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Leitlinienprogramm Onkologie

Seit > 5 Jahren nicht aktualisiert, Leitlinie wird zur Zeit überarbeitet

Leitlinienreport zur S3-Leitlinie Diagnostik, Therapie und Nachsorge der Keimzelltumoren des Hodens

Version 1.0 – Mai 2019
AWMF-Registernummer: 043/049-OL

Leitlinienreport

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

Inhaltsverzeichnis

1. Informationen zum Leitlinienreport

1.1. Autoren des Leitlinienreports

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1.2. Herausgeber

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

1.3. Federführende Fachgesellschaft der Leitlinie

Deutsche Gesellschaft für Urologie e.V. (DGU)

Deutsche Krebsgesellschaft (DKG) vertreten durch:
German Testicular Cancer Study Group (GTCSG)

1.4. Finanzierung der Leitlinie

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

1.5. Kontakt

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1.6. Zitierweise des Leitlinienreports

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Diagnostik, Therapie und Nachsorge der Keimzelltumoren des Hodens, Leitlinienreport 1.0, 2019, AWMF Registernummer: 043/049-OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/hodentumoren, (abgerufen am TT.MM.JJJJ).

1.7. Weitere Dokumente zur Leitlinie

Die Leitlinie wird als Lang- und Kurzversion vorliegen. Außerdem wird es eine Patientenleitlinie (Laienversion der Leitlinie). Alle Dokumente zur Leitlinie sind über die folgenden Seiten zugänglich:

- AWMF (http://www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- Leitlinienprogramm Onkologie https://www.leitlinienprogramm-onkologie.de/leitlinien/hodentumoren

1.8. Allgemeine Informationen zur Leitlinie

In der Langversion der Leitlinie sind die Adressaten der und diejenigen Ziele aufgeführt, die mit der Erstellung und Implementierung der Leitlinie verfolgt werden.

Darüber hinaus enthält die Langversion Angaben zur Gültigkeit, dem geplanten Aktualisierungsverfahren und den Personen und Institutionen, die an der Erstellung der Leitlinien beteiligt waren.

1.9. Abkürzungsverzeichnis

Tabelle 1: Abkürzungsverzeichnis

Abkürzung	Bedeutung
ACT	adjuvant chemotherapy
AFP	α-Fetoprotein
AHR	adjusted hazard ratio
AJCC	American Joint Committee on Cancer
ALT	GPT (Glutamat-Pyruvat-Transaminase)
AMC	academic medical center
AML	acute myeloid leukaemia
API	Asian/Pacific Islander men
ASR	age-standardized rates
AST	GOT (Glutamat-Oxalacetat-Transaminase)
ATSP	high-dose chemotherapy regimen with stem cell transplantation
AUC	area under the curve
AYA	adolescent and young adult
BEP/PEB	bleomycin, etoposide, cisplatin

Abkürzung	Bedeutung
BM	brain metastases
BMI	Body Mass Index
BOMP	bleomycin, vincristine, methotrexate, cisplatin,
BOMP-E	bleomycin, vincristine, methotrexate, cisplatin followed by etoposide, ifosfamide, cisplatin
CarboPEC (T)	carboplatin, etoposide, cyclophosphamide (paclitaxel)
CAV/IE	cyclophosphamide/doxorubicin/vincristine ifosfamide/etoposide
CBOP	carboplatin, bleomycin, vincristine, cisplatin
CCI	crude cumulative incidence
CDC	Centers for Disease Control and Prevention
CDCT	conventional-dose chemotherapy
CDDP	cis-Diammindichloroplatin (Cisplatin)
CDFS	conditional disease free survival
CDUS	color-doppler ultrasound
CE	carboplatin, etoposide
CECT	Contrast-enhanced computer tomography
CEI	carboplatin, etoposide, ifosfamide
CG	control group
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMB	China Medical Board
CMV	Cytomegalie-Virus
CO	cryptorchidism

Abkürzung	Bedeutung
COI	conflict of interest
COS	conditional overall survival
CR	complete response
cRR	conditional risk of relapse
CRUK	Cancer Research UK
cSI	clinical stage I
CSS	cancer specific survival
CT	Computer tomography *oder auch* Chemotherapy
CTC	common toxicity criteria
CVB	cisplatin, vinblastine, bleomycin
CVE	cardiovascular events
CXCL 12	CXC-Motiv-Chemokin 12
CXR	chest X-Ray
D	day
DFS	disease free survival
DFSR	disease free survival rate
DGU	Deutsche Gesellschaft für Urologie
DKG	Deutsche Krebsgesellschaft
DKH	Deutsche Krebshilfe
DLCO	diffusing capacity of the lungs for carbon monoxide
DOR	diagnostic odds ratio
DSG	Disease Site Group
DSS	disease specific survival
DVT	deep vein thrombosis

Abkürzung	Bedeutung
DWD	dead without disease
EP	cisplatin, etoposide
EAU	European Association of Urology
EBRT	external beam radiotherapy
EBV	Epstein Barr Virus
EC	embryonal carcinoma
EFS	event-free survival
EG	experimental group
EGCCCG	European Germ Cell Cancer Consensus Group
EGGCT	extra gonadal germ cell tumour
EK	Expertenkonsens
EMF	electromagnetic fields
EOR	excess odds ratio
EPI	epididymis
Fav-BEP	Favorable BEP-Group
FDG PET/CT	fluorodeoxyglucose positron emission tomography
FFS	failure-free survival
FTGCT	familial testicular germ cell tumor
GCC	germ cell cancer
GCNIS	germ cell neoplasia in situ
G-CSF	granulocyte colony-stimulating factor
GCT	germ cell tumor
GFR	glomerular filtration rate
GIS	gastrointestinal

Abkürzung	Bedeutung
GIST	gastrointestinal stromal tumors
GO	gemcitabine plus oxaliplatin
GOP	gemcitabine plus oxaliplatin plus paclitaxel
GTCSG	German Testicular Cancer Study Group
H&P	history and physical
hCG	human chorion gonadotropin
HDCT	high-dose chemotherapy
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HR	hazard ratio
HTA	health technology assessment
ICD	International Classification of Diseases
ICR	Institute of Cancer Research
IGCCCG	International Germ Cell Cancer Collaborative Group
IQR	inter-quartile range
ITGCNU	intratubular germ cell neoplasia of unclassified type
IU	Indiana University
IVC	inferior vena cava
JSC	Johnsen Score Count
kA	keine Angabe
KZT	Keimzelltumor des Hodens
LDH	Laktatdehydrogenase
LH	Luteinisierendes Hormon
LoE	level of evidence

Abkürzung	Bedeutung
L-PCLND	laparoscopic postchemotherapy retroperitoneal lymph node dissection
LR	likelihood ratio
LVI	lymphovascular invasion, lymphatic or vascular invasion
MA	meta-analysis
MAPE	mean absolute percentage error
MCE	major cardiac event
MDC	multidisciplinary clinic
MDS	myelodysplastic syndrom
ME	malignant event
MHL	marker half life
MIR	magnetic resonance imaging
miR	micro RNA
mo	month
MPE	mean percentage error
MRC	Medical Research Council
MRI, MRT	magnetic resonance imaging
mSV	millisievert
MTOL	more than one line of treatment
MV	mega voltage
n	number
NCI	National Cancer Institute
NCTW	noncancerous testicular tissue width
NED	no evidence of disease
NHL	non-Hodgkin lymphoma

Abkürzung	Bedeutung
NHS	National Health Service
NIH	National Institute of Health
NLR	negative likelihood ratio
NR	not reported
NS	nonseminomatous
OAS	overall survival
Onco-TESE	onco-testikuläre Spermien Extraktion
O-PCLND	open postchemotherapy retroperitoneal lymph node dissection
OR	odds ratio
ORR	overall response rate
OS	overall survival
PA-strip	para-aortic strip
PBSCT	peripheral blood stem cell transplant
PCa	prostate cancer
PC-RPLND	postchemotherapy retroperitoneal lymph node dissection
PE	physical rvaluation
PEB=BEP	Cisplatin, etoposide, bleomycin
PEI	cisplatin, etoposide, ifosfamide
PET	positron emission tomography
PFS	progression free survival
PLAP	placental alkaline phosphatase
PLR	positive likelihood ratio
PNET	primitiver neuroektodermaler Tumor
PR	partial response

Abkürzung	Bedeutung
pT	pathologisches Tumorstadium
QoL	quality of life
RATC	rapid access testicular clinic
RC	regression coefficient
RCT	randomised controlled trial
RFI	relapse free intervall
RFS	recurrence-free survival
RLA	retrograde Lymphadenektomie
RoB	risk of bias
ROC	receiver operating characteristic
RoRR	ratio of RR estimates
RPLND, RLND	retroperitoneal lymph node dissection
RR	relatives Risiko
RS	relative survival
RT	radiotherapy
RTI	rete testis invasion
RTR	residual tumor resection
SCIN	Scale for Chemotherapy-Induced Neurotoxicity
SD	standard deviation
SE	standard error
SEER	Surveillance, Epidemiology, and End Results
SIGN	Scottish Intercollegiate Guideline Network
SIR	standardized incidence ratio
SMN	second malignant neoplasms

Abkürzung	Bedeutung
SMR	standardised mortality ratio
SPM	second primary malignancies
SR	systematic review
SROC	summary receiver operating characteristic
STM	serum tumour marker
T-BEP	paclitaxel, bleomycin, etoposide, and cisplatin
TC, TCa	testicular cancer
TEE	thrombo embolic event
TESE	testikuläre Spermienextraktion
TGCC, TGCT	testicular germ cell cancer/tumor
TIN	testikuläre intraepitheliale Neoplasie
TIP	paclitaxel, ifosfamide, cisplatin
TM, TML	testicular microlithiasis
TNM	Tumour Node Metastasis
TSE	testicular self examination
UDT	undescended testis
UICC	Union for International Cancer Control
UK	United Kingdom
ULN	upper limit of normal
Unfav-BEP	unfavorable BEP-Group
US	ultrasound
USPSTF	US Preventive Task Force
VASC-	vascular invasion negative
VASC+	vascular invasion positive

Abkürzung	Bedeutung
VI	vascular invasion
VIP	cisplatin, etoposide, ifosfamide

2. Fragestellungen und Gliederung

2.1. Entwicklung der Schlüsselfragen

Durch die Koordinatoren der Leitlinie in Zusammenarbeit mit den Arbeitsgruppen-Leitungen wurde ein Vorschlag für mögliche Schlüsselfragen sowie relevanten Endpunkten auf Basis der gefundenen Literatur (Leitliniensynopse, systematische Übersichtsarbeiten und Europäische Konsensusleitlinien) erarbeitet. Die finale Konsentierung der Schlüsselfragen wurde von der Leitliniengruppe beim Kick-off Treffen im Januar 2017 definiert. Ingesamt sind 78 Schlüsselfragen entstanden, zu denen die Leitlinie Stellung nehmen sollte. 15 Schlüsselfragen wurden durch eine DeNovo-Recherche (DeNovo) beantwortet, 54 durch aggregierte Evidenz und Leitlinienanpassung (AE) und 7 durch Expertenkonsens (EK).

Tabelle 2: Schlüsselfragen

Arbeitsgruppe	Fragestellungen	De Novo	AE	EK
AG 1 Epidemiologie, Risikofaktoren, Screening, Prävention	Wie hoch sind Inzidenz und Prävalenz von Keimzelltumoren des Hodens in Deutschland?		x	
	Welche Gründe gibt es, die einen Anstieg der Inzidenz in den letzten zehn Jahren erklären?		x	
	Wie ist die Mortalität des Keimzelltumors des Hodens?		x	
	Wie ist die regionale Verteilung / Häufigkeit bei Keimzelltumoren des Hodens?		x	
	Ist ein generelles Screening aller Männer zwischen 14 und 45 Jahren notwendig?		x	
	Welche Risikofaktoren (Genetik, Umwelt, Lifestyle) existieren für die Entstehung von Keimzelltumoren des Hodens?		x	
	Existieren präventive Maßnahmen für die Entstehung von Keimzelltumoren des Hodens?		x	
AG 2 Klassifikations-systeme, Diagnostik, Prognose	Gibt es zusätzlich zur vaskulären Invasion relevante prognostische Marker für ein Tumorrezidiv beim nichtseminomatösen Keimzelltumor im Stadium I?	x		
	Wie verhält sich die Kernspintomographie des Abdomens/ Beckens in der Primärdiagnostik/in der Nachsorge des testikulären Keimzelltumors des Hodens bezüglich diagnostischer Genauigkeit?		x	
	Haben Patienten, wenn sie eine kontralaterale Biopsie im Rahmen der Ablatio testis erhalten, ein besseres		x	

Arbeitsgruppe	Fragestellungen	De Novo	AE	EK
	Überleben als Patienten, bei denen diese nicht durchgeführt wird?			
	Sollten Patienten mit einer testikulären Mikrolithiasis zum Ausschluss einer GCNIS eine Hodenbiopsie bekommen?		x	
	Ist die zusätzliche Bestimmung der miRNA371a-3p gegenüber den klassischen Hodentumormarkern AFP, beta HCG und LDH in der Diagnosestellung/in der Ausbreitungsdiagnostik / in der Rezidivdiagnostik des testikulären Keimzelltumors des Hodens überlegen? a: bei Männern mit histologisch gesichertem Keimzelltumor des Hodens b: bei Männern mit definitiv therapiertem Keimzelltumor des Hodens		x	
	Haben Patienten mit organerhaltender Enukleationsresektion des testikulären Keimzelltumors des Hodens und anschließender adjuvanter Radiatio des Resthodens mit mind. 18 Gy häufiger Lymphknoten- oder Fernmetastasen („distant failure“) im weiteren Krankheitsverlauf als Patienten mit Ablatio testis?		x	
AG 3 Primär- und Erstlinien-therapie	Wie sind Patienten mit einer nach Ablatio testis geringen und im kurzfristigen Verlauf stabilen AFP-Wert-Erhöhung zu behandeln?		x	x
	Ist für Patienten mit einem Keimzelltumor des Hodens, die eine skrotale Ablatio testis erhalten haben, eine Aktive Überwachungsstrategie im Stadium I kontraindiziert?		x	x
	Haben Patienten, die nicht inguinal, sondern skrotal eine Ablatio testis erhalten haben, eine schlechtere Prognose bezüglich tumorfreiem und Gesamtüberleben?		x	
	Ist die Strahlentherapie der GCNIS der Aktiven Überwachung oder Chemotherapie überlegen?		x	
	Was sind relevante Prognosefaktoren für eine okkulte Metastasierung bei einem nichtseminomatösen Keimzelltumor des Hodens? a) bei Patienten mit einem nichtseminomatösen Keimzelltumor des Hodens cSI niedriges Risiko		x	

Arbeitsgruppe	Fragestellungen	De Novo	AE	EK
	Was sind relevante Prognosefaktoren für eine okkulte Metastasierung bei einem nichtseminomatösen Keimzelltumor des Hodens? b) bei Patienten mit einem nichtseminomatösen Keimzelltumor des Hodens cSI		x	
	Welche adjuvante Behandlung des nichtseminomatösen Keimzelltumor des Hodens im cSI ist sinnvoll? (Intervention: 1 Zyklus PEB)		x	
	Welche adjuvante Behandlung des nichtseminomatösen Keimzelltumor des Hodens im cSI ist sinnvoll? (Intervention: 2 Zyklen PEB)		x	
	Ist eine risikoadaptierte adjuvante Behandlung des nichtseminomatösen Keimzelltumor des Hodens im cSI sinnvoll?	x		
	Ist eine risikoadaptierte adjuvante Behandlung des nichtseminomatösen Keimzelltumor des Hodens im cSI sinnvoll? a) bei Hochrisikopatienten	x		
	Welchen Stellenwert hat die Carboplatin-Monotherapie beim Seminom I im Vergleich zu Aktiver Überwachung?	x		
	Welche Effekte hat Überwachung als alleinige Therapie bei Patienten im Stadium I auf das Gesamtüberleben, Lebensqualität, Rezidivrate im Vergleich zur Strahlentherapie oder Chemotherapie?	x		
	Welchen Effekt zeigt ein Zyklus Chemotherapie im Vergleich zu zwei Zyklen Chemotherapie bei Patienten mit einem Stadium I des nichtseminomatösen Keimzelltumor des Hodens?		x	
AG 4 Metastasierte Keimzelltumoren des Hodens	Wie werden verifizierte testikuläre Keimzelltumoren im CS1S behandelt?		x	
	Welches weitere Vorgehen sollte bei seminomatösen/nichtseminomatösen Keimzelltumoren des Hodens bei V.a. ein klinisches Stadium IIA, S0 gewählt werden?		x	
	Was ist die optimale Therapie für Seminome im klinischen Stadium IIA/IIB?	x		

Arbeitsgruppe	Fragestellungen	De Novo	AE	EK
AG 4 Metastasierte Keimzelltumoren des Hodens	Wie werden nichtseminomatöse Keimzelltumoren des Hodens im gesicherten klinischen Stadium IIA/IIb behandelt?		x	
	a) Spielt der inadäquate Markerabfall unter primärer Chemotherapie beim metastasierten Keimzelltumor des Hodens in der „schlechte Prognose-Gruppe“ eine Rolle? b) Wie erfolgt die Therapie des metastasierten Keimzelltumors des Hodens in der „schlechte Prognose- Gruppe“ unter Chemotherapie bei inadäquatem Markerabfall? c) Welcher Zeitpunkt wird dem inadäquaten Markerabfall zu Grunde gelegt? d) Wie ist die Halbwertszeit definiert, die einen inadäquaten Markerabfall beschreibt?	x x x	x	
	In welchen klinischen Situationen des metastasierten Keimzelltumors des Hodens erfolgt eine primäre Chemotherapie ohne vorherige Ablatio testis?		x	
	Ist beim testikulären Keimzelltumor eine Orchiektomie nach primärer Chemotherapie indiziert?		x	
	Ist bei einer Ausnahmepopulation HIV-positiver Keimzelltumorpatienten eine Anpassung der Wahl und Dosis der Chemotherapie notwendig?		x	
	Ist bei einer Ausnahmepopulation niereninsuffizienter Keimzelltumorpatienten eine Anpassung der Wahl und Dosis der Chemotherapie notwendig?		x	
	Was sind allgemeine Kontraindikationen für eine Therapie mit Bleomycin?		x	
	Welche Alternativen gibt es für eine Therapie mit BEP bei Kontraindikationen für Bleomycin?		x	
	Was ist die optimale Therapie für Patienten mit primär zerebral metastasierenden Keimzelltumoren?		x	
	Was ist die optimale Therapie für Patienten mit primär ossär metastasierenden Keimzelltumoren?		x	
	Was ist die optimale Therapie von nichtseminomatösen Keimzelltumoren des Hodens mit Teratomanteil und maligner somatischer Transformation?		x	

Arbeitsgruppe	Fragestellungen	De Novo	AE	EK
	Was ist die optimale Therapie für Patienten mit primär mediastinalen nichtseminomatösen Keimzelltumoren des Hodens?		x	
AG 5 Restaging und Therapie der Residualtumor-erkrankung	Wann ist die Indikation zur Residualtumorresektion beim metastasierten nichtseminomatösen Keimzelltumor des Hodens gegeben?		x	
	Wann ist die Indikation zur Residualtumorresektion beim metastasierten Seminom gegeben?		x	
	Bei welchen metastasierten Keimzelltumor-Patienten ist eine Chemotherapie nach Residualtumorresektion indiziert?		x	
AG 6 Therapierefrakt äre Tumore und Rezidive	Wie wird ein Spätrezidiv definiert? Wie wird ein Serumtumormarker negatives Spätrezidiv therapiert? Wie wird ein Serumtumormarker positives Spätrezidiv therapiert? Wie wird ein multilokuläres Spätrezidiv therapiert? In welcher Sequenz werden Residualtumoren an verschiedenen Lokalisationen operativ saniert? Wie wird ein Progress aus einem klinischem Stadium I behandelt? A) beim Seminom B) beim nichtseminomatösen Keimzelltumor des Hodens			x
	Wie wird ein Progress aus einem klinischem Stadium I behandelt? A) beim Seminom B) beim nichtseminomatösen Keimzelltumor des Hodens			x
	Welche Chemotherapie sollte in der Rezidivsituation angewendet werden?	x		
	Welche Chemotherapie ist bei einer malignen somatischen Transformation einzuleiten?	x		
	Ist eine Residualtumorresektion bei Marker-positivem Residualtumor indiziert?	x		

Arbeitsgruppe	Fragestellungen	De Novo	AE	EK
	Ist bei der „Desperation Surgery“ eine extendierte oder eine retrograde „pick-up“ Lymphadenektomie erforderlich?		x	
	Wie sollen Patienten mit einem Rezidiv und Knochenmetastasen behandelt werden?			x
	Ist eine Bildgebung des zentralen Nervensystems bei allen Patienten gerechtfertigt?		x	
	Sollen zentrale Nervensystem-Metastasen reseziert werden?		x	
	Welche Therapie ist indiziert bei Größenprogression der Metastasen und Normalisierung der Serumtumormarker während der Chemotherapie bei Patienten mit „Growing Teratoma Syndrome“?		x	
AG 1 Sonderformen	Wie hoch sind Inzidenz und Prävalenz des spermatocytischen Seminoms?		x	
	Wie hoch ist die Mortalität des spermatocytischen Seminoms?		x	
	Wie ist die Altersverteilung beim spermatocytischen Seminoms?		x	
	Wie unterscheiden sich der spermatocytische Tumor und das klassische Seminom in Hinblick auf Diagnostik, Therapie und Nachsorge?		x	
	Wie häufig treten Keimzelltumoren extragondal auf?		x	
	Wie ist die prozentuale Verteilung der Lokalisationen der extragonadalen Keimzelltumoren?		x	
	Wie werden die extragonadalen Tumoren in Hinblick auf das klinische Stadium und die IGCCCG-Prognosegruppe klassifiziert, therapiert, diagnostiziert und nachgesorgt?	x		
	Wie wird ein ausgebrannter Tumor definiert?			x
	Sollte ein ausgebrannter Tumor operativ entfernt werden?			x

Arbeitsgruppe	Fragestellungen	De Novo	AE	EK
AG 7 Nachsorge	Kann die MRT-Diagnostik in der Nachsorge des Keimzelltumor des Hodens als Alternative die CT ersetzen?	x		
	Wie verändert sich das rezidivfreie Überleben bzw. das individuelle Rezidivrisiko und das Gesamtüberleben eines Keimzelltumor-Patienten im weiteren Verlauf in Abhängigkeit vom bereits erlebten rezidivfreien Überleben?	x		
AG 7 Toxizität	Führt die Risikostratifizierung in der Behandlung eines nichtseminomatösen Keimzelltumors des Hodens im cS1 zur Reduktion der Langzeittoxizität?		x	
	Führt die Reduktion der PEB-Therapie bei einem nichtseminomatösen Keimzelltumors des Hodens im cS1 zu einer Reduktion der Langzeittoxizität?		x	
	Welche Auswirkungen hat Carboplatin beim Seminom im cSI?		x	
	Gibt es Unterschiede beim Auftreten von Langzeittoxizitäten bei unterschiedlichen Behandlungsregimen von Patienten mit einem metastasiertem Keimzelltumor des Hodens?		x	
	Kann das Auftreten von thromboembolischen Ereignissen bei einer Chemotherapie vom Patienten mit metastasierten Keimzelltumoren des Hodens durch begleitende Thromboseprophylaxe mittels Heparinisierung verringert werden?		x	
	Führt die Reduktion der Gesamt-Chemotherapie-Dosis zu einer Reduktion der Langzeit-Toxizität ohne erhöhtes Rezidivrisiko?		x	

Abkürzungen: EK = Expertenkonsens, AE= Aggregierte Evidenz durch Leitlinienadaptation oder systematische Übersichtsarbeiten, DeN = DeNovo-Recherche (systematische Literatursuche nach Primärstudien)

3. Methodisches Vorgehen

3.1. Leitliniensynopse

Leitlinienrecherche (Quellen, Suchzeitraum, Suchbegriffe, Treffermenge)

Die Recherche nach internationalen evidenzbasierten Leitlinien erfolgte auf folgenden Internetseiten:

- G-I-N (Guidelines International Network)
- AUA (American Urology Association)
- NCCN (The National Comprehensive Cancer Network
- ASCO (American Society of Clinical Oncology)
- CCO (Cancer Center Ontario)
- SIGN (Scottish Intercollegiate Guideline Network)
- NICE (National Institute of Clinical Excellence)
- EAU (European Association of Urology)
- Oncoline
- IKNL (Quality institute for oncological and palliative research and practice)
- Ebm-guidelines.com
- Domusmedica.be
- KCE Belgien (Federaal Kenniscentrum voor de Gezondheidszorg
- Medline (Pubmed)

Als Suchbegriffe in Medline wurden folgende Begriffe genutzt:

- ("testicular neoplasms"[MeSH Terms] OR ("testicular"[All Fields] AND "neoplasms"[All Fields]) OR "testicular neoplasms"[All Fields] OR ("testicular"[All Fields] AND "neoplasm"[All Fields]) OR "testicular neoplasm"[All Fields]) OR ("rete testis"[MeSH Terms] OR ("rete"[All Fields] AND "testis"[All Fields]) OR "rete testis"[All Fields]) OR ("germinoma"[MeSH Terms] OR "germinoma"[All Fields])
- (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]) AND ("germ cells"[MeSH Terms] OR ("germ"[All Fields] AND "cells"[All Fields]) OR "germ cells"[All Fields] OR ("germ"[All Fields] AND "cell"[All Fields]) OR "germ cell"[All Fields]) AND embryonal [All Fields])
- (("gonadoblastoma"[MeSH Terms] OR "gonadoblastoma"[All Fields]) AND ("male"[MeSH Terms] OR "male"[All Fields]))
- (("teratoma"[MeSH Terms] OR "teratoma"[All Fields]) AND ("male"[MeSH Terms] OR "male"[All Fields]))

Zur Eingrenzung auf Leitlinien wurden die Filter von Pubmed “guideline” und “practice guideline“ aktiviert. Als Suchzeitraum wurden Publikationen ab 2010 eingeschlossen. Die Recherche nach Leitlinien wurde im Oktober 2016 durchgeführt. Zur Suche auf den Internetseiten wurden die Begriffe “testicular cancer” oder „testis cancer“ genutzt.

Nach insgesamt 103 identifizierten Treffern, dem Ausschluss von 24 Duplikaten und dem weiteren Ausschluss von 51 Treffern nach Inhalt im Titel bzw. Abstract wurden schlussendlich 28 Treffer im Volltext gelesen. Nach der Volltextprüfung wurden 13 Leitlinien in die Endauswahl eingeschlossen, 15 Leitlinien wurden nach der Volltextsichtung wegen fehlender inhaltlicher Relevanz ausgeschlossen.

Europäische Konsensus-Empfehlungen wurden zusätzlich in Pubmed (MEDLINE) zur Identifizierung weiterer offener Fragen recherchiert.

Auswahl der im Volltext gesichteten Leitlinien

Als Einschlusskriterien wurden das inhaltliche Zutreffen bzgl. der Patientengruppe, die Verfügbarkeit als Vollversion und die englische und deutsche Sprache festgelegt.

Die folgenden Leitlinien wurden eingeschlossen:

- Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, Quinn G, Wallace WH, Oktay K, American Society of Clinical Oncology. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013 Jul 1;31(19):2500-10.
- Yacoub, J. H., Oto, A., Allen, B. C., Coakley, F. V., Friedman, B., Hartman, M. S. Eberhardt, S. C. (2016). ACR Appropriateness Criteria Staging of Testicular Malignancy. Journal of the American College of Radiology, 13(10), 1203–1209. https://doi.org/10.1016/j.jacr.2016.06.026
- U.S. Preventive Services Task Force. Screening for testicular cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2011 Apr 5;154(7):483-6.
- Motzer RJ, Jonasch E, Agarwal N, Beard C, Bhayani S, Bolger GB, Chang SS, Choueiri TK, Costello BA, Derweesh IH, Gupta S, Hancock SL, Kim JJ, Kuzel TM, Lam ET, Lau C, Levine EG, Lin DW, Michaelson MD, Olencki T, Pili R, Plimack ER, Rampersaud EN, Redman BG, Ryan CJ, Sheinfeld J, Shuch B, Sircar K, Somer B, Wilder RB, Dwyer M, Kumar R. Testicular Cancer, Version 2.2015. J Natl Compr Canc Netw. 2015 Jun;13(6):772-99.
- Gilligan TD, Seidenfeld J, Basch EM, Einhorn LH, Fancher T, Smith DC, Stephenson AJ, Vaughn DJ, Cosby R, Hayes DF; American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. J Clin Oncol. 2010 Jul 10;28(20):3388-404.
- Chung P, Mayhew LA, Warde P, Winquist E, Lukka H; members of the Genitourinary Cancer Disease Site Group. Management of stage I seminoma. M Lock and J Brown, reviewers. Toronto (ON): Cancer Care Ontario; 2008 Jan 30 [Endorsed 2014 Feb 27]. Program in Evidence-based Care Practice Guideline No.:3-18 Version 2.
- Alberta Provincial Genitourinary Tumour Team. Extragonadal germ cell tumours. Edmonton (Alberta): CancerControl Alberta; 2013 Mar. 8p. (Clinical practice guideline; no. GU-007, Version 1).
- Alberta Provincial Genitourinary Tumour Team. Testicular germ cell tumours. Edmonton (Alberta): CancerControl Alberta; 2016 Sep. 23p. (Clinical practice guideline; no. GU-001, Version 7).
- Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, Horwich A, Laguna MP, Nicolai N, Oldenburg J; European Association of Urology. Guidelines on Testicular Cancer: 2016
- Richenberg J, Belfield J, Ramchandani P, Rocher L, Freeman S, Tsili AC, Cuthbert F, Studniarek M, Bertolotto M, Turgut AT, Dogra V, Derchi LE. Testicular microlithiasis imaging and follow-up: guidelines of the ESUR scrotal imaging subcommittee. Eur Radiol. 2015 Feb;25(2):323-30.
- Oldenburg J, Fosså SD, Nuver J, Heidenreich A, Schmoll HJ, Bokemeyer C, Horwich A, Beyer J, Kataja V; ESMO Guidelines Working Group. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi125-32.
- Scottish Intercollegiate Guidelines Network (SIGN). Management of adult testicular germ cell tumours. A national clinical guideline. Edinburgh, (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2011 Mar. 63 p. (SIGN publication; no. 124)
- Tombal B, Vlayen J, Stordeur S, De Meerleer G, Gil T, Renard L, Rorive S, Rottey S, Salmon I, Schrijvers D, Villeirs G. Wetenschappelijke ondersteuning van het College

voor Oncologie: een update van de nationale richtlijn voor testiskanker. KCE (BE) 2010 (in englisch)

Methodische Bewertung der Leitlinien

Die 13 eingeschlossenen Leitlinien wurden durch einen Reviewer mit dem AGREE-2 Instrument [1] bezüglich ihrer methodischen Qualität bewertet. Es wurde kein cut-off Wert zum Ausschluss von Leitlinien festgelegt, sodass alle Leitlinien, die inhaltlich relevant waren, eine systematische Literaturrecherche und erkennbare Empfehlungen mit Evidenzlevel und/oder Empfehlungsgrad zeigten, eingeschlossen wurden.

Sechs der 13 eingeschlossenen Leitlinien waren vollständige Leitlinien, d.h. sie beinhalteten Ausführungen zu Diagnose, Therapie und Nachsorge. Die weiteren sieben Leitlinien adressierten einzelne Aspekte wie Screening oder Fertilität. Keine der Leitlinien erreichte den vollen Punktwert in der AGREE-Bewertung. Generell wurde die Domaine Klarheit der Präsentation am höchsten bewertet (n=10 >80% der Punkte), die niedrigste Bewertung wurde in der Domaine Anwendbarkeit erreicht (n=9 <20% der Punkte). Acht der 13 Leitlinien erreichten in der Bewertung eine Gesamtpunktzahl von über 50%. In der Domaine Entwicklung der Leitlinie erreichten 5 der 13 Leitlinien Werte von über 50% der maximal erreichbaren Punktzahl.

Eine Synopse mit den inhaltlichen Kernaussagen der eingeschlossenen Leitlinien findet sich im Anhang unter 11.1. Aus vier Leitlinien wurden insgesamt fünf Empfehlungen adaptiert.

3.2. Systematische Literaturrecherchen

3.2.1. Suche nach systematischen Übersichtsarbeiten für ausgewählte Schlüsselfragen

Recherchestrategie

Die Suche nach aggregierter Evidenz in Form von systematischen Übersichtsarbeiten, Metaanalysen und HTA Berichten erfolgte für den Suchzeitraum von Januar 2010 bis November 2016. Eine Update-Suche erfolgte im Frühjahr 2018. Englische und deutsche Literatur wurde berücksichtigt. Die Suche erfolgte in MEDLINE über OVID, in der Cochrane Review Library und bei DIMDI. Folgende Suchstrategie lag der Suche zu Grunde:

Suchstrategie für MEDLINE:

1. Meta-Analysis as Topic/
2. meta analy$.tw.
3. metaanaly$.tw.
4. Meta-Analysis/
5. (systematic adj (review$1 or overview$1)).tw.
6. exp Review Literature as Topic/
7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.
11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list$.ab.
18. bibliograph$.ab.
19. hand-search$.ab.
20. relevant journals.ab.
21. manual search$.ab.
22. or/17-21
23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. Review/
27. 25 and 26
28. Comment/
29. Letter/
30. Editorial/
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27

36. 35 not 34
37. Testicular Neoplasms/
38. Rete Testis/
39. Germinoma/
40. seminoma/
41. non-seminoma.mp.
42. (testi* adj3 (cancer* or tumo* or neoplas* or carcinom* or malign*)).tw.
43. (Germ* adj3 (cancer* or tumo* or neoplas* or carcinom* or malign*)).tw.
44. (teratom* adj2 testi*).mp.
45. or/37-44
46. 36 and 45
47. children/
48. female/
49. 47 or 48
50. 46 not 49
51. limit 50 to yr=2010-2016

Suchstrategie für die Suche in der Cochrane Library

#1	(testi* near (cancer* or tumo* or neoplas* or carcinom* or malign*))
#2	Germ* near (cancer* or tumo* or neoplas* or carcinom* or malign*)
#3	seminoma
#4	#1 or #2
#5	#4 and #3

Insgesamt wurden in Medline, Cochrane und bei DIMDI (DAHTA-Datenbank) 564 Quellen identifiziert, und nach Duplikatentfernung wurden 366 Treffer einer Titel-Abstractprüfung unterzogen. 54 Treffer erfüllten die Einschlusskriterien (Inhaltliche Relevanz bzgl. Patientengruppe) nach der Volltextsichtung. Das Screening von Titel und Abstract und das Volltextscreening erfolgte durch einen Reviewer. Der Suchverlauf ist im PRISMA Flowchart dargestellt (siehe Kapitel 11.2).

Bewertung der systematischen Übersichtsarbeiten

Systematische Reviews und Metaanalysen wurden mit dem AMSTAR Instrument (siehe Anlage 11.12.) bewertet [2]. Die Bewertung erfolgte durch einen Reviewer. Keine der eingeschlossenen systematischen Übersichtsarbeiten erreichte eine hohe Punktbewertung zwischen 9 und 11 Punkten (maximale Punktzahl 11 Pkt.). 33 Übersichtsarbeiten erreichten Werte zwischen 0 und 4 Punkten (niedrige Bewertung) und 21 Arbeiten wurden im Bereich zwischen 5 und 8 Punkten bewertet (mittlere Bewertung). Die Übersichtsarbeiten decken die Themen Screening, Prävention, Diagnose, Prognose, Therapie und Toxizität ab. Es wurde eine Evidenztabelle aller eingeschlossenen Übersichtsarbeiten erstellt (siehe Kapitel 11.3).

3.2.2. Suche nach Primärliteratur für ausgewählte Schlüsselfragen

Recherchestrategie

Als Zeitraum für die Suche nach Primärliteratur wurde Januar 2010 bis Mai 2017 festgelegt. Englische und deutsche Literatur wurde berücksichtigt. Die Suche nach Primärliteratur in

Form der DeNovo-Recherchen wurde in einer Hauptsuche organisiert, der Suchverlauf ist in einem PRISMA-Suchverlauf abgebildet (Anlage 11.7.) Ausnahme bildete das Kapitel 11 Sonderformen. Für dieses Kapitel erfolgte eine Extrasuche (PRISMA Suchverlauf Anlage 11.5; Suchstrategie Anlage 11.6). Zusätzlich wurden klinische Studienregister (clinical trials.gov und das WHO Register) nach Studien durchsucht.

Durchsucht wurden die Datenbanken MEDLINE (via OVID) und die Cochrane Library. Zur Identifizierung möglichst hoher Evidenz wurden folgende Studiendesigns und Publikationsformen ausgeschlossen: Fallberichte, Fallserien, Editorials, Kommentare, Konferenzabstracts.

Die folgende Suchstrategie wurde für MEDLINE via OVID genutzt:

1. exp seminoma/
2. seminom*.tw.
3. *testicular neoplasms/
4. ((testicular or testis or testes) adj2 (tumor* or cancer* or carcinoma* or tumour* or neoplasm* or neoplasia)).tw.
5. germ cell tumor.tw.
6. (germinomatous or non*germinomatous).tw.
7. non*seminom*.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. "review"/
10. case reports/ or case reports.tw.
11. conference abstract.pt. or congresses as Topic/
12. note/ or editorial/ or letter/ or Comment/ or news/ or opinion/
13. 9 or 10 or 11 or 12
14. 8 not 13
15. exp animals/ not humans.sh.
16. 14 not 15
17. cancer-testis antigen*.tw.
18. 16 not 17
19. limit 18 to male
20. limit 19 to (english or german)
21. limit 20 to yr="2010-current"

Die Suche ergab 1785 Treffer. Eine Updatesuche nach Primärstudien erfolgte im Februar 2018. Es wurde die gleiche Suchstrategie genutzt. Es wurden zusätzlich 412 Treffer identifiziert. Pro PICO-Fragestellung wurden relevante Treffer identifiziert und zugeordnet.

Auswahl Publikationen

Diese wurden nach inhaltlicher und formaler Relevanz gemäß den festgelegten Ein- und Ausschlusskriterien zunächst im Titel- und Abstractscreening und anschließend im Volltextscreeening durch einen Reviewer geprüft. Der Suchverlauf wurde in einem Prisma-Flowchart festgehalten (siehe Anlage 11.7.)

Zusammenfassung der Information

Die identifizierte Literatur wurde durch UroEvidence in Evidenztabellen zusammengefasst (siehe Anlage 11.4.). Diese Tabellen wurden an die AGs zur Finalisierung der

Hintergrundtexte weitergeleitet. UroEvidence erstellte eine Beschreibung der identifizierten Studien inklusive systematischer Bewertung als Arbeitsgrundlage für die AGs.

Bewertung des Risikos für Bias der Literatur

Für Therapiestudien wurden entweder das Cochrane Risk of Bias tool (für RCTs) [3] oder die SIGN-checklist für Kohortenstudien verwendet [4]. Diagnostikstudien werden mit dem QUADAS-2 Instrument bewertet (Whiting 2011), Prognosestudien mit dem QUIPS Tool [5].

Qualitätsbewertung der Literatur

Für die Qualitätsbewertung der Evidenz der Therapiestudien wird die GRADE Methodik verwendet [6]. Diese bemisst sich an: Risiko für Bias, Inkonsistenz, Indirektheit, fehlende Präzision und Publikationsbias. Eine GRADE-Bewertung der Literatur erfolgte für die Therapiekapitel 9 und 10 für die entsprechenden De Novo-Recherchen. Eingeschlossen in die GRADE-Bewertung wurden Studien, die mindestens zweiarmig sind. Eine GRADE-Bewertung erfolgte nur, wenn mindestens zwei Studien zu einem Endpunkt vorlagen (siehe Anlage 11.8).

Tabelle 3: Bewertungsinstrumente

Studiendesign	Instrument	Quelle
RCT	RoB Tool Cochrane	[3]
Kohortenstudie	SIGN Tool for cohort studies	https://www.sign.ac.uk/checklists-and-notes.html, [4]
Prognostische Studien	QIPS-Tool	[5]
Diagnostische Studien	Quadas-Tool	https://www.sign.ac.uk/checklists-and-notes.html [7]

3.3. Schema der Evidenzklassifikation

Tabelle 4: Schema der Evidenzgraduierung nach Oxford 2009*

Eviden-zgrad	Diagnostikstudien	Studien zu Therapie/ Prävention/ Ätiologie
1a	Systematische Übersichtsarbeit mit Level 1 Diagnostik (mit hohem Homogenitätsgrad), diagnostische Entscheidungsregel begründet auf Ib Studien, validiert in verschiedenen klinischen Zentren	Systematische Übersichtsarbeit (mit hohem Homogenitätsgrad) mit randomisierten klinischen Studien (RCTs)
1b	Validierungs- Kohortenstudie mit gutem Referenzstandard oder diagnostische Entscheidungsregel, validiert in einem Zentrum	Einzelne RCT (mit engem Konfidenzintervall)
1c	Alle-oder-Keiner-Prinzip (absolute SpPins und SnNouts)	Alle-oder-Keiner-Prinzip
2a	Systematische Übersichtsarbeit mit Level >2 Diagnostikstudien (mit hohem Homogenitätsgrad).	Systematische Übersichtsarbeit (mit hohem Homogenitätsgrad) mit Kohortenstudien
2b	Explorative Kohortenstudie mit gutem Referenzstandard, diagnostische Entscheidungsregel nach Herleitung oder nur validiert nach split-sample oder Datenbanken	Einzelne Kohortenstudie oder ein RCT minderer Qualität
2c		Wirkungsstudien, ökologische Studien
3a	Systematische Übersicht mit Level 3 Diagnostikstudien	Systematische Übersichtsarbeit (mit hohem Homogenitätsgrad) mit Fall-Kontroll-Studien
3b	Nicht-konsekutive Studie; oder ohne Konsistenz der angewendeten Referenzstandards	Eine Fall-Kontrollstudie
4	Fall-Kontrollstudie, schlechte oder nicht unabhängige Referenzstandards	Fallserien oder Kohorten- und Fall-Kontrollstudien minderer Qualität
5	Expertenmeinung ohne explizite Bewertung der Evidenz oder basierend auf physiologischen Modellen/Laborforschung	Expertenmeinung ohne explizite kritische Bewertung der Evidenz oder basierend auf physiologischen Modellen/Laborforschung

* Übersetzung ins Deutsche durch UroEvidence.

Es erfolgte eine Einordnung bezüglich des Evidenzlevels aller eingeschlossenen Referenzen. In der Bezeichnung des Evidenzlevels der Empfehlungen und Statements wurde das jeweils höchste Evidenzlevel ausgewählt, auch wenn im Hintergrundtext mehrere Quellen mit unterschiedlichen Evidenzleveln zitiert wurden.

3.4. Formulierung der Empfehlungen und formale Konsensusfindung

3.4.1. Schema der Empfehlungsgraduierung

In der Leitlinie wird zu allen Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in der Leitlinie drei Empfehlungsgrade unterschieden (siehe Tabelle 5), die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.

Tabelle 5: Verwendete Empfehlungsgrade

Empfehlungs-grad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Schwache Empfehlung	sollte/sollte nicht
0	Offene Empfehlung	kann

3.4.2. Festlegung des Empfehlungsgrades

Methodisches Vorgehen bei der Formulierung der Empfehlungen/Statements

Die Empfehlungen und Statements der Leitlinie wurden von den einzelnen AGs ausgearbeitet und anschließend der gesamten Leitliniengruppe vorgelegt und von dieser konsentiert. Um von der Evidenz zur Empfehlung zu gelangen, wurden folgende Aspekte berücksichtigt: Qualität der Studien (GRADE-Ergebnisse für die Therapiestudien) oder Evidenzlevel (https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/), Konsistenz der Studienergebnisse; klinische Relevanz der Endpunkte und Effektstärken; Nutzen-Risiko-Verhältnis; ethische, rechtliche, ökonomische Erwägungen; Patientenpräferenzen; Anwendbarkeit und Umsetzbarkeit.

Grundsätzlich erfolgte eine Anlehnung der evidenzbasierten Empfehlungen hinsichtlich ihres Empfehlungsgrades an die Stärke der verfügbaren Evidenz, d.h. ein hoher Evidenzgrad (z.B. Metaanalysen/systematische Übersichten von RCTs oder mehrere methodisch hochwertige RCTs führt in der Regel auch zu einer starken Empfehlung (Empfehlungsgrad A, „soll“).

Zusätzlich wurden weitere Kriterien bei der Wahl des Empfehlungsgrades berücksichtigt. Diese konnten zu einem Abweichen der Empfehlungsstärke nach oben oder unten führen:

- Konsistenz der Studienergebnisse
- Klinische Relevanz der Endpunkte und Effektstärken
- Nutzen-Risiko-Verhältnis
- Ethische Verpflichtungen
- Patientenpräferenzen
- Anwendbarkeit, Umsetzbarkeit in der Versorgung

3.4.3. Formale Konsensusverfahren und Konsensuskonferenz

Für die Verabschiedung von Empfehlungen galten die Konsensregeln gemäß AWMF Regelwerk.

Die formulierten Empfehlungen und Statements der Kapitel 4-9 und 11 -15 wurden in einem zweiphasigen Abstimmungsvorgang strukturiert konsentiert. D.h. alle Empfehlungen und Statements wurden vorab via Online-Umfrage vorabgestimmt. Grundsätzlich wurden mit starkem Konsens angenommene Empfehlungen/Statements als verabschiedet gewertet.

Erreichten die Empfehlungen und Statements weniger als einen 95%igen Konsens, so wurden sie in der zweitägigen Konsensuskonferenz abgestimmt (14./15. Mai 2018). Auch wurden Empfehlungen und Statements >95% Konsens besprochen, die Kommentare aus der Online-Abstimmung enthielten. In der Regel ging dies mit einer inhaltlichen Korrektur der Aussage einher. Die Empfehlungen und Statements von Kapitel 10 wurden in der Konsensuskonferenz vor Ort abgestimmt, da sie erst kurzfristig vor der Konferenz final vorlagen und daher nicht online vorabgestimmt werden konnten. Es gab keine relevanten Widersprüche. Die Konsensuskonferenz wurde durch zwei AWMF-zertifizierte Leitlinienberater (Dr. Nothacker, Dr. Follmann) moderiert; alle Verfahren der Konsensusfindung folgten dem Regelwerk Leitlinien der AWMF [8] nach dem Verfahren einer strukturierten Konsensuskonferenz nach dem NIH-Typ moderiert:

- - Vorstellung des Kapitels und der Empfehlungen durch die AG Leiter
- - ggf. inhaltliche Klärung und Aufnahme von Änderungsvorschlägen
- - Abstimmung aller Vorschläge
- - falls kein Konsens >75% erzielt wurde, erneute Diskussion und Abstimmung.

Alle Empfehlungen und Statements konnten im Konsens oder starken Konsens verabschiedet werden. Sonder- oder Minderheitsvoten zu bilden als Lösung für Meinungsunterschiede war nicht erforderlich.

Abstimmungsberechtigt waren die jeweiligen Mandatsträger (in ihrer Abwesenheit der jeweilige Stellvertreter) der Fachgesellschaften und Arbeitskreise, die beiden Leitlinienkoordinatoren, der Patientenvertreter. Ausgeschlossen waren die AG-Leitungen, Methodiker und externe Experten. Für die Abstimmung wurde ein TED-System genutzt.

Tabelle 6: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	> 50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

4. Ableitung der Qualitätsindikatoren

Im Rahmen des Leitlinienprogramms Onkologie werden Qualitätsindikatoren in einem standardisierten Prozess aus den Empfehlungen der Leitlinien abgeleitet und aktualisiert. Die detaillierte Beschreibung der Methodik findet sich auf der Homepage des Leitlinienprogramms Onkologie [9].

Die Generierung der Qualitätsindikatoren wurde in folgenden Schritten durchgeführt:

4.1. Bestandsaufnahme

Bei der Suche nach bereits definierten internationalen und nationalen Qualitätsindikatoren außerhalb des OL-Verfahrens erfolgte eine Einschränkung des Suchzeitraums auf die letzten zehn Jahre (01.07.2008 bis 17.07.2018). Es erfolgte keine Einschränkung der Sprache.

Die Suche wurde in folgenden Quellen durchgeführt:

- Literaturdatenbanken: Medline über https://www.ncbi.nlm.nih.gov/ & Cochrane über http://www.cochranelibrary.com/
- Webseiten von nationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Webseiten von internationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Suchmaschine: www.google.de

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und sind in der Anlage 11.9. aufgeführt.

Die Recherche führte zu keinem nationalen QI und einer Reihe von internationalen QI, die ebenfalls in dem Dokument zusammengefasst wurden (Anlage 11.10).

4.2. Vorbereitung Anwesenheitstreffen (Erstellung einer Primärliste potentieller Qualitätsindikatoren)

Soweit möglich, wurden im Vorfeld des Anwesenheitstreffens (siehe 6.3) aus den starken Empfehlungen der Leitlinie (n= 88) potentielle Indikatoren mit Definition von Zähler und Nenner abgeleitet. Diese Liste und das Dokument mit den internationalen QI wurden den Mitgliedern der AG im Vorfeld des Anwesenheitstreffens zugesandt.

4.3. Anwesenheitstreffen (Diskussion und primäre Sichtung)

Das Treffen der AG QI, die aus Mitgliedern der Leitliniengruppe, Vertretern der klinischen Krebsregister, des Zertifizierungssystems und des OL bestand, fand am 30.08.2018 statt. In dem Treffen wurde den Teilnehmern der Prozessablauf der QI-Erstellung sowie das Bewertungsinstrument des OL erläutert.

Im Anschluss wurde die unter 6.2 generierte Zusammenstellung aus den Empfehlungen der Leitlinie und der internationalen Qualitätsindikatoren diskutiert und entschieden, ob

aus der jeweiligen Empfehlung ein potentieller Qualitätsindikator generiert werden könne. Folgende Ausschlusskriterien kamen bei diesem ersten Screening zur Anwendung:

Tabelle 7: Gründe für einen Ausschluss der Empfehlung aus der Liste der potentiellen Qualitätsindikatoren

Nr.	1	2	3	4
Begründung	Empfehlung ist nicht operationalisierbar (Messbarkeit nicht gegeben)	Fehlender Hinweis auf Verbesserungs potential	Fehlende Verständlichkeit u/o großer Erhebungsaufwand in Verhältnis zu Nutzen	Sonstiges (mit Freitexteingabe in Liste der Empfehlungen)

Die Diskussion und primäre Sichtung ergab ein Set von 12 potentiellen Qualitätsindikatoren.

4.4. Bewertung

Das vorselektierte Set der 12 potentiellen Qualitätsindikatoren wurde mit dem Bewertungsinstrument des Leitlinienprogramms Onkologie durch die Mitglieder der AG QI bewertet. Jeweils mit dem unten abgebildeten Bogen erhielten die Bewertenden seitens der Krebsregister und des Zertifizierungssystems der DKG pro Indikatorvorschlag die Informationen zur Datenverfügbarkeit. Angenommen wurden die Qualitätsindikatoren, bei denen mind. 75% der Teilnehmer die Kriterien 1,2,3 und 5 mit „Ja“ und das Kriterium 4 mit „Nein“ bewertet haben. Die Auswertung dieser Abstimmungen erfolgte durch einen Methodiker, der nicht am Qualitätsindikatoren-Entwicklungsprozess teilgenommen hatte.

Tabelle 8: Bewertungsinstrument des Leitlinienprogramms Onkologie

QI-Nr.	Möglicher Qualitätsindikator		Empfehlung	Angaben der S3 Leitlinie im Hinblick auf a) Qualitätsziel und b) Evidenzgrundlage
1.	Z			
	N			

Information zur Datenverfügbarkeit (Stand 09/2018):

[dies wird von den Registern und den Zentren ausgefüllt]

Die Erfassung ist seitens der Klinischen Krebsregister über den einheitlichen Onkologischen Basisdatensatz und seiner Module gewährleistet: ja / nein

Die Erfassung ist Teil des Zertifizierungssystems der DKG: ja / nein

Ggf. welche Ergänzungen wären erforderlich?

	Nein	Ja
1. Kriterium: Der Qualitätsindikator erfasst für den Patienten relevante Verbesserungspotentiale.		

QI-Nr.	Möglicher Qualitätsindikator	Empfehlung	Angaben der S3 Leitlinie im Hinblick auf a) Qualitätsziel und b) Evidenzgrundlage	
2.	**Kriterium:** Der Indikator ist klar und eindeutig definiert.			
3.	**Kriterium:** Der Qualitätsindikator bezieht sich auf einen Versorgungsaspekt, der von den Leistungserbringern beeinflusst werden kann.			
4.	**Kriterium:** Gibt es Risiken zur Fehlsteuerung durch den Indikator, die nicht korrigierbar sind?			
5.	**Kriterium:** Die Daten werden beim Leistungsbringer routinemäßig dokumentiert oder eine zusätzliche Erhebung erfordert einen vertretbaren Aufwand			

Zusätzlich bestand die Möglichkeit, zu den im Folgenden genannten Kriterien Kommentare abzugeben:

	Kommentar
Risikoadjustierung Können spezifische Merkmale von Patienten z.B. Alter, Komorbidität oder Schweregrad der Erkrankung die Ausprägung des QI beeinflussen?	
Implementierungsbarrieren Gibt es Implementierungsbarrieren, die es zu beachten gilt?	

4.5. Telefonkonferenz:

Nach der schriftlichen Bewertung erfolgte am 09.10.2018 eine moderierte Telefonkonferenz, in der die Ergebnisse der Bewertung diskutiert wurden. Auf Basis der Bewertungen und der Diskussion wurde ein finales Set von 11 Qualitätsindikatoren konsentiert.

Die Primärliste der potentiellen Qualitätsindikatoren inklusive der Ausschlussgründe, die o.g. Zusammenstellung der internationalen Qualitätsindikatoren und die Ergebnisse der schriftlichen Bewertung sind auf Anfrage im Leitliniensekretariat oder Office des Leitlinienprogramms Onkologie erhältlich.

5. Review-Verfahren und Verabschiedung

Diese Leitlinie sowie der Leitlinienreport wurden nach Fertigstellung von der AWMF (Frau Dr. Nothacker, Frau Dr. Blödt) sowie dem Leitlinienprogramm Onkologie (Dr. Follmann, Dipl. Soz. Wiss. Langer) abschließend begutachtet.

Die Konsultationsphase dauerte vom 14. November 2018 bis zum 20.Dezember 2018. Insgesamt gingen 33 Kommentare ein. Sie beinhalteten redaktionelle Hinweise, Vorschläge zur Verbesserung der Übersichtlichkeit in Tabllen, inhaltliche Präzisierungen von Formulierungen des Hintergrundtextes, Literaturverweise und Formulierungsänderungen von Empfehlungen. Alle eingegangenen Kommentare mit inhaltlichen Anmerkungen zu Empfehlungen oder Hintergrundtexten sowie der Umgang der Leitliniengruppe mit Ihnen sind in Kapitel 9.11 aufgeführt.

An den Empfehlungen wurden im Rahmen der Konsultation keine Änderungen vorgenommen. Einge Änderungsvorschläge wurden allerdings für die zukünftige Überarbeitung vorgemerkt.

6. Unabhängigkeit und Umgang mit Interessenkonflikten

Beim Kick-off-Treffen wurde beschlossen, dass eine Arbeitsgruppe geschaffen wird, welche die Interessenkonflikte sichten und ein Management zum Ungang von Interessenkonflikten innerhalb der Leitlinie vorschlagen sollte (Mitglieder: Dr. Follmann, Dr. Nothacker, T. Langer, ein Vertreter des MDK, Prof. Kliesch, Dr. Schmidt). Die Interessenkonflikte der Leitliniengruppenmitglieder wurden mit dem AWMF-Formblatt erhoben. Diese wurden von der Arbeitsgruppe gesichtet und in einer Telefonkonferenz wurden Definitionen vorgeschlagen, auf deren Grundlage das Management erfolgen sollte.

Folgende Kriterien zum Management der Interessenkonflikte wurden von der Leitliniengruppe beschlossen: Als GERING wurden bezahlten Vorträge, industrielle Drittmittelforschung und bezahlte Vorträge bis <10.000€ pro Jahr pro Firma eingeordnet. Als MODERAT wurden eine Advisory Board-Tätigkeit oder bezahlte Gutachtertätigkeiten eingeordnet. Als HOCH wurden eingestuft, wenn das Haupteinkommen aus Medizinprodukten-/Pharmaindustrie stammt oder Patent- oder Aktienbesitz vorliegt.

Die Bewertung der Formulare ergab, dass hinsichtlich der Leitlinieninhalte Interessenkonflikte mit geringer Relevanz in der Leitliniengruppe vorlagen. Ein Interessenkonflikt mit hoher Relevanz wurde bzgl. des Themas ‚Tumormarker miRNA' identifiziert. Dieses Thema war jedoch nicht Gegenstand dieser Leitlinienversion.

Die Ergebnisse der Interessenkonflikterklärung sind in Anlage 11.11 dargestellt.

7. Verbreitung und Implementierung

Die Publikation erfolgt primär über die Websites des Leitlinienprogramms Onkologie und der AWMF. Darüber hinaus soll die Leitlinie über Kongresse und Fachzeitschriften bekannt gemacht werden. Eine Vorstellung auf dem Deutschen Krebskonkress 2019 und dem Jahreskongress der Deutschen Gesellschaft für Urologie (DGU) 2019 erfolgen. Weitere Kongresspräsentationen werden geplant. Zur Leitlinie wird nach der finalen Publikation eine Laienversion (Patientenleitlinie) erstellt und ebenfalls frei verfügbar sein. Ebenfalls

nach Publikation der Leitlinien wird voraussichtlich die Implementierung der Qualitätsindikatoren in das Zertifizierungssystem der DKG und die Krebsregister erfolgen. Es wird ebenfalls, zeitgleich zur Langversion, eine Kurzversion der Leitlinie publiziert. Eine englische Publikation zur Disseminierung auf internationaler Ebene ist geplant.

8. Tabellenverzeichnis

9. Anlagen

9.1. Leitliniensynopse

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
Risikofaktoren			
	ALAM SS, 2010 Maternal body mass index and risk of testicular cancer in male offspring: A systematic review and meta-analysis. SR (6/11)	The meta-analysis provides some evidence that higher pre-pregnancy maternal weight may be associated with a decrease in testicular cancer risk in male offspring.	2a
	BALISE VD, 2016 Systematic review of the association between oil and natural gas extraction processes and human reproduction SR (5/11)	The evidence is low and inadequate for testicular, breast, or female reproductive cancers, birth outcomes associated with paternal exposures, and stillbirth.	2a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	BANKS K, 2013 Cryptorchidism and testicular germ cell tumors: comprehensive meta-analysis reveals that association between these conditions diminished over time and is modified by clinical characteristics. SR (8/11)	Modifying factors may provide insight into testicular germ cell tumour (TGCT) aetiology and suggest improved approaches to managing cryptorchidism (CO). Based on available data, CO patients and their parents or caregivers should be made aware of elevated TGCT risk following orchidopexy, regardless of age at repair, unilateral vs. bilateral non-descent, or position of undescended testes.	2a
	COOK MB, 2010 A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer-experiences of the son SR (5/11)	Through systematic review and meta-analysis we find associations of low birth weight, gestational age, cryptorchidism, inguinal hernia and twinning with risk of testicular cancer.	2a
	GURNEY J, 2015 Cannabis exposure and risk of testicular cancer: A systematic review and meta-analysis. SR (7/11)	Using meta-analysis of published studies, we observed that a) current, b) chronic, and c) frequent cannabis use is associated with the development of TGCT – particularly non-seminoma TGCT – at least when compared to never-use of the drug. We found inconclusive evidence regarding the relationship between ever- and former-use of cannabis and TGCT development. However, it must be noted that these observations were derived from only three published studies;	3a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		that these studies were all conducted in the United States; and the majority of data collection occurred during the 1990's.	
	JIANG W, 2016 Predictive value of GGN and CAG repeat polymorphisms of androgen receptors in testicular cancer: A meta-analysis. SR (5/11)	We found that long GGN repeats were associated with an increased risk of TC compared with a reference group. Furthermore, an association between GGN repeats in AR and the risk of TC was found in studies with a sample size > 200 and in the mid-latitude and seminoma subgroups. We found that CAG repeat polymorphisms with > 25 and < 21 + > 25 repeats might confer a protective effect to the patients with TC in the PB, high-latitude, seminoma, and non-seminoma subgroups. However, it CAG repeat polymorphisms with > 25 and < 21 + > 25 repeats in the mid-latitude subgroup were associated with an increased risk of TC.	3a
	LIP SZL , 2013 A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. SR (6/11)	Boys with isolated cryptorchidism are three times more likely to develop testicular cancer. The limitations of this study must be acknowledged, in particular, possible publication bias and the lack of high quality evidence focusing on the risk of malignancy in boys with isolated cryptorchidism.	2a
	Marrie R, 2015 A systematic review of the incidence and prevalence of cancer in multiple sclerosis SR (7/11)	The complexity of understanding cancer risk in MS is augmented by inconsistencies in study design, and the relative paucity of age, sex and ethnicity-specific risk estimates from which the strong impact of age on the incidence of cancers can be assessed. Among the incidence studies, the risks of prostate and testicular cancer were consistently lower in the MS population than in the general population, although some of the findings were not statistically significant.	Einstufung nicht möglich, Datenbasis sind Registerdaten

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	WANG T, 2015 A Meta-Analysis of the Relationship between Testicular Microlithiasis and Incidence of Testicular Cancer. SR (6/11)	The present meta-analysis suggests that testicular microlithiasis (TM) is significantly associated with risk of testicular cancer. More researches are warranted to clarify an understanding of the association between TM and risk of testicular cancer.	2a
	YOUSIF L, 2010 Testicular cancer risk associated with occupational radiation exposure: a systematic literature review. SR (5/11)	Overall, there was very limited evidence for associations between occupational ionising radiation and testicular cancer, while there were some positive associations for electromagnetic fields (EMF). Testicular cancer mortality is generally low and was not associated with radiation.	2a
	YOUSIF L, 2013 Testicular cancer and viral infections: A systematic literature review and meta-analysis: SR (5/11)	A specific causative virus for testicular cancer could not be identified with certainty due to the large discrepancy between different studies. However, the evidence for HIV as causative agent is comparatively strong, and similarly, high ORs for EBV and CMV infection suggest that these viruses may be involved in the development of testicular cancer.	2a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
Screening / Prävention			
	US Prev Task Force 2011 114 Pkt / 71%	The USPSTF recommends *against* screening for testicular cancer in adolescent or adult males.	D
	ASCO 2010 (#) 92 Pkt / 57%	*Asymptomatic adults:* The Panel recommends *against* use of STMs or any other blood tests to screen for GCTs.	
	EAU 2016 (*) 81 Pkt / 50%	There are no high level evidence studies proving the advantages of screening programmes, but it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, self-physical examination by the affected individual is advisable.	
	ILIC D, MISSO ML 2011 Screening for testicular cancer. Cochrane Review (1/11)	A total of 19 studies were identified through the search. Of the 19 studies assessed for inclusion all 19 were assessed as not being eligible for inclusion in this review since none of the studies was a randomised controlled trial of screening for testicular cancer.	Keine Einschätzung (keine passenden RCT konnten ausgewertet wurden)
	ROVITO MJ, 2015 Interventions Promoting Testicular Self-Examination (TSE) Performance: A Systematic Review.	Testicular Self-Examination (TSE) is a viable and useful method to detect testicular cancer and may contribute to healthier lifestyles for at-risk males, including learning the value of self-awareness in terms of their overall wellness.	1a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	SR (5/11)		
	SAAB MM, 2016 Promoting Testicular Cancer Awareness and Screening: A Systematic Review of Interventions. SR (5/11)	The majority of the reviewed interventions succeeded in increasing men's awareness of TC and TSE and in enhancing their intentions to undergo screening and perform TSE. Examples of interventions that succeeded in enhancing men's TC and TSE awareness include TC facts and TSE advice, a university campaign, information about TSE using shower gel sachets and waterproof stickers and posters, and high self-efficacy messages. A number of interesting channels through which men can learn about TC were identified. Examples include social media and mass media.	1a
Pathologische Klassifikation (mit Abgrenzung zu Stromatumoren und extragonadalen KZT)			
	WHO 2016	Neue WHO Klassifikation 2016	
Primärdiagnostik			
Klinische Untersuchung			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Stage I Nonseminoma Clinical history and physical	
	EAU 2016 81 Pkt / 50%	Testicular cancer presents as a painless, unilateral testicular scrotal mass, as a casual US finding or is revealed by a scrotal trauma. Scrotal pain may be the first symptom in 20% of cases and it is present in up to 27% of patients with TC.	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		Gynaecomastia appears in 7% of cases (more common in non-seminomatous tumours). Back and flank pain due to metastasis is present in about 11% of cases. Diagnosis is delayed in around 10% of cases of testicular tumour that mimic orchioepididymitis, physical examination reveals the features of the mass and must always be carried out together with a general examination to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. US must be performed in any doubtful case. A correct diagnosis must be established in all patients with an intrascrotal mass.	
	KCE 2010 (∞) 115 Pkt / 79%	Patients with a clinical suspicion of testicular malignancy should undergo urgent urological assessment, including clinical exam and bilateral testicular ultrasonography	1C
	SIGN 2011 132 Pkt / 82%	Patients presenting with a swelling in the scrotum should be examined carefully and an attempt made to distinguish between lumps arising from the body of the testis and other intrascrotal swellings. Those patients suspected of harbouring a testicular malignancy, ie a lump in the testis, doubtful epididymo-orchitis or orchitis not resolving within two to three weeks, should be referred urgently for urological assessment.	best practice D
Sonographie			
	NCCN 2015 (¥) 65 Pkt/ 40%	Empfehlung: Testicular Ultrasound (US)	2a
	EAU 2016	Perform testicular US in all patients with suspicion of testicular cancer.	A

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	81 Pkt / 50%		
	ESMO 2013 55 Pkt / 34%	In patients with a testicular mass, testicular sonography (7.5 MHz transducer) should be carried out, also noting the size and any structural alterations of the contralateral testis.	
	SIGN 2011 132 Pkt /82%	An ultrasound, if available at this stage, should be performed to make a distinction.	best practice
	KCE 2010 115 Pkt / 79%	Patients with a clinical suspicion of testicular malignancy should undergo urgent urological assessment, including clinical exam and bilateral testicular ultrasonography	1C
Serumtumormarker			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Stage I Seminome, Stages IIA and IIB Seminomas, Stages IIC, and III Seminomas, Stage I, II, III Nonseminomas Tumour markers (β-hCG, LDH, άFP) zum Staging	
	NCCN 2015 65 Pkt / 40 %	Further evaluation includes measurement of the serum tumor markers, and a chest x-ray. Serum tumor markers are critical in the assignment of prognosis and management during treatment as well. Serum tumor markers are prognostic factors and contribute to diagnosis and staging.Markers are assessed before orchiectomy and repeated after orchiectomy. Elevated values of	2a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		beta-hCG, LDH, or AFP should be followed up with repeated tests to allow precise staging.	
	EAU 2016 81 Pkt / 50%	Perform serum determination of tumour markers (AFP, hCG, and LDH), both before and 5-7 days after orchiectomy for staging and prognostic reasons.	A
	ESMO 2013 55 Pkt / 34%	Elevation of 'tumour markers', i.e. serum levels of α-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG) support the diagnosis. Tumour markers (AFP, HCG, LDH) should be determined before orchiectomy and followed until normalisation or lack of further decrease. The half-life for HCG is up to 3 days and 5–7 days for AFP. Serum levels of total testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be determined.	
	SIGN 2011 132 Pkt /82%	Serum markers should be checked pre-orchidectomy, 24 hours after orchidectomy and weekly thereafter until normal. Measurement of serum AFP and HCG is essential in the follow up of patients with non-seminomatous germ cell tumours.	best practice C
	ASCO 2010 92 Pkt / 57%	The Panel recommends drawing blood to measure serum AFP and hCG before orchiectomy for all patients suspected of having a testicular GCT to help establish the diagnosis and interpret postorchiectomy levels. However, the Panel recommends against use of STM assay results to guide decision making on need for an orchiectomy. Concentrations in the normal range do not rule out testicular neoplasm or the need for diagnostic orchiectomy	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		The Panel recommends against using serum AFP and hCG assay results to guide treatment of patients with CUP and indeterminate histology, because evidence is lacking to support this use. Consider treatment with a chemotherapy regimen for disseminated GCT in patients presenting with undifferentiated midline carcinoma even if serum hCG and AFP concentrations are within normal ranges. In rare male patients presenting with testicular, retroperitoneal, or anterior mediastinal primary tumor and whose disease burden has resulted in an urgent need to start treatment, substantially elevated serum AFP and/or hCG may be considered sufficient for diagnosis of GCT. For such rare, medically unstable patients, treatment need not be delayed until after tissue diagnosis.	
	KCE 2010 115 Pkt / 79%	Preoperative assessment of tumour markers (AFP, HCG, LDH) is recommended for postoperative management of patients with testicular cancer	expert opinion
Operative Diagnostik/inguinale Exploration des Hodens (inkl. Organerhalt)			
	NCCN 2015 65 Pkt / 40%	Radical inguinal orchiectomy, Consider inguinal biopsy of contralateral testis if: Suspicious ultrasound for intratesticular abnormalities, Cryptorchid testis, Marked atrophy.	2a
	EAU 2016 81 Pkt / 50%	Perform orchiectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, start chemotherapy before orchiectomy.	A
	ESMO 2013	‘Radical orchiectomy’ provides the histological diagnosis and should be carried out before any further treatment, unless the clinical situation requires	

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	55 Pkt / 34%	immediate chemotherapy in patients with a clear germ cell malignancy based on elevated tumour markers. Any testicular mass of uncertain ranking must be explored by the inguinal approach to verify or exclude malignancy. As benign testicular lesions are recognised with increasing frequency, frozen section analysis should be considered intra-operatively, which differentiates malignant from benign testicular lesions. Tumour marker analysis should be carried out before and after surgery until normalisation, progression or plateau development, since this information is used for final staging. Radical orchiectomy is carried out through an inguinal incision. Any scrotal violation for biopsy or open surgery should be avoided. The tumour-bearing testis is resected with the spermatic cord at the level of the internal inguinal ring. In experienced centres, 'organ-preserving surgery' may be feasible in case of a small tumour, particularly in patients with synchronous bilateral testicular tumours, tumour in a solitary testis or contralateral atrophic testis. However, mandatory postresection testicular radiotherapy renders the residual testicular tissue azoospermic but retains some testosterone production.	B/IV A/III B/IV
	SIGN 2011 132 Pkt /82%	Where possible an inguinal orchidectomy should be performed. A testicular prosthesis should be offered to all patients.	D D
	KCE 2010 115 Pkt / 79%	In patients with a high suspicion of testicular malignancy after urological assessment, radical orchidectomy through inguinal approach is indicated.	expert opinion
Pathologische Untersuchung des Hodengewebes (inkl. TIN)			

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	NCCN 2015 65 Pkt / 40 %	Biopsy may also be considered if a suspicious intratesticular abnormality, such as a hypoechoic mass or macrocalcification, is identified on ultrasound. In contrast, if microcalcifications without any other abnormality can be observed, testicular biopsy is not necessary. Pathologic Diagnosis: Pure seminoma (pure seminoma histology and AFP negative; may have elevated beta-hCG). Nonseminomatous germ cell tumor (NSGCT) (includes mixed seminoma/nonseminoma tumors and seminoma histology with elevated AFP).	2a
	EAU 2016 81 Pkt / 50%	Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralaterial TIN.	A
	ESMO 2013 55 Pkt / 34%	Diagnosis of a testicular germ cell cancer (TGCC) is based on histology of the testicular mass. Biopsy of mid-line extragonadal tumours is mandatory, unless the patient is very sick and has high tumour markers. The biopsy should be preceded by testicular sonography to exclude a TGCT. Histology of GCT should be reported according to the World Health Organisation (WHO) classification, specifying tumour size, multiplicity, extension of tumour (e.g. in rete testis or other tissue), pT category (according to the American Joint Committee on Cancer, AJCC, Union for International Cancer Control, UICC), all histological components with corresponding percentages, and presence or absence of vascular invasion and testicular intraepithelial neoplasia (TIN). In seminomas, the presence of syncytiotrophoblasts should be reported. Increased copy numbers of iso-chromosome 12p are found in both TGCT and EGGCT and provide a	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		pathognomonic test, which might be useful in challenging histologic diagnoses, e.g. somatically transformed teratoma. *Biopsy for diagnosis of TIN in the contralateral testis and subsequent management* In 2%–5% of TGCT patients, a contralateral TGCT is diagnosed either metachronously or synchronously. Accordingly, between 3% and 5% of testicular cancer patients have TIN in the contralateral testis with the highest risk (~30%) in men with testicular atrophy (volume <12 ml) and age <40 years, and in patients with EGGCT. The majority of European Germ Cell Cancer Consensus group (EGCCCG) experts did not consider a routine biopsy of the contralateral testis as indicated. If a biopsy is carried out and TIN is diagnosed, however, the condition may be managed by surveillance, irradiation with 20 Gy in 2 Gy fractions (with potential damage to the contralateral, nonaffected testis by scattered radiation) or orchiectomy, depending on fertility issues. In patients with metastatic disease treated with three or more cycles of cisplatin-based chemotherapy, TIN in the contralateral non-resected testicle may be eradicated or progression may be slowed down, although the risk of developing an invasive tumour is still substantial.	C/V
	KCE 2010 115 Pkt / 79%	The distal margin has to be cut prior to incision of the testis to avoid tumour cell contamination of the spermatic cord. If the tumour is classified as a mixed type germ cell tumour, the pathologist has to estimate the amount of each component (as a percentage).	expert opinion 1C
Ausbreitungsdiagnostik,			

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
Stadieneinteilung und Prognose			
	YACOUB 2016 48 Pkt / 30%	In most instances, the diagnosis of testicular tumours is established with a carefully performed physical examination and scrotal ultrasonography. - Tumour markers are useful for determining the presence of residual disease. - Cross-sectional imaging studies (CT, MRI) are useful in determining the location of metastases. - FDG PET scans have slightly higher sensitivity than CT, but their role in staging testicular cancer has not been determined in a large study. FDG PET may play a role in follow-up of higher stage seminoma after chemotherapy. - Bone scans are useful in the absence of FDG PET scans and should be used when bone metastases are suspected.	
	EAU 2016 81 Pkt / 50%	For staging purposes recommendations are: Test Recommendation GR Serum tumour markers AFP, hCG, LDH (A) Abdominopelvic CT, All patients (A) Chest CT, All patients (A) Testis ultrasound (bilateral), All patients (A) Bone scan or MRI columna In case of symptoms Brain scan (CT/MRI) In case of symptoms and patients with metastatic disease with multiple lung metastases and/or high beta-hCG values.	Grad der Empf. Siehe Spalte links

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		Further investigations Fertility investigations: Total testosterone, LH, FSH, Semen analysis, (B) Discuss sperm banking with all men prior to to starting treatment for testicular cancer. (A) Assess the state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera in testicular cancer (A) Risk factors for occult metastatic disease in stage I testicular cancer For seminoma Pathological (for stage I) Histopathological type Tumour size (> 4 cm) Invasion of the rete testis For non-seminoma Pathological (for stage I) Vascular/lymphatic in or peri-tumoural invasion Proliferation rate > 70% Percentage of embryonal carcinoma > 50%	
	NCCN 2015 65 Pkt / 40 %	Postdiagnostic workup: · Abdominal/pelvic CT	2a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		· Chest CT if: Positive abdominal CT or abnormal chest x-ray · Repeat beta-hCG, LDH, AFP since TNM staging is based on postorchiectomy valuese · Brain MRI, if clinically indicated · Bone scan, if clinically indicated · Discuss sperm banking	
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Staging: CXR CT abdomen/pelvis; CT chest if positive abdominal CT or abnormal CXR. CBC Creatinine Tumour markers (β-hCG, LDH, άFP)	
Bildgebende Verfahren			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	CXR CT abdomen/pelvis; CT chest if positive abdominal CT or abnormal CXR. Bone scan, if clinically indicated, CT brain, if clinically indicated PET if indicated	
	NCCN 2015 65 Pkt / 40 %	Chest X-ray (workup) Abdominal/pelvic CT (postdiagnostic workup) Chest CT if: positive abdominal CT or abnormal chest X-ray (postdiagnostic workup) Brain MRI, if clinically indicated (postdiagnostic workup)	2a

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		Bone scan, of clinically indicated (postdiagnostic workup)	
	ESMO 2013 55 Pkt / 34%	Computed tomography (CT) scan of the abdomen and pelvis is mandatory. Thoracic CT should be carried out in case of non-seminoma, but can be omitted in seminoma patients without infradiaphragmatic metastases. Magnetic resonance imaging (MRI) of the central nervous system is indicated in advanced stages, particularly in case of choriocarcinoma/high HCG, or in those with cerebral symptoms. Positron emission tomography (PET) scanning does not contribute to initial staging.	B/III D/II
	SIGN 2011 132 Pkt / 82%	Preoperative investigations should include assay of AFP, HCG, and LDH, bilateral testicular ultrasound, and a chest X-ray.	D best practice für CT, MRT und PET LE3
	KCE 2010 115 Pkt / 79%	Contrast-enhanced CT of the thorax, abdomen and pelvis is recommended in patients with confirmed testicular cancer for the detection of (nodal and extranodal) metastatic disease (2C). In patients with confirmed testicular cancer, magnetic resonance imaging is an alternative for the detection of abdominal metastatic disease if contrastenhanced CT is contraindicated (expert opinion). The evidence supporting other staging techniques is too weak to recommend their routine use for the staging of testicular cancer (1C).	

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		In selected patients, targeted diagnostic interventions are indicated (expert opinion). Treatment options for patients with testicular cancer should be discussed at the multidisciplinary team meeting (expert opinion).	
	EAU 2016 81 Pkt / 50 %	MRI of the scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis.	
	TREGLIA G, 2014 Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography in the postchemotherapy management of patients with seminoma: Systematic review and meta-analysis. SR (6/11)	F-FDG-PET and PET/CT were demonstrated to be accurate imaging methods in the post-chemotherapy management of patients with seminoma.	1a
	ZHAO JY, 2014 Diagnostic accuracy of 18F-FDG-PET in patients with testicular cancer: a meta-analysis. SR (5/11)	In conclusion, 18F-FDG-PET is an accurate noninvasive and useful diagnostic tool for the patients with testicular cancer. FDG-PET is able to differentiate between nonvital and vital lesions in patients with testicular cancer. A negative PET eliminates viability in large lesions and contributes to avoid unnecessary surgery. On the other hand, a positive PET is a predictor of a viable tumor with the relapse risk. FDG-PET demonstrated a good specificity, being potentially useful tools if combined with other imaging methods such as MRI, CT. In	Level nicht festlegbar

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		addition, FDG-PET can provide uptake values, which can used as a prognostic factor in many tumors, and this is a new research hotspot.	
Postoperative Tumormarkerbestimmung			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	*Siehe vorne bei Serumtumormarkerbestimmung*	
	NCCN 2015 65 Pkt / 40%	Repeat beta-hCG, LDH, AFP since TNM staging is based on postorchiectomy values (elevated values should be followed after orchiectomy with repeated determination to allow precise staging)	2a
	EAU 2016 81 Pkt / 50%	Perform serum determination of tumour markers (AFP, hCG, and LDH), both before and 5-7 days after orchiectomy for staging and prognostic reasons.	A
	ESMO 2013 55 Pkt / 34%	Tumour markers are to be determined immediately before the start of each new chemotherapy cycle.	
	SIGN 2011 132 Pkt /82%	Serum markers should be checked pre-orchidectomy, 24 hours after orchidectomy and weekly thereafter until normal. Measurement of serum AFP and HCG is essential in the follow up of patients with non-seminomatous germ cell tumours.	best practice C
	ASCO 2010	NSGCT	

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	92 Pkt / 57%	*Monitoring during treatment (or observation)* For staging and prognosis before chemotherapy and/or additional surgery: Although evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes for these patients, the Panel recommends measuring serum AFP, hCG, and LDH for all patients with testicular NSGCT shortly after orchiectomy and before any subsequent treatment. The magnitude of postorchiectomy STM elevations is used to stratify risk and select treatment but must be interpreted appropriately. Serial STM measurements may be needed to determine whether STM levels are rising or falling and, if falling, whether the decline approximates the marker's biologic half-life. To predict response to or benefit from treatment: The Panel recommends measuring AFP and hCG shortly before RPLND in patients with clinical stage I or II NSGCT; those with rising concentrations are beyond stages IA or IB and need systemic therapy similar to the regimens used for patients with stage III disease. Although direct evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes when compared with decisions made without assay results, the Panel recommends measuring hCG, AFP, and LDH immediately prior to chemotherapy for stage II/III testicular NSGCT. The magnitude of marker elevations guides chemotherapy regimen choice and treatment duration.	

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		To monitor response or progression during or soon after therapy: Although direct evidence is lacking to determine whether monitoring treatment response with STM assays during chemotherapy improves survival or other health outcomes of patients with NSGCT, the Panel recommends measuring serum AFP and hCG at the start of each chemotherapy cycle and again when chemotherapy concludes. However, the Panel sees no indication to delay the start of chemotherapy until after results of STM assays are known. Rising AFP and/or hCG levels during chemotherapy usually imply progressive disease and the need to change regimen. However, tumor lysis from chemotherapy, particularly during the first cycle, may result in a transient spike in STM levels, and such a spike does not represent treatment failure. Resect all residual disease for patients whose STM levels have normalized and who have resectable residual mass(es) following chemotherapy. Slow decline during treatment conveys higher risk of treatment failure but does not indicate need to change therapy. Persistently elevated but slowly declining postchemotherapy levels do not indicate immediate need for additional chemotherapy; resection of residual masses need not be delayed until STM levels normalize. *For surveillance* After presumably definitive therapy: Although direct evidence is unavailable to determine whether monitoring STM concentrations during surveillance and following definitive therapy for NSGCT improves patients' survival or other health outcomes, the Panel recommends measuring AFP and hCG at each visit during surveillance after definitive therapy for NSGCT, regardless of stage. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used by the available uncontrolled series: every 1 to 2 months in the first year, every 2 to 4 months in the second	

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		year, every 3 to 6 months in the third and fourth years, every 6 months in the fifth year, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed. *Seminoma* Monitoring during treatment (or observation) For staging and prognosis before RPLND, radiation, or chemotherapy: Although direct evidence is lacking to determine whether measuring STM concentrations improves survival or other health outcomes of these patients, the Panel recommends measuring postorchiectomy serum concentrations of hCG and/or LDH for patients with testicular pure seminoma and preorchiectomy elevations. However, the Panel recommends against using postorchiectomy serum concentrations of either hCG or LDH to stage or predict prognosis of patients with involved nodes and/or metastasis. To predict response to or benefit from treatment The panel recommends against using tumor marker levels to guide treatment decisions for seminoma. Evidence is lacking that selecting therapy based on tumor marker levels yields better outcomes. To monitor response or progression during or soon after therapy The Panel recommends against using tumor markers to monitor response or progression of seminomas during treatment. However, serum hCG and AFP should be measured when seminoma treatment concludes. Rising	

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		concentrations usually indicate progressive disease and the need for salvage therapy (usually chemotherapy). *For surveillance* After presumably definitive therapy Conclusive evidence is lacking for clinical utility of STMs in post-treatment surveillance for stage I seminoma, and the Panel recommends against this use. However, while direct evidence is unavailable to determine whether monitoring STM concentrations improves survival or other health outcomes of patients who have completed therapy for advanced seminoma, rising levels may be the earliest sign of relapse, and the Panel recommends measuring STMs at each visit for these patients. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used in the available uncontrolled series: every 2 to 4 months in the first year, every 3 to 4 months in the second year, every 4 to 6 months in the third and fourth years, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed	
Stadieneinteilung (UICC)			
	EAU 2016 81 Pkt / 50%	TNM classification for testicular cancer (UICC, 2009, 7th ed.)	
	NCCN 2015 65 Pkt / 40 %	TNM classification	

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	ESMO 2013 55 Pkt / 34%	Post-orchiectomy management should be the responsibility of clinicians with experience in the classification and treatment of TGCT. Staging and risk group categorisation' are carried out according to the AJCC/UICC and the International Germ Cell Cancer Collaborative Group (IGCCCG), reflecting the extent of the disease based on clinical and radiological examinations and the results of serum tumour markers after orchiectomy, including serum lactate dehydrogenase (LDH) For stage I disease different risk factors have been identified for seminoma and non-seminoma based on histological features in the primary tumour. For metastatic cases the IGCCCG has identified three prognostic groups (see Table 1). If treatment is carried out correctly, the 5-year survival rate of patients with TGCT approximates 99% in stage I, and 91%, 79% and 48% in metastatic disease with good, intermediate and poor prognosis, respectively. The IGCCCG provided prognostic information for chemotherapy-treated metastatic disease. For patients with nonseminoma, a good, intermediate or poor risk group is identified. Patients with seminoma are categorised as either good or intermediate risk (there is no poor-risk group). However, not all patients with metastases receive chemotherapy, e.g. radiotherapy for seminoma IIA or retroperitoneal lymph node dissection (RPLND) for non-seminoma IIA.	A/V
	SIGN 2011 132 Pkt / 82%	CECT scanning of the thorax, abdomen and pelvis is an essential part of the staging of all germ cell tumours. Meticulous and reproducible technique is important for accuracy and comparability between examinations.	D best practice

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		Magnetic resonance imaging may be helpful when CT scanning is inconclusive, is contraindicated because of allergy to contrast media, or where there is concern about radiation dose. Either MRI or CT scanning of the brain should be considered where there are multiple lung metastases and/or HCG >10,000 IU/L. All staging should be completed and reviewed at a meeting of the uro-oncology multidisciplinary team no later than three weeks after surgery, although immediate postoperative scans may be misleading.	best practice best practice
Prognoseklassifikation			
	EAU 2016 81 Pkt / 50%	IGCCCG staging system	
	NCCN 2015 65 Pkt / 40 %	IGCCCG staging system AJCC classification7th ed. 2010	
	SIGN 2011 132 Pkt / 82%	Marker - Konzentration IGCCC G staging system	D best practice
	KCE 2010 115 Pkt / 79%	IGCCCG staging system	
Therapie			

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Stadium I Seminome, Nichtseminomatöser KZT			
Auswirkungen auf die Fertilität und damit verbundene Aspekte			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	The possibility of sperm banking should be discussed.	
	NCCN 2015 65 Pkt / 40%	Discuss sperm banking.	2a
	EAU 2016 81 Pkt / 50%	Sperm abnormalities are frequently found in patients with testis tumours. Furthermore, chemotherapy and radiation treatment can also impair fertility. In patients in the reproductive age group, pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) should be performed, and semen analysis and cryopreservation should be offered. If cryopreservation is desired, it should preferably be performed before orchiectomy, but in any case prior to chemotherapy treatment. In cases of bilateral orchiectomy or low testosterone levels after treatment of TIN, life-long testosterone supplementation is necessary. Patients with unilateral or bilateral orchiectomy should be offered a testicular prosthesis. For more detailed information, the reader is referred to the EAU Male Infertility Guidelines.	

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	LOREN AW 2013 97 Pkt / 60%	Discuss fertility preservation with all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy • Refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists • Address fertility preservation as early as possible, before treatment starts • Document fertility preservation discussions in the medical record • Answer basic questions about whether fertility preservation may have an impact on successful cancer treatment • Refer patients to psychosocial providers if they experience distress about potential infertility • Encourage patients to participate in registries and clinical studies Adult Males • Present sperm cryopreservation (sperm banking) as the only established fertility preservation method • Do not recommend hormonal therapy in men; it is not successful in preserving fertility • Inform patients that other methods (eg, testicular tissue cryopreservation, which does not require sexual maturity, for the purpose of future reimplantation or grafting of human testicular tissue) are experimental	

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		• Advise men of a potentially higher risk of genetic damage in sperm collected after initiation of chemotherapy	
	ESMO 2013 55 Pkt / 34%	Semen analysis and sperm banking should be discussed with all patients.	
	SIGN 2011 132 Pkt / 82%	When appropriate, sperm storage should be offered to men who may require chemotherapy or radiotherapy.	D
	KCE 2010 115 Pkt / 79%	Pre-treatment sperm storage should be offered to men who may require chemotherapy or radiotherapy.	expert opinion
Stadium I Seminome Überwachung			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Therapeutic options include surveillance or adjuvant chemotherapy. Surveillance is indicated for the individual who will comply with the surveillance protocol. Patients with a higher risk for recurrence (e.g. presence of a tumour >4 cm and/or rete testes involvement) should discuss risk factors with oncologists and could be offered radiotherapy; however, even patients in the high risk group have a greater than 65% chance of being relapse free without adjuvant treatment, as such surveillance remains an preferred option.	
	NCCN 2015	Stage Ia, Ib:	

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	65 Pkt/ 40%	Surveillance for pT1-pT3 tumors (category 1) (preferred) OR: Single-agent carboplatin (AUC=7 x 1 cycle or AUC=7 x 2 cycles OR: RTf (20 Gy)g Stage IS: Repeat elevated serum tumor marker and assess with abdominal/pelvic CT scan for evaluable disease	2a
	EAU 2016 81 Pkt. / 50%	Offer surveillance as a management option if facilities are available and the patient is compliant. Do not perform adjuvant treatment in patients at very low risk. Do not perform radiotherapy as adjuvant treatment.	A
	CANCER CARE ONTARIO 2014 104 Pkt / 65%	The DSG recommends surveillance as the preferred option, because adjuvant therapy is associated with important short and long-term toxicities and second malignancy risks with no evidence of improved survival. Surveillance or adjuvant therapy (radiation therapy [RT]) ultimately yields equivalent disease control in stage I seminoma. Patients should be informed of all treatment options, including the potential benefits and side effects of each treatment. A table of benefits and risks associated with each management option is available in Section 1: Appendix A. A treatment plan should be developed that includes the patient's preferences and clinical judgement of that specific case.	

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	ESMO 2013 55 Pkt / 34%	Approximately 80% of the patients with seminoma present with stage I disease, with a survival of ~99%, independent of the chosen strategy, if accepted by the patient. In light of this very high cure rate, minimising toxicity is the priority. Surveillance is considered the preferred strategy.	
	SIGN 2011 132 Pkt / 82%	Patients with stage I seminoma should have the advantages and disadvantages of the various post-orchidectomy management options discussed with them, including surveillance, single-dose adjuvant carboplatin and adjuvant radiotherapy. Patients in whom compliance for follow up is likely to be poor may be advised to pursue adjuvant therapy over surveillance. In patients with stage I seminoma post-orchidectomy, active surveillance may be considered as a management option.	C best practice B
	KCE 2010 115 Pkt / 79%	In patients with stage I seminoma post-orchidectomy, active surveillance can be considered as a management option	2B
	CHUNG P, 2010 Management of stage I seminomatous testicular cancer: a systematic review. SR (5/11)	The optimal management of stage I seminoma remains to be defined. Surveillance seems to be the preferable option, as this strategy minimises the toxicity that might be associated with adjuvant treatment, while preserving high cure rates. The currently available evidence should be presented to patients in order to select the most appropriate option for the individual.	1a
	CHUNG P, 2011	Surveillance (avoids toxicity associated with adjuvant radiotherapy or chemotherapy, increased risk of relapse)*	**No RCTs. Based on observational evidence and consensus

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	Testicular Cancer: seminoma SR (5/11)		
Stadium I Seminome Adjuvante Chemotherapie			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Chemotherapy (carboplatin AUC 7 x 2 courses) can be considered in select cases.	
	NCCN 2015 65 Pkt / 40%	Stage Ia, Ib: OR: Single-agent carboplatin (AUC=7 x 1 cycle or AUC=7 x 2 cycles	2a
	EAU 2016 81 Pkt / 50%	Offer one course at AUC 7, if carboplatin-based chemotherapy is considered.	A
	CANCER CARE ONTARIO 2014 104 Pkt / 65%	When neither surveillance nor RT is suitable, adjuvant chemotherapy is the preferred option. Single-agent carboplatin is typically used. In patients treated with adjuvant therapy, post-treatment monitoring for disease relapse is still necessary. The follow-up after adjuvant therapy should be as thorough as the surveillance conducted in the absence of adjuvant therapy.	
	ESMO 2013 55 Pkt / 34%	The predictive value of ‘risk factors’, such as rete testis infiltration and tumour size ≥4 cm, is controversial, but these factors are sometimes used to apply one course of carboplatin (AUC 7) or radiotherapy (20 Gy/10 ractions to para-aortic	A/I

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		target volume) as adjuvant treatment. Compared with radiotherapy, one course of carboplatin results in similar relapse rates, but less protracted treatment-related lethargy, sick leave and probably treatment-induced malignancies. Although the true long-term adverse effects after >10 years are still unknown. If a relapse occurs, it is usually located in the retroperitoneal or iliac lymph nodes. Rarely, late occurring relapses may contain non-seminoma components.	B/IV
	SIGN 2011 132 Pkt / 82%	In patients receiving a single dose of adjuvant carboplatin, the dose should be AUC7 (ie that dose required to achieve an area under the concentration time curve of 7 mg/ml per minute) based on EDTA clearance. In post-orchidectomy patients with stage I seminoma, adjuvant carboplatin chemotherapy may be considered as a management option.	best practice A
	KCE 2010 115 Pkt / 79%	In patients with stage I seminoma post-orchidectomy, single-dose carboplatin can be considered as a management option.	2B
	CHUNG P, 2011 Testicular Cancer: seminoma SR (5/11)	Trade off between benefits and harms Adjuvant chemotherapy (reduced risk of relapse compared with surveillance, increased immediate toxicity, and possible long-term fertility problems and development of secondary malignancies)* Unknown effectiveness Comparative effects of different drug combinations for adjuvant chemotherapy. Comparative effects of different number of cycles of adjuvant chemotherapy.	*No RCTs. Based on observational evidence and consensus 1a

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		MAINTENANCE CHEMOTHERAPY Unlikely to be beneficial Maintenance chemotherapy	
Stadium I Seminome Risikoadaptierte Behandlung			
	EAU 2016 81 Pkt / 50%	Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided into a low-and high-risk group of occult metastatic disease. Patients with and without both risk factors have a 32% and 12% risk of occult disease respectively. These risk factors were introduced through an analysis of retrospective trials. A prospective trial based on no risk factors, surveillance, both risk factors and two courses of carboplatin AUC 7 showed the feasibility of a risk-adapted approach. Early data with limited follow up indicate that patients without either risk factor have a very low risk, 6.0% - 14.8%, of relapse at 5 years. Patients in the high-risk group treated with carboplatin experienced a 1.4% - 3.2% relapse rate at mean follow up of 34 months.	
Stadium I Seminome Adjuvante RT			
	CANCER CARE ONTARIO 2014 104 Pkt / 65%	For patients who prefer immediate treatment, or who are unsuitable for primary surveillance, adjuvant RT is the recommended option. When adjuvant RT is the preferred option, a radiation dose of at least 20 Gy and no more than 30 Gy is recommended.	

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		When adjuvant RT is the preferred option, para-aortic and extended-field (i.e., “dogleg”) RT are equivalent in prevention of para-aortic recurrence, but are different in terms of short- and long-term toxicity and follow-up requirements. In patients treated with adjuvant therapy, post treatment monitoring for disease relapse is still necessary. Except in the specific case of extended-field radiotherapy, the follow-up after adjuvant therapy should be as thorough as the surveillance conducted in the absence of adjuvant therapy.	
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Radiotherapy: 20-25 Gy in 10-20 fractions, to para-aortic ± ipsilateral pelvic lymph nodes (“dog leg” or “hockey stick”).	
	SIGN 2011 132 Pkt / 82%	In patients with stage I seminoma who have undergone no previous inguinoscrotal surgery and who are to receive adjuvant radiotherapy following orchidectomy, the volume should be limited to the para-aortic nodal strip. If para-aortic nodal irradiation is used, CT scanning of the pelvis may be considered during follow up. In patients with stage I seminoma who have undergone previous inguinoscrotal surgery and who are to receive adjuvant radiotherapy following orchidectomy, the para-aortic nodal strip volume should be extended to include the ipsilateral pelvic nodes (‘dog-leg radiotherapy’). In patients with stage I seminoma who are to receive adjuvant 'dog-leg' or para-aortic strip radiotherapy, a dose of 20 Gy in ten fractions over two weeks should be prescribed to the International Commission on Radiation Units (ICRU) reference point.	A best practice D A

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		The potential risk of second malignant neoplasms should be outlined to patients where adjuvant radiotherapy is being considered.	C
	ESMO 2013 55 Pkt / 34%	The predictive value of 'risk factors', such as rete testis infiltration and tumour size ≥4 cm, is controversial, but these factors are sometimes used to apply one course of carboplatin (AUC 7) or radiotherapy (20 Gy/10 fractions to para-aortic target volume) as adjuvant treatment. Compared with radiotherapy, one course of carboplatin results in similar relapse rates, but less protracted treatment-related lethargy, sick leave and probably treatment-induced malignancies. Although the true long-term adverse effects after >10 years are still unknown. If a relapse occurs, it is usually located in the retroperitoneal or iliac lymph nodes. Rarely, late occurring relapses may contain non-seminoma components.	A/I B/IV
	CHUNG P, 2011 Testicular Cancer: seminoma SR 5/11	GOOD-PROGNOSIS STAGE 1 SEMINOMA (CONFINED TO TESTIS) *Beneficial* Adjuvant irradiation of 20 Gy in 10 fractions to paraaortic area compared with 30 Gy in 15 fractions to paraaortic area and iliac nodes (similarly effective but less toxicity). Adjuvant radiotherapy (reduced risk of relapse compared with surveillance, increased immediate toxicity, and possible long-term fertility problems and development of secondary malignancies)*	1a *No RCTs. Based on observational evidence and consensus
Stadium I Seminome Retroperitoneale Lymphknotenentfernung			
	EAU 2016	In a prospective, non-randomised study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of	

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	81 Pkt / 50%	retroperitoneal relapses (9.5%) after RPLND as primary treatment. Therefore, RPLND is *not recommended* in stage I seminoma	
Nichtseminomatöser KZT Stadium I Überwachung			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Surveillance (see below) or template RPLND; the decision for surveillance should consider the higher risk of metastatic disease in patients with pure embryonal histology and lymphovascular invasion.	
	NCCN 2015 65 Pkt / 40%	Surveillance (preferred) for Stage Ia OR: Surveillance for T2 only for Stage Ib	2a
	EAU 2016 81 Pkt / 50%	Inform patients with stage 1 NSGCT about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and RPLND) including treatment-specific recurrence rates as well as acute and long-term side effects. In patients with stage 1 NSGCT, offer surveillance or risk-adapted treatment based on vascular invasion (see below). If patients are not willing to undergo surveillance, offer one course of BEP as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	A / LE 2a A/LE 2a A / LE1b

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		In patients with marker-positive recurrent and/or progressing lesion during surveillance, perform salvage treatment consisting of three or four courses of BEP chemotherapy according to the IGCCCG classification, followed by post-chemotherapy retroperitoneal lymph node dissection if necessary.	A / LE2a
	ESMO 2013 55 Pkt / 34%	Stage I disease implies excellent survival rates of 98%–100% and is categorised by absence or presence of vascular invasion into 'low risk' (20% relapse rate) or 'high risk' (40%–50% relapse rate), respectively. low-risk non-seminoma stage I Surveillance is the standard for low-risk disease. high-risk non-seminoma stage I There are two standard treatment options: surveillance with 40%–50% relapse rate or adjuvant chemotherapy (one or two cycles of BEP, relapse rate of 3%–4%). Survival is the same whichever option is used.	
	SIGN 2011 132 Pkt / 82%	Patients with stage I NSGCT or mixed seminoma/NSGCT of the testis with no high-risk features should be managed by surveillance following inguinal orchidectomy. Patients on surveillance should be seen in a designated clinic following a strict protocol. In low-risk patients under surveillance CT scanning at three and 12 months postorchidectomy is recommended. A pelvic CT scan is only indicated where there are known risk factors for pelvic disease.	C best practice B D

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	KCE 2010 115 Pkt / 79%	Primary surveillance is recommended for patients with stage I nonseminoma (without vascular or lymphatic invasion and without predominant embryonal component) post-orchidectomy, with treatment at relapse	2B
Nichtseminomatöser KZT Stadium I Adjuvante Chemotherapie			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	If lymph node metastases are present and completely excised, consider adjuvant chemotherapy.	
	EAU 2016 81 Pkt / 50%	If patients are not willing to undergo surveillance, offer one course of BEP as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	A / LE 1b
	ESMO 2013 55 Pkt / 34%	low-risk non-seminoma stage I If surveillance is not feasible, e.g. due to difficulties with repeated imaging, low compliance or patient's preference, adjuvant chemotherapy with one or two cycles of BEP is given. Efficacy appears to be similar between one and two cycles of BEP.	C/III
	SIGN 2011 132 Pkt /82%	Risks and benefits of adjuvant chemotherapy and surveillance, in particular risk of relapse, should be discussed with patients to agree an appropriate management strategy. Two courses of adjuvant BEP chemotherapy should be offered to patients with stage I NSGCT or mixed seminoma/NSGCT of the testis following inguinal	best practice

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		orchidectomy if high-risk features are present (blood vessel and/or lymphatic invasion) or if the patient is unable or unwilling to comply with a policy of surveillance.	D
	CHUNG P, 2011 Testicular Cancer: seminoma SR (5/11)	INTERMEDIATE PROGNOSIS NON-STAGE 1 SEMINOMA Unknown effectiveness Chemotherapy GOOD-PROGNOSIS NON-STAGE 1 SEMINOMA Likely to be beneficial Chemotherapy using etoposide plus cisplatin with or without bleomycin (increased relapse-free survival compared with other combined regimens) Chemotherapy using bleomycin added to vinblastine plus cisplatin (reduced relapse rates and mortality compared with two-drug regimen of vinblastine plus cisplatin alone) Unknown effectiveness Adding higher compared with lower doses of cisplatin or vinblastine to a two-drug chemotherapy regimen. Unlikely to be beneficial Chemotherapy using single-agent carboplatin (may be less effective than combined chemotherapy in increasing relapse-free survival)	1a
Nichtseminomatöser KZT Stadium I Risikoadaptierte Behandlung			

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	EAU 2016 81 Pkt / 50%	Stage 1A (pT1, no vascular invasion): low risk Offer surveillance if the patient is willing and able to comply. In low-risk patients not willing (or suitable) to undergo surveillance, offer adjuvant chemotherapy with one course of BEP. Stage 1B (pT2-pT4): high risk Offer primary chemotherapy with one course of BEP. Inform patients having adjuvant chemotherapy about the advantages and disadvantages of one vs. two cycles of BEP. Offer surveillance or nerve-sparing RPLND in high-risk patients not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, discuss further chemotherapy as well as observation with the patient. *Zusätzliche Abbildung der Risiko-adaptierten Behandlung in einem Flow-Chart.*	A
Nichtseminomatöser KZT Stadium I Retroperitoneale Lymphknotenentfernung			
	NCCN 2015 65 Pkt / 40%	OR: Nerve-sparing RPLND bei Stage 1a OR: Nerve-sparing RPLND bei Stage 1b	2a
	EAU 2016 81 Pkt / 50%	In view of the high CSS rates of surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary diagnostic RPLND has diminished. A randomised phase III trial of the German Testicular Cancer Study group compared RPLND to BEP x 1 as adjuvant	

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		treatment, with a 7% difference in favour of chemotherapy. One course of BEP showed a significantly lower recurrence rate as compared to surgery. When RPLND is performed in a multicentre setting, higher rates of in-field recurrences and complications were reported. Therefore, nerve-sparing RPLND - if indicated - should be performed by an experienced surgeon in specialised centres. About 18-30% of patients are found to have retroperitoneal lymph node metastases on RPLND, corresponding to pathological stage II (PS2) disease. If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites. If metastases are present and not treated with adjuvant chemotherapy, recurrence will occur in 31% of patients. The presence of vascular invasion, predominant embryonal carcinoma, pT category as well as a high number of extranodal extension in metastatic nodes may be associated with an increased risk of recurrence in PS2 cases without adjuvant chemotherapy. As yet, the clinical significance of these further parameters remains limited and not applicable in clinical practice. The follow-up after RPLND is simpler and less costly than that carried out during post-orchiectomy surveillance because of the reduced need for abdominal CT scans. If there is an indication to perform a staging RPLND, a laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimal-invasive approach cannot be recommended as the standard approach outside of a specialised laparoscopic centre.	
	ESMO 2013 55 Pkt / 34%	low-risk non-seminoma stage I In patients not suitable for surveillance or adjuvant chemotherapy, open nervesparing RPLND in highly experienced centres is an option. Some experts	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		consider nerve-sparing RPLND the preferred treatment of patients with teratoma and somatic transformation in the primary tumour. high-risk non-seminoma stage I Nerve-sparing RPLND may be carried out in case of contra-indications against the strategies recommended above. Some experts consider nerve-sparing RPLND the preferred treatment of patients with teratoma and somatic transformation in the primary tumour.	
Nichtseminomatzöser KZT Stadium I RT			
	CHUNG P, 2011 Testicular Cancer: seminoma SR (5/11)	GOOD-PROGNOSIS NON-STAGE 1 SEMINOMA Likely to be beneficial Radiotherapy (30–36 Gy in 15–18 fractions)* Trade off between benefits and harms Radiotherapy versus chemotherapy (less toxicity with radiotherapy compared with chemotherapy; higher risk of relapse)*	*No RCTs. Based on observational evidence and consensus
Metastasierender Keimzelltumor			

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
Stage I mit erhöhten Serumtumormarkern			
	NCCN 2015 65 Pkt / 40%	Stage IS: Primary chemotherapy: EP for 4 cycles (category 1) OR BEP for 3 cycles	2a
	EAU 2016 81 Pkt / 50%	Serum tumour markers should be followed closely until levels fall into the reference values according to the expected half-life values for AFP and hCG. If the marker level increases after orchiectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum. An US examination of the contralateral testicle must be performed, if this was not done initially. The treatment of true CS1S patients is still controversial. They may be treated with BEP x 3 chemotherapy and with follow-up as for CS1B patients (high risk, see below) after primary chemotherapy, or by RPLND.	
	ESMO 2013 55 Pkt / 34%	Patients with good prognosis should receive three cycles of BEP or four cycles of EP if contra-indications against bleomycin exist. BEP can be substituted by VIP. Four cycles of BEP still represent standard treatment of patients with intermediate or poor prognosis.	A/I
Metastatic disease (stage IIA/B) Seminom			

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	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Stages IIA and IIB Seminomas Staging Tumour markers (β-hCG, άFP, LDH) CT chest, abdomen and pelvis Bone scan, if clinically indicated. Preparation for Therapy Baseline CBC, Creatinine Discuss sperm banking with the patient. Primary Therapy External-beam radiotherapy. Include para-aortic and ipsilateral pelvic nodes to 20-30Gy (“dog leg” or “hockey stick”). Boost grossly involved nodes by 10 Gy. Chemotherapy. Consider BEP × 3 cycles when optimal radiotherapy not possible; EP × 4 cycles may be considered in patients with contraindication to bleomycin. Consider BEP × 3 cycles, in extensive stage IIB disease (same as stage IIC); EP × 4 cycles may be considered in patients with contraindication to bleomycin. Residual Disease: If the residual mass >3 cm, consider a PET scan 4-12 weeks after day 21 of the last cycle. If PET scan is positive, decisions should be made using a multi-disciplinary approach. Due to the difficulty of surgical resection and radio-sensitivity of seminoma, consider biopsy and/or radiotherapy. If required, surgery can be performed in the future.	
	NCCN 2015 65 Pkt / 40%	Stage IIA:	2a

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		RT to include para-aortic and ipsilateral iliac lymph nodes to a dose of 30 Gyf (preferred) OR: Primary chemotherapy: EP for 4 cycles or BEP for 3 cycles for multiple positive lymph nodes Stage IIb: Primary chemotherapy (preferred): EP for 4 cycles or BEP for 3 cycles RT in select non-bulky cases to include para-aortic and ipsilateral iliac lymph nodes to a dose of 36 Gyf	2a
	EAU 2016 81 Pkt / 50%	Treat seminoma CSII A/B initially with radiotherapy. When necessary, use chemotherapy as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.) In seminoma stage CS IIA/B, offer chemotherapy (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	B / LE 2 A / LE1
	ESMO 2013 55 Pkt / 34%	stage IIA (lymph nodes 1–2 cm) The treatment options consist of either cisplatin-based chemotherapy or radiotherapy to para-aortic and ipsilateral iliac lymph nodes with 30 Gy in 2 Gy fractions (Figure 1). A recent study reported three relapses among 29 irradiated stage IIA patients (10.9%), compared with no relapses after cisplatinbased chemotherapy among six stage IIA and 79 stage IIB patients.	B / II

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		Neoadjuvant carboplatin before radiotherapy may further reduce relapse rates, according to a recent single centre pilot study in 51 seminoma patients, but this strategy needs further validation. stage IIB/IIC Three cycles of BEP represent the standard therapy. If there are arguments against bleomycin, e.g. reduction in lung capacity, emphysaema, heavy smoking (including former smokers) or poor renal function, four cycles of etoposide, cisplatin (EP) are used (Table 2). Patients unsuitable for chemotherapy should receive paraaortic and ipsilateral iliac field radiotherapy to 36 Gy in 2 Gy fractions.	B / III
	SIGN 2011 132 Pkt / 82%	Sequential chemotherapy and radiotherapy can be considered as an alternative to radiotherapy alone in stage IIB. In stage IIA seminoma both chemotherapy and radiotherapy treatment options should be considered and discussed with the patient. The optimal treatment for an individual patient will depend on clinical judgement and patient preference.	D best practice
	KCE 2010 115 Pkt / 79%	Patients with stage IIA or IIB seminoma should be treated with chemotherapy or radiotherapy	2C
	GIANNATEMPO P, 2015 Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: A systematic	Despite the statistical equivalence between the two modalities across the CSs and treatment patterns, a difference in the trend of relapses was observed favouring the use of CT in CSIIB. This information, together with the observed (confirmed) incidence of late toxicities and second cancers after RT, actually	1a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	review and meta-analysis of patient outcomes. SR (5/11)	provides a valuable proof of principle for the use PEB/EP CT as the preferred choice for all stage II cases.	
Metastatic disease Stadium IIA/B Nichtseminomatöser KZT			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Stage II Nonseminomas Indications include: Clinical T1-4, N0, M0, (S+): failed marker normalization post radical orchidectomy for clinical stage I disease Clinical T1-4, N+, M0: a. Relapsed disease in the retroperitoneal lymph nodes (RPLN) on surveillance post radical orchidectomy b. Clinical N+: RPLN+ on staging CT at presentation c. Pathologic T1-4, N+, M0: pathologic N + post RPLND (see below) Staging Tumour markers (άFP, β-hCG, LDH) CT chest, abdomen, and pelvis Bone scan, CT brain, if clinically indicated Preparation for Therapy Baseline CBC, biochemistry, liver function tests, alkaline phosphatase Discuss sperm banking with the patient Primary Therapy Cisplatin-based combination chemotherapy. Good risk (IGCCC): BEP x 3 Intermediate/poor risk (IGCCC): BEP x 4; VIP may be considered if there is contraindication to bleomycin or in patients at increased risk to bleomycin	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		induced pulmonary toxicity. Consider complete bilateral RPLND if post chemotherapy RP masses > 1.0 cm. Role of consolidation chemotherapy is unclear. Post-resection treatment depends on histology: Necrosis/fibrosis (40-50% of cases): observe Teratoma (30-40% of cases): observe Residual embryonal, yolk sac, choriocarcinoma, or seminomatous elements (15-20% of cases): adjuvant chemotherapy with EP x 2, TIP x 2, or VIP x 2 RPLND as primary treatment can be considered for selected clinical stage IIA patients with normal markers, ipsilateral LN within landing zone, patient's preference or refusal of chemotherapy. Treatment options following RPLND based on pathological staging (PS); also include pathologic stage II following RPLND for clinical stage I: o Pathologic stage N0 or mature teratoma: observe o Pathologic stage IIA: observation preferred, may use adjuvant EP x 2 or BEP x 2 o Pathologic stage IIB: adjuvant EP x 2 or BEP x 2 o Pathologic stage IIC: primary chemotherapy as for good risk disease	
	NCCN 2015 65 Pkt / 40%	Stage IIA: Markers negative: Nerve-sparing RPLND, OR Primary chemotherapy (category 2B): EP for 4 cycles or BEP for 3 cycles Stage IIA: Persistent marker elevation, Primary chemotherapy: EP for 4 cycles (category 1) OR	2a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		BEP for 3 cycles (category 1)	
	EAU 2016 81 Pkt / 50%	Treat low volume NSGCT stage IIA/B with elevated markers like 'good or intermediate prognosis' advanced NSGCT, with three or four cycles of BEP. In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either RPLND or biopsy. If not possible, repeat staging after 6 weeks of surveillance before making a final decision on further treatment. Perform surgical resection of residual masses after chemotherapy in NSGCT in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.	A / LE 2 B / LE 3 A / LE 2
	ESMO 2013 55 Pkt / 34%	stage IIA (IIB), marker-negative Metastatic non-seminoma not purely consisting of teratoma should be treated according to the IGCCCG's recommendations (Figure 2). Small lymph nodes might not represent metastases thus implying the risk of over-treatment, which may be avoided by the following two strategies: Close follow-up with abdominal imaging every 6 weeks until regression or progression, resulting in observation only or treatment, respectively. Treatment may consist of primary nerve-sparing RPLND in case of a single progressing lymph node, and the presence of normal markers suggestive of teratoma or chemotherapy. In case of multiple progressive lymph nodes and/or rising tumour markers suggestive of non-teratomatous TGCT, chemotherapy (3 cycles of BEP) is indicated. Lymph node biopsy or primary nerve-sparing RPLND. The latter approach comprising both diagnostic and therapeutic potential. Adjuvant chemotherapy	

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		post-RPLND in form of two cycles BEP may be considered, in case of vital GCT in the specimen. Completely resected teratoma warrants follow-up only.	
	SIGN 2011 132 Pkt / 82%	Patients with a good prognosis metastatic non-seminomatous germ cell tumour should receive three cycles of BEP chemotherapy in either a 3-day or 5-day schedule.	A
Metastatic disease (stage IIC and III)			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	Stages IIC, and III Seminomas Staging Tumour markers (β-hCG, άFP, LDH) CT chest, abdomen, pelvis CT head (if symptomatic) Bone scan, CT brain, if clinically indicated PET if indicated 19 Preparation for Therapy Baseline CBC, biochemistry, liver function tests, alkaline phosphatase Discuss sperm banking with the patient Primary Therapy Cisplatin-based combination chemotherapy. Good risk as per IGCCC: BEP × 3; EP × 4 may be considered if bleomycin is contraindicated. Intermediate risk as per IGCCC: BEP × 4. Management of Residual Disease If residual mass > 3 cm, consider PET scan 4-12 weeks after day 21 of the last cycle. If PET is positive, decisions should be made using a multi-disciplinary approach due to the difficulty of surgical resection and radio-sensitivity of	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		seminoma. Consider biopsy and/or radiotherapy. If required, surgery can still be performed in the future. Stage III Nonseminomas Staging Tumour markers (άFP, β-hCG, LDH) CT abdomen/pelvis CT chest Bone scan, CT brain, if clinically indicated. Preparation for Therapy Baseline CBC, biochemistry, liver function tests, alkaline phosphatase Discuss sperm banking with the patient. Primary Therapy Cisplatin-based combination chemotherapy is preferred: a. Good risk (IGCCC): BEP × 3 or EP × 4 may be considered if contraindication to bleomycin. b. Intermediate/poor risk (IGCCC): BEP × 4; VIP may be considered if there is contraindication to bleomycin or in patients at increased risk to bleomycin induced pulmonary toxicity. Consider surgical resection of post chemotherapy RP masses >1.0 cm or <90% volume shrinkage from pre-chemotherapy size with normalization of tumour markers if previously elevated. Consider resection of any residual mass in mediastinum/ lung; these sites are associated with higher risk of teratoma and viable NSGCT. PET remains investigational due to high false negative rate and difficulty in detecting mature teratoma in studies. Post resection treatment depends on histology. a. Necrosis/fibrosis – observe	

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		b. Teratoma – observe c. Residual embryonal, yolk sac, choriocarcinoma, or seminomatous elements - chemotherapy with EP × 2, TIP × 2, or VIP × 2 Patients with brain metastases should be given whole brain radiotherapy (to be given up-front while chemo-therapy is ongoing) ± neurosurgical opinion for isolated disease.	
	NCCN 2015 65 Pkt / 40%	Stage IIC, Stage IIIA: Primary chemotherapy: EP for 4 cycles (category 1) OR BEP for 3 cycles (category 1) Intermediate Risk Stage IIIB: Primary chemotherapy: BEP for 4 cycles (category 1) Poor risk Stage IIIC: Primary chemotherapy: BEP for 4 cycles (category 1) or VIP for 4 cycles in selected patients (category 1)	2a
	EAU 2016 81 Pkt / 50%	In metastatic NSGCT (> stage IIC) with good prognosis, treat with three courses of BEP. In metastatic NSGCT with an intermediate prognosis, treat with four courses of standard BEP.	A / LE 1 A / LE 1

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		In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, followed by tumour marker assessment after 3 weeks: in the case of an unfavourable decline, initiate chemotherapy intensification. In the case of a favourable decline, continue BEP up to a total of four cycles	A / LE 1
	ESMO 2013 55 Pkt / 34%	stage III Chemotherapy with BEP is standard treatment: three cycles for good prognosis patients according to IGCCCG (alternatively four cycles of EP) and four cycles for intermediate prognosis patients according to IGCCCG (alternatively four cycles of etoposide, ifosfamide and cisplatin (VIP), if there are arguments against bleomycin) Stage IS/II/III Patients with good prognosis should receive three cycles of BEP or four cycles of EP if contra-indications against bleomycin exist. BEP can be substituted by VIP (Table 2). Four cycles of BEP still represent standard treatment of patients with intermediate or poor prognosis. In case of contraindication against bleomycin, four cycles of VIP are used. Firstline high-dose chemotherapy has not been proven superior to standard dose chemotherapy in three randomised trials. A prospective randomised trial has indicated that poor prognosis patients with an insufficient tumour marker decline after the first cycle of BEP might benefit from dose intensification of first-line therapy, rather than continuation of standard BEP treatment, though the evidence of an optimal dose-dense regimen is still needed.	A/I

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	SIGN 2011 132 Pkt /82%	For patients with stage IIC or IID seminoma, chemotherapy is the recommended initial treatment.	C
		Scheduling of chemotherapy is similar to that used for NSGCTs, although the risks of bleomycin pulmonary toxicity may be higher in this generally older age group and bleomycin omission should be considered.	C
		Where chemotherapy is contraindicated, radiotherapy may be an acceptable alternative.	
		Patients with stage III and IV seminoma should be treated with cisplatin-based chemotherapy.	C
		In patients with stage III and IV seminoma carboplatin should only be used as an alternative to cisplatin in exceptional circumstances.	B
		Patients with a *good prognosis* metastatic non-seminomatous germ cell tumour should receive three cycles of BEP chemotherapy in either a 3-day or 5-day schedule.	A
		In patients with good prognosis metastatic non-seminomatous germ cell tumours carboplatin should only be given in circumstances in which cisplatin is contraindicated.	A
		Patients with good prognosis metastatic non-seminomatous germ cell tumour and in whom bleomycin is contraindicated should receive four cycles of EP chemotherapy (with 500 mg/m2 etoposide and 100 mg/m2 cisplatin per cycle).	A
		Chemotherapy should only be given in a specialist centre and overseen by a clinician experienced in the management of germ cell tumours.	D
			D

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		Patients with adverse prognostic factors should be treated in specialist centres. Where possible, patients should be entered into well designed multicentre studies to define the optimal treatment for this group.	B
		Outwith the trial setting standard initial chemotherapy for patients with intermediate and poor-risk germ cell tumours is four courses of 5-day BEP.	best practice
		In patients with a residual mass post-chemotherapy, FDG-PET/CT is not routinely recommended, however may be used as a problem solving tool.	best practice
		FDG-PET/CT scans should not take place less than two weeks after chemotherapy due to false positives secondary to inflammatory responses.	best practice
		Surgery is not routinely indicated for patients with seminoma who have residual masses.	D
		Patients with NSGCT who have residual masses after chemotherapy and whose markers have normalised should be treated by complete excision.	D
		If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time as retroperitoneal lymph node dissection.	best practice
		Surgery for metastatic NSGCTs should be performed in a specialist centre with experience in the operative management of these patients.	D
		Patients with seminoma who have residual masses following chemotherapy can generally be managed by a policy of observation rather than radiotherapy.	D
		Surgery should be considered the mainstay of treatment for late relapse where feasible.	D

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		Patients with testicular germ cell cancer who relapse after first line cisplatin based chemotherapy should be managed in specialised centres. The International Prognostic Factors Study Group's model should be applied to guide prognostic information for patients who relapse after first line platinum based chemotherapy. Due to the low survival predicted for the Beyer poor prognosis group (score >2) such patients should not be subjected to high-dose chemotherapy. Those with intermediate and good Beyer prognostic score (0 to 2) may be considered for high-dose chemotherapy. High-dose chemotherapy is not routinely recommended as salvage therapy for germ cell cancer patients who relapse after standard platinum based chemotherapy. The aim of treatment following progression after high-dose chemotherapy or where high-dose chemotherapy is not considered beneficial should be for palliation. Careful consideration should be given to benefit/risk ratios of standard cytotoxics in this setting due to heavy prior treatment. Recruitment to clinical trials is strongly recommended in patients with relapsed disease, where appropriate	C B Best practice Best practice
	KCE 2010 115 Pkt / 79%	In patients with stage IIC seminoma chemotherapy is the treatment of choice. In patients with stage III seminoma cisplatin-based chemotherapy is recommended.	2C 1B
Primäre Chemotherapie			

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
Alle Risikogruppen			
	NCCN 2015 65 Pkt / 40%	Seminome, Stage IIA, Stage IIB (Preferred) Non-Seminome: Stage IB, Stage IIA with persistent marker elevation, Stage IIB, markers negative, lymph node metastases Stage IIB, markers negative, multifocal, symptomatic or lymph node metastases with abberant lymphatic drainage Stage IIC, IIIB, IIIC, Brainmetastases	2a
	EAU 2016 81 Pkt / 50%	Treat seminoma stage IIC and higher with primary chemotherapy according to the same principles used for NSGCT.	A / LE 1
	KCE 2010 115 Pkt / 79%	Patients with good prognosis metastatic NSGCT should be treated with 3 cycles of first-line BEP chemotherapy or 4 cycles of first-line EP chemotherapy (1A). Patients with intermediate prognosis metastatic NSGCT should receive first-line BEP chemotherapy in 4 cycles (2A). Patients with poor prognosis metastatic NSGCT should be treated with first-line BEP chemotherapy in 4 cycles (2A). Patients with intermediate and poor prognosis metastatic NSGCT should be enrolled in clinical trials when available (expert opinion).	
	SIGN 2011 132 Pkt / 82%	Patients with metastases where the diagnosis is not in doubt, on account of high markers and the presence of a testicular mass, may be referred for immediate chemotherapy. In such cases, when examination or ultrasound scan demonstrates that there is a testicular tumour, delayed orchidectomy should be	best practice

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		performed, either at the time of excision of residual masses or following chemotherapy, for those patients who are not undergoing additional surgery.	
Nachsorge nach der kurativen Therapie			
	CANCER CONTROL ALBERTA 2016 77 Pkt / 48%	T1-4, N0, M0 (Stage I Seminomas) Surveillance protocol 7 Years 1-3: P/E, tumour markers, CT abdomen and pelvis every 6 months; CXR every 12 months. Years 4-10: P/E, tumour markers, CT abdomen every 12 months. Pelvic imaging may be added at the discretion of the physician. Follow-up: Evaluation post-radiotherapy or chemotherapy (re-staging), then: Years 1-3: P/E, tumour markers, CT abdomen and pelvis every 6 months; CXR every 12 months. Years 4-10: P/E, tumour markers, CT abdomen every 12 months. Pelvic imaging may be added at the discretion of the physician. Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner. Years 4-10 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner. Stages IIA and IIB Seminomas	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		Follow-up Post-Therapy Evaluation P/E tumour markers CXR (or CT thorax) CT abdomen/ pelvis (baseline post-RT) Evaluation of Residual Disease PET scan for evaluation of residual disease. 15-18 If there is no residual disease, evaluate post-completion of therapy with CT abdomen/pelvis. Post-Therapy Surveillance Year 1: P/E, tumour markers, CXR, CT abdomen and pelvis every 4 months. Year 2: P/E, tumour markers, CXR, CT abdomen and pelvis every 6 months. Year 3-10: P/E, tumour markers every 12 months. CXR, CT as clinically indicated. Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner. Years 4-10 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner. Stages IIC, and III Seminomas Follow-up Evaluation post completion of therapy should include baseline restaging and then: Year 1: P/E, tumour markers, CXR, CT abdomen and pelvis every 4 months. Year 2: P/E, tumour markers, CXR, CT abdomen and pelvis every 6 months. Year 3-10: P/E, tumour markers every 12 months. CXR and CT as clinically indicated. Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner. Years 4-10 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		Stage I Nonseminomas Follow-up Surveillance protocol Year 1: P/E, tumour markers, CXR every 2 months; CT abdomen and pelvis every 4 months.** **For patients at higher risk of relapse (i.e. lymphovascular invasion, rete testis invasion, or embryonal subtype on pathology), measure tumour markers monthly in year 1. Year 2: P/E, tumour markers, CXR every 3 months. CT abdomen and pelvis every 6 months. Year 3: P/E, tumour markers, CXR every 4 months. CT as clinically indicated. Years 4-5: P/E, tumour markers, CXR every 6 months. CT as clinically indicated. At the end of year 5, CT abdomen and pelvis. If pathologically node negative post-LN dissection, the risk of relapse in the abdomen is very low. CT of the abdomen may be done at decreased frequency at physician's discretion. Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner. Years 4-5 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner. Stage II Nonseminomas Follow-up Evaluation post chemotherapy or RPLND should include baseline restaging and then: Year 1: P/E, tumour markers, CXR every 2 months. CT every 4 months of area of known disease based on IGCCC risk group. Year 2: P/E, tumour markers, CXR every 3 months. CT every 6 months of area of known disease based on IGCCC risk group. Year 3: P/E, tumour markers, CXR every 4 months. CT as clinically indicated based on IGCCC risk group. Years 4-5: P/E, tumour markers, CXR every 6 months. CT as clinically indicated. At the end of year 5, CT abdomen and pelvis. Years 1-3 follow-up should be conducted in a cancer	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner. Years 4-5 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner. Stage III Nonseminomas Follow-up Post chemotherapy or surgical intervention should include baseline restaging and then: Year 1: P/E, tumour markers, CXR every 2 months. CT area of known disease every 4 months based on IGCCC risk group. Year 2: P/E, tumour markers, CXR every 3 months. CT area of known disease every 6 months based on IGCCC risk group. Year 3: P/E, tumour markers, CXR every 4 months. CT as indicated based on IGCCC risk group. Years 4-5: P/E, tumour markers, CXR every 6 months. CT as clinically indicated. At the end of year 5, CT abdomen and pelvis. Years 1-3 follow-up should be conducted in a cancer centre by an oncologist, family physician/general practitioner in oncology, clinical associate, or nurse practitioner. Years 4-5 follow-up can be conducted in the community by a family physician, clinical associate, or nurse practitioner.	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	NCCN 2015 65 Pkt / 40%		2a

Table 1 Clinical Stage I Seminoma: Surveillance after Orchiectomy

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 3–6 mo	Every 6–12 mo	Every 6–12 mo	Annually	Annually
Abdominal/ Pelvic CT	At 3, 6, and 12 mo	Every 6–12 mo	Every 6–12 mo	Every 12–24 mo	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

Table 2 Clinical Stage I Seminoma: Surveillance after Adjuvant Treatment (Chemotherapy or Radiatic

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 6–12 mo	Every 6–12 mo	Annually	Annually	Annually
Abdominal/ Pelvic CT	Annually	Annually	Annually	------	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Table 3 Clinical Stage IIA and Non-Bulky IIB Seminoma: Surveillance after Radiotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal/ Pelvic CT	At 3 mo, then at 6–12 mo	Annually	Annually	As clinically indicated	
Chest x-ray[3]	Every 6 mo	Every 6 mo	------		

Table 4 Bulky Clinical Stage IIB and Stage III Seminoma: Surveillance Post-Chemotherapy with No I and Normal Tumor Markers

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[2]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT[4]	• Abdominal/pelvic CT at 3–6 months, then as clinically indicated • PET scan as clinically indicated				
Chest x-ray[3]	Every 2 mo[5]	Every 3 mo[5]	Annually	Annually	Annually

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Table 5 Clinical Stage IA, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Every 4–6 mo	Every 6–12 mo	Annually	---	---
Chest x-ray[2]	At mo 4 and12	Annually	Annually	Annually	Annually

Table 6 Clinical Stage IB, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Every 4 mo	Every 4–6 mo	Every 6 mo	Annually	---
Chest x-ray[2]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Table 7 Clinical Stage IB NSGCT: Treated with 1–2 Cycles of Adjuvant BEP Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 3 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Annually	Annually	---	---	---
Chest x-ray[2]	Every 6–12 mo	Annually	---	---	---

Table 8 Clinical Stage II-III NSGCT: Surveillance After Complete Response to Chemotherapy ± Post-chemotherapy RPLND

	Year (at month intervals)				
	1	2	3	4	5
H&P and marker[1]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal/ Pelvic CT[3]	Every 6 mo	Annually	---	---	---
Chest x-ray[2,4]	Every 6 mo	Every 6 mo	Annually[5]	Annually[5]	---

If Recurrence, see TE

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Table 9 Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and Treated with Adjuvant Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 6 mo	Every 6 mo	Annually	Annually	Annually
Abdominal/ Pelvic CT	After RPLND	As clinically indicated			
Chest x-ray[2]	Every 6 mo	Annually	Annually	Annually	Annually

If Recu

Table 10 Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and NOT Treated with Adjuvant Chemotherapy[6]

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	At 3–4 mo[7]	As clinically indicated			
Chest x-ray[2]	Every 2–4 mo	Every 3–6 mo	Annually	Annually	Annually

If Recurrence,

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AMSTAR-Bewertung bei Systematic Reveiws (SR)</th><th>Fazit/Schlussfolgerung // Empfehlung/Inhalt</th><th>Empfehlungs-grad bei Leitlinien
oder
Level of Evidence (LoE) bei Systematic Reviews</th></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>EAU 2016
81 Pkt / 50%</td><td>Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma
<table>
<tr><td></td><td colspan="3">Year</td></tr>
<tr><td>Procedure</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Physical examination</td><td>4 times</td><td>4 times</td><td>4 times</td></tr>
<tr><td>Tumour markers</td><td>4 times</td><td>4 times</td><td>4 times</td></tr>
<tr><td>Plain radiography chest</td><td>Twice</td><td>Twice</td><td>Twice</td></tr>
<tr><td>Abdominopelvic CT</td><td>Twice at 3 and 12 months</td><td>Once at 24 months</td><td>Once at 36 months</td></tr>
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AMSTAR-Bewertung bei Systematic Reveiws (SR)</th><th>Fazit/Schlussfolgerung // Empfehlung/Inhalt</th><th>Empfehlungs-grad bei Leitlinien
oder
Level of Evidence (LoE) bei Systematic Reviews</th></tr>
<tr><td></td><td></td><td>CT = computed tomography

Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma
<table>
<tr><td></td><td colspan="4">Year</td></tr>
<tr><td>Procedure</td><td>1</td><td>2</td><td>3</td><td>4-5</td></tr>
<tr><td>Physical examination</td><td>4 times</td><td>4 times</td><td>4 times</td><td>Once/year</td></tr>
<tr><td>Tumour markers</td><td>4 times</td><td>4 times</td><td>4 times</td><td>Once/year</td></tr>
<tr><td>Plain radiography chest</td><td>Twice</td><td>Twice</td><td>Twice</td><td></td></tr>
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Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Abdominopelvic CT	Once	Once	Once	Once/year

CT = computed tomography.

Recommended minimum follow-up schedule for post-orchiectomy surveillance, radiotherapy or chemotherapy: stage I seminoma

	Year		
Procedure	1	2	3-5
Physical examination	3 times	3 times	Once/year
Tumour markers	3 times	3 times	Once/year
Plain radiography chest	Twice	Twice	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Abdominop elvic CT	Twice	Twice	at 36 and 60 months

CT = computed tomography.

Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

	Year		
Procedure	1	2	3-5
Physical examination	4 times	4 times	Twice/year
Tumour markers	4 times	4 times	Twice/year
Plain radiography chest	4 times	4 times	Twice/year

<table>
<tr><th>Themen gebiet</th><th>Quelle
AGREE-Bewertung bei Leitlinien (XY Pkt / XY%)
AMSTAR-Bewertung bei Systematic Reveiws (SR)</th><th>Fazit/Schlussfolgerung // Empfehlung/Inhalt</th><th>Empfehlungs-grad bei Leitlinien
oder
Level of Evidence (LoE) bei Systematic Reviews</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Abdominopelvic CT*</td><td>Twice</td><td>Twice</td><td>Once/year</td></tr>
<tr><td>Chest CT†‡</td><td>Once/year</td><td>Once/year</td><td>Once/year</td></tr>
<tr><td>Brain CT§</td><td>Once/year</td><td>Once/year</td><td>Once/year</td></tr>
</table>
CT = computed tomography.

* An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.

† If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT

should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDGPET/

CT can be performed.

‡ A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.

§ In patients with headaches, focal neurological findings, or any central nervous system symptoms.
</td><td></td></tr>
<tr><td></td><td>ESMO 2013</td><td>Follow-up</td><td></td></tr>
</table>

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
	55 Pkt / 34%	Early detection and treatment of relapse represents the primary objective of follow-up visits during the first 5–10 years. Recommendations for the follow-up schedule need to be adapted according to national and institutional requirements. Many follow-up recommendations that have been published most likely expose TGCT survivors to unnecessary radiation, increasing the risk of a radiation-induced second cancer. Replacing CT by MRI scan would reduce this risk, but is not considered feasible for the majority of European countries. However, effort should be made to reduce the frequency of CT scans and limit their overall number. PET-CT scanning has no role in the routine follow-up of TGCT patients.	
		salvage treatment of seminoma and non-seminoma	C /IV
		Conclusive recommendations as to an optimal salvage approach in patients relapsing after cisplatin-based first-line treatment cannot be made at present. The prognosis of relapsing GCC patients is variable as shown by the 'International Prognostic Factor Study Group' who categorised 1594 relapsing GCC patients into five prognostic groups, with 2-year survival rates ranging from 75% (very low risk) to 6% (very high risk), Table 3	
		The same group demonstrated superior survival rates for patients treated with high-dose chemotherapy [n = 812, 51.2% 5-year overall survival (OS)] compared with conventional dose chemotherapy (n = 773, 5-year OS 42.8)	C / IV
		The retrospective nature of this study limits its conclusive power, such that an international prospective study randomising relapsing patients to either four cycles of paclitaxel, ifosfamide cisplatin (TIP) or high-dose chemotherapy with three cycles of paclitaxel, ifosfamide, carboplatin and etoposide (TI-CE) is under preparation. In 2005, Pico et al. reported on 280 relapsing TC patients randomised to either four cycles of cisplatin, ifosfamide and etoposide/vinblastine or three such cycles followed by high-dose carboplatin,	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		etoposide and cyclophosphamide (CarboPEC) with haematopoietic stem cell support without significant differences of OS or progression-free survival (PFS)	D / II
		Alternative conventional dose cisplatin-based regimens with similar efficacy comprise TIP, VeIP (vinblastine, ifosfamide, cisplatin) or VIP/PEI (etoposide, ifosfamide, cisplatin). Carboplatinbased high-dose chemotherapy has been reported to achieve complete remissions in relapsing patients as third line or later and is the preferred option of some authorities, despite absence of randomised trials in this area.	B/III
		In refractory patients, i.e. those not reaching a markernegative complete response after first-line treatment or those without favourable response to salvage treatment, further treatment must be individualised by GCT experts	B/V
		These patients should be included in clinical trials, if available. Surgery should be part of the strategy whenever possible, particularly in those patients with localised or late relapse, and with poor response to chemotherapy.	
	SIGN 2011 132 Pkt / 82%	Patients who undergo surveillance or adjuvant therapy for stage I seminoma should be followed up according to protocols which take into account the likely site and timing of first relapse to define the frequency of clinic visits, blood tests and radiology investigations. This should include cross-sectional imaging of the abdomen in patients under surveillance and after adjuvant carboplatin, and chest imaging in all patients. Cross-sectional imaging of the pelvis may also be indicated in selected patients (eg after para-aortic radiotherapy alone, or where the risk of pelvic nodal disease is considered to be elevated).	B

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Table 7: Suggested follow-up protocol for stage I seminoma post-treatment

STRATEGY	Year 1	Year 2	Year 3	Year 4	Year 5	Years 6-10
Surveillance	3-monthly clinic visit*	3-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	annual clinic visit
	6-monthly CT of abdomen§	6-monthly CT of abdomen§	annual CT of abdomen§	annual CT of abdomen§		
Adjuvant para-aortic nodal RT	3-monthly clinic visit*	3-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	discharge from clinic
	annual CT of pelvis	annual CT of pelvis	annual CT of pelvis			
Adjuvant 'dog-leg' RT	3-monthly clinic visit*	3-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	discharge from clinic
Adjuvant carboplatin	3-monthly clinic visit*	3-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	annual clinic visit
	annual CT of abdomen§	annual CT of abdomen§	annual CT of abdomen§			

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Table 8: Suggested follow-up protocol for stage I post orchidectomy low-risk NSGCT

STRATEGY	Year 1	Year 2	Year 3	Year 4	Year 5	Years 6-10
Surveillance	monthly clinic visit*	2-monthly clinic visit*	3-monthly clinic visit*	4-monthly clinic visit*	6-monthly clinic visit*	annual clinic visit
	CT scan of abdomen at 3 and 12 months§	Consider stopping in uncomplicated cases				
Adjuvant chemotherapy	monthly clinic visit* for 6 months, then 2-monthly for 6 months	3-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	annual clinic visit*
	CT of chest, abdomen after adjuvant treatment and if CT appears normal, no further routine CT scans.					

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews

Table 9: Suggested follow-up protocol for metastatic seminoma (postradiotherapy for stage IIA/B, postchemotherapy for stages II-IV)

STRATEGY	Year 1	Year 2	Year 3	Year 4	Year 5	Years 6-10
After radical radiotherapy or chemotherapy	3-monthly clinic visit*	3-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	6-monthly clinic visit*	annual clinic visit*
	If post-treatment CT abdomen and pelvis scan is normal, no further routine CT scans. If post-treatment CT scan is abnormal, repeat the CT scan every six months for 18 months but stop as soon as CT scan is normal or appearance is stable.					

* each clinic visit involves an assessment of symptoms, clinical examination, chest X-ray and tumour markers (AFP and HCG): LDH has not been shown to be helpful in the follow up in patients with germ cell tumours (*see section 4.2*);

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		Table 10: Suggested follow-up protocol for metastatic NSGCT **STRATEGY** / **Year 1** / **Year 2** / **Year 3** / **Year 4** / **Year 5** / **Years 6-10** **After chemotherapy (+/- resection of residual masses)** / monthly clinic visit* for 6 months, then 2-monthly for 6 months / 3-monthly clinic visit* / 6-monthly clinic visit* / 6-monthly clinic visit* / 6-monthly clinic visit* / annual clinic visit* CT of chest, abdomen after treatment and if CT appears normal, no further routine CT scans. If post-treatment CT is abnormal, then ongoing imaging of the area of abnormality is required. * each clinic visit involves an assessment of symptoms, clinical examination, chest X-ray and tumour markers (AFP and HCG): LDH has not been shown to be helpful in the follow up in patients with germ cell tumours (*see section 4.2*);	
	KCE 2010 115 Pkt / 79%	In patients with stage I seminoma under primary surveillance, physical examination and blood serum marker tests (AFP, HCG, LDH) should be conducted every 3 months in the first and second years, and every six months in the third, fourth and fifth years	expert opinion
		Although the evidence is insufficient to propose a standard scheme for CT follow-up in patients with stage I seminoma under primary surveillance, at least an abdomeno-pelvic CT every 6 months during the 2 first years postorchidectomy is desirable.	expert opinion
		In patients with stage I non-seminoma under primary surveillance, physical examination and blood serum marker tests (AFP, HCG, LDH) should be conducted every month in the first year, every two months in the second year,	expert opinion

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		every three months in the third year, and every six months in the fourth and fifth years. Although the evidence is insufficient to propose a standard scheme for CT follow-up in patients with stage I non-seminoma under primary surveilance, at least an abdomino-pelvic CT at 3 and 12 months is recommended. In patients treated with chemotherapy or radiotherapy post-orchidectomy or as primary treatment, physical examination and blood serum marker tests (AFP, HCG, LDH) should be conducted every 3 months in the first and second years, and every six months in the third, fourth and fifth years. There is insufficient evidence to define a standard scheme for CT follow-up in patients with advanced stage testicular germ cell cancer (expert opinion). Ultrasonography of the contralateral testis can be considered during the follow-up of patients with testicular germ cell cancer.	2B expert opinion expert opinion
Treatment of relapsing or refractory disease			
	KCE 2010 115 Pkt / 79%	Patients with relapsing or refractory GCT should be enrolled in clinical trials when available. · In patients with testicular GCT relapsing after cisplatin-based first-line chemotherapy, high-dose chemotherapy with autologous bone marrow support is not recommended outside a clinical trial.	expert opinion 1A
	ESMO 2013 55 Pkt / 34%	A late relapse occurs in 2%–3% of survivors and is defined as new tumour growth >2 years after at least three cycles of preceding chemotherapy. These	C / IV

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		relapses do not respond so well to new chemotherapy (often yolk sac tumour, usually AFPpositive, or slow-growing teratoma). In particular, in marker-negative relapses histological assessment of the relapsing lesions should be carried out by radical surgical resection of all lesions, if technically feasible. Further chemotherapy must be individualised based on the histology of the late relapse and tumour marker development. If salvage chemotherapy is the first treatment option of a late relapse, radical post-chemotherapy surgery should be conducted whenever possible.	
Langzeittoxizität			
	EAU 2016 81 Pkt / 50%	The vast majority of patients will be cured and 5-year relative survival rates approximate 95% in Western Europe. Furthermore, TC patients are usually between 18 and 40 years at diagnosis such that life expectancy after cure extends over several decades. Patients should be informed before treatment of common longterm toxicities, which are probably best avoided by adherence to international guidelines. Treatment of stage I TC is controversial with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy, whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with its known long-term toxicities as quite appealing. Unfortunately, it is not known which treatment spares most patients long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy. During follow-up, patients should be screened and treated for known risk factors such as high blood pressure, hyperlipidaemia and testosterone deficiency. When follow-up by the TC expert is discontinued, a written cancer survivorship plan addressing late toxic effects,	

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		lifestyle recommendations, recurrence risk, and cancer-specific follow-up might be helpful. The following overview is not complete and interested readers are referred to review articles on this topic. Second malignant neoplasms (SMN), Leukaemia, Infections, Pulmonary complications, Cardiovascular toxicity, Raynaud-like phenomena, Neurotoxicity, Ototoxicity, Nephrotoxicity, Hypogonadism, Fatigue.	
	SIGN 2011 132 Pkt / 82%	Oncologists should advise survivors of testicular cancer and their GPs of the increased risk of cardiovascular disease. GPs should reinforce advice to survivors of testicular cancer on prevention of cardiovascular disease as outlined in SIGN 97. Survivors of testicular cancer should be advised not to smoke. Oncologists should advise patients and their GPs of the increased risk of non-germ cell second malignancies. It should be noted that the risks are greatest for those treated before age 30 years. Increased risks continue beyond 15 years following treatment. General health advice should be reinforced, particularly avoidance of smoking, and patients should be encouraged to maintain a healthy diet and level of physical activity in order to reduce cancer risk (see also section 2 of SIGN 67: Management of Colorectal Cancer). Patients should remain vigilant of any unusual or alert symptoms, particularly relating to the gastrointestinal, respiratory or urinary tract, and report these promptly to their GPs. There should be increased awareness of the risk of haematological malignancies especially after chemotherapy and solid malignancies in or near	best practice Best practice C Best practice

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		the fields of radiotherapy. There should be a low threshold for further investigation and appropriate referral to secondary care if any alert symptoms are reported. Annual urinalysis for haematuria may be considered.	
	ESMO 2013 55 Pkt / 34%	Besides early detection of relapse, follow-up should be directed towards prevention, detection and treatment of late toxicity for the increasing number of GCC survivors. Semen cryopreservation should be considered in each patient. Compared with the general population the 10-year posttreatment paternity rate is significantly reduced, in part due to pre-existing fertility problems. Nevertheless, the 15-year fatherhood rate among testicular cancer survivors wishing to father a child is ~70%, with a strong association with treatment intensity [IV, B] [25]. Hypogonadism is present in 11%–35% of TGCT survivors, depending on cut-off levels of testosterone used, age, cumulative cisplatin dose and follow-up duration. Therefore, determination of testosterone levels is recommended during follow-up, although it is not always clear when and at what testosterone level replacement should be offered. Compared with the general population, there is about a twofold increased risk of late post-chemotherapy cardiovascular disease (coronary heart disease, myocardial infarction, congestive heart failure and stroke) among TGCT survivors. Early-onset (starting 3–5 years after treatment) metabolic syndrome occurs in about 20%–30% of long-term survivors. Therefore, survivors need to be counselled on a healthy lifestyle (no smoking, regular physical exercise) and screened for other known risk factors such as hypertension, dyslipidaemia and excessive weight gain. Pulmonary and renal toxicity, oto- and neurotoxicity are further dose-related sequelae. The relative risk (RR) of a second solid non-germ cell tumour, particularly in the gastro-intestinal and urinary tract, is approximately doubled after radiotherapy (latency ≥10 years) and is probably also increased after chemotherapy. The estimated	C/IV

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
		cumulative risk of leukaemia depends on the cumulative etoposide dose and occurs earlier in the course of follow-up, i.e. usually <10 years.	
	DUVAL M, 2012 Meta-analysis of the efficacy of amifostine in the prevention of cisplatin ototoxicity. SR (5/11)	This meta-analysis reveals toward decreased ototoxicity in patients receiving amifostine infusion prior to receiving cisplatin chemotherapy. However, the results did not reach statistical significance.	1a
	LINDNER OC, 2014 A meta-analysis of cognitive impairment following adult cancer chemotherapy. SR (7/11)	The likelihood to identify impairments rests on the type of design employed, as memory and attention impairments are only detected in cross-sectional studies.	Keine Einstufung auf ein Level * *Longitudinal studies waren eingeschlossen, jedoch gab es keine Schluss-folgerungen aufgrund der enormen Heterogenität der Studien, UND es gibt kein Level für cross-sectional studies
	LYMAN GH, 2010 Acute myeloid leukaemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: A systematic review. SR (7/11)	Delivered chemotherapy dose-intensity and risk of AML/MDS are increased but all-cause mortality is decreased in patients receiving chemotherapy with G-CSF support. Greater reductions in mortality were observed with greater chemotherapy dose-intensity.	1a

Themen gebiet	Quelle AGREE-Bewertung bei Leitlinien (XY Pkt / XY%) AMSTAR-Bewertung bei Systematic Reveiws (SR)	Fazit/Schlussfolgerung // Empfehlung/Inhalt	Empfehlungs-grad bei Leitlinien oder Level of Evidence (LoE) bei Systematic Reviews
Quality of Life			
	EAU 2016 81 Pkt / 50%	Quality of life (QoL) is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social and physical functions. When comparing three or four cycles of BEP in good risk patients, all outcomes favour treatment with three courses. After one and two years, one third of patients reported an improvement in global QoL after chemotherapy, while one fifth of patients reported deterioration, with no difference between treatment groups. In adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (5 year) QoL between RPLND or one course of BEP.	
	ESMO 2013 55 Pkt / 34%	Health-related quality of life in long-term TGCT survivors appears to be similar to the normal male population, but persisting long-term treatment-related side-effects show a strong association with both impaired physical and mental quality of life. Furthermore, anxiety levels are higher in GCC survivors than in the general male population. Perhaps most importantly, TGCT survivors and their family doctors should be adequately informed (verbally and using written information) about potential late toxicity and their prevention, both during and at the end of treatment and in the course of specialised follow-up.	

Anlage: Erläuterungen zum Grad der Empfehlungen

(#)**ASCO (American Society of Clinical Oncology)** Guideline nutzt keine Empfehlungsgrade

(*)**EAU (European Association of Urology**) nutzt die Classification of Oxford Centre for Evidence-Based Medicine Levels of Evidence für den Grad der Empfehlung und für den Level der Evidenz (LE) (GR)

CANCER CONTROL ALBERTA (Clinical practice guideline) Keine Angaben zu LoE, keine Angaben zum Grad der Empfehlung

(¥) **NCCN (National Comprehensive Cancer Network)** Kategorien der Empfehlungen:
The specific definitions of the NCCN categories for recommendations are included below:
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

(∞) **KCE (Kenniscentrum voor de Gesondheitszorg Brüssel, Belgien)** nutzt GRADE zur Klassifizierung der Empfehlungen Ia-c, 2a-c

SIGN (Scottish Intercooleguiate Guideline Network)
GRADES OF RECOMMENDATION
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.
A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

LEVELS OF EVIDENCE
1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 - Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High quality systematic reviews of case control or cohort studies, High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytic studies, eg case reports, case series

4 Expert opinion

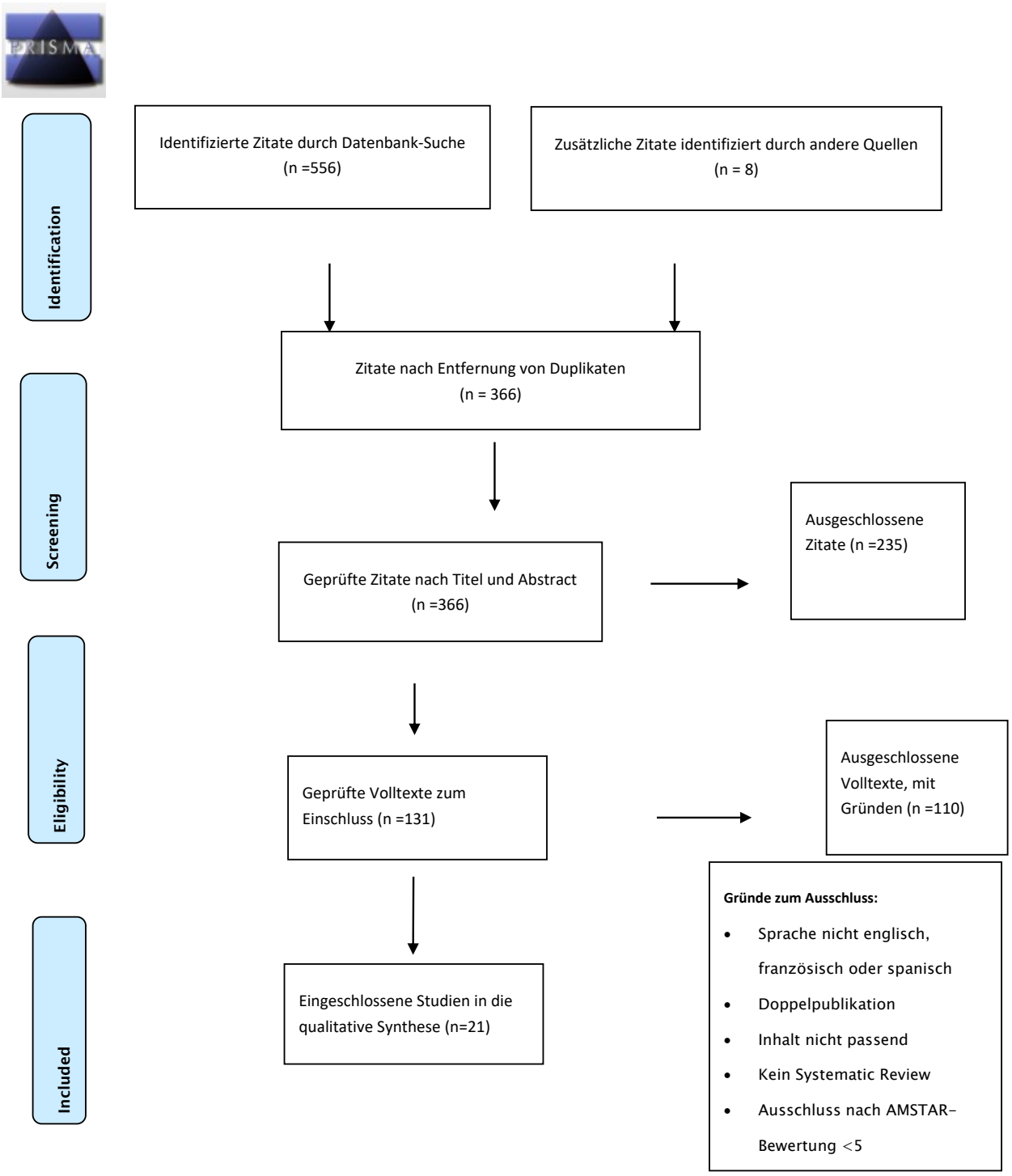
ESMO (European Society of Medical Oncology) Clinical practice guideline
Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service)

Levels of evidence
I Evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III Prospective cohort studies
IV Retrospective cohort studies or case–control studies
V Studies without control group, case reports, expert opinions

Grades of recommendation
A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs..,), optional
D Moderate evidence against efficacy or for adverse outcome, generally not recommended
E Strong evidence against efficacy or for adverse outcome, never recommended

Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

9.2. PRISMA-Flowchart Systematische Übersichtsarbeiten



9.3. Evidenztabelle Systematische Übersichtsarbeiten

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
Alam S 2010	7 observational studies case-control, retrospective Sweden, UK, USA, Ca, DK, Japan 1983-2008	no information about patient characteristics, inclusion criteria n=5322	Maternal weight: high vs normal BMI high: >25 oder >26 moderate/normal: BMI 18-25	High compared with normal maternal BMI is associated with a decrease in testicular cancer risk (OR = 0.82; 95% CI 0.65—1.02)	no information about coi	6/11 LOE: 3a
Balise VD 2016	45 studies, retrospective, cross sectional, case-control-studies Taiwan, USA, S, Ecuador, China, Brazil, France, Saudi Arabia, Canada, Australia	no information about patient characteristics, inclusion criteria total n=851.918 in studies with testicular cancer	Oil and natural gas extraction processes and human reproduction In detail:	Endpoint: reproductive cancer: testicular cancer no pooled analysis SIR* of 1.24 (95% CI 0.68 - 2.08)	National Institute of Health, University of Missouri	5/11 LOE: 3a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	1984-2015		[1] birth outcomes associated with maternal Exposure [2] semen quality, fertility, and birth outcomes associated with adult paternal exposure [3] reproductive Cancers [4] disruption of human sex steroid hormone Receptors	SIR of 1.33 (95% CI 0.80 - 2.08) no trend (p>0.1) SIR of 1.0 (95% CI 0.2 - 2.8) SIR of 0.82 (95% CI 0.45 - 1.37) SIR=standardized incidence ratio		
Bandak M 2016	retrospective no information about design of included studies	inclusion criteria: treated for TGCC (P), CT (regimens, cycles and doses),	Outcome: risk of Testosterone deficiency exper.	standard CT compared with patients treated with orchiectomy alone OR 1.8 (95% CI 1.3–2.5), (p = 0.0007) (I^2 = 2%)	no coi no information about funding	3/11

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	no information about countries 1986-2013	RT (fields and doses) (I), compared with orchiectomy alone (C). Follow-up-time: 2 months – 12 yrs total n=1.858 patients total n=11 studies	orchiectomy + standard CT control: orchiectomy alone exper. compared orchiectomy + non-conventional therapy control: orchiectomy alone exper. orchiectomy + RT control orchiectomy alone	non-conventional therapy compared with orchiectomy alone OR 3.1 (95% CI 2.0–4.8), (p < 0.0001) (I^2 = 12%) infradiaphragmatic RT compared with orchiectomy alone OR 1.6 (95%CI 1.0–2.4), (p = 0.03) (I^2 = 0%)		LoE nicht eindeutig festzulegen, da keine Angaben zu Designs der eingeschlossenen Studien
Banks K 2013	147 studies Case-control, cohort studies	no information about patient characteristics, inclusion criteria	History of cryptorchidism vs.	History of CO is associated with fourfold increased TGCT risk	Grants California Cancer	8/11

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	Retrospective, prospective USA, Canada, England, Denmark, Greece, Germany, Sweden, France, Czech rep, Norway, Netherlands, Ireland, Australia, Japan 1971-2008	Total n=27.558	no history of cryptorchidism	RR = 4.1 (95% CI = 3.6–4.7). Subgroup analyses identified five determinants of stronger association: bilateral CO, unilateral CO ipsilateral to TGCT, delayed CO treatment, TGCT diagnosed before 1970, and seminoma histology.	Research Program, National Cancer Institute, Whittier Foundation to the Norris Comprehensive Cancer Center.	LOE 2a-3a
Beranger R 2013	retrospective Cohort, case control, ecological study, cluster USA, Brazil, Norway, Germany, France, UK, Sweden, Italia, Denmark, Canada, Iceland, Netherland, Bulgaria,	inclusion criteria: Age: no limits Diagnostic periods: 1943-2008 publication period: 1990-2012	Occupational, environmental exposures and TGCT: Industrial exposure White-collar workers, professionals and higher social-economic status	no results with effect estimates provided no pooled analysis conclusion: Current evidence does not allow concluding on existence of any clear association between TGCT	no coi Funding: French national cancer institute, Public funding, Cancéropole CLARA	4/11 LoE 2a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	Ireland, Finland, Australia, New Zealand, 1990-2012	included patients: Total n=12.395.623* In cohort studies Total n=839.080* Cases n=12.311* Controls n=826.769* In case-control-studies included studies: n=72 *=Eigenberechnung	Construction and related occupations Firemen, policemen and military workers Farmers, agricultural workers and occupational exposures to pesticides Magnetic and electric field exposure Organochlorines, pesticides Leather working, food processing, cleaning agents, disinfectant, insecticides, Parental exposure Agriculture-related	and adulthood occupational or environmental exposure. Despite of the numerous factors investigated in many studies, the reasons for the rapid increase of TGCT incidence remain unclear. Occupational exposures during adulthood are unlikely to be involved in TGCT aetiology because of the young age of patients.		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
Bozcuk H 2011	retrospective trials, prospective trials RCT, non randomised trials 1994-2007 no information about countries Single-centre and multi-centre-studies	Median age (24-37,4) Total n=2176 no information about follow-up	Identification of prognostic factors: Treatment, patient disease, trial features NED (no evidence of disease) OAS	multivariate analysis: Publication year: Survival with NED: ß=0.40 t=3.55 P=0.001 Cisplatin Refractory Fraction* Survival with NED: β=-0.43 t= -3.77 P=0.001	no information about funding and coi	0/11 LoE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				Poor Risk Fraction* Survival with NED: β=0.15 t=1.08 P=0.288 HDC cycles administered (1 vs. 1 to 2 vs. ?2 cycles) Survival with NED: β=0.42 t=3.88 P=0.001 OAS: β=0.20 t=2.46 P=0.021		

Referenz (Autor, Jahr)	**Studiendesigns in den SR/MA: Land, Zeitraum**	**Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up**	**Intervention Zielgröße/Outcome**	**Hauptergebnisse und Richtung (direction)**	**Finanzierung/ Interessen-konflikte**	**AMSTAR Bewertung Evidenz-stufe LoE**
				Line of Chemotherapy Index* Survival with NED β=-0.26 t=-1.24 P=0.224 OAS: β=-0.18 t=-10.44 P=<0.001		
Calabro F 2012	prospective RCT retrospective no information about countries	no information about patient characteristics total n=4988* *=Eigenberechnung	CR complete response OS Overall survival DFS disease free survival	no pooled analysis conclusion: Currently, three cycles of the BEP regimen remain the standard treatment of good-risk metastatic GCTs, and four cycles of the same regimen are the best option	no coi no information about funding	1/11 LoE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	1987-2010	no information about time period		for patients with intermediate- and poor-prognosis tumours. Four cycles of EP and four cycles of VIP can be used in patients with good and intermediate-to-poor prognosis at high risk of developing bleomycin-induced pulmonary toxicity. At the present time, there is no established role for HDCT in the firstline setting of patients with poor prognosis. Patients with recurrent or refractory disease have a poor prognosis.		
Chan E 2014	retrospective prospective non – RCT, RCT study period: 1950-2008	no information about patient characteristics total n= 3776* no information about countries	timing of orchiopexy outcomes: fertility	no pooled analysis conclusion: fertility: Orchiopexy should be performed after 6 months of age, to allow for possible natural descent. If the testis remains cryptorchid after 6	no information about coi and funding	4/11 LoE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	no information about countries	*=Eigenberechnung	testicular malignancy	months, orchiopexy should be performed as soon as possible—and certainly before 1 year of age—to optimize fertility outcomes testicular malignancy risk for cancer is greatly increased when orchiopexy is delayed until after 10–11 years in cryptorchid boys to protect against the increased risk of testicular cancer, we recommend that orchiopexy should be performed as early as possible (ideally between 6 and 12 months of age, as this would also optimize fertility potential)		
Chung P 2010	RCT, non-randomised studies of treatment, non-randomised long-term-toxicity studies	no information about patient characteristics, inclusion criteria	Survival, recurrence, relapse-free survival, long-term toxicity including	no pooled analysis RCT: Radiation therapy:	no information about coi and funding	5/11 LOE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	Keine Verblindung in den RCT no information about countries 1990 – 2008	RCT Total n=2580 n IG=? Non-randomised trials Total n=10.002 n=6.401 n=3.601 IG	second malignancy, quality of life	Relapse free- survival at 2 bzw. 3 years: 95,9% - 97,7% Non-randomised trials: Radiation therapy: OS: 95%-100% Surveillance: OS at 5 ys 97,1%-100 At 10 ys 94.4% At 15 ys 86%% Carboplatin: OS At 4,5 ys 94%-100% Second malignancy RR 1.9 among 10 ys-survivors		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				Second tumor in the radiation field: RR 2.0 (CI 1.6-2.7) oder 3.4 (CI 2.5-4.6) Cardiac events: Radiation therapy vs. surveillance RR 2.74 (CI 1.23-6.08) OS at 10, 20 , 30 ys 93% (CI 90-95%), 79% (CI 74-84%), 59% (CI 50-67%) Quality of life Vergleich radiation vs. carboplatin-therapy: better QoL at month 1 in 11 domains, at month 4 in two domains and at month 12 in five domains Conclusion:		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				Surveillance seems to be the preferable option, as this strategy minimises the toxicity that might be associated with adjuvant treatment, while preserving high cure rates.		
Chung P 2011	RCT, Cohort studies, SR von RCT prospective 1988-2010	kA KA total n=8.015 RCT n=5540 Cohort studies	Mortality, cure rates, relapse rate, including relapse-free survival, quality of life, adverse effects of treatment	no pooled analysis Leading question: What are the effects of treatments in *men with stage 1 seminoma* (confined to testis) who have undergone orchidectomy? Adjuvant radiotherapy vs. adjuvant chemotherapy: Relapse rates: Adjuvant radiotherapy compared with adjuvant chemotherapy Adjuvant radiotherapy does not increase the rate of relapse-	no information about coi and funding	5/11 LOE 1a-2b

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
		n=224 SR n=2251		free survival at 2 to 5 years in men with stage 1 seminoma, compared with adjuvant chemotherapy (high quality evidence). Adverse effects: Siehe Tabelle in Publikation 11 beschriebene Effekte Surveillance Relapse rates: Surveillance compared with adjuvant radiotherapy Surveillance may be less effective than adjuvant radiotherapy at 5 years at reducing relapse rates in men who have undergone orchidectomy for stage 1 seminoma (very low-quality evidence).		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				Adverse effects: Siehe Tabelle in Publikation 5 beschriebene Effekte Surveillance versus adjuvant chemotherapy in men who have undergone orchidectomy: Relapse rates Surveillance compared with adjuvant chemotherapy Surveillance may be less effective than adjuvant chemotherapy at reducing relapse rates in men who have undergone orchidectomy for stage 1 seminoma (low-quality evidence Adverse effects: Siehe Tabelle in Publikation 5 beschriebene Effekte		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				OPTION DIFFERENT ADJUVANT RADIOTHERAPY REGIMENS. Relapse rates Para-aortic strip compared with para-aortic plus ipsilateral iliac lymph node irradiation Para-aortic strip (restricted) irradiation is as effective as para-aortic plus ipsilateral iliac lymph node irradiation at 3 years in men who have undergone orchidectomy for stage 1 seminoma (high-quality evidence). Note: Toxicity increases with increases in irradiation field. Adverse effects: Men receiving para-aortic irradiation had less severe and less frequent acute toxicities such as nausea,		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				vomiting, and leukopenia than did men receiving para-aortic plus ipsilateral iliac lymph node irradiation, and had higher sperm counts at 18 months (no further data reported) Secondary malignancies (adenocarcinoma or non-seminomatous testicular tumours) 2/478 (0.4%) with para-aortic strip (restricted field) irradiation (30 Gy in 15 fractions for 3 weeks) 1/478 (0.2%) with para-aortic strip plus ipsilateral iliac lymph node (traditional field) irradiation (30 Gy in 15 fractions for 3 weeks)		

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				20 Gy adjuvant radiotherapy versus 30 Gy adjuvant radiotherapy: Relapse rates 20 Gy compared with 30 Gy irradiation 20 Gy irradiation in 10 fractions is as effective as 30 Gy irradiation at reducing relapse rates at 61 months in men who have undergone orchidectomy for stage 1 seminoma (high-quality evidence). Note: Toxicity increases as dose increases DIFFERENT ADJUVANT CHEMOTHERAPY DRUG COMBINATIONS. Relapse rates One cycle compared with two cycles of carboplatin One cycle of carboplatin may be as effective as 2 cycles at		

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				reducing relapse rates at 2 years (low-quality evidence). Mortality One cycle compared with two cycles of carboplatin We don't know whether 1 cycle of carboplatin reduces mortality rates at 9 years compared with 2 cycles (very low-quality evidence). SRM 0.89 (CI 0.36-1.83) Adverse effects Myelotoxicity A low myelotoxicity rate was found, and suggested that carboplatin was associated with low gonadal toxicity. The cohort study did not compare rates of myelotoxicity between 1 and 2 cycles-		

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				Absolute results not reported. Leading question: What are the effects of treatments in men *with good-prognosis non-stage 1 seminoma* who have undergone orchidectomy? CHEMOTHERAPY USING ETOPOSIDE PLUS CISPLATIN (WITH OR WITHOUT BLEOMYCIN). Relapse rates Etoposide plus cisplatin compared with etoposide plus carboplatin Etoposide plus cisplatin may increase relapsefree survival rates at about 2 years in men with good-prognosis non-stage 1 seminoma or non-seminoma, compared with etoposide		

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				plus carboplatin (low-quality evidence). Absolute results reported graphically. Mortality Etoposide plus cisplatin compared with etoposide plus carboplatin Etoposide plus cisplatin and etoposide plus carboplatin may be equally effective for increasing overall survival in men with good-prognosis non-stage 1 seminoma or non-seminoma (low-quality evidence). Absolute results reported graphically. Overall survival , median 22.4 months, P = 0.52 Adverse effects		

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				The RCT found that etoposide plus cisplatin was associated with In review [9] significantly less anaemia (P = 0.005), thrombocytopenia (P <0.005), and neutropenia (P = 0.004) than etoposide plus carboplatin. Etoposide plus cisplatin plus bleomycin versus etoposide plus cisplatin: Relapse rates Etoposide plus cisplatin plus bleomycin compared with etoposide plus cisplatin Etoposide plus cisplatin plus bleomycin may reduce relapse rates at about 4 years in men with good-prognosis non-stage 1 seminoma, teratoma, or mixed tumours, compared with etoposide plus cisplatin alone (very low-quality evidence).		

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				Relapse rates , median 4.1 years 8/81 (10%) with etoposide plus cisplatin plus bleomycin 17/75 (23%) with etoposide plus cisplatin Mortality Etoposide plus cisplatin plus bleomycin compared with etoposide plus cisplatin Etoposide plus cisplatin plus bleomycin may increase survival rates at 3 years in men with good-prognosis non-stage 1 seminoma and non-seminoma, compared with etoposide plus cisplatin alone (very low-quality evidence). Survival, 3 years P = 0.01 95% with etoposide plus cisplatin plus bleomycin		

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				86% with etoposide plus cisplatin Adverse effects Drug-related mortality The RCT found that 2 people receiving additional bleomycin and one person receiving etoposide plus cisplatin had drug-related mortality. Two-drug regimen versus five-drug regimen : Relapse rates Two-drug compared with five-drug regimen A 2-drug regimen of etoposide plus cisplatin may be as effective as a 5- drug regimen of cisplatin plus vinblastine plus bleomycin plus cyclophosphamide plus dactinomycin in reducing		

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				relapse rates at 5 years in men with good-prognosis non-stage 1 seminoma, teratoma, or mixed tumours, and may reduce toxicity (very low-quality evidence). Mortality Two-drug compared with five-drug regimen A 2-drug regimen of etoposide plus cisplatin may be as effective as a 5- drug regimen of cisplatin plus vinblastine plus bleomycin plus cyclophosphamide plus dactinomycin in increasing overall survival at 5 years in men with good-prognosis non-stage 1 seminoma, teratoma, or mixed tumours, and may reduce toxicity (very low-quality evidence). Adverse effects		

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				The RCT found that etoposide plus cisplatin reduced toxicity compared with cisplatin plus vinblastine plus bleomycin plus cyclophosphamide plus dactinomycin (emesis: P = 0.05; mucositis: P = 0.06). CHEMOTHERAPY USING VINBLASTINE PLUS CISPLATIN PLUS BLEOMYCIN. Relapse rates Bleomycin plus vinblastine plus cisplatin compared with cisplatin plus vinblastine alone Adding bleomycin to 2-drug regimens containing vinblastine plus cisplatin seems more effective at 4 years at reducing relapse rates, in men with non-stage 1 good-prognosis tumours, than cisplatin plus vinblastine alone (moderate-quality evidence).		

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				Mortality Bleomycin plus vinblastine plus cisplatin compared with cisplatin plus vinblastine alone Adding bleomycin to 2-drug regimens containing vinblastine plus cisplatin reduces tumour-related mortality at 4 years, in men with non-stage 1 good-prognosis tumours, compared with cisplatin plus vinblastine alone (moderate-quality evidence). Adverse effects: Treatment-related mortality 6/110 (5%) P = 0.06 with adding bleomycin to vinblastine plus cisplatin 1/108 (1%) with cisplatin plus vinblastine alone.		

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				ADDING HIGHER COMPARED WITH LOWER DOSES OF CISPLATIN OR VINBLASTINE TO A TWO-DRUG CHEMOTHERAPY REGIMEN. Cure rates Higher-dose cisplatin compared with lower-dose cisplatin Adding higher-dose cisplatin to vinblastine-plus-bleomycin regimens may increase cure rates at 1 year in men with good-prognosis non-stage 1 seminoma, teratoma, or nonseminoma, compared with adding lower-dose cisplatin (very low-quality evidence). Adverse effects Thrombocytopenia , 1 year The RCT found that less than 10% of people in both groups had severe thrombocytopenia.		

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				Adding higher versus lower doses of vinblastine to two-drug regimens: Cure rates Higher-dose vinblastine compared with lower-dose vinblastine Adding higher-dose vinblastine to cisplatin-plusbleomycin regimens may not increase complete remission rates at 1 year in men with good-prognosis non-stage 1 seminoma, teratoma, or non-seminoma, compared with adding lower-dose vinblastine (very low-quality evidence). Adverse effects Leukocytopenia, Granulocytopenic fever		

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				THREE VERSUS FOUR CYCLES OF CHEMOTHERAPY. Relapse rates Three cycles compared with four cycles of chemotherapy. We don't know whether 3 cycles of chemotherapy increases relapse rates or relapse-free survival in men with both seminomas and non-seminomas compared with 4 cycles, but 3 cycles may cause less toxicity (low-quality evidence). Mortality Three cycles compared with four cycles of chemotherapy We don't know whether 3 cycles of chemotherapy may increase progression-free or overall survival rates in men with both seminomas and non-seminomas compared with 4 cycles, but 3 cycles		

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				may cause less toxicity (low-quality evidence) Adverse effects 5 Effekte warden beschrieben CHEMOTHERAPY USING SINGLE-AGENT CARBOPLATIN VERSUS COMBINED CHEMOTHERAPY REGIMENS. Relapse rates Single-agent compared with combined chemotherapy. We don't know whether single-agent carboplatin reduces relapse rates compared with combined chemotherapy regimens (very low-quality evidence). Mortality		

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				Single-agent compared with combined chemotherapy We don't know whether single-agent carboplatin reduces mortality compared with combined chemotherapy regimens at 2 years (low-quality evidence). Leading question: What are the effects of maintenance chemotherapy in men who are *in remission after orchidectomy and chemotherapy for good-prognosis non-stage 1 seminoma?* MAINTENANCE CHEMOTHERAPY. Relapse rates Maintenance chemotherapy compared with no maintenance chemotherapy Maintenance chemotherapy		

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				may not reduce relapse rates at 1 to 5 years in men with complete remission after initial chemotherapy, compared to no maintenance chemotherapy (low-quality evidence).		
Chung P 2016	RCT prospective no information about countries 1991-2011	no information about patient characteristics no information about follow-up total n=4.595* *Eigenberechnung	mortality, cure rates, relapse rates, including relapse-free-survival, quality of life, adverse effects	no pooled analysis conclusion: effects of treatments following orchidectomy in men diagnosed with stage 1 germ cell tumours (confined to testis) good prognosis Stage 1: beneficial adjuvant irradiation of 20 Gy in 10 fractions to para-aortic area compared with 30 Gy in 15 fractions to para-aortic area and iliac nodes in patients with seminoma	no coi no information about funding	3/11 LoE 1a

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				(Lower dose irradiation is similarly effective and associated with less toxicity) trade off between benefits and harms adjuvant chemotherapy adjuvant radiotherapy adjuvant surgery in patients with non-seminoma surveillance unknown effectiveness comparative effects of different drug combinations for adjuvant chemotherapy comparative effects of different number of cycles of adjuvant chemotherapy		
Cook MB 2010	67 studies	no information about patient characteristics, inclusion criteria	Perinatal variables:	Association with risk of cancer:	National Institutes of Health,	5/11

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	case-control or cohort study retrospective und prospective Sweden, Norway, USA, Canada, Denmark, UK, Czech Rep, France, Germany, Greece, Italy, Japan, 1976-2008	total n=kA	birth length, birth weight, gestational age, cryptorchidism, inguinal hernia, neonatal jaundice, twinship, having been breast fed	Birth length: OR 1.00 (95% CI 0.98-1.01) birth weight: (OR 0.94, 95% (CI) 0.88–1.01) low birth weight (OR=1.34, 95% CI 1.08–1.67) high birth weight (OR=1.05, 95% CI 0.96–1.14) gestational age (per week (OR=0.95, 95% CI 0.92–0.98) low vs not (OR=1.31, 95% CI 1.07–1.59) cryptorchidism (OR=4.30, 95% CI 3.62–5.11) inguinal hernia (OR=1.63, 95% CI 1.37–1.94) neonatal jaundice (OR=1.05, 95% CI 0.86-1.28) twinning (OR=1.22, 95% CI 1.03–1.44)	National Cancer Institute	LOE 2a-3a

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				breast fed (OR=0.96, 95% CI 0.68-1.36)		
Cooper KL 2011	RCT prospective 1992-2009 no information about countries	Age range: 15-90 Stage II-III, IV, metastatic, poor prognosis total n=4.710 Exp n=2.459 control n=2.251	Granulocyte colony-stimulating factors Experimental (G-CSFs) Comparison no primary G-CSF prophylaxis G-CSF with one another outcome: incidence of febrile neutropenia	Pegfilgrastim No primary G-CSF RR 0.30 (0.14 to 0.65) p = 0.002 (76% Heter.) Filgrastim No primary G-CSF RR 0.57 (0.48 to 0.69) p < 0.00001 (50% Heter.) Lenograstim No primary G-CSF 0.62 (0.44 to 0.88) p = 0.007 (64% Heter.) Any G-CSF No primary G-CSF RR 0.51 (0.41 to 0.62) p < 0.00001 (Heter.)74% Pegfilgrastim Filgrastim	Funded by Amgen Ltd (production of the manuscript) Amgen staff reviewed and made suggested edits to the manuscript, but final content, authorship and right to publication remained with the research team.	3/11 LoE 1a

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				RR 0.66 (0.44 to 0.98) p = 0.04 (0% Heter.) favours primary G-CSF		
Daneshmand S 2012	no information about number or designs of included studies	patients with metast. GCT after first line therapy	no outcomes or endpoints provided	no pooled analysis Evidence synthesis: Approximately one-third of patients who undergo chemotherapy for metastatic GCTs have residual retroperitoneal disease. All patients with residual masses >1 cm after chemotherapy for nonseminomatous GCTs should undergo postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) because of the risk of mature teratoma in 40–45% of cases	no information about funding and coi	0/11 keine Bestimmung des LoE möglich

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				and of viable GCT in 10–15% of cases. Patients who obtain a complete serologic remission and radiographic residual <1 cm after chemotherapy have a 6–9% risk of relapse. Patients with a completely resected teratoma in only the PC-RPLND specimen have a >90% chance of cure, while patients with viable GCTs should be considered for additional therapy, depending on the percentage of viable tumor. In patients with disseminated seminoma, postchemotherapy masses <3 cm may be safely observed, while patients with masses >3 cm should be evaluated with positron emission tomography (PET)/computed tomography 2 mo after completion of chemotherapy, with very selective administration of		

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				PC-RPLND. Late relapse occurring >2 yr after chemotherapy is rare, and surgery remains the mainstay of therapy in cases of resectable masses independent of tumor markers. There is still controversy on whether high-dose chemotherapy confers a survival benefit compared with conventional-dose chemotherapy in the salvage setting. Surgery should always be considered for resectable masses following salvage therapies or in chemoresistant disease to maximize chance of cure.		
De Souza KW 2011	retrospective case series, cohort, expert opinion prospective	no information about patient characteristics	Testicular Cancer Prevention Strategies	no pooled analysis Testicular Cancer Prevention Strategies: Perform the self-exam after a warm bath or shower: the testicle should be examined	no information about coi and funding	3/11 LoE 2a

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	quasi-experimental 1984-2007 no information about countries	no information about included patients		delicately between the thumb and the other fingers, observing the presence of nodes, swellings or other alterations. The process should be repeated with the other testicle. Remember that a normal testicle is oval-shaped, with firm and elastic consistency. Perform the testicle self-exam every 6 months. Submit to orchiopexy in the pre-puberty phase in case of cryptorchidism. Construct a multidisciplinary protocol for testicular cancer prevention. Theoretical-practical training for the team. Identify children who had cryptorchidism. Perform the physical testicular exam, observing the person's age and risk factors. Train secondary education teachers on risk		

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				factors and prevention measures, and discuss the main aspects involving testicular cancer prevention and testicular self-exam in health education programs for a secondary education public. Promote strategies for testicular cancer prevention in companies with a high number of male employees, and also in commercial establishments and waiting rooms. Perform health education by showing testicular self-exam videos		
Djaladat H 2014	cohort, case-control, case series retrospective 1983-2010	no information about patient characteristics total n= 503* cases n=135 controls n= 368*	association between TGCT and semen abnormalities before orchiectomy sperm count sperm concentration	no pooled analysis mean/ median sperm count: below 20 · 106/mL (oligospermia) total sperm count: 45.3 · 106/ejaculate	no competing financial interests exist no information about funding	4/11 LoE 2a-4

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		*Eigenberechnung	sperm motility sperm morphology infertility	mean/median sperm motility: below 50% Sperm morphology: < 50% TGCT before orchiectomy was associated with semen abnormalities, a surrogate for infertility.		
Duval M 2012	Non-blinded RCT Prospective KA zu Ländern 1999-2009	Patients of all ages With any type of tumor, receiving cisplatin chemotherapy, audiography performed at baseline and after completion of all cycles of cisplatin ct	Intervention: Infusion of amifostine vs. no infusion Primary endpoint: incidence of ototoxicity	Ototoxicity: Grade 2 and greater: OR = 0.73 (95% CI 0.39-1.37) Grade 3 and greater: OR 0.85 (95% CI 0.30-2.36) Side effects: Angaben als n	no information about coi and funding	5/11 LOE 1a

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		total n=215 (105 adults, 110 children)	Secondary endpoint: Side effects from amifostine infusion	Hypocalcemia (asymptomatic) 15/15; 2/37 Hypotension 17/36 Sneezing 6/36		
Giannarini G 2010	case series series retrospective non-randomised no information about countries 1989-2009	age: 26-44 total n=244 follow up: 9-73 mo	organ-sparing surgery	no pooled analysis conclusion: Testis-sparing surgery (TSS) should be considered for (1) small malignant GCTs with imperative indications for surgery and normal preoperative endocrine function; (2) small Leydig cell tumours even with elective indications, and (3) small nonpalpable, ultrasound-detected tumours with elective indications, provided that definitive histology fails to reveal malignancy. In the case of malignant GCTs, TSS	no coi no Funding	2/11 LoE 3a

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				should be coupled with local adjuvant radiotherapy.		
Giannatempo P 2015	Retrospective and prospective studies no information about countries 1998-2013	CSIIA and/or CSIIB seminoma patients Median age: 32-41 Median follow-up: RT-studies: 90 mo (range 36-228) CT-studies: 72.2 months (28-112.8) total n=890	Primary endpoint: Relapse rate (RR) Secondary endpoint: incidence of acute, long-term-toxicities, second cancers, mortality rate, OS (overall survival), RFS (relapse-free-survival)	Radiotherapy: Relapse rate 0.11 (0.08–0.14) P for heterogeneity = 0.096, I^2 = 38%, Chemotherapy: Relapse rate 0.08 (0.01–0.15) P for heterogeneity <0.001, I^2 = 82.5%, Mortality: Radiotherapy: [0.02 (95% CI <0.01–0.04), P for heterogeneity = 0.017, I^2 = 63.7%,	no conflicts of interest no information about funding	5/11 LOE 2a

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				Chemotherapy: [0.01 (95% CI <0.01–0.02), P for heterogeneity = 0.319, I^2 = 14.6%, Second cancers overall incidence of nontesticular second malignancies: 0.04 (95% CI 0.01–0.02) in the RT group and 0.02 (95% CI 0.003–0.04) in the CT group.		
Goede J 2012	prospective retrospective Turkey, Iran, USA, Italy, Israel, Canada, Denmark, UK, Argentina, Spain,	range age: 2 days-70 yrs follow up: 1-9 yrs total n=3401	testicular microlithiasis “outcomes”: prevalence	no pooled analysis prevalence: 1.6% in symptomatic boys 3,5% with undescended testes	no coi no Funding	2/11 LoE 4

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	Netherlands, Hong Kong, Germany, India, Greece 1970-2010	included Boys n=3085	Association with benign anomalies Association with testicular malignancies follow - up	benign anomalies: hydrocele, varicocele, undescended testis, testicular asymmetry, testicular pain, torsion of the testis, torsion of the appendix of the testis chromosomal abnormalities: Down syndrome (29% compared to 7% in controls) McCune-Albright syndrome (6 out of 10 boys) pseudoxanthoma elasticum fragile X syndrome Cornelia de Lange syndrome Peutz-Jeghers syndrome mumps, urethroperineal fistula, retro-iliac ureter, hypogonadotropic hypogonadism, b-thalassemia		

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				development of a testicular malignancy in boys after TM (yolk sac tumor, mixed germ cell tumor) co-existence of TM and testicular tumor follow-up self-examination, testicular ultrasound, screening tumor markers and/or hormone profiles		
Greco F 2014	no information about designs no information about countries	no information about patient characteristics no information about cases	“outcome” image-guided surgery for genitourinary (GU) oncologic diseases	no pooled analysis conclusion SLNs could be detected in all patients examined on static imaging. In right tumours, hot uptakes were observed at the interaortocaval, paracaval, or common iliac	no coi no Funding	2/11 LoE ????

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
	1995-2013			region; for left tumours, positive uptakes were detected in the para-aortic region. the utility of SLN identification in testicular tumours is controversial with limited research on this topic.		
Gurney J 2015	3 studies case-control Study retrospective USA 2009-2012	Inclusion criteria: kA Exclusion criteria: -Non-germ cell tumours -Chorio-carcinoma -Age (<18 or >44) -No telephone -Non-English-speaking	Cannabis use	Ever-use compared to never-use: OR 1.19, 95% CI 0.72-1.95 Former use and TGCT: OR 1.54, 95% CI 0.84-2.85 Current use and TGCT: OR 1.62 95% cI 1.13-2.31)	No conflicts of interest. funded by the Health Research Council of New Zealand	7/11 LOE 3a

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		-Age (<18 or >50) -Extragonadal tumours -Age (<18 or >35) -Born in U.S.A., Canada, Europe or Middle East total n=2138 719 cases 1419 controls		Frequency (weekly and greater use) and TGCT: OR 1.92, 95% CI 1.35-2.72 Duration (>= 10 ys vs. never use) and TGCT: OR 1.50, 95% CI 1.08-2.09 Cannabis-use and non-seminoma development: OR 2.09, 95% CI 1.29-3.37		
Heidenreich A 2010	no information about designs until 2009 no information about countries	no information about patient characteristics no information about cases	appropriate imaging technique and the most useful time interval in metastatic urogenital cancer patients undergoing systemic therapy	no pooled analysis conclusion Contrast-enhanced CT remains the standard imaging of choice for monitoring of pulmonary, hepatic, mediastinal and retroperitoneal lymph node metastases. In young testicular cancer patients, CT might be replaced by MRI in	no information about coi and funding	3/11 LoE ????

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				order to decrease radiation exposure in long-term cancer survivors.		
Heidenreich A 2012	retrospective no information about countries Suchzeitraum: 1990-2012	no information about patient characteristics no information about cases	surgical resection of urological tumor metastases	no pooled analysis conclusion 30% to 50% of metastatic nonseminomatous germ cell tumors show residual metastases after chemotherapy. Post-chemotherapy resection of retroperitoneal, intraabdominal, and intrathoracic residual tumors larger than 1 cm in patients with negative tumor markers or a tumor marker plateau, performed in experienced reference centers, is the therapy of choice with	possible coi of at least 5 authors no information about Funding	2/11 LoE 2b- 3

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				curative intention (evidence level IIA).		
Hotte SJ 2010	RCT non-randomised studies prospective no information about countries	no information about patients charactersitics total n=3199 follow-up: range 19.5 mo – 5 yrs	Management of Stage I Non-seminomatous Testicular Cancer relapse free survival cancer specific survival	no pooled analysis conclusion Cancer cure rates were excellent regardless of the management option selected. Overall and disease-free survival rates were over 95% for all management approaches; recurrence rates were higher in the patients managed by surveillance. In conclusion, patients with CS I NSTC should be assessed and managed at multidisciplinary centres by health care professionals experienced in the treatment of testicular	no information about coi and funding	4/11 LoE 1a

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			OS	cancer. On the basis of the available evidence, the Genitourinary Disease Site Group recommended primary surveillance for all patients with CS I NSTC, with treatment if relapse occurs. As cancer cure rates are similar with primary surveillance, adjuvant chemotherapy and retroperitoneal lymphadenectomy, patient preference with respect to the risk of recurrence and the timing and toxicities of treatment must be considered. For patients who prefer immediate treatment, or who are unsuitable for primary surveillance, adjuvant chemotherapy with two cycles of bleomycin, etoposide (500 mg/m2/cycle) and cisplatin was recommended. Surgeons involved in the development of this guideline suggested		

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				that retroperitoneal lymphadenectomy may be a useful option for patients at high risk of relapse. There is currently insufficient evidence from prospective trials to support or refute this position.		
Hu Z 2016	7 Guidelines and 4 Systematic reviews included USA, Canada, Europe, UK, Spain, Italy 2002-2015	no information about patient characteristics total n=3.083	Cisplatin Chemotherapie OS, DFS, relapse rate, CR, adverse events	no pooled analysis Effectiveness: cisplatin-based chemotherapy significantly improved in response rates and overall survival for more advanced disease (stage II and stage III). Bleomycin, etoposide, and cisplatin (BEP) — should be considered as the standard treatment of good prognosis patients with survival rates of 90% and as the best option for intermediate or poor-prognosis patients with	no coi CMB grant	4/11 LoE ???

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				survival rates of 75% and 50%. Safety/adverse effects nephrotoxicity, ototoxicity, peripheral neuropathy		
Ilic D 2011	RCT	Adult men No exclusion criteria based on ethnicity or age Inclusion criteria: men with a history of undescended testes or testicular atrophy	Physical examination by a physician or patient self-examination Primary outcome: mortality: testicular-cancer specific and al-cause Secondary outcomes: Incidence of testicular cancer, stage and grade of	empty review no studies eligible with inclusion criteria	no information about coi	1/11 (empty review) LOE 1a (?)

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			cancer classification, quality of life, harms of screening			
Krajewski W 2016	no infromation about designs, countris until Oct 2015	no information about patient characteristics, cases, follow-up	Intervention: Vitamin D Control: KA Outcome: prevention, therapy of cancers	no pooled analysis conclusion VDR is present in various normal testicular cells. VDR expression was also found in almost every type of TGCT. Significant antiproliferative VD3 effect on TGCT cells was proved in in-vitro studies. exact mechanism of VD3 influence on TGCT is complex and not fully understood	no coi no information about funding	1/11 LoE ????

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Lerro CC 2010	retrospective cohort, case-control UK, Denmark, Canada, Greece, Germany, USA, Sweden, Norway 1989-2009	no information about patient characteristics total n=14.262	height weight BMI Overweight Obese vs. normal weight Odds Ratio OR	overall: OR 1.13 (1.07-1.19) weight OR 1.0 (1.00-1.01) bmi OR 0.99 (0.97-1.00) overweight 25<bmi<30 OR 0.92 (0.86-0.98) obese BMI >30 OR 0.93 (0.75-1.15)	National Cancer Institute, NIH no information about coi	2/11 LoE 3a

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Lin K 2010	prospective cohort retrospective cohort diagnostic accuracy study 2001-2004 no information about countries	men with microlithiasis, men with germ-cell tumours	screening for testicular cancer. follow-up-sonography Detection of unmethylated (abnormal) XIST DNA with specifically designed polymerase chain reaction primer Orchiectomy (12 men) vs. testis-sparing surgery (15 men)	no pooled analysis No new testicular tumors detected after a mean follow-up of 45 mo (range, 12 to 90 mo) Unmethylated XIST DNA was found in 16 of 25 plasma samples in men with testicular germ-cell tumors; none of the plasma samples in the comparison groups contained unmethylated XIST DNA. No recurrent tumors in either group after a mean follow-up of 9 mo (range, 1 to 19 mo)	no coi no infromation about funding	1/11 LoE 2a
Lindner OC 2014	Longitudinal and cross-sectional studies	Mean age:	Intervention:	All subgroups:	no information about coi	7/11

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	no information about countries 1995-2011	51.57 ys (SD=6.29) Total n=3940 n=1940 adult patients n= 2000 controls average of 2 ys posttreatment	Patients exposed to chemotherapy Control group: Studies comparing patients with norms, healthy controls, or cancer patients who were not treated with Chemotherapy Outcome: cognitive function: memory, verbal memory, visual memory, immediate free recall, delayed memory, delayed recognition, attention, motor function	visual memory (0.22* (95% CI 0-0.4), p=o.04 visual immediate free recall (0.22* (95% CI 0-0.45) P=0.05 selective attention (-0.26* (95%CI -0.51-0) p=0.04. *Hedge's *g* effect size Analysis by study design (cross-sectional) low to moderate impairments relative to controls. These were observed in memory, immediate free recall, delayed memory, delayed recognition, verbal memory,	Medical Research Council, UK	LOE unklar *Longitudinal studies waren primär eingeschlossen, jedoch gab es keine Schlussfolgerungen aufgrund der enormen Heterogenität der Kohorten-Studien. Es gibt kein Level für cross-sectional studies

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				verbal immediate free recall, verbal delayed free recall, verbal delayed recognition, selective attention, and capacity of attention. Analysis by study design (longitudinal studies) improvement in patients for immediate free recall, verbal immediate free recall, visual immediate free recall, visual delayed memory, focused attention, capacity of attention, and verbal abilities.		
Lip SZL 2013	9 case-control studies 3 cohort studies retrospective	exclusion criteria: boys at risk of testicular cancer for reasons other than cryptorchidism (eg, hypospadias, subfertility, carcinoma	Isolated cryptorchidism	case-control studies RR=2.47, 95% CI 1.91 to 3.18; p<0.0001 cohort studies	Competing interests None. no information about Funding	6/11 LOE 2a-3a

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	USA, Czech Rep., Canada, Germany, France, Sweden, Denmark, UK 1980-2010	in situ, microlithiasis or cancer families total n= 2.185.033		RR=3.77, 95% CI 2.65 to 5.37; p=0.01 overall significant risk of having cryptorchidism and developing testicular malignancy: RR=2.90, 95% CI 2.21 to 3.82		
Lotti F 2014	no information about design, countries until March 2014	no information about patient characteristics	color-Doppler ultrasound CDUS	no pooled analysis conclusion Even if medical care for men suffering childlessness is growing, in andrology, diagnostic and therapeutic measures have not yet reached a critical mass to ensure a reasonable understanding of the underlying problem and the consequent evidence-based treatment. Nowadays, scrotal and transrectal imaging of	no coi no information about funding	0/11 LoE ?

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				the male genital tract (MGT) has greatly helped in the deciphering anatomy, physiology and pathology of male infertility. Table IV offers a provisional summary of seminal, US and hormonal correlates of some recognized causes of male infertility. However, sonographic imaging of MGT still suffers from a lack of standardization and often tends to produce subjective and vague diagnoses.		
Lyman GH 2010	RCT prospective kA zu Ländern 1990-2008	no information about patient characteristics, inclusion criteria mean and median follow-up: 60 and 53 months	patients with cancer receiving conventional dose chemotherapy for solid tumors or malignant lymphoma Exper. Group: initial G-CSF	AML/MDS RR 1.92 (95% CI 1.19-3.07) p=0.007 Second malignancies 114 control patients (3.25%) 115 patients receiving G-CSF–supported chemotherapy (3.28%) RR 1.01 (95% CI, 0.78 to 1.3; P = .941) for second	Consultant or Advisory Role: Dale, Amgen Honoraria: Lyman, Amgen; Dale, Amgen;	7/11 LOE 1a

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		total n=12.804 n= 6058 n=6746 controls	control group: without initial G-CSF primary outcome: occurrence of AML or MDS Secondary outcomes: secondary malignancies, number of deaths	malignancies for patients randomly assigned to primary G-CSF– supported chemotherapy compared with control patients AR 0 (95% CI, -0.002 to 0.009; P=.942) across studies All-cause mortality N=1.845 (30.5%) exper. group N=2.099 (31.1%) control patients. RR 0.897 (95% CI, 0.857 to 0.938; P=.001) for all-cause mortality associated with G-CSF AR decrease 3.40% (AR=3.40%; 95% CI, 2.00% to	Kuderer, Amgen Research Funding: Lyman, Amgen; Dale, Amgen; Culakova, Amgen; Kuderer, Amgen	

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				4.80%; P=.001) for mortality in patients randomly assigned to receive G-CSF across studies		
Marrie RA 2015	hospital register, cancer registers administrative data sources 1953-2010 North America, Europe, Asia	no information about patient characteristics, total n=174.775* *eigene Berechnung	incidence and prevalence of cancer in MS	prevalence of testicular cancer =0%	Funding by: National Multiple Sclerosis Society, Don Paty Career Development Award from the MS Society of Canada. Ruth Ann Marrie receives research funding from: Canadian Institutes of Health Research, Public Health	7/11 LOE nicht eindeutig zuzuordnen (Oxford-Schema berücksichtigt keine Registerdaten)

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					Agency of Canada, Manitoba Health Research Council, Health Sciences Centre Foundation, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Rx & D Health Research Foundation, and has conducted clinical trials funded by Sanofi-Aventis.	

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					Nadia Reider reports no disclosures. Olaf Stuve is an associate editor of JAMA Neurology, and he serves on the editorial boards of the Multiple Sclerosis Journal, Clinical and Experimental Immunology, and Therapeutic Advances in Neurological Disorders. He has participated in data and safety monitoring committees for Pfizer and	

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					Sanofi. Dr. Stuve has received grant support from Teva Pharmaceuticals. Jeffrey Cohen reports personal compensation for consulting from EMD Serono, Genentech, Genzyme, Innate Immunotherapeutics, Novartis, and Vaccinex. Dr. Cohen receives research support paid to his institution from Biogen Idec,	

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					Consortium of MS Centers, US Department of Defense, Genzyme, US National Institutes of Health, National MS Society, Novartis, Receptos, Synthon, Teva, and Vaccinex. Per Soelberg Sorensen has received personal compensation for serving on scientific advisory boards, steering committees, independent data monitoring	

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					boards in clinical trials, or speaking at scientific meetings.	
Maule M 2012	retrospective case control USA, UK, CA, DK 1983-2010	total n=10.800 cases total n= 14.807 controls	exposure: age when started shaving, age at voice change, age at puberty	shaving; late shaving: OR of testicular cancer of 0.84, (95% CI: 0.75–0.95, I^2: 0%) early shaving: OR of 0.98 (95% CI: 0.85–1.12, I^2: 12%,) age at voice change: late change: OR of 0.87 (95% CI: 0.75–1.01, I^2: 76%) early change: OR of 1.04 (95% CI: 0.90–1.21, I^2:0%) age at puberty onset	Funding: Piedmont Region and the Compagnia di San Paolo/FIRMS. ERACOL (Erasmus-Columbus 2013) Erasmus Mundus Programme no information about coi	3/11 LoE 3a

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				for late onset OR 0.67 (95% CI: 0.54–0.83, I^2: 0%) for early onset OR 0.89 (95% CI: 0.71–1.11, I^2: 0%)		
Müller J 2011	no information about designs, countries 1999-2005	total n=130 (161 Läsionen) mean age: 39,5 yrs Follow-up: 23,6 mo	FDG-PET vs. CT	FDG-PET / CT: specifity: 92% / 59% sensitivity: 72% / 63% estimation of res. tumor size: FDG-PET / CT: positiv predictive: 70% / 28% negativ predictive: 93% / 86%	no coi no information about Funding	2/11 LoE ?

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Petrelli F 2015	retrospective prospective 1998 – 2014 no information about countries	total n=12.075 (7.351 for RT, 908 for CT, 3816 for observation) Follow up: 33-174 mo	adjuvant radiotherapy (RT) or chemotherapy (CT) compared with surveillance alone in Stage I Seminoma prim endpoint: 5 year RFS sec endpoint 5-year-OS, cancer-spec. survival, 5-year-noncancer-related mortality	5 year RFS adjuvant RT or CT reduces the risk of relapse by 83% (OR 0.17; 95% CI, 0.1-0.29; P < .00001) favours CT or RT relapse rates: 3.9% versus 14.8% in the adjuvant therapy and surveillance arms ARR 10.9% in favour of adjuvant therapy (95% CI, -9.3 to -12.5), NNT 10 (95% CI, 7.9-10.7) 5-year-OS: OR 1.03; 95% CI, 0.46-2.28; P =.94	no coi no information about funding	3/11 LoE 1a

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				mortality rates: 1.8% versus 2.6% in the adjuvant therapy and surveillance arms Cancer-specific survival: 99.7% versus 99.3% in the adjuvant therapy and surveillance arms ARR 0.7% in favour of adjuvant therapy (95% CI, 0.1 to 1.4; P < .00001) NNT 130 (95% CI, 70-528) Five-Year Noncancer-Specific Mortality (OR 1.1; 95% CI, 0.47-2.56; P= .82) mortality rates adjuvant therapy 1.5%		

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				versus surveillance 1.9%		
Poon R 2016	no information about designs and countries 07-12/2015	no information about patient characteristics, follow up and cases	diagnostic accuracy; change in patient clinical management, clinical outcomes, or treatment response; survival; quality of life; prognostic indicators; time until recurrence; or safety outcome (e.g., avoidance of unnecessary surgery)	no pooled analysis conclusion Current Recommendations for the Utilization of PET/CT in Testicular Cancer: Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the routine staging of patients with testicular cancer. PET is recommended for the assessment of treatment response in patients with seminoma and residual masses after chemotherapy.	Funding by Ontario Ministry of Health and Long-Term Care no information about coi	2/11 LoE expert opinion

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				PET is not recommended for the assessment of treatment response in patients with nonseminoma. Due to insufficient evidence, a recommendation cannot be made for or against the routine use of PET for evaluation of recurrence.		
Ravi P 2014	"surveillance studies" no information about designs, countries 1992-2011	median age (DFCI): 31 Database (DFCI surveillance cohort) total n=47 and literature total n=966 Follow up: 3 – 15,5 yrs	with and without a PC-RPLND outcomes: histological rates of necrosis, Teratoma, active malignancy number of all relapses, RP-only relapses, overall survival	pooled incidence: necrosis: 71% (95% CI: 67–75%) teratoma: 24% (95% CI: 20–27%) active cancer: 4% (95% CI: 1–7%) proportion of relapses in men undergoing surveillance:	no funding no coi	4/11 LoE ?

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				All relapses: 5% (95% CI 0–10%) Q = 19.2; I^2 = 84%; P = 0.00) RP-only relapse: 3% (95% CI 0–5%)] Q=9.37; P=0.02; I^2 =68%		
Rove KO 2015	no information about designs, countries, time	median age 5.7 (0.1-21) median size 2.0 (0.5-8.0= median follow up 45.6 mo (4-360) total n=100	rate of OMD (occult metastatic disease) in cases of children and adolescent with clinical stage I TST's histologic risk factors	no pooled analysis OMD n=0 12 years and below: 99% 0 to 1 pathologic risk factors above 12 years 95% 0 to 1 pathologic risk factors (P=0.38)	Funding by a NCI grant no coi	1/11 LoE ? am ehesten Case series (LoE 4)

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Rovito MJ 2015	RCT's, quasi-experimental prospective kA zu Ländern 1985-2014	no information about inclusion criteria exclusion criteria: Participants who have sought care at a genitourinary medical clinic as these individuals may be more apt to follow recommended pelvic (i.e., testicular) health regimens than others. total n= 2.786	Outcome: TSE behavioural outcomes: Information on testicular cancer risks, TSE knowledge, behaviours (discussions with health care professionals about testicular cancer and TSE), preferences (intentions to self-screen or not), and behavioural outcomes (exercising of TSE)	Knowledge $\chi 2 = 9.69$, $p < .05$ (patient–volunteer group compared with others) Knowledge $\chi 2 = 9.69$, $p < .01$ (physician-conversation vs. no physician discussion) Knowledge $F = 10.59$, $p < .0001$ (comparing experimental groups with control condition; more comprehensive curriculum associated with higher reported TSE) Knowledge/awareness $\chi 2 = 11.11$, $p < .004$ (TPB-group compared with others). Attitudes and beliefs about TSE and TC $t (276) = 8.68$, $p < .001$ (Read + practice compared with others; read + read also	no conflicts of interest no financial support	5/11 LOE 1a

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				higher than control condition) Completeness of TSE r = .37, p < .05 (for mailed postcards compared with performance efficacy; authors related self-reported TSE performance should equate with better performance technique posttest) Duration of TSE t(46) = .98, p > .30 (for social support vs. control group analysis) Knowledge χ2 = 4.61, p < .05 (intervention group vs. control group) Knowledge χ2 = 7.59, p < .006 (posttest TSE report vs. pretest TSE report)		

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				Knowledge $\chi 2 = 1.38$, $p < .50$ (across all groups for reported TSE) Attitude $F = (1, 169) = 6.084$, $p < .015$ (shower cards and attendance at campaign events only for mean change in behaviors) Intention to perform $F = (1, 169) = 12.190$, $p = .001$ (exposure to events explained 4.6% of posttest TSE behavior)		
Saab MM 2016	RCT quasi-experimental design: pre-posttest-design, posttest-design only, prospective	Inclusion criteria: men, age from 15-86	Knowledge, awareness, attitude towards TC and TC screening, TC screening interventions and TC screening practice	(Q1) knowledge, awareness, and attitude toward TC; (Q2) knowledge, awareness, attitude, toward TC screening; (Q3) TC screening intentions; (Q4) TC screening practices.	no conflicts of interest no funding	5/11 LOE 1a

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	USA, UK, France, Pakistan, 2004-2014	total n=8.528		Q1: T1: on a scale of 0-9, 50.6% (n = 80) scored <3 on items related to TC causes and outcomes (mean, 3.62), 92.2%(n = 147) did not know that TC is more prevalent among whites. Q2: T1: 46.8% (n = 74) were not aware that most abnormalities are found during TSE. Q3: T2: no difference between EG and CG in terms of intentions to perform TSE (not statistically significant). Q4: T2: 65.2% (n = 30) of EG performed TSE compared with 40% in CG (n = 12) (#2 = 4.61, P <.05)		

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				Q1: T2: on a scale of 0-10, EG had higher knowledge scores about Q2: T2: EG had greater knowledge (P<.001) and a more positive attitude (P<.001) toward TSE. Q3: T2: EG had a greater intention to perform TSE (R2 = 0.01, P<.001). Q4: NR Q1: Knowledge TC risks such as age increased significantly from T1 (47.5%, n = 48) to T2 (93.1%, n = 94) up until T3 (84.2%n = 80) (P<.05) Knowledge of TC treatment increased significantly between T1 (73%, n = 73) and T2 (92%, n = 92) (P<.05)		

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				T1: on a scale of 0-5, the EG and CG had similar TC knowledge (median score, 3) T2: EG scored significantly higher (median score, 4; P = .014) Q2, Q3: NR Q4: T1: No difference in TSE practice between EG and CG (P not reported) T2: EG scored higher than CG on TSE practice (P = .006) Q1: NR Q2: TSE knowledge increased significantly from 4% (n = 3) at T1 to 72% (n = 41) at T2(P<.001) Q3: NR		

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				Q4: TSE practices increased significantly from 2% (n = 1) at T1 to 26% (n = 15) at T2 (P<.001) Q1: T2: participants who read the low vulnerability information (mean, 19.31) and high severity condition information (mean, 19.34) perceived themselves to be more susceptible to TC than those who read the high vulnerability (mean, 16.3) and low severity information (mean, 16.27) (P<.05) Q2: T2: participants exposed to the high self-efficacy message perceived themselves as more capable of performing TSE (mean, 22.16) than those who read the low-self efficacy message (mean, 19.31) Attitude		

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				toward TSE increased significantly in T2 (P<0001). Q3:T2: men in the high self-efficacy group and high-vulnerability group intended to perform TSE (P G .06) Intentions to perform TSE increased significantly in T2 (P<.0001). Q4:T1: 58.6% (n = 75) performed TSE in the past year and had their testes checked by a clinician T2: 75.7% (n = 56) Reported performing TSE in the past month; those in the high-efficacy condition had higher odds of performing TSE (OR, 3.09). Q1:		

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				Part I: T1: 26.75% (n = 107) received information about TC, 7.75% (n = 31) were educated about TC risk factors, 63.3% (n = 253) did not know about TC prognosis. Q2: Part I: T1: 16.3% (n = 65) were educated about the importance of TSE, and 9.5% (n = 38) have been taught how to perform TSE. Q3: Part I: T2: mean degree of willingness did not increase significantly (mean, 7.09 at T1 and mean, 7.43 at T2) (not statistically significant); 2.75% (n = 11) became less willing to have testicular palpation, and 15% (n = 60) became more willing to have testicular palpation.		

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				Part II: 14.17% (n = 51) Declined examination before the briefing. Q4: Part II: Of those who declined examination (n = 51), 31.37% (n = 16) accepted testicular palpation following the briefing. Q1: T2: on a scale of 0Y10, EG2 had the highest knowledge scores (mean, 8.9; CI, 8.3-9.14) and the lowest perceived severity of TC (P = .007). Q2: T2: EG2 had the highest TSE response efficacy (mean, 6.34; CI, 6.19-6.49; P = .023)		

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				and TSE self-efficacy (mean, 6.24; CI, 6.06-6.42; P = .004) EG2 reported significantly greater learning from the message (P = .004). Q3: EG2 had the greatest intentions to perform TSE at T2 (P = .002) and T3 (P = .011). Q4: NR Q1: T2: 92.6% (n = 25) of EG1, 90.5% (n = 19) of EG2, and 86.4% (n = 38) of CG knew about TC. There was no significant difference between the groups regarding TC knowledge (P = .7). Q2:		

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				T2: 74.1% (n = 20) of EG1, 95.2% (n = 20) of EG2, and 75.6% (n = 34) of CG knew about TSE. There was no significant difference between the groups regarding TSE knowledge (P = .13) Overall, 93.5% (n = 87) agreed that TSE improves chances of recovery, and 74.2% (n = 69) agreed that men do not perform TSE because they have now knowledge about this practice. Q3: NR Q4: T2: 25.9% (n = 7) of EG1, 33.3% (n = 7) of EG2, and 20% (n = 9) of CG performed monthly TSE 51.9% (n = 14) of EG1, 47.6% (n = 10) of EG2, and 20% (n = 9) of CG were never screened for TC by a clinician. Q1:		

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				T1: deaf men had less TC Knowledge (P<.002) than hearing men T2: TC knowledge among deaf men (P<.001) and hearing men (P<.001) increased. Postintervention, hearing men had a greater mean change in knowledge (mean difference, 3.82) compared with deaf men (mean difference, 3.46) Q2-Q4: NR Q1: EG: TC awareness increased significantly from T1 to T2 (P<.001) T2: TC awareness in EG was higher than CG (P<.001) T2:		

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				Significant increase in awareness among EG (p<.001). Q2: NR Q3: EG: intention to within a month increased significantly from T1 to T2 (P<.001) as compared with CG. EG: compared with T1, there was a significant increase in monthly TSE (P<.001) T2: EG was more likely to perform TSE than the CG (P<.001).		

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Srigley JR 2014	retrospective 1999-2008 UK, Germany	total n=942	What types of specimens suspected to be or diagnosed as genitourinary cancer should or should not have routine secondary pathology review?	no pooled analysis Specimens with suspicion of, or diagnosis of, testicular cancer should have secondary pathology review or direct referral to an expert genitourinary pathologist. Central management (including pathology review) in specialized centers should be considered.	Funding by Ontario Ministry of Health and Long-Term Care. JB declared grants or research support (Medicalm Advisory Board) from Abbott, Amgen, Astellas, Astra Zeneca, Ferring, Palladin, Sanofi and was a co-author/investigator for clinical trials in BHOS-Bone Health Observational Study (Astra	3/11 LoE unclear

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					Zeneca), Delay Trial: Firmagon for the management of castrate resistant prostate cancer (Ferring). The other members did not declare any conflicts.	
Stang A 2011	case-control cohort studies no information about time, countries	total n= 1148 (risk estimates)	RR estimates RoRR (ratio of RR estimates) etiologic differences among seminoma and non-seminoma	no pooled analysis 30.9% lifestyle factors, 20.9% pregnancy related factors, 12.7% family history, 10.8% genetic factors ratios of RR estimates were symmetrically distributed	no coi no information about Funding	2/11 LoE 2a-3a

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Suominen JS 2015	case reports or series no information about time, countries	total n=421 with TM mean follow up: 3.3 ys (0.2-11 ys)	to address association of Testic Microlith TM with testicular neoplasms among pediatric patients	n=15 (3.6%) with neoplasm n=1 mediastinal Teratoma n=1 retroperitoneal yolk sac tumour n=13 varied testicular neoplasm no calculations of risk estimates	no coi no information about funding	2/11 LoE 4
Tan IB 2010	case-control, cohort studies 1992-2008 no information about countries	total n=40.379* *=eigene Berechnung	Testic Microlith TM endpoints: TGCT, intratubular germ cell neoplasia of unclassified type, interval TGCT	TGCT in the presence of TM: RR 8.46 (95% CI 4.45-16.08) intratubular germ cell neoplasia in the presence of TM: RR 10.48 (95% CI 5.28-20.81) interval TGCT: no pooled data provided	Funded by National Research Foundation Singapore and Singapore Millenium Foundation no information about coi	4/11 LoE 2a-3a

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Trabert B 2012	observational studies 1979-2012 US, UK, GR, DK	no information about cases, time	childhood infections and TGCT OR	no association between history of mumps without orchitis and TGCT (OR: 0.98; 95% CI: 0.76–1.27) Overall history of orchitis was associated with an increased risk of TGCT (OR: 2.38; 95% CI: 1.56–3.63), however, this association was limited to orchitis diagnosed within one calendar year of the reference date (OR: 23.16; 95% CI: 5.53–96.99) Orchitis at ≥10 years of age (OR: 1.12; 95% CI: 0.67–1.90)	Funding durch National Cancer Institute no coi	2/11 LoE keine Einordnung von observational studies in den Oxford Levels of Evidence 2009

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				and mumps infection at ≥10 years of age were not associated with TGCT (OR: 1.34; 95% CI: 0.71–2.51) History of measles, chicken pox, roseola/sixth disease and mononucleosis were not associated with TGCT overall or by histological type. mumps OR 1.03 (95% CI: 0.89–1.20) mumps orchitis or orchitis OR 1.80 (95% CI: 0.74–4.42).		
Treglia G 2014	Retrospective and prospective and monocentric or multicentric	Included: Patients with seminoma (including evaluation of residual masses after chemotherapy and	Sensitivity, specificity, accuracy, positive and negative predictive value, positive and negative likelihood	Sensitivity (95% CI) 0.78 (0.67-0.87) $\chi 2 = 23.50$; df = 8 (P = 0.0028) Inconsistency (I^2) = 66.0%	no conflict of interests no funding	6/11 LOE 1a

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	Italy, EU-Countries, Canada, Poland, Germany, USA, Austria, Netherlands, UK 1999-2014	restaging) were eligible for inclusion. Excluded: patients with seminoma at initial staging total n=375	ratio (LR), and diagnostic odd ratio (DOR) of 18FFDG- PET or PET/CT in the postchemotherapy management. Diagnostic performance of the PET/PET CT The reference standard used to validate the 18F-FDG-PET or PET/CT findings was quite different in the included studies. Follow-up including chest radiograph, tumor markers, physical examination, and	Specificity (95% CI) 0.86 (0.81 to 0.89) $\chi 2$ = 36.14; df = 8 (P = 0.0000) Inconsistency (I^2) = 77.9% Symmetric SROC AUC = 0.9012 SE (AUC) = 0.0346 $Q*$ = 0.8326 SE($Q*$) = 0.0371 Positive LR (95% CI) 4.59 (2.55 to 8.25) Cochran's Q = 22.63; df = 8 (P = 0.0039) Inconsistency (I^2) = 64.6% τ^2 = 0.4152		

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			CT Histology or clinical follow-up (minimum of 18 months) Histology in 2 patients and clinical follow-up in 8 patients (serum tumour markers, CT, and the duration of the event-free follow-up) (median of 12 months) Histology (11 resected masses) or follow-up (median of 34 months) Histology or clinical follow-up Histology Histology or follow-up (at least 24 months) Histology (7 patients) or follow-up. Histology or follow-up.	Negative LR (95% CI) 0.26 (0.09 to 0.71) Cochran's Q = 60.62; df = 8 (P = 0.0000) Inconsistency (I^2) = 86.8% τ^2 = 1.6377 Diagnostic OR (95% CI) 22.71 (8.79 to 58.68) Cochran's Q = 10.50; df = 8 (P = 0.2317) Inconsistency (I^2) = 23.8% τ^2 = 0.4805		

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Wang T 2015	14 studies retrospective 12 cohort-studies, 2 case-control studies UK, USA, The Netherlands, Turkey, Taiwan, Italy 2000-2014	no information about patient characteristics, inclusion criteria total n=35.578 Cohort-studies: n=29.302 Case-control-studies: n=6.276 1493 TM cases 34085 controls	testicular microlithiasis (TM)	TM was strong associated with an increased incidence of testicular cancer (RR = 12.70, 95% CI: 8.18-19.71, P < .001) Sub group analysis: Geographical region: North America (USA): RR 9.43 (4.58-19.44) European countries: RR 16.31 (11.12-23.94) Asia RR 16.06 (10.04-25.69) Study design Cohort study	National Natural Science Foundation of China Natural Science Foundation of Guangdong Province Conflict of interest: None declared.	6/11 LOE 2a

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				RR 13.62 (8.08-22.96) Case-control study RR 7.68 (5.54-10.64) Age <18 RR 13.04 (0.92-184.64) Age >18 RR 12.11 (7.76-18.89) No. of participants ≤ 1000 RR 6.58 (2.32-18.68) No. of participants > 1000 RR 14.80 (10.07-21.76)		

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Yousif L 2010	37 studies 7 case-control studies, 30 cohort studies Retrospective/prospective USA, UK, Denmark, New Zealand, Sweden, Canada, Germany, Finland, Iceland, Norway, France 1990-2007	no information about patient characteristics, inclusion criteria total: n=1.226.311 Case-control: Cases: n=1087 Controls: n=3405 Cohort-studies: n=1.221.819	Ionising and non-ionising radiation exposure	no pooled analysis Conclusion: "An association between occupational ionising radiation exposure and development of testicular cancer seems unlikely. Risks of internal exposure still need to be assessed, as the few studies with details on internal exposure reported a somewhat increased testicular cancer risk. For non-ionising radiation, several studies point to a possible association with testicular cancer."	DAAD (German Academic Exchange Service)	5/11 LOE 2a
Yousif L 2013	21 Epidemiological cohort, case-control studies, Histopathological laboratory studies	no information about patient characteristics, inclusion criteria	EBV, CMV, Parvovirus B19, HPV, HIV	EBV: OR 4.80 95% CI 0.98-23.54 CMV:	Conflict of interest: None. DAAD (German Academic	Amstar 5/11 LOE 2a-3a

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	USA, UK, Denmark, Sweden, Germany, Norway, Japan, Switzerland, Austria 1986-2008	number of studies pro Virus: EBV 8, CMV 5, Parvovirus B19 4, HPV 2, HIV 8 TN in EBV-studies: Cases: n=480 Controls: n=583 TN in CMV-studies: Cases: n=340 Controls: n=411 TN in Parvovirus B19: Cases: n=690 TN in HPV-studies: Cases: n=58 Controls: 867		OR 1.85 95% CI 0.92-3.70 Parvovirus B19: OR 2.86 95% CI 0.35-23.17 HIV: OR 1.79 95% CI 1.45-2.21 no pooled analysis for HPV comment of authors: “However, the evidence for HIV as causative agent is comparatively strong, and similarly, high ORs for EBV and CMV infection suggest that these viruses may be involved in the development of testicular cancer.”	Exchange Service)	

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		TN in HIV-Studies (cohort-studies) N=282.268				
Zequi S 2012	case series, case reports, cohort study (1) no information about countries 1991-2011	total n=602	incidence pathological features clinical outcomes (DSS, OS)	261 (43.4%) with synchronous tumours 341 (56.6%) with metachronous tumours prevalence: 1.82% men with metachronous tumours: average age of 30.02 years at diagnosis of the first tumours men with synchronous tumours: average age of 33.54 years (P < 0.001) at diagnosis of the first tumours 5-year OS synchronous 88%	no information about Funding no coi	2/11 LoE 2b-4

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				5-year OS metachronous 95% 5-year DSS synchronous tumour 89% 5-year DSS metachronous 95% synchronous tumour group: higher clinical stage, discordant histology negatively impacted on OS and DSS rates metachronous tumour group: higher clinical stage, a time interval between tumours of > 60 months, presence of bilateral concordant histology (mainly seminomatous tumours) negatively influenced OS and DSS rates		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
Zhao JY 2014	diagnostic accuracy studies Germany, Europe, Israel, Canada, Austria, England, Denmark, Netherlands, Poland, Turkey 1999-2012	patients with testicular cancer n=957 examination in n=807 patients	Diagnostic accuracy of 18F-FDG-PET Sensitivity, specificity, accuracy, positive and negative predictive value, positive and negative likelihood ratio (LR), and diagnostic odd ratio (DOR) of 18FFDG- PET or PET/CT, SROC Vergleich: histopathologic, follow-up data	pooled sensitivity 0.75 (95% CI, 0.70-0.80) pooled specificity 0.87 (95% CI, 0.84-0.89) pooled PLR 7.80 (95% CI, 3.73-16.32 pooled NLR 0.31 (95% CI, 0.23-0.43) pooled DOR 35.57 (95% CI, 12.87-98.29) SROC 0.88	no conflict of interest no information about funding	5/11 LOE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschlusskriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenz-stufe LoE
				Heterogeneity: SPE (X2 P <0.001, I^2 =89.8% PLR (X^2 P < 0.001, I^2 =89.7%) DOR (X^2 P =0.001, I^2 =78.5%)		

9.4. Evidenztabellen der Primärstudien

9.4.1. Kapitel 4

Referenz	Studientyp	Studienziel	Patienten	Intervention	Endpunkt	Ergebnis	Schlussfolgerung
Albany C 2018	retrospective data base study 1998 – 2014 USA	to compare our overall survival (OS) to that of the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program	n=704 with metastatic germ-cell tumor (GCT) and started first-line chemotherapy	SEER database patients 2000 – 2014 SEER historical stage of distant n=1283	PFS, OS probabilities at 5 yrs	IU testis cohort: 5-year OS 94% (95% CI 91% - 96%) SEER 'distant' cohort: 5-year OS 75% (95% CI 73% - 78%)	The MDC approach to GCT at high-volume cancer center associated with improved OS outcomes in this contemporary dataset. OS is significantly higher in the IU cohort compared with the IGCCCG and SEER 'distant' cohort.
Carey K 2016	prospective Evaluation	Präsentation von Erfahrungen nach 12 Monaten mit der „rapid access outpatient clinic“	All adult males with scrotal swellings or discomfort suggestive of TCa n=74	„rapid access outpatient clinic“	primary outcome: incidence of TCa in the referred patient cohort. Secondary outcome: waiting times prior to clinical review and waiting times prior to radical orchidectomy in patients diagnosed with TCa.	TCa was the most common diagnosis and was found in 18 (25 %) patients. Patients diagnosed with TCa underwent radical orchidectomy, a median of 3 (range 1–5) days after their initial GP referral. Patients requiring surgical intervention for benign scrotal pathology underwent their procedure a median of 32 (range 3–61) days after their initial referral. Of the 18 patients diagnosed with TCa, 9 (50 %) were	The RATC is a new initiative in Ireland that provides expedient and definitive treatment of patients with newly diagnosed TCa. Early treatment will ultimately improve long-term prognosis in this patient cohort.

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						diagnosed with a seminomatous germ cell tumour on histopathology.	
Collette L 1999	randomized trial 30895/TE13	Explored whether there is an association between experience of the treating institution with this disease and the long-term clinical outcome of patients, particularly patients with a poor prognosis.	380 nonseminoma patients 49 institutions (65% of patients with IGCCCG poor prognosis)	1 of 4 treatments: 4 cycles of bleomycin–etoposide–cisplatin followed by two cycles of etoposide–cisplatin (BEP/EP) 3 cycles of bleomycin–vincristine–cisplatin followed by three cycles of etoposide–ifosfamide–cisplatin–bleomycin (BOP/VIP-B) either granulocyte colony-stimulating factor (filgrastim) nothing. Institutions were divided into four groups based on the total number of patients entered in the trial: <5, 5-9, 10-19, ≥20	Overall Survival time to progression failure-free survival rate of complete response	Patients in institutions with fewer than 5 patients had an overall survival statistically significantly worse (P = .010; hazard ratio = 1.85; 95% CI = 1.16–3.03) Overall survival and failure-free survival were similar among institutions that entered at least five patients.	patients treated for poor-prognosis germ cell cancer in institutions that entered fewer than five patients in the EORTC/MRC trial 30895/TE13 have a poorer outcome than those treated in larger institutions. the treating institution appears to be a prognostic factor of the same magnitude as the established pretreatment characteristics. Potential explanations are related to the protocol treatment compliance and management of treatment-related toxicity.
Cost N 2016	retrospective analyse of	to compare oncologic	n= 183 patients,	no intervention	Staging	Patients initiating care outside were	AYA patients initially treated for TC in the

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	institutional TC database	outcomes of adolescent and young adult (AYA) patients with TC treated from the outset at an AMC to those whose care was initiated elsewhere with subsequent referral.	n=59 initiated TC care outside n=124 were managed initially at an AMC		histology	more likely to have non-seminoma histology and more often presented with metastatic disease (Stage II [30.5%] or III [35.6%] vs. Stage II [19.4%] or III [19.4%]; p=0.007). Lower 3-year event-free survival (EFS) was observed in those initiating treatment outside an AMC (60.6% vs. 78.7%; p=0.027). However, on multivariate analysis adjusting for stage and histology, the location of initiating TC care was no longer significant (hazard ratio=1.5, 95% confidence	community and subsequently referred to an AMC were initially observed to experience worse EFS than those who were managed at an AMC from the outset. However, on multivariate analysis, these findings were largely explained by referral bias, where AYA patients with advanced disease were more likely to be referred to AMCs.
Gschwend JE 2011	Narrative review	Bericht über Zweitmeinungszentren Hodentumor	Rationale: Im Vgl zum MammaCa und PCa besitzt der KZT eine geringe Inzidenz. Daher hier keine Zertifizierung von spezialisierten Zentren sondern Zweitmeinung zur Verbesserung der Versorgungsqualität. Im Gegensatz zur Versorgung von Patienten mit PCa ist bei der Primärtherapie	Initiator: Deutsche Hodentumorstudiengruppe plus DGU Ziel: Urologen bei dezentraler Versorgungsstruktur unkompliziert und flächendeckend die Einholung einer Expertenmeinung zu ermöglichen sowie	Beschreibung des Ablaufs	Systemablauf: Nach einmaliger Nutzerregistrierung erfolgt Anonymisierung der Patientendaten. Patienten Datensatz auf 21 Therapie relevante Datenfelder minimiert. Der Nutzer kann eins von aktuell 32 Zentren selektieren und die Anfrage an das gewählte	mittlerweile fast 1500 Zweitmeinungen zu komplexen Behandlungsfällen Ansätze zur Verbesserung der Versorgungsqualität waren: Klinische Studien: haben nach allgemeiner Einschätzung, die Behandlungsergebnisse nur geringfügig verbessert.

Referenz	Studientyp	Studienziel	Patienten	Intervention	Endpunkt	Ergebnis	Schlussfolgerung
			die operative Expertise eher nachrangig.	leitlinienkonforme Therapie zu gewährleisten. Projekt ab 2006, initial von der DKH gefördert		Zentrum senden (Schritt 1). Arzt des jeweiligen Zweitmeinungszentrums gibt daraufhin eine Therapieempfehlung (Schritt 2). Das Projekt wird von einem Datenzentrum begleitet, welches 3 Monate nach Anfrage an Zweitmeinungszentrum recherchiert, welche Therapie schlussendlich erfolgte (Schritt 3 und 4). Durch das Datenzentrum wird zudem 2 Jahre nach Anfrage ein Follow-up durchgeführt. Durch ein Audit erfolgt in jährlichen Abständen eine Kontrolle der Leitlinienkonformität von Zweitmeinungsempfehlungen, die diskrepant zur Erstmeinung waren.	Evidenzbasierte Leitlinien: seit 1997, aufgrund fehlender flächendeckender Implementierung Versorgungsergebnisse nur punktuell verbessert Zweitmeinungszentren: aktueller Ansatz, flächendeckendes Angebot zur Konsultation von Zweitmeinungen vor der initialen therapeutischen Weichenstellung nach erfolgter Orchiektomie und Ausbreitungsdiagnostik; online via Datenmaske
Harari SE 2017	Single center Database study	Study compares the experience at a large academic institution with a uniquely high	2014-2015 enrolled 221 consecutive cases	Cases were evaluated for comparison of final diagnoses between the outside institution	Concordance of pathology evaluation	31% showed some discrepancy of histologic subtype Overall, reporting of Lymphovascular	study revealed significant discrepancy involving multiple parameters between original and second opinion pathology

Referenz	Studientyp	Studienziel	Patienten	Intervention	Endpunkt	Ergebnis	Schlussfolgerung
		volume of orchiectomy cases vs. that of other hospitals		and central pathology review		invasion changed in 22% of cases of those, initially called positive 23% were changed to negative of those initially called negative 12% were changed to positive overall discrepancy for spermatic cord invasion was 9%, an initial positive diagnosis was negated in 35% pathologic stage was altered in 23%, mostly secondary to differences interpreting lymphovascular and spermatic cord invasion.	reports. Pathologists evaluating orchiectomy specimens should be aware of the major pitfalls in classification and staging, many of which may affect patient management
Jeldres C 2014 Abstract data	National Cancer Data Base, retrospective	to measure the effect of expertise in TGCT in the US. We hypothesized that hospital volume is associated with overall survival in clinical stage III (CSIII) TGCT.	79119 TGCT patients Inclusion criteria: CSIII at diagnosis and chemotherapy Median age at diagnosis 32 yrs (18-84)	Hospital volume defined as the number of TGCTs diagnosed per hospital per Year. since its distribution was bimodal with an early peak and a second peak of volumes above 60, we	Overall survival OS	Therapy delivered in community, "comprehensive" community and academic hospitals in 10.0%, 47.3% and 40.5% PC-RPLND performed in 1295 (15.8%) patients Median hospital volume was 8 (from 1 to 115 cases per year)	Patients with advanced metastatic testicular cancer treated at high volume hospitals exhibit better overall survival rates compared to their counterparts. results suggest that broad efforts should be made to develop and improve collaborative care models among institutions in order to

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			median follow-up 5.7 yrs	categorized by tertiles below 60 (1-5, 6-10, 11-60) and a fourth group of “>60”.		Death in 1225 (24.8%) patients At 5 years, OS was 74.3%, 76.9%, 75.2%, 86.1% for hospital volume categories 1-5, 6-10, 11-60 and >60 greatest disparity for risk of death was between groups 1-5 and >60 (HR: 0.85, p=0.03).	disseminate the experience of higher volume centers.
Moynihan C 2009	Prospective single center database study	To identify predictive factors of adherence to medical advice, specifically the likelihood of attendance to a recommended follow-up regimen in patients with newly diagnosed testicular cancer.	Enrolment 1992 and 1995 Median follow up 7 yrs	self-reported questionnaires to score a range of psychosocial factors followed by analysis of subsequent attendance behaviour	nonadherence to medical advice	184/209 eligible patients with complete data 17% were classified as nonattenders No significant differences found between attenders and nonattenders in the majority of psychosocial and medical variables that might have predicted nonadherence to medical advice highly significant association between nonattendance and a patient’s perception of an unsatisfactory affective relationship with his clinician (P = .005; hazard ratio,	patients who perceived an unsatisfactory affective relationship with their clinician that included an inability to trust the clinician and a perception that they were not being treated as a person were subsequently more likely to disregard medical advice regarding follow-up. Improved communication that embraces the needs of patients with testicular cancer to establish a satisfactory doctor–patient relationship may lead to improved adherence to medical advice.

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						3.1; 95% CI, 1.4 to 6.6).	
Paffenholz P 2017	Database study, retrospective, single center	investigation of frequently occurring mistakes in the diagnosis of and therapy for TC considering EAU guidelines	Enrolled 2015-5016 147 patients identified, 131 eligible	None-guideline-concordant treatment was defined as treatment that was not in line with the EAU guidelines. It was further subdivided into overtreatment, undertreatment, inappropriate treatment, and misdiagnosis, similar to the categories used in a recent study patients subdivided into 2 groups according to whether the none-guideline-concordant care had occurred at an outside, low-volume hospital before referral to our institution or at our high-volume institution.	Recurrence OS (not available for 5 patients)	Of the 131 primary treated patients, 23 (18%) had received a none-guideline concordant treatment. The most common error was undertreatment (n= 12; 52%), mainly due to missing chemotherapy cycles. Overtreatment occurred in 30% of patients (n = 7); however, inappropriate treatment (n = 2; 9%) and misdiagnosis (n = 2; 9%) were rarely observed. In salvage therapy, none-guideline concordant treatment was observed less frequently compared to patients receiving primary therapy (12% vs. 18%). Of the 131 patients, 35 developed a relapse, 23 of whom were treated correctly and	Despite the standardization of treatment by interdisciplinary guidelines, its integration into daily practice remains limited. Undertreatment of TC patients is associated with significantly reduced relapse-free survival and should thus be avoided.

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						6 of whom were undertreated. Undertreatment of patients resulted in significantly reduced relapse-free survival compared with guideline-concordant management in primary treated patients (P= .005).	
Rigaud J 2014	Survey, crosssectional	to conduct a declarative survey on professional practices among urologists of the French Association of Urology (AFU) and pathologists of the International Academy of Pathology, French Division, concerning their management of testicular cancer.	997 urologists 1200 pathologists	Self-designed questionnaires	Management of TC	289/997 answers 84/1200 answers 75% of urologists performed <5 orchidectomies per year. Pathologists examined < 5 orchidectomy specimens per year in 24% of cases. The laboratory work-up (only alpha fetoprotein [AFP], lactate dehydrogenase [LDH], and total	failure to comply with clinical practice guidelines concerning the staging to be performed as part of the initial diagnostic assessment, because only 31.8% of urologists performed this staging at least according to guidelines (AFP, LDH, total hCG, testicular ultrasound, and chest, abdomen and pelvis CT scan). Similarly, less than 15% of urologists were familiar with the prognostic factors used to determine the indications for adjuvant therapy of stage I tumors.

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						human chorionic gonadotropin [hCG]) strictly according to guidelines in 15.9% radiological workup (only testicular ultrasound and chest, abdomen, and pelvis CT scan) were performed strictly according to guidelines 65.7% 31.8% of urologists performed the minimum assessment required by guidelines (AFP, LDH, total hCG, testicular ultrasound and chest, abdomen, and pelvis CT scan plus other examinations not recommended). Prognostic factors of stage I tumors, to define the indications for adjuvant therapy, correctly declared in 7.3% of nonseminoma (vascular and/or lymphatic emboli) Prognostic factors of stage I tumors correctly declared in 13.8% of seminomas (tumor size >4 cm	Resulting questions: how can we ensure that guidelines are more rigorously applied? Should testicular tumors be treated exclusively in referral centers or expert centers able to apply the appropriate guidelines to ensure optimal management, resulting in better survival, and quality of life for patients?

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						and rete testis invasion)	
Rusner C 2013	database study (health insurance data from BKK)	to explore the patterns of care regarding the use of CT imaging in management of testicular cancer patients in Germany.	177 newly diagnosed Cases Enrolment 2004-2009	compared the number of CT scans actually applied with the contemporary guideline recommendations for follow-up	Guideline adherence effective radiation dose attributable to the use of CT scans	im Mittel 4,4 CT-Untersuchungen (Standardfehler: 0,4), während gemäß Leitlinien im Mittel 6,2 Untersuchungen erwartet worden wären. Die geschätzte diagnostische Strahlenexposition war im Median 30 mSv (Interquartilenabstand:10–54 mSv).	Abdominal CT imaging was considerably less frequently Employed during follow-up than advocated in contemporary national guidelines. This deviation from guideline recommendations may be attributed to several competing factors including unfamiliarity of clinicians with guidelines in follow-up care of testicular cancer patients as well as poor acceptance of the high numbers of CT scans scheduled. In future, a prospective cohort study should be initiated
Salsman JM 2016	Prospective single center database study	to examine rates of and factors predictive of oncologists' compliance with national guidelines for discussing potential treatment-related infertility	young adults with cancer (ages 18–39) comprehensive cancer center enrolment 2010-2012		fertility preservation	454/1018 patients included (M=31.5 years old, 67.8% women) 83% of patients were informed about potential treatment-related infertility (of those patients with TC 100% informed)	Reported compliance with fertility preservation guidelines was greater than published rates. Higher compliance rates in female patients and in patients with cancers more common among young adults may reflect greater awareness of fertility-related concerns among

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						significant effect for patient gender (OR=3.57, CI: 1.33, 9.60, p=0.012) with females being more likely to be informed than males.	these patients and their providers.
Schrader M 2009	Data from Second-opinion centers	Dieser Artikel gibt einen Überblick über die Zwischenergebnisse des Projekts.	Enrolment 2006 to 2008	Comparison of expert opinion	Diskrepanz der Erstmeinung vs. Zweitmeinungs Therapiewechsel	Eine Diskrepanz zwischen Therapieplan des Anfragenden und Therapieempfehlung des Zweitmeinungszentrums bestand in 32,3%. Bei diskrepanter Empfehlung war die definitive Therapie in 71,8% der Fälle mit der Zweitmeinung kongruent. Eine diskrepante Zweitmeinung führte in 40,3% (26,5%) zur Vermeidung von Über- bzw. Untertherapie.	Die bisher vorliegenden Ergebnisse des „Zweitmeinungsprojekts Keimzelltumoren“ zeigen, dass eine gemeinsam von Niedergelassenen und Klinikern mit Zweitmeinungszentren erfolgte Therapieplanung zu einer Verbesserung der Implementierung von Leitlinienempfehlungen beiträgt. Die alleinige Publikation von Therapieleitlinien weist dagegen einen limitierten Effekt auf, wie die Abweichung der primären Therapieplanung von der Leitlinienempfehlung von 32,3% unterstreicht. Wir appellieren angesichts der bisherigen Ergebnisse an alle Kollegen das Zweitmeinungsnetzwerk bei der Therapieplanung zu nutzen.
Schrader M 2010	Data from Second-opinion centers	Describe aims and	Enrolment 2006 to 2008	Comparison of expert opinion	Discrepancy in opinions	discrepant second opinions in a third of	Published guidelines for germ cell cancer are applied only sporadically

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		preliminary results of the second opinion project.			Change in treatment Guideline adherence	the cases, their treatment scope related to that of the first opinion, and their degree of implementation, it appears that second opinions prevented overtreatment in 10.7 cases and undertreatment in 16. Approximately every sixth second opinion resulted in a relevant change in the scope of therapy.	and should be supported by second-opinion systems
Schrader M 2016	Datenbankstudie Zweitmeinungsprojekt	Zwischenbilanz des Zweitmeinungsprojekts zur Verbesserung der Versorgungsqualität	2515 />4750 Zweitmeinungsanfragen (Stand 05/2016) Anfrage von 536 Ärzten (in etwa 22% der Hodentumorpatienten in Deutschland) Nicht-Seminome (47,1%) Seminome (47,8%)	Vergleich der Erst- und Zweitmeinung	Diskrepanz der Erstmeinung vs. Zweitmeinungs Therapiewechsel rezidiv- bzw. Progressionsfreier Verlauf	Rücklaufquote für die Therapieangaben betrug 77% (1328/1737) und 72% (575/800) für das 2-Jahres-Follow-up fast die Hälfte der Primärbehandler niedergelassene Urologen sind, in etwa ein Viertel als Oberarzt und 13% bzw. 4% als Chef- oder 6% als Assistenzarzt in 32% der Fälle eine Diskrepanz zwischen Erst- und Zweitmeinung.	Das Zweitmeinungsprojekt trägt maßgeblich zu einer Verbesserung der Behandlung des Hodentumors in Deutschland bei.

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			klinisches Stadium I: 59% vs. klinisches Stadium II-III: 37 %			Erhöhte Diskrepanz bei zunehmendem Tumorstadium (<0,001) In 40% weniger intensiven Therapievorschlag als vom Anfragenden In 16% Zweitmeinung therapieintensiver jede 6. Zweitmeinung führt zu einer relevanten Änderung der Therapie (Reduktion in etwa 3-mal häufiger war als eine Intensivierung) progressionsfreie Überleben im Gesamtkollektiv 90,0%	
Silva MV 2012	Retrospective database study, single center	determined the total amount of diagnostic radiation that a patient with testicular cancer receives during the course of treatment and the associated risk of secondary malignancy	55 seminoma 64 nonseminoma Enrolment 2002-2010	Using the nomograms by Brenner et al the average amount of ionizing radiation for a given imaging study was determined using a typical exposure of 20 mSV per abdominopelvic CT with or	total amount of diagnostic radiation Rate of secondary malignancy	Between the groups no difference was found in the lifetime (215.5 and 214.1 mSV, p = 0.96) or the annual (104.6 and 104.6 mSV, respectively, p = 1.0) radiation dose. Of the 41 patients with more than 5-year followup 32 (78%) were in violation of	Radiographic followup protocols for GCT vary based on patient risk characteristics and institutional paradigms. Patients with GCT seem to be at increased risk for secondary malignancy even when they are not treated with chemotherapy or

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				without contrast medium, 40 mSV per abdominopelvic CT with and without contrast medium, and 6.5 mSV per chest CT.9 Chest x-rays were initially tabulated with an expected dose of 0.01 mSV per examination.		guidelines by exceeding 20 mSV per year of radiation. 74 patients (61.7%) received 50 mSV or greater of radiation during a 1-year period. Using the previously calculated excess relative risk for solid cancer and leukemia, excluding chronic lymphocytic leukemia, the RR was 68 and 329, respectively, with a 2.1% lifetime risk of fatal cancer over the baseline risk	therapeutic radiation. Since patients with GCT are generally young men with long life expectancy, their additive exposure to radiation accrues for decades. At a tertiary care center with experience with managing testicular cancer the amount of radiation exposure in a contemporary cohort exceeded current national and standard radiation safety limits in 78% of patients followed longer than 5 years. Imaging should be done judiciously in this population at high risk for radiation overexposure and the expanded use of magnetic resonance imaging must be considered.
Vlayen J 2012	Systematic review	developing and measuring an indicator set to monitor the quality of testicular cancer care, to make comparisons over time and to support quality	TC patients	preliminary list of 32 indicators, resulting from the literature search and addition of guideline-based indicators, was subjected to a formal assessment by six	Quality indicators evolution over time	From the original set of 32 quality indicators, 12 were finally retained Table 1 for process and outcome indicators (see below). Of the 12 finally selected indicators,	feasibility to develop a multidisciplinary set of quality indicators for testicular cancer. Using national cancer registry data linked to claims data, eight indicators were measurable, showing a mixed picture of the quality of care for

Referenz	Studientyp	Studienziel	Patienten	Intervention	Endpunkt	Ergebnis	Schlussfolgerung
		improvement for all practitioners and centres involved		experts based on four criteria: reliability, relevance, interpretability and actionability. Measurability was no selection criterion a priori.		5 were fully and 1 was partly measurable, while 2 indicators were measurable using proxy information. Five-year relative survival was 97%, 95% and 76% for pStage I–III, respectively. Overall 5-year survival slightly improved from 91% in 2001 to 94% in 2004. Between 2004 and 2006, 14 of 97 centres performedP10 orchidectomies. Large variability was found between centres. The nine centres with a 5-year observed survival below the lower limit treated less than 20 patients between 2001 and 2006.	testicular cancer patients in Belgium. Survival is good, but there are indications of over- and underuse of certain interventions. Above this, the results suggest an important variability and dispersion of care.
Wayment RO 2011	Cross-sectional, multicenter	to evaluate the utility of second opinion pathology in patients who are seen in consultation for urologic malignancy.	Mixed oncologic patient population	Comparison of opinions	Disagreement between opinions Change in care	264 patients, of those testis cancer 5 (2%) Disagreement with the original diagnosis was found in 22 cases (10%), of which 18 (8%) were	A second opinion review of surgical pathology for urologic malignancy can result in major therapeutic and prognostic changes, which can impact patient care.

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						classified as major, and 4 (2%) were classified as minor.	Our results support the review of all pathology by the urologist and pathologist as part of the consultation in patients with urologic malignancy.
Woldu SL 2018	retrospective analysis of National Cancer Database (NCDB) data	to review the degree to which TGCT care is centralized in the United States, and to assess the effect of TGCT-specific hospital volume on testicular cancer outcomes andt reatment patterns	n=33.417 patients with TGCT n=1.239institutions	no intervention	Overall survival OS analysis of patient characteristics seeking care stratified by case volume at different centers and the effect of hospital volume on treatment patterns.	multivariate analysis: volume hospitals and overall mortality: high-intermediate HR 1.28 (95% CI 1.01-1.63) intermediate HR 1.45 (95% CI 1.15-1.81) low-intermediate HR 1.48 (95% CI 1.18-1.85) low HR 1.83 (95% CI 1.36-2.46) favours case volume	TGCT case volume appears to play an important role in treatment patterns and survival in more advanced TGCT, however, we could not discern a survival difference among hospital volume in patients presenting with localized TGCT. This may be due to the excellent survival of patients with stage I disease, regardless of subsequent management strategy. These findings should inform discussion of the appropriateness of centralizing care for rare disease such as TGCT.
Yu HY 2009	private insurance claims database study	compliance with follow-up protocols developed at referral centers within the community	patients with stage I testis cancer	Comparison of protocols	Compliance rate	Surveillance was widely used in the community. Compliance with surveillance and postadjuvant therapy follow-up	Surveillance is a widely accepted strategy in clinical stage I testicular cancer treatment in the community. However, follow-up care recommendations

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						testing was poor and degraded with increasing time from diagnosis. Nearly 30% of all surveillance patients received no abdominal imaging, chest imaging, or tumor marker tests within the first year of diagnosis. Patients who elected RPLND were most compliant with recommended follow-up testing within the first year. Recurrence rates were consistent with previously reported literature, despite poor compliance.	developed at referral centers are not being adhered to in the community. Although recurrence rates are similar to those of reported literature, the clinical impact of noncompliance on recurrence severity and mortality are not known. Further prospective work needs to be done to evaluate this apparent quality of care problem in the community.
Zengerling F 2013	Nutzerbefragung	Umfrage an Nutzer zum Zweitmeinungsportal	440 Primärbehandler angeschrieben	24 item questionnaire	Ergebnisse der Nutzer	Rücklauf 192/440 Antworten Teilnehmer: niedergelassener Urologe 47,4%, 24,2% Oberarzt, 13,2% Chefarzt, 10,5% Assistenzarzt neu diagnostizierte Patienten: ≥5/Jahr: 59,4% der Teilnehmer	Das „Zweitmeinungsprojekt testikuläre KZT“ der GTCSG stößt auf breite Akzeptanz bei Primär- behandlern von KZT Patienten. Für mehr als 2500 KZT Patienten wurde bislang eine Zweitmeinung eingeholt (Stand: Juli 2013). aktuellen Überarbeitung der Homepage:

Referenz	Studientyp	Studienziel	Patienten	Intervention	Endpunkt	Ergebnis	Schlussfolgerung
						≥10 Patienten/Jahr: 25,9% „2–4 Patienten/Jahr“ 36,8% „0–1 Patienten/Jahr“ 3,8%	Einführung eigener Eingabepfad für Patienten mit Rezi- div oder Progression Die Teilnehmer befürworten zum großen Teil (77,1% der Fälle) dieses System
Zengerling F 2014	Database study	results of the ‘National Second-Opinion Project on Testicular Cancer’ after a period of 5 years, including data from the first 2 years of follow-up.	1,284 requests with 926 eligible cases 350 urologists/ physicians to interim analysis, with only the requests from urologists working in private practice or hospital departments (but not one of the 31 second-opinion centers) November 2006 to October 2011.	Comparison of opinions	Rate of discrepancy among 1. And 2. Opinion Degree of complicance with recommended treatment PFS	discrepancy between first and second opinion: 39.5% Discrepant second opinions led to less extensive treatment in 28.1% and to more extensive treatment in 15.6%. 2-year PFS: 90.4%	Approximately every 6th second opinion led to a relevant change in therapy. data from every 8th testicular cancer patient in Germany were submitted to second-opinion centers. Second-opinion centers can help to improve the implementation of evidence into clinical practice.

9.4.2. Kapitel 5

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
Bueno ATP 2017	Review of Cochrane systematic reviews	Inclusion criteria: Only Cochrane systematic reviews on effectiveness and safety, including randomized, quasi-randomized or non-randomized clinical trials as primary studies. Systematic reviews focusing on diagnostic accuracy were excluded.	screening and diagnostic tests for cancer	However, 6 of the 17 reviews did not find any clinical trial that met the inclusion criteria, and therefore the authors of those “empty reviews” were unable to provide recommendations on the benefits and risks of screening. These last reviews were on screening for bladder, breast, nasopharyngeal, esophageal, *testicular* and cervical cancer.	Sources of funding: None declared Conflict of interest: None declared	3/11 LoE nicht bestimmbar, da “leeres Review”
Chan E 2014	retrospective prospective non – RCT, RCT study period: 1950-2008	no information about patient characteristics total n= 3776* no information about countries	timing of orchiopexy outcomes: fertility testicular malignancy	no pooled analysis conclusion: fertility: Orchiopexy should be performed after 6 months of age, to allow for possible natural descent. If the testis remains cryptorchid after 6 months, orchiopexy should be performed as soon as possible—and certainly before 1 year of age—to optimize fertility outcomes	no information about coi and funding	4/11 LoE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
	no information about countries	*=Eigenberechnung		testicular malignancy risk for cancer is greatly increased when orchiopexy is delayed until after 10–11 years in cryptorchid boys to protect against the increased risk of testicular cancer, we recommend that orchiopexy should be performed as early as possible (ideally between 6 and 12 months of age, as this would also optimize fertility potential)		
Cook MB 2010	67 studies case-control or cohort study retrospective und prospective Sweden, Norway, USA, Canada, Denmark, UK, Czech Rep, France, Germany, Greece, Italy, Japan, 1976-2008	no information about patient characteristics, inclusion criteria total n=kA	Perinatal variables: birth length, birth weight, gestational age, cryptorchidism, inguinal hernia, neonatal jaundice, twinship, having been breast fed	Association with risk of cancer: Birth length: OR 1.00 (95% CI 0.98-1.01) birth weight: (OR 0.94, 95% (CI) 0.88–1.01) low birth weight (OR=1.34, 95% CI 1.08–1.67) high birth weight (OR=1.05, 95% CI 0.96–1.14) gestational age (per week (OR=0.95, 95% CI 0.92–0.98) low vs not (OR=1.31, 95% CI 1.07–1.59) cryptorchidism (OR=4.30, 95% CI 3.62–5.11) inguinal hernia (OR=1.63, 95% CI 1.37–1.94) neonatal jaundice (OR=1.05, 95% CI 0.86-1.28)	National Institutes of Health, National Cancer Institute	5/11 LoE 2a-3a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
				twinning (OR=1.22, 95% CI 1.03–1.44) breast fed (OR=0.96, 95% CI 0.68-1.36)		
De Souza KW 2011	retrospective case series, cohort, expert opinion prospective quasi-experimental 1984-2007 no information about countries	no information about patient characteristics no information about included patients	Testicular Cancer Prevention Strategies	no pooled analysis Testicular Cancer Prevention Strategies: Perform the self-exam after a warm bath or shower: the testicle should be examined delicately between the thumb and the other fingers, observing the presence of nodes, swellings or other alterations. The process should be repeated with the other testicle. Remember that a normal testicle is oval-shaped, with firm and elastic consistency. Perform the testicle self-exam every 6 months. Submit to orchiopexy in the pre-puberty phase in case of cryptorchidism. Construct a multidisciplinary protocol for testicular cancer prevention. Theoretical-practical training for the team. Identify children who had cryptorchidism.	no information about coi and funding	3/11 LoE 2a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
				Perform the physical testicular exam, observing the person's age and risk factors. Train secondary education teachers on risk factors and prevention measures, and discuss the main aspects involving testicular cancer prevention and testicular self-exam in health education programs for a secondary education public. Promote strategies for testicular cancer prevention in companies with a high number of male employees, and also in commercial establishments and waiting rooms. Perform health education by showing testicular self-exam videos		
Gurney J 2015	3 studies case-control Study retrospective USA 2009-2012	Inclusion criteria: ni information provided Exclusion criteria: -Non-germ cell tumours -Chorio-carcinoma -Age (<18 or >44) -No telephone -Non-English-speaking -Age (<18 or >50)	Cannabis use	Ever-use compared to never-use: OR 1.19, 95% CI 0.72-1.95 Former use and TGCT: OR 1.54, 95% CI 0.84-2.85 Current use and TGCT: OR 1.62 95% cI 1.13-2.31) Frequency (weekly and greater use) and TGCT: OR 1.92, 95% CI 1.35-2.72	No conflicts of interest. funded by the Health Research Council of New Zealand	7/11 LoE 3a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
		-Extragonadal tumours -Age (<18 or >35) -Born in U.S.A., Canada, Europe or Middle East total n=2138 719 cases 1419 controls		Duration (>= 10 ys vs. never use) and TGCT: OR 1.50, 95% CI 1.08-2.09 Cannabis-use and non-seminoma development: OR 2.09, 95% CI 1.29-3.37		
Huang SV 2018	cohort studies case control studies 1991 - 2009	Inclusion Criteria: Males Intensity- moderate-strenuous Frequency- e.g. >5 days/wk Duration- e.g. 1h/day Intensity- sedentary-light Frequency- e.g. < 5 days/wk Duration- e.g. <1h/day Any testicular cancer	no intervention physical activity as risk factor	no meta-analysis On balance, there is presently no strong evidence of an association between physical activity and risk of subsequent TC.	Cancer Society of New Zealand (Wellington Division) no coi	8/11 LoE 2a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
		Seminoma Non-seminoma No limit placed on initial search criteria Exclusion criteria Animal studies Studies that do not report association between exposure and outcome no information about patient characteristics no total numbers of patients				
Ilic D 2011	RCT 19 potentially relevant articles identified until June 2010	randomised controlled trials and quasi randomised controlled trials Adult men either physical examination by a	testicular cancer-specific mortality quality of life, adverse outcomes	empty review, because after fulltext screening no RCT met the inclusion criteria	no coi no funding	LoE 5 empty review

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
		physician or patient self-examination				
Lerro CC 2010	retrospective cohort, case-control UK, Denmark, Canada, Greece, Germany, USA, Sweden, Norway 1989-2009	no information about patient characteristics total n=14.262	height weight BMI Overweight Obese vs. normal weight Odds Ratio OR	overall: OR 1.13 (1.07-1.19) weight OR 1.0 (1.00-1.01) bmi OR 0.99 (0.97-1.00) overweight 25<bmi<30 OR 0.92 (0.86-0.98) obese BMI >30 OR 0.93 (0.75-1.15)	National Cancer Institute, NIH no information about coi	2/11 LoE 3a
Lip SZL 2013	9 case-control studies 3 cohort studies	exclusion criteria: boys at risk of testicular cancer for reasons other than cryptorchidism (eg,	Isolated cryptorchidism	case-control studies RR=2.47, 95% CI 1.91 to 3.18; p<0.0001 cohort studies	Competing interests None.	6/11 LoE 2a-3a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
	retrospective USA, Czech Rep., Canada, Germany, France, Sweden, Denmark, UK 1980-2010	hypospadias, subfertility, carcinoma in situ, microlithiasis or cancer families total n= 2.185.033		RR=3.77, 95% CI 2.65 to 5.37; p=0.01 overall significant risk of having cryptorchidism and developing testicular malignancy: RR=2.90, 95% CI 2.21 to 3.82	no information about funding	
Pedersen MR 2016	no information about study designs Turkey, Netherlands, USA, Italy, Singapore, Brazil, Korea, Greece 1998 - 2015	inclusion criteria: if TML was diagnosed by US if a risk condition was reported if the particular risk condition was reported in more than one article there were no criteria on number of patients enrolled in each study patient characteristics:	no intervention testicular cancer testicular microlithiasis as risk factor	no meta-analysis data available Data in the literature seem to support the conclusion that TML is not an independent risk factor for testicular cancer. In male infertility, TML appears to be related to an increased risk possibly as part of a testicular dysgenesis syndrome	no coi no information about funding	2/11 LoE?

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
		Fallzahl: n=9920 kA zum Follow-Up mean age: 2,4 – 28,3 yrs				
Rovito MJ 2015	RCT's, quasi-experimental prospective kA zu Ländern 1985-2014	no information about inclusion criteria exclusion criteria: Participants who have sought care at a genitourinary medical clinic as these individuals may be more apt to follow recommended pelvic (i.e., testicular) health regimens than others.	Outcome: TSE behavioural outcomes: Information on testicular cancer risks, TSE knowledge, behaviours (discussions with health care professionals about testicular cancer and TSE), preferences (intentions to self-screen or not), and behavioural outcomes (exercising of TSE)	Knowledge $\chi 2 = 9.69$, $p < .05$ (patient–volunteer group compared with others) Knowledge $\chi 2 = 9.69$, $p < .01$ (physician-conversation vs. no physician discussion) Knowledge $F = 10.59$, $p < .0001$ (comparing experimental groups with control condition; more comprehensive curriculum associated with higher reported TSE) Knowledge/awareness $\chi 2 = 11.11$, $p < .004$ (TPB-group compared with others). Attitudes and beliefs about TSE and TC	no conflicts of interest no financial support	5/11 LoE 1a

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		total n= 2.786		t (276) = 8.68, p < .001 (Read + practice compared with others; read + read also higher than control condition) Completeness of TSE r = .37, p < .05 (for mailed postcards compared with performance efficacy; authors related self-reported TSE performance should equate with better performance technique posttest) Duration of TSE t(46) = .98, p > .30 (for social support vs. control group analysis) Knowledge χ2 = 4.61, p < .05 (intervention group vs. control group) Knowledge χ2 = 7.59, p < .006 (posttest TSE report vs. pretest TSE report) Knowledge χ2 = 1.38, p < .50 (across all groups for reported TSE) Attitude F = (1, 169) = 6.084, p < .015 (shower cards and attendance at campaign events only for mean change in behaviors)		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
				Intention to perform F = (1, 169) = 12.190, p =.001 (exposure to events explained 4.6% of posttest TSE behavior)		
Saab MM 2016	RCT quasi-experimental design: pre-posttest-design, posttest-design only, prospective USA, UK, France, Pakistan, 2004-2014	Inclusion criteria: men, age from 15-86 total n=8.528	Knowledge, awareness, attitude towards TC and TC screening, TC screening interventions and TC screening practice	(Q1) knowledge, awareness, and attitude toward TC; (Q2) knowledge, awareness, attitude, toward TC screening; (Q3) TC screening intentions; (Q4) TC screening practices. Q1: T1: on a scale of 0-9, 50.6% (n = 80) scored <3 on items related to TC causes and outcomes (mean, 3.62), 92.2%(n = 147) did not know that TC is more prevalent among whites. Q2: T1: 46.8% (n = 74) were not aware that most abnormalities are found during TSE. Q3: T2: no difference between EG and CG in terms of intentions to perform TSE (not statistically significant). Q4: T2: 65.2% (n = 30) of EG performed TSE compared with 40% in CG (n = 12) (#2 = 4.61, P <.05) Q1: T2: on a scale of 0-10, EG had higher knowledge scores about	no conflicts of interest no funding	5/11 LoE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
				Q2: T2: EG had greater knowledge (P<.001) and a more positive attitude (P<.001) toward TSE. Q3: T2: EG had a greater intention to perform TSE (R2 = 0.01, P<.001). Q4: NR Q1: Knowledge TC risks such as age increased significantly from T1 (47.5%, n = 48) to T2 (93.1%, n = 94) up until T3 (84.2%n = 80) (P<.05) Knowledge of TC treatment increased significantly between T1 (73%, n = 73) and T2 (92%, n = 92) (P<.05) T1: on a scale of 0-5, the EG and CG had similar TC knowledge (median score, 3) T2: EG scored significantly higher (median score, 4; P = .014) Q2, Q3: NR Q4: T1: No difference in TSE practice between EG and CG (P not reported) T2: EG scored higher than CG on TSE practice (P = .006) Q1: NR Q2: TSE knowledge increased significantly from 4% (n = 3) at T1 to 72% (n = 41) at T2(P<.001) Q3: NR		

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				Q4: TSE practices increased significantly from 2% (n = 1) at T1 to 26% (n = 15) at T2 (P<.001) Q1: T2: participants who read the low vulnerability information (mean, 19.31) and high severity condition information (mean, 19.34) perceived themselves to be more susceptible to TC than those who read the high vulnerability (mean, 16.3) and low severity information (mean, 16.27) (P<.05) Q2: T2: participants exposed to the high self-efficacy message perceived themselves as more capable of performing TSE (mean, 22.16) than those who read the low-self efficacy message (mean, 19.31) Attitude toward TSE increased significantly in T2 (P<0001). Q3:T2: men in the high self-efficacy group and high-vulnerability group intended to perform TSE (P G .06) Intentions to perform TSE increased significantly in T2 (P<.0001). Q4:T1: 58.6% (n = 75) performed TSE in the past year and had their testes checked by a clinician T2: 75.7% (n = 56) Reported performing TSE in the past month; those in the high-efficacy condition had higher odds of performing TSE (OR, 3.09). Q1: Part I: T1: 26.75% (n = 107) received information about TC, 7.75% (n = 31) were		

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				educated about TC risk factors, 63.3% (n = 253) did not know about TC prognosis. Q2: Part I: T1: 16.3% (n = 65) were educated about the importance of TSE, and 9.5% (n = 38) have been taught how to perform TSE. Q3: Part I: T2: mean degree of willingness did not increase significantly (mean, 7.09 at T1 and mean, 7.43 at T2) (not statistically significant); 2.75% (n = 11) became less willing to have testicular palpation, and 15% (n = 60) became more willing to have testicular palpation. Part II: 14.17% (n = 51) Declined examination before the briefing. Q4: Part II: Of those who declined examination (n = 51), 31.37% (n = 16) accepted testicular palpation following the briefing. Q1:T2: on a scale of 0Y10, EG2 had the highest knowledge scores (mean, 8.9; CI, 8.3-9.14) and the lowest perceived severity of TC (P = .007). Q2:T2: EG2 had the highest TSE response efficacy (mean, 6.34; CI, 6.19-6.49; P = .023) and TSE self-efficacy (mean, 6.24; CI, 6.06-6.42; P = .004) EG2 reported significantly greater learning from the message (P = .004).		

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				Q3: EG2 had the greatest intentions to perform TSE at T2 (P = .002) and T3 (P = .011). Q4: NR Q1:T2: 92.6% (n = 25) of EG1, 90.5% (n = 19) of EG2, and 86.4% (n = 38) of CG knew about TC. There was no significant difference between the groups regarding TC knowledge (P = .7). Q2:T2: 74.1% (n = 20) of EG1, 95.2% (n = 20) of EG2, and 75.6% (n = 34) of CG knew about TSE. There was no significant difference between the groups regarding TSE knowledge (P = .13) Overall, 93.5% (n = 87) agreed that TSE improves chances of recovery, and 74.2% (n = 69) agreed that men do not perform TSE because they have now knowledge about this practice. Q3: NR Q4:T2: 25.9% (n = 7) of EG1, 33.3% (n = 7) of EG2, and 20% (n = 9) of CG performed monthly TSE 51.9% (n = 14) of EG1, 47.6% (n = 10) of EG2, and 20% (n = 9) of CG were never screened for TC by a clinician. Q1: T1: deaf men had less TC Knowledge (P<.002) than hearing men		

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				T2: TC knowledge among deaf men (P<.001) and hearing men (P<.001) increased. Postintervention, hearing men had a greater mean change in knowledge (mean difference, 3.82) compared with deaf men (mean difference, 3.46) Q2-Q4: NR Q1: EG: TC awareness increased significantly from T1 to T2 (P<.001) T2: TC awareness in EG was higher than CG (P<.001) T2: Significant increase in awareness among EG (p<.001). Q2: NR Q3:EG: intention to within a month increased significantly from T1 to T2 (P<.001) as compared with CG. EG: compared with T1, there was a significant increase in monthly TSE (P<.001) T2: EG was more likely to perform TSE than the CG (P<.001).		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
Tan IB 2010	case-control, cohort studies 1992-2008 no information about countries	total n=40.379* *=eigene Berechnung	Testic Microlith TM endpoints: TGCT, intratubular germ cell neoplasia of unclassified type, interval TGCT	TGCT in the presence of TM: RR 8.46 (95% CI 4.45-16.08) intratubular germ cell neoplasia in the presence of TM: RR 10.48 (95% CI 5.28-20.81) interval TGCT: no pooled data provided	Funded by National Research Foundation Singapore and Singapore Millenium Foundation no information about coi	4/11 LoE 2a-3a
Wang T 2015	14 studies retrospective 12 cohort-studies, 2 case-control studies UK, USA, The Netherlands, Turkey, Taiwan, Italy	no information about patient characteristics, inclusion criteria total n=35.578 Cohort-studies: n=29.302 Case-control-studies: n=6.276	testicular microlithiasis (TM)	TM was strong associated with an increased incidence of testicular cancer (RR = 12.70, 95% CI: 8.18-19.71, P < .001) Sub group analysis: Geographical region: North America (USA): RR 9.43 (4.58-19.44) European countries: RR 16.31 (11.12-23.94) Asia RR 16.06 (10.04-25.69)	National Natural Science Foundation of China Natural Science Foundation of Guangdong Province Conflict of interest: None declared.	6/11 LoE 2a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessen-konflikte	AMSTAR Bewertung Evidenzstufe LoE
	2000-2014	1493 TM cases 34085 controls		Study design Cohort study RR 13.62 (8.08-22.96) Case-control study RR 7.68 (5.54-10.64) Age <18 RR 13.04 (0.92-184.64) Age >18 RR 12.11 (7.76-18.89) No. of participants ≤ 1000 RR 6.58 (2.32-18.68) No. of participants > 1000 RR 14.80 (10.07-21.76)		

9.4.3. Kapitel 7 Diagnostik Systematische Übersichtsarbeiten

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessenkonflikte	AMSTAR Bewertung Evidenzstufe LoE
Campobasso D 2017	Case series USA, Turkey, D	Synchronous bilateral testis cancer series with more than three patients and containing relevant information about clinical and oncological features in relation to histology and stage n=13 studies n=73 pts median follow-up: 45.4 mo, range 6–145	no intervention overall survival stage histology	no Meta-analysis overall survival of 100% 72.7% (8/11) of bilateral NSGCT are stage III, with 62.5% (5/8) mortality for disease progression. mixed form has a heterogeneous stage presentation: 44.4% (12/27) stage I, 29.6% (8/27) stage II, 26% (7/27) stage III. Only one death for disease was reported in patients with stage III (seminoma + embryonal carcinoma) In conclusion, with modern therapeutic options and the introduction of cis-platinum chemotherapy, most patients with synchronous bilateral testicular germ cell tumours will become long-term survivors with	no coi no information about funding	1/11 LoE 4

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessenkonflikte	AMSTAR Bewertung Evidenzstufe LoE
				the same overall survival and disease specific survival than metachronous patients		
Djaladat H 2014	cohort, case-control, case series retrospective 1983-2010	no information about patient characteristics total n= 503* cases n=135 controls n= 368* *Eigenberechnung	association between TGCT and semen abnormalities before orchiectomy sperm count sperm concentration sperm motility sperm morphology infertility	no pooled analysis mean/ median sperm count: below 20 · 106/mL (oligospermia) total sperm count: 45.3 · 106/ejaculate mean/median sperm motility: below 50% Sperm morphology: < 50% TGCT before orchiectomy was associated with semen abnormalities, a surrogate for infertility.	no competing financial interests exist no information about funding	4/11 LoE 2a-4

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessenkonflikte	AMSTAR Bewertung Evidenzstufe LoE
Müller J 2011 Urologe	no information reported about designs no information about countries 1999-2005	total n=130 (161 lesions) mean age: 39,5 J mean follow-up: 23,6 mo	FDG-PET vs. CT	FDG-PET / CT: Specificity: 92% / 59% Sensitivity: 72% / 63% Größenbestimmung des Residualtumors: FDG-PET / CT: positive predictive value: 70% / 28% negative predictive value: 93% / 86%	no coi no information about funding	2/11 LoE ?
Poon R 2016	no information about designs and countries 07-12/2015	no information about patient characteristics, follow up and cases	diagnostic accuracy; change in patient clinical management, clinical outcomes, or treatment response; survival; quality of life; prognostic indicators; time until recurrence; or safety outcome (e.g., avoidance of unnecessary surgery)	no pooled analysis conclusion Current Recommendations for the Utilization of PET/CT in Testicular Cancer: Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the routine staging of patients with testicular cancer. PET is recommended for the assessment of treatment response in patients with seminoma and residual masses after chemotherapy. PET is not recommended for the assessment of treatment response in patients with nonseminoma. Due to insufficient evidence, a recommendation cannot be made for or	Funding by Ontario Ministry of Health and Long-Term Care no information about coi	2/11 LoE ?

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessenkonflikte	AMSTAR Bewertung Evidenzstufe LoE
				against the routine use of PET for evaluation of recurrence.		
Tan IB 2010	case-control, cohort studies 1992-2008 no information about countries	total n=40.379* *=eigene Berechnung	Testic Microlith TM endpoints: TGCT, intratubular germ cell neoplasia of unclassified type, interval TGCT	TGCT in the presence of TM: RR 8.46 (95% CI 4.45-16.08) intratubular germ cell neoplasia in the presence of TM: RR 10.48 (95% CI 5.28-20.81) interval TGCT: no pooled data provided	Funded by National Research Foundation Singapore and Singapore Millenium Foundation no information about coi	4/11 LoE 2a-3a
Treglia G 2014	Retrospective and prospective and monocentric or multicentric Italy, EU-Countries, Canada, Poland, Germany, USA, Austria, Netherlands, UK 1999-2014	Included: Patients with seminoma (including evaluation of residual masses after chemotherapy and restaging) were eligible for inclusion. Excluded: patients with seminoma at initial staging total n=375	Sensitivity, specificity, accuracy, positive and negative predictive value, positive and negative likelihood ratio (LR), and diagnostic odd ratio (DOR) of 18FFDG- PET or PET/CT in the postchemotherapy management. Diagnostic performance of the PET/PET CT	Sensitivity (95% CI) 0.78 (0.67-0.87) $\chi 2$ = 23.50; df = 8 (P = 0.0028) Inconsistency (I^2) = 66.0% Specificity (95% CI) 0.86 (0.81 to 0.89) $\chi 2$ = 36.14; df = 8 (P = 0.0000) Inconsistency (I^2) = 77.9%	no conflict of interests no funding	6/11 LoE 1a

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessenkonflikte	AMSTAR Bewertung Evidenzstufe LoE
			reference standard used to validate the 18F-FDG-PET or PET/CT findings was quite different in the included studies.	Symmetric SROC AUC = 0.9012 SE (AUC) = 0.0346 $Q*$ = 0.8326 SE($Q*$) = 0.0371 Positive LR (95% CI) 4.59 (2.55 to 8.25) Cochran's Q = 22.63; df = 8 (P = 0.0039) Inconsistency (I^2) = 64.6% τ^2 = 0.4152 Negative LR (95% CI) 0.26 (0.09 to 0.71) Cochran's Q = 60.62; df = 8 (P = 0.0000) Inconsistency (I^2) = 86.8% τ^2 = 1.6377 Diagnostic OR (95% CI) 22.71 (8.79 to 58.68)		

Referenz (Autor, Jahr)	Studiendesigns in den SR/MA: Land, Zeitraum	Ein- und Ausschluss-kriterien Patienten-merkmale Fallzahl n Follow-up	Intervention Zielgröße/ Outcome	Hauptergebnisse und Richtung (direction)	Finanzierung/ Interessenkonflikte	AMSTAR Bewertung Evidenzstufe LoE
				Cochran's Q = 10.50; df = 8 (P = 0.2317) Inconsistency (I^2) = 23.8% τ^2 = 0.4805		
Zhao JY 2014	diagnostic accuracy studies Germany, Europe, Israel, Canada, Austria, England, Denmark, Netherlands, Poland, Turkey 1999-2012	patients with testicular cancer n=957 examination in n=807 patients	Diagnostic accuracy of 18F-FDG-PET Sensitivity, specificity, accuracy, positive and negative predictive value, positive and negative likelihood ratio (LR), and diagnostic odd ratio (DOR) of 18FFDG- PET or PET/CT, SROC comparison: histopathologic, follow-up data	pooled sensitivity 0.75 (95% CI, 0.70-0.80) pooled specificity 0.87 (95% CI, 0.84-0.89) pooled PLR 7.80 (95% CI, 3.73-16.32 pooled NLR 0.31 (95% CI, 0.23-0.43) pooled DOR 35.57 (95% CI, 12.87-98.29) SROC 0.88 Heterogeneity: SPE (X2 P <0.001, I^2 =89.8% PLR (X^2 P < 0.001, I^2 =89.7%) DOR (X^2 P =0.001, I^2 =78.5%)	no conflict of interest no information about funding	5/11 LoE 1a

9.4.4. Kapitel 7

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
Dieckmann KP 2013	retrospective multicenter cohort study n=228 2006-2010 D	men with unilateral GCTs and biopsy-proven contralateral TIN Mean (SD) age: 30.5 (6.9) n=107 (surveillance N = 6, radiotherapy N = 29, 2× PEB N = 23, ≥3 PEB N = 37, carboplatin N = 12) underwent control biopsy	Of the 122 patients with local radiotherapy, 33 (27%) had additional chemotherapy with carboplatin (N = 11), 2 courses of PEB (N = 12), and 3 courses of PEB (N = 10).		primary end point: occurrence of a malignant event (ME) during follow-up, defined either by detection of TIN upon testicular control biopsy or by clinical detection of contralateral GCT upon follow-up visit secondary end point: occurrence of hypogonadism during follow-up	n= 45 malignant events (MEs) (19.7%) Median event free survival (EFS): total group: 11.08 yrs (95% CI 9.83–15.92) Hypogonadism rates: in radiotherapy 30.8%, in chemotherapy (two cycles) 13%, in chemotherapy (three cycles) 17.8%, in carboplatin 40%, in surveillance 40%	no coi no information about funding	LoE 2b SIGN RoB (+) acceptable
Dieckmann KP 2017	multicenter prospective two arm cohort study	age: 38.5 (30.3–46.0)	n=166 patients with GCT	n=106 male participants	diagnostic accuracy of microRNAs (miRNAs) miR-	miR-371a-3p performed best, with 88.7% sensitivity (95% CI 82.5–93.3%)	Funding/Support and role of the sponsor: This study was supported by Wilhelm Sander-Stiftung (Grant No.	LoE 2b

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
	n=178 + 106 June 2011 to September 2015 D	tumour diameter in mm 29.0 (18.0–45.0)	n=12 patients with Leydig cell tumour (LCT)	(12 healthy men and 94 patients with benign scrotal conditions such as hydrocele, spermatocele, epididymitis, and varicocele)	371a-3p, miR-372-3p, miR- 373-3p, and miR-367-3p as sensitive and specific GCT serum biomarkers (sensitivity, specificity)	93.4% specificity (95% CI 86.9–97.3%) an area under the curve of 0.94, outperforming AFP, bHCG, and LDH (combined sensitivity 50%)	2014.178.1) and Albertinen- Stiftung Hamburg (1-3, 2015). The sponsors played a role in the design and conduct of the study. Klaus-Peter Dieckmann certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: K.-P. Dieckmann, M. Spiekermann, and G. Belge hold stock in miRdetcet GmbH, Bremen, a biotech company aiming to develop a commercially available laboratory test for measuring microRNAs in body fluids.	Quadas-Tool Low RoB

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
							This company was founded after the submission of this manuscript to European Urology. Mrs. Meike Spiekermann has been an employee of miRdetect GmbH since May 2016. miRdetect GmbH holds a patent for measurements of microRNAs in body fluids at the limit of detection. No other authors have declared coi.	
El Sanharawi I 2016	retrospective cohort study n=31 F 2006 - 2014	patients with non-palpable tumors incidentally found using US and who had normal levels of tumor markers Benign (n = 12) Malignant (n = 12) Burned-out tumors (n = 7)	diagnostic test dynamic contrast-enhanced (DCE)-MRI	no reference test	diagnostic accuracy: sensitivity specificity ROC AUC	Two-group comparison between benign tumors and malignant + BO tumors: ROC curves (AUC): maximal relative enhancement: 0.919 (CI0.825–1.000), time to peak: 0.868 (CI 0.738–0.999)	no coi no information about funding	LoE 4 Quadas-Tool: RoB unclear

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
						initial slopes: 0.950 (CI 0.879–1.000) AUC of ROC curves: Ktrans 0.978(CI 0.938–1.000) Kep 0.934 (CI 0.852–1.000)		
Rives N 2012	retrospective multi center cohort study n=1158 F January 1999 - December 2003	mean age: 29.70 yrs (±6.57 yrs) n=230 history of urological disease, n=158 history of cryptorchidism, n=49 (4%) scrotal injury, n=43	Cryopreservation	no control	prefreeze and postthaw sperm parameters	conclusion: sperm banking should be performed before orchiectomy in all men with testicular cancer independent of disease stage. At present, TESE concurrent with orchiectomy should be included systematically in fertility preservation management for patients who fail to bank semen samples or those with severe spermatogenesis impairment.	Supported by a research grant from FARO (Organon, France) no information about conflict of interest	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
		(4%) genital infections, n=33 patients (3%) testicular torsion, n=33 (3%) varicocele, n=14 (1%) testicular cancer prior to the current episode						
Suzuki K 2015	retrospective single center cohort study n=102 Japan April 2002 - April 2014	n=102 pts n=104 testes Seminoma (n= 26) Non-seminoma (n =78) Mean age (+SD) seminoma 40.1+9.2 Range 20-62 nonseminoma	no intervention pat underwent all inguinal orchiectomie	no control	relations between age, tumor histopathologic type, tumor size (maximum diameter), distance from the tumor, non-tumor tissue width and JSC	single regression analysis: age and spermatogenesis: RC= -0.017, P = 0.37, maximum diameter and spermatogenesis: RC=-0.422, P< 0.001 Multiple regression analysis: tumor diameter and spermatogenesis:	No external funding no coi	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
		34.2+7.3 Range 22–48				RC=-0.437, P<0.001 Mature spermatozoa: 93.0% of patients with NCTW ≥7.5 mm 41.3% of those with NCTW 7.5 mm (P< 0.001)		
van Casteren NJ 2010	retrospective single center cohort study n=764 January 1983 - August 2006 NL	median age: 26.9 years, range 13.8–56.9 majority diagnosis: TGCT (n = 292, 38%) Hodgkin lymphoma (HL) (n = 173, 23%)	cancer treatment	no control	semen parameters reproductive hormones	Semen characteristics for complete group: median spermatozoa concentration 20 · 106⁄mL (range 0–749), total sperm count 39.6 · 106 (range 0–1282), sperm volume 2.4 mL (range 0.1–10.8) progressive motility 39.0% (range 0–80) Patients with TGCT/ extragonadal germ-cell tumours (extragonadal GCT) showed a significant lower sperm concentration than		LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
						the other patients ($p < 0.05$). TGCT and extragonadal GCT: 28 and 10% respectively had normal sperm concentrations. n=74 patients were diagnosed with an azoospermia of which 38.5% were diagnosed with a TGCT 1/17 patients with an extragonadal GCT was diagnosed with an azoospermia Median serum levels for the complete cohort: FSH 3.9 U/L, inhibin B 117 ng/L, LH 3.5 U/L		

Referenz (Autor/Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten	Intervention	Kontrolle	Endpunkt	Ergebnisse	Finanzierung, Interessenkonflikte	Risiko eines Bias (RoB) LoE
						testosterone 15 nmol /L Patients diagnosed with TGCTs, extragonadal GCTs and brain tumours showed significant lower median levels of inhibin B compared with patients diagnosed with HL, NHL, leukaemia and carcinomas		

9.4.5. Kapitel 8

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
Aparicio J 2014	prospective risk adapted cohort study Spain 1994 – 2008 database	n=744 stage I seminoma	patient age (≤30 versus >30 years), tumor size (≤4 versus >4 cm), histological variant (classical versus anaplastic), pT stage (pT1–2 versus pT3–4), presence of vascular invasion, rete testis invasion, and preoperative BHCG levels (negative versus positive)	disease-free survival (DFS) relapse	multivariate analysis	multivariate model: presence of rete testis invasion (P < 0.001) tumor size (P = 0.052). no HR estimates provided in publication	no information about funding no coi	Quips Low RoB LoE 4
Arai E 2012	cross sectional design National Cancer Center Hospital, Tokyo, Japan samples of seminoma tissue	n=88 seminoma, n= 35 (39.8%) of which showed widely scattered nuclear immunoreactivity for DNMT3B, n=53 (60.2%) of which were completely negative.	DNA methyltransferase 3B expression (DNMT3B)	relapse	chi-squared test	Tumour relapse Negative Focal DNMT3B expression negative 42 positive 19 Tumour relapse Positive Focal DNMT3B expression negative 3 positive 6 p=0.037	no information about coi and funding	NO Correlational statistical method used, only differences in groups LoE 3b

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
		mean (±standard deviation) age: 38.8 ± 9.2 years (range 21–66 years)						
Chung P 2015	retrospective multicentric cohort study DK, Ca 1998 – 2005 prospectively managed databases	n=685 stage I seminoma surveillance patients median age: 36 years (range = 16–82) median tumor size 3 cm (range = 0.2–13) median follow-up of 3.85 years (range = 0.1–10.29)	age at diagnosis, primary tumor size, rete testis invasion, small vessel invasion	time to relapse	multivariable analysis	multivariable analysis: patients with primary tumor size ≥3 cm: 1.87 times higher risk of relapse, (95% CI 1.15–3.06) P = 0.01) rete testis invasion: HR 1.36 (95% CI 0.81–2.28) P = 0.25	no coi no funding information provided	Quips Low RoB LoE 4
Daugaard G 2014	mono centric retrospective	n= 1.226 patients with stage I NSGCC	prognostic factor of relapse and survival	overall survival	multivariable analysis	Relapse free survival: Final multivariable model: *Vascular invasion present:*	Supported by Danish Regions, the	Quips Low RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
	Denmark 1984 to 2007 patient files, pathology reports plus register data	median age: 30 range: 15-79	Embryonal carcinoma, Vascular invasion (VI), Epididymis invasion, Invasion of rete testis, Tunica albuginea invasion, hCG elevated Choriocarcinoma, York sac tumor, AFP elevated Seminoma, Teratoma	disease-specific survival relapse		HR 2.20 (95% CI 1.64 - 2.99) p=0.001 *Rete testis invasion:* HR 1.47 (95% CI 1.10 - 1.98) p=0.010 *Embryonal carcinoma:* HR 3.85 (95% CI 2.03 - 7.32) p=0.001 relapse rate: 59% (n=225) within the first 6 months n=6 relapses (1.6%) after 5 years of follow-up median time to relapse: 5 months (range, 1 to 308 months) Overall survival OS: 5 yrs 97,6%, 10 yrs 96,2% 15 yrs 94,5% Disease specific survival DSS: 99,3% 5 yrs 99,3% 10 yrs 99,1% 15 yrs	Danish Cancer Society, and the Preben and Anna Simonsens Foundation no coi	

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
Dong P 2013	mono centric retrospective China January 1997 - December 2009 Sun Yat-Sen University Cancer Center patient records	n= 89 CS I NSGCT inclusion criteria: CS I NSGCT excluded: stage IS stage I yolk sac tumors at pediatric age Mean age, years (range) Surveillance 18.4 (3-46) RPLND 29.7 (13-47) Chemo	cryptorchidism Side Age predominat EC Lymphatic or vascular invasion (LVI)	Odds ratio OR, Cumulative 5-year progression free survival PFS rates, 5-year disease specific survival DSS, overall survival OS, rate of relapse	Multivariate analysis	Multivariate analysis: factors to predict relapse: *All patients* Treatment options OR 0.22 (0.06-0.92) p=0.04 History of cryptorchidism OR 0.07 (0.01-0.34) p= 0.001 Side OR 1.62 (0.42-6.23) p=0.48 Age OR 1.01 (0.95-1.05) p=0.96 Predominant EC OR 0.71 (0.14-3.67) p=0.69 LVI OR 5.02 (1.17-21.62) p=0.02 *Surveillance patients* History of cryptorchidism OR 0.09 (0.01-0.56) p=0.01 Side OR 0.97 (0.19-4.84) p=0.97 Age OR 1.16 (0.78-2.01) p=0.05	no information about funding no coi	Quips High RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
		33.0 (8–66) dropouts not reported				Predominat EC OR 1.67 (0.26–10.77) p=0.06 LVI OR 12.10 (2.56–18.42) p=0.01 Cumulative 5-year PFS rates: surveillance 74.1% chemotherapy 92,3% RPLND groups 100 % 5-year DSS, OS rates: 100 % relapse rate of events surveillance group n=8 patients chemotherapy group n=1		
Gilbert DC 2016	multicentre prospective UK, Canada Medical Research Council (MRC) trial TE08	n=190 stage I NSGCT inclusion criteria: patients with stage I NSGCTs managed by surveillance with negative tumor markers	CXCL12, %EC, MIB1 prognostic biomarkers for relapse %EC as quintiles (0%, 1%–25%, 26%–75%, 76%–99%, 100%)	relapse-free rate (RFR)	multivariate analysis	TE08/TE22 multivariate analysis Model 1: VI (present vs absent) HR 3.28 (95% CI 1.68. 6.40) p<0.001 EC (continuous) HR 1.01 (95% CI 1.00 - 1.01) p=0.012	Medical Research Council (MRC) Biomarkers Grant G0801477 D.M. Berney reports receiving	Quips Moderate RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
	Medical Research Council (MRC) trial TE22	and CT scan confirming stage I or patients with stage I NSGCTs undergoing FDG-PET imaging followed by surveillance dropouts not reported	absent/weak CXCL12 if <1% cells across the whole tumor stained positive for CXCL12 <10% cells staining for CXCL12 as CXCL12 absent/ weak Analysis for MIB1: separately using both intensity and % cells positive using cutoffs described in the previous studies, i.e., ≥70% and ≥40% (15–18) as well as additional exploratory analyses			Model 2 VI (present vs absent) HR 3.28 (95% CI 1.68 - 6.38) p<0.001 EC ≤25% HR 1 (reference) EC 26-99% HR 1.67 (95% CI 0.73 -3.83) p=0.019 EC 100% HR 3.11 (95% CI 1.39 - 6.98) Model 3: VI (present/absent) HR 4.33 (95% CI 2.23 - 8.40) p=0.001 CXCL12 (absent/weak vs moderate/high) HR 0.43 (95% CI 0.22 - 0.86) p=0.01 CXCL12 with 2-year RFRs: 94.3% (95% CI, 89.4%–99.2%)	speakers bureau honoraria from Sanofi. No potential conflicts of interest were disclosed by the other authors.	

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
						CXCL12 with 2-year RFRs of 63.9% (52.9%–74.9%) CXCL12 with 2-year RFRs 30% (1.6%–58.4%) 76.4% 2-year relapse free rate		
Hatakeyama S 2010	cross sectional study Japan samples of seminoma and NSGCT tissue	n=130 n=65 seminoma n=65 NSGCT median follow-up 52 months (range 13–144)	anticore 2 N-acetylglucosaminyltransferase-1 (C2GnT-1) antibody expression	recurrence free survival	Chi square test	Seminoma: positive C2GnT-1 in: stage I: 12/43 (28%), stage II: 8/13 (62%), stage III: 8/9 (89%) NSGCT: positive C2GnT-1 in: stage I: 9/28 (28%), stage II: 13/13 (100%), stage III: 21/24 (88%)	Grant sponsor: Japan Society for the Promotion of Science; CREST, Japan Science and Technology Agency; no coi	NO Correlational statistical method used, only differences in groups LoE 3b
Howard SA 2014	multicentre	n=118	craniocaudal nodal length, nodal volume, embryonal	endpoint of relapse:	multivariable models	multivariate analysis: n=62 Craniocaudal nodal length (cm)	no information about funding and coi	Quips Low RoB

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
	retrospective Boston, USA 1997 – 2010 electronic medical records	n=66 (56%) NSGCT n=52 (44%) SGCT inclusion criteria: Patients with clinical stage I disease (defined as axial lymph node ≤ 10 mm in greatest short-axis dimension and negative tumor markers after orchiectomy) managed with surveillance at least 2 years of oncologic follow-up underwent imaging underwent retroperitoneal lymph node dissection	predominance (with a tumor defined as embryonal-predominant if embryonal histology was the most common subtype found in the pathologic specimen), presence or absence of LVI, and greatest short-axis diameter	pathologically proven nodal involvement in patients who had retroperitoneal lymph node dissection		OR 1.15 (1.01, 1.31) Estimates for every 3-mm increase OR 1.52 (1.03, 2.25) Embryonal-predominant OR 1.63 (0.37, 7.09) LVI OR 8.67 (1.38, 54.37) Nodal volume (cm3) OR 0.78 (0.21, 2.96)		LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
		without adjuvant chemotherapy. available imaging						
Keskin S 2012	mono centric retrospective Institute of Oncology, Istanbul University, Turkey January 2001 - December 2009	nonrelapsed (n = 37) relapsed (n = 28) inclusion criteria: NSGCT elevated levels of AFP and/or b-HCG after orchiectomy Median age nonrelapsed 28 years (range, 16 to 48 y) Median age relapsed	half-life of AFP and β-HCG (d) MHL: logarithmic formula: $t/2 = (-0.693 \times \Delta T) / \ln(concT / concT_0)$ where ‘‘t/2’’ is half-life, ‘‘DT’’ is time (d) between marker measurements, ‘‘ln’’ is natural logarithm, ‘‘concT’’ is current marker level, and ‘‘concT0’’ is baseline level	MHL (Marker Half-Life)	χ2-Test	Half-life of STM Median (Range) and relapse in (d) nonrelapsed AFP 6.7 (0.9-10.2) b-HCG 3.1 (1.2-6.5) relapsed AFP 11.5 (6.5-163) b-HCG 9.1 (4.4-27) p<0.001 STM and IGCCCG Risk Group Risk group 1 Nonrelapsed n=22 Half-life of AFP: 6.4 Half-life of β-HCG: 3.7	no information about funding no conflicts of interest	Quips Moderate RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
		26 years (range, 19 to 46 y) Median follow-up 25 mo (6-96) no information about dropouts				relapsed n=7 Half-life of AFP: 7 Half-life of β-HCG: 8.5 Risk Group 2 Nonrelapsed n=9 Half-life of AFP: 7.1 Half-life of β-HCG: 2.9 Relapsed n=7 Half-life of AFP: 12.3 Half-life of β-HCG: 8.9 Risk group 3 Nonrelapsed n=6 Half-life of AFP:6.5 Half-life of β-HCG: 5 Relapsed n=14 Half-life of AFP: 24.6 Half-life of β-HCG: 11 *U'schiede alle stat. sign.		

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
						Germ cell components and Marker Half-life Embryonal Yes n=48 Half-life of AFP: 7.0 (0.91-163) half-life of β-HCG: 4.0 (1.2-10.5) Embryonal no n= 17 Half-life of AFP: 11.3 (7.3-104) Half-life of β-HCG: 9.75 (2.2-27) *stat. sign. Endodermal Yes n=39 Half-life of AFP: 7.3 (0.9-35.4) half-life of β-HCG: 4 (1.2-16.8) Endodermal No n= 26 Half-life of AFP: 8.6 (4.9-163) half-life of β-HCG: 6.4 (2.8-27) Mature teratoma Yes n=29 Half-life of AFP: 7.9 (0.9-104) Half-life of β-HCG: 6.2 (1.2-27) Mature teratoma No n=36		

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						Half-life of AFP: 7.6 (4.2-163) Half-life of β-HCG: 4.7 (1.7-16.8) Immature Teratoma Yes n=13 Half-life of AFP 7.6: (5.3-11.5) Half-life of β-HCG: 8.3 (2.9-16.8) Immature Teratoma No n=52 Half-life of AFP: 7.8 (0.9-163) Half-life of β-HCG: 4.8 (1.2-27) Choriocarcinoma Yes n=18 Half-life of AFP: 6.8 (5.3-35.4) Half-life of β-HCG: 5.7 (2.3-14.8) Choriocarcinoma No n=47 Half-life of AFP: 7.9 (0.9-163) Half-life of β-HCG: 5.2 (1.2-27) Seminoma Yes n=22 Half-life of AFP: 7.6 (4.2-104) Half-life of β-HCG: 4.1 (2.2-16.8)		

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
						Seminoma No n= 43 Half-life of AFP 7.8 (0.9-163) Half-life of β-HCG: 5.7 (1.2-27)		
Kier MG 2017	nationwide population-based cohort of GCC patients 1984– 2007 DK database	n=1889 treated with first-line BEP Seminoma: n=420 (22% NSGCT: n=1469 (78%)	Age at BEP per 10 yr Year of BEP Relapse from stage I Disseminated gonadal Retroperitoneal primary Mediastinal primary Nonpulmonary visceral metastases Pulmonary metastases Lactate dehydrogenase	5 yr-progression	multivariate analysis	multivariable analysis for 5-yr progression: Age at BEP per 10 yr HR 1.46 (95% CI 1.18–1.80) p < 0.001 Lactate dehydrogenase 1.5–10 x ULN HR 2.25 (95% CI 1.29–3.95) p<0.05 Lactate dehydrogenase >10 x ULN HR 4.62 (95% CI 1.56–13.73)	Danish Cancer Society no coi	Quips Low RoB LoE 2b
Kollmannsberger C 2015[1]	two-arm retrospective Cohort study n=2483 (total)	Nonsem-patients CS I	Active Surveillance LVI positive n=183	no prognostic factors examined	Disease-specific survival (DSS) Relapse	LVI-positive: Median time to relapse: 4 months (1-61)	information about coi: Honoraria: Tom Powles,	SIGN (+) Acceptable RoB LoE 2b

[1] zitierte Studie im Hintergrundtext, aber Zitierung bezieht sich nicht auf die prognostischen Faktoren

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
	CSI-Nonsem I n=1139 CSI Sem I n=1344 1983-2012 Canada Sweden Norway UK	histologically confirmed NONSEM CS I median follow up: 62 months (1-277)	Active Surveillance LVI negative n=935			LVI-negative: 8 months (2-77) no rates per groups: total 5 ys DSS: 99,7% 10 ys DSS: 99,7% Alive NED (no evidence of disease) Nonsem LVI positive 98% Nonsem LVI negative 95% Relapse rate: Nonsem LVI positive: 44% Nonsem LVI negative: 14%	GlaxoSmithKline, Pfizer, Astellas Pharma no information about funding	
Kvammen O 2016[2]	retrospective cohort study Cancer Registry of Norway (CRN) 1953 – 2012	n=8,736 men with testicular cancer as diagnosis 6 cohorts median age at diagnosis	RPLND radiation CVB regimen BEP regimen surveillance	no prognostic factors were examined	estimates of long-term RS, method developed by Perme and colleagues comparison with that of the general	RS was significantly reduced among the TGCT patients, regardless of cohort of diagnosis and follow-up time	grants from St. Olavs University Hospital no coi	SIGN (+) Acceptable RoB LoE 2b

[2] zitierte Studie im Hintergrundtext, aber Zitierung bezieht sich nicht auf die prognostischen Faktoren

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
	N	across the cohorts: 32 - 36 years seminoma 27 - 30 years nonseminomas			population: relative survival (RS)			
Li, X 2015	mono centric retrospective Sun Yat-sen University Cancer Center Guangzhou, China 1999 – 2013	n=163 CSI NSGCT inclusion criteria: Patients that underwent active surveillance as their initial treatment after orchiectomy and had been followed for more than 12 months n=78 of 163 (47.9 %) active surveillance	Age LVI T classification EC Mature teratoma Immature teratoma Seminoma Yolk sac tumor Preoperative AFP levels Preoperative HCG levels Primary tumor size	Relapse-free survival: from the date of orchiectomy to the date of tumor recurrence recurrence-free survival (RFS)	multivariate analysis	multivariate analysis: LVI Lymph vascular invasion OR 6.521; 95 % CI 1.872–22.721;(p = 0.003) Predominant presence of yolk sac tumor OR 3.537; 95 % CI 1.076–11.628; p = 0.038) Overall survival (OS) 98.7 % Relapse (23.1 %) n=18 median time of 5.6 (range 1–47) months 72.2 % relapsed within the first year after orchiectomy	no coi no information about funding	Quips Low RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
		60 of 78 (76.9 %) patients were classified as stage T1 Median follow-up time: 6.2 (range 1–15) years 65 patients (83.3 %) were followed for greater than 2 years Age median 29.5 Range 14–56				3.8 % relapsed beyond 2 years (25, 46, and 47 months) after orchiectomy Recurrence-free survival according to LVI and yolk sac tumor in the primary testicular tumors: Low-risk group: 41 patients, 3 relapse (7.3%) Intermediate-risk group: 29 patients, 9 relapse (31.0 %) High-risk group: 8 patients, 6 relapse (75.0 %)		
Mead GM, 2011[3]	RCT TE 19 trial n=1477	Seminom CS I mean age: kA	radiation n=904	carboplatin n=573 AUC7	5-year Relapse-free rate Overall CSS for all	radiation: 5-year relapse-free rate: 96.0% (95% CI, 94.5% -97.1%)	MRC Clinical Trials Unit	Low RoB LoE 1b

[3] zitierte Studie, aber Zitierung bezieht sich nicht auf die prognostischen Faktoren

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
	1996-2001 UK	median follow up: radiation: 6,4 y carboplatin 6,5 y followed for 5 years: radiation 79.7% carboplatin 75.8%	randomly assigned to 20 or 30 Gy or between 20 Gy and 30 Gy standard treatment: Para-aortic radiation therapy dogleg radiation therapy recommended for patients with previous inguinoscrotal surgery	single injection	(n=2466) TE 10, TE18, TE19	carboplatin: 5-year relapse-free rate: 94.7% (95% CI = 92.5% to 96.3%) Overall cancer-specific survival: 99.8% (95% CI = 99.6% to 99.9%)	no information about coi	
Mortensen MS 2014	nationwide retrospective, population-based cohort study 1984 - 2008 DK	Seminom CS I n=1954 Median follow-up time 15.1 yr	tumor size, invasion of rete testis, epididymis (EPI), small vessels (vascular and/or lymphatic) (VI+), and invasion of tunica albuginea, as well as histology at relapse	relapse	Multivariate analysis	Multivariate analysis: Model 1: Complete case, reduced model VI+: Tumor size HR 1.59 (95% CI 1.31–1.92), p<0.0001 VI+ HR 1.46 (95% CI 1.05–2.02), p=0.0257	Danish Cancer Society no coi	Quips Low RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
						Model 2: Complete case, reduced model EPI Tumor size HR 1.63 (95% CI 1.34–1.98), p<0.0001 EPI HR 1.57 (95% CI 1.04–2.38), p=0.0333 Model 3 Imputed, reduced model VI+ Tumor size HR 1.38 (95% CI 1.20–1.60) p<0.0001 VI + HR 1.41 (95% CI 1.05–1.89), p=0.0217 Model 4: Imputed, reduced model EPI Tumor size		

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
						HR 1.41 (95% CI 1.22–1.62), p<0.0001 EPI HR 1.60 (95% CI 1.14–2.23), p=0.0064		
Nicolai N 2010	mono centric retrospective Fondazione IRCCS Istituto Nazionale die Tumori of Milan, Italien 1985 – 1995	n=322 inclusion criteria: consecutive CS1 patients with NSGCT underwent RPLND median follow-up: 17.3 yr (interquartile range [IQR]: 14.9–19.9 yr) age median (IQR) 27 (22–32)	pT, VI, percentage of embryonal carcinoma (%ECa), teratoma (T), and nodal metastasis at RPLND (pN)	tumour recurrence including distant and abdominal metastases crude cumulative incidence (CCI) of recurrence Time to event: from the date of RPLND to the first occurrence of the event	multivariable analysis OR (95% CI)	no recurrence: 271 patients (84.2%) multivariate logistic regression model: Pathologic N stage at RPLND pN+ vs pN0 OR 2.9 (1.3–6.5) p=0.009 T category pT2/3 vs pT1 OR 4.4 (1.7–11.7) p=0.003 Vascular invasion Present vs absent OR 2.7 (1.2–6.2) p=0.019 Percentage of embryonal carcinoma*	Funding: None no conflicts of interests	Quips Moderate RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
						50 vs 6 OR 3.5 (1.4–9.0) p= 0.019 Percentage of embryonal carcinoma* 85 vs 6 OR 1.6 (0.6–4.5) Teratoma Present vs absent OR 1.1 (0.5–2.4) p=0.891 * With multiple imputation of prognostic factor missing values		
Sturgeon JF 2011	mono centric retrospective Toronto, Canada 1981 – 2005 database-data	n = 371 inclusion: clinical stage I NSGCT managed by active surveillance exclusion: pure choriocarcinoma patients	different patient characteristics	Recurrence rates, time to relapse, risk factors predictive for recurrence, disease-specific survival, overall survival	multivariate model	multivariate model: risk factors for relapse LVI Lymphovascular invasion HR 3.22; 95% CI, 2.17–4.78; p < 0.0001) presence of pure EC HR 1.74; 95% CI, 1.10–2.74; p = 0.02 Relapse rate: 28.0% (n= 104) median time to relapse: 7.1 months	Funding: None conflicts of interest: none	Quips Moderate RoB LoE 4

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
		mean age (SD) 30.5 (8.6) Range, yr 13.2–76.6 Median follow-up: 6.3 yr (0.08–25.9 yr);				DSS: 5-yr disease-specific survival 99.1% 5 yr estimated recurrence-free survival: 72.5%		
Tandstadt T 2011	three arm prospective Cohort study n=1384 2000 – 2006 Norway, Sweden	Seminom CS I mean age: 37 ys median follow up: 5,2 ys (all patients) 6,1 ys radio 5,0 ys surveillance	Vascular invasion Tumor size, cm Elevated hCG Age, years	relapse	multivariate analysis	No significant prognostic factor in Cox proportional hazards survival regression	Swedish Cancer Society, the Gunnar Nilsson Foundation for Cancer Research, and the Nordic Cancer Union no coi	RoB SIGN (+) Acceptable RoB LoE 2b

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
		3,4 ys carboplatin 1x						
McCleskey BC 2017	retrospectiv multi-institutional USA two arm cohort study	n=44 that contained LVI within the spermatic cord without soft tissue invasion of the cord cohort of control n=32 who had NSGCT diagnosed as pT2 because of the presence of LVI confined to the testis without LVI present in the spermatic cord.	Lymphovascular Invasion (LVI) of the Spermatic Cord Lymphovascular invasion was defined as tumor cells adherent to the luminal aspect of a vascular or lymphatic channel (Figure). The presence of fibrin among tumor cells was also used to help discriminate true LVI from artifact	Clinical stage Dominant tumor histology Rete testis involvement Hilar soft tissue involvement Any disease recurrence/progression Recurrence/progression after chemotherapy Death	differences between groups 2-tailed Student t test for continuous variables Pearson v2 test with Fisher exact modification categoric values	no significant differences between the 2 groups regarding patient age at presentation, rete testis involvement, or presence of embryonal carcinoma as the dominant histology Patients with LVI present in the spermatic cord had larger tumors (P = .008). More patients with spermatic cord LVI had hilar soft tissue involvement (P = .004). 76% of pts with LVI in the spermatic cord presented with advanced clinical stage disease CS II, III 50% of pts with LVI in Testis Only (p=0,01) no significant difference in: any disease recurrence/progression disease recurrence/progression after chemotherapy (P=.40; P=.90)	no relevant financial interest in the products or companies described in this article no information about funding	Quips high RoB LoE 4 (Einstufung, weil hohes RoB)

Referenz (Autor, Jahr)	Studiendesign, Land, Zeitraum, Datenquelle	Patienten, Patienten-merkmale	prognostischer Faktor Definition	Endpunkt	statistische Analyse	Hauptergebnisse Events n OR/RR/HR	Finanzierung Interessenkonflikte	Risk of Bias Evidenzlevel (LoE)
						no difference in mortality between the 2 groups (P =.50).		
Williams SB 2011	multicentric retrospective Boston, USA 1993 to 2009 database-data	n=90 Mean age (ys) Pathol Stage I:29 Pathol Stage II: 30 Median follow up: 1.1 ys	patient characteristics	association with positive lymph nodes at RPLND	multivariate analysis	multivariate analysis: embryonal carcinoma OR 1.02, 95% CI 1.001–1.040, p = 0.038 LVI lymphovascular invasion OR 3.52, 95% CI 1.43–8.67, p =0.006	no information about funding no informationabout coi	Quips Moderate RoB LoE 4
Zengerling F 2017	systematic review of 19 included studies	CS I Seminoma	26 potential prognostic factors	tumor recurrence	systematic review	tumor size (continuous or dichotomized): significantly associated with relapse in 10/14 studies with a hazard ratio(HR) ranging from 1.33 (95%confidence interval[CI]:1.14–1.56) to 3.17 (95%CI:1.08–9.26). Rete testis invasion significantly associated with relapse in only 4/13 studies with a HR ranging	no information about coi no information about funding	AMSTAR 7/11 LoE 2a

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						from 1.18 (95%CI:0.92–1.51) to 1.36 (95%CI:0.81–2.28)		

9.4.6. Kapitel 9 Primär- und Erstlinientherapie Stadium I

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Andreassen KE 2011	retrospective data base analysis (cohort study) n=7.102 men with unilateral TGCT 1953 – 2007 NO	patients diagnosed with histologically verified invasive TGCT 55% seminoma 45% nonseminoma Median age at diagnosis of first TGCT: 36 yrs seminoma 30 yrs nonseminoma n=175 (2.5%) diagnosed with an invasive metachronous contralateral TGCT	1953–1979 Chemotherapy/ RAD* *Adjuvant abdominal radiotherapy 1980–2007 Seminoma Chemotherapy+ RAD/surgery Nonseminoma Chemotherapy+ surgery n=175	no control	follow-up (median 10.9 yrs, range 0.16–54.7 yrs)	SIR standardized incidence ratio RR relative risk	Period I: cumulative incidences: of developing a metachronous contralateral TGCT: 10- year cumulative incidences: 1.3% (95% CI 0.9–1.9%) 20-year cumulative incidences: 1.9% (95% CI 1.4–2.6%) Period II 10- year cumulative incidences: 2.7% (95% CI 2.2–3.2%) 20-year cumulative incidences: 3.9%	funding: Norwegian Cancer Society no information about coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							(95% CI 3.3–4.7%) HR 0.5, (95% 0.33–0.77)		
Aparicio J 2011	2 arm prospective Cohort study n=227 2004-2008 Spain	Seminom CSI mean age: 33 (range 21-59)	0-1 Risk factor: surveillance n=153	2 risk factors: Carboplatin n=74 tumours >4 cm, invasion of rete testis two courses of adjuvant single-agent carboplatin (area under the curve of 7, with 21-day interval)	median follow-up: 34 mon	Disease free survival DFS Overall survival OS	surveillance 3-year DFS: total: 88.1% (95% CI 82.3% - 93.9%) 3-year DFS: no risk factors 93.5% with tumour size 4 cm 83.7% with rete testis involvement 78.3%	no information to funding source	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							3 year OS: 100% adjuvant chemotherapy 3-year-DFS: 98.0% (95% CI, 94.0% -100%) 3 year OS: 100% adverse events: uncomplicated thrombocytopenia (8%), afebrile neutropenia (4%), anemia (2%), emesis (2%)		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Bamias A 2011	single-arm retrospective cohort study n=142 October 1994 – December 2004 Greece	NSGCT I high risk inclusion criteria: at least 1 of the following risk factors: LVI in the tumour specimen, embryonal carcinoma >50% of the tumour, invasion of tunica vaginalis, spermatic cord, rete testis, or scrotal wall	2 cycles bleomycin/etoposide/cisplatin n=142	without control group	median follow-up time: 79 months (range 2–155)	relapse mortality toxicity	Relapse n=1 CSS:n=0 Grade 3 toxicities n/% Anemia 1 (0.6%) Thrombocytopenia 3 (2%) Neutropenia 8 (6%) Nausea/vomiting 10 (7%) Alopecia 77 (54%) Infection 3 (2%) Grade 4 toxicities n/% Neutropenia 7 (5%)	no information about funding no information to COI	LoE 4 SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Beard CJ 2013	single arm retrospective Cohort study n=9561 1973-2001 USA	Seminom CSI mean age: no information	radiotherapy n=7179	not treated with radiation no further information about the therapies	median follow up: 12,7 ys	15 Year OS causes of death	15 Year OS: 91.2% (95% CI, 90.5-91.9) 5 most common causes of death: Second malignant neoplasms n=291 cardiovascular disease n=5201 testicular cancer n=573 infection (n=558 suicide n=539	National Cancer Institute no coi	LoE 4 RoB SIGN (+) acceptable
Bilici A 2015	three arm retrospective Cohort study n=282	Seminom CS I median age total group: 35 ys Surveillance: 33,5	Surveillance n=72 Carboplatin for high risk patients: n=80		median follow up: 38,5 Months (6,5-192)	Relapse rate DFS OS	Relapse Rate: Surveillance: 22,3% Carboplatin: 1,2% Radiotherapy: 7,7% p<0,001	no financial support no coi	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
	1997-2013 Turkey	(19-85) Carboplatin: 33,5 (18-64) Radiotherapy: 36 (17-74)	one or two cycles single-agent carboplatin (area under the curve of 7) every 3 weeks Radiotherapy n=130 RT included paraaortic lymph node area (from the tenth thoracic vertebra to the fifth lumbar vertebra) and dog-leg fields (including the paraaortic and iliac lymph node areas) treatment: five consecutive days per week for 3 weeks, and the total dose ranged from 20 to 25 Gy				5 -year DFS: Surveillance: 64,2% Carboplatin: 97,7% Radiotherapy: 91,9% p<0,001 5-year OS: Surveillance: 100% Carboplatin: 92,3% Radiotherapy: 97,4% p=0,44		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Braband S. 2012	retrospective single center cohort study n=61 1986 – 2010 NO	patients with intratubular germ cell neoplasia unclassified (IGCNU) treated for first-time invasive germ cell cancer n=61 Age at diagnosis: Median 29 yrs Range 16-55 yrs (1) unilaterally orchiectomized and IGCNU in the contralateral testicle or EGCC and IGCNU in at least one testicle,	Chemotherapy group Any chemotherapy (n = 35) LOW group 1-3 cycles of chemotherapy (n = 18) HIGH group ≥ 4 cycles of chemotherapy (n = 17)	NO group No chemotherapy (n = 26)	observation time: median 53 mo (range 1 - 244 mo)	primary endpoint: diagnosis of subsequent testicular cancer (STC)	NO group and the chemotherapy group: 5-year probability: NO group: 54% (95% CI 33% - 78%) Chemotherapy group (any chemotherapy 23% (95% CI 11% - 45%) HIGH group, 5- and 7.5-year probability: 22% (95% CI, 8% to 54%), LOW group: 5- and 7.5-year probability of STC: 24% (95% CI,9%to 58%,) 58%	no coi no information about funding	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
		(2) no invasive tumor in the IGCNU-affected testicle, (3) at least 1 month of observation between the diagnosis of IGCNU and STC, IGCNU-definitive treatment (radiotherapy or orchiectomy), emigration, death, or end of follow-up.					(95% CI, 30% to 88%) combined group compared with the HIGH group: probability of STC: 5-year probability of STC: 42% (95% CI 27% - 62%)		
Cathomas R. 2014	retrospective multi center cohort study n=426 1999-2012 CH UK	Seminoma stage I median age: 39 yrs (range 19–60 yrs) median measured GFR 118 ml/min (51–209)	Carboplatin dose AUC7 (mg) Cockcroft-Gault, Jelliffe, Martin, Wright, Mayo, MDRD and CKD-EPI formulae for eGFR values	no control	no information about observation time	underdosing of carboplatin	Cockcroft-Gault, MPE of +2.1 MAPE 11 underdosing 18% Wright formulae MPE +0.4 MAPE 11 underdosing 24%	no coi no information about funding	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
		median administered carboplatin dose 1000 mg (532–1638)	n=426				flat dosing algorithm MPE +1.9 MAPE 11 underdosing 19% Jelliffe MPE −13 MAPE 15 underdosing 63% MDRD formulae MPE −7.8 MAPE 13 underdosing 49%		
Chau C 2015	single arm retrospective Cohort study n=517	Seminom CSI Median age at diagnosis: 38 years (range 18–73 years)	Carboplatin single dose of adjuvant AUC7 dose was calculated on radioisotope measured glomerular filtration rate (GFR)		Hospital median follow-up: 3.9 years (range 0–17.8 years).	RFS (5 year) OS CSS	5 years relapse free survival (RFS) 95.0% (95%CI 92.8% - 97.3%) CSS: 100%	no conflicts of interest no information about Funding source	LoE 4 RoB SIGN (-) not acceptable

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	1996-2013 UK		uncorrected for body surface area using the Calvert formula		Virtual median follow-up: 6.5 years (range 0.3–17.8 years)	incidence of contralateral GCT incidence of secondary malignancies	5 ys OS: 99% (n=511 von 517) metachronous CTGCT: n =17/517 (3.3%) (9 seminoma, 8 non-seminoma) during follow-up median time to CTGCT of 8.8 years (range 0.8–22 years) secondary malignancy n= 6/517 (1.2%) (plasmacytoma, renal cell carcinoma, GIST, rectal cancer, malignant melanoma, mantle cell lymphoma)		
Cummins S 2010	single arm retrospective Cohort study n=164 1980-2004	Seminom CS I mean age: no information	surveillance		median follow up: 13,5 y	relapse rate time to relapse	relapse rate: 13% (n=22) median time to relapse: 15,5 months (6-55 months)	no coi Royal Mardsen NHS Foundation Trust	LoE 4 RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
	UK								
Detti B 2011	single arm retrospective Cohort study n=320 1960-2009 Italy	Seminom CS I mean age: 37 y (20-72)	radiation PA strip: n=73 (22.8%) dog leg (DL) volume including PA and ipsilateral iliac lymph nodes n= 155 patients (48.4%) RT to DL volume and prophylactic RT to the supradiaphragmatic region n= 80 (25%)		median follow-up: 22.7 years (range: 1-48)	5 y DSS 5,10 y RFS median time to relapse Toxicity	5- y DSS all RT: 98.4 10-y DSS all RT: 97.7% 5-year DSS: infradiaphragmatic lymph nodes, DL 98.9% prophylactic RT to the supradiaphragmatic region: 97.5%, (p = 0.06) 5-year DSS:	no coi no information to funding source	LoE 4 RoB SIGN (+) acceptable

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			conventional fractionation (2 Gy/day), treating each field daily 5 times a week				RT to the DL: 98.7 5-year DSS: PA only: 100% 5, 10-year RFS: 97.7% 5-year RFS: infradiaphragmatic lymph nodes and DL volume: 97.8% with RT to the supradiaphragmatic region: 97.5% (p = 0.88) median time to relapse: 14,8 Months (13-40) nausea and/or epigastric discomfort and/or loose stools during treatment:		

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							45% at least 5 years from the testicular cancer diagnosis: cardiovascular disease: n= 8 acute myocardial infarction n= 4 angina pectoris: n=4		
Dieckmann KP, 2016	four arm prospective Cohort study n=1050 2008-2013 Germany	Seminom CS I 4 groups n=725 mean age: Surveillance 40y (20-75) Radiotherapy 39y (25-65)	Surveillance n=256 Radiotherapy n=41 20 GY no information about duration of treatment Carboplatin 1x AUC7		median follow up: 30 mon (0-60 Mon)	primary endpoint: relapse rate secondary endpoint: association of tumour size, RTI with relapse in various treatment modalities	relapse rate: Surveillance: n=21 (8,2%) Radiotherapy: n=1 (2,4%) 1x Carbo: n=18 (5%) 2x Carbo: n=1 (1,5%) DWD: Surveillance: 0 Radiotherapy: 0 1x Carbo: n=2 (0,6%) 2x Carbo: n=0	Funding source: Hamburger Stiftung zur Förderung der Krebsbekämpfung no COI	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
		n=362 1x Carboplatin 42y (19-82) 2x Carboplatin 43,5y (21-81)	Carboplatin 2x n=66			RTI: rete testis invasion DWD: dead without disease	median follow up: Surveillance: 24 Mon Radiotherapy: 36 Mon 1x Carbo: 30 Mon 2x ‘Carbo: 30 Mon DSS: 100% Surveillance Gruppe: keine Unterschiede in den Relapse-Raten nach Stratifizierung (Tumorgröße </> 4 cm und rete testis invasion) Relapse rate 1x Carbo: tumor size < 4cm: 2,3% tumor size: >4cm: 6,8% p=0,04 1x Carbo: tumor size >4cm vs tumor size <4 cm:		

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							HR 3,03 (95% CI 0,97-9,44)		
Diminutto A 2016	single arm retrospective Cohort study n=115 2005-2014 Italy	Seminom CS I mean age: 35 ys (18-65)	Carboplatin single dose median dose 900 mg n=115		median follow up: 22,1 Months	relapse rate time to relapse PFS (1 y ,2 ys) acute toxicity	Relapse rate: n=6 patients (5.2%) overall PFS: 98.3% at 1 year 94.8% at 2 years median time to relapse: 13.7 months (range, 11.1-16.6 months) acute toxicity: fatigue grade 1 to 2: 40% nausea/vomiting grade 1 to 2: 41.7% neutropenia grade 1 to 2: 8.7% anaemia grade 1: 20%	no conflicts of interest no information to Funding source	LoE 4 RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							No infections, no nephrotoxicity transient neutropenia grade 3: 2.6% thrombocytopenia grade 3 to 4: 5,2% no long-term toxicities after a median follow-up 22.1 months		
Gamulin M 2011	single arm prospective Cohort study n=115 no information about time frame of data collection Kroate	Seminom CS I mean age: 34 (19-72)	radiation paraaortic lymph nodes with 15 MV linear accelerator photons from two opposite anteroposterior fields. 24 Gy divided in 16 daily fractions Para-aortic field borders included superior T10/T11 intervertebral disk,		mean follow up: 28 Months	side effects during and after rt	most side effects during and after radiation in %: nausea 25 nausea and fatigue 27 same weight as before radiotherapy, no anorexia 46 anorexia with weight loss ≤ 5 % 28 anorexia with weight loss ≤ 15 % 23 worried and anxious 35 worried, anxious and depressed 32	no information about coi no information to Funding source	LoE 4 RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
			inferior L5/S1 intervertebral disk, lateral margins to the vertebral bodies including the transverse process bilaterally and left renal hilum for the left testicular seminoma				financial problems due to absence from work 21 social problems (social life and going out) 23 Physical condition in the last week of radiotherapy in % poor, very poor 23 medium 20 good/excellent 57 Quality of life in the last week of radiotherapy in % poor, very poor 14 medium 20 good/excellent 66		

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Haughnes HS 2014	three arm retrospective Cohort study n=232 1986-2010 Norway	Seminom CS I AFTER SWENOTECA V n=111 median age: 38 (24-77)	Radiation: n=23 (21%) dog leg field 25,2 Gy Carboplatin: n=15 (13%) AUC7	Surveillance: n=73 (66%)	median follow up: not reported	Relapse-free survival Cancer-specific survival Time to relapse	Time to relapse for all: 15 months (4-93) Relapse-free survival for all: 93% relapse rate: radiation: 1,9% carboplatin: 0% surveillance: 11% Cancer-specific survival for all: 100%	no coi Norwegian Cancer Society	LoE 2b RoB SIGN (+) acceptable
Horwich A 2014	single arm retrospective Cohort study n=2629 1960-1992 UK, Norway	Seminom CS I at risk of second cancer n=2543 mean age: 37,2	radiation: abdominal and pelvic lymph nodes RT 91% para-aortic node RT 6.3%		median overall follow-up 21.8 years (interquartile range 17.5–27.5 years	SIR of second malignancies	second cancers: total n=468 SIR for second cancer incidence 1.61 (95% CI: 1.47–1.76, P<0.0001) testis cancer SIR 9,45, 95% CI 6,68-13,36	ICR, CRUK, MRC-Funding source no information about conflicts of interests	LoE 4 RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
		interquartile range 31.3–44.7	thoracic or neck irradiation in addition to abdominal fields 1% dose: 30 Gy, or 35/36 or 40 Gy given over 3–4 weeks				bladder cancer SIR 2.46, 95% CI: 1.86–3.26 pancreatic cancer SIR 3.14, 95% CI: 2.13–4.60 stomach cancer SIR 1.93, 95% CI: 1.31–2.83		
Jones G 2013	two arm retrospective Cohort study n=6764 1973-2003 USA	Seminom CSI n=6764	radiation n=5265 mean age: 36,7 ys no information about dosing	observation n=1499 mean age: 36,6 ys	median follow up: radiation: 96 months (0-.354) observation: 78 months (0-340)	5y, 10y, 20y OS 5y, 10y, 20y CSS second malignancies third malignancies	Overall survival radiation: 5y OS: 97,7% 10y OS: 94.8% 20 Y OS: 83.5% observation: 5y OS: 95.0% 10y OS: 92.2% 20y OS: 84.1% P = 0.0047	no coi no information about Funding source	LoE 2b RoB SIGN (+) acceptable

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							Cause specific survival Radiation 5y CSS: 99.6 (95% CI 99.4-99.8) 10y CSS: 99.4 (95% CI 99.2-99.7) 20y CSS: 99.2 (95% CI 98.8-99.6) Observation: 5 yr-CSS: 98.7% (98.1-99.4) 10 yr CSS: 98.7% (98.1-99.4) 20 yr CSS: 98.7% (98.1-99.4) Freedom from second malignancy diagnosis radiation:		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							5 y: 97.7 (95% CI 97.3-98.2) 10y: 95.8 (95% CI 95.1-96.5) 20y: 87.9 (95% CI 86.0-89.8) observation: 5y: 98.5 (95% CI 97.8-99.2) 10y: 97.3 (95% CI 96.2-98.4) 20y: 95.0 (95% CI 92.9-97.1) p= 0.0029 Freedom from third malignancy diagnosis: radiation: 5y: 99.2 (95% CI 98.1-100) 10y: 97.8 (95% CI 95.6-100) 20y: 76.1 (95% CI 65.0-89.0) observation: 5y: 95.5 (95% CI 87.1-100)		

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							10y: 95.5 (95% CI 87.1-100) 20y. 70.7 (95% CI 45.7-100) p=0.2669		
Kamba T 2010	three arm retrospective Cohort study n=425 1985-2006 Japan	Seminom CS I	Surveillance median age: 36 (19–84) n=186 Chemotherapy median age: 40 (24–66) n=57 carboplatin: n=51 (89.5%) etoposide and cisplatin: n=1 (1.8%)	Radiation median age: 36 (22–64) n=182 para-aorta and ipsilateral pelvis: n=130 (71.4%) para-aorta and bilateral pelvis n=18 (9.9%) para-aorta alone: n=11 (6.0%) unspecified	median follow up: Surveillance: 44.9 (0.1–218.7) Chemotherapy: 58.4 (2.5–205.6) Radiation 60.8 (0.9–248.5)	time to relapse OS RFS	median time for relapse: surveillance: 21.0 mo chemotherapy 42.8 mo radiotherapy 37.9 mo 10 yr-OS: surveillance 100% chemotherapy 100% radiotherapy 99.4%% 5 years RFS: surveillance 90% chemotherapy 94% radiotherapy 95% 10 years RFS: surveillance 79% chemotherapy 94% radiotherapy 94%	no coi no information about funding source	LoE 2b RoB SIGN (+) acceptable

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			bleomycin, etoposide and cisplatin n=1 (1.8%) cisplatin, vinblastine and bleomycin or vinblastine, actinomycin-D and bleomycin: n=4 (7.0%)	n= 23 (12.6%) information about dose in Gy and duration of treatment not reported					
Khader J 2012	two arm retrospectively Cohort study n=74 2003-2010 Jordan	Seminom CS I mean age: 34 years (17–51 years)	radiation n=71 radiotherapy via para-aortic fields in 63 (88.7%) patients or dog-leg fields in 7 patients (9.9% total dose ranging from 2000 to 2500 cGy given over a period of 2 to 3 weeks (daily fractions in 5	surveillance n=3 no calculation of effect estimates	mean follow up: 33 Months	acute toxicity late toxicity 3 y-RFS (entire cohort)	keine konkreten Angaben zur Häufigkeit von Akut-Toxizität (Acute radiotherapy-related side effects were mild in all patients) (none demonstrated late toxicity at the time of follow-up) 3 y-RFS (entire cohort) 95.9%	no coi no information about funding source	LoE 2b RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
			consecutive days of the week						
Kier MG 2016	4 arm retrospective Cohort study n=5190 1984-2007 DK	Seminom n=2804 no information to age	stage I GCT surveillance program for 5 ys Chemotherapy (1x BEP) retroperitoneal Radiation RT-Dose was reduced during the study period from 46 Gy to 30 Gy to 36 Gy (no further information about duration of RT reported more than 1 line of treatment (MTOL)		mean follow up: 14,4 ys (8,6 ys – 20,5ys)	incidence of second malignancies (SMN) risk for SMN probability of death	SMN at 20 ys: surveillance: 7,8% BEP: 7,6% Radiotherapy: 13,5% MTOL (9,2%) risks for SMN: surveillance: HR 1,0 BEP HR 1,7 RT HR 1,8 MTOL HR 3,7 20 ys probability of death: surveillance: 9,3% BEP 13,6% RT 14,7% MTOL 74,5%	Danish Cancer Society and several more foundations No conflicts of interests	LoE2b RoB SIGN (+) acceptable

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Kollmannsberger C 2011	three arm retrospective Cohort study n=649 1999-2008 Canada	Seminom CS I n=545 mean age: surveillance 37 [range 18–83] radiation 39 [range 19–76] carboplatin 36 [range 19–62]	Active surveillance n = 313 Adjuvant RT n = 159 Adjuvant RT: 25 Gy in 15 fractions over 3 weeks with anterior to posterior parallel pair technique using megavoltage photons. Fields were usually restricted to the paraaortic chain Adjuvant carboplatin n = 73		median follow-up: surveillance 34 months [range 2–136] radiation 65 months [range 3–120] carboplatin 33 months [range 4–106]	5-y-RFS median time to relapse DSS	5-year relapse-free survival: surveillance 80.7%, adjuvant RT 98% carboplatin 98% Median time to relapse: surveillance:14 (3–36) mo Carboplatin: 20 mo total DSS: 100%	no conflict of interest no information about funding source	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Koutsoukus K 2016	single arm retrospective Cohort study n=138 2003-2011 Greece	Seminom CSI mean age: 34	2x Carboplatin AUC6		no information to mean follow up minimum follow up: 12,3 Months	5-y-RFR Acute Toxicity	5-year RFR: 96.8 % [95 % CI 91.6–98.8]) Toxicity Grade 3 Neutropenia 2,1% AST/ALT elevation 0,7% Constipation 0,7%	no coi no information to Funding source	LoE 4 RoB SIGN (-) not acceptable
Lee H 2015	single arm retrospective Cohort study n=41 1996-2007 Korea	Seminom CSI median age: 34 (21-56)	radiation median treatment period of radiotherapy: 23 days (range 21–27 days) for fractional doses of 1.5 Gy, 19 days (range 17–23 days) for 1.67 Gy, and 19 days (range 13–22 days) for 1.8 Gy		median follow-up: 112 months (range 50–200 months)	5,10 Y OS 5,10 Y RFS Toxicity	5-year OS: 100% 10-year OS: 96.0% 5-year and 10-year relapse-free survival (RFS) rates: both 97.1% Toxicity no grade 3–4 acute toxicity	no coi no information to Funding source	LoE 2b RoB SIGN (+) acceptable

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							Grade 1–2 hematologic toxicity: n=22 patients (54%): grade 1 leukopenia n= 8 (20%) grade 2 leukopenia n= 14 (34%)		
Leung E 2013	two arm retrospective Cohort study n=764 1981-2004 Canada	Seminom CS I mean age: no information	surveillance n=484	radiation n=280 megavoltage radiation using parallel-opposed fields with appropriate shielding para-aortic nodes, ipsilateral ilac nodes the inferior	median follow-up: surveillance 6.6 ys adjuvant RT 8.5 ys	OS relapse	Surveillance: 5-ys OS: 98.6% 10-ys OS: 97.7% n=72 (15%) relapsed median time to relapse: 14 Months adjuvant RT: 5-ys-OS: 97.2% 10-ys-OS: 91.4% n= 14 (5%) relapsed	no coi no information to funding source	LoE 2b RoB SIGN (+) acceptable

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				border of the RT field was placed at the cranial aspect of the acetabulum median (range) RT dose: 35 (25–37) Gy duration of RT not reported			median time to relapse: 15 mo		
Lewinshtein D 2011	single arm retrospective Cohort study n=5994 1973-2000 USA	Seminom CS I mean age: 37	radiation doses of 25 Gy to the para-aortic lymph nodes	compared to the general population	mean follow up: 15,1 Ys	SIR for SPM (standardized incidence ratio) SPM (Second primary malignancies)	All solid and blood-based malignancies, including secondary testicular cancer O/E 1.51 95% CI 1.38 1.64 All solid and blood-based malignancies, excluding secondary testicular cancer O/E 1.19 95% CI 1.08 1.31 SPM risk exposed to EBRT	no coi no information about Funding source	LoE 4 RoB SIGN (+) acceptable

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							SIR 1.51; 95% CI, 1.08 – 1.31 thyroid cancer SIR 2.32; 95% CI, 1.16 – 4.16 pancreatic cancer SIR 2.38; 95% CI, 1.43 – 3.72 non-bladder urothelial malignancies SIR 4.27; 95% CI, 1.57 – 9.29 bladder cancer SIR 1.47; 95% CI, 1.01 – 2.28 all haematological malignancies SIR 1.44; 95% CI, 1.08 – 1.89 specifically, NHL SIR 1.77; 95% CI, 1.22 – 2.48 stratified for time: SPM risk exposed to EBRT SIR 1.29; 95% CI, 1.10 – 1.49 thyroid cancer SIR 3.44; 95% CI, 1.12 – 8.03		

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							non-bladder urothelial carcinoma SIR 7.01; 95% CI, 1.91 – 17.96 bladder cancer SIR 1.77; 95% CI, 1.01 – 2.87 stratified for age SPM risk exposed to EBRT cohort of 25 – 29-year-olds SIR 1.61; 95% CI, 1.09 – 2.28		
Mahantshetty U 2012	two arm retrospective Cohort study n=137 1990-1998 India	Seminom CSI mean age: 37 (20-68)	radiation: n=96 mean dose: 30 GY (20-45 Gy) radiation with Cobalt 60 gamma rays or 6MV X -rays by conventional dose fractionation and schedule of 180 - 200 cGy / Fraction, 5 Fr / week.	observation: n=41	median follow up: radiation: 33 months observation: 29 months (mean follow up: 55 months, 8-218)	DFS DSS Toxicity second cancer	5 Y-DFS: observation: 73,5% radiation: 91% p=0,004 5-Y-DSS: observation: 89% radiation: 93% p=0,18 second cancer n=0	no information about coi and about Funding source	LoE 2b RoB SIGN (-) not acceptable numbers in abstract are different

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
			All the patients received radiation to para- aortic and pelvic nodes by simple parallel opposing antero-posterior and postero-anterior beams.				late Grade III toxicity: n=0		from numbers in full text
Martin JM 2010	two arm retrospective Cohort study n=23 1989-2007 Australia	Seminom CSI plus Cryptorchidism mean age: 37,7 ys	Surveillance n=5	Radiation n=18 median dose of 25 Gy (range, 20–30) in 15 fractions (range, 10–20). para-aortic region, 12 included ipsilateral common iliac, 5 the ipsilateral external iliac, and 2 the	median follow up: surveillance: 88 Months radiation: 47 Months	5 y relapse free rate RFR 5 y- OS cause specific survival malignant events	radiation: 5 y-RFR: 100% 5-y-OS: 100% 5-y-CSS: 100% surveillance: 5-y-RFR: 80% 5-y-OS: 100% 5-y-CSS: 100% malignant events: total n=2 n=1 (relapse in the para-aortic region and ipsilateral pelvis) after surveillance	no coi no information to funding source	LoE 2b RoB SIGN (-) not acceptable very small number of cases

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
				ipsilateral inguinal lymph nodes			n=1 (relapse in the contralateral testis) after radiation		
Mead GM, 2011	RCT TE 19 trial n=1477 1996-2001 UK	Seminom CS I mean age: kA	radiation n=904 randomly assigned to 20 or 30 Gy or between 20 Gy and 30 Gy standard treatment: Para-aortic radiation therapy dogleg radiation therapy recommended for patients with	carboplatin n=573 AUC7 single injection	median follow up: radiation: 6,4 y carboplatin 6,5 y followed for 5 years: radiation 79.7% carboplatin 75.8%	5-year Relapse-free rate Overall CSS for al (n=2466) TE 10, TE18, TE19	radiation: 5-year relapse-free rate: 96.0% (95% CI, 94.5% -97.1%) carboplatin: 5-year relapse-free rate: 94.7% (95% CI = 92.5% to 96.3%) Overall cancer-specific survival: 99.8% (95% CI = 99.6% to 99.9%)	MRC Clinical Trials Unit no information about coi	LoE 1b low RoB

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			previous inguinoscrotal surgery						
Mortensen MS 2014	retrospective, population-based cohort study n = 1954 DK 1984 - 2008	CS I Seminoma Age, yr, median (range): 37 (16–82)	surveillance	no control	Median follow-up time: 15.1 yrs (range: 0.6–28.7 yr)	Disease-specific survival (DSS), overall survival, relapse rates, time to relapse, prognostic factors for relapse	Relapse rate 18.9% (369 of 1954) time to relapse: 13.7 mo (range: 2.3–173.6 mo) relapse rate during the first 2 yr after orchiectomy: 73.4% (271 of 369) relapse rate between years 3 and 5: 22.2% (82 of 369) relapse rate >5 yr after	Danish Cancer Society, The Danish Cancer Research Foundation, and the Preben & Anna Simonsen Foundation	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							orchiectomy: 4.3% (16 of 369) 5 yr-OS: 98.1% 10 yr-OS: 95.5% 15 yr OS: 91.6% 5 yr DSS: 99.6% 10 yr-OS: 99.4% 15 yr-OS: 99.3% prognostic factor: Tumor size: HR 1.59 (1.31–1.92), <0.0001		
Oliver RT 2011	RCT TE 19 trial n=1477 1996-2001 UK	Seminom CS I mean age: kA	radiation n=904 randomly assigned to 20 or 30 Gy or	carboplatin n=573 AUC7 single injection	median follow up: radiation: 6,4 y carboplatin 6,5 y	5-year Relapse-free rate Overall CSS for all (n=2466) TE 10, TE18, TE19	radiation: 5-year relapse-free rate: 96.0% (95% CI, 94.5% -97.1%) carboplatin: 5-year relapse-free rate: 94.7% (95% CI = 92.5% - 96.3%)	Supported by United Kingdom Medical Research Council no potential conflicts of interest	LoE 1b unclear RoB

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			between 20 Gy and 30 Gy standard treatment: Para-aortic radiation therapy dogleg radiation therapy recommended for patients with previous inguinoscrotal surgery		followed for 5 years: radiation 79.7% carboplatin 75.8%	contralateral GCT-free rates at 5 years	Overall cancer-specific survival: 99.8% (95% CI = 99.6% - 99.9%) 5 year- contralateral GCT-free rates: carboplatin: 99.8% radiation: 98.8% relative reduction in risk of nearly 80% HR 0.22 (95% CI 0.05- 0.95 P=.03) adverse events not reported		
Ondrusova M 2015	two arm retrospective Cohort study n=90 2008-2015	Seminom CS I mean age: 36,6 y	low risk group: Surveillance n=74	high risk group: Carboplatin n=16 one single course (7AUC)	mean follow up: for OS: 27 mo (range 6.5-84)	progression rate PFS OS	Surveillance: progression rate: .9.5 % Mean time to relapse: 14.5 mo Progression-free survival n=67 (90.5 %) OS 100%	no conflict of interest supported by the Slovak Research and Development Agency	LoE 2b RoB SIGN (-) not acceptable

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	Slovakia						Carboplatin progression rate 12.5 % Mean time to relapse: 13,8 mo Progression-free survival n=14 (87.5 %) OS 100%		very small number of cases in Carbo-group
Robinson R 2016	Retrospective Cohort study Three time cohorts n=904 1999 - 2002 2002 - 2005 2007 - 2009 UK	radical orchidectomy for testis cancer median (range): age 35 (14–88) yrs	Prosthesis n=228 median (range) age of 33 (16–72) yrs	No prosthesis n not reported 37 (14–88) yrs	no information to mean follow up	use of prostheses and associated postoperative complications, LOS, re-admission rate and return to theatre rate in men undergoing orchidectomy	Outcomes no significant difference -- LOS (1.98 and 2.10 days, *P* = 0.387) 30-day hospital - re-admission rates: 2.6% (95% CI 1.04–5.56%) 4.2% (95% CI 2.85–6.01%) (*P* = 0.539) - 30-day return to theatre rates: 1.3% and 1.5%, *P* = 0.999 Removal prosthesis: Haematoma (1=n) Wrong size (1=n)	no COI no information about Funding source	LoE 2b RoB SIGN (+) acceptable

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							abscess formation (1=n) overall removal/revision rate of 1.3%		
Serdar L 2015	single arm retrospective Cohort study n=68 1997-2013 Turkey	Seminom CS I mean age: 39 (24-74)	radiation para-aortic RT 85.3% dog-leg field RT 14.7% median RT dose: 23.4 (23.4–30.6) Gy. 10 received dog-leg field RT. The median time between surgery		median follow up: 77,5 Months (6,7-198,5 Months)	5,10,15 OS 5,10,15 CSS PFS toxicity	5, 10, and 15-year OS: 94.7%, 89.6%, 89.6% 5, 10, and 15-year CSS 98.5%, 96%, 96% 5, 10, and 15-year PFS rate: 96.1% Grade 1–2 gastrointestinal (GIS) toxicity: n=28 patients (41.2%) grade 3–4 disease-related toxicity: n=0	no coi Source of Support: Nil	LoE 4 RoB SIGN (+) acceptable

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			and RT was 47 (18–307) days. RT was applied with 1.8 Gy/day fractionation and an overall median dose of 23.4 (23.4–30.6) Gy. The median RT dose was 23.4 (23.4–25.2) Gy among patients receiving paraaortic RT and 23.4 (23.4–30.6) Gy among patients receiving dog-leg RT.				paraaortic RT: GIS toxicity: n=23 (39.7%) dog-leg RT GIS toxicity: n=4 (40%)		
Soper MS 2014	three arm retrospective Cohort study n=502 1990-2009	Seminom CS I mean age: Radiation: 36 Chemotherapy: 32 Observation: 38	Radiation (n = 329) (117 to a pelvic and para-aortic [dog-leg] field [DL], 205 to a para-aortic field [PA], and 7 to other or unknown fields),		median follow-up: radiation 7.5 years (range, 0.3 mo to 21 y) chemotherapy	RFS OS CSS	2 yr-Relapse-free survival Radiation 97.6% (95.8, 99.4) Chemotherapy 98.3% (94.9, 100) Observation 89.2% (81.4, 95.4)	no coi no information to Funding source	LoE 2b RoB SIGN (+) acceptable

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	USA		RT dose and duration of RT not reported Chemotherapy (n = 79) 1x carboplatin n=33 2 x carboplatin n=36 other agents n=10 Observation (n=94)		2.6 years (range, 1mo to 15.2 y) observation (5.2 years (range, 1mo to 16.7 y)		5 yr-Relapse-free survival Radiation 97.2% (95.2, 99.1) Observation 89.2% (81.4, 95.4) 2 yr Overall survival Radiation 99.6% (97.7, 100) Chemotherapy 100% (100, 100) Observation 98.8% (96.2, 100) 5 yr Overall survival Radiation 98.0% (95.2, 99.3)		

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							Observation 98.8% (96.2, 100) 2 yr Cause-specific survival Radiation 99.6% (98.2, 100) Chemotherapy 100% (100, 100) Observation 100% (100, 100) 5 yr Cause-specific survival Radiation 99.3% (98.2, 100) Observation 100% (100, 100)		

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Steiner H 2010	single arm retrospective Cohort study n=276 1990-2008 Austria, Italy	Seminom CS I mean age: 36,7	2 cycles Carboplatin (2× 400 mg/m²) n=276		follow-up period of 75.2 (0.5–250.2) months	acute toxicity contralateral second tumour relapse free rate second malignancies	acute toxicity: transient leucopoenia: 36.7% Thrombocytopenia: 50.5% contralateral second tumour 5 von 263 patients (1.9%) 2y relapse-free rate: 98.6%, 4y relapse-free rate: 98.4%, 4y relapse-free rate: 98.1% 10y relapse-free rate: 93.9% second malignancies: prostate cancer (n = 2) melanoma (n = 2) kidney cancer (n=1) hypertension (n=3) cardiovascular disease: apoplectic stroke n=1 symptomatic coronary heart disease n=1	no conflicts of interests no information to funding source	LoE 4 RoB SIGN (+) acceptable

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							myocardial infarction n=1 peptic ulcer (n=1)		
Tandstad T 2014b	two arms prospective cohort study n=1003 1995-2005 Sweden, Norway	CS I NSGCT mean age: no information about age	ACT n= 494 cisplatinbased chemotherapy in combination with 1x CVB or BEP In case of ITGCNU: RT to a minimum dose of 16 Gy in 8 fractions	Surveillance n=494 In case of ITGCNU: RT to a minimum dose of 16 Gy in 8 fractions	median follow-up: 8.3 years	incidence ITGCNU and bilateral TGCC according to biopsy status effect of adjuvant chemotherapy	Incidence ITGCNU: 9/282 (3.2%) Biopsy status 9/282 ACT 4/494 Surveillance 5/494 Incidence bilateral TGCC: 3.6 %	no COI Founding: National Cancer Fund of Sweden	LoE 2b SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							bilateral TGCC ACT 11/494 (2.5%) surveillance 13/494 (3.4%) p = 0.41 time to relapse: median: 3.7 yrs (0.2 – 8.1 yrs) OS: 100% Relapse after radiotherapy: n=1/8 patients after 3 yrs		
Tandstadt T 2011	three arm prospective Cohort study n=1384	Seminom CS I und weitere Stadien mean age: 37 ys	radiotherapy n=481 Treatment of two parallel opposed equally	Carboplatin 1x AUC7 n=188 surveillance n=512	median follow up: 5,2 ys (all patients) 6,1 ys	RFI (relapse free interval) CSS OS	Relapse rate: Surveillance: 14,3 % median time to relapse: 1,4 ys Relapse rate: Carboplatin 1x: 3,9%	Swedish Cancer Society, the Gunnar Nilsson Foundation for Cancer Research, and the Nordic	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
	2000 – 2006 Norway, Sweden		weighted fields 25.2 Gy (14 fractions of 1.8 Gy). ipsilateral iliac and para-aortal lymph nodes up to the level between the 10th and 11th thoracic vertebra (L-field) within 6 weeks of orchiectomy		radio 5,0 ys surveillance 3,4 ys carboplatin 1x		median time to relapse: 1,8 ys Relapse rate: Radiation: 0,8% median time to relapse: 1,1 ys adjuvant carboplatin vs radiotherapy HR, 4.7; 95% CI, 1.1 - 14.4; P=0.031) risk of relapse: Surveillance vs. adjuvant carboplatin HR 3.9 (95% CI, 1.6 to 9.3) P=0.02) RFI: Surveillance: 85,7% Carbo 1x: 96,1% Radiation: 99,2% 5-ys-OS:	Cancer Union. no coi	

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							Surveillance: 98,4% Carbo 1x: 99,2% Radiation: 98,7% 5 ys-CSS: Surveillance: 99,8% Carbo 1x: 100% Radiation: 100%		
Tandstadt T 2016	two arm prospective Cohort study n=897 SWENOTECA VII 2007-2010 plus: n=221 SWENOTECA V	Seminoma CS I mean age: no information about age	risk adapted protocol with no or one risk factor: surveillance n=422 risk factors: largest tumour diameter >4 cm and/or stromal invasion of rete testis	risk adapted protocol with two risk factors: Carbo 1x AUC7 n=469	median follow up: surveillance: 5.4 ys (4.5–6.3) Carbo: 5.7 ys (4.3, 7.3)	Median time to relapse 5-year OS 10-year OS 5-year CSS 10-year CSS	Median time to relapse: surveillance: 1,3 ys (0,4-5,6) Carbo 1x: 1,7 ys (0,2-6,5) 5-years OS: surveillance: 99,2% Carbo 1x: 98,9% 10-years-OS: surveillance: 96,8% Carbo 1x: 98,5%	Research Committee at St Olavs Hospital, Trondheim. The Swedish Cancer Society, the Swedish Association of Local Authorities and Regions, the Norwegian Regional Health Authorities, and the Norwegian Urological Cancer Group no coi	LoE 2b RoB SIGN (+) acceptable wahrscheinlicher Selektionsbias in der Carboplatin Gruppe Empfehlung war: low risk

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	total n=1118 Norway, Sweden						5-years-CSS: surveillance: 100% Carbo 1x: 100% 10-years-CSS: surveillance: 99,6% Carbo 1x: 100%		Patienten erhalten Surveillance und high risk Patienten erhalten Carbo Mono, nur 11% der Stichprobe hatten 2 Risikofaktoren, aber 53% der Patienten wählte Carbo als Therapie

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Terbruch A 2017	Retrospective cohort study n=950 1994-2013 Austria	Seminom CS I Mean age: 37.3 [32.4 to 44.1] yrs	surveillance n=406	adjuvant therapy with single shot carboplatin n=37 patients	median follow up: 8.6 yrs (21 days to 21.6 yrs)	CVE rate	CVE rate after single shot carboplatin: 0/37 patients median follow up: 3.4 yrs	no COI Founding: Medical University of Graz	LoE 2b SIGN RoB (+) acceptable
Daugaard G 2014	single-arm retrospective cohort n=1226 1984-2007 Denmark	NS GCT CS I n=1226 median age: 30 (15-79)ys	Surveillance	no control group	median follow-up time: 180 months (range, 1 to 346 months)	time to relapse Risk of relapse relapse rate OS, DSS	median time to relapse: 5 months (1 -308 months) 5-year relapse rate without any risk factors: 12% 5-year relapse rate with all risk factors: 50% 5-y-OS: 97.6% 10-y-OS: 96.2%	no coi no information about funding	LoE 4 RoB SIGN (+) acceptable

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							15-y-OS: 94.5% 5-y-DSS: 99.3% 10-y-DSS: 99.3% 15-y-DSS: 99.1%		
Dieckmann KP 2013	multi center retrospective cohort study n=228 Germany Austria 2006-2010	patients with unilateral GCTs and biopsy-proven contralateral TIN Age Mean (SD): 30.5 yrs (6.9) Non-seminoma: n=116 Seminoma: 112	n=122 local radiotherapy n=33 (27%) additional chemotherapy with carboplatin (N = 11), 2 courses of PEB (N = 12), 3 courses of PEB (N = 10)	no controls	median follow-up of all patients: 4 yrs (range 0.1–13.1 yrs)	primary end point: occurrence of a malignant event (ME) during follow-up secondary end point: hypogonadism during follow-up	n=45 MEs (19.7%) Hazard ratios of developing malignant event (ME): Radiotherapy HR 1.0 Chemotherapy two or more cycles PEB: HR 29.1 (95% CI 8.41–100.85) Chemotherapy three or more cycles PEB: HR 11.5 (95% CI 3.15–42.30) Carboplatin HR 63.6	no coi no information about funding	LoE 4 SIGN RoB (+) acceptable

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							(95% CI 17.21–235.11) Surveillance HR 12.3 (95% CI 2.88–52.35) Hypogonadism: n=55/205 eligible pts Surveillance n=4 (40%) (95% CI 12.16–73.76) Radiotherapy n=36 (30.8%) (95% CI 22.41–39.13) Two or fewer cycles PEB n=3 (13.0%) (95% CI 2.78–33.59) Three or more cycles PEB:		

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							n=8 (17.8%) (95% CI 8.0–32.05) Carboplatin n=4 (40%) (95% CI 12.16–73.76)		
Dieckmann KP 2015	multi center cross sectional study 1997 – 2014 n=475 Germany	n=293 pure seminoma n= 183 nonseminoma	testicular prosthesis implantation having the implant for at least half a year and no longer than 10 years	no control	not applicable	acceptance rate patient satisfaction	acceptance rate: n=128 (26.9%) (95% CI 23.0% - 31.2%) Over-all satisfaction with the implant: “very high”31.1% “high” 52.4%	no coi no information about coi	LoE 3b
Fan G 2015	two-arm retrospective Cohort study n=81	NSGCT I low risk inclusion criteria: non-lymphatic vascular invasion (non-	Surveillance n=54	RPLND n=27 (n=4 lap. RPLND/ n=23 open RPLND	Median follow-up: surveillance: 66,2 months (6-164)	Disease-free-survival rates (DFSR) Overall survival (OS) after 66 mo	DFSR: Surveillance 89,9% RPLND 87% p=0.743 OS: 100% both groups	Fundamental Research for the central Universities of Central South University, China.	LoE 2b RoB SIGN (+) acceptable

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	January 1999-October 2013 China	LVI), percentage of embryonal carcinoma is <50% (%ECa <50%), and negative or declining tumor markers (AFP: a-fetoprotein; hCG: human chorionic gonadotropin) to their half-life			RPLND: 65,9 Mon. (8-179)		DFSR RPLND: HR 0,779 (95% KI 0,175-3,464) p=0,743 adverse events RPLND: infection (one case), obstruction (two cases) ejaculatory dysfunction (six cases) overall occurrence in 39.1% (9/23) most events: mild or treated easily no adverse events in Surveillance		

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Hallemeier CL 2014	retrospective single center cohort study n=199 1972 - December 31, 2009 USA	CS I Seminoma median age: 36 years (range: 18-80)	adjuvant megavoltage radiation (RT) median RT dose: 25.5 Gy (interquartile range: 25-30)	no control	median follow-up after RT: 13 yrs (range: 0.1-37)	Overall survival (OS), cause-specific survival, relapse rate, major cardiac event (MCE), second malignancy (SM)	10 yr-OS: 92% 20 yr-OS: 77% 10-yr-Cause-specific survival: 99% 20-yr-Cause-specific survival: 99% 10 yr Risk of relapse: 1% 20 yr Risk of relapse: 2% 20 yr Risks of MCE: 12% 20 yr Risks of SM: 19%	no information about coi no information about funding	LoE 4 RoB SIGN (+) acceptable

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Keskin S 2011	single-arm retrospective cohort study n=80 2002-2009 Turkey	NS GCT CS I n=70 Median age: 27.8 years (16-67).	Surveillance	no control group	Median follow-up period: 18.5 ± 16.1 mo (6-76)	relapse rate	Relapse rate: n=12 (17%) Relapse within 1 year: n=10 (83%)	no coi no information about funding	LoE 4 Rob SIGN (+) acceptable
Kier MG 2015	retrospective two arm cohort study n=5409 patients with GCC diagnosed in 1984-2007 DK	Median age at diagnosis, years (IQR) Screened cohort: 34 (28-42) Unscreened cohort: 34 (28-43)	n=4130 with GCC diagnosed in 1984-2007 (screened cohort)	n=462 with GCC diagnosed in 1984-1988 (unscreened cohort)	Median follow-up, years (IQR) Screened cohort: 14 (9-19) unscreened cohort: 26 (24-27)	cumulative incidence of metachronous GCC	screened cohort: Contralateral CIS: n=181 [4.4%; 95% (CI) 3.8-5.0 Metachronous GCC n=5/181 (2.8%) with contralateral CIS Metachronous GCC = 53/3949 (1.3%) without CIS	The Danish Cancer Society (grant number DP08 094); Anna and Preben Simonsen Foundation (no grant number); Clemmesen Foundation	LoE 2b SIGN RoB (+) acceptable

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							unscreened cohort: 15 (3.2%) cases of metachronous GCC 20-year cumulative incidence of metachronous GCC: screened population 1.9% (95% CI 1.4–2.5) unscreened cohort 3.1% (95% CI 1.5–4.6) (P = 0.097) HR 1.59 (95% CI 0.85–2.95) for the unscreened cohort in comparison with the screened cohort (P = 0.144) second tumour: stage I for 85% of all patients with metachronous GCC (62/73)	no coi	

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Kobayashi 2013	two-arm retrospective cohort study n=158 1980-2008 Japan	NS GCT CS I n=40 mean age: 31,2 ys (1-54)	Surveillance n=36	Chemotherapy n=4		Relapse time to relapse RFS-	relapse rate: surveillance: n=9 (25%) chemotherapy n=0 time to relapse: mean 6 months (2-13) 5-year / 10-y-relapse free survival: surveillance: both 75%	not been funded by any commercial company or grant no coi	LoE 2b RoB SIGN (+) acceptable
Kollmannsberger C 2015	two-arm retrospective Cohort study n=2483 (total) CSI-Nonsem I n=1139	Nonsem-Patienten CS I histologically confirmed NONSEM CS I	Active Surveillance LVI positive n=183	Active Surveillance LVI negative n=935	median follow up: 62 months (1-277)	Disease-specific survival (DSS) Relapse	LVI-positive: Median time to relapse: 4 months (1-61) LVI-negative: 8 months (2-77) no rates per groups: total 5 ys DSS: 99,7%	Honoraria: Tom Powles, GlaxoSmithKline, Pfizer, Astellas Pharma	LoE 2b RoB SIGN (+) acceptable

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	CSI Sem I n=1344 1983-2012 Canada Sweden Norway UK						10 ys DSS: 99,7% Alive NED (no evidence of disease) Nonsem LVI positive 98% Nonsem LVI negative 95% Relapse rate: Nonsem LVI positive: 44% Nonsem LVI negative: 14%		
Kollmannsberger C 2010	single-arm retrospective cohort study n=233 1998-2007 Canada	NS GCT CS I n= 2223 median age: 29ys (15-63)	Surveillance	no control group	Median follow-up: 52 mo (range 3-136)	relapse rate DSS	Relapse rate: n=59 (26%) Median time to relapse: 4 months (range 2-49) 85% patients relapsed within the first year after diagnosis median follow-up: 52 months (range 3-136 months)	no information about coi no information about funding	LoE 4 RoB SIGN (+) acceptable

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							DSS:100%		
Li X 2015	single-arm retrospective cohort study n=163 1999-2013 China	NS GCT CS I n=78 median age: 29,5 ys (14-56)	Surveillance	no control group	Median follow-up time: 6.2 ys (range 1-15)	relapse rate time to relapse OS	Relapse rate: n= 18 (23.1 %) median time to relapse: 5.6 (range 1-47) months n=13 (72.2 %) relapsed within first year after orchiectomy median follow up time: 6,2 ys OS: 98.7 %	no coi no information about funding	LoE 4 RoB SIGN (+) acceptable
Lv ZJ 2013	three-arm retrospective Cohort study n total= 492	NSGCT I n tumour stage Ia=40 Ib=12 IS=37	active surveillance: If vascular or lymphatic invasion was not present or there was less than 50% embryonal carcinoma, with strict follow-ups	RPLND: patients with predominant Teratoma or for those who were opposed to chemotherapy or surveillance	median follow-up: 92 Months (6-149)	5 yr-Overall survival rate OS 4-yr recurrence rate	OS: 98,9% 4 y-recurrence-free rate: 80.2% surveillance (low-risk-patients)	four public funding sources no information about coi	LoE 2b RoB SIGN (+) acceptable

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	1997-2011 n total NSGCT= 205 China	vascular or lymphatic invasion of the primary tumour yes/no low-risk / high-risk patients n=58 low risk n=31 high risk	n=37	n= 34 Adjuvant chemotherapy: patients with vascular invasion, lymphatic invasion, more than 50% embryonal carcinoma or some combination n=18			92.0% RPLND (low and high risk patients) 100% adjuvant chemotherapy (low and high risk patients) recurrence free rate: stage Ia: 100% stage Ib: 84,7% p<0,001 no Grade 3/4 chemotherapy-related toxicity		
Nicolai 2010	single-arm retrospective cohort study n=322 1985-1995 Italy	NS GCT CS I median age: 27 (IQR 22-32)	RPLND n=322	no control group	median follow-up: 17.3 yr	CCI of recurrence contralateral GCTT	tumour recurrence 10-yr-CCI: 15,2% (11,7%-19,8%) contralateral GCTT: 2,0% (0,7%-6,1%)	no coi no funding	LoE 4 RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
						CCI=crude cumulative incidence			
Ondrus D 2015	two-arm prospective Cohort study n total=454 January 1992 – August 2014 Slovakia	NSGCT I low risk n=287 (negative LVI) high risk n=167 (with LVI and/ or > 50% embryonal cell carcinoma)	active surveillance (low risk patients) n=287	adjuvant Chemotherapy (CT) (high risk patients) n=167 adjuvant CT: two cycles BEP	median follow up: 142 months	Relapse Progression-free survival (PFS) Overall survival after 142 mo (low risk) and after 135 mo (high risk)	low risk: Relapse: n=48 (16.7%) after mean follow-up of 11.2 mo Progression-free survival (PFS): 83.3% (median follow-up 113.9 mo) OS: n=281/ 287 (97.9%) median follow-up 142 mo high risk: relapse: n=2 (1.2%) meantime 56.2 mo	Slovak Research and Development Agency	LoE 2b RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							PFS: 98.8% median follow-up 134 mo low risk group OS: n=166/ 167 (99.4%) median follow-up 135.7 mo high risk group OS: 166/ 167 (99.4%) median follow-up of 135.7 mo PFS 83.3% vs. 98.8% p < 0.001		
Ondrusova M 2017	Prospective two arm cohort study n=485 1992-2017	NSGCT CS I Low risk and high risk	Low risk N=301 Active surveillance	High risk n=184	Low risk: 7,2 mo High risk: 56 mo	Relapse rate OS	Active surveillance: Relapse rate: 17,3% median follow up 7,2 mo OS: 97,8% Late Relapse rate 11,5%	No information about funding No coi	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
	Slovak republic			adjuvant chemotherapy 2xBEP			Adjuvant chemotherapy: Late relapse rate: 1,1% median follow up 56,2 mo OS: 99,5%		
Sturgeon JF 2011	single-arm retrospective cohort study n=371 1981-2005 Canada	NS GCT CS I	Surveillance n=371	no control group	Median follow-up: 6.3 yr (0.08–25.9 yr)	recurrence rate, time to relapse, DSS	Relapse rate: n= 104 (28.0%) median time to relapse: 7.1 mo 78.9% relapsed in first year of follow-up 5-yr DSS: 99.1% 5 yr recurrence-free survival: 72.5%	no coi no funding	LoE 4 RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Tandstad T 2014a	two arm prospective Cohort study n=517 May 1998 – December 2010 Norway Sweden	NS GCT I with LVI without LVI LVI (lymphovascular invasion)	adjuvant Chemotherapy (ACT) bleomycin, etoposide, cisplatin (BEP) with LVI: one course of adjuvant BEP n=258	adjuvant Chemotherapy ACT bleomycin, etoposide, cisplatin (BEP) without LVI: surveillance or one course of adjuvant BEP n=255 none of the patients choose Surveillance n=4 LVI Status unclear BEP 1x	median follow up all: 7,9 ys with LVI: 8,0 Jahre without LVI: 7,9 ys	5 ys OS 10 ys OS 5 ys CSS 10 ys CSS Relapse Rate CSS=Cancer specific survival	5 ys OS total: 99,0 % with LVI: 98,7% without LVI 99,2% LVI uncertain: 100% 10 ys OS total: 96,9% with LVI: 96,9% without LVI: 96,9% LVI uncertain: 100% 5 ys CSS total: 100% with LVI: 100% without LVI 100% LVI uncertain: 100% 10 ys CSS total: 99,6% with LVI: 99,3% without LVI: 100%	National Cancer Fund of Sweden no COI	LoE 2b RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							LVI uncertain: 100% Relapses: total: n=12 (2,4%) with LVI: n=8 (3,2%) without LVI: n=4 (1,6%) LVI uncertain: n=0, 0%		
Tandstad T, 2014b	two arm prospective Cohort study n total: 1003 July 1995-July 2005 Norway Sweden	NSGCT CS I with lymphovascular invasion (LVI): adjuvant chemotherapy without LVI: surveillance or adjuvant chemotherapy	patients with LVI: adjuvant chemotherapy: n=494 protocol violations: radiotherapy (n = 2) RPLND (n=1)	patients without LVI: surveillance n=494 or adjuvant chemotherapy	median follow up: 8,3 ys	incidence of metachronous contralateral cancer time to develop contralateral cancer	metachronous TGCC n=31 (3,6%) median time to metachronous TGCC 3.7 yrs (0.2 – 8.1) incidence of bilateral cancer: surveillance: 3,4% chemotherapy: 2,5% p=0,41	no coi funded by the National Cancer Fund if Sweden	LoE 2b RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Tanstad T 2010	RCT n total=232 July 1995-January 1998 Sweden Norway	NS GCT I VASC- n=165 VASC+ n=67	Study 1: VASC- n=40 CVBx1 VASC unclear n=1 CVBx1 study 2: VASC+ n=55 CVBx2 VASC +: CVBx1 n=1 VASC +: CVBx1 & BEP x1	control study 1: VASC- n=124 surveillance study 2: VASC+ n=5 surveillance	median follow-up: 122 mo minimum follow up: 13 mo	relapse free survival RFS overall survival OS after 122 Mon	VASC- CVBx1 10% relapse rate (n=4) surveillance 12,9% relapse rate (n=16) VASC+ CVBx2 1,8% relapse rate (n=1) surveillance relapse rate 60% (n=3) OS surveillance: n=2 / 129 (98,5%) CVBx2: n=1 / 55 (98,2%) DSS total =100%	no information about funding or coi	LoE 2b (low quality RCT) RoB: high risk

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
			n=4 CVB: cisplatin, vinblastine, bleomycin VASC+: VASC+, mit vascular Invasion VASC-: without vascular Invasion				OS total =98,4% toxicity: 90%-95% of all cases tox WHO Grade 3/4 n= 23 (27%) pts receiving CVB n=10 (12%) paralytic ileus n=21 (25%) neutropenic infections Grade 3/4 Leucopenie n=53 (60%) Grade 3 Neuropathie n=3 (4%) Pulmonary, renal, thrombocytic toxicity: not reported grade 3 or 4		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Tandstad T 2016	two arm prospective Cohort study n=897 SWENOTECA VII 2007-2010 plus: n=221 SWENOTECA V total n=1118 Norway, Sweden	Seminoma CS I mean age: no information about age	risk adapted protocol with no or one risk factor: surveillance n=422 risk factors: largest tumour diameter >4 cm and/or stromal invasion of rete testis	risk adapted protocol with two risk factors: Carbo 1x AUC7 n=469	median follow up: surveillance: 5.4 ys (4.5–6.3) Carbo: 5.7 ys (4.3, 7.3)	Median time to relapse 5-year OS 10-year OS 5-year CSS 10-year CSS	Median time to relapse: surveillance: 1,3 ys (0,4-5,6) Carbo 1x: 1,7 ys (0,2-6,5) 5-years OS: surveillance: 99,2% Carbo 1x: 98,9% 10-years-OS: surveillance: 96,8% Carbo 1x: 98,5% 5-years-CSS: surveillance: 100% Carbo 1x: 100% 10-years-CSS: surveillance: 99,6% Carbo 1x: 100%	Research Committee at St Olavs Hospital, Trondheim. The Swedish Cancer Society, the Swedish Association of Local Authorities and Regions, the Norwegian Regional Health Authorities, and the Norwegian Urological Cancer Group no coi	LoE 2b RoB SIGN (+) acceptable wahrscheinlicher Selektionsbias in der Carboplatin Gruppe Empfehlung war: low risk Patienten erhalten Surveillance und high

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
									risk Patienten erhalten Carbo Mono, nur 11% der Stichprobe hatten 2 Risikofaktoren, aber 53% der Patienten wählte Carbo als Therapie
Tandstad T 2011	three arm prospective Cohort study n=1384 2000 – 2006	Seminom CS I und weitere Stadien mean age: 37 ys	radiotherapy n=481 Treatment of two parallel opposed equally weighted fields	Carboplatin 1x AUC7 n=188 surveillance n=512	median follow up: 5,2 ys (all patients) 6,1 ys radio	RFI (relapse free interval) CSS OS	Relapse rate: Surveillance: 14,3 % median time to relapse: 1,4 ys Relapse rate: Carboplatin 1x: 3,9% median time to relapse: 1,8 ys	Swedish Cancer Society, the Gunnar Nilsson Foundation for Cancer Research, and the Nordic Cancer Union.	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
	Norway, Sweden		25.2 Gy (14 fractions of 1.8 Gy). ipsilateral iliac and para-aortal lymph nodes up to the level between the 10th and 11th thoracic vertebra (L-field) within 6 weeks of orchiectomy		5,0 ys surveillance 3,4 ys carboplatin 1x		Relapse rate: Radiation: 0,8% median time to relapse: 1,1 ys adjuvant carboplatin vs radiotherapy HR, 4.7; 95% CI, 1.1 - 14.4; P=0.031) risk of relapse: Surveillance vs. adjuvant carboplatin HR 3.9 (95% CI, 1.6 to 9.3) P=0.02) RFI: Surveillance: 85,7% Carbo 1x: 96,1% Radiation: 99,2% 5-ys-OS: Surveillance: 98,4%	no coi	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							Carbo 1x: 99,2% Radiation: 98,7% 5 ys-CSS: Surveillance: 99,8% Carbo 1x: 100% Radiation: 100%		
Vidal AD, 2015	single-arm-prospective phase-II-study 1995-1999 n =44 Switzerland	NSGCT CS I high risk with VI and/or EC >50% n=40	CT within 4 weeks after orchiectomy 1 modified-BEP cycle daily dose of 20 mg/m2 of bleomycin (given as a continuous i.v. infusion over 24 h to decrease the risk of pulmonary side-effects), 120 mg/m2 of etoposide and 40 mg/m2 of cisplatin administered i.v. on days 1–3	no control	Median follow-up: 186 (10–224) months	Primary end point: rate of relapse after adjuvant chemotherapy, with or without elevation of tumour markers Secondary end points: rates of metachronous testicular tumours, secondary neoplasia, late	relapse rate after 15 ys: n=1 (2,5%) rate of metachronous tumour: n=3 (7,5%) secondary neoplasia: n=3 (7,5%) (leukemia, colorectal cancer) chemotherapy-side-effects: n=1 (grade 2 peripheral polyneuropathy) Intermittent grade 1 tinnitus: n=2 (5%)	no information about funding no coi	LoE 4 RoB SIGN (-) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
						postchemotherapy toxicity Intervals to relapse, death, or secondary malignancies were calculated from the date of orchiectomy	Intermittent grade 2 tinnitus n=1 (2.5%) glomerular filtration rate of 53 ml/min/1.73 m2 and non-ST elevation myocardial infarction (210 months of follow-up) n=1 No overt nephrotoxicity, cardiotoxicity, or pulmonary toxicity registered in other patients		
Weiner AB, 2017	three-arm retrospective cohort study n=6660 2004-2013 USA (National Cancer Data Base)	NS GCT CS IA n=4080 NS GCT CS IB n=2580	NSGCT CS IA surveillance n=2873 (70,4%) RPLND n=676 (16,6%) Chemotherapy n=531 (13,0%) NSCGT CS IB	NS GCT S0 n=944	median follow-up: 45.0 mo (IQ range: 25,1-69 mo)	overall survival OS based on living vital status and date of last follow-up after diagnosis of NSGCT.	Clinical stage IA 5-Year OS: Surveillance 97.3% (KI 96.3-98.0) RPLND 99.1% (KI 97.6-99.7) Chemotherapy 98.0% (KI 96.2-99.0) 10-Year OS	No specific funding was disclosed no coi	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
			surveillance n=1195 (46,3%) RPLND n= 503 (19,5%) Chemotherapy n=882 (34,2%) unclear, which kind of Chemo				Surveillance 94.2% (KI 91.2-96.2) RPLND 97.5% (KI 93.6-99.1) Chemotherapy 95.1% (KI 89.8-97.7) p=0,064 Clinical stage IB 5-Year-OS: Surveillance 96.5% (KI 94.8-97.7) RPLND 97.8% (KI 95.5-99.0 Chemotherapy 96.0% (KI 94.1-97.3) 10-Year OS: Surveillance		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
							95.8% (KI 93.4-97.4) RPLND 97.0% (KI 93.7-98.6) Chemotherapy 91.7% (KI 77.7-97.0) p=0,411		
Yap St A 2017	three-arm retrospective Cohort study n=3951 1988 – 2010 USA-California	NS GCT I	Surveillance n=1903	Chemotherapy n=962 RPLND n=1049	median follow up: 96 months	5 ys CSS 5 ys OS	5-ys OS RPLND 98% Chemotherapy 92% Surveillance 97 % 5 – ys (CSS) RPLND 99% Chemotherapy 94% Surveillance 99 %	no coi no information about funding	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
Yuasa T 2015	two-arm-retrospective cohort study n=84 Stage I GCT March 1999-February 2013 Japan	NS GCT CS I n=30 Vascular invasion LVI n=13 (43%) no LVI n=11 (20%) n=6 uncertain LVI	surveillance low risk-group n=11	surveillance high risk group n=13	median follow-up: 5.1 years (inter-quartile range (IQR): 2.3–7.7 years	recurrence-free survival (RFS) overall survival (OS)	recurrence rate: NS GCT I: n=3 (10%) NS GCT I low risk: n=0 (0%) NS GCT I high risk: n=3 (23%) p=0,10 5-yr-OS: 100%	Smoking Research Foundation, Takeda Science Foundation, Grants-in- Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. Yuasa T. received remuneration for a lecture from Pfizer Japan (Tokyo, Japan) and Novartis Pharma Japan (Tokyo, Japan).	LoE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention	Kontrolle	Beobachtungszeitraum	Endpunkt	Effekte und Unerwünschte Wirkungen	Finanzierung COI	Evidenzstufe LoE RoB
								no conflict of interest of the other authors	

9.4.7. Kapitel 9 metastasierte KZT

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
Ahmed KA 2015	two-arm retrospective cohort study n=241 1988-2003 USA	CS IIA Seminoma CS IIB Seminoma CSIIA n=145 CSIIB n=96	Radiation n=136 RT and chemotherapy details, including dosages, are not included in the SEER database	other approaches (chemotherapy), but not clearly described which ones n=105	median follow up: 10 ys	5-, 10-, and 15-year overall survival (OS) 5-, 10-, and 15-year cause-specific survival (CSS) rates	CSIIA: Radiation: 5-yr-OS: 96% 10-yr-OS: 96% 15-yr-OS: 96% other approaches: 5-yr-OS: 88% 10-yr-OS: 77% 15-yr-OS: 77%	Comparison of therapy is limited due to missing data to doses in the SEER database and “other approaches” is not defined	no information about coi no information about funding	LOE 2b RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
							p=0,008 CSIIA: Radiation: 5-yr-CSS: 97% 10-yr-CSS: 97% 15-yr-CSS: 97% other approaches: 5-yr-CSS: 96% 10-yr-CSS: 92%, 15-yr-CSS: 92% P = 0.30 CSIIB Radiation 5-yr-OS: 98% 10-yr-OS: 96% 15-yr-OS: 88%			

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
							other approaches: 5-yr-OS: 90% 10-yr-OS: 86% 15-yr-OS: 86% p=0,03 CSIIB Radiation 5-yr-CSS: 98% 10-yr-CSS: 98% 15-yr-CSS: 98% other approaches: 5-yr-CSS: 98% 10-yr-CSS: 96% 15-yr-CSS: 96% P = 0.60			

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
Albany C 2018	retrospective data base study 1998 – 2014 USA	n=704 with metastatic germ-cell tumor (GCT)	first-line chemotherapy at IU	SEER database patients 2000 – 2014 SEER historical stage of distant n=1283	median follow-up: 4.4 yrs	PFS, OS probabilities at 5 yrs	IU testis cohort: 5-year OS 94% (95% CI 91% - 96%) SEER 'distant' cohort: 5-year OS 75% (95% CI 73% - 78%) conclusion: The MDC approach to GCT at high-volume cancer center associated with improved OS outcomes in this contemporary dataset. OS is significantly higher in the IU cohort compared with the IGCCCG and SEER 'distant' cohort.		Walther Cancer Foundation, Walther Scholars Program (grant number 0053.01 to CA); Slovak Research and Development Agency (contract number APVV-0016-11 and APVV-15-0086 grants to MC).	LoE 4

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
Daugaard G. 2011	randomized phase III, multicenter study n=137 April 1999 and June 2007 DK, PL, NO, NL, D, ES, A, B 27 European centers	Adult male patients aged 15–50 years with previously untreated metastatic poor-prognosis nonseminoma GCC according to IGCCCG classification of either testicular or extragonadal origin Median yrs (range) age: BEP: 27 (16–50) HD-CT: 30 (16–49)	BEP regimen 4 cycles Cisplatin every 21 days: 20 mg/m2 i.v. on days 1–5 Etoposide every 21 days 100 mg/m2 i.v. on days 1–5 Bleomycin every week 30 mg bolus i.v. on days 1, 8, and 15	VIP followed by high-dose chemotherapy with peripheral stem-cell support [high-dose chemotherapy]	median follow-up: 4.4 yrs	primary end point: FFS secondary end points: Response to treatment, overall survival, and toxicity	1-year FFS rate: 48% [95% CI35.5%–59.5%] after BEP 1-year FFS rate: 66.1% (95% CI 53.1%–76.2%) after HD-CT 2-year FFS rate: 44.8% (95% CI 32.5%–56.4%) after BEP 2-year FFS rate: 58.2% (95% CI 48.0–71.9) after HD-CT		no coi National Cancer Institute (Bethesda, MD) (5U10 CA11488-27 through 5U10 CA011488-40); EORTC Charitable Trust	LoE 1b Cochrane RoB-Tool Bewertung: low Risk of Bias

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
							1 yr OS BEP: 83% (95% CI 71.3%–90.2%) 2 yr OS: BEP: 65.5% (95% CI 52.4%–75.8%) 1-yr OS: HD-CT 86.1% (95% CI 74.9%–92.5%) 2-yr OS: HD-CT: 72.9% (95% CI 60.0%–82.3%) PFS: HR 0.62			

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
							(in favor of HD-VIP) adjusted 95% CI 0.38 -1.02 toxicity: leukopenia grade 4: after 3 cycles BEP: n=2 (3.0%) after 3 cycles HD-CT: n=38 (61.3%) neutropenia grade 4: after 3 cycles BEP: n=6 (9.1%) after 3 cycles HD-CT: n=25 (40.3%)			

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
							Total no. of days with leukopenia grade 4: Median (range) BEP 4.0 (1.0–13.0) HD-CT 20.0 (4.0–33.0) Total no. of days with neutropenia grade 4: Median (range) BEP 5.0 (1.0–21.0) HD-CT 17.0 (4.0–29.0)			
de Wit R 2012	Randomized, open-label, multi center Phase III Study n=337	intermediate-prognosis metastatic GCC	BEP (n = 169) Standard BEP consisted of cisplatin 20 mg/m2 days 1 through 5 and	T-BEP T-BEP received paclitaxel 175	median follow-up: 5.3 yrs	response rate progression free survival PFS	intent-to-treat population: 3-year PFS rate: 71.1% in the BEP group		no coi Financial support: Ronald de Wit	LoE 1b Cochrane RoB tool: low risk of Bias

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
	November 1998 - April 2009 12 countries	Age, years Median 28 in both groups	etoposide 100 mg/m2 administered days 1 through 5 for four cycles. Bleomycin was administered at a dose of 30 mg weekly for 12 weeks (total dose of bleomycin, 360 mg)	mg/m2 given as a 3-hour infusion on day 1, before starting standard BEP, for four cycles. n = 168)		overall survival OS	79.4% in the T-BEP group PFS (HR, 0.73; CI, 0.47 -1.13; P=0.153) favours T-BEP per-protocol analysis: 3-yr PFS rates: 83.2 versus 70.6%, respectively (HR, 0.59; CI, 0.37 to 0.96; P=0.0289) overall survival; intent-to-treat population HR, 0.89; 95% CI, 0.46 - 1.74; P=0.7382 HR, 0.58; CI, 0.26 - 1.29; P=0.17 in the			

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							per-protocol analysis			
Domont J 2013	two-arm-retrospective cohort study 1980-2001 n=67 France	CS IIA Seminoma CS IIB Seminoma CS IIC Seminoma mean age: 40 (23-64)	radiation n=37 CS IIA, CSIIB: n=33 CS IIA n=5 CS IIB <3cm n=19 CSIIB >3cm n=9 CSIIC n=4 megavoltage radiation (4 to 20 MV) with antero-posterior parallel opposed fields, at a dose of 2 Gy	chemotherapy n=30 but: CSIIA and CSIIB: n=3 CSIIB<3cm: n=1 CSIIB>3cm: n=2 CSIIC: n=27	median follow-up: 9.4 yrs	relapse rate time to relapse 5-yr-Overall Survival (OS) toxicity second neoplasms	relapse rate: radiotherapy 30% chemotherapy 27% median time to relapse: 13,5 mo (3-51) 5-yr OS: chemotherapy 88% (CI 95%: 53–98) radiotherapy 82% (CI 95%: 52–95)	no different analysis for tumour stages	no information about coi no information about funding	LOE 2b RoB SIGN (+) acceptable

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			per fraction per day over 5 days per week only the ipsilateral pelvic lymph nodes with a “dog-leg” technique and the para-aortic nodes up to the T9-T10 vertebral level. total dose of 20 Gy was delivered over 2 weeks to the para-aortic and pelvic lymph nodes, with a boost dose of 16 Gy in 8 fractions to involved para-aortic lymph nodes. Prophylactic mediastinal or supraclavicular radiotherapy (20 Gy over 2 weeks)				P= 0.83 immediate toxicity radiation Grade 1, 2, and 3 nausea 46%, 46%, 8% Grade -2 diarrhoea 51% late toxicity: chemotherapy: Fertility disorders (n=2) pulmonary fibrosis (n=1) mild elevation of serum creatinine (between 120 and 140 µmol/l) (n=2)			

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			was delivered for stage IIB and IIC (22 patients, 59%) until 1992.				second tumor, after follow-up of 5, 9, 20 yrs second cancers radiotherapy n=3 for stage II seminoma, (colorectal carcinoma, duodenal cancer, medullary thyroid carcinoma) second cancers: chemotherapy n=2 (colorectal and esophageal carcinoma)			

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Feldman DR 2016	multi center retrospective cohort study n=582 46 centers 13 countries United States, Canada, Australia, Europe 1990-2013	n=523 patients with synchronous brain metastases (BM) at initial diagnosis (group A; n=228) metachronous brain metastases BM at relapse (group B; n=295)	Group A: multimodality treatment vs single-modality first-line treatment	Group B: multimodality treatment vs single-modality salvage treatment	median time from previous response to occurrence of metachronous BM in patients who experienced disease relapse from group B: 3 months (range, 0 to 74 months)	overall survival (OS), progression-free survival (PFS)	Group A Single-modality treatment: n= 103 patients (45%) multimodality treatment: n= 125 patients (55%) multimodality treatment versus single-modality treatment: OS: HR 0.57; 95% CI, 0.40 -0.80; p<0,001 high-dose chemotherapy OS:		7/21 authors declare research funded by industry or honoraria by industry or travel, accomodations, expenses funded by industry no informationa about funding of the study	LOE 2b RoB SIGN (+) acceptable

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							HR 0.86; 95% CI of HR, 0.46 to 1.59; P =0.62 Group A vs Group B: chemotherapy alone or in combination with other therapies: 99% vs. 58%; p= 0,05 OS in univariable analysis: Chemotherapy HR, 0.64; 95% CI, 0.49 - 0.83; p=0.001 surgery HR, 0.55;			

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							95% CI, 0.41 -0.72; p=0.001 radiation therapy HR, 0.70; 95% CI, 0.53 - 0.92; p=0,01 high-dose chemotherapy HR, 0.51; 95% CI, 0.34 - 0.77; p=0,001 OS multivariate analysis: multimodality treatment: HR, 0.52; 95% CI, 0.37 - 0.73; p=0.001) high-dose chemotherapy HR, 0.41; 95% CI, 0.24 - 0.69; p=0,001			

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Fizazi K 2014 GETUG S99	three-arm-prospective cohort study n=132 1999-2008 France	good-risk group (IGCCCG): with any stage II seminoma and those with supradiaphragmatic (lymph nodes or lung) dissemination and a serum LDH level less than two times the upper limit of normal (ULN). intermediate-risk group (IGCCCG): included only patients with extrapulmonary visceral metastases	good-risk group: N=81 (CS II) four cycles of EP regimen (cisplatin 20 mg/m2 per day and etoposide 100 mg/m2 per day for 5 d, repeated every 3 wk)		median follow-up: 4.5 yr (range: 0.4–11.6 yr)	3-yr-progression free survival PFS 3-yr-overall survival OS 5-yr-OS acute toxicity	good prognosis group: 3-yr-PFS: 93% (range: 85–97%) 3-yr OS: 99% (range: 92–100%) 5-yr OS: 93% grade 3/4 acute toxicity: Neutropenia n=48 (47%) Anemia n=5 (5%)	limitation: good prognosis group definition is not in line with definition of CDS II A or CS IIB	no funding no coi	LOE 2b RoB SIGN (+) acceptable

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		poor-risk group Medical Research Council (MRC) extrapulmonary visceral metastases and also those with supradiaphragmatic (lymph nodes or lung) dissemination and serum LDH two or more times the ULN median age: 37 yr (interquartile range: 33–43)					Thrombocytopenia n=2 (2%) Neutropenic fever n=13 (12%) Nausea and vomiting n=4 (4%) Audio n=1 (1%)			
Fizazi K 2014 GETUG 13	phase 3 multi-center randomised trial	poor prognosis germ cell tumour patients	unfavourable decline n=203	favourable decline favourable BEP-group	4,1 ys (IQR 0·3–8·8)	primary endpoint: progression-free	3-year-progression-free survival PFS: Unfav-dose-dense group		Funding: Institut National du Cancer and sponsored by Unicancer, and	LOE 1b Low RoB

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	n=254 2003-2012 France, USA, Slovakia	(IGCCCG-classification) unfav-BEP median age: 27 (17-72) unfav-dose-dense median age: 29 (16-51) fav BEP median age: 27 (19-54) BEP: Bleomycin, Etoposide, Cisplatin	randomly assigned: unfavourable dose-dense-group n=105 regime: one cycle BEP plus two cycles of T-BEP-oxaliplatin after evaluation of tumormarkers unfavourable BEP-group n=98 regime: 1x BEP plus 3x BEP after	n=51 regime: 1xBEP plus 3xBEP after evaluation of tumormarker		survival, PFS Secondary endpoints: overall response, overall survival, safety, complete response normal tumour markers no clinical or radiological evidence of disease	59% (95% CI 49–68) Unfav-BEP group 48% (95% CI 38–59) HR 0·66 [95% CI 0·44–1·00] 3-year progression-free survival: Fav-BEP group: 70% (95% CI 57–81) Unfav-BEP group 48% (38–59) in the complete response Unfav-dose-dense: n=42 (40%) Unfav-BEP: n= 29 (30%)		cosponsored by the University of Texas MD Anderson Cancer Center for the USA no coi	

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			evaluation of tumormarker				(p=0,12) Fav-BEP: n=23 (45%) 3-year overall survival OS: Unfav-dose-dense 73% (95% CI 64–81) Unfav-BEP 65% (95% CI 55–75) HR 0,78 (95% CI 0·46–1·31) 3-year overall survival OS: Fav-BEP 84% (95% CI 71–92) Unfav-BEP 65% (55–75)			

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							toxicity: grade 3-4 neutropenia unfav dose-dense: 60% unfav BEP: 63% grade 3-4 anaemia: unfav dose-dense: 44% unfav BEP: 26% grade 3-4 thrombocytopenia: unfav dose-dense: 31% unfav BEP: 26% grade 3-4 nausea or vomiting unfav dose-dense: 23%			

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							unfav BEP: 2% grade 3-4 mucositis: unfav dose-dense: 8% unfav BEP: 0% grade 3-4 dyspnoea unfav dose-dense 9% unfav BEP: 11% grade 1-2 febrile neutropenia unfav dose-dense: 17% unfav BEP: 18% 3-y-progression free survival PFS: high serum tumour marker no			

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							HR 0,54 (95% CI 0,24-1,23) favours unfav dose-dense high serum tumour marker yes HR 0,73 (95% CI 0,46-1,16) favours unfav dose-dense			
Gilbert ES 2017	pooled analysis study n=327 cases n=678 controls Hodgkin lymphoma, testicular cancer,	testicular cancer n=86 cases n=174 controls mean age of 5-yr-survivors: 39,4 ys	external beam radiotherapy mean radiation dose: 24,7 Gy (0,39-59,1) treatment time of radiation: 1953-1992		mean time between first cancer and stomach cancer: 17,9 ys	risk for radiation related stomach cancer Excess Odds Ratio (EOR)	dose-response relationship: EOR/Gy 0.27 95% CI 0.054–1.44		funded by: intramural research program of the NIH and the NCI no information about coi	LOE 3a RoB moderate

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	cervical cancer Denmark, Sweden, Norway, Finland, Canada, USA, Netherlands	(18,3-71,8)								
Girones R 2014	double-arm retrospective cohort study n=33 Spain 1994-2012	n=19 patients with brain metastases at the time of diagnosis (synchronous) age at diagnosis of TGCT: 31 (18-53) n=13 patients with brain metastases at the time at recurrence	first treatment synchronic cases: orchiectomy followed by chemotherapy n = 18 patients; n= 1 chemotherapy without orchiectomy. Chemotherapy consisted of cisplatin-based combinations (8 BEP, 6 BOMP-EPI, 1 BEP followed by TIP, 1 EP, 1 BOMP, 1 TIP followed by high-dose	first treatment of metachronous cases: orchiectomy and chemotherapy: BEP schedule (62 %) and BOMP-EPI (31 %). n=2 consolidation with high-dose	Median follow-up; 16 mo (1–228)	median overall survival OS 2-year OS	group 1 (synchronous) alive without disease 33 % group 2 (metachronous) alive without disease 36 % median overall survival for all patients: 1.385 yrs (95 % CI 0.116–2.655)		no coi no information about financing	LOE 2b RoB SIGN (+) acceptable

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		(metachronous) age at diagnosis of TGCT: 29 (20-38)	chemotherapy with stem cell support). After chemotherapy: n=5 (26 %) surgery for residual masses excision; n=5 (26 %) irradiation of residual mass. treatment of brain metastases: n=13 (68.4 %) whole brain radiotherapy part of primary treatment	chemotherapy and ATSP (14 %). n=3 Surgery for residual disease n=1 radiotherapy Treatment for brain metastasis: n=9 brain metastases as the single site of recurrence (70 %). n=3 (33 %) surgery (resection) n=1 chemothera			OS (group 2 vs group 1) 1.91 yrs versus 1.18, p= 0.857) 2-year survival rates: group 1: 37.5% group 2: 38.9 %			

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				py (TIP: cisplatin, ifosfamide paclitaxel), n=1 holocraneal radiotherapy n=1 resected after chemotherapy (GEMOX: gemcitabine–oxaliplatin) and holocraneal radiotherapy						
Grimison PS 2010	prospective, multicenter randomized phase III trial n=166	good-prognosis metastatic germ cell tumors (Memorial Sloan-	three cycles BEP, repeated every 21 days, of 30 kU bleomycin on days 1, 8, and 15; 100 mg/m2 etoposide on days 1–5; and 20	four cycles BEP, repeated every 21 days, of 30 kU bleomycin on day 1, 120	median follow-up: 8.5 yrs	overall survival (OS) progression-free survival (PFS)	OS 8-year survival: 92% vs 83%; HR of death = 0.38, 95% CI = 0.15 to 0.97, P = .037)		National Health and Medical Research Council to NHMRC Clinical Trials Center (Unit Grant), New South Wales Cancer Council	LoE 1b Cochrane RoB Tool low risk of Bias

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	February 1994 and April 2000 Australia New Zealand	Kettering criteria) Median age (range), y 28 (14–60) 3xBEP 32 (17–62) 4xBEP	mg/m2 cisplatin on days 1–5; n = 83	mg/m2 etoposide on days 1–3, and 100 mg/m2 cisplatin on day 1; n = 83		quality of life, side effects	favours 3xBEP PFS 8-year progression-free survival: 86% vs 79%; HR of progression = 0.6, 95% CI = 0.3 to 1.1, P = .15) favours 3xBEP 12 weeks after randomization: average scores for most scales were higher (ie, the side effect was worse) for patients allocated to 4xBEP than for those allocated to 3xBEP.		(Program Grant), and Apex Foundation and Apex Clubs of Australia (Donation). no coi	

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Hallemeier CL 2013	single arm retrospective cohort study n=52 1974-2007 USA	CS II Seminoma median age at diagnosis: 36 ys (22-71)	radiation Megavoltage external beam RT para-aortic lymph nodes ± pelvic lymph nodes with anterior- posterior (AP) and posterior-anterior (PA) fields median infradiaphragmatic RT dose 30.7 Gy	no control group	median follow up: 19 ys (0.4 –37)	Overall survival (OS), relapse-free survival (RFS), cause-specific survival (CSS) second malignancy (SM)	10 ys-OS 94% 20 ys-OS 83% 10 ys- OS: IIA: 96% IIB: 83%, IIC: 94% II NOS: 100% (log-rank P=0.46) 10-ys-RFS IIA: 83% IIB: 54% IIC: 81% II NOS:100%, P=0,21		no information about coi no information about funding	LOE 4 RoB SIGN (+) acceptable

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							10 ys-CSS 96% 20 ys CSS 96% 10 ys CSS IIA: 100% IIB: 83% IIC: 94% II NOS: 100% Major cardiac event (MCE) n=10 19% at a median of 18 years (range 7–30) after RT. median age at time of MCE: 53 years (range, 34 –76)			

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							First MCE: myocardial infarction (n=7), valve replacement (n=2), coronary artery stent placement (n=1) second malignancies (SM): SM n=5 (10%) at a median of 27 years (range 20–34) after RT SM: esophageal adenocarcinoma (n=2), periampullary			

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							adenocarcinoma (n=1), retroperitoneal undifferentiated neoplasm (n=1), papillary thyroid cancer (n=1)			
Hardt A 2014	single center retrospective cohort study n=39 1993 – 2012 UK	consecutive patients with germ cell tumors and brain metastases median patient age: 29 yrs (range, 20-53 years) n=17 (44%) group 1 (those who presented	chemotherapy n=37 GAMEC regimen: cisplatin 100 mg=m2 in weeks 1, 3, 6, and 8 plus 50 mg=m2 in weeks 2 and 4; actinomycin D 1 mg=m2 in weeks 1, 3, 6, and 8; highdose methotrexate 8 g=m2 (with dose		Median follow-up: 8.2 yrs	OS Time OS	3-year median OS: whole cohort: 38%, 69% for group 1 22% for group 2 0% for group 3 median OS: whole cohort: 10.6 mo (range, from 5.5 mo to not evaluable [NE])		No specific funding was disclosed no coi	LoE 4 SIGN RoB (-) not acceptable

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		with brain metastases), n=16 (41%) group 2 (those who developed metastases after the completion of chemotherapy), n=6 patients (15%) group 3 (those who developed metastases during chemotherapy	adjustments for renal impairment) in weeks 1, 3, 6, and 8; and etoposide 360 mg=m2 in weeks 1, 3, 6, and 8. The IPO regimen consisted of oxaliplatin 100mg/m2 day 1, irinotecan 200mg/m2 day 1, paclitaxel 80mg/m2 day 1,8 and 15 every 21 days. The IPO regimen consisted irinotecan 200 mg=m2 on day 1; paclitaxel 80 mg=m2 on days 1, 8, and 15; and irinotecan 200				group 1 not yet reached (range, from 7.4 mo to NE) group 2 6.2 mo (range, 2.1- 15.3 mo), group 3 2.7 mo (range, from 0.6 mo to NE)			

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			mg=m2 on day 1 repeated every 3 weeks for a maximum of 4 cycles with high-dose consolidation using carboplatin at an area under the receiver operating characteristic curve of 21, topotecan 30 mg=m2, and thiotepa 500 mg=m2.							
Haugnes HS 2012	three-arm-prospective cohort study n=882 1995-2007	poor prognosis patients n=138 median age	poor response to treatment: n=29 with slow marker decline slow tumor marker decline (HCG $T_{1/2}$ >3 days,		Median follow-up 7.5 years (range 0 – 14).	overall survival (OS) failure-free survival (FFS) observation time	group slow marker decline: OS (after median 7.2 ys) 76% failure free survival:		The Swedish Cancer Society, Gunnar Nilsson Foundation for Cancer Research, Nordic Cancer Union	LOE 2b RoB SIGN (-) not acceptable

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	Sweden, Norway	poor responders: 29 ys (18-56) A) patients with poor response to treatment intensification step 1 (slow marker decline, n=29; progressive disease, n=7; in total n=36); B) patients with vital cancer at surgery after intensified chemotherapy (n=7); and C) relapses as specified above (n=12)	AFP $T_{1/2}$ >7 days) after two BEP high dose chemotherapy: first HDCT cycle: daily carboplatin 7x (GFR +25) mg Day 1 – 4, cyclofosfamide 1500 mg/m 2 Day 1 – 4 and etoposide 440 mg/m 2 Day 1 – 4. second HDCT cycle: etoposide was substituted by tiotepa 120 mg/m 2 Day 1 – 4			acute toxicity	69% progression after high dose: 14% relapse after high dose: 14% toxicity grade 4 Nephrotoxicity n=3 (8.3%) Bleeding n=3 (8.3%) Neurotoxicity n=1 (2.8%) Diarrhea/obstipation		no coi	

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							n=1 (2.8%)			
Hauptmann M 2016	population-based case control study n=23 982 5-yr survivors Sweden, Denmark, Norway, Ontario (Canada), Finland, Iowa (USA) NL TC diagnosis: 1947-1991	median age at diagnosis of pancreatic cancer 61 yrs; range, 41–81 yrs 48% occurred >20 years after TC diagnosis (median, 20 years; range, 6–38 years), 69% located in pancreas head	n=80 with pancreatic cancer surgery and radiotherapy (81% cases, 74% controls); surgery, radiotherapy, and chemotherapy (8% cases, 6% controls); surgery only (6% cases, 15% controls); or surgery and chemotherapy (4% cases, 6% controls)	two controls per case controls: who survived TC without a second cancer at least as long as the corresponding case n=145 controls for	second primary invasive pancreatic cancer diagnosed during 1965–2004	second primary invasive pancreatic cancer incidence	cumulative incidence: 15 yrs after TC diagnosis 0.14% (95% CI 0.07– 0.20%) 30 yrs after TC diagnosis. 1.08% (95% CI 0.83–1.34%)		no coi no information about funding	LoE 3b low RoB

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				n= 80 cases						
Hauptmann M 2015	population based case-control study Denmark (1943–1999), Finland (1953–2002), Iowa, USA (1973–2001), Ontario, Canada (1964–2003), Sweden (1958–2002) Norway (1953–2000). 2003–2009	Median age at TC diagnosis: 38 yrs (range, 18–71) 67% seminoma 92% stage I or II disease (at TC diagnosis) Median age at stomach cancer diagnosis: 58 yrs; (range, 31–80) 37% occurred ≥20 years	n=92 patients who developed stomach cancer Treatment for TC included surgery and radiotherapy only (80% cases and 78% controls); surgery, radiotherapy and chemotherapy (14% cases and 6% controls); surgery only (3% cases and 9% controls); and surgery and chemotherapy only (1% cases and 7% controls).	n=180 matched controls	second stomach cancer diagnosed during 1975–2004	second stomach cancer incidence	cumulative incidence of second primary invasive stomach cancer: 0.30% (95% CI 0.20– 0.39%) at 15 years 1.45% (95% CI 1.15–1.74%) at 30 years after TC diagnosis radiotherapy (87 (95%) cases, 151 (84%) controls) had a 5.9-fold (95% confidence interval (CI) 1.7–20.7) increased risk of stomach cancer.		no coi no information about funding	LoE 3b low Risk of Bias

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	n=22 269 5-year survivors of histologically confirmed TC TC diagnosis 1959–1987	after TC diagnosis (median, 17; range, 7–39)					Risk increased with increasing stomach dose (P-trend <0.001), OR 20.5 (3.7–114.3) for ≥50.0 Gy compared with <10 Gy. Radiation-related risks remained elevated ≥20 years after exposure (P<0.001). Risk after any chemotherapy: OR=1.1; 95% CI 0.5–2.5; 14 cases and 23 controls			
Helleberg M 2014	population-based cohort study	HIV-infected individuals who receive care at Danish HIV centres	n=3503 HIV patients	n=12 979 matched population controls	who were followed for a total of 18 679 and 55 957 person-	cancer	Testis Cancer HIV patients n=3 IR/10 000 PY		N.O. has received research funding from Bristol-Myers	LoE 3b RoB SIGN (+)

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	n=3503 HIV patients 1995–2011 DK	HIV-1-infected individuals who were 16 years or above at HIV diagnosis, alive	proportion of ever-smokers 67%	proportion of ever-smokers 53%	years, respectively.		2.1 (0.7–6.4) Population controls n=12 IR/10 000 PY 2.7 (1.5–4.7)		Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, and Gilead. C.P. has received research funding from Abbott, Roche, Bristol- Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Swedish Orphan, Jansen Pharma/Tibotec and Boehringer Ingelheim. J.G. has received research funding from Abbott, Roche, Bristol-Myers Squibb, Merck Sharp	acceptable

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									& Dohme, ViiV, Swedish Orphan and Gilead. All other authors: no coi no information about funding	
Huddart RA 2015	randomised phase 2 multicenter trial n=89 2005-2009 UK (16 centers)	poor prognosis GCT n=89 mean age: 30 yr (16-68)	CBOP/BEP six cycles over 15 wk n=43 mean age: 28,5ys CBOP/BEP (carboplatin, bleomycin,	BEP four 3-weekly cycles of Indiana-style BEP n=46 mean age: 31,3 ys BEP:	median follow up: 58 months	primary end point: favourable response rate (FRR) Secondary end points: progression-free survival (PFS), overall survival (OS), toxicity	FRRs: CBOP/BEP arm: 74.4% (90% CI, 61.2–84.9) BEP arm: 60.9% (90% CI, 47.7–73.0) 1-yr PFS: CBOP/BEP arm: 65% (95% CI, 49–77%)		Cancer Research UK (CRUK/05/014) with additional support from the Medical Research Council through the Clinical Trials Unit no coi	LOE 1b low RoB

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			vincristine, cisplatin/BEP)	bleomycin, etoposide, cisplatin			BEP arm: 43% (95% CI,29–57) HR:0.59 (95% CI, 0.33–1.06) 2-yr-OS: CBOP/BEP arm: 67% BEP arm: 61% HR: 0.78 [95% CI, 0.41–1.50]) toxicity grade 3-4: neutropenia: CBOP/BEP arm: n=36 (84%) BEP arm: n=25 (54%)			

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							neutropenic fever grade 3: CBOP/BEP arm: n=7 (16%) BEP arm: n=0 grade 3-4 thrombocytopenia: CBOP/BEP arm n=23 (54%) BEP arm: n=8 (18%)			
Jamal-Hanjani M 2013	single arm retrospective cohort study n=2550	GCT patients with bone metastases found at diagnosis or at relapse	n=13 one-line chemotherapy: BEP, bleomycin, etoposide, cisplatin or BOP, bleomycin,		median (IQR) duration of follow-up: 18 mo (10, 42)	complete response partial response	chemotherapy any given line: complete response: (4/19, 21%),		no coi no information about funding	LOE 4 RoB SIGN (-)

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	UK 2005-2011	IGCCCG group: intermediate prognosis: 26% poor prognosis: 68% n=19 mean age: 40 ys (11,8)	vincristine, cisplatin OR BCa, etoposide, bleomycin, carboplatin n=5 four to six lines of chemotherapy: POMBACE, cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, etoposide; 4. IPO, irinotecan, paclitaxel and oxaliplatin plus stem cell			stable disease progressive disease mortality	partial response (11/19, 58%) stable disease (1/19, 5%) progressive disease: (1/19, 5%) one line of chemotherapy: remaining in remission: 9/19 (47%) further chemotherapy due to subsequent relapse: 6/19 (32%)			not acceptable

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			collection; 5. GAMEC, granulocyte colony stimulating factor, actinomycin-D, methotrexate, etoposide, cisplatin; 6. HD ToPCat + PBSCT, IPO followed by tandem high dose chemotherapy and peripheral blood stem cell transplantation; 7. VIP, etoposide, ifosfamide, cisplatin; 8. IPO, irinotecan, paclitaxel and oxaliplatin; 9. TP, docetaxel, cisplatin; 10. Cisplatin and epirubicin; 11. Cisplatin and gemcitabine; 12. ToPCat, topotecan, thiotepa,				3/19 (16%) died 1/19 lost to follow-up mortality: bone metastases at diagnosis: 23% (3/13) metastases at relapse: 50% (3/6)			

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			carboplatin; 13. VelP, vinblastine, ifosfamide, cisplatin; 14. Paclitaxel and gemcitabine; 15. Oral etoposide; 16. paclitaxel priming for stem cell harvest.							
Kier MG 2017	population-based cohort study n= 1889 1984–2007) DK	Good, intermediate and poor prognosis pts	BEP as first-line treatment for disseminated disease n=420 SGCC n=1469 NSGCC four cycles of BEP; after 2001, patients with good prognosis received three cycles of BEP and patients with intermediate or	No control group	median follow-up of 15.3 yr	5-yr-OS, PFS, DSS	SemGCT: good prognosis: 5-yr PFS 87% 5-yr DSS 95% 5-yr OS 93% After 15 yr, the difference in OS between patients with good prognosis and the background population disappeared.		funding from The Danish Cancer Society no coi	LoE 4 RoB SIGN + (acceptable)

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			poor prognosis continued to receive four cycles. Standard BEP comprised bleomycin 15[6TD$DIF] 000 IU/m2 [4TD$DIF] on days 1, 8, and 15; etoposide 100 mg/m2 on days 1–5; and cisplatin 20 mg/m2 on days 1–5 every 3 wk. Patients				NonSemGCC 5 yr-PFS: Good: 90% Intermediate 76% Poor: 55% 5 yr DSS: Good: 97% Intermediate: 87% Poor 66% 5 yr OS: Good: 95% Intermediate: 85% Poor: 64% In the first 15 yr, the survival of the group with good prognosis was slightly lower than that of the			

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							background population.			
Kollmannsberger C 2011	multiple arm retrospective cohort study n=649 1999-2008 Canada	CS II Seminoma n=87 median age: 41 (19-68)	radiation n=19 treated with 35 Gy in 20–25 fractions with standard paraaortic and ipsilateral pelvic techniques [4]. Twenty-five gray was delivered to the paraaortic and ipsilateral pelvic lymph nodes in 15–20 fractions over 3–4 weeks with anterior to posterior parallel pair technique	chemotherapy n=65 Good prognosis disease patients: three cycles of BEP or four cycles of etoposide/ cisplatin (EP). Patients with intermediat	median follow up: 46 months (2-110)	5-yr-relapse free survival 5-yr-overall survival (OS)	5-yr actuarial relapse-free survival: 94% for all CSII seminomas radiation: 91.7% chemotherapy 95.5% Actuarial 5-yr overall survival: chemotherapy 90.7%		no coi no information about funding	LOE 2b RoB SIGN (+) acceptable

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			using megavoltage photons. Subsequently, a boost of 10 Gy in five fractions was given to the nodal mass with a margin using an anterior to posterior parallel pair technique	e prognosis: primarily four cycles of BEP. BEP: Bleomycin, Etoposide, Cisplatin			radiation 92.3% (P = 0.67)			
Lauritsen J. 2016	single arm single center retrospective cohort study n=565 1984 – 2007 DK	all patients with germ cell cancer (GCC) age > 15 years who received treatment with BEP from 1984 to 2007 at Rigshospitalet	BEP, which consisted of bleomycin 15 IU/m2 once per week, etoposide 100 mg/m2 days 1 to 5 every 3 weeks, cisplatin 20mg/m2 days 1 to 5 every 3 weeks	no control	before, during, and after treatment with BEP for 5 years of follow-up	diffusing capacity of the lungs for carbon monoxide (DLCO), forced expiratory volume in 1 second, and forced vital capacity	Overall Pulmonary Function According to Time: long-term restrictive disease 4.1%; (95% CI, 1.8% - 6.3%) obstructive disease 2.7%; (95% CI, 0.8% - 4.6%)		Conflict of interest: Frederik Birkebæk Thomsen Honoraria: Astellas Pharma Travel, Accommodations, Expenses: Ipsen all others: no coi	LoE 4 SIGN RoB (+) accepatable

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							Diffusion capacity abnormality: 15.6% (95% CI, 11.3% - 19.9%) at 5 yrs follow-up compared with 20.7% (95% CI, 16.6% - 24.8%) pretreatment Post-treatment DLCOc decreased significantly, with a rebound during follow-up. Forced expiratory volume in 1 second and forced vital capacity remained unchanged after BEP but increased significantly to levels above pretreatment during follow-up.		Financial support: Gedske Daugaard	

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Oechsle K 2012	retrospective analysis of data of 2 multicenter phase II studies n=434 1993-2004 Germany	poor prognosis patients (IGCCCG) n=434 n=40 with bone metastases at initial diagnosis mean age: 33 ys (17-54) n=394 without bone metastases mean age: 30 ys (16-58)	high dose chemotherapy without prior radiation or surgical treatment of bone metastases one cycle of conventional dose combination chemotherapy with 20 mg/m2 cisplatin, 75 mg/m2 etoposide and 1,200 mg/m2 ifosfamide for 5 days (VIP) for stem cell mobilization in both trials. In case of successful stem cell asservation, patients received a maximum of 3			complete response CR tumor marker negative partial remission PR- tumor marker positive partial remission PR+ stable disease SD progressive disease PD	CR n=1 / 2% PR- n=20 / 50% PR+ n= 13 / 33 SD n= 5 / 13% PD/early death n=1 / 2% Median PFS: 11 mo (3-115+) Median OS: 24 mo (5-115+) Progression-free survival rate after primary treatment: 63% overall long-term survival (120 mo): 75%		no coi no information about financing	LOE 4 RoB SIGN (-) not acceptable

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			consecutive cycles of high-dose chemotherapy plus PBSCT either with cisplatin, etoposide and ifosfamide alone (HD-VIP) (Bokemeyer et al. 1999), or in combination with paclitaxel (HD-TaxVIP) (Hartmann et al. 2007)			progression free survival PFS overall survival OS				
Olofsson SE 2011	multiple-arm prospective cohort study n=610 1995-2003	metastatic Nonseminomatous GCT poor prognosis group n=94	poor prognosis group with large and very large volume disease n=94 1.) two cycles of bleomycin,		median follow up: 99 mo (24-162)	Overall survival (OS) Progression-free survival (PFS)	relapse n=9 (13%) cumulative incidence at 2 yrs: 12.9% 10-year OS:		Supported by the Swedish Cancer Society, Gunnar Nilsson Foundation for Cancer Research, and Nordic Cancer Union	LOE 2b RoB SIGN (+) acceptable

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	Sweden, Norway	median age: 28 (16-62) poor tumor markers: (AFP >10,000 ng/mL or β-HCG >50,000 mU/mL or LDH >10 times the upper limit of normal [ULN])	etoposide, and cisplatin (BEP) 2.) patients with poor response: BEP-if BEP-if/PEI 3.) patients with poor response: HDCT 1+2 BEP: bleomycin, etoposide, cisplatin PEI:			Cancer-specific survival (CSS) toxicity	67.4% 95% CI 56.7 -76.1 10 yr-CSS: 68,5% 95% CI 57.5 - 76.8 10 yr-PFS 63,8% 95% CI 53.2 -72.6 10-yr OS: patients with poor markers only: 81.6% patients with nonpulmonary visceral metastases: 58,1% (P =0,032)		no coi	

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			etoposide, cisplatin plus ifosfamide, mesna				died as a result of treatment-related complications: sepsis (n =3), myocardial infarction (n =1), intracerebral haemorrhage (n=2), kidney failure (n=1), liver cirrhosis (n=1), complications to surgery (n = 1), not further specified (n=2) died during standard BEP (n=7) during BEP-if (n=2) received HDCT and died as a result of treatment (n=2)			

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Paffenholz P 2017	Database study, retrospective, single center	investigation of frequently occurring mistakes in the diagnosis of and therapy for TC considering EAU guidelines	Enrolled 2015-2016 147 patients identified, 131 eligible	None-guideline-concordant treatment was defined as treatment that was not in line with the EAU guidelines. It was further subdivided into overtreatment, undertreatment, inappropriate treatment, and misdiagnosis, similar to the categories used in a		Recurrence OS (not available for 5 patients	Of the 131 primary treated patients, 23 (18%) had received a none-guideline concordant treatment. The most common error was undertreatment (n= 12; 52%), mainly due to missing chemotherapy cycles. Overtreatment occurred in 30% of patients (n = 7); however, inappropriate treatment (n = 2; 9%) and misdiagnosis (n = 2; 9%) were rarely observed. In salvage therapy, none-guideline concordant treatment was observed less frequently compared to patients receiving		no information about funding no coi	LoE 4

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				recent study patients subdivided into 2 groups according to whether the none-guideline-concordant care had occurred at an outside, low-volume hospital before referral to our institution or at our high-volume institution.			primary therapy (12% vs. 18%). Of the 131 patients, 35 developed a relapse, 23 of whom were treated correctly and 6 of whom were undertreated. Undertreatment of patients resulted in significantly reduced relapse-free survival compared with guideline-concordant management in primary treated patients (P= .005). Conclusion: Despite the standardization of treatment by interdisciplinary			

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							guidelines, its integration into daily practice remains limited. Undertreatment of TC patients is associated with significantly reduced relapse-free survival and should thus be avoided.			
Paly JJ 2016	multiple arm retrospective cohort study n=1885 1998-2012 USA National Cancer Data Base	CSIIA and CSIIB Seminoma n=1885 CSIIA n=1080 CSIIB 805	radiation CSIIA n=780 CSIIB n=380 CS IIA radiation	chemotherapy CS IIA n=300 CSIIB n=425 no further information about	Median follow-up: 4.2 ys (IQR, 5.6 ys)	5-year overall survival (OS) risk of 5-year all-cause mortality	CS IIA 5-year OS: radiation: 99.4% (95% CI, 98.4-99.8) chemotherapy 91.2% (95% CI, 86.4-95.5) P<0,01	risk of bias due to limited availability of 80% data to radiation dose risk of bias due to lacking information about treatment details in chemotherapy	supported by the American Cancer Society intramural research funding no coi	LOE 2b RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
		Median age at diagnosis: 37 years [IQR], 14 ys	median regional dose: 25.5 Gy (IQR, 5.0 Gy) and median boost dose: 4.5 Gy (IQR, 10.0 Gy). CS IIB radiation: median regional dose: 25.5 Gy (IQR, 5.4 Gy) and median boost dose: 10.0 Gy (IQR, 10.5 Gy)	treatment details			CS IIB 5-year OS: radiation: 96.1% (95% CI, 93.0-96.6) chemotherapy 92.8% (95% CI, 89.1-95.3) P = 0.08 CS IIA: risk of 5-year all-cause mortality HR 13.3 p <0 .01) compared chemotherapy vs. RT CS IIB:			

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							risk of 5-year all-cause mortality HR 1.39 p = 0.45 compared chemotherapy vs. RT			
Tandstadt T 2011	multiple arm prospective cohort study n=1384 2000-2006 Norway, Sweden	CS IIA Seminoma n=35 CS IIB Seminoma n=67 median age: CS IIA RT: 33 ys CS IIA CT	radiation CS IIA n=29 RT including lymph node metastases total dose of 27 Gy (15 fractions of 1.8 Gy)	chemotherapy CS IIA n= 6 CS IIB n=67 four courses of etoposide 100 mg/m2 days 1 to 5 and cisplatin 20	median follow up: CS IIA Radiation: 5,7 ys chemotherapy 5,2 ys CS IIB: 5,5 ys	Relapse free interval (RFI) median time to relapse: 5-ys-overall survival (OS) 5-ys-Cancer specific survival (CSS)	RFI: CS IIA radiation: 88,7% chemotherapy: 100% CS IIB chemotherapy: 100% median time to relapse: 2,1 ys		no coi Supported by the Swedish Cancer Society, the Gunnar Nilsson Foundation for Cancer Research, and the Nordic Cancer Union	LOE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
		42 ys CS IIB 38 ys		mg/m2 days 1 to 5 (EP). In large-volume disease, addition of bleomycin 30,000 IU (30mg) days 1, 5, and 15 (BEP).			(1,5-3,3 ys) 5-ys-OS, 5-ys-CSS for all groups: 100%			
Thibault C 2014	cross sectional analysis of retrospective collected database data n=82 2000 – 2010 F	relapsed metastatic GCT after first-line chemotherapy Age, median (range) 33 (19–54)	Salvage (second-line) chemotherapy	comparison to recommended standard treatment French Urology Association guidelines for the 1998–2004 period,		Compliance with guidelines, predictive factors for non-compliance, impact on outcome	non-adherence to the planned dose (16%), an inappropriate interval between first-line chemotherapy cycles (16%), the lack of post-chemotherapy surgery (16%) and a long interval to post-chemotherapy surgery (48%). Compliance with standard care was		no coi no information about funding	LoE 3b

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				European guidelines from 2005 to 2010			better in cancer centres than in other hospitals (private or public) (Odd Ratio (OR): 6.9, P = 0.001).			
Tookman L 2013	single arm retrospective cohort study n=61 1997 – 2010 UK	IGCCCG good prognosis group Seminoma n=61 stage IIA/IIB disease: 48% CSIIA n=15 CSIIB n=13	Carboplatin: AUC 10 based on the Calvert formula {total dose (mg) =target AUC x [GFR (ml/min) +25]}		median follow-up: 36 mon	response rate acute toxicity	Complete response CSIIA: n=14 (93%) CSIIB: n=9 (69%) Marker negative partial response: CS IIA: n= 1 (7%) CSIIB: n=2 (15%) Marker negative stable disease		no information about funding no coi	LOE 4 RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
							CSIIB: n=2 (15%) acute toxicity: grade 3/4 neutropenia: 70% grade 3 or 4 thrombocytopenia: 54% grade 3 or 4 anaemia: 26%			
Tryakin A 2011	phase 2, single arm cohort study n=51 2004-2008	poor prognosis non-seminomatous GCT n=51	poor prognosis NSGCT n=49 4-6 cycles of T-BEP (paclitaxel 175 mg/m2 as 3-hour infusion on day 2; bleomycin 30 mg on days 1,		median follow up: 36 months (6-72)	primary endpoint: progression free survival (PFS) at 1 year	1-year PFS 58% (95% [CI] 46%-72%) 2-year PFS 57% (95% CI 43%-70%)	paclitaxel was discontinued permanently because of toxicity (grade 2-3 infections)	Funding support: This study was partly supported by an unrestricted grant from OJSC Veropharm; medical writing support was funded by F.	LOE 4 RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
	Russia	median age: 27 (17-48)	3, and 5; cisplatin 20 mg/m2 on days 1-5; and etoposide 100 mg/m2 on days 1-5 of every 21-day cycle) with G-CSF support of filgrastim 300 g administered on days 6-10.			secondary endpoint Overall survival (OS) Adverse events	1- OS rate 80% (95% CI 69%-91%) 2-year OS rate 67% (95% CI 54%-80%) adverse events: excessive toxicity at cycle 1: 22% grade 3-4 infection that resulted in 2 toxic deaths grade 3-4 T-BEP-related adverse events: neutropenia (71%) febrile neutropenia 33% infection (14%) anaemia (8%)	slow decline in tumor markers: n=38 patients (75%) received >4 cycles of chemotherapy	Hoffman-La Roche Ltd. From the NN Blokhin Russian Cancer Research Center, Moscow, Russia no information about coi	

Referenz (Autor, Jahr)	Studientyp Gesamt- n Zeitraum der Datenerhebung Land	Patienten-merkmale	Intervention	Kontrolle	Beobach-tungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE Risk of Bias RoB
Wortel RC 2015	single arm prospective cohort study n=238 1999-2013 Netherlands	CS I Seminoma n=145 CS II Seminoma with radiation after orchiectomy n=16 median age: 36 ys (18-70)	radiation 26 Gray (Gy) in 2 Gy fractions to para-aortic region with an additional 10 Gy boost to enlarged nodes visible on computer tomography (CT) scan for stage II		median follow-up time 55 months (range 3–148)	incidence and severity of short-term effects of orchiectomy and radiotherapy on body image and sexual function	fertility concerns: 48% changes in body images: 61%		funding by Dutch Society for Sexual Medicine (NVVS) Fund for Stimulation and Development of Sexology no coi	LOE 4 RoB SIGN (+) acceptable

9.4.8. Kapitel 9 Restaging und Therapie der Residualtumorerkrankung

Referenz (Autor, Jahr)	Studientyp RCT, retrospektive oder prospektive Kohortenstudie, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patientenmerkmale	Intervention Anzahl der Patienten	Kontrolle Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt Primary Endpoint, Secondary Endpoint	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LoE Risk of Bias RoB
Arai Y 2012	retrospective cohort study n=20 Japan April 2002 - February 2010	Median age 27 yrs (18–49) metastatic NS GCT	Extraperitoneal laparoscopic retroperitoneal lymph node dissection after chemotherapy	no control group	median follow-up: 45 mo	Median operative time Median estimated blood loss Blood transfusion Intraoperative complications Postoperative complications: Prolonged lymphorrhea Chyle leakage Pneumonia Conversion to open surgery	Median operative time (r 223 (137–399) min Median estimated blood loss 20 (10–520) ml Blood transfusion: None Intraoperative complications: None Prolonged lymphorrhea (>5 days) n=4 (grade I) Chyle leakage n=9 (grade I) Pneumonia n=1 (grade II) disease recurrence: n=0		no coi no information about funding	LoE 4 RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp RCT, retrospektive oder prospektive Kohortenstudie, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patientenmerkmale	Intervention Anzahl der Patienten	Kontrolle Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt Primary Endpoint, Secondary Endpoint	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LoE Risk of Bias RoB
						tumor recurrence				
Busch J 2012	two-arm single-center-cohort study n=67 Germany	Median age at the time of surgery: L-PCLND: 32.0 yrs (range 26.5–37.5) O-PCLND 28.0 yrs (range 22.0–34.0)	L-PCLND n=46	O-PCLND n= 21	Median follow up; months (IQR) L-PCLND 30.1 (12.1 – 47.1) O-PCLND 54.5 (22.0 – 87.7)	Lost to follow up Tumor relapse Estimated OS since PCLND in months	Lost to follow up L-PCLND n=1 (2.2%) O-PCLND n=2 (9.5%) Tumor relapse: L-PCLND n=4 (8.6%) O-PCLND 3 (14.2) Estimated OS since PCLND in mo: L-PCLND 83.3 ± 1.9 (95% CI 79.6 - 87.3) O-PCLND		no coi no information about funding	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp RCT, retrospektive oder prospektive Kohortenstudie, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patientenmerkmale	Intervention Anzahl der Patienten	Kontrolle Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt Primary Endpoint, Secondary Endpoint	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LoE Risk of Bias RoB
							95.0 ± 7.4 (95%CI 80.5 – 109.6)			
Decoene J 2015	retrospective case series n=22 July 2003 and September 2013 Germany	Median age at PC-RPLND (range) 43.9 (28–53)	n=22 patients with a pure seminoma underwent PC-RPLND	no control group	Median follow-up in months 2 (0–134)	diagnostic accuracy	n=11 FDG-PET before surgery n=7 (64%) false positive results		no information about coi no information about funding	LoE 4 Quadas-Tool: Risk of bias: unclear

Referenz (Autor, Jahr)	Studientyp RCT, retrospektive oder prospektive Kohortenstudie, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patientenmerkmale	Intervention Anzahl der Patienten	Kontrolle Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt Primary Endpoint, Secondary Endpoint	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LoE Risk of Bias RoB
Ehrlich Y. 2010 Long-term follow up… JCO	retrospective single arm cohort study n=141 USA 1984-2005	n=3 apparent primary retroperitoneal NSGCT n=19/75 and n=8/33 with retroperitoneal mass 2.0 to 5.0 cm and more than 5.0 cm, respectively, contained teratoma in the primary tumor	primary chemotherapy (BEP, EP, HD, VIP)	no control group	Median follow-up 15.5 yrs (range, 6 months to 24 yrs)	Recurrence-free survival (RFS) Cancer-specific survival (CSS)	15-yr RFS: 90% (95% CI, 84.8% to 95.7%) 15-yr-CSS: 97% (95% CI, 94.3% to 100%)		no coi no information about funding	LoE 4 RoB Sign (+) acceptable
Fizazi K 2014	R(C)T Phase III Nov 2003-May 2012 Frankreich, USA, Slovakei	IGCCCG poor prognosis group patients	n=203 with unfavourable decline randomly assigned n=105 assigned	n=51 with favourable decline (Fav-BEP group)	median follow up 4·1 years (IQR 0·3–8·8).	PFS OS adverse events	3-year PFS: Unfav-dose-dense group versus Unfav-BEP group (HR 0·66 [95% CI 0·44–1·00]; p=0·05 3-year		Unicancer, Univ. Cancer Center	LOE 1b RoB low

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	n=263		(Unfav-dose-dense group) n=98 assigned (Unfav-BEP group)				59% (95% CI 49-68) Unfav-dose-dense group 48% (95% CI 38-59) Unfav-BEP group 3-year PFS: 70% (95% CI 57-81) Fav-BEP group 48% (38-59) Unfav-BEP group 3-year OS: 73% (95% CI 64-81) Unfav-dose dense group 65% (95% CI 55-75) Unfav-BEP (HR 0·78, 95% CI 0·46-1·31) p=0·34 3-year OS 84% (95% CI 71-92)			

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							Fav-BEP group 65% (95% CI 55–75) Unfav-BEP group			
Kollmannsberger C 2010	population based retrospective study n=276 1999 – 2007 CA, USA	disseminated nonseminomatous testicular cancer Median age: 27 yrs (range) 16-63 Teratoma in the primary tumor was seen in 40% of cases. 84% low stage, IGCCCG good risk 5% intermediate risk	cisplatin-based combination chemotherapy as primary treatment modality	no control group	median follow-up: 45 mo (range, 3 - 135 mo)	response to chemotherapy (CR, PR - ≤1 cm)	CR, PR - ≤1 cm: Of our 276 patients, 161/276 pts (59%) after primary chemotherapy and were observed without adjunctive surgery complete remission with complete resolution of all metastatic lesions: n=115/161 (71%) n=46/161 (29%) PR-; ≤1cm)		no coi no information about funding	LoE 4 SIGN RoB (-) unacceptable

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		11% poor risk disease								
Oechsle K 2011	two Phase II studies (prospective single arm) GO-Study plus GOP-Study n=76 pts Germany August 2001 - March 2003 (GO-study) April 2003 - October 2006 (GOP-study)	n=35 GO n=41 GOP Age at study entry: Median 37 yrs range 21-54 GO-study Age at study entry: Median 38 range 25-62 GOP-study Location of primary tumor Gonadal	GO-study: Gemcitabine dose: 1,000 mg/m2 on days 1 and 8; oxaliplatin dose: 130 mg/m2 on day 1 GOP-study: 800 mg/m2 gemcitabine, 80 mg/m2 paclitaxel	no control groups	updated follow-up (cut-off date: November 2010) after a median time of 19 mo (range: 2-86 mo) GO study median follow-up: 6 mo (range,	OS	68 of 76 pts in both studies (89%) had died. Median overall survival for all 76 pts: 8 mo (range: 1-84 mo) Median overall survival time: 17 mo (range: 6-84 mo) for 37 pts showing any response to treatment (49%) In total, 8 of 76 pts (11%), 1 after GO (1 in 35; 3%) and 7 after GOP (7 of 41; 17%) with or without additional surgery or		GO study Supported by an educational grant from Sanofi-Synthelabo Inc, Berlin, Germany GOP-study: fundin g by	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor, Jahr)	Studientyp RCT, retrospektive oder prospektive Kohortenstudie, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patientenmerkmale	Intervention Anzahl der Patienten	Kontrolle Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt Primary Endpoint, Secondary Endpoint	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LoE Risk of Bias RoB
		n=30 (86%) GO-study Location of primary tumor Gonadal n=32 (78%)	(Taxol), both on days 1 + 8, and oxaliplatin 130 mg/m2 on day 1 of a 3-week cycle for a minimum of two cycles		0.5 to 18 mo) GOP-study: 5 mo (range, 0–20 mo)		salvage chemotherapy remain relapse free long term		Sanofi-Aventis	
Ramsey S 2013	retrospective cohort study UK n=21 1982-2006	Age, years: median/mean (range) 37/34 (19 – 51) Risk factors: none/family history/UDT 16/1/4 Initial diagnosis: seminoma/NSGCT 7/14	Prim. Chemotherapy before Ablatio testis n=21 orchiectomy	no control group	Time from diagnosis to orchidectomy, months: median/mean (SD, range) 7/16.5 (2.25, 3 – 68)	n alive n deceased Follow-up-in yrs	Group Early n=13 testis patho scar/necrosis n=6 alive n= 12 follow-up-years: 4.4	very small sample	no information about funding	LOE 4 RoB SIGN (+) acceptable

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		Marsden stage: I/II/III/IV 1/3/8/9 IGCCC risk classification: good/intermediate/poor 8/8/5	median 7 mo after chemotherapy (range 3–68 mo)				deceased n= 1 Early n=3 testis patho: tumour RPLND n=3 alive n=0 follow up years 4.6 deceased: n=3 Group Delayed n=2 testis patho: scar/necrosis			

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							RPLND n=0 alive n=2 follow-up years: 8.4 deceased: n=0 Group: Delayed n=3 testis patho: tumour RPLND n=1 alive: n=2 follow-up years: 7.5			

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							deceased n=1			
Schirren J 2012	retrospective single center cohort study n=124 2000-2006 Germany	age 33.1 ± 8.4 yrs NSGCT after CT and/or HDCT	intrathoracic residual tumor resection (RTR)		median follow-up: 48.9 ±27.2 mo (range, 1 - 98 mo)	Morbidity and mortality rates Mean survival overall 5-yearsurvival and 10-year survival rates	Morbidity rate: 12.7% mortality rate: 0.5% Mean survival: 86.6 ±2.6 mo 5-yr OS: 87% 10-yr OS:85% Completeness of RTR Mean survival: Complete: 87.8 mo ±2.5 (95% CI 82.8–92.8) 5-yr-survival: 88% Mean survival:		no information about coi no information about funding	LoE 4 SIGN RoB (+) acceptable

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							Incomplete 39.5 mo ± 23.8 (95% CI 0.0–86.2) 5-yr-survival: 33%			
Winter C 2012	retrospective analysis n=402 GCT who underwent 414 RTRs in 9 centers Germany January 1995 - July 2011	median age: 31 yr of (range: 14–67) Histopathology: 88% nonseminomatous GCTs (NSGCT) 12% pure seminoma Good prognosis: 43%, intermediate prognosis: 24%,	postchemotherapeutic RTR	no control group	median follow-up: 36 mo (range: 0–192)	prediction of additional vascular procedures during RTR	Tumor size and IVC: probability of 20.4% with an intermediate or poor prognosis feature and a residual tumor size ≥5 cm needs an IVC intervention during a planned RTR good prognosis patients with a tumor size <5 cm, probability of 6.4% for a possible vena cava procedure		no coi no fundin g	LoE 4 SIGN RoB (+) acceptable

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		poor prognosis: 32% according to IGCCCG classification								

Adverse events aus: Fizazi 2014

	Unfav-BEP (n=98)			Unfav-dose-dense (n=105)			Fav-BEP (n=51)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Rash	18 (18%)	0	0	27 (26%)	0	0	16 (31%)	0	0
Nausea or vomiting	70 (71%)	2 (2%)	0	66 (63%)	24 (23%)	0	36 (71%)	1 (2%)	0
Diarrhoea	19 (19%)	1 (1%)	0	45 (43%)	6 (6%)	0	12 (23%)	1 (2%)	0
Mucositis	18 (18%)	0	0	36 (34%)	7 (7%)	1 (1%)	13 (25%)	3 (6%)	0
Liver	40 (41%)	3 (3%)	0	31 (30%)	5 (5%)	0	15 (29%)	0	0
Motor neuropathy	1 (1%)	0	0	6 (6%)	2 (2%)	0	1 (2%)	0	0
Sensory neuropathy	20 (20%)	1 (1%)	0	73 (70%)	6 (6%)	0	13 (25%)	0	0
Auditory	28 (29%)	0	0	48 (46%)	2 (2%)	0	10 (20%)	0	0
Dyspnoea	23 (23%)	5 (5%)	6 (6%)	34 (32%)	9 (9%)	0	4 (8%)	9 (9%)	1 (2%)
Renal	9 (9%)	0	0	27 (26%)	2 (2%)	0	3 (6%)	0	0
Fatigue	69 (70%)	7 (7%)	0	71 (68%)	19 (18%)	0	35 (69%)	1 (2%)	0
Infection	14 (14%)	8 (8%)	1 (1%)	23 (22%)	9 (9%)	1 (1%)	12 (24%)	3 (6%)	0
Haemoglobin	71 (72%)	18 (18%)	8 (8%)	58 (55%)	36 (34%)	11 (10%)	39 (76%)	8 (16%)	2 (4%)
Neutropenia	16 (16%)	17 (17%)	45 (46%)	21 (20%)	18 (17%)	45 (43%)	10 (20%)	13 (25%)	18 (35%)
Thrombocytopenia	55 (56%)	15 (15%)	1 (1%)	56 (53%)	27 (26%)	5 (5%)	35 (69%)	4 (8%)	0
Febrile neutropenia	18 (18%)	0	0	18 (17%)	0	0	7 (14%)	0	0
Transfusion	31 (32%)	0	0	55 (52%)	0	0	6 (12%)	0	0
Platelet transfusion	6 (6%)	0	0	16 (15%)	0	0	2 (4%)	0	0

Unfav-BEP=patients with an unfavourable marker decline who were randomly assigned to receive BEP. Unfav-dose-dense=patients with an unfavourable marker decline who were randomly assigned to receive a dose-dense regimen. Fav-BEP=patients with a favourable marker decline who continued BEP. Infection=infectious event without neutropenic fever.

Table 2: Adverse events

9.4.9. Kapitel 10

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
Adra N 2017	Retrospective single-arm cohort study n=364 December 2004 - December 2014 USA Indiana University, Indianapolis median follow-up: 3.3 yrs	metastatic GCT that progressed after one or more standard cisplatin-etoposide–based combination chemotherapy regimens	High dose chemotherapy (HDCT) Patients who had platinum-refractory disease, defined as tumor progression within 4 weeks of cisplatin-based chemotherapy, proceeded directly to HDCT. Patients who had platinum-sensitive disease received one or two cycles of standard-dose chemotherapy, most commonly vinblastine plus ifosfamide plus cisplatin, before proceeding to HDCT	No control group	2-year PFS of patients with relapsed GCT treated with HDCT. Secondary end points: 2-year OS	total of 364 patients: 2-year PFS: 60% (95% CI, 55% - 65%) 2-year OS: 66% (95% CI, 60% to 70%) HDCT as second-line: 2-yr PFS: 63% (95% CI, 57% - 68%) 2-yr OS: 67% (95% CI, 61% - 72%) HDCT as third-line or later therapy: 2-yr PFS: 49% (95% CI, 36% to 61%;		Rafat Abonour Research Funding: Amgen (Inst) Nasser H. Hanna Research Funding: Merck (Inst), Bristol-Myers Squibb (Inst) Lawrence H. Einhorn Stock or Other Ownership: Amgen, Biogen Idec Consulting or Advisory Role: Celgene All other authors: no coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						P = .03). 2-yr-OS: 60% (95% CI, 46% - 71%) (P = .05) Patients with platinum-refractory disease: 2-yr PFS: 33% (95% CI, 24% - 41%) vs 75% (95% CI, 69% to 80%) for platinum-sensitive patients 2-yr OS rates: Patients with platinum-refractory disease: 37% (95% CI, 30% - 45%) platinum-sensitive patients: 80% (95% CI, 75% - 85%)		Supported in part by the National Cancer Institute	

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
Al-Hader A 2015	single-arm retrospective cohort study n=86 1998-2012 USA Indiana University Database no information about follow-up	total: n=18 treated with PNET-specific chemotherapy (CAV/IE) median age: 29 (20-53) unresectable PNET n=12 adjuvant chemotherapy after surgery n=6	cyclophosphamide (1000 to 1200 mg/m2), doxorubicin (50 to 75mg/m2), vincristine (2 mg) alternating with ifosfamide (1.8 g/m2) plus etoposide (100mg/m2) for 5 consecutive days (CAV/IE)	no control	remission CSS NED no evidence of disease	unresectable PNET-group: n=12 median survival: 36 mo (range 3 - 114 mo) median duration of remission: 10 mo 1-yr-CSS: 80% 2-yr-CSS: 50% adjuvant chemotherapy: n=6 still alive with NED after 9, 13, 15, 24, 45, 90 mo median survival: 32.7 mo		no information about funding no coi	LOE 4 SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
Berger LA 2014	retrospective, multi center registry study n=143 Germany January 2007 – January 2013	patients with relapsed or refractory metastatic germ cell cancer after firstline cisplatin-based conventional-dose combination chemotherapy median age: 31 years (range 15–58)	first salvage treatment: conventional- or high-dose chemotherapy HD-Chemo: sequential regimen in 95 % of patients with a planned number of three cycles consisting of carboplatin 500 mg/ m2 and etoposide 500 mg/m2 on days 1–3 with autologous stem cell transplantation 2 days later	conventional-dose regimens: VIP (etoposide, ifosfamide, cisplatin) TIP (paclitaxel, ifosfamide, cisplatin	Progression-free survival Overall survival relapse	progression-free interval since first-line chemotherapy: 7 mo (range 1–313) relapse rate: 55 % 91% relapsed within the first 2 years progression-free survival: 15 mo (95% CI 9–21) overall survival: 59 mo (95% CI 33–85) 2 yr-PFS: 43 % 2 yr OS:		no information about coi no information about funding	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						67 % 5 yr PFS 33% 5 yr OS: 52% 2yPFS: CD-CX versus HD-CX 22% versus 53 % (p < 0.001)* 2yOS: CD-CX versus HD-CX 65 versus 68 % (p = 0.644)			

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
Cary C 2015	single arm retrospective cohort study n=92 1987-2011 USA median follow-up for the entire cohort: 80.6 months (range, 1.2-305.2 months	Patients with advanced germ cell tumor receiving HDCT before PC-RPLND n=39 in desperation setting with elevated markers	postchemotherapeutic RPLND	no control	Overall survival OS predictive factors of overall mortality Hazard ratio	desperation group: 5-yr-OS: n=15/39 5-year OS of the entire cohort: 70% (95% CI, 60%-79%) 5-year OS first-line salvage HDCT: 72% 5-year OS for second-line salvage HDCT: 62% (p=0,34) predictive factors of OS: Desperation PC-RPLND (p<0,001)		no funding no coi	LOE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						RP histology (p=0,003) HR: First- vs second-line salvage HDCT HR 0.67 (95% CI 0.28-1.6) Desperation PC-RPLND HR 4.29 (95% CI 1.87-9.8)			
Ehrlich Y 2010	single arm cohort study n=81 1988-2007 USA Indiana University testis cancer database	n=76 with PNET in primary tumor or in surgical specimen following initial chemotherapy mean age: 28 (16-68) n=12	PNET-specific chemotherapy: cyclophosphamide 1200 mg/m², doxorubicin 75 mg/m², and vincristine 2 mg i.v. alternating with ifosfamide 1.8 g/m² x 5 days plus etoposide 100 mg/m² x 5 days (CAV/IE)	no control group	NED (no evidence of disease) ADW Alive with disease DOD dead of disease	n=1 NED at 33mo n=4 AWD at 21 to 73mo from initiation of CAV/IE n=5 DOD		no coi no information about funding	LOE 4 SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
	no information about follow-up	PNET specific chemotherapy CAV/IE n=2 CAV/IE adjuvant to surgery n=10 CAV/IE not suitable for surgery							
Feldman DR 2010	single-institution phase II trial USA n=10	Median age, y (range) 33 (19–51) clinically refractory to standard platinum-based salvage therapy with progression or relapsed after high-dose chemotherapy with autologous stem cell rescue,	initial dosing schedule of sunitinib: 50 mg, administered daily for four consecutive weeks followed by a two-week break (4/2 schedule), constituting one six-week cycle	no control	toxicities	no grade 4 toxicities grade 3 mucositis: n=1 grade 3 lymphopenia: n=6 grade 3 neutropenia: n=2 grade 3 hemorrhage into a progressive splenic metastasis: n=1	to alter the dosing schedule midway through the trial	sponsored by Pfizer and Sidney Kimmel Center for Prostate and Urologic Cancers no information about coi	LoE 4 no critical appraisal (more or less a case report)

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
		or they had declined or were not candidates for high-dose therapy			tumor status Responses serum tumor marker levels	response: stable disease (SD) in five pat progressive disease (PD) in five pat Four of five patients experienced some tumor marker decline (without radiographic progression) during the four-week “on” period, with subsequent marker rise during the two-week break			
Giannatempo P 2016	multi center retrospective database study n=320 June 1981 – August 2014 USA	Patients with Teratoma with Somatic-Type Malignant Transformation n=130 median	GCT chemotherapy TMT chemotherapy: doxorubicin based chemotherapy, which was often combined with cyclophosphamide or ifosfamide as primary or salvage therapy		5 yr OS	5-yr overall survival; 83.4% (95% CI 61.3 – 93.5) in patients with clinical stage I good prognosis: 69.8% (95% CI 57.3-79.3),		Supported by the Conquer Cancer Foundation of the American Society of Clinical Oncology Merit Award (PG)	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
	CA Italy France	age of 28 years (IQR 24-35) median follow up: 25.1 mo (IQR 5.4-63.8)	surgery only			intermediate prognosis: 49.1% (95% CI 27.7-67.4) poor prognosis: 47.9% (95% CI 34.4-60.2)		no information about coi	
Heidenreich A 2017	retrospective single center two arm cohort study n=185 PC-RPLNDs Germany 1/2009 – 12/2015	n= 25 complex cases n=25 (13.5%) patients who needed complex adjunctive vascular (n=16, 8.6%), skeletal (n=5, 2.7%) pancreaticoduodenal (n=4, 2.2%) surgeries	standard PC-RPLND n=138	complex PC-RPLND n=25	surgery-related complications progression-free, overall and cancer specific survival	surgery related complications: 41.7% versus 7.2%, P=0.02 patients with pancreaticoduodenal surgeries developed more severe complications Vascular surgery: relapse: n=1 OS: 100% PFS: 100%		no funding no coi	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
		Age 26.4 (19-46) standard group 24.5 (18-52) complex group				Skeletal surgeries: overall survival: 100% progression-free survival: 60% Pancreaticoduodenal adjunctive surgery: overall survival and progression-free survival: 75%			
Hosni A 2016	retrospective single center two arm database analysis n=1060 1981 – 2011 CA	CS I Seminoma median age at initial diagnosis: 34 yrs (range 20e83) median follow-up: 10.6 yrs (range 1.2e30)	active surveillance n=744	adjuvant therapy (radiotherapy) n=294 no information provided about RT dosing	OS relapse time to relapse (median)	active surveillance relapse rate: 17% time to relapse: 14 months (range 3-129) adjuvant radiotherapy: relapse rate: 5% time to relapse: 15 mo (range 5-72)		no information about coi no information about funding	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						active surveillance: 10 yr OS: 97% 10 yr CSS 99%			
Kollmannsberger C 2010	population-based retrospective cohort study n=276 1999 – 2007 CA USA	disseminated non seminomatous testicular cancer	good prognosis disease patients: three cycles of BEP or Intermediate or poor prognosis received primarily four cycles of BEP	four cycles of etoposide, cisplatin in case of contraindications to bleomycin	Complete response (CR) DSS	complete remission with complete resolution of all metastatic lesions: n=115 patients (71%) Disease-specific survival for the CR group: 100% after a median follow-up of 52 mo (range, 3 to 135 mo) complete response IGCCCC good: 84% IGCCCG intermediate 5%/		no coi no information about funding	LoE 2b SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						IGCCCG poor 11%			
Kurobe M 2015	single-arm retrospective cohort study n=43 2000-2012 Japan median follow-up: 58 months (range 19–166 months)	n=41 with primary testicular tumor n=2 with extragonodal GCT (retroperitoneum) median age: 31 ys (20-54) IGCCCG: Poor: n=20/74% Intermediate: n=4/15% Good: n=3/ 11%	TIP paclitaxel 175 mg/m2 by 24-h infusion on day 1, followed by ifosfamide 1.2 g/m2 infusion over 2 h and cisplatin 20 mg/m2 given over 2 h on days 2–6 indication of TIP: Elapsed: n= 10/23% Refractory: n= 6/14% Consolidation n=27/63%	no control group	complete response CR partial response with normalized markers PRm- partial response without normalized markers PRm+ no change NC	CR to chemotherapy ± resection of necrosis/teratoma: refractory: n=1/6 (17%) Relapse: n=4/10 (40%) Consolidation n=16/27 (59%) CR to chemotherapy + resection of viable germ cell tumor Refractory: n=0 Relapse:		no coi no information about funding	LOE 4 SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
					progressive disease PD 5 y-overall survival OS toxicity	n=1/10 (10%) Consolidation n=2/27 (7%) PRm− Refractory: n=2/6 (33%) Relapse: n=1/10 (10%) Consolidation: n=5/27 (19%) PR 171+ Refractory: n=1/6 (17%) Relapse: n=2/10 (20%) Consolidation: n=1/27 (4%) NC			

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						Refractory n=2/6 (33%) Relapse n=2/10 (20%) Consolidation: n=1/27 (4%) PD Refractory: n=0 Relapse: n=0 Consolidation: n=2/27 (7%) 5-y-OS: refractory cases: 33% relapsed cases 66 %			

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						good- or intermediate-prognosis: 100 % poor-prognosis: 78 % toxicity all grades: Hematological: Leukocytopenia: n=43 (100%) Thrombocytopenia: n=42 (98%) Anemia: n=43 (100%) Febrile neutropenia: n=23 (53%) Non-hematological:			

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						Nausea or vomiting n=23 (53%) Neuropathy (sensory): n=17 (40%) Myalgia/arthralgia n=11 (26%) Acoustic nerve disorder: n=2 (5%) AST/ALT n=4 (9%) Dysgeusia: n=1 (2%)			

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
Lee DJ 2014	single-arm retrospective cohort study n=15 2005-2012 USA mean follow up of 13.7 months	n=15 patients with post-chemotherapy retroperitoneal lymphadenectomy with growing teratoma syndrome median age at diagnosis: 23 years median rate of linear tumor growth : 0.5 cm/month, increase in tumor volume: 9.2 cm3/month	All received systemic chemotherapy before RPLND	no control group	OS, CSS	OS, CSS after 13.7 mo: 100%		no information about funding no coi	LOE 4 SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
Lorch A 2010a JCO Int Progn factors study group	retrospective multi center database study n=1984 September 2007 – December 2008 38 centers and cooperative groups worldwide	relapsed and/or refractory GCT Median age: 30 yrs (range, 15 to 63 yrs) Median follow-up: 58 mo (range, 1 to 206 mo)	Conventional dose n=773 (48.5%) Consolidation after salvage: No further treatment n=917 (57.5%) Surgery n=495 (31.1%) Radiotherapy n=134 (8.4%) Surgery & radiotherapy n=47 (3.0%)	High dose n=821 (51.5%)	Progression-free survival (PFS) at 2 yrs Overall survival (OS) at 2 yrs	Median PFS: 9.8 mo (95% CI, 8.8 – 11.0 mo) median OS: 41 mo (95% CI, 30 – 57 mo)		Ownership: Lawrence H. Einhorn, Amgen, Biogen Idec, GlaxoSmithKline Research Funding: none	LoE 2b SIGN RoB (+) acceptable
Lorch A 2011	retrospective multi center database study n=1984 September 2007 – December 2008	metastatic GCT Median follow-up time: 58 mo (range, 1 to 206 mo)	Salvage chemotherapy CDCT n=773 patients (49%)	Salvage chemotherapy HDCT n=821 patients (51%)	progression free survival PFS Overall survival OS	median PFS for all: 9.8 mo (95% CI, 8.8 – 11.0 mo) median OS for all: 41 months (95% CI, 30 – 57 mo)	Patients who had received CDCT were younger, had slightly more favourable responses to firstline	Financial support: Joerg Beyer no coi	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
	38 centers and cooperative groups worldwide	CDCT: median age: 32 (15-64) HDCT: median age: 32 (16-60)				PFS at 2 years: favours HDCT compared with CDCT: HR for PFS: very low risk: 0.18 (95% CI, 0.06 – 0.55) low risk: 0.43 (95% CI, 0.28 - 0.66) intermediate: 0.46 (95% CI, 0.37 – 0.56) high: 0.47 (95% CI, 0.37 0.60) very high:	treatment, and had lower HCG values at salvage		

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						0.36 (95% CI, 0.23 – 0.56)			
Lorch A 2012	Prospective Randomized Trial n=211 November 1999 – November 2004	patients with relapsed or refractory GCT arm A median age: 36 (16-59) arm B 36 (17-55)	CE, arm A one cycle of cisplatin 100 mg/m2, etoposide 375 mg/m2, and ifosfamide 6 g/m2 (VIP) plus three cycles of high-dose carboplatin 1,500 mg/m2 and etoposide 1,500 mg/m2 n=108	CEC, arm B three cycles of VIP plus one cycle of high-dose carboplatin 2,200 mg/m2, etoposide 1,800 mg/m2, and cyclophosphamide 6,400 mg/m2 (followed by autologous stem-cell reinfusion	Progression free survival PFS overall survival OS	PFS arm A: PFS at 2 yrs: 52% (95% CI, 42% to 61%) PFS at 5 yrs: 48% (95% CI, 38% to 57%) PFS arm B: PFS at 2 yrs: 47% (95% CI, 36% -57%) PFS at 5 yrs: 46% (95% CI, 35% - 56%)		no coi Financial support: Joerg Beyer	LoE 1b RoB Tool Bewertung. High risk of bias

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
				n=103		OS in arm A: OS at 2 yrs: 58% (95% CI, 48% - 66%) OS at 5 yrs: 50% (95% CI, 40% - 59%) OS arm B: OS at 2 yrs: 50% (95% CI, 40% - 59%) OS at 5 yrs: 40% (95% CI, 30% - 49%)			
Lorch A, 2010b	retrospective data base study of two centers n=534	patients with multiple relapsed or refractory germ-cell tumors	HDCT consisted of one, two or three cycles of high-dose carboplatin and etoposide or of one cycle of high-dose carboplatin, etoposide	no control	Overall survival OS, response rate, rate of progression and treatment-	overall rate of favourable responses (complete remission with or without surgery and PRm2):		no information about coi no information about funding	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
	1989 – 2008 Germany	Median age at SST: 32 yrs (range 19–52 yrs) Median follow-up for surviving patients: 4 yrs (range 1.7–8.5 yrs)	and ifosfamide, cyclophosphamide or thiotepa n=71		related toxic effects	n=27 of 49 (55%) Relapses or progression: n=36 of 49 (74%) 5 yr-OS: for the entire group of patients: 17% (95% CI 7% - 30%) Evaluations of toxic effects not reported			
Loriot Y 2017	secondary analysis of data from the GETUG 13 trial see Fizazi 2014 n=254 France USA	testicular, retroperitoneal, or mediastinal NSGCT and highly elevated serum hCG or AFP levels, with IGCCCG poor-prognosis criteria: a	personalised chemotherapy based on tumour marker decline in patients with poor-prognosis germ-cell tumour (GCT) favourable tumour marker decline	patients with an unfavourable decline: randomly assigned (1:1) to receive either BEP (Unfav-BEP group) or	PFS OS	no significant treatment effect on OS risk of deaths (HR) marker progression only: HR 14.14 [95% CI 6.26-31.95]		no information about funding no coi	LoE 1b RoB Bewertung low risk of bias

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
	Slovakia 28th November 2003 – 16th May 2012	primary mediastinal NSGCT, or non-pulmonary visceral metastases and/or high serum tumour markers (hCG> 50,000 UI/l, AFP > 10,000 ng/ml, or LDH> 10- fold the upper normal value)	n=51	a dose-dense regimen (Unfav-dose-dense group) n=98 Unfav-dose-dense group n=105		radiographic progression only: HR 40.4 [95% CI 16.41-99.45] both: HR 18.02 [95% CI 7.84-41.38] risk of death for patients within the first year with a marker progression only HR 15.8; 95% CI 3.62-69.05 a radiographic progression only HR 24.09; 95% CI 3.90 -148.8			

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
						both HR 9; 95% CI 1.98-40.96			
Maroto P 2011	phase II multicenter trial n=20 Spain UK 1999 -2001	cisplatin-refractory germ cell cancer patients Median age (range), yrs 38 (27–56)	temozolomide 150 mg/m 2 /day p.o. for 5 days every 4 weeks; doses were raised to 200 mg/m 2 /day if grade II toxicity was not observed in the first cycle	no control	toxicity (CTC) response	overall response rate 10%, 95% CI 1.2–31.7 median time to progression: 1.47mo (95% CI 1.32–1.61 median overall survival 3.1 mo (95% CI 2.5–3.8)		no coi no information about funding	LoE 4 SIGN RoB (+) acceptable
Narayan V 2016	single center retrospective cohort study n=37 2005 – 2013	relapsed or refractory GCT undergoing systemic salvage therapy	risk adapted approach favourable risk CDCT (TIP 4x) n=16	no controls	complete response CR partial response PR	n=21 (57%) CR or PR-negative response n=3 (8%) CR with post-chemotherapy surgical resection		no coi no information about funding	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
	USA median follow-up from start of initial salvage therapy: 31 mo (1-118 mo)		unfavourable risk HDCT (TIP 2x plus Carboplatin 2x plus Etoposide plus autologous stem cell re-infusion) n=21		incomplete response IR PFS OS	favourable response rate TIP: 69% favourable response rate HDCT: 62% TIP-Group: favourable response rate: favourable-risk pat: n=9 (67% unfavourable-risk pat: n=7 (71% 2-yr-PFS: all pat: 45,8% (95% CI 29,4-60,8) TIP: 61,9% (95% CI 33,9-80,8) HDCT: 33,3,% (95% CI 14,9-53,1) 2-yr-OS: all pat: 59% (95% CI 41,1-72,9) TIP: 75% (95% CI 46,3-89,8)			

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						HDCT: 47,6% (95% CI 25,7-66,7) 4-yr PFS: all pat: 45,8% (95% CI 29,4-60,8) TIP: 61,9% (95% CI 33,9-80,8) HDCT: 33,3,% (95% CI 14,9-53,1) 4-yr-OS: all pat: 49,7% (95% CI 32,5-64,9) TIP: 67,5% (95% CI 38,4-85,1) HDCT: 37,5% (95% CI 18,0-57,4)			
Necchi A 2017	multicenter retrospective single arm cohort study EU	pure seminoma GCT median age: 38 yrs (IQR 35-46)	HDCT (Carbo PEC, Carbo PECT, CE, CEI)	no controls	PFS OS	5-yr-PFS: 58,3% (95% CI 42,4-80,2) 5-yr-OS: 61,2% (95% CI 44,6% - 83,9%)		no coi no information about funding	LoE 4 SIGN Rob (+) acceptable

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	n=46 2002 – 2012 median follow up: 22 mo (IQR 8-56)					multivariate analysis for prognostic factors: chemosensitivity HR 6,04 (95% CI 1,86-19,64) for PFS chemosensitivity HR 3,93 (95% CI 1,07-14,45) for OS			
Nieto Y 2015	single arm single center cohort study n=43 May 2008 – August 2014 USA	poor-risk relapsed or refractory germ-cell tumors median follow-up of 46 (9–84) months	HDC regimen combining infusional gemcitabine with docetaxel/melphalan/carboplatin (GemDMC	no control	RFS toxicity	ORR 89% (32% CR, 35% PRm−, 22% PRm+) RFS 55.8% [95% CI 41% - 70.6%] OS 58.1% (95% CI 43.4% - 72.8%)		no coi no information about funding	LoE 4 SIGN RoB (+) acceptable

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						RFS: testicular site 66% mediastinal site 28.5% retroperitoneal site 25% Median post-relapse OS: 4 (2–24) mo toxicity: Long-term toxicities included end-stage renal failure (n = 3) hypertension (n = 4). N=2 second cancers (lung adenocarcinoma, leiomyosarcoma)			

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Oechsle K, Honecker F 2011 Ann Oncol	open-label, multicenter phase II trial n=33 Germany UK, USA CA February 2007 – January 2010	seminomatous or nonseminomatous GCT, and relapse within 2 months after cisplatin-based chemotherapy, tumor progression during or relapse after salvage HD-CT, tumor progression during salvage cisplatin-based chemotherapy, or ineligibility for cisplatinbased chemotherapy or HD-CT due to severe comorbidities Median age, yrs (range) 32 (22–54)	Sunitinib was given at a dose of 50 mg daily for 4 weeks followed by a 2-week break to form 6-week cycles	no control	response rate. TolerabilityPFS, and overall survival (OS) time	No complete remission observed Median PFS for all patients: 2.0 mo 95% (CI) 1.4–2.60 11% progression free at 6 mo 3.7% progression free at 12 mo Median OS: 3.8 mo 95% CI 3.0–6.6 36.4% alive at 6 mo 9.9% alive at 12 mo		funding: Pfizer Inc., New York (investigator-initiated research grant) no coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
Oechsle K, Kollmannsberger C 2011 Eur Uro	two phase II studies (GO and GOP studies) Gos study n=35 August 2001 – March 2003 subsequent GOP study n=41 April 2003 – October 2006 Germany	histologically confirmed germ cell tumors, relapse within 3 mo after cisplatin-based chemotherapy, or tumor progression after at least two previous lines of platinum-based chemotherapy Patients ineligible for cisplatin-based salvage treatment or high-dose chemotherapy and patients presenting with a late relapse after treatment failure of at least one cisplatin-based combination regimen in the late	GO study: gemcitabine 1000 mg/m2 was given intravenously (IV) over 30 min on days 1 and 8 of a 3-wk cycle, and oxaliplatin was administered as a 2-h infusion after gemcitabine at a dose of 130 mg/m2 on day. GOP study, gemcitabine was given at a dose of 800 mg/m2 as a 30-min infusion with paclitaxel 80 mg/m2 as a 1-h infusion on days 1 and 8 of a 3-wk cycle. Oxaliplatin was administered only on day 1 with 130 mg/m2 IV over 2 h. Premedication for paclitaxel with 20 mg dexamethasone IV and 50 mg diphenhydramine plus 300 mg cimetidine	no control	response rate. Tolerability progression-free and overall survival time	GO Study: Median overall survival for all 35 patients: 6 mo (range: 1–84 mo) for 16 patients responding to treatment: 15 mo (range: 6–84 mo) GOP-study: median progression-free survival time: 31 mo (range: ≥28–48 mo) Median overall survival for all 41 patients: 11 mo (range: ≥2–48 mo)		no funding no coi	LoE 4 SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
		relapse situation follow-up: 19 mo (range: 2–86 mo)	IV 20 min prior to infusion was mandatory			for 21 patients responding to treatment: 18 mo (range: ≥7–48 mo) 89% died Median overall survival for all 76 patients 8 mo (range: 1–84 mo) Median overall survival time: 17 mo (range: 6–84 mo) for the 37 patients showing any response to treatment			
Oing C 2015	retrospective database analysis International Prognostic Factor Study Group (IPFSG) database	GCT patients with Brain Metastases at first relapse	Salvage treatment CD-CTX in 35 (34 %)	Salvage treatment HD-CTX in 69 patients (66 %)	Median progression-free survival (PFS)	for the entire cohort: Overall response rate (ORR) to salvage chemotherapy: 68 %		no coi no information about funding	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
	n=1594 patients with unequivocal relapse or progression after at least three cycles of cisplatin-based first-line CTX 38 international centers	Median age of patients at initial GCT diagnosis: 30 yrs (range 16–53)			Median overall survival (OS) 1-year PFS 1-year OS	Median follow-up: 14 mo (range 1–161) n=73 patients (70 %) progressed at a median of 8 mo (range 1–161) n=62 patients (60 %) died at a median of 11 mo(range 1–95) for entire cohort (n = 104) median PFS: 8 mo (95 % CI 7–10) median OS: 15 mo (95 % CI 11–20) 1-yr PFS: 37% 1-yr OS: 59 % ORR: HD-CTX: 81% ORR: CD-CTX: 43 % p < 0.01			

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						complete remission CR: HD-CTX: 21% CD-CTX: 0 % p < 0.01 Median PFS: HD-CTX 9 mo (95 % CI 6–12) CD-CTX: 5 mo (95 % CI 3–7; p < 0.01). Median OS: HD-CTX: 18 mo (95 % CI 12–24) CD-CTX: 13 mo (95 % CI 8–18; p = 0.078) 1-yr PFS HD-CTX: 41%			

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						CD-CTX: 29% p = 0.23 1-yr OS HD-CTX: 19% CD-CTX: 65% p = 0.056			
Park S 2011	single-arm cohort study n=14 1998-2009 Korea median follow-up: 41.0 months (range 11.1–137.6)	relapsed or cisplatin-refractory patients median age: 26 years (range 19–60	salvage TIP: paclitaxel 175 mg/m2 administered by infusion over 3 h on day 1, ifosfamide 1,200 mg/m2 administered by infusion over 2 h on days 1–5, and cisplatin 20 mg/m2 given intravenously over 1 h on days 1–5	no control group	response rate defined as the proportion of patients with CR or PR (PR, PR–, PR+) PFS, OS toxicity	favourable response with TIP alone: n=5 (37.5%) (CR n=1, partial response (PR) n=4) CR with subsequent surgery: n=1 overall survival for all patients: 21.1 months (range 5.0–112.6)		no coi no information about funding	LOE 4 SIGN RoB (-) not acceptable

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						PFS only reported by case numbers, not cumulative toxicity: Neutropenia Grade 3: n=2 (14%) Grade 4: n=9 (64%) Thrombocytopenia Grade 3: n=5 (36%) Grade 4: n=3 (21%) Anemia Grade 3: n=3 (21%) Grade 4: n=4 (29%) Nausea/vomiting Grade 3: n=4 (33%) Grade 4: n=0			
Rice KR 2014	retrospective analysis of Indiana University testis cancer database	Germ cell tumors with somatic type malignancy	orchiectomy or subsequent resection	no control	CSS	5-year cancer specific survival: 64%		no information about funding	LoE 4

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	n=121 1979 – 2011 USA	Mean age (range) 28.36 ysr (15-54) median follow up: 71 mo			predictors for CSS	at median follow up of 66 months median CSS: 166 mo Predictors of poorer cancer specific survival: somatic type malignancy diagnosed at late relapse (p=0.017) referral to Indiana University for reoperative retroperitoneal lymph node dissection (p= 0.026) grade (p= 0.026)		no information about coi	SIGN RoB (+) acceptable
Schirren J 2012	single center single arm retrospective cohort study	patients who underwent intrathoracic residual tumor resection (RTR)	residual tumor resection (RTR)	no control	Survival overall survival OS	Mean survival: 86.6 ±2.6 months (95% CI 81.5–91.8)		no information about coi	LoE 4

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	n=124 Germany January 2000 - December 2006	for TNSGCT after Chemotherapy (CT) age 33.1 (± 8.4 yrs) median follow-up: 48.9 ±27.2 months (range, 1 to 98 mo)				5-yr-OS 87% 10-yr OS 85%		no information about funding	SIGN RoB (+) acceptable
Seidel C 2016	retrospective multicenter registry study n=63 Germany CH	patients with refractory GCC who received GOP because of progression under cisplatin-based treatment or relapse after high-dose CTX Median time of follow-up: 8.1mo	GOP Chemotherapy: gemcitabine, oxaliplatin, paclitaxel	no control	response rate, toxicity, progression-free and overall survival	grade III and IV toxicities in n=29 thrombocytopenia n=20, leukopenia n=17, anaemia n=9, infection n=4, polyneuropathy n =3 Complete remissions (CR):		Funding by Klaus Möller foundation no information about coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
		(range:0.03– 52.27)				n=8/61 (13%) Partial Remission: n=19/61 (31%) Overall Response rate ORR 44% stable disease: n=14/61 (23%) progression: 20/61 (33%) Median PFS: 4.0 mo (95% CI: 3.08–4.94) Median OS 13.3 mo (95%CI: 9.50–17.06)			

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Selle F 2014	Multicentric TAXIF II study (phase II trial) n=54 France September 2004 - December 2007	nonrefractory patients failing Cisplatin-based chemotherapy seminomatous GCT in relapse after two lines of chemotherapy nonseminomatous GCT in relapse after first or second lines, partial remission after first line, primary mediastinal GCT in first relapse. median follow-up time: 26 mo (range, 4–51)	Thiotepa (Thio-Tax) association and two using the 5-day Ifosfamide–Carboplatin–Etoposide regimen	no control	complete response rate	overall response rate ORR: 48.8% median progression-free survival (PFS) 22 mo [95% CI 2–not reached] overall survival (OS) 32 mo (95% CI 4–49) 2-year PFS was a plateau setup at 50% (95% CI 32–67) 2-year OS: 66% (95% CI 44–81)		no coi sponsored by Assistance Publique—Hôpitaux de Paris French Ministry of Health Bristol-Myers-Squibb Lab, 3, Rue Joseph Monier, 92500 Rueil-Malmaison, France—for the supply of Paclitaxel for the 45 patients (no grant numbers). · Baxter Lab, 6, Avenue Louis Pasteur, 78310	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp, Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung, Beobachtungs-zeitraum	Patienten-merkmale	Intervention	Kontrolle	Untersuchter Endpunkt	Ergebnis	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenz-stufe LOE RoB
								Maurepas, France —with a grant of 10 000 Euros (no grant numbers)	

9.4.10. Kapitel 11

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
Assi T 2015	single center retrospective cohort study n=244 1992 – 2014 F	germ cell tumors n=201	no intervention	no control	no information provided	no estimation of endpoints	50% seminomatous GCT 48% non-seminomatous GCT 2%s permatocytic seminoma subtype of non-seminomatous tumors: mixed germ cell tumors (63.9%) embryonal carcinoma (18.6%) teratoma (15.4%) yolk sac tumor (2.1%)		no information about coi or funding	LoE 4 SIGN RoB (-) not acceptable
Banerji JS 2016	retrospective cohort study of National Cancer Data Base n=79.120 1998 – 2011	n=315 (0.39%) primary malignant Leydig or Sertoli cell tumors	Orchiectomy, chemotherapy, RPLND, XRT XRT (external beam radiotherapy)	no control	no information provided	Overall survival OS	Stage I Leydig cell tumors 1 yr-OS 98% (95% CI 96-100) 5 yr-OS 91% (95% CI 85-96) Stage I Sertoli cell tumors		no information about coi or funding	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
	USA	median age: 43 yrs for both tumors n=250 (79%) malignant Leydig cell tumors n= 65 (21%) malignant Sertoli cell tumors					1 yr-OS 93% (95% CI 83-100) 5 yr-OS 77% (95% CI 62-95)			
Bozzini G 2013	multicenter retrospective clinical study n=22 1987 - 2006	Leydig cell tumor n=22 Mean age: 35 yrs (range, 5-61 years)	testicle-sparing surgery	no control	Mean follow-up: 180 mo (range, 77-290 mo)	DSS	disease-free survival 100%		no coi no information about funding	LoE 4 SIGN RoB (-) not acceptable

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	6 European centers									
De Latour B 2012	single arm retrospective cohort study n=21 (20 male, one female) France 1983 - 2010	primary mediastinal non-seminomatous germ cell tumours patients with high serumtumormarkers (STM) levels who underwent surgery with persistent STM elevation after chemotherapy and even those	first-line chemotherapy: n=16 BEP n=5 VIP Second-line chemotherapy: n=11 (52%) surgery before end of second line treatment n=10 After chemotherapy,	no control group	median follow-up: 98 months	OS disease-free survival adverse events	Overall survival: 1-year: 41% 5-year: 36% disease-free survival: 1-year: 38% 5-year: 33% adverse events: n=4 (19%) n=1 pneumonia n=1 mediastinitis requiring surgical debridement		Conflict of interest: none declared no information about funding	LOE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
		whose STM levels were lower after than before chemotherapy median age of 30 ys (range: 19–49 ys)	all 21 patients underwent aggressive surgery				n=2 need for prolonged mechanical ventilation (5 and 8 days) 5-yr- survival in patients with tumours confined to the mediastinum compared to patients with extra-mediastinal involvement: 50% vs. 27%; P = 0.320) 5-year survival: 42% with second-line chemo 30% without second-line chemotherapy treatment (P = 0.610)			
Dechaphunkul A 2016	single arm retrospective cohort study n=40 (one female)	mediastinal germ cell tumors n=7 seminoma	n=37 (92.5%) received chemotherapy as first treatment modality n=3 (7.5%) underwent upfront surgery	no control	median follow-up time for all patients: 13 months (range 1–132 months)	5-yr-OS	5-yr OS: seminoma: 71.4% non-seminoma: 27.3% (p = 0.051)		supported by the Faculty of Medicine, Prince of	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
	Thailand 2003-2013	n=33 non-seminoma median age at time of diagnosis: 24 years (range 15–52 years)	all patients received cisplatin-based chemotherapy: 87% BEP (bleomycin 30 mg intravenous (IV) days 1, 8 and 15; etoposide 100 mg/m2 IV days 1–5; cisplatin 20 mg/m2 IV days 1–5; every 3 weeks) 13% EP (etoposide 100 mg/m2 IV days 1–5; cisplatin 20 mg/m2 IV days 1–5; every 3 weeks)				5-yr OS: 72.7% for those who received chemotherapy followed by surgical resection with no viable tumor or only mature Teratoma 5 yr OS: 20.7% for those without surgical resection (p = 0.02)		Songkla University, Songkhla, Thailand no coi declared	

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Fedyanin M 2014	single arm retrospective cohort study n=61 Russia 1986 - 2011	mediastinal nonseminomatous germ cell tumors median age: 23 (18–44) ys	BEP regimen n = 27 (44.2 %) TBEP and CBOP regimen n = 34 (55.8 %) Secondary surgery: BEP-regime: n=8 (30 %) TBEP and CBOP regimen: n=20 (59 %) p=0.04	no control	Median follow-up for surviving patients was 60 months (range, 4–180)	overall survival OS	2-yr OS: 66 % without any of this factors (age <24 years and/or size of mediastinal tumor <19 cm) 2-yr OS: 40 % with at least one factor (age ≥24 years and/ or size of mediastinal tumor ≥19 cm) (p = 0.03, HR 0.4, 95 % CI 0.19–0.91) resection of residual tumor (59 %) versus (30 %) pts in BEP group (p = 0.04) 3-yr OS 46 % for all pts		no conflicts of interest no information about funding	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
							2- yr-OS: CBOP and TBEP regimen: 63% BEP-regimes: 35 % 5-yr OS: CBOP and TBEP regimen: 55% BEP-regimes: 21%			
Fukui N 2013	single arm retrospective cohort study n=13 Japan 1998 - 2011	extragonadal nonseminomatous germ cell tumors n=6 mediastinum n=7 retro-peritoneum	n=13 cisplatin or carboplatin-based chemotherapy as initial treatment n=7 post-chemotherapy surgery as a part of their primary treatment	no control	median observation time: 34 months (range, 0–150 months	5 yr-overall survival OS 5-yr-cancer specific survival CSS	5-yr OS: 62 % 5-yr CSS: 68 %		no coi funding not reported	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
		median age: 39 ys (range 16–48 ys)								
Ghazarian AA 2015	retrospective analysis of SEER database n=21.271 1992 – 2011 USA	Testicular germ cell tumors (TGCT)	no intervention	no control	1992 – 2011	incidence	n=12 419 seminomas n=8715 non-seminomas n=137 spermatocytic seminomas incidence of TGCT: non-Hispanic white men (6.97 per 100 000 man-years) American Indian/ Alaska Native (AI/AN; 4.66) Hispanic white (4.11)		supported by the intramural research program of the National Cancer Institute (NCI) no coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
							Asian/Pacific Islander (A/PI; 1.95) black men (1.20)			
Kowalski DM 2014	single arm retrospective cohort study n=5 (4 males, 1 female) Poland 1999 - 2009	germ cell tumour with primary location in the mediastinum median age 27.8 ys (range 23–30 ys)	chemotherapy according to the BEP regimen (3-6 cycles) combined with surgical treatment n=3 second line chemo n=3 third line chemo: n=1 radiotherapy n=3	no control	not reported	median survival time	median survival time: 55.8 mo (range 8.0–120.0)		no financial disclosure no coi	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
Kuwano H 2014	single arm retrospective cohort study n=11 (all male) Japan 1995 – 2011	primary