgical margin	Multicentre Study (12 centers worldwide) Retrospective

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Germany, Canada, Italy	3	lymphadenectomy for urothelial carcinoma of the bladder (UCB) without neoadjuvant chemotherapy. No patient received preoperative chemotherapy and/or radiotherapy. No metastatic disease at the time of surgery as shown by radiographic and/or nuclear imaging. A total of 999 patients received adjuvant chemotherapy at	with radical cystectomy.		outcomes was evaluated in patients treated with RC and bilateral lymphadenectomy for UCB. We estimated the probability of experiencing disease recurrence or dying of UCB within different age groups.	status ($P = 0.004$). Elderly patients were less likely to receive postoperative chemotherapy ($P < 0.001$). Higher age was associated with disease recurrence, cancer-specific, and overall mortality ($P < 0.001$). Patients ≥ 80 years had a significantly greater risk of cancer-specific mortality than patients <50 years (HR 1.763, P < 0.001). Age minimally improved the accuracy of a base model that included standard pathologic features for prediction of disease recurrence (+0.2–0.3%) and cancer-specific survival (+0.3%). Follow Up: median 43 months Postoperatively at least every 3–4 months in year 1, semiannually in year 2, and annually thereafter.	Study Limitations: Inherent to retrospective analyses Extent to which patient age factored into the selection of RC and/or perioperative chemotherapy. A careful analysis of other factors, such as the impact of comorbidities, is needed. Lack of date regarding such as access to care and timing of surgery.

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		the investigator's discretion. Indication for radical cystectomy was muscle-invasive disease or invasion into the prostatic stroma, or recurrent Ta, T1 or CIS refractory to TUR or intravesical chemo- or immunotherapy. The median patient age was 67 years.					
Chromecki 2013 USA, Austria, Germany, Canada,	Multi-institutional, Case series/ prognostic cohort study 3	4118 patients treated with Radical Cystectomy (RC) and pelvic lymphadenectomy for urothelial	Effect of BMI on disease recurrence, cancer-specific mortality and overall mortality.	No control	Investigate the association between body mass index (BMI) and oncological outcomes in patients after	Median BMI was 28.8 kg/m^2 (interquartile range 7.9); 25.3% had a BMI < 25 kg/m^2, 32.5% had a BMI between 25 and 29.9 kg/m^2, and 42.2% had a BMI _30 kg/m^2. Patients with a higher BMI were older (P < 0.001), had higher tumour grade (P <	Retrospective design Multicentre Study (12 centers worldwide)

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Italy, Czech Republic		carcinoma of the bladder (UCB). Patients receiving preoperative chemotherapy or radiotherapy were excluded.			radical cystectomy (RC) for urothelial carcinoma of the bladder (UCB).	0.001), and were more likely to have positive soft tissue surgical margins (P = 0.006) compared with patients with lower BMI. In multivariable analyses that adjusted for the effects of standard clinicopathological features, BMI > 30 was associated with higher risk of disease recurrence (hazard ratio (HR) 1.67, 95% confidence interval (CI) 1.46–1.91, P < 0.001), cancer-specific mortality (HR 1.43, 95% CI 1.24–1.66, P < 0.001), and overall mortality (HR 1.81, CI 1.60–2.05, P < 0.001). Obesity is associated with worse cancer-specific outcomes in patients treated with RC for UCB. Focusing on patient-modifiable factors such as BMI may have significant individual and public health implications in patients with invasive UCB. We found that obesity (BMI ≥ 30 kg/m^2) was associated with features of	Specifically designed to investigate the association between BMI and cancer-specific outcomes in UCB. Study strengths include its large cohort size and the duration of follow-up. Limitations: Retrospective analyses We are unable to comment on the extent to which BMI factored into the selection of RC among other available treatment options for patients, or how many patients

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						biologically aggressive UCB and clinical outcomes after RC and, even when adjusting for the effects of standard clinicopathological features, obesity remained an independent predictor of cancer recurrence, cancer-specific mortality and overall mortality. Follow Up: Median 44 months Postoperatively at least every 3–4 months in year 1, semi-annually in year 2, and annually thereafter.	were not treated with RC. Outcomes from multiple surgeons and surgical techniques were evaluated. ts. The worse outcome in obese patients may be the result of delay in diagnosis or definitive therapy with curative intent. Metabolic syndrome is an important area of investigation and therapy in patients with UCB.
Horovitz 2012 Canada,	Multi-institutional, Case series/prognos	605 Patients with bladder cancer (BC) undergoing RC at two	Patients were divided into four age groups: ≤ 59, 60 – 69, 70 – 79	No control	Analyse the impact of patient age on survival after radical cystectomy	Compared with younger patients (age ≤ 79 years), elderly patients (age ≥ 80 years) had higher ASA scores ($P < 0.001$), a greater number of lymph nodes	Retrospective design Although RC is an

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Finland	tic cohort study. 3	academic centres (University Heath Network, Toronto, Canada, 1992 – 2008 and University of Turku, Turku, Finland, 1986 – 2005). Exclusion: Salvage RC after failed radiotherapy or neoadjuvant chemotherapy and Non-urothelial malignancies. Considered factors: Gender (134 women, 471 men). American Society	and ≥ 80 years. Demographic, clinical and pathological data were compared, as well as recurrence free survival (RFS), disease-specific survival (DSS) and overall survival (OAS) rates.		(RC).	removed during surgical dissection (P < 0.001), and underwent less adjuvant treatment (P < 0.001). Choice of urinary diversion differed among the groups, with ileal conduit being used for all patients ≥ 80 years (P < 0.001). No differences were noted between age groups with respect to RFS (P = 0.3), DSS (P = 0.4) or OAS (P = 0.4). No differences were noted among the groups in terms of gender, clinical stage, treatment delay from the time of last TUR to RC or rates of neoadjuvant treatment. Follow-up: Every 3 months for the first year, bi-annual follow-up until 5 years and annual follow-up thereafter. Follow-up time was defined as the period from the date of the RC to the patient's last visit, death or recurrence. The present findings suggest that	operation with significant morbidity, it is a viable treatment option for carefully selected elderly patients.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		of Anesthesiologists (ASA) score (n=348[1-2]; n=223 [3-4]; 34 missings). Conduit (n=346); Neobladder (n=159); Continent cutaneous diversion (n=48); Ureterosigmoide ostomy (n=2); other (n=3) CIS/cTa cT1 (n=87) cT2 (n=170) cT3 (n=49) cT4 (n=28) Neoadjuvant treatment (n=56) Median number				carefully selected elderly patients have similar recurrence free survival (RFS), disease-specific survival (DSS) and overall survival (OAS) compared with younger patients undergoing the same procedure.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		of days between last transurethral resection (TUR) and RC (6-395). Pathological specimens.					
Johar 2013 Germany, South Korea, Spain, Sweden, Turkey, United Kingdom, USA	Multi-institutional, Case series/ prognostic cohort study 3	939 patients who underwent robot-assisted radical cystectomy (RARC), had available complication data, and had at least 90 days of follow-up. The median age was 68 years (interquartile range [IQR]: 60–76), and median BMI was 27 kg/m^2 (IQR: 24–30).	Complications after Robot-assisted Radical Cystectomy Logistic regression models were used to define predictors of complications and readmission.	No control	Describe the complications after robot-assisted radical cystectomy (RARC) using a standardized and validated reporting methodology (Memorial Sloan-Kettering Cancer Center [MSKCC] system and were defined and stratified by organ system).	41% (n = 387) and 48% (n = 448) of patients experienced a complication within 30 and 90 d of surgery. The highest grade of complication was grade 0 in 52%, grade 1–2 in 29%, and grade 3–5 in 19% patients. Gastrointestinal, infectious, and genitourinary complications were most common (27%, 23%, and 17%). On multivariable analysis, increasing age group, neoadjuvant chemotherapy, and receipt of blood transfusion were independent predictors of any and high-grade complications. 30 and 90-d mortality was 1.3% and 4.2%.	Retrospective design 16 participating institutions As a multi-institutional database, a disparity in patient selection, operating standards, postoperative management, and reporting of complications can be considered a major limitation of the study.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		considered factors: Age, Gender, BMI, ASA Score (American Society of Anesthesiologists), Prior abdominal surgery, Neoadjuvant chemotherapy, Preoperative radiation, Diversion type, Diversion location.				Surgical morbidity after RARC is significant when reported using a standardized reporting methodology. The majority of complications are low grade.	
Koppie 2008 USA	Single-institutional Case series. 3	1121 patients who underwent Radical Cystectomy (RC) as initial treatment for clinically localized transitional cell carcinoma of the bladder from	Radical Cystectomy for transitional cell carcinoma of the bladder.	No control	The association between age and comorbidity (measured by age-adjusted Charlson comorbidity index (ACCI)) on overall and disease-specific survival and progression free survivial	ACCI scores (age-adjusted Charlson comorbidity index) increased during the study period (P = 0.009). Extravesical disease was present in 43% of patients with ACCI ≤ 2, 49% with ACCI 3–5, and 56% with ACCI > 5 (P = 0.051). Patients with higher ACCI were less likely to have lymph-node dissection (odds ratio, 0.55 and 0.35, for ACCI 3–5 and >5	Single institution Retrospective design Limitations: We used the ACCI to quantify age and comorbidity in this study. The Charlson

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		1990 through 2004. Considered factors: Age, sex, American Society of Anesthesiologists (ASA) score, pathologic stage, nodal status, postoperative chemotherapy, lymph-node dissection status, lymphnode counts, and urinary diversion type.			(progression was defined as the earlier of postoperative development of local or distant recurrence or death from bladder cancer) after RC by using a competing risk analysis. We also compare the clinicopathologic and treatment characteristics of patients undergoing RC for transitional cell carcinoma of the bladder among various age adjusted comorbidity risk groups.	vs ≤ 2; P = 0.005), and when it was performed, fewer lymph nodes were evaluated (P < 0.0005). Patients with higher ACCI were also less likely to have postoperative chemotherapy (odds ratio, 0.70 and 0.66, for ACCI 3–5 and >5 vs ≤ 2; P = 0.04). Higher ACCI was significantly associated with lower overall (P < .005) but not recurrence-free (P = 0.17) survival after RC. ACCI Status and Overall Survival: There were 559 deaths observed during the follow-up period. Median follow-up for survivors was 3.0 years. Median overall survival for patients with low, moderate, and high ACCI scores was 6.3, 3.9, and 1.7 years. Compared with patients who had low ACCI scores, patients with moderate scores had a hazard ratio of 1.46 (95% confidence interval [95% CI], 1.20–1.78).	comorbidity score has been used to assess disease specific and overall survival for various cancers, this instrument does not address the full breadth of comorbid conditions common among patients with bladder cancer.

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						ACCI Status and Progression-Free Survival: Overall, 374 patients progressed, and another 234 patients died from causes other than bladder cancer (without evidence of disease). Median follow-up for patients who were progression-free and alive at last follow-up was 3.0 years. The 5-year cumulative incidence of progression, adjusted for death as a competing risk, for patients with low, moderate, and high ACCI scores was 39% (95% CI, 34–46%), 34% (95% CI, 31–39%), and 47% (95% CI, 38–59%), (P = 0.07). Analysis for pathologic stage and nodal status found no significant association between ACCI status and progression-free survival (P = 0.17).	
May 2011 Germany	Multi-institutional national Case series/prognos	477 patients with Lymphnode (LN)-positive tumours (pN1–2, M0) for	Lymph Node Density Affects Cancer-Specific Survival in	No control	To evaluate prognosis criteria using a large cohort of Radical	The median number of LNs removed was 12 (range: 1–66), and the median number of positive LNs was 2 (range: 1–25).	Multi institutional study Retrospective

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	tic cohort study. 3	whom data were available concerning the following study criteria: pT, pN stage, grading, associated Tis, adjuvant chemotherapy or radiation therapy (RT), number of LNs removed, and number of positive LNs. The exclusion criteria were having received neoadjuvant chemotherapy, morphological evidence of organ metastasis on imaging, and data missing and incongruent with the study	Patients with Lymph Node–Positive Urothelial Bladder Cancer Following Radical Cystectomy.		Cystectomy (RC) patients with LN-positive urothelial BCa and to define factors associated with long-term survival.	Median follow up: 16 months 290 (60.8%) of the patients presented with stage pN2 disease. The median and mean Lymphnode (LN) density was 17.6% and 29% (range: 2.3–100), where 268 (56.2%) and 209 (43.8%) patients exhibited am LN density of ≤ 20% and >20%. In separate multivariable Cox regression models adjusted for age, sex, pTN stage, grade, associated Tis, and adjuvant chemotherapy, the interval-scaled LN density (hazard ratio [HR]: 1.01; p = 0.002) and the LN density, ordinal-scaled by 20% (HR: 1.65; p < 0.001) exhibit independent effects on cancer-specific survival (CSS). In addition, an independent contribution appears from the pT but not the pN stage.	design Our study is the first to document that LN density (threshold value = 20%) has a significant effect on CSS, both for limited PLND (<12 LNs) as well as for standard/ extensive PLND. Limitations: Long timeframe for the investigation (modifications in the staging modalities, development of surgical techniques, including PLND techniques). Surgeon selection

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		criteria. The median follow-up period for all living patients was 28 months. Considered factors: Age, Sex, Radical Cystectomy time frame, pT stage, pN stage, Grade, Associated Tis, Adjuvant chemotherapy, Total no. Lymphnodes, Total no. positive Lymphnodes, LN density.					bias when determining the extent of lymphadenectomy. Absence of centralised pathologic reviews. Different, clinicspecific diagnostic protocols, therapies, and follow-up. Before LN density can be integrated into the pNclassification and the clinical decisionmaking process, however, the present results should be validated by prospective studies with

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							defined LN dissection areas and standardised histopathologic examination methods.
Mc Cabe 2007 United Kingdom	Multi-institutional national Case series 3	All cystectomies performed for bladder cancer in England over 5 years (1998–2003) were analysed. 6308 patients were identified who underwent cystectomy for urological malignancy. 4787 were male and 1521 female, with an overall mean age of 66.1 years.	Cystectomy for urological malignancy. The surgeon's outcomes were then analysed with respect to the overall level of activity in their operating centre.		Comparison of patient demographics and outcomes according to case volume of operating surgeon (high volume surgeon (>8). Analysis was undertaken to describe the relationship between each surgeon's annual case volume and two outcome measures: in-hospital mortality rate (rate of death	The overall mortality rate for the 5 year period was 5.6%. Mean duration of hospital stay was 21.9 days. The number of surgeons who performed cystectomy annually decreased from 346 in 1998–99 to 309 in 2002–03, overall annual mortality rates from 7.3% to 5.2%. A significant inverse correlation (Pearson coefficient -0.968, $p < 0.01$) was found between case volume and mortality rate. Applying 95% confidence interval estimation, the minimum caseload required to achieve the lowest mortality rate was eight procedures per year. Our data suggest that the threshold is eight operations per surgeon annually for radical cystectomy.	Multi-institutional Retrospective design Our study is the first to examine the relationship between individual surgeon volume and mortality for radical cystectomy in the UK.

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					before hospital discharge), and hospital stay. Derive the minimum caseload a surgeon requires to achieve optimum outcomes and to examine the effect of the operating centre size upon individual surgeon's outcomes.	Increasing caseload beyond eight operations per year did not produce a significant reduction in mortality rate. Analysis of HES data confirms an inverse relationship between surgeon's caseload and mortality for radical cystectomy. A caseload of eight operations per year is associated with the lowest mortality rate.	
Messer 2014 11 institutions in Canada, Germany, Italy, USA	Multi-institutional international Case series/prognostic cohort study. 3	4216 patients (890 women, 21% and 3326 men, 79%), who underwent radical cystectomy with bilateral lymphadenectomy between 1979 and 2008 for	Radical cystectomy with bilateral lymphadenectomy.	No control	The association of gender with disease recurrence and cancer-specific mortality was examined using a competing risk analysis.	Disease recurred in 1430 patients (33.9%) (36.8% of women and 33.1% of men) at a median of 11 months after surgery. Death from any cause was observed in 46.0% of men and 50.1% of women. Cancer-specific death was observed in 33.0% of women and 27.2% of men. The median 5-year overall survival	Multi-institutional Study Retrospective design Limitations: The inability to account for additional potential

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		transitional cell carcinoma (TCC) of the bladder, who did not receive radiotherapy or chemotherapy before radical cystectomy, and who did not have distant metastatic disease at the time of cystectomy.				estimates for the entire cohort was 56.1% (95% confidence interval [CI], 54.5%-57.8%). The 5-year overall survival estimates for women and men were 51.9% (95% CI, 48.3%-55.4%) and 57.3% (95% CI, 55.4%-59.1%), (P = 0.006). The 5-year cancer-specific mortality cumulative incidence rates adjusted for competing risks for women and men were 37.0% (95% CI, 33.4%-40.5%) and 30.4% (95% CI, 28.6%-32.2%). The 5-year disease recurrence cumulative incidence rates adjusted for competing risks for women and men were 40.8% (95% CI, 37.2%-44.3%) and 36.7% (95% CI, 34.9%-38.5%). Gender was significantly associated with an increase in cancer-specific mortality on univariable analysis (hazard ratio [HR], 1.25; 95% CI, 1.10-1.43; P = 0.001). Multivariable regression with competing	confounders, such as differences in environmental exposures, treatment selection, and histologic subtypes between men and women. We were unable to fully characterize the disease stage because of lack of pathologic substaging. Insufficient numbers of patients within substages may explain the lack of an association of gender with cancer-specific survival within substages. Adjuvant chemotherapy was

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						risk found that female gender was associated with an increased risk for disease recurrence and cancer-specific mortality (hazard ratio, 1.27; 95% confidence interval, 1.108-1.465; P = 0.007) compared with male gender. Follow-up: At least every 3-4 months for the first year after cystectomy, every 6 months for the second year, and annually thereafter. The median follow-up duration was 31.5 months for all patients. Our analysis identified female gender as a poor-risk feature for patients undergoing radical cystectomy. This adverse prognostic factor was independent of standard clinical and pathologic features and competing risk from none cancer-related death.	associated with a surprisingly lower disease-specific survival on multivariable analysis, which suggests that confounding was not completely eliminated in the model. Failure to properly adjust for factors influencing adjuvant therapy would indicate the presence of residual confounding which could also influence the association of gender with mortality. A degree of selection bias

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							undoubtedly contributed to the lack of difference in stage between men and women in our cohort.
Novara 2010 Canada, Germany, Italy, USA	Multi-institutional international Case series. 3	4,410 patients who underwent Radical Cystectomy (RC) with bilateral lymphadenectomy between 1980 and 2008. No patient received preoperative radiotherapy or chemotherapy. No patient had distant metastatic disease at the time of RC.	Radical Cystectomy (RC) with bilateral lymphadenectomy. The entire cystectomy surgical specimen was inked, and multiple sections were obtained from the tumor, the bladder wall, and mucosa adjacent to and distant from the tumor in addition to the ureters and regional lymph nodes.	No control	We evaluated the association of soft tissue surgical margins with characteristics and outcomes of patients treated with radical cystectomy for urothelial carcinoma of the bladder. To validate the significance of soft tissue surgical margin (STSM) and to bypass the statistical limitations of previous efforts.	Positive soft tissue surgical margins were identified in 278 patients (6.3%). The most common locations were the posterior (23%) and lateral (12.2%) bladder walls of the bladder, and periprostatic (10%) and periurethral (9.3%) soft tissue. On univariate analysis positive soft tissue surgical margin was significantly associated with advanced pT stage, higher tumor grade, lymphovascular invasion and lymph node metastasis ($p < 0.001$). Actuarial 5-year recurrence-free and cancer specific survival probabilities were 62.8% ± 0.8% and 69% ± 0.8% for patients without soft tissue surgical margins vs 21.6% ± 3.1% and 26.4% ± 3.3% for those with positive soft tissue surgical margins	Retrospective design Multinstitutional Study To our knowledge this is the largest series evaluating the prognostic role of soft tissue surgical margins (STSMs) in urothelial carcinoma of the bladder (UCB). Solid pieces of evidence are lacking and prospective

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		Overall 996 patients (22.6%) received adjuvant chemotherapy at investigator discretion based on patient tumor stage and overall health status.	In men tissue was obtained from the seminal vesicles and prostate. In women sections were obtained from ovaries, uterus and vagina. Pelvic lymph node dissections were examined grossly and all lymphoid tissue was submitted for histological examination.			(p < 0.001). On multivariable analyses adjusting for the effect of standard clinicopathological features and adjuvant chemotherapy positive soft tissue surgical margin was an independent predictor of disease recurrence and cancer specific mortality (HR 1.52 and HR 1.51, p < 0.001). Soft tissue surgical margin retained independent predictive value in subgroups with advanced disease such as pT3Nany, pT4Nany or Npositive. Follow Up: median 37 months Postoperatively at least every 3 to 4 months for the first year, semiannually for the second year and annually thereafter. Patients with positive STSMs should be considered for studies of adjuvant local and/or systemic therapy after RC.	randomized studies on adjuvant therapies are strongly needed in this category of patients. Limitations: Patients for whom we obtained largely incomplete information, which could possibly create selection bias, were excluded. RC by multiple surgeons and had specimens evaluated by multiple pathologists. All specimens were examined by dedicated genitourinary

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							pathologists at selected centers. The study period spans more than 25 years and the data in the present study may not represent current practice patterns. STSM status should always be reported in the pathological reports.
Ramani 2009 United Kingdom	Single Centre Case series. 3	846 patients (between 1970 and 2005) had a Radical Cystectomy (RC), of whom 647 had a bladder primary tumour and 199 a primary tumour elsewhere (gynaecological,	Radical Cystectomy (RC)	No control	Changes in peri-operative outcomes (mortality, reoperation rate) over time, irrespective of the previous treatment or pathology. Establish a contemporary	There was a progressive reduction in 30- and 60-day mortality rates, such that the current perioperative mortality (1999–2005) was 0.4% and 2.6%. There was a significant reduction in the re-operation rate over the decades (P=0.01), which is currently 4.7%. Patient age was a significant factor in 30- and 60-day mortality rates (P<0.001 for both) but not for complications	Unselected single-centre series. Data were collected retrospectively from 1970 to 1998 and then prospectively from 1999.

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		colorectal and others). There were 536 men (63%) and 310 women (37%), with a median (range) age of 63 (23–87) years. Patients previously treated by definitive radiotherapy, chemotherapy, and cases of Radical Cystectomy where the primary tumour involved the bladder but was not of bladder origin.			standard for peri-operative outcome for surgery of this type. Identify prognostic factors for perioperative morbidity and mortality.	(*P*=0.09).There was no significant association between either American Society of Anesthesiologists grade or T stage with complication rates (*P*=0.61and 0.12). The overall early complication rate was 35.5% for all pelvic surgery; this compared with 39.5% for those with bladder Transitional Cell Carcinoma (TCC) as the primary. The late complication rate was 25.5% overall, and 26.7% for those with a bladder TCC primary. Age was a statistically significant risk factor (both *P*<0.001) for the 30- and 60-day mortality, There was no significant association between pathological stage and either mortality rate (*P*=0.12 and 0.22). In all, 420 patients had RT before surgery; there was no significant difference between the complication	

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		Variables recorded: patient demographics, ASA grade, tumour characteristics, adjuvant therapy, complication rates, and 30- and 60-day mortality rates, complication rates.				rates after surgery in these patients, at 36.9% after RT vs 34.0% with no previous RT (*P*=0.40). There has been a progressive reduction in mortality related to Radical Cystectomy, associated with both cases of Radical Cystectomy and pelvic exenteration. The contemporary standard for 30-and 60-day mortality rates for these operations is 0.4% and 2.6%.	
Shariat 2006 USA	Multi-institutional national Case series/prognostic cohort study 3	Data from three U.S. academic centers . Of 958 patients, 227 were excluded. This left 731 consecutive patients treated with radical cystectomy and bilateral pelvic	Radical cystectomy and bilateral pelvic lymphadenectomy . .	No contraol	To develop multivariate nomograms that determine the probabilities of all-cause and bladder cancer-specific survival after radical cystectomy and to compare their predictive accuracy to that of American Joint Committee on	During a mean follow-up of 36.4 months, 290 of 731 (39.7%) patients died; 196 of 290 patients (67.6%) died of bladder cancer. Actuarial all-cause survival estimates were 56.3% [95% confidence interval (95% CI), 51.8-60.6%] and 42.9% (95% CI, 37.3-48.4%) at 5 and 8 years after cystectomy. Actuarial cancer-specific survival estimates were 67.3% (62.9-71.3%) and 58.7% (52.7-64.2%) at 5 and 8 years.	Multi-institutional, national Study Retrospective design 200 bootstrap resamples were used to reduce overfit bias and for internal validation. Limitations: Multiple internal

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		lymphadenectomy for bladder transitional cell carcinoma. Female 17,6% Male 82,4% Mean age 64,5 years pT0 7.7% pTis 12.6% pTa 3.1% pT1 12.9% pT2 22.4% pT3 29.5% pT4 11.8% pN0 76.2% pN1 9.2% pN2 12.7% pN3 1.9% AJCC stage: 0* 7.4% 0is 12.2% 0a 3.1%			Cancer (AJCC) staging. Variables considered included age, gender, pathologic stage (pT), pathologic grade, carcinoma in situ, lymphovascular invasion (LVI), lymphnode status (pN), neoadjuvant chemotherapy (NACH), adjuvant chemotherapy (ACH), and adjuvant external beam radiotherapy (AXRT).	The accuracy of a nomogram for prediction of all-cause survival (0.732) that included patient age, pT, pN, LVI, NACH, ACH, and AXRT was significantly superior (P = 0.001) to that of American Joint Committee on Cancer (AJCC) staging-based risk grouping (0.615). Similarly, the accuracy of a nomogram for prediction of cancer-specific survival that included pT, pN, LVI, NACH, and AXRT (0.791) was significantly superior (P = 0.001) to that of AJCC staging-based risk grouping (0.663). Multivariate nomograms provide a more accurate and relevant individualized prediction of survival after cystectomy compared with conventional prediction models, thereby allowing for improved patient counseling and treatment selection.	and external reviews of our consortium data set Exclusion of patients with incomplete information (selection bias) Radical cystectomy by multiple surgeons and specimens evaluated by multiple pathologists. The lack of central pathology represents a potential weakness of our work. As the study period spans over 20 years, the data in the present study may not

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		I 12.0% II 17.8% III 23.1% IV 24.4% Presence of LVI 37.5% Concomitant carcinoma in situ at cystectomy 53.6% NACH 5.2% ACH 25.6% Adjuvant radiotherapy 4.7%					represent current practice patterns. External and prospective validation is needed to control for differences in diagnosis and treatment preferences.
Shariat 2006 USA	Multi-institutional national Case series. 3	Analysis was limited to patients with TCC. A total of 67 patients with nonTCC	Recurrence-free survival Bladder cancer-specific survival Cancer recurrence	No control	We present cancer related clinical outcomes in a large, contemporary, consecutive series of patients with complete	Of the patients 25% had extravesical tumor extension with negative lymph nodes and 23% had lymph node metastasis. The rate of lymph node involvement increased with advancing pathological stage.	Retrospective design Retrospective and prospective data were collected Multi-institutional

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		histology were excluded. This left 888 consecutive patients (19% female and 81% male) with bladder transitional cell carcinoma who were treated with radical cystectomy and pelvic lymphadenectomy at 3 academic centers in the United States between 1984 and 2003. Median patient age was 66.2 years (range 33.1 to 89.2).	Progression-free survival Disease recurrence Disease specific survival		preoperative and postoperative data available who were treated with pelvic lymphadenectomy and radical cystectomy. In addition, we determined the association of established clinical and pathological characteristics with recurrence-free and disease specific survival.	Mean recurrence-free and bladder cancer specific survival ± SE was 58% ± 2% and 66% ± 2% at 5 years. On preoperative multivariate analysis clinical tumor stage and neoadjuvant systemic chemotherapy were associated with cancer recurrence, while more advanced age, clinical tumor stage and preoperative carcinoma in situ were associated with bladder cancer specific mortality. On postoperative multivariate analysis pathological tumor stage, lymph node metastasis, lymphovascular invasion, adjuvant radiotherapy and adjuvant chemotherapy were associated with cancer recurrence, while higher pathological tumor stage, more advanced age, lymph node metastasis, lymphovascular invasion and adjuvant radiotherapy were associated with disease specific survival. Patients with metastasis to regional	study Limitations: Multiple internal and external reviews. Exclusion of patients with incomplete information (selection bias). As the study period spans over 20 years, the data in the present study may not represent current practice patterns. Surgical techniques, indications for surgery and follow-up protocols have changed with time. Assigning cause of death in retrospect

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		The indications for radical cystectomy were tumor invasion into the muscularis propria or prostatic stroma, or Ta, T1 or carcinoma in situ refractory to transurethral resection with intravesical chemotherapy and/or immunotherapy. No patient had distant metastatic disease at cystectomy.				lymph nodes (pT any N1-3) were at significantly higher risk for bladder cancer recurrence and death than patients with extravesical tumor extension (pT3N0), who in turn were at significantly higher risk than patients with organ confined disease (pT2 N0 or less). Patient sex and age were not associated with any clinical and pathological tumor characteristics. Follow Up: Patients were generally seen postoperatively at least every 3 to 4 months for year 1, semiannually for year 2 and annually thereafter. We found that 7% of patients had no evidence of cancer in the cystectomy specimen, 94% had pathological grade III disease, 43% had extravesical disease and 23% had metastasis to regional LNs. The discrepancy between clinical and pathological stage was substantial with	could have resulted in an ascertainment bias. Data are representative of the quality of cystectomy performed by specialist trained in urological oncology at high volume academic institutions. No prospective data on outcomes with regard to functional status and quality of life.

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						up staging at cystectomy in 42% of patients. In contrast, clinical and pathological grades were identical in 86% of patients. At a median followup of 39 months 35% of patients experienced disease recurrence and 28% had died of bladder cancer. The risk of recurrence and bladder cancer death increased significantly with increasing pathological tumor grade and advancing final pathological stage. The results of this large, contemporary, multi-institutional series show that radical cystectomy and pelvic lymphadenectomy provide durable local control and disease specific survival in patients with localized invasive transitional cell carcinoma.	
Shariat 2010 12 centres in Canada,	Multi-institutional international Case series.	N=4257 The indications for RC were tumour invasion	Radical Cystectomy) and pelvic lymphadenectomy for UCB (urothelial	No control	To externally validate the prognostic value of lymphovascular invasion (LVI) (	LVI was detected in 1407 patients (33.1%); the proportion of LVI increased with advancing stage, higher grade, soft-tissue surgical margin involvement, and lymph node metastasis (*P*<0.001 for all).	Multi-institutional Study Retrospective design, but this is

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Germany, Italy, USA	3	into the muscularis propria or prostatic stroma or Ta, T1, or carcinoma in-situ refractory to transurethral resection, with intravesical chemotherapy and/or immunotherapy. No patient had distant metastatic disease at the time of RC, as shown by chest radiography, bone scan and CT or MRI of the abdomen and pelvis. 954 patients	carcinoma of the bladder), without neoadjuvant chemotherapy. Association of LVI with clinical and pathological characteristics (Gender was missing in 20 patients (0.5%), pathological grade in 23 (0.5%), pathological stage in 12 (0.3%), surgical margin status in 18 (0.4%), concomitant CIS in 4 (0.1%), lymph node status in 64 (1.5%) and adjuvant		defined as presence of nests of tumour cells within an endotheliumlined space.) in a large international cohort of patients treated with radical cystectomy (RC) for urothelial carcinoma of the bladder (UCB). factors considered: Age, Gender, pT-stage, Grade, soft tissue surgical margin status, concomitant carcinoma in situ, number of lymph nodes removed, lymph nodes status, adjuvant chemotherapy.	In standard multivariate models, LVI was associated with both disease recurrence (HR 1.43, *P*<0.001) and cancer specific mortality (HR1.45, *P*<0.001). In the entire cohort, adding LVI to a base model that included standard features improved only minimally its predictive accuracy for both recurrence and cancer-specific mortality (by 1.1% and 1.2%, respectively). In 3122 patients with negative lymph nodes, LVI remained independently associated with and improved the predictive accuracy of the standard predictors for recurrence (hazard ratio 1.68, *P*<0.001; +2.3%) and cancer specific mortality (1.70, *P*<0.001;+2.4%). By contrast, in 1071 node-positive patients, LVI only marginally improved the prediction of cancer-specific recurrence (hazard ratio 1.20, *P*<0.001;+0.2%) and survival (1.23, *P*<0.001;+0.5%).	one of the largest reported series of patients treated with RC for UCB, and it is unlikely that large prospective randomized trials will be organized to test the predictive value of LVI. Limitations: Inherent difficulty in determining the presence of LVI at the morphological level, with significant differences between local pathologists and central pathology review. We did not address the effect

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		(22.4%) received adjuvant chemotherapy Women 20.4% Men 79.6% Median Age 67 years T0 5.4% Ta 3.0% Tis 10.3% T1 13.3% T2 23.8% T3 31.1% T4 13.0% Grade None 5.4% 1 1.8% 2 41.6% 3 51.2% Soft-tissue surgical margin status	chemotherapy status in two (0.1%). Recurrence-free survival (RFS) and cancer-specific survival (CSS) estimates with pathological stage and number of lymph nodes removed.			The disease recurred in 1414 of 4257 patients (33.2%); 1947 (45.7%) had died at the time of analysis, 1156 (27.2%) from bladder cancer. Overall the 3-, 5- and 10-year recurrence-free survival (RFS) estimates (SEM) were 63 %, 59 % and 57 %, respectively. Overall, the 3-, 5- and 10-year cancer specific survival (CSS) estimates were 70%, 65% and 61%, respectively. Follow Up: Every 3–4 months for the first year, semi-annually for the second, and annually thereafter. The median (range) follow-up for all patients was 43 (0.1–324) months. LVI is strongly associated with clinical outcome in node-negative patients treated with RC. The assessment of LVI might help to identify patients who could benefit from adjuvant therapy after RC.	of LVI location, or the differential effect of lymphatic vs blood vasculature on outcomes. Patients were treated by various physicians and the specimens were evaluated by various pathologists over a long period. The long study period implies that the data might not represent current practice patterns. The assessment of LVI might help to identify patients who could benefit from adjuvant therapy after RC.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Negative 93.7% Positive 6.3% Concomitant carcinoma in-situ Negative 50.9% Positive 49.1% Number of lymph nodes removed 19% Lymph nodes status pN0 74.5% pN1-2 25.5% Adjuvant chemotherapy Negative 77.5% Positive 22.4%					After confirmation in different populations, LVI should be included in the staging of UCB.
Takada 2012 Japan	Multi-institutional national Case series. 3	928 patients (716 men, 77%, 212 women, 23%), median age 70 years, with carcinoma	Standard surgical approach of RC, pelvic lymphadenectomy and urinary diversion.	No control	To determine the type, incidence and severity of 90-day morbidity in accordance with a standard reporting	At least one complication was observed in 635 (68%) patients and a major (grade 3–5) complication was observed in 156 (17%) patients. The most common complication	Multi-institutional study Retrospective design

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		invading bladder muscle or high-grade carcinoma not invading bladder muscle between 1997 and 2010.			methodology (Clavien system). Identify independent predictive factors of any complications or major complications (grade 3–5). Considered factors: The variables analyzed were sex (man vs woman), age (continuous and continuous vs < 70 years),(ASA) score (I vs = II), body mass index (BMI) (continuous and < 23 kg/m, vs = 23 kg/m), mean annual cystectomy volume (< 5 per	categories were infectious (30%), gastrointestinal (26%), wound-related (21%) and genitourinary (15%). The 30-day mortality rate was 0.8% and the 90-day mortality rate was 2%. A multivariate regression model showed that previous cardiovascular comorbidity and type of urinary diversion (i.e. ileal conduit or neobladder) were significant factors for any and major complications. gatrointestinal, infectious and genitourinary complications were more frequent in patients who were undergoing ileal conduit/neobladder than cutaneous ureterostomy (exact data not shown). No association was observed between the rate of complications and annual surgical volume. Surgical complication-related radical cystectomy is significant and both previous cardiovascular comorbidity and	Data from Japan Our report is the largest one regarding perioperative morbidity and mortality in Asian patients who underwent radical cystectomy. Limitations: It is possible that some minor complications were not recorded. We did not have strict prospective criteria and each doctor collected data from medical charts, which may lead to an under-reporting of postoperative paralytic ileus.

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					year vs = 5 annual volume < 10 per year vs = 10 per year), previous cardiovascular comorbidity (yes vs no), previous surgical history (yes vs no), previous pulmonary comorbidity (yes vs no), previous cerebrovascular comorbidity (yes vs no), organ-confined disease (yes vs no), type of urinary diversion (ileal conduit or neobladdder vs others), operating time (continuous and < 400 min vs = 400 min) and estimated blood loss (continuous	the type of urinary diversion were found to be significant factors for any and major complications. The 90-day mortality rate was 2%, which is compatible with reports from Western high-volume centres.	Major complications or deaths were probably not missed because these events are described in the medical charts by the use of numerous notes. Regarding surgical techniques and postoperative management, we did not follow any strict prospective guidelines and, as such, there could have been some variation among institutions. We could not identify any significant differences in complication rates during the study

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					and < 1300 mL vs = 1300 mL).		periods.
Tilki 2010 Canada, Germany, Italy, USA	Multi-institutional international Case series. 3	565 patients with pT2 disease, 249 patients (44.1%) had substage pT2a; 316 patients (55.9%) had pT2b. Adjuvant chemotherapy was administered to 101 patients (17.9%) at the investigator's discretion. The median age was 66.2 years. None of the patients received preoperative systemic chemotherapy or	Patients' characteristics and outcome were evaluated. We compared the clinicopathologic characteristics and outcomes between patients with T2a versus pT2b American Joint Committee on Cancer (AJCC) substage.	No control	To compare the clinicopathologic characteristics and outcomes between patients with pT2a versus pT2b AJCC substage. Outcomes: Recurrence-free survival Cancer-specific survival Cancer-specific death Disease recurrence	Disease recurrence occurred in 169 patients (29.9%). A total of 265 (46.9%) were deceased at the time of analysis including 139 patients (24.6%) who died of UCB. 111 patients (19.6%) had metastases to regional lymph nodes. Follow Up: Postoperatively at least every 3 to 4 months for the first year, semiannually for the second year, and annually thereafter. Median follow-up was 50.5 months. Recurrence-free survival (73.2% [(95% CI, 67–79] vs 58.7% [(95% CI, 52–65]) and cancer-specific survival (78.0% [(95% CI, 72–83] vs 65.1% [(95% CI, 59–71]) estimates were significantly better for pT2a patients compared with those with pT2b (p = 0.002 and p = 0.001).	Multi-institutional study Retrospective desing Limitations: We did not review all pathologic specimens. We excluded all patients treated with preoperative chemotherapy, potentially creating a bias. Surgery by multiple surgeons and specimens evaluated by multiple pathologists. The analysis of patients treated in referral centers

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		radiotherapy. Charactersitics: Age, Lymph Nodes removed, Gender, Grade, Lymph Node status, soft-tissue surgical margin (STSM) status, Lymphovascular Invasion (LVI), Concomitant CIS, Adjuvant chemotherapy. Exclusion: Patients treated with preoperative chemotherapy.				Pathologic T2 substaging was associated with worse recurrence-free and cancer-specific survival after adjusting for the effects of standard pathologic features (p = 0.011 and p = 0.006). We found that patients with pT2b UCB had a significantly worse outcome compared with patients with pT2a disease regardless of other classic pathologic features such as lymph node status and the presence of LVI. In this large international cohort, we found that pT2 substaging based on depth of muscle invasion can stratify patients into statistically significantly different risk groups with regard to outcomes. This strong association was independent of lymph node status and other clinicopathologic features. Therefore, we believe that pT2 substaging should be maintained in the American Joint Committee on Cancer	may have biased the results. The study period spans >25 years, the data may not represent current practice patterns.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						(AJCC) TNM staging because it may add prognostic value and may help in the application of future therapeutic approaches.	
Turker 2012 Canada, Finland	Multi-institutional international Case series. 3	678 (602 were analysed) consecutive patients undergoing Radical Cystectomy (RC) at University Health Network, Toronto, Canada (1992 – 2010) and University of Turku, Turku, Finland (1986 – 2005). Exclusion: Patients with non-urothelial Bladder Cancer (BC) (*n* = 46), or salvage RC after failed	Radical Cystectomy (RC) and lymphadenectomy for urothelial BC. Indications for RC included carcinoma invading the bladder muscle or non-muscleinvasive BC failing intravesical therapy. In addition to removal of bladder and distal ureters, RC included removal of seminal vesicles and the	No control	Compare the cancer-specific outcomes Cancer-specific survival Recurrence-free survival Disease recurrence Study rate and time trends, as well as risk factors for upstaging, especially clinical factors associated with staging errors after RC. Factor considered: age, gender, initial	306 (51%) had a discordance in clinical and pathological stages. Upstaging occurred in 240 (40%) patients and 192 (32%) patients were upstaged from organ-confined (OC) to non-organ-confined (nOC) disease. During the study period, upstaging became more common in both centres. In multivariate analyses, T2 disease at initial presentation (*P* = 0.001, odds ratio [OR] = 2.62, 95% confidence interval [CI]: 1.44 – 4.77), high grade disease (*P* = 0.01, OR = 2.85, 95% CI: 1.21 – 6.7), lymphovascular invasion (LVI) (*P* < 0.001, OR = 5.17, 95% CI: 3.48 – 7.68), female gender (*P* = 0.038, OR = 0.6, 95% CI: 0.38 – 0.97, and histological variants (*P* < 0.001, OR = 2.77, 95% CI: 1.6 – 4.8) were associated with a risk of upstaging from OC to nOC disease.	Multi-institutional study Retrospective design Limitations: Data on time to RC (no significant effect) were available for 336 patients only. Long study time period. Lack of systemic pathology review in the Toronto cohort. During the course of the study, the

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		radiotherapy or neoadjuvant chemotherapy (*n* = 30). Median (range) patient: 67 (32–88) years 78% were males. The primary stage :< T2 in 50% and ≥ T2 in 50% of the patients 30% received intravesical instillations. High grade disease: 88%.	prostate in males and the uterus, ovaries and interior vaginal wall in females.		BC presentation, intravesical therapies, date of surgery, extent of lymphadenectomy, clinical stage before RC, lymphovascular invasion (LVI), the presence of concomitant carcinoma *in situ* (CIS) and pathological stage after RC.	Upstaged patients had worse survival rates than patients with correct staging. This was especially significant among patients with carcinoma invading bladder muscle before undergoing RC (16% vs 46% 10-year disease-specific mortality, *P* < 0.001). Upstaging is a common problem and unfortunately no improvements have been observed during the last two decades. LVI and the presence of histological variants are strong predictors of upstaging at the time of RC. Tumours with LVI or histological variants were noted to be at a very increased risk of upstaging. Pathologists should be encouraged to report LVI and any histological variant at the time of TURBT. Patients with cT2 disease were most likely to experience upstaging and, in this group of patients, upstaging had the	BC grading system was changed, therefore definitions can be imperfect. Association between upstaging and prognosis identified, but no causal relation deducible.

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						most dramatic effect on survival.	
Karl 2014 Germany	RCT 1 +	101 patients Randomization ratio was 2 ERAS (Early Recovery After Surgery) 1 CR (conservative regimen). Median age was 69.5 years (range 44 to 92). ASA (American Society of Anesthesiologists) scores were ASA 1, 2 and 3 in 7%, 42% and 51% of patients. Median BMI: 27.2 kg/m^2. Neobladder surgery: 49	ERAS group (Early Recovery After Surgery). N=62. No extensive orthograde or retrograde bowel preparation except the oral administration of 2 bisacodyl coated tablets in the afternoon before the operation. On the day before surgery high calorie, protein based drinks were offered to all patients at least 3 times. On the morning of the operation all patients were offered clear fluids and high calorie drinks again up to 2	Conservative group N= 39 Stomach tube remained in position for 2 to 3 days or until the first suffcient bowel movement was registered. Enteralization with solid food started after the beginning of bowel movement. Fluid intake was permitted on postoperative day 1 with limited and small portions only. If no bowel activity was registered,	Differences in quality of life (The EORTC QLQ-30 questionnaire was used preoperatively, on postoperative days 3 and 7, and at discharge home). Secondary end points included postoperative morbidity, demand for analgesics, time spent in the intermediate care unit, mobility and number of gastrointestinal events during hospital stay.	Primary End Point: Quality of Life in most categories the ERAS group fared significantly better than the CR group at discharge home. Quality of life parameters did not change significantly between postoperative days 3 and 7 and at discharge from hospital in the conservative regimen group, whereas a significant improvement was observed in the early recovery after surgery group. By analyzing the emotional functioning score exclusively, we found a stable score during hospitalization in the CR group whereas continuous improvement was found in the ERAS group. Secondary End Points: Postoperative morbidity was lower in the ERAS group in terms of wound healing disorders (p =0.006), fever (0.004) and deep venous thrombosis (0.027). CR was not superior in any of the determined parameters (Hydronephrosis,Urinary tract infection, Antibiotics for urinary tract infection,	Single-institutional study Open label, prone to bias patient reported outcomes. Drop Outs are not reported No masked randomization The main limitations of this study were the lack of long-term data as well as the single center approach.

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		patients, ileal conduit: 52 patients. For all urinary diversions only terminal ileum was used.	hours before the beginning of surgery. The perioperatively placed stomach tube was removed right after the operation in all cases. Unrestricted fluid intake was permitted 6 hours after the end of surgery including yogurt and high calorie protein drinks. Bowel movement was stimulated on postoperative day 1 using magnesium powder (200 mg per unit) 3 times a day until sufficient movement was reached. If possible,	stimulation was routinely initiated per protocol using substances like neostigmine, metoclopramide and dexpanthenol on postoperative day 2.		Cardiovascular complications , deep venous thrombosis, Lung emboli, Wound healing disorders, Paralytic ileus, Fever). The demand for analgesics was significantly lower in the early recovery after surgery group. The amount of food consumed in relation to the amount of food offered was significantly higher for the early recovery after surgery group as early as day 3 (p = 0.02). Time spent in the intermediate care unit was significantly shorter for the early recovery after surgery group (p<0.001). There were no significant differences between the groups with respect to gastrointestinal events. ERAS patients who underwent radical cystectomy appears to have significant benefits compared to a conservative regimen in terms of postoperative morbidity, quality of life, use of analgesics and time spent in the	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			patients were mobilized as early as possible on the day of surgery.			intermediate care unit.	
Parekh 2013 USA	RCT (pilot study) 1+	47 patients have been randomized data available on 40 patients for analysis from July 2009 to June 2011. Inclusion: Biopsy proven bladder cancer of clinical stage T1–T3, N0, M0. Exclusion: 1) Inability to give informed consent, 2) multiple prior abdominal and pelvic open surgical procedures that	Open Radical Cystectomy with pelvic lymph node dissection (16 Male and 4 Female).	Robotic Assisted Radical Cystectomy (18 Male, 2 Female).	The primary aim of the study was to demonstrate the feasibility of randomizing and enrolling patients in a pilot setting to obtain enough outcome measures in several variables to determine the optimal sample size to conduct future multi-institutional studies.	Primary End Points: Oncologic Efficacy (Soft Tissue Margins, Lymph Node counts, Pathologic Stage) Perioperative Outcomes Secondary Endpoints: Quality of Life Outcomes - Vanderbilt Cystectomy Index at 3,6,9 and 12 months Functional Recovery - Activities of Daily Living (ADL), Instrumental ADL, Timed Get up and Go/Grip Strength at 3,6 months. We observed no significant differences between oncologic outcomes of positive margins (5% each, p = 0.50) or number of lymph nodes removed for open radical cystectomy (23, IQR 15–28) vs robotic assisted laparoscopic radical cystectomy (11, IQR 8.75–21.5) groups (p = 0.135). The robotic assisted laparoscopic radical	Single-institutional study Almost all of the patients in our study underwent surgery at a single institution by a single surgeon proficient in both approaches. This significantly reduced surgeon induced bias. The prospective randomized nature eliminates selection biases. Limitations: Sample size Lack of power to

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		would preclude a safe robotic approach, 3) morbid obesity that would preclude the robotic approach, 4) clinical T4 bladder cancer, 5) clinical lymph node positive bladder cancer with grossly enlarged pelvic or retroperitoneally mph nodes, 6) any pre-existing condition that precludes safe initiation or maintenance of pneum-operitoneum for a prolonged period, 7) age				cystectomy group (400 ml, IQR 300–762.5) was noted to have decreased estimated blood loss compared to the open radical cystectomy group (800 ml, IQR 400–1,100) and trended toward a decreased rate of excessive length of stay (greater than 5 days) (65% vs 90%, p =0.11) compared to the open radical cystectomy group. The robotic group also trended toward fewer transfusions (40% vs 50%, p =0.26). Our results suggest no significant differences in surrogates of oncologic efficacy.	detect differences in oncologic efficacy. Measures of oncologic efficacy in perioperative pathological parameters. Our results need to be validated in a larger multicenter prospective randomized clinical trial. Drop Out are not reported No marked randomisation Robotic assisted laparoscopic radical cystectomy demonstrates potential benefits of decreased

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		younger than 30 or older than 90 years and 8) pregnancy.					estimated blood loss and decreased hospital stay compared to open radical cystectomy.

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Bi 2014 Systematic Review and Meta Analysis	No randomized controlled trial was identified. As the number of included studies was only six, there was apparent publication bias in most of the outcomes. 2 -	Comparative studies assessing different PLND templates in patients undergoing radical cystectomy for bladder cancer. Comprehensive search of the PubMed, Embase and Cochrane Library databases in September 2012. Exclusion:	Extended pelvic lymph node dissection (ePLND) vs non-extended pelvic lymph node dissection (non-ePLND).	Number of lymph nodes removed. Positive lymph node rate Recurrence free survival rate.	1 prospective, nonrandomized study and 5 retrospective comparative studies (total of 2824 patients) Extended pelvic lymph node dissection was associated with: A better recurrence free survival rate than non-extended pelvic lymph node dissection (HR 0.66, 95% CI 0.56–0.78, P < 0.001). A better recurrence free survival for both patients with negative lymph nodes (HR: 0.68, 95% CI 0.51–0.90, P = 0.007) and those with positive lymph nodes (HR: 0.58, 95% CI 0.47–0.72, P < 0.001). A better recurrence free survival rate for patients with pT3–4 (non -organ-confined) disease (HR 0.61, 95% CI 0.52–0.63, P <	Six studies with a were identified: Abol-Enein H Eur Urol 2011; 60:572–7 Dhar NB J Urol 2008; 179:873–8 Holmer M World J Urol 2009; 27: 521–6 Jensen JB Int J Urol 2012; 19: 39–47 Poulsen AL J Urol 1998; 160: 2015–9; discussion 20

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
		No extractable survival data Conference abstracts without complete data			0.001), but not for patients with ≤ pT2 (organ-confined) disease (HR 0.95, 95% CI 0.64–1.41, P = 0.81). A higher number of Lymphnodes than non-ePLND (weighted mean difference 19.06, 95% CI 12.38–25.74, P < 0.001). A higher positive rate than non-ePLND (odds ratio 1.26, 95% CI 1.06–1.50, P = 0.009). The duration of follow-up varied from 23.5 to 96 months.	Simone G Int J Urol 2012; 20: 390–7
Goossens-Laan 2011 Systematic Review and Meta Analysis	Relationship between procedural volume and outcome of cystectomies. Two reviewers independently screened titles and/or abstracts of all retrieved articles. All studies had an observational design, and two used clinical data. Multi-institutional	Inclusion criteria: (1) The subject of the study is cystectomy for BCa (2) Hospital or surgeon volume is reported as a variable (3) The outcome parameter is postoperative mortality or survival (4) The study describes multiple hospitals or surgeons (5) The study uses primary data.	Radical cystectomy (RC) for bladder cancer (BCa). Impact of Volume (surgeon/hospital) on postoperative mortality and survival.	1. Hospital volume as the defined variable. 2. Surgeon volume as the independent factor. 3. Hospital and surgeon volume as an independent factor.	10 studies of good methodologic quality were included for metaanalysis. All studies had an observational design, and two used clinical data. Countries: United States, United Kingdom, Canada, Netherlands. Zu 1. 7 studies were included with hospital volume as the defined variable, - The perioperative mortality varied from 2.2% to 5.0%. - Beneficial effect of hospital volume on mortality - Hospital mortality showed a pooled estimated effect of odds ratio (OR) 0.55 (range: 0.44–0.69), moderate heterogeneity (I2 = 50). - One study showed a positive effect of hospital volume on survival (hazard ratio [HR]: 0.89; p = 0.06).	Elting LS Cancer 2005;104:975–84. Birkmeyer JD N Engl J Med 2002;346:1128–37. Birkmeyer JD N Engl J Med 2003;349:2117–27. Birkmeyer JD Ann Surg 2007;245:777–83. Hollenbeck BK Urology 2007;69:871–5. Gilbert SM Urology 2008;71:906–10.

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	studies Observational design 2+	Editorials, Systematic Reviews, opinion articles, and surveys were excluded. Systematic search in PubMed, Embase, and the Cochrane Library.			Zu 2. Surgeon volume and outcome(2 studies): - Surgeon volume and postoperative mortality showed a significant effect in favour of high-volume surgeons (OR: 0.55, 95% CI, 0.41–0.73 and OR: 0.64; 95% CI, 0.44–0.91). - Surgeon volume and survival did not show a significant effect (HR: 0.83, 95% CI, 0.6–1.14; p = 0.26). Zu 3. Hospital and surgeon volume (1 study): In the United Kingdom is still reduced mortality in higher surgeon and hospital volume providers, which suggests that selective referral does not play a key role in the volume–outcome relationship.	Gore JL Cancer 2010;116:331–9. Fairey AS J Urol 2009;182:85–92. Goossens-Laan CA Eur J Surg Oncol 2010;36 (Suppl 1):S100–7. Mayer EK BMJ 2010;340:c1128.
Li 2013 Systematic Review and Meta-Analysis	Only 1 RCTs included Minority of eligible studies Small sample size Unmeasurable selection bias might limit the power	Comparative studies that selected patients with different clinical stages in two groups, as well as editorials, comments, letters to the editor, review articles, case reports, conference abstracts, and	Robot Assisted Radical Cystectomy (RARC) compared with Open Radical Cystectomy (ORC).	Overall perioperative complication rates. Positive surgical margins (PSMs) rates. Lymph node yield (LNY). The secondary	3 studies (1 RCT, 8 studies with prospectively collected data, 4 retrospective studies) including 962 cases (364 cases for Robot Assisted Radical Cystectomy and 598 cases. Primary Outcomes: Perioperative complications in 474 patients: Significantly lower rate of overall perioperative complications in the RARC versus ORC groups (OR: 0.68; 95% CI, 0.46–0.98; p = 0.04). Intraoperative and postoperative complication rates showed no significant difference (p =	Richards KA Urology 2010;76:1400–4. Nix J Eur Urol 2010;57:196–201. Styn NR Urology 2012;79:1303–8. Ng CK Eur Urol 2010;57:274–82. Galich A JSLS

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	Short follow-up period Long-term outcomes of RARC compared with ORC remained to be proved. Two authors independently extracted and summarized the data. Any disagreement was resolved by the adjudicating senior authors. 2 +	experimental animal studies were excluded. Database search of PubMed, Scopus, and the Cochrane Library on July 8, 2012.		outcomes were operative time, estimated blood loss (EBL), perioperative transfusion rates, and length of stay (LOS).	0.36 and p = 0.15). No significant difference in minor complications (p = 0.92). Significantly lower major complication rates in the RARC versus ORC groups (p = 0.002). Significantly lower rate of myocardial infarction and pulmonary diseases in the RARC versus the ORC group (p = 0.04 and p = 0.009). No significant difference in other complications. Positive surgical margins (PSMs, assessed in 579 patients):No significant difference between the RARC and ORC groups (OR: 0.85; 95% CI, 0.48–1.49; p = 0.57). Urethral/ureteric and soft tissue PSMs showed no significant differences between the two groups (p = 0.63 and p = 0.57). Lymph node yield (LNY, counted in 874 patients): Significantly more LNY in RARC than the ORC group (weighted mean difference (WMD): 2.25; 95% CI, 0.57–3.94; p = 0.009). Secondary Outcomes: Operative time (668 patients): Significantly longer operative time in the	2006;10:145–50. Pruthi RS J Urol 2007;178:814–8. Sterrett S World J Urol 2007;25:193–8. Wang GJ BJU Int 2008;101:89–93. Martin AD Urology 2011;77:621–5. Abaza R J Urol 2012;187:1200–4. Gondo T Jpn J Clin Oncol 2012;42:625–31. Sung HH et al. J Endourol 2012;26:670–5. Nepple KG et al. Urol Oncol, http://dx.doi.org/10.1016/j.urolonc.2011.06.009.

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					RARC than the ORC group (p < 0.001). Using ileal conduit method, no significant differences between the two groups (p = 0.57, p < 0.001, and p = 0.02). Estimated blood loss (EBL, 668 patients): Significantly lower blood loss in the RARC than the ORC group (p < 0.001). Perioperative transfusion (272 patients): Significantly lower rate in the RARC than the ORC group (p < 0.001). Intraoperative transfusion: Significant difference favoring the RARC group (p < 0.001). Postoperative transfusion: No data. Length of stay (668 patients): Significantly shorter in the RARC versus ORC groups (p < 0.001). Subgroup analysis: Significantly more LNY of Pelvic Lymph Node Dissection (PLND) to level II in RARC than ORC (p = 0.04).	

7.2. AG 6 Schlüsselfrage 2 (Harnableitung)

„Welche Harnableitung ist für welche Patientengruppe inkl. Geschlecht in Bezug auf Morbidität, Mortaliät und Lebensqualität indiziert?“

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Cody 2012 Cochrane Review	LoE: 1++ Data extraction were undertaken independently by 3 review authors and cross checked. Risk of bias: Small sizes of the trials Randomised trials but no details about methods of randomisation or concealment. Methods of blinding were not reported. Lack of data in	5 trials were included and had a total of 355 participants. All randomised or quasi-randomised controlled trials of surgery involving transposition of an intestinal segment into the urinary tract. Cochrane Incontinence Group Specialised Trials Register (searched 28 October 2011), which contains trials from CENTRAL, MEDLINE and CINAHL.	Comparisons: Continent diversion vs conduit diversion. One segment vs another for conduit diversion. One segment vs another for bladder replacement. Anti-reflux uretero-intestinal anastomotic technique vs freely refluxing for bladder replacement. Anti-reflux uretero-intestinal anastomotic	Quality of life Patient symptoms Clinical endpoints Health economic measures Physiological/radiological measures Urodynamic measures Endoscopic assessment	5 included trials, n= 355 **Continent diversion vs conduit diversion** (Kristjansson 1995) N=94 participants (3 arms, n=38 formation of ileal conduit, n=30 formation of colonic conduit, n=26 formation of a continent caecal reservoir; only 56 patients were evaluable, mean age = 60 years for ileal conduit and colonic conduit group, 50 years for caecal reservoir group, Follow-up: 121 months [ileal conduit], 117 months [colonic conduit], 132 months [continent caecal reservoir]. No statistically significant differences in the relative risks of upper urinary tract infection, number with uretero-intestinal stenosis, incidence of glomerular filtration rate deterioration (of more than 25%) and renal scarring. Confidence intervals were all wide, and did not rule out clinically important differences. **One segment vs another for conduit diversion (Kristjansson 1995, see above)**	Chen 2009 {published data only} Chen Z, Lu G, Li X, Li X, Fang Q, Ji H, et al. Urology 2009; 73(4):838-43; discussion 843-4. Khafagy 2006 {published data only} Khafagy M, Shaheed FA, Moneim TA. BJU International 2006;97(4): 799–804. [: 21954]. Kristjansson 1995 {published data only} Kristjansson A, Bajc M, Wallin L, Willner J, Mansson W. British Journal of Urology 1995;76:546–50. [MEDLINE: 96138003]. Kristjansson A, Wallin

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	symptoms, quality of life and clinical endpoints. No data regarding health economic measures. No reported drop-outs or losses to follow-up. Effects of interventions	Handsearching of journals, conference proceedings, and the reference lists of relevant articles. Exclusion: Not prospective randomised or quasi-randomised trials for patients with intractable incontinence or following cystectomy. Number of patients in each treatment group was not report.	technique vs freely refluxing for conduit diversion.		Only 2 outcome measures. No statistically significant differences in the relative risks of upper urinary tract infection and uretero-intestinal stenosis. Confidence intervals were wide and compatible with large clinical differences. **One segment vs another for bladder replacement (Chen 2009; Khafagy 2006)** No difference in daytime incontinence but with wide confidence intervals. Heterogeneity for the nocturnal incontinence outcome. No statistically significant result for nocturnal incontinence (RR 0.62: 95% CI 0.13 to 2.87). Chen 2009 (n=71, male, (ileocolonic segment (Le Bag) or ileal segment (Studer technique). Urodynamic parameters and continence rates were measured at 6 months did favour the ileal neobladder over the ileocolonic segment using the “Le Bag” technique which used a freely refluxing technique (RR 0.35, 95%CI 0.15 to 0.79). Khafagy 2006 (n=60 with radical cystectomy for muscle invasive bladder cancer; ileal neobladder reconstruction vs. ileocaecal neobladder reconstruction following radical cystectomy) used a non-refluxing technique	L, Mansson W. British Journal of Urology 1995;76:539–45. [MEDLINE: 96138003]. ManssonW, Ahlgren G, White T. Scandinavian Journal of Urology and Nephrology 1989;23: 195–200. [MEDLINE: 90019354]. Shaaban 2006 {published data only} Shaaban AA, Abdel-Latif M, Mosbah A, Gad H, Eraky I, Ali-El-Dein B, et al. BJU International 2006;97(5):1057–62. [: 21881]. Studer 1996 {published data only} Hugonnet CL, Danuser H, Thalmann GN, Studer UE. Progres en Urologie

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					with the ileocaecal segment. Similar continence rate between the two procedures. Higher rate of acidosis, infections and high residual urine in the ileal neobladder group. **Anti-reflux uretero-intestinal anastomotic technique vs freely refluxing for bladder replacement (Studer 1996; Shaaban 2006)** Studer et al.; n=70 (2 groups – n=35 anti-reflux nipple mechanism vs. n=35 refluxing mechanism afferent ileal tubular segment). Male patients, (median age 66.6 years, median follow-up 57 months in the anti-reflux nipple mechanism group and 63.8 years, median follow-up 45 months in the afferent ileal tubular segment group). No statistically significant differences in upper urinary tract infection, daytime incontinence, nighttime incontinence, and uretero-intestinal anastomotic strictures. Confidence intervals were all wide and clinically important differences were not ruled out. Marginally statistically significant difference in the incidence of upper tract dilatation, suggesting a higher rate after nipple value treatment, but this was based on only 11 cases and the confidence interval was wide	1997;7:960-6. [MEDLINE: 98108882]. Studer U, Danuser H, Thalmann G, Springer J, Turner W. Journal of Urology 1996;156:1913-7. [MEDLINE: 97068026]. Studer U, Spiegel T, Casanova G, Springer J, Gerber E, Ackermann D, et al. European Urology 1991; 20:315-26. [MEDLINE: 92267076].

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					(RR 0.22; 95% CI 0.05 to 0.96). Shaaban et al 2006 (n=60 with ileal bladder replacement. Mean follow-up 23 months for 53 patients. No major co-morbidity. Compared refluxing and antirefluxing techniques of uretero-enteric anastomosis in different renal units for the same patient. The total of the antireflux group was 11 out of 53. Glomerular filtration rates have no statistically significant difference between the two groups of the renal units. **Anti-reflux uretero-intestinal anastomotic technique vs freely refluxing for conduit diversion. (Kristjansson 1995b)** The trial compared an anti-reflux technique and a freely refluxing anastomosis used in the formation of ileal and colonic conduit diversion. Data were only available for the incidence of renal scarring. Renal units affected rather than the number of patients affected. No statistically significant difference was found between the two techniques and the confidence intervals were wide (risk ratio 1.94; 95% CI 0.92 to 4.08).	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Hautmann 2013 Austria, China, Egypt, Germany, Norway, Sweden, Switzerland, United Kingdom, USA	LoE 3 Most publications, searched 28 October 2011, based on retrospective single institutional experiences with nonstandardized reporting of complications and varying duration of follow-up. No randomized controlled studies comparing conduit diversion with neobladder or continent cutaneous diversion have been performed. Risk of bias:	Data published between 1970 and 2012 on patients with Urinary Diversion (UD) following Radical Cystectomy (RC) for bladder cancer. 17 758 urinary diversions.	Urinary diversion after pelvic irradiation. Orthotopic bladder substitution in men. Orthotopic diversion in women. Continent cutaneous urinary diversion.	Reconstructive options after RC due to Bladder Carcinoma, the criteria for selection of the most appropriate procedure, and the outcomes and complications associated with the available Urinary Diversion options. Indications, surgical details, postoperative care, complications, functional outcomes, as well as quality-of-life measures of patients with different forms of urinary diversion (UD).	Indications and patient selection criteria have significantly changed. Renal function impairment is primarily caused by obstruction. Complications such as stone formation, urine outflow, and obstruction at any level must be recognized early and treated. In patients with orthotopic bladder substitution, daytime and nocturnal continence is achieved in 85–90% and 60–80%, respectively. Continence is inferior in elderly patients with orthotopic reconstruction. Urinary retention remains significant in female patients, ranging from 7% to 50%. Significant disparity on how the surgical complications were reported makes it impossible to compare postoperative morbidity results. Complications rates overall following RC and UD are significant, and when strict reporting criteria are incorporated, they are much higher than previously published.	122 Publications were cited.

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	Retrospective single institutional experiences. Nonstandardized reporting of complications. Varying duration of follow-up. RC and UD only performed at high-volume hospitals (40–50 cases per year). Minimum annual caseload of 25 surgeries, by not more than two surgeons. Only an experienced team will master the challenges of RC and UD safely and guarantee a minimum of				Fortunately, most complications are minor (Clavien grade 1 or 2). Complications can occur up to 20 years after surgery, emphasizing the need for lifelong monitoring. Evidence suggests an association between surgical volume and outcome in RC; the challenge of optimum care for elderly patients with comorbidities is best mastered at high-volume hospitals by high-volume surgeons.	

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	long-term complications by regular follow-up.					
Lee 2014 Narrative Review	1- 105 Articles were identified, the highest level of evidence were selected and reviewed. Reviews and other secondary data sources were excluded. Details are not reported, major limitations of currently published studies: Lack of preoperative baseline assessment, lack of longitudinal studies using valid and reliable	A MEDLINE search of original articles, review articles, and editorials on urinary diversion in patients treated with RC (Radical Cystectomy). Searches were limited to the English language. No search date stated 105 articles were identified, those with the highest level of evidence were selected and reviewed. Reviews and other secondary data sources were excluded.	Continent diversions Incontinent diversions Orthotopic neobladders Ileal conduits	Function and oncological outcomes, complications, and factors influencing choice of procedure with urinary diversion after Radical Cystectomy for bladder carcinoma. Functional goals of an orthotopic neobladder are to maintain day- and night-time continence and to allow consistent emptying of the neobladder without the need for CISC, while preserving renal function.	10 studies, n=2127 Functional Outcomes: In several large series comprised predominantly of men, day and night-time continence rates ranged from 87 to 100%, and 70 to 95%. Continence rates improve gradually postoperatively as the neobladder volume increases. (Barre, P; 1996, Cancrini, A; 1996, Elmajian, D; 1996, Hautmann et al. 1999, Steven et al. 2000, Abol-Enein, H; 2001, Madersbacher et al. 2002, Carrion, R; 2004, Sevin, G; 2004, Stein, J; 2004). The number of patients reporting simultaneous day- and night-time continence is lower, ranging from 12 to 58%. (Ali-el-Dein, B; 2002, Arai, Y; 1999, Hautmann, R; 2000, Stenzl, A; 2001, Stein, J; 2002). A single institution series of 655 men by Simon et al. reported incomplete emptying, defined by a residual urine volume of >100 mL, was observed in 75 (11.5%) cases. Daytime continence rates range from 75 to	Barre PH, Herve JM, Botto H, Camey M., orld J Urol 1996; 14: 27-8 Cancrini A, De Carli P, Pompeo V et al., Eur Urol 1996; 29: 204-9 Elmajian DA, Stein JP, Esrig D et al., J Urol 1996; 156: 920-5 Hautmann RE, de Petriconi R, Gottfried HW, Kleinschmidt K, Mattes R, Paiss T., J Urol 1999; 161: 422-8 Steven K, Poulsen AL., J Urol 2000; 164: 288-95 Abol-Enein H, Ghoneim MA., J Urol 2001; 165: 1427-32 Madersbacher S, Mohrle K, Burkhard F, Studer UE., J Urol 2002; 167: 2052-7 Carrion R, Arap S,

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	measures, and the absence of a validated instrument to measure bladder cancer-specific HRQOL.	Search period was not reported.		Definition of continence, method of assessing continence, and timeframe of assessment relative to surgery.	93% in women at average follow-ups of 20–33 months; night-time rates were also similar to men at 72–84% (Steers WD. et al.; 2000, Farnham SB et al.; 2004). Health-related quality of life (HRQOL): Insufficient data were available to conclude that any one form of urinary diversion was associated with a better HRQOL. Lack of preoperative baseline assessment, lack of longitudinal studies using valid and reliable measures, and the absence of a validated instrument to measure bladder cancer-specific HRQOL as major limitations of currently published studies. Factors influencing choice of procedure: Primary goals in selecting a urinary diversion are to provide the lowest potential for complications and the highest HRQOL, while allowing for the timely completion of chemotherapy and therapeutic goals. The decision process is complex and involves consideration of issues related to cancer stage, patient comorbidities, treatment needs, and patient desires related to HRQOL.	Corcione G et al., BJU Int 2004; 93: 803–6 Sevin G, Soyupek S, Armagan A, Hoscan MB, Oksay T., BJU Int 2004; 94: 355–9 Stein JP, Dunn MD, Quek ML, Miranda G, Skinner DG., J Urol 2004; 172:584–7 Ali-El-Dein B, El-Tabey N, Abdel-Latif M, Abdel-Rahim M, El-Bahnasawy MS., Urol 2002; 167: 84–8 Arai Y, Okubo K, Konami T et al., Urology 1999; 54: 44–9 Hautmann RE, de Petriconi R, Kleinschmidt K, Gottfried HW, Gschwend JE., Int Urogynecol J Pelvic Floor Dysfunct 2000; 11: 224–9; discussion 30 Stenzl A, Jarolim L, Coloby P et al.,

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					While patient preference is important, absolute and relative contraindications for the use of various bowel segments and continent urinary reservoirs do exist. Patients should be informed that intraoperative findings may dictate a change in the planned form of urinary diversion. Even when an orthotopic neobladder is planned, all patients should have a stoma site marked preoperatively by an enterostomal therapist in the event that orthotopic diversion becomes unfeasible. Complications: Surgery Related Complications Morbidity rates ≤ 30 days after surgery range between 20 and 56%, while long-term morbidity >30 days ranges from 28 to 94%. (Madersbacher S et al.; 2002, Killeen KP et al.; 1988, Perimenis P et al.; 2004). Diversion-related complications are specific to the type of diversion (Farnham SB et al.; 2004). Illeal conduits: The 4 most common complications reported	Cancer 2001; 92: 1864-71 Stein JP, Ginsberg DA, Skinner DG., Urol Clin North Am 2002; 29: 725-34, xi Simon et al. Simon J, Bartsch G Jr, Kufer R, Gschwend JE, Volkmer BG, Hautmann RE., J Urol 2006; 176: 1468-72 Steers WD., World J Urol 2000; 18: 330-7 Farnham SB, Cookson MS., World J Urol 2004; 22: 157-67 Madersbacher S, Mohrle K, Burkhard F, Studer UE., J Urol 2002;167: 2052-7 Madersbacher S, Schmidt J, Eberle JM et al., J Urol 2003; 169: 985-90 Killeen KP, Libertino JA., Urol Clin North Am 1988; 15:183-94 Perimenis P, Burkhard FC, Kessler TM,

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
					are pyelonephritis in 5–23%, ureteric obstruction in 2–22%, urinary calculi in 3–16%, and stomal complications in 2–62% of cases in a series of 412 patients with a median follow-up of 98 months (Madersbacher S et al.; 2002, Madersbacher S et al.; 2003). The frequency of complications increased over time from 45% at 5 years to 94% at >15 years. The most frequent complications reported were renal insufficiency in 27%, stomal problems in 24%, bowel problems in 24%, UTIs in 24%, ureteric obstruction in 14%, and urinary calculi in 9%.	Gramann T, Studer UE., Eur Urol 2004; 46: 604–9

7.3. AG 6 Schlüsselfrage 3 (Laparoskopische vs. roboterassistierte vs. offene Harnableitung)

„Ist die laparoskopische oder roboterassistierte laparoskopische Harnableitung der klassisch offenen Harnableitung in Bezug auf Operationszeit, peri- und postoperative Morbidität und Funktionalität sowie Lebensqualität gleichwertig?“

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Ahmed 2014	Diagnostic Accuracy Study 3	935 patients who had undergone RARC (robot-assisted radical cystectomy) and PLND (pelvic lymph node dissection) between 2003 and 2011 at 18 participating institutions. Of these patients, 768 had ECUD (Extracorporeal urinary diversion), (570 conduits and 198 neobladders, 26%), and 167 patients had their urinary diversion constructed	Robot-assisted ICUD (Intracorporeal urinary diversion)	ECUD (Extracorporeal urinary diversion)	The postoperative parameters of interest were the 30- and 90-d complication and readmission rates. The operative outcomes measured were operative time, EBL (estimated blood loss), blood transfusion requirement, and LOS (length of stay).	Postoperative complications data were available for 817 patients, with a minimum follow-up of 90 d. No difference in the reoperation rates at 30 d was noted between the groups. The 90-d complication rate was not significant between the two groups, but a trend favoring ICUD (Intracorporeal urinary diversion) over ECUD (Extracorporeal urinary diversion) was noted (41% vs 49%, p = 0.05). Of the patients who developed complications, 43% in the ECUD (Extracorporeal urinary diversion) group and 35% in the ICUD (Intracorporeal urinary diversion) group presented with a complication within 30 d of surgery (p = 0.07). The readmission rate for ICUD (Intracorporeal urinary diversion) compared with ECUD (Extracorporeal urinary diversion) at 30 d was 5% and 15% (p ≤ 0.001), and the 90-d	Retrospective Multicenter, of the 18 institutions in the IRCC, 10 performed their urinary diversions only extracorporeally, while 8 participating centers carried them out both intracorporeally and extracorporeally. Being a retrospective study was the main limitation. This study has a few limitations. First, this multiinstitutional database may contain some disparity in terms of patient selection, operating standards, surgical techniques, postoperative management, and reporting of

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		intracorporeally (106 conduits and 61 neobladders, 36.5%). The mean age was 68 ± 11 yr (ECUD, Extracorporeal urinary diversion) and 66 ± 11 yr (ICUD, Intracorporeal urinary diversion), the majority of patients being males (82% vs 81% for ECUD, Extracorporeal urinary diversion) and ICUD, Intracorporeal urinary diversion).				readmission rate was 12% and 19%, (p = 0.016). The 90-d mortality events were higher in the ECUD (Extracorporeal urinary diversion) group than the ICUD (Intracorporeal urinary diversion) group (4.9% vs 1.6%, p = 0.043). An independent multivariable logistic regression analysis showed a significant correlation between intraoperative BT (blood transfusion) and 90-d mortality (p = 0.004). Most of the complications were gastrointestinal, followed by infection and complications involving the genitourinary tract. Outcomes of the present series suggest that ICUD (Intracorporeal urinary diversion) following RARC (robot-assisted radical cystectomy) is feasible, safe, and has excellent short-term surgical and pathologic outcomes.	complications, all of which can have a significant influence on operative outcomes and complication rates. Second, postoperative complications may be underreported, as these data were available for only 817 patients. Third, the length of follow-up is relatively short. Selection bias may influence outcomes. It is also possible that a degree of selection bias toward RARC and diversion type may have occurred at the participating institutions.

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		Characteristics were Age, Gender, BMI, American Society of Anesthesiologists grade, or rate of prior abdominal surgery.					
De Ger 2004	Case Series 3	Between April 2000 and January 2004, 20 patients underwent laparoscopic radical cystectomy with urinary diversion for transitional cell carcinoma (TCC) at the Charité Hospital. Of the 20 patients, 12 received a rectosigmoid pouch for urinary	Rectosigmoid pouch for urinary diversion. The procedures were performed completely laparoscopically, including free-hand laparoscopic suturing and in situ knot tying techniques. The mobilized specimens were removed in an	None (case series)	We evaluated the intermediate functional and oncologic outcomes. To present our experience with the first series of rectosigmoid pouch creation performed completely laparoscopically for continent urinary diversion	Two patients required reoperation. The median follow-up was 33 months, the longest follow-up after laparoscopic cystectomy. No patient developed local recurrence, but 3 patients had systemic progression. The median operating time was 485 minutes (range 365 to 830). All specimens had negative surgical margins. No patient had an electrolyte imbalance intraoperatively, postoperatively, or	Retrospective, Mono-institutional We present the first oncologic and functiona data of laparoscopic rectosigmoid pouch creation for continent urinary diversion with follow-up for longer than 2 years. Our clinic has had experience with the rectosigmoid pouch as continent urinary diversion in women since 1994.

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		diversion. The male patients had urethral involvement of TCC (transitional cell carcinoma) or urethral strictures before surgery. Those who had urethral involvement underwent urethrectomy in the same or in a separate session. Three patients had bacillus Calmette-Guérin resistant T1G3 urothelial carcinoma, the others had muscle-invasive	endoscopy bag by way of the rectum or vagina. All operations were completed laparoscopically by two surgeons without conversion to open surgery. The median patient age was 65 years.		after radical cystectomy to treat transitional cell carcinoma of the bladder.	perioperatively. All patients had daytime and nighttime continence when they left the hospital. During follow-up, all reported daytime continence. Although 50% of the patients needed bicarbonate when leaving the hospital, only 33% needed it during follow-up. No patient developed local recurrence, but three developed systemic disease (two bone metastases and one liver and lung metastases). Two of these patients died of the disease 15 and 24 months after surgery. Postoperative pain management for these patients was standardized. They received the same pain medication as the patients who had undergone open surgery with creation of a Mainz II pouch. We had no episodes of pyelonephritis in our patient population.	Our follow-up is the longest reported in laparoscopic groups; however, more time is needed to address the oncologic outcome. Our intermediate oncologic data after 33 months are comparable with the data after open surgery studies.

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		urothelial carcinoma. The pathologic features were pT1G3 plus carcinoma in situ (CIS) in 2 patients, pT3bG3 in 2 patients, and pT3aG3 plus CIS, pT1G3, pT2bG3, pT3aG2, pT2bG3 plus CIS, pT3aG3, pT2aG3 plus CIS, and pT2aG2 plus CIS in 1 patient each.				The rectosigmoid pouch is not a very popular urinary diversion because of concerns about metabolic problems, especially hyperchloremic metabolic acidosis and infection. 77% of our patients did not require medication for metabolic problems. We had no urinary diversion-related infections, probably because of our nonrefluxing ureteral implantation technique. Most patients had additional risk factors, including concomitant CIS in 50% (6 of 12) and pT3a-bG3 bladder cancer in 42% (5 of 12).	
Guru 2010	Case Series 3	26 patients diagnosed with invasive transitional cell carcinoma of the bladder underwent a robot-assisted	13 patients who underwent robot-assisted intracorporeal ileal conduit (IC) after RARC (robot-assisted radical cystectomy) and	13 patients who underwent RARC (robot-assisted radical cystectomy), pelvic lymph node dissection (PLND) with extracorporeal	Operative data and short-term outcomes between the 2 groups were assessed.	Overall operative time and intraoperative complications were similar. No significant differences were noted between the 2 groups (IC (intracorporeal, EC, extracorporeal) in terms of diversion time or estimated blood loss.	Retrospectice, comparative This study represents the largest series in robot-assisted intracorporeal ileal conduit using a novel

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		radical cystectomy with bilateral extended pelvic lymphadenectomy with ileal conduit diversion. The intracorporeal group (IC) included 2 female and 11 male patients (mean age 71 years). The extracorporeal group (EC) included 4 female and 9 male patients (mean age 66 years). Charactersitics:	extended lymph node dissection.	ileal conduit (EC).		There were no significant differences seen between the groups in terms of patient age, body mass index, sex, American Society of Anesthesiologists (ASA) score, and previous surgical history (P = .93, P = .65, P = 1.00, and P = 1.00). Mean lymph node yield for IC (intracorporeal) was 25 and 26 for EC (extracorporeal) (*P* = .83). There was 1 positive margin in EC (extracorporeal). There was no statistical difference between the 2 groups in terms of pathologic stage or lymph node positivity. There were 4 complications in the IC (intracorporeal) group: nonspecific colitis; small bowel obstruction 3 weeks postoperatively, requiring exploratory laparotomy with lysis of adhesions; a urine leak that eventually resolved but required a temporary nephrostomy tube; and a fever of unknown origin that	technique. Ileal conduit was performed by a single surgeon. Robot-assisted intracorporeal ileal conduit can be accomplished safely wit acceptable operative times even during early experience. Larger series with favorable results will be required to add this new paradigm to minimally invasive surgery for bladder cancer.

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		Age, BMI, sex, American Society of Anesthesiologists (ASA) score, prior surgery, or pathologic stage.				resolved without intervention. There were 5 complications in the EC (extracorporeal) group: a wound infection; a pelvic collection requiring computed tomography– guided drainage; pyelonephritis; an ureteroileal anastomotic stricture requiring revision; and a partial small bowel obstruction managed conservatively with bowel rest.	
Haber 2007	Case Series 3	A total of 54 patients (37 men and 17 women) with a mean age of 65 years (range 26 to 87) underwent laparoscopic radical cystectomy for muscle invasive (n = 35) or high-risk non-muscle-invasive (n = 19) bladder cancer. The mean follow-	17 patients underwent a pure laparoscopic (group 1, 8 conduit and 9 neobladder) procedure. In group 1, the EndoCatch bag containing the specimen was removed from the vagina or by way of a slight extension of the umbilical port	37 patients underwent an open-assisted laparoscopic (group 2, 18 conduit and 19 neobladder) procedure. In group 2, the specimen was removed through a minilaparotomy midline incision, which was then used for extracorporeal	Perioperative outcomes and associated morbidity.	Anastomotic leak, bowel obstruction, or sepsis requiring reexploration developed in 5 patients (29%) in group 1 and 4 patients (11%) in group 2. A “learning curve” was observed for both procedures, but it was particularly steep for the pure laparoscopic technique, and this approach was eventually abandoned. No significant differences were found between groups 1 and 2 with respect to mean patient age (63 versus 66 years, P = 0.5), comorbidities (Charlson comorbidity index 2.25 versus 2.38; P = 0.69), history of abdominal surgery, or operative indications.	Retrospective, comparative, single site.

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		up was 25 months. An ileal conduit was created in 26 patients (48%) and an orthotopic neobladder in 28 patients (52%). Eleven patients had a history of abdominal surgery. All ureterointestinal anastomoses were stented, and a standard pelvic drain was used in all cases. The mean body mass index was 27 kg/m2 (range 17.4 to 34.6),	site. Mean follow-up 28 months.	construction of the urinary diversion. Mean follow-up 23 months.		The tumor was organ confined (Stage pT2N0 or less), non-organconfined (Stage pT3-T4N0), and lymph node positive (Stage pTanyN+) in 59%, 18%, and 23% of group 1 patients and 67%, 19%, and 14% of group 2 patients, (P = 0.62). Group 2 had superior outcomes regarding operative time (3.1 hours shorter; P < 0.0001), blood loss (decreased 52%; P = 0.0002), transfusion requirement (decreased 7.6-fold; P = 0.01), time to oral intake (quicker by 50%; P = 0.005), time to ambulation (quicker by threefold; P < 0.0001), and overall in-patient complications (reduced from 70% to 22%; P = 0.0005). A major postoperative complication, defined as the need for open repeat surgery, occurred in 5 (29%) of 17 patients in group 1 and 4 (11%) of 37 patients in group 2. This difference approached, but did not reach, statistical significance (P = 0.08).	

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		and 85% of the patients had an American Society of Anesthesiologists score of 2 or more.				When comparing LRC (Laparoscopic radical cystectomy) with ileal conduit in group 1 (n = 8) versus group 2 (n = 18), similar trends were noted, with a distinct advantage for group 2 with respect to operative time, blood loss, time to convalescence, and postoperative complications. The most substantial difference was in the postoperative complication rate at 87% for group 1 versus 28% for group 2 (P = 0.004). The overall complication rate for patients receiving an ileal conduit was 46% (12 of 26) versus 32% (9 of 28) for patients undergoing neobladder diversion (P = 0.29). Major postoperative complications occurred in 5 (19%) of 26 versus 4 (14%) of 28 of the ileal conduit and neobladder groups (P = 0.62). The results have shown that the extirpative portion of LRC (Laparoscopic	

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						radical cystectomy) is efficiently performed by purely laparoscopic techniques, but that most of the morbidity appears to be associated with the urinary diversion.	
Torrey 2012	Case series Retrospective, mono-institutional 3	From February 2004 to March 2010, 141 patients with bladder cancer underwent RARC (robot-assisted radical cystectomy) at the City of Hope Cancer Center, and 34 of these patients underwent Indiana pouch continent cutaneous urinary diversion reconstruction. Most of the patients had	34 patients undergoing RARC (robot-assisted radical cystectomy) with extracorporeal Indiana pouch continent cutaneous urinary diversion reconstruction.	No control	After surgery, the complications were identified, categorized, and graded using an established 5-grade modification of the original Clavien grading system, and continence was assessed.	175 (123 early and 52 late) complications after surgery were reported in 32 (94%) of 34 patients. Within 90 days of surgery, 31 (91%) of 34 patients experienced ≥ 1 early complication. Of 34 patients, 15 (44%) reported ≥ 1 late complications (> 90 days). Most (85% and 69%) early and late complications were graded as minor (grade II or less). The most common complication in both intervals was infection, reported in 22% and 37% of patients with early and late complications. The median number of lymph nodes removed was 27.5, and 6 patients (18%) had positive nodes.	Retrospective, mono-institutional Overall, more male patients underwent the procedure than female patients. In our study, we were careful to include any and all complications possibly related to the cystectomy or Indiana pouch portion of the surgery. To ensure that the complications were adequately assessed and included, 1 physician reviewed each of the 34 charts in detail.

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		pathologically localized disease (Stage T2 or less; 62%). 12 patients (35%) had a history of chemotherapy. Of the 12 patients, 8 (24%) received adjuvant chemotherapy, 3 (9%) neoadjuvant chemotherapy, and 1 (3%) chemotherapy within 8 months of surgery for metastatic breast cancer. 3 patients (9%) had a history of radiotherapy for prostate cancer.				The 5-year overall disease-specific survival rate was 81.4% (95% CI 60.6%-91.9%). Continence information at a mean was available for 31 (91%) of 34 patients. Of the 31 patients analyzed, at a mean follow-up of 20.1 months all but 1 (97%) reported current daytime and nighttime continence, providing they catheterized and cared for their pouch appropriately. Complications tend to be greater for Indiana pouch reconstruction at cystectomy compared with other urinary diversion types.	

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Xylinas 2013	Diagnostic Accuracy Study 3	From March 2004 to August 2011, 175 consecutive patients underwent RARC (robot-assisted radical cystectomy) with extracorporeal urinary diversion at our institution by a single surgeon. 145 men and 30 women with a median age of 73 years and a median body mass index of 27 kg/m^2 underwent RARC (robot-assisted radical cystectomy). 91 patients (52%)	RARC (robot-assisted radical cystectomy) with extracorporeal diversion by a single surgeon. Recurrence-free survival and cancer-specific survival curves were generated using the Kaplan-Meier method.	No control	Complications rates and the midterm oncologic outcomes (Recurrence-free survival (RFS) and cancer-specific survival (CSS)). Perioperative parameters and postoperative complications were prospectively collected using the modified Clavien system.	The median follow-up was 37 months (IQR: 21.5-53.5). 4 patients (2.3%) required conversion to open surgery because of difficulty to progress, 109 patients (62%) underwent a transcutaneous ileal conduit, 40 patients (23%) an orthotopic neobladder, and 26 (15%) a continent cutaneous conduit. The perioperative mortality rate was 2.8%. The positive soft tissue surgical margins rate was 5%. The median number of lymph nodes removed was 19 (IQR: 12-28). Actuarial recurrence-free survival and cancer-specific survival at 2, 3, and 5 years after RARC (robot-assisted radical cystectomy) were 67%, 63%, 63% and 73%, 68%, 66%, respectively. Early surgery-related complications (<30 days) occurred in 74 patients (42%).	The study design was prospective. This study has noteworthy limitations. First and foremost are the limitations inherent to its design. Although the data collection was prospective, the analyse performed were retrospective. In addition, we did not perform a review of all specimens and therefore relied on the dedication and attention of our uropathologists. Furthermore, our experience does not represent a comparative effectiveness study of RARC (robot-assisted radical cystectomy) vs

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		had an American Society of Anaesthesiologists score of 3 or more. Clinical stage was T2 or less in 168 patients (97.1%). 64 patients (36.6%) had a history of previous abdominal surgery; 18 patients (10%) had a previous radiotherapy for other cause than bladder cancer.				The rates of early complications were not significantly different according to the type of urinary diversion (40%, 47%, and 48%, for ileal conduit, orthotopic neobladder, and contienent diversion. Reoperation was necessary in 7 patients because of wound dehiscence (n = 3), enterocutaneous fistula (n = 1), bowel obstruction (n = 2), and ileal anastomic leakage (n = 1). Late surgery-related complications (30-90 days) were observed in 59 patients (34%), from which 54 (91.5%) had early complications. The rates of late complications were not significantly different according to the type of urinary diversion (30%, 40%, and 39%, for ileal conduit, orthotopic neobladder, and continent diversion, respectively). Five patients died in the postoperative setting to ileal anastomotic leakage (perioperative mortality rate of 2.8%).	ORC (open radical cystectomy). Comparative studies of RARC (robot-assisted radical cystectomy) and ORC (open radical cystectomy) are needed to confirm our results in a randomized clinical trial setting. A single surgeon series consecutive nature of patient inclusion.

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						The median follow-up in patients alive at the last followup was 37 months (IQR: 21.5-53.5). Disease recurrence occurred in 51 patients (29.1%); 44 patients (25.1%) died of UCB (urothelial carcinoma of the bladder), and 67 patients (38.3%) died of any cause. The results suggest, as other studies have also shown, a general noninferiority of RARC (robot-assisted radical cystectomy) when compared with open radical cystectomy (ORC).	
Jonsson 2011	Case series from 2004-2009 3	45 selected patients (38 male, 7 female) with high-grade and/or muscleinvasive urothelial cancer of the bladder. Median patient age was 62	RARC (robot-assisted radical cystectomy) and total intracorporeal urinary diversion.	No control	Perioperative variables, pathology data, early and late complication rates, urinary continence, potency, and cancer-specific survival were evaluated as	Median Follow-up:25 months. An orthotopic ileal neobladder was constructed in 36 patients (3 women). An ileal conduit was created in 9 patients (four women). Operative time was 477 min (range: 325–760). Four patients died due to metastatic	Single site case series, nonrandomised The study is limited by a relative small sample size and no comparative group. The fact that only regional patients were assessed by IIEF-5 score

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		years.			outcome measures.	disease. Overall patient recurrence-free survival was 84%. There was no statistical difference in complication rates between neobladder- and conduit-operated patients. Patients with neobladder had daytime and nocturnal continence rates of 97% and 83%, respectively. In 20 male patients, bilateral nerve-sparing surgery was done. Potency outcome was reported by 16 patients and only one patient was impotent. One year after RARC (robot-assisted radical cystectomy), excellent daytime continence and potency rates were reported.	and no other quality-of-life instrument was used can cause an observer bias and that is a limitation of this study.
Nazmy 2014	Case series Retrospectiv, Single site 3	A total of 254 RARCs (robot-assisted radical cystectomy) were performed from 2003 to 2012.	Robot-assisted radical cystectomy	No control	Perioperative complications, including severity, time period (early and late) and diversion type.	The American Society of Anesthesiologists (ASA) score was 3 or greater in 80% of patients and continent diversion was performed in 68%. Within 90 days 77.5% of patients	Retrospective, consecutive single site Limitations of our study include its retrospective nature and lack of

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		209 patients were included. Median Age: Patients with illeal conduit 78.7 years Patients with Indiana Pouch 71.1 years Patients with orthotopic bladder substitute 64.4 years.				experienced any complication and 32% experienced a major complication. The 90-day mortality rate was 5.3%. Most complications were gastrointestinal, infectious and hematological. On multivariate analysis patients with ileal conduit diversion had a decreased likelihood of complications compared to patients with Indiana pouch and orthotopic bladder substitute diversion despite the selection of a more comorbid population for conduit diversion. Continent diversion was associated with a higher likelihood of urinary tract infection. Although patients with an ileal conduit had more comorbidities, they experienced fewer complications than those with an orthotopic bladder substitute or Indiana pouch diversion.	comparison to a contemporary group of patients with ORC. Since our institution is a tertiary referral center, accurate readmission data may also be lacking. Large standardized analysis and prospective randomized trials are anxiously awaited.
Pruthi 2010	Case series	12 Patients (2 patients	Robotic-assisted laparoscopic	Historical comparisons to a	Perioperative and pathologic	12 patients (mean age: 60.9 years) underwent an intracorporeal diversion.	Single-institution, retrospective case series

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	Retrospective 3	undergoing for a noncompliant dysfunctional bladder refractory to more conservative management) between December 2008 to June 2009. Mean age was 60.9 years. Clinically localized urothelial carcinoma of the bladder. 20 patients with robotic radical cystectomy and extracorporeal urinary diversion. Mean age was	intracorporeal urinary diversion (N=10).	consecutive case series of 20 patients undergoing robotic radical cystectomy and extracorporeal urinary diversion.	outcomes.	Mean operating-room time of all patients was 5.3 h. 11 of the 12 patients were discharged on or before postoperative day 5. There were 6 postoperative complications in 5 patients (42%), with one complication being Clavien grade 3 or higher. Our initial experience with robotic-assisted laparoscopic intracorporeal diversion appears to be favorable with acceptable operative and short-term clinical outcomes.	The major limitations of the study are the small sample size and the nonrandomized nature of the compared treatment groups (intracorporeal vs extracorporeal), which limits the ability to directly compare the techniques at a high level of scientific confidence. Certainly larger case series and, more significantly, randomized trials, would be required to demonstrate superiority or at least noninferiority of the intracorporeal diversion. Some bias did occur with regard to selection of

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		66.9 years.					patients for the initial intracorporeal experience. Although well-defined selection criteria were not utilized A bias toward healthier patients was reflected in the trend toward a lowe mean age in the robotic population compared with our simultaneous extracorporeal series. This study only addresses perioperative results with short-term follow-up. 3) This is a relatively small case series of only 12 patients. More extensive experiences will be required to better asses the appropriateness and true potential of this technique.

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Aboumohamed 2014	Case-Series, retrospective 3	182 patients who underwent either RARC (robot-assisted radical cystectomy) (n = 82, 40 extra- and 42 intracorporeal) or ORC (open radical cystectomy) (n = 100) met the inclusion criteria and were included in this retrospective case series. Patients undergoing radical cystectomy with ileal conduit urinary diversion between January 2009 and December 2012	Robot-assisted radical cystectomy (RARC) n=82.	Open radical cystectomy (ORC), N=100.	The primary outcome measure was difference in interval and baseline BCI (Bladder Cancer Index) and BIS (Body Image Scale) scores in each group.	Follow-up: 30 months Compared with RARC (robot-assisted radical cystectomy), more patients undergoing ORC (open radical cystectomy) had an American Society of Anesthesiology score ≥ 3 (66% vs 45.1% RARC; P = .007) and shorter median operative time (350 vs 380 minutes; P = .009). Longitudinal postoperative analysis revealed better sexual function in ORC (open radical cystectomy) group (P = .047), with no significant differences between both the groups in the other 3 domains (P = .11, .58, and .93). Comparisons regarding diversion techniques showed similar findings in baseline and postoperative health-related quality of life (HRQL) data, with no significant differences in the HRQL and body image domains. RARC (robot-assisted radical cystectomy) has comparable HRQL (health-related	Retrospectiv case series multi-institutional Validated health-related quality of life (HRQL) assessment measures were used: bladder cancer index (BCI) and body image scale (BIS). Limitations: The study compares different surgical techniques performed b different surgeons at separate institutions. The 2 techniques should have ideally been assessed in a randomized fashion to improve the overall evidence presented. Only 2 postoperative evaluations were required for inclusion in the study.

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		were included.				quality of life) outcomes to ORC (open radical cystectomy) using validated bladder cancer index (BCI) and body image scale (BIS). The diversion technique used does not seem to affect patients' quality of life. No quality of life differences were noted based on the diversion technique used.	
Schumacher 2011	Case-Series 3	45 patients ((7 women and 38 men, median age 62 years, range 37-79) with bladder cancer. Exclusion criteria for RARC (robot-assisted radical cystectomy) were a history of extensive abdominal surgery and/or a contraindication to the steep	RARC (robot-assisted radical cystectomy) with lymph node dissection and total intracorporeal urinary diversion.	No control	The following parameters were assessed: operative time, blood loss, urinary diversion type, lymph node yield, surgical margin status, and length of hospital stay.	In 9 (20%) of the 45 patients an ileum conduit urinary diversion and in 36 (80%), an orthotopic bladder substitution (Studer) was performed intracorporeally. The mean operative time was 476 ± 96 minutes (range 325-760). Early surgery-related complications were noted in 40% of the patients and late complications in 30%. The early Clavien grade III complications remained significant (27%) and did not decline with time. Overall, fewer complications were	Retrospective Study, multi-institutional, consecutive recruitment The study had several limitations: The sample size of only 45 patients was very small. Patient selection bias might have influenced our results and could certainly explain the high proportion of patients undergoing orthotopic urinary diversion.

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		Trendelenburg position. Patients with decreased pulmonary compliance and spinal stenosis were also excluded.				observed between the groups over time, with a significant decrease in late versus early complications (P = .005 and P = .058). The mean operative times declined from the first group to the second and third groups (P = .005) and the hospital stays shortened (P = .006). No significant difference was observed between groups regarding the lymph node yield at cystectomy (P = .108), with a mean of 22.5 nodes (range 10-52) removed. More patients received an orthotopic bladder substitute (Studer) in each of the latter 2 groups than in the first. Our results need to be confirmed by others before robot-assisted radical cystectomy with totally intracorporeal urinary diversion can be accepted as a treatment option for patients with bladder cancer.	The continuous improvement in our surgical technique makes a direct comparison among the groups questionable.

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Huang 2008	Retrospectice, Single site case series 3	Between December 2002 and May 2006, 85 patients (77 men and 8 women) ages 39 to 81 years (mean 62.4 years) with bladder carcinoma	Laparoscopic radical cystectomies or laparoscopic radical prostatocystectomy with orthotopic illeal neobladder.	No control		Follow-up: 1 to 41 months (average 21.3 months). The median operative time was 320 min, and the median blood loss was 280 ml. Conversion to open surgery was not necessary in any of the patients. The average time to oral intake after operation was 3.9 days. There were no perioperative mortalities. The complication rate was 14.1% (12/85). The daytime continence rate was 91.2%, and the nighttime continence rate was 82.4% at 6 months postoperatively. The neobladder capacity was about 343 ml. Of the 8 patients who underwent a nerve-sparing procedure, 4 patients had potency for intercourse.	Retrospectice, Single sit study. Long-term follow-up is needed to confirm the oncologic outcomes.

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						During a follow-up period of 1 to 41 months (average 21.3 months), 3 patients had local recurrence, 1 patient had trocar site seeding, and 5 patients had distant metastasis, of whom 4 died. Most of the patient could ambulate 2 to 3 days postoperatively and returned to normal activity in 2 weeks. 40 patients were followed for more the 2 years. The overall survival rate was 90% (36/40), and the overall 2-year recurrence-free rate was 85% (34/40).	
Azzouni 2013	Cohort Study 2+	The first 100 consecutive patients who underwent Robot-assisted radical cystectomy (RARC) and robotassisted intracorporeal ileal conduits (RICIC), and had ≥ 3 months of	Robotassisted intracorporeal ileal conduits (RICIC).	This cohort was divided into four groups (25 patients each) to study the evolution of our surgical technique.	Comparisons were made in terms of demographics, and pathologic, perioperative, and 90-d postoperative outcomes.	Overall operative and specific diversion times were 352 and 123 min, respectively. Estimated blood loss was 300 ml, lymph node yield was 24, and positive surgical margin rate was 4%. Length of hospital stay increased from 7 d for group 1 to 9 d for group 4. The overall 90-d complication rate was 81%; 19% of complications were high	Retrospective Study, Single Site Larger series with longe follow-up are needed to validate the procedure and define its place in the minimally invasive urologic armamentarium. Quality of life studies need to be conducted to

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		postoperative follow-up were included.				grade. Infections were the most common complications, representing 31% of all complications. There were no statistically significant intergroup differences except in diversion time, intraoperative transfusions, and length of stay.	compare benefits of intracorporeal urinary diversion. Limitations: It is retrospective and therefore subject to selection bias. It is not a randomized study Follow-up was short and the number of patients included in the study may not be adequate to reveal any other significant statistical differences.
Tyritzis 2013	Single- site, prospective 3	Between 2003 and 2012 70 patients (62 men and 8 women) aged 37 – 76 years	RARC (robot-assisted radical cystectomy) with totally intracorporeal modified Studer ileal neobladder formation.	No control	Surgical margin status, recurrence and cancer specific death at 24 months, 30-d and 90-d complication rates, daytime and nighttime continence, and potency. We also looked at sexual	Median follow-up of the cohort was 30.3 months (interquartile range: 12.7–35.6). We recorded negative margins in 69 of 70 patients (98.6%). Clavien 3–5 complications occurred in 22 of 70 patients (31.4%) at 30 d and 13 of 70 (18.6%) at >30 d. At 90 d, the overall complication rate was 58.5%. Clavien < 3 and Clavien ≥ 3 complications were	Data were collected prospectively and reviewed retrospectively Single-site (expert center) Limitations of this study include its retrospective design, selection bias due to the learning curv

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					function.	recorded in 15 of 70 patients (21.4%) and 26 of 70 (37.1%), respectively. Recurrence-free, cancer-specific, and overall survival at 24 months were 80.7%, 88.9%, and 88.9%, respectively. Daytime continence and satisfactory sexual function or potency at 12 months ranged between 70% and 90% in both men and women.	phase, and missing data The missing data represented patients who live outside of Sweden. In addition, the number of female patients was very small. Our study represents the largest and longest published follow-up of RARC with totally intracorporeal neobladder to date, the numbers are still too small to reach definitive conclusions.

8. AG 7: Neoadjuvante/adjuvante Therapie und palliative Chemotherapie

8.1. AG 7 Schlüsselfrage 1 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

8.2. AG 7 Schlüsselfrage 2 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

8.3. AG 7 Schlüsselfrage 3 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

8.4. AG 7 Schlüsselfrage 4 (Marker für neo-/adjuvante Chemotherapie)

„Können anhand von histopathologischen, klinischen und molekularen Markern Patienten identifiziert werden, die von einer neoadjuvaten/adjuvanten Chemotherapie profitieren?“

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Font 2001 Spain	Study of Diagnostic Accuracy 3	n=98 Transurethral resection with muscle-invasive locally advanced	n=57 With BRCA1 assessment.	n=41 Without BRCA1 assessment (insufficient tumor tissue).	Assessement of BRCA1 messenger RNA expression levels. Correlation	Patient characteristics: Median follow-up of 45 months. Median disease-free survival 49 months. Median survival 54 months. 5-year survival was 48%.	Multi-institutional study Retrospective design BRCA1 expression may predict the efficacy of

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		bladder cancer subsequently treated with neoadjuvant cisplatin-based chemotherapy (1991 and 2007). Median age 63 years. Male n=93 Female n=5 Transitional Cell Carcinoma: TCC n=76 TCC with other n=22 Lymphovascular invasion: Present n=14 Absent n=84 Hydronephrosis: Yes n=40			between BRCA1 mRNA levels, pathological response and survival.	A significant pathological response (pT0-1) was attained in 66% (24 of 39) of patients with low/intermediate BRCA1 levels compared with 22% (4 of 18) of patients with high BRCA1 levels (P = 0.01). Median survival was 168 months in patients with low/intermediate levels and 34 months in patients with high BRCA1 levels (P = 0.002). Analysis for survival, only BRCA1 expression levels and lymphovascular invasion emerged as independent prognostic factors. BRCA1 mRNA expression and outcome: Median overall survival in patients with low levels was 124 months and 34 months in those with high levels (P=0.008). Patients with low/intermediate BRCA1 levels had a higher pathological response rate.	cisplatin-based neoadjuvant chemotherapy and may help to customize therapy in bladder cancer patients. Limitations: Limited number of patients. Further studies with a larger number of patients and other molecular markers are warranted to confirm these results.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		No n=58 Clinical stage: T2N0M0 n=3 T3N0M0 n=55 T4N0M0 n=24 T1-4N+M0 n=13 TxNxM1 n=3 Chemotherapy regimen: CMV (cisplatin, methotrexate, and vinblastine) n=66 Cisplatin/gemcitabine n=32 BRCA1 levels: Low (<13.57) Intermediate (13.57-26.77) High (>26.77)					
Frank 2004 USA	Study of Diagnostic Accuracy	n=139 Cystectomy for Transitional Cell	Entire cohort n=139	Adjuvant chemotherapy n=37	Prognostic value of p53 and MIB-1 protein expression.	The median p53 and MIB-1 indices were 45.2% and 30.3%. The median follow-up was 4.5 years.	Single-institutional study. Retrospective design.

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	3	Carcinoma of the urinary bladder, metastatic to regional lymph nodes. (1970-1998). Patients with evidence of prior or concurrent systemic disease (pM1) and with inadequate tissue blocks were excluded.			Assess their ability to predict response to chemotherapy.	No statistically significant associations between p53 and MIB-1 indices and outcomes. p53 index limited to adjuvant chemotherapy (n = 37) no prognostic value. Significant association between MIB-1 and distant metastases (P = 0.049). Disease-specific survival rates, stratified according to p53 index and chemotherapy, response to chemotherapy regardless of p53 index. No statistically significant association between p53 and death from TCC, distant metastases, or local recurrence.	Lymph node specimens, not primary tumor specimens were used fo immunohistochemical staining. Limitations: Chemotherapy regimens differed significantly (new chemotherapeutic agents were introduced. Very limited number of patients (n=37), limited power to detect significant differences. Further multi-institutional, prospective, randomized studies will be required to substantiate the results.
Hoffmann 2010	Study of Diagnostic Accuracy	n=108 With locally	n = 56 Methotrexate and		Correlation of MDR1 and ERCC1with Overal	Expressions of MDR1 and ERCC1 were independently associated with overall survival or progression-free survival	Multi-institutional Study Retrospective design.

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Germany, Switzerland, USA	3	advanced bladder cancer, who had been enrolled in AUO-AB 05/95, a phase 3 trial randomizing a maximum of three courses of adjuvant cisplatin and methotrexate (CM) versus methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC). Tumor category: pTis/pT1 pN+ n=4 (3.7%) pT2 pN+ n=18 (16.7%) pT3 pN0 n=34 (31.5%) pT3 pN+ n=34 (31.5%)	Cisplatin Group (CM). n = 52 Methotrexate, Vinblastine, Epirubicin, and Cisplatin Group (M-VEC).		Survival. Progression-free Survival.	(P=0.001, relative risk = 2.9 and P=0.01, relative risk = 2.24). The correlation of high MDR1 expression with inferior outcome was stronger in patients receiving M-VEC. MDR1 expression below the 75th percentile (P=0.0006, hazard ratio [HR] = 0.25, 95% CI = 0.11-0.55) had a higher chance for prolonged survival. After 5 years, only 23% of patients with high MDR1 expression were still alive, 62% of patients with low MDR1 expression survived 5 years. Association was still significant, when each treatment arm, CM (P=0.01, HR = 0.26, 95% CI = 0.09-0.74) and M-VEC (P=0.02, HR = 0.27, 95% CI = 0.083-0.88) was analyzed separately. Patients with low MDR1 expression had a lower risk for early progression (P=0.002, HR = 0.28, 95% CI = 0.13-0.62). After 2 years, only 25% of patients with	Clinicopathologic parameters were equally balanced in the present study group and the entire trial population. Clinicopathologic characteristics of all patients were reviewed by one surgical pathologist. Prospective studies are warranted to define a role for MDR1 and ERCC1 analysis in individualizing multimodality treatment in locally advanced bladder cancer. Limitations: The results may have been influenced by confounders that have occurred during follow-up (not reported) and by

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		pT4a pN0 n=8 (7.4%) pT4a pN+ n=10 (9.3%) Nodal status: pN0 n=42 (38.9%) pN+ n=66 (61.1%) 1 lymph node n=28 (25.9%) 2-5 lymph nodes n=31 (28.7%) >5 lymph nodes n=7 (6.5%) Median Age 59 years. Male n=85 (78.7%)				low MDR1 expression experienced disease progression, more than 65% of patients with high MDR1 expression had progressed. Significant associations for progression-free survival in relation to MDR1 expression (CM: P=0.01, HR = 0.26, 95% CI = 0.09-0.76; M-VEC: P=0.05, HR = 0.34, 95% CI = 0.11-1.04). Significant associations for progression-free survival in low ERCC1 expression (P=0.03, HR = 0.52, 95% CI = 0.27-1.01). Overall survival: M-VEC-group, high MDR1 expression exhibited significant (P=0.008, 95% CI = 0.56-0.82) sensitivity of 69% (true-positive rate) and specificity of 72% (true-negative rate). CM-group (P=0.91, 95% CI = 0.37-0.65), sensitivity of 46% and specificity of 56%. MDR1 and ERCC1 expressions are independent markers for overall survival and progression-free survival. in patients	additional bias (tissue blocks were only available from one third of the patients. Lack of an observation arm in AUO-AB 05/95 makes it impossible to decide whether expressions of MDR1 and ERCC1 are prognostic or predictive markers.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						undergoing cisplatin-based adjuvant chemotherapy.	
Matsumoto 2004 Japan	Single-arm Cohort study 3	n=62 Transitional cell carcinoma of the bladder (pT1G3–pT4M0) treated with chemoradiotherapy (CRT) (median dose: 40.5 Gy of radiation and 230 mg of cisplatin) between November 1994 and August 2000. Male n=47 (75.8%) Median Age 68 years, range 45–89 years	Mucosal biopsy was performed before and after CRT. Tumor specimens were examined immunostained for Ki-67, p53, Bcl-2 and Bax; the Bax/Bcl-2 ratio and apoptosis index (AI). Clinical features and response to CRT were compared with data.	No control.	Correlation to histopathological grade and clinical stage with immunohistostaining of p53, Bcl-2, Bax, Ki-67 index, apoptotic index and Bax/Bcl-2 ratio. Correlation to pathological response with immunohistostaining of p53, Bcl-2, Bax, Ki-67 index, apoptotic index and Bax/Bcl-2 ratio in pretreatment specimens.	Median follow-up of 34 months (range, 3–84 months). Responses to CRT: Complete Remission (CR) n=21 (34%) Partial Remission (PR) n=28 (45%) No Change (NC) n=13 (21%). Survival rate of patients with Ki-67-positive tumors was significantly lower than those with Ki-67-negative tumors (P < 0.05). Positive p53 IHC, n=21 (34%), was associated with tumor grade (P=0.005) or stage (P=0.0454). Significant correlations between Bax/Bcl-2 ratio and CR rate (P=0.0289), histological grade (P=0.0120) or clinical stage (P=0.0159). Cause-specific survival rate of Ki-67 positive patients was significantly lower than that of negative patients (P=0.0148).	Single-institutional Study Retrospective design Limitations: Combined assessment o Bcl-2 and Bax protein expression may be used to predict a clinical response to CRT based on the Bax/ Bcl-2 ratio determined before therapy. The Ki-67 index may be a useful predictor of prognosis in patients treated by CRT. Bax/Bcl-2 ratio could be used to predict the response to CRT by analysis of pretreatment biopsy specimens from

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Histopathology: Transitional cell carcinoma n=62 (100%) Pathological grade: G2 n=15 (19.4%) G3 n=53 (80.6%) Clinical stage: T1, G3 n=12 (19.4%) T2 n=20 (32.2%) T3 n=25 (40.3%) T4 n=5 (8.1%) Lymph node metastasis: N(+) n=1 (1.6%) N(–) n=61 (98.4%)				The Ki 67 index (hazard ratio: 5.76, 95% CI: 1.42–38.44, P=0.0126) was an independent predictive factor for cancer-specific survival. The Bax/Bcl-2 ratio was not available as a predictor of survival (data not shown).	bladder tumors.
Pinho 2009 Brazil	Case series 3	n=14 Paired samples Treated with a	XAF1-high subset (n=5) XAF1-low subset (n=9)	No control	Correlation from XAF1 and XIAP with response to neoadjuvant treatment.	XAF1-high subset had a 3,9-fold decreased chance of dying from disease (hazard ratio (HR) 0,257; (CI 95%) 0,043-1,536, P=0,036).	Single-institutional Study Prospectively accrued into a phase II trial of neoadjuvant gemcitabin

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		combination of neoadjuvant gemcitabine and cisplatin. June 2002 – March 2005 Median Age 64 years (range 55 to 68 years) Male n=12 (85,7%) Tumor-Status: T2 n=7 (50%) T3 n=2 (14,3%) T4 n=5 (35,7%) Nodal Status: N0 n=14 (100%) N1-3 n=0 N > 3 n=0	XIAP mRNA		Clinical response Pathological response Progression-free survival Overall survival	Clinical response: Expression of XIAP mRNA - no statistically significance Clinical response in XAF1-high subset (n=5) was higher compared with XAF1-low subset (n=9) (100% vs. 44,4%, P=0,038). XAF1-high subset had a 2,25-fold increased chance for positive clinical response (HR 2,250; CI 95%; 1,084-4,671). XAF1 and XIAP mRNA before and after treatment – no statistically significance (data not shown). Pathological response: Inverse correlation between expression of XIAP mRNA and pathological response Expression of XAF1 – higher level in responding tumors (1,60 vs. 0,62; P=0,109). XAF1 and XIAP mRNA before and after treatment – no statistically significance (data not shown). Progression-free survival: Improvement in XAF1-high subset	and cisplatin. Paired samples narrow focus on changes and minimize facts of inter-individual genetic variability. XAF1 is a novel predictive and prognostic factor. XAF1 point towards as a tumor-suppressor gene. Additional studies, mechanistic and translational, are warranted. Limitations: Very small sample size Limited patient material

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Expression of XIAP mRNA - no statistically significance with length of PFS. Overall survival: Expression of XIAP mRNA - no statistically significance	
Sun 2012 South Korea	Study of Diagnostic Accuracy 3	n=93 transitional cell carcinoma, treated with radical cystectomy and bilateral pelvic lymphadenectomy between January 2004 and December 2010. Median age 63 (range 34 – 79) Men n=79 (84.9%) Pathological T stage	ERCC1 expression in 57 patients treated with adjuvant gemcitabine plus cisplatin chemotherapy.	ERCC1 expression in 36 patients who were not treated.	Predictive and prognostic values of excision repair crosscomplementation 1 (ERCC1). Overall survival. Disease-free survival.	Overall survival and ERCC1 expression: 5-year overall survival rate was 56.0% (95% CI, 51.8%–60.3%) ERCC1-positive tumors compared with ERCC1-negative tumors had no prognostic value (HR for death, 1.15; 95% CI, 0.55-2.40; P = 0.71). ERCC1 positivity was significantly associated with longer survival (adjusted HR for death, 0.12, 95% CI 0.014-0.99; P = 0.049) without adjuvant chemotherapy. ERCC1 positivity was associated with shorter survival with adjuvant chemotherapy (adjusted HR for death, 2.64; 95% CI 1.01-6.85; P = 0.047). Assessment of ERCC1 expression:	Single-institutional study. Retrospective design. ERCC1 may potentially be a novel biomarker with clinical predictive and prognostic values. Limitations: Different patient characteristics Retrospective nature Difference and bias were minimized because the value of ERCC1 expression was analyzed independently in each

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		T1*n=4 (4.3%) T2 n=15 (16.1%), T3 n=52 (55.9%), T4 n=22 (23.7%) Pathological N stage Node negative n=61 (65.6%) Node positive n=32 (34.4%) Histologic type Squamous differentiation n=11 (11.8%) Other types n=82 (88.2%) Pathological grade G2 n=10 (10.8%) G3 n=83 (89.2%) ERCC1 expression Positive n=54				Median H-score was 50 (range, 0–300) H-score > 50 were ERCC1 positive n=54 (58.1%) were ERCC1 positive n=39 (41.9%) were ERCC1 negative No significant differences in clinicopathologic parameters between ERCC1-positive and ERCC1-negative tumors. Prognostic value of ERCC1 expression according to adjuvant chemotherapy: ERCC1 positivity (HR for death, 0.12; 95% CI 0.014–0.99; P = 0.049), negative lymph node (HR for death, 0.066; 95% CI 0.005–0.82; P = 0.035), and histologic types other than squamous cell differentiation (HR for death, 0.033; 95% CI 0.002-0.62; P = 0.022) were significantly associated with longer survival. ERCC1 positivity was significantly associated with shorter survival in the group with adjuvant chemotherapy (HR for death, 2.64; 95% CI 1.01-6.85; P =	group. The adjuvant chemotherapy was homogenous with an identical regimen of gemcitabine plus cisplatin. Future prospective, randomized studies are warranted to confirm ou findings.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		(58.1%) Negative n=39 (41.9%) Adjuvant chemotherapy (gemcitabine plus cisplatin) Yes n=57 (61.3%) 4 cycles n=24 (25.8%) 3 cycles n=28 (30.1%) 2 cycles n=4 (4.3%) 1 cycle n=1 (1.1%) No n=36 (38.7%) Exclusion: Not completely resected Neoadjuvant chemotherapy,pTa/pT1 with negative node No available				0.047). Disease-free survival, ERCC1 expression, and adjuvant chemotherapy: 2-year disease-free survival rates for ERCC1-positive and ERCC1-negative tumors were 64.6% and 44.2% (P = 0.28) without adjuvant chemotherapy and 46.5% and 64.5% (P = 0.19) with adjuvant chemotherapy. ERCC1 expression and adjuvant chemotherapy showed borderline significance for disease-free survival (P = 0.20). Clinical benefit from adjuvant chemotherapy was associated with ERCC1 negativity as measured by overall survival (P = 0.034) and by disease-free survival (P = 0.20).	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		tissue for immunohistochemical analysis for ERCC1. Considered factors: age at operation, sex, histology, tumor stage, tumor grade.					
Takata 2005 Japan	Study of Diagnostic Accuracy 3	n=27 cancer samples Histologically confirmed transitional cell carcinoma of the bladder n=7 women, median age, 66; range, 53-77 years Inclusion: No node	n=9 Responders (patient who achieved downstaging ≤ pT1or ≤ T1 after two courses of M-VAC neoadjuvant chemotherapy).	n=9 Non-Responders (patient who could not achieve downstaging ≥ pT2 or ≥ T2 after two courses of M-VAC neoadjuvant chemotherapy).	Develop a prediction system for MVAC neoadjuvant chemotherapy on the basis of gene expression profiles of purified populations of bladder cancer cells.	14 of 50 genes showed significantly different levels of expression between responders and non-responders. The system accurately predicted the drug responses of 8 of 9 test cases that were reserved from the original 27 cases.	Multi-institutional Study Retrospective design Very limited number of samples The sensitivity of an invasive bladder cancer to the M-VAC neoadjuvant chemotherapy can be predicted by expression patterns. A larger scale study is

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		metastasis at the clinical stage of T2a N0 M0 to T3b N0 M0 and expected to undergo radical cystectomy without prior radiation therapy. No serious abnormality in renal, hepatic, or hematologic function, ECOG ≤ 2. Considered factors: Sex, Age, Stage, Grade, Response, Prediction, Post treatment.					certainly warranted. Limitations/ Bias are not reported.
Takata 2007 Japan	Study of Diagnostic Accuracy	n=22 bladder cancer patients Histologically	n=10 Responder, patient who archived downstaging	n=12 Non-responder, patient who could not archive	Further evaluation of the prediction system to M-VAC neoadjuvant	Validation of the microarray-based prediction system: Sensitivity (proportion of the patients predicted to have the responder	Multi-institutional Study Very limited number of samples.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
	3	confirmed transitional cell carcinoma of the bladder. n=16 men n=6 women Mean age 66.7 years in a range of 58–75 years. Inclusion: No node metastasis at the clinical stage of T2a N0 M0 to T3b N0 M0 and expected to undergo radical cystectomy without prior radiation therapy. Considered factors: Sex, Age, Stage,	(≤pT1 or ≤T1) after two courses of treatment.	downstaging (>pT1 or >T1) after two courses of treatment.	chemotherapy using additional test cases. 2-year-disease-free survival. Overall survival.	phenotype among responders) is estimated to be 1.0. Specificity (proportion of the patients predicted to have the non-responder phenotype among non-responders) is estimated to be 0.727. PPV (proportion of responders among the patients predicted to have the responder phenotype) is estimated to be 0.786 (11 of 14 cases). NPV (proportion of non-responders among the patients predicted to have the non-responder phenotype) is estimated to be 1.0 (8 of 8 cases). Validation of the quantitative RT-PCR-based prediction system: PPV is estimated to be 0.769 NPV is estimated to be 1.0. Predictive value of the scoring system for prognosis of patients treated with M-VAC therapy: 2-year disease-free survival rate of patients with a negative score was significantly lower than for those with a positive score (75.9% vs 41.7%).	Retrospective design. Limitations/ Bias are not reported. The predicting system for M-VAC could be used for advanced bladder therapy, and provides opportunities for achieving better prognosis and improved quality of life for patients.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Grade, Response, Prediction, Post treatment				Overall survival of patients with a negative score was also significantly shorter than those with a negative score.	
Urushibara 2007 Japan	Study of Diagnostic Accuracy 3	n=54 Clinically invasive (T2-4N0M0) or high-risk superficial (T1 and G3) bladder cancer. Considered factors: Median age 68.5 years (range 45–83 years). Female n=19 (35%) Pathological grade: G2 n=11 (20%) G3 n=43 (80%) Clinical stage:	Neoadjuvant low-dose chemoradiotherapy (CRT) followed by cystectomy between March 1997 and December 2004.	No control.	Association between Heat shock protein (HSP) expression and pathological response to treatment. 5-year cause-specific survival. 5-year overall survival.	Positive HSP60 expression prior to CRT was found to be marginally associated with good pathological response to CRT (P = 0.0564). None of clinicopathological factors was associated with HSP60 expression level. 5-year cause-specific survival in good pathological responders was 88% and significantly better than survival in poor responders (51%) (P = 0.0373). 5-year overall survival in good responders was 85% and significantly better than in the poor pathological responders (46%) (P = 0.0463). 5-year overall survival in the positive HSP60 (89%) 5-year overall survival in the negative HSP60 (59%) (P = 0.1599).	Single-institutional study. Retrospective design. First report demonstrating significance of HSP expression in clinical settings especially in CRT for the treatment of bladder cancers. Positive HSP60 expression prior to CRT may predict good pathological response to low-dose neoadjuvant CRT in invasive or high-risk superficial bladder cancer. Bias/ limitations are not reported.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		T1 (G3) n=9 (17%) T2 n=32 (59%) T3 n=11 (20%) T4 n=2 (4%) Cystectomy: Partial n=11 (20%) Radical n=43 (80%) Pathological response to CRT: Good n=33 (61%) Poor n=21 (39%) Exclusion: Impossible Follow Up.				5-year cause-specific survival in positive HSP60 (89%) 5-year cause-specific survival in negative HSP60 (64%) (P = 0.2626).	

8.5. AG 7 Schlüsselfrage 5 (Adjuvante RT/RCT nach Zystektomie)

„Ist die adjuvante RT/RCT nach radikaler Zystektomie indiziert in Abhängigkeit vom Resektionsstatus?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
El-Monim 2013 Egypt	Prospective randomized trial. 1-	N=100 patients with non-metastatic muscle invasive bladder cancer.	Postoperative radiotherapy (50 Gy/25 Fs/5 wk) after cystectomy n=50	Preoperative radiotherapy (50 Gy/25 Fs/5 wk) before cystectomy n=50	- 3-year overall survival - disease-free survival - metastases-fee survival - complication rates - locoregional control	Median follow-up: 32 months (range 0-69 months). 3-year overall survival of all patients: 51%. 3-year overall survival of preop. radiotherapy vs. postop. radiotherapy: 53,4% vs. 51,8% (p=0,689). Disease-free survival for all patients: 37%. Disease-free survival of preop. radiotherapy vs. postop. radiotherapy: 47,4% vs. 34,1% (p=0,952). Locoregional control of preop. radiotherapy vs. postop. radiotherapy: 89,3% vs. 80,6% (p=0,410). Metastases-free survival of preop. radiotherapy vs. postop. radiotherapy: 61,5% vs. 55,7% (p=0,575). None of the patients had serious radiation reactions. Authors conclusion: In our study, preoperative radiotherapy was almost equivalent to postoperative radiation therapy as regard OS, DFS, as well as complication rates. Given the	Small sample size, single center Treatment arms differ significantly in terms of tumor grade questioning success of randomization and allocation concealment and therefore validity There is no information on power calculations. Therefore it is unclear (rather unlikely) that the trial is designed as a noninferiority trial, allowing the conclusion of equivalent outcomes It seems as there are some

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						recent physical developments in radiation therapy techniques and the biological rationale for treating the pelvis after cystectomy, adjuvant radiotherapy should be re-evaluated world wide. Preoperative radiotherapy may re-emerge as a useful tool for adjuvant treatment.	mistakes in this publication: Reported follow-up time 32 (range 0-69) vs. 37 (range 1-68) months.

8.6. AG 7 Schlüsselfrage 6 (Erstlinien-Chemotherapie)

„Welchen Nutzen hat die Erstlinien-Chemotherapie im metastasierten Stadium von Blasentumorpatienten in Bezug auf das tumorspezifische Überleben und Gesamtüberleben stratifiziert nach Alter (biologisch vs. kalendarisch), Geschlecht, Komorbiditäten und Prognosefaktoren?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Bamias 2013 Greece	Prospective randomized phase III trial 1-	N=130 patients with inoperable, metastatic or relapsed urothelial cancer.	Two dose-dense (DD) regimens MVAC (methotrexate, vinblastine, adriamycin, cisplatin) [M 30 mg/m², V 3 mg/m², A 30	DD-Gemcitabine/ cisplatin [G 2500 mg/m², C 70 mg/m² q 2 weeks]. n=64	- Overall survival - Progression-free survival - Toxicity - Feasibility	Excluded patients from analysis: n=4. Median follow-up: 52,1 months (range 0,1-82,5 months). Survival: - Median overall survival of DD-MVAC vs. DD-GC: 19 vs. 18 months (P=0,98). - 3-year survival rate of DD-MVAC vs.	12 study centers in Greece. Randomization and allocation concealment not adequate reported, significant

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
			mg/m², C 70 mg/m² q 2 weeks]. n=66			DD-GC: 27,6% vs. 26,7%. Progressin-free survival: - Progressin-free survival of DD-MVAC vs. DD-GC: 8,5 vs. 7,8 months (P=0,36). - 3-year progression-free survival rate of DD-MVAC vs. DD-GC: 11,0% vs. 22,8% (p-value not reported). - Toxicity (analysis of n=120): - Grade 3-5 toxicities of DD-MVAC vs. DD-GC: 50% (n=30) vs. 44% (n=26). - Neutropenic infections of DD-MVAC vs. DD-GC: 8% vs. 0%. - Anemia of DD-MVAC vs. DD-GC: 92% vs. 89%. - Thromobocytopenia of DD-MVAC vs. DD-GC: 51% vs. 55%. - Fatique of DD-MVAC vs. DD-GC: 55% vs. 43%. - Feasibility of DD-MVAC vs. DD-GC: - 6 cycles of treatment: 63% (n=36) vs. 85% (n=50) (P=0,011). - Discontinuation rate: 13% vs. 3%. - Full dose of treatment: n=36 vs. n=39 patients. Univariate analysis: - Improved OS and PFS: due to PS of 0 and good MSKCC risk caterory.	differences between study groups according to number of metastatic sites, no blinding reported Study closed prematurely, due to slow accrual and lack of adequate funding, Authors argue that a conditional power assessment at the timepoint the trial stopped would have resulted in a decision of not continuing the trial due to futility. (low probability to detect the predicted 15% differnence for OS based on the

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- Inferior PFS: due to visceral metastases and > 3 metastatic sitesy Authors conclusion: Although DD-GC was not superior to DD-MVAC, it was better tolerated. DD-GC could be considered as a reasonable therapeutic option for further study in patient population.	interim analysis.
Bellmunt 2012	Multicenter randomized phase III study 1+	N=626 patients with locally advanced or metastatic urothelial carcinoma	Paclitaxel + cisplatin + gemcitabine (PCG) n=312	Gemcitabine + cisplatin (GC) n=314	- Overall survival - Progression-free survival - Overall response rate - Toxicity	N=607 patients were included for safety analysis. N=578 patients in treatment after excluding ineligibile patients. Median follow-up: 4,6 years. Overall survival: - Median overall survival of PCG vs. GC (ITT analysis): 15,8 vs. 12,7 months (HR 0,85; 95%CI 0,72-1,02); p=0,075). - 4-year overall survival of PCG vs. GC: 17,2% vs. 15,4%. - unplanned, post hoc analysis: overall survival of PCG vs. GC (eligible patient population): 15,9 vs. 12,7 months 3.2 months (HR 0,82; p=0,03). - Overall survival of upper urinary tract vs. bladder (not preplanned for analysis): 15,9 vs. 11,9 months (HR 0,80; p=0,025). - Overall survival in subgroup of	137 study centers Open label Randomization and allocation concealment not adequate reported.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						patients with primary tumors: 2 months (HR 0,82; p=003). Prognostic factors (ITT analysis, independent of the treatment): - WHO performance status: 1 vs. 0 (HR 1,5; p<0,001) - metastatic disease: precence vs. absence (HR 1,74, p<0,001). - visceral metastases: precence vs. absence (HR 1,74; p<0,001). - number of Memorial Sloan-Kettering Cancer Center risk factors: 2 risk factors vs. 1 or 0 risk factors (HR 2,17; p<0,001). Progression-free survival: - Progression-free survival of PCG vs. GC (in eligible population n=547): 8,3 vs. 7,6 months (HR 0,87; p=0,113). Overall response rate of PCG vs. GC: 55% vs. 43,6% (p=0,0031). Toxicity: - Severe acute toxicity of PCG vs. GC: 20,2% (incl. 6 toxic deaths) vs. 14,8% (incl. 3 toxic deaths).	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- grade 4 neutropenia of PCG vs. GC: 35,8% vs. 20% (p<0,001). - febrile neutropenia of PCG vs. GC: 13,2% vs. 4,3% (p<0,001). - thrombocytopenia grade 3/4 of PCG vs. GC: 4,0% vs. 6,2% (p=0,03). Authors conclusion: The addition of paclitaxel to GC provides a higher response rate and a 3,1-months survival benefit that did not reach statistical significance. Novel approaches will be required to obtain major improvements in survival of incurable urothelial cancer.	
Mead 1998 UK	Multicenter randomized trial 1-	N=214 patients with advanced or metastatic transitional cell carcinoma	Methotrexate + vinblastine (MV) n=106	Cisplatin + methotrexate + vinblastine (CMV) n=108	- Overall survival - Progression-free survival - Disease progression - Progression of cancer-related symptoms - Clinical response - Toxicity - Prognostic factors	Median number of cycles received with CMV vs. MV: 4 vs. 3 cycles. Overall suvival with CMV vs. MV: 7 vs. 4,5 months (HR 0,68; 95% CI 0,51-0,90; p=0,0065). 1-year survival with CMV vs. MV: 29% vs. 16%. Progression-free survival with CMV vs. MV: 5,5 vs. 3 months (HR 0,55; 95% CI 0,41-0,73; p=0,0001). Disease progression with CMV vs. MV: 34 (32%) vs. 72 (68%) patients (no p-value reported).	16 centers in the UK

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Symtomatic progression-free survival with CMV vs. MV: 4,5 vs. 2 months (HR 0,48; 95% CI 0,36-0,64; p=0,0001). Clinical response: - Complete response with CMV vs. MV: 10% vs. 7%. - Partial response with CMV vs. MV: 36% vs. 12%. Toxicity: - Treatment-related deaths with CMV vs. MV: 5 (4%) vs. 0 deaths. - Excessive toxicity with CMV vs. MV: 16 (15%) vs. 0 patients. - Leucopenia or thrombocytopenia with CMV vs. MV: 5 vs. 0 patients. - Neutropenic fever with CMV vs. MV: 11 vs. 2 patients. - Long-term neurological toxicity 9 vs. 1 patient. Prognostic factors: - for overall survial: only WHO performance status and the extent of disease are relevant prognostic factors. Authors conclusion: We conclude that the addition of cisplatin to methotrexate and vinblastine should be considered in patients with tranistional cell	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						carcinoma, taking into account the increased toxicity.	
Sternberg 2006	Randomized phase III trial 1-	N=263 patients with metastatic or advanced transitional-cell carcinoma with no prior chemotherapy.	High-dose-intensity methotrexate, vinblastine, doxorubicin, cisplatin + recombinant human granulocyte colony-stimulating factor (HD-MVAC) in 2-week cycles. n=134	MVAC in 4-week cycles. n=129	- Overall survival - Progression-free survival - Time to progression - Response rate - Toxicity	Median follow-up: 7,3 years. ITT analysis: Survival: - Median overall survival time 15,1 vs. 14,9 months. - 7,3-year overall survival rate of HD-MVAC vs. MVAC: 21,8% vs. 13,5% (p=0,042; HR 0,76; 95% CI 0,58-0,99). Progression: - Median progression-free survival time of HD-MVAC vs. MVAC: 9,5 vs. 8,1 months (HR 0,73; 95% CI 0,56-0,95; p=0,017). Response rates: - Complete response of HD-MVAC vs. MVAC: 28 (21%) vs. 12 (9%) (p=0,009). - Parial response of HD-MVAC vs. MVAC: 55 (41%) vs. 53 (41%) (p=0,06). - Overall response of HD-MVAC vs. MVAC: 64% vs. 50% (p=0,06). Toxicity: - WBC toxicity grade II of HD-MVAC vs.	21 study centers in 8 countries in Europe. Study started as a phase II study. Long period of follow-up.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						MVAC: 21% vs.22% (p=0,001). - Platelets toxicity grade II of HD-MVAC vs. MVAC: 22% vs. 12% (p=0,033). - Neutropenic fever of HD-MVAC vs. MVAC: 10% vs. 26% (p<0,001). - Mucositis grade II of HD-MVAC vs. MVAC: 18% vs. 20% (p=0,034). - Creatinine toxicity grade II of HD-MVAC vs. MVAC: 2% vs. 2% (p=0,815). Authors conclusion: With longer follow-up initial results have been confirmed, and shows that HD-MVAC produces a borderline statistically significant relative reduction in the risk of progression and death compared to M-VAC.	
Von der Maase 2005 (2000)	Randomized phase III study. 1+	N=405 patients with locally advanced or metastatic transitional-cell carcinoma (TCC) of the urothelium (stage IV) and no prior chemotherapy.	Gemcitabine (1000 mg/m^2; days 1, 8, 15) + cisplation (70 mg/m^2; day s) (GC) n=203	Methotrexate + vinblastine + doxorubicin + cisplatin (MVAC) n=202	- Overall survival - Progression-free survival - Prognostic factors (- Toxicity)	Patients for analysis n=396. Follow-up: > 5 years after the last patient had been enrolled onto the study. Overall survial: - Median overall survival of GC vs. MVAC: 14,0 vs. 15,2 months (p=0,66; HR 1,09; 95% CI 0,88-1,34). - 5-year overall survival rate: 13,0% (n=27 patients) vs. 15,3% (n=31) (p=0,53). - 5-year overall survival for patients with	Update analysis of the publication of van der Maase et al. 2000. Long time of follow-up. Open label

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						vs. without visceral metastases: 6,8% vs. 20,9%. Significant prognostic factors for overall survival: - performance score > 70 - TNM staging M0 vs. M1 - low/normal alkaline phosphatase level - number of disease sites < 3 - no visceral metastases Progression-free survival: - Median progression-free survival of GC vs. MVAC: 7,7 vs. 8,3 months (p=0,63; HR=1,09; 95% CI 0,89-1,34). - 5-year progression-free rate of GC vs. MVAC: 9,8% vs. 11,3% (p=0,63). Significant prognostic factors for progression-free survival: - poor (70) performance score - TNM staging M1 - measurable disease - high alkaline phosphatase level - number of disease sites > 3 - visceral metastases Toxicity (as reported in van der Maase et al. 2000): - Toxic death rate of GC vs. MVAC: 1% vs. 3%.	

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- Grade 3 or 4 anemia of GC vs. MVAC: 27% vs. 18%. - Thrombocytopenia of GC vs. MVAC: 57% vs. 21%. - Transfusion rate of RBC of GC vs. MVAC: 13 of 100 cycles vs. 13 of 100 cycles. - Transfusion rate of platelets of GC vs. MVAC: 4 of 100 cycles vs. 2 of 100 cycles. - Neutropenia grade 3 or 4 of GC vs. MVAC: 71% vs. 82%. - Neutropenic fever of GC vs. MVAC: 2% vs. 14%. - Mucositis grade 3 or 4 of GC vs. MVAC: 1% vs. 22%. Authors conclusion: Long-term overall survival and progression-free survival after treatment with GC or MVAC are similar. These results strengthen the role of GC as a standard of care in patients with locally advanced or metastatic TCC.	

8.7. AG 7 Schlüsselfrage 7 (Prädiktive Faktoren für Erst- und Zweitlinientherapie)

„Gibt es prädiktive Faktoren, anhand derer die Wirksamkeit einer Erstlinien-Chemotherapie bzw. Zweitlinien-Chemotherapie des metastasierten Urothelkarzinoms abgeschätzt werden kann?“

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
Li 2014 Meta-analysis	Sensitivity analysis: results are statistically robust. Publication bias was found for ERCC1 and OS. The Newcastle-Ottawa Qualitiy Assessment Scale for cohort studies was used to assess the quality of the studies: all included studies were scored high. But unclear if assessed by two reviewers. All studies were retrospective observational studies No systematic search, literature search by related	Inclusion criteria: - utilized platinum-based regimens for patients with path. proven bladder cancer. - measured ERCC1 with immunhistochemistry or RT-PCR - presented the data of the objective response rate, overall survival and/or progression-free survival according to the ERCC1 status - reported or allowed calulation of hazard ratio.	s. unter Endpunkte	Correlation of expression levels of excision repair cross-complementation group 1 (ERCC1) with: - objective response - overall survival - progression-free survival	3 studies with n=356 patients: - n=138 (38,8%) with high/positive ERCC1 expression - n=218 (61,2%) with low/negative ERCC1 expression. - Objective response rate of low/negative ERCC1 expression vs. high/positive ERCC1 expression: OR 0,86; 95% CI 0,36-2,06; p=0,734 [reported by 3 studies]. - Overall survival time of low/negative ERCC1 expression vs. high/positive ERCC1 expression: prolonged with low/neg. ERCC1ex.; HR 0,76; 95% CI 0,66-0,89; p=0,000 [reported by 6 studies, n=356]. - Progression-free survival time of low/negative ERCC1 expression vs. high/positive ERCC1 expression: prolonged with low/neg. ERCC1ex.; HR 0,69; 95% CI 0,54-0,89; p=0,004 [reported by 4 studies, n=242]. No heterogenity was found in the overall and subgroup analysis (asian vs. not asian, method of ERCC1 detection, number of chemotherapy drugs). Authors conclusion: Large prospective clinical studies using	Hoffmann 2010 Kawashima 2012 Sun 2012 Matsumura 2011 Ozcan 2012 Bellmunt 2007

Referenz Studientyp	methodische Bemerkungen Evidenz-graduierung	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Literaturbelege/ eingeschlossene Publikationen
	articles function of pubmed, Authors declared no conflicts of interest 2-				standardized unbiased methods are needed... to confirm our findings	

8.8. AG 7 Schlüsselfrage 8 (Cisplatin-ungeignete Patienten)

„Welche Patienten sind für eine cisplatinhaltige-Chemotherapie ungeeignet?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
De Santis 2012 (and 2009)	Multicenter randomized controlled phase III study 1+	N=236 patients with bladder cancer and impaired renal function (< 30 ml/min < glomerular filtration rate [GFR] < 60 ml/min and/or PS 2). All patients were	GC (gemcitabine 1000 mg/m² on days 1 and 8 and carboplatin area under the serum concentration-time curve [AUC] 4,5 for 21 days. n=118	M-CAVI (methotrexate 30 mg/m² on days 1, 15, 22; carboplatin AUC 4,5 on day 1; vinblastin 3 mg/m² on	- Overall survival - Overall response rate - Progression-free survival - Severe acute toxicity - Quality of life	Median follow-up: 4,5 years. - Median overall survival of GC vs. M-CAVI: 9,3 vs. 8,1 months (HR 0,94; 95% CI 0,72-1,22; p=0,64). - Confirmed and unconfirmed overall response rates of GC vs. M-CAVI: 41,2% vs. 30,3% (p=0,08). - Confirmed overall response rates of	Adequate time of follow-up. No p-values given for the endpoint toxicity. Quality of life was assessed at

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		chemotherapy naive.		days 1, 15, 22 for 28 days. n=118		GC vs. M-CAVI: 36,1% vs. 21%. Patients with only one reason for being unfit for cisplatin had a better overall survival than patients with both reasons (GFR < 60 ml/min, and performance status 2). Overall survival decreased with the increasing numbers of Bajorin risk factors. - Median progression-free survival: 5,8 vs. 4,2 months (HR 1,04; 95% CI 0,80-1,35; p=0,78). Treatment "modifications": - Treatment stopped due to toxicity in GC vs. M-CAVI: 21,4% vs. 21%. - Dose reduction in GC vs. M-CAVI: 72,9% vs. 84,7%. - Delays in GC vs. M-CAVI: 71,2% vs. 60,2%. Severe acute toxicity of GC vs. M-CAVI: 9,3% vs. 21,2%: - Leucopenia grade 3 or 4 in GC vs. M-CAVI: 44,9% vs. 46,6%. - Neutropenia in GC vs. M-CAVI: 52,5% vs. 63,5%. - Febrile neutropenia in GC vs. M-CAVI: 4,2% vs. 14,4%. - Thrombocytopenia in GC vs. M-CAVI:	baseline, after every two cycles and at the time of stopping treatment by using the EORTC Quality of Life Questionaire C30 (QLQ-C30) Version 3.0. Due to low compliance (90% at baseline, less than 50% afterward) for quality of life, the results remain inconclusive. Study planed as inferiority trial (powered to detect 50 % HR for overall survival) Study supported by Eli Lilly, several authors declared

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						48,3% vs. 19,4%. - Infection in GC vs. M-CAVI: 11,8% vs. 12,7%. Quality of life: no differences (p=0,47). Authors conclusion: There were no significant differences in efficacy between the two treatmet groups. The incidence of severe acute toxicities was higher for those receiving M-CAVI.	financial relationships with Lilly (conflicts of interest)
Galsky 2007 USA	Single-institutional phase II trial (case series) 3	N=25 patients with advanced urothelial bladder cancer, ineligible for cisplantin because of solitary kidney and creatinine clearance < 60 ml/min.	Doxorubicin + gemcitabine every other week for 5 cycles followed by paclitaxel plus carboplatin weekly for 12 weeks		- Toxicities - Effecitveness - Response - Survival	Drug delivery: - Completition of all 17 cycles: 60% (n=15). - Completition of ≥ 15 cycles: 84% (n=21). - At least 1 dose delay: 56% (n=14). - Dose reduction: 12% (n=3). Toxicities: - Neutropenia grade III-IV: 28%. - Febrile neutropenia: 8% (n=2). - Thrombotic episodes ≥ III: 16% (n=4). Response (ITT): - Overall response rate: 56% (95% CI 35%-76%). - Complete response: 20%; n=5 (95% CI 6%-41%). - Partial response: 36%; n=9 (95% CI 18%-58%).	Very small sample size.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Survival: - Median survival: 15 months (95% CI 11-30 months). - 2-year survival: 32%. - 3-year survival: 25%. - Follow-up of 45 months (range 14-68 months): 7 patients (28%) are disease-free. Authors conclusion: Dose-dense sequential chemotherapy is tolerable and active in patients with urothelial carcinoma and renal impairment. Prolonged disease-free survival is achievable in a subset of patients with primary unresectable disease or lymph-node only metastases treated with carboplatin-based therapy plus/minus surgical consolidation. Randomized trials are needed to define the optimal regimen in patients with advanced urothelial carcinoma and renal impairment.	
Hussain 2007	Multicenter phase II trial (case series) 3	N= 44 patients with advanced urothelial carcinoma and prospectively evaluated human epidermal growth factor receptor-2 (Her-2/neu)	Trastuzumab 4 mg/kg followed by 2 mg/kg on days 1, 8, 15; paclitaxel 200 mg/m^2 on day 1; carboplatin (C;		Primary endpoint: - Cardiac toxicity Secondary endpoints: - Toxicities - Response rate - Time to disease	Median cycles: 6 (range 1 to 12 cycles). Toxicities: - Death: n=2 (5%). - Cardiac toxicities grade I-III: n=10 (22,7%). - Cardiac toxicity grade III: n=2 (4,5%).	Very small sample size.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		overexpression rates. Her-2/neu status: - n=57 patients (52%) positive with at least one method. - All of the 44 Her-2-positive treated patients had serum available. - Her-2/neu positive patients had a trend for more liver/bone metastases (no p-value given), higher median number of metastatic sites (p=0,14) and a higher incidence of two or more metastatic sites (51% vs. 31%; p=0,51).	area under the curve, 5) on day 1; gemcitabine 800 mg/m^2 on days 1, 8.		progression - Survival - Prospective evaluation of Her-2/neu overexpression rate.	Response: - Overall response: n=31 (70%). - Complete response: n=5 (11%). - Partial response: n=26 (59%). - Stable disease: n=5 (11%). Survival: - Median time to progression: 9,3 months (95% CI 6,7-10,2 months). - Median duration of response: 7,1 months (95% CI 4,8-8,0 months). - Median survival: 14,1 months (95% CI 11,5-17,1 months). Authors conclusion: We prospectively characterized Her-2/neu status in advanced urothelial carcinoma patients. Trastuzumab/Paclitaxel/Carboplatin/Gemcitabine is feasible; cardiac toxicity rates were higher than projected, but the majority were grade two or lower. Determining the true constribution of trastuzumab requires a randomized trial.	

8.9. AG 7 Schlüsselfrage 9 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

8.10. AG 7 Schlüsselfrage 10 (Monosubstanzen und Kombinationen in der Zweitlinientherapie)

„Welche Monosubstanzen bzw. Substanzkombinationen und wie viele Therapiezyklen sollen bei einer Zweitlinientherapie des metastasierten Urothelkarzinoms der Harnblase zum Einsatz kommen?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Bellmunt 2009	Multicenter randomized controlled phase III trial 1-	N= 370 patients with advanced bladder cancer who had experienced progress after first-line platinum-containing regimen.	Vinflunine (320 or 280 mg/m^2 + best supportive care (BSC) n=253	BSC n=117	- Toxicity - Overall survival - Response rate - Disease control - Progression-free survival - Quality of life - Clinical benefit	Median follow-up: 22,1 months. Toxicities for Vinflunine + BSC: - Neutropenia grade III-IV: 50%. - Febrile neutropenia: 6%. - Anemia: 19%. - Fatique: 19%. - Constipation: 16%. Survival (ITT analysis): - 2-months survival benefit for vinflunine + BSC vs. BSC: 6,9 vs. 4,3 months (HR 0,88; 95% CI 0,69-1,12; p=0,287). - Overall survival (multivariate analysis for ITT) for vinflunine + BSC vs. BSC: HR 0,77; 95% CI 0,61-0,98; p=0,036. Survival (eligible population n=357): - 2-months survival benefit for vinflunine + BSC vs. BSC: 6,9 vs. 4,3	Adequate follow-up time. Randomization 2:1. No adequate information according to randomization, allocation concealment and blinding reported. Significant baseline differences according to performance status

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						months (HR 0,78; 95% CI 0,61-0,99; p=0,040). Overall response rate for vinflunine + BSC vs. BSC: 8,6% vs. 0% (p=0,006). Disease controll for vinflunine + BSC vs. BSC: 41,2% vs. 24,8% (p=0,002). Median progression-free survival for vinflunine + BSC vs. BSC: 3,0 vs. 1,5 months (p=0,001; HR 0,68; 95% CI 0,54-0,86). Quality of life: Vinflunine did not induce a decrease in health-related quality of life (p=0,66). Clinical benefit: Vinflunine did not produce a worsening of the clinical benefit of patients. Authors conclusion: Vinflunine demonstrates a survival advantage in second-line treatment for advanced transitional cell carcinoma of urothelial tract. Consistency of results exists with significant and meaningful	questioning successful randomization. Primary outcome in the ITT not significant. Adjusted multivariate or per protocol analysis are significant but with wide KI. Insufficient reporting of quality of life data. Study sponsored by Pierre Fabre and some authors are employees or consultants of Pierre Fabre (high risk of Conflict of interest).

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						benefit over all efficacy parameters. Safety profile is acceptable, and therefore, vinflunine seems to be a reasonable option for transitional cell carcinoma of urothelial tract progressing after first-line platinum-based therapy.	
Bellmunt 2012	Multicenter randomized controlled phase III trial 1-	N= 370 patients with advanced bladder cancer who had experienced progress after first-line platinum-containing regimen.	Vinflunine (320 or 280 mg/m² + best supportive care (BSC) n=253	BSC n=117	Survival	Median follow-up: 45,4 months. Survival (ITT analysis): - Median overall survival: 6,9 vs. 4,6 months (HR 0,88; 95'% CI 0,70-1,10; p=0,2613). - 12-months survival: 27% vs. 27%. - 24-months survival: 11% vs. 11%. - Overall survival (multivariate analysis for ITT) for vinflunine + BSC vs. BSC: HR 0,719; 95% CI 0,570-0,906; p=0,0052. Survival (eligible population n=357): - Overall survival benefit for vinflunine + BSC vs. BSC: 6,9 vs. 4,3 months (HR 0,78; 95% CI 0,61-0,96; p=0,0227). - 12-months survival: 27% vs. 22%. - 24-months survival: 11% vs. 8%. Authors conclusion: The updated overall survival data confirm the positive treatment effect of vinvlunine on survival that was previously reported. These results are consistent over time and confirm that	Original data see Bellmunt 2007. Long-term suvival data + updated overall survival is presented here.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						vinflunine is a valuable option for second-line treatment in patients with advanced transitional cell carcinoma of urothelial tract after failure of platinum-based regimens.	
Albers 2010 Germany	Multicenter randomized phase III trial 1-	N= 96 patients with metastatic urothelial cancer after failure of cisplatin-based first-line therapy.	Second-line short-term gemcitabine 1000 mg/m² on days 1 and 8 + paclitaxel 175mg/m² on day 1. n=48	Second-line long-term gemcitabine 1000 mg/m² on days 1 and 8 + paclitaxel 175mg/m² on day 1. n=48	- Overall survival - Progression-free survival - Objective response-rate - Toxicity	Overall survival of short-term vs. long-term: 7,8 [95% CI 4,2-11,4] vs. 8,0 [95% CI 4,9-11,1] months (p=0,772). Progression-free survival of short-term vs. long-term: 4,0 [95% CI 0-8,0] vs. 3,1 [95% CI 1,9-4,2] months (p=0,488). Objective response rate of short-term vs. long-term: 37,5% vs. 41,5% (p=0,715). Toxicitiy: - Anemia grade III/IV of short-term vs. long-term: 6,7% vs. 26,7% (p=0,011). - 2 patients died due to treatment-related toxic effects. Authors conclusion: Due to rapid tumor progression and toxicity at this dosage and schedule in a multicenter setting, it was not feasible to deliver a prolonged regimen. However, a high response rate of about 40% makes gemcitabine + paclitaxel a promising second-line treatment option for patients with metastatic urothelial	Small sample-size. Study was powered to detect a OS-difference of 9,1 months. Studies shows that a prolonged treatment is not feasible (3 cycles vs. 4 cycles) Study funded by Lilly and Bristol Myers Squibb.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						carcinoma.	

8.11. AG 7 Schlüsselfrage 11 (Erhaltungstherapie in der Zweitlinie)

„Welchen Nutzen hat die Erhaltungstherapie im Vergleich zu begrenzten Therapiezyklen in der Zweitlinientherapie des metastasierten Urothelkarzinoms der Harnblase?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Albers 2011	RCT 1+	November 2001 to November 2005. n=102 Histologically confirmed metastatic Urothelial Carcinoma (bladder, urethra or upper urinary tract), with recurrence or progression.	Arm A (n = 51) Short-term gemcitabine and paclitaxel (GP) followed by best supportive care (BSC).	Arm B (n = 51) Prolonged gemcitabine and paclitaxel (GP).	Primary end point: Overall survival (OS). Secondary end points: Progression-free survival (PFS), objective response rates (ORR) and toxicity. Identification of	No significantly difference in: OS [arm A: 7.8 (95% CI: 4.2–11.4), arm B: 8.0 (95% CI: 4.9–11.1) months]. PFS [arm A: 4.0 (95% CI: 0–8.0), arm B: 3.1 (95% CI: 1.9–4.2) months]. ORR (arm A: 37.5%, arm B: 41.5%). Toxicity: Severe anemia (arm A: 6.7% versus arm B: 26.7% grade III/IV anemia; P = 0.011).	Multi-institutional study (30 German centers) Open-labeled randomized phase III trial Study was powered (90% to detect a difference or OS of 9,1 months (superiority). Limitations:

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Primary tumor localization: Bladder n=76 Kidney, ureter, urethra n=18 Combination of bladder and upper urinary tract n=2 Hepatic and/or bone metastasis n=34 Lymphatic metastasis only n=27. Surgery carried out before chemotherapy: Cystectomy n=65 Nephroureterectomy n=17 TUR-B only n=10 Others n=4. Modality of first-line treatment:			prognostic factors.	Treatment was stopped during the first cycle due to disease progression or toxicity (n=6), Death due to treatment-related toxic effects in arm B (n=2). Prognostic factor for OS: lymph node metastases only (13,8 Months) vs. additional oder other metastasis (6,5 months). Prognostic factors for PFS: duration of response to first line treatment. Superior OS and PFS of prolonged compared with short-term GP in second-line treatment after failure to cisplatin-based chemotherapy was not possible to demonstrate. Prolonged second-line chemotherapy was not feasible in this population (Arm A: 3 cycles; arm B: 4 cycles).	A more homogeneous population would have provided clearer results in terms of prognostic factors for response. Funding: Lilly Oncology Inc.; Bristol Myers Squibb Inc.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
		Adjuvant after surgery n=42 Primary inductive chemotherapy n=50 Neoadjuvant chemotherapy n=4. Prior chemotherapy regimen: GC n=53 Cisplatin n=2 GC/paclitaxel n=2 GC/amifostine n=2 MVAC/MVEC/MC n=37.					

8.12. AG 7 Schlüsselfrage 12 (Indikation zur Metastasenresektion nach Chemotherapie)

„Wann wird die Indikation zur Metastasenresektion nach Chemotherapie von metastasierten Blasentumorpatienten in Hinblick auf die Morbidität, Mortalität und Lebensqualität gestellt?“

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Abe 2007 Japan	Case series 3	N=48 patients with metastatic urothelial cancer which underwent systemic chemotherapy. N=12 patients with metastasectomy.	Conventional cisplatin-based chemotherapy.		The impact of multimodal treatment including metastastectomy on survival. Endpoint: - median survival	Median survival-time of all patients: 17 months (range 9-27 months). Independent predictors of survival (multivariate model) [selected due to significance in univariate analysis and perceived clinical relevance]: - ≥ 5 chemotherapy cycles (p=0,0022). - no liver, bone and local recurrence (p=0,0146). - resection of metastasis (p=0,0006). Median survival in patients with metastasectomy (n=12) vs. no metastasectomy: 42 [95% CI 19-42 months] vs. 10 months [95% CI 6-17 months]. Authors conclusion: The number of chemotherapy cycles, sites of metastasis, and metastasectomy had an impact on survival. In selected patients, a multi-modal approach including metastasectomy may contribute to long-term disease control.	Small number of patients; especially patients with metastasectomy (n=12). Patient characteristics (gender, sex, origin, site of metastases, number of metastases, time of resection, inducion chemotherapy, response) of patients with metastases are very inconsistant.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Abe 2014 Japan	Case servies 3	N=42 patients with urothelial carcinoma and resection of metastases	Metastasectomy with curative intend (mostly) after and/or after chemotherapy.		To determine prognostic factors associated with prolonged survival after metastasectomy. Endpoint: - overall suvival	Side of resection: - lymph node dissection: n=20 - pulmonary resection: n=12 - pelvic exenteration: n=3 - resection of local recurrence: n=2 - resection of subcutaneous met.: n=2 - liver resection: n=1 - others: n=2. Median overall survival from initiation of treatment for metastases: 29 months . (18-80 months). Median overall survival from metastasectomy: 26 months (11-90 months). 5-year overall survival from metastasectomy: 31% . Univariate analysis: Median survival of metastasectomy of solitary lung or lymph node resection vs. other kinds of metastasectomy: 81 months vs. 19 months (p=0,0296). Authors conclusion: Long-term cancer control could be achieved in a subgroup of patients undergoing metastasectomy, especially in those with solitary lung or solitary lymph node metastasis.	Multicenter: 4 hospitals. 41 of 42 patients underwent systemic chemotherapy before and/or after metastastectomy . Small number of patients.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
Herr 2001 USA	Case series 3	N=80 patients with unresectable or regionally metastatic bladder cancer.	Surgical rescetion of residual cancer (after cisplatin based chemotherapy treatment; n=60 patients with MVAC).		- Response - Relapse-free survival	Post-chemotherapy surgical outcome in 80 patients: - N=49: residual cancer; Response to chemotherapy: n=9 complete, n=35 partial, n=5 none - N=24: no residual cancer; Response to chemotherapy: n=15 complete, n=7 partial, n=2 none - N=7: unresectable disease; Response to chemotherapy: n=2 partial, n=5 none. Overall survival: n=34 (42%) survived 9 months to 5 years. Results of surgery: - N=49 (61%): cancer completely resected. 20 of these 49 patients (41%) survived after 5 years. - N=24 (30%): pathologically cancer-free. 14 of these 24 patients (58%) survived 9 months to 5 years. Authors conclusion: Post-chemotherapy surgical rescetion of residual cancer may result in disease-free survival in some patients who would otherwise die of disease. Optimal candidates include those in whom the pre-chemotherapy sites of disease are restricted to the bladder and pelvis or	Information concerning chemotherapy regimen only given for 60 patients with MVAC.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						rgional lymph nodes, and who have a major response to chemotherapy.	
Lehmann 2008 Germany	Retrospective case series 3	N=44 patients with bladder cancer and removal of urothelial carcinoma metastases.	Complete resection of all detectable metastases. N=35 patients with chemotherapy before and/or after surgery.		- overall survival - cancer-specific survival - progression-free survival from time of diagnosis and metastasectomy	Resection metastatic sites: - retroperitoneal lymph nodes: 56,8% - distant lymph nodes: 11,3% - lung: 18,2% - bone: 4,5% - adrenal gland: 2,3% - brain: 2,3% - small intestine: 2,3% - skin: 2,3% Median overall survival from initial time of diagnosis:35 months (5-year survival rate: 28,0%). Median overall survival from metastasectomy: 27 months (5-year survival rate: 27,7%). Cancer-specific survival from initial time of diagnosis:38 months (5-year survival rate: 33,8%). Cancer-specific survival from metastasectomy: 34 months (5-year survival rate: 32,5%). In summary, surgical resection was well tolerated, with no perioperative deaths. Progression-free survival from initial time of diagnosis:19 months (5-year survival rate: 23,6%).	Mulitcenter: 15 uro-oncologic centers in Germany. Small number of patients. No significant prognostic factors could be determined due to limited patient number. Administrion of systemic chemotherapy was heterogeneous.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						Progression-free survival from metastasectomy: 15 months (5-year survival rate: 24,0%). 5-year overall survival for the entire cohort was 28%. Authors conclusion: Long-term cancer control and possible cure can be achieved in a subgroup of patients following surgical removal of urothelial cancer metastasis. Metastasectomy in patients with disseminated urothelial cancer metastasis remains investigational and should only be offered to those with limited disease as a combined-modality approach with systemic chemotherapy.	
Otto 2001 Germany	Prospective phase II trial (case series) 3	N=70 with bladder cancer metastases (lung, lymph nodes, skin, bone, peritoneum, liver) refractory to MVAC chemotherapy.	Complete surgical resection of bladder cancer metastases.		Outcome of surgical removal of metastases. Endpoints: - suvival - quality of life/ performance score	Patients: - Patients with multiple metastases: 76%. - Patients with different localisations: 41%. Survival: - Median survival time: 7 months. - 1-year survival rate: 30,7%. - 2-year survival rate: 19,3%. - No difference in survival by site of metastasis. Performance score:	Short time of follow-up.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- N=42 (83%) of the 51 symptomatic patients did benefit from surgery in terms of tumor-related symptoms and performance score: WHO performace score changed from 3,3 to 2,1 (p=0,005). - N=19 of 19 asymptomatic patients complained of a reduced sense of well-being postoperatively (p=0,007). Authors conclusion: Surgical removal of metastases from bladder cancer refactory to systemic therapy has an impact on the quality of life in patients with symptomatic disease only. Asymptomatic patients felt worse after surgery and no survival advantage appeared to be gained.	
Siefker-Radtke 2004 USA	Retrospective case series 3	N=31 patients with metastatic urothelial cancer undergoing metastasectomy.	metastasectomy		- Overall-survival - Time to progression	Resection sites: - lung n=24 (77%) - distant lymph nodes n=4 (13%) - brain n=2 (7%) - subcutaneous metastasis n=1 (3%). Resection wih negative margins in 30 patients. Overall-survival: - from time of diagnosis of metastasis: 31 months. - from time of metastasectomy: 23 months.	Small sample size.

Referenz	Studientyp Evidenz-graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkungen
						- 5-year survival from metastasectomy: 33%. Of this group of long-term survivors 5 are alive and free of disesase. No differences in survival were observed when comparing site of resection for pathological subtypes of metastases. Progression: - time to progression from metastasectomy: 7 months. Authors conclusion: The results in this highly selected cohort, with 33% alive at 5 years after metastasectomy, suggest that resection of metastatic disease is feasible and may contribute to long-term disease controll especially when integrated with chemotherapy. Further prospective studies should be undertaken to better characterize the selection criteria and benefit from this intervention.	

9.6. AG 8 Schlüsselfrage 6 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

9.7. AG 8 Schlüsselfrage 7 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

9.8. AG 8 Schlüsselfrage 8 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

9.9. AG 8 Schlüsselfrage 9 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche

9.10. AG 8 Schlüsselfrage 10 – keine Evidenztabelle erstellt wegen Expertenkonsens oder externe De-Novo-Recherche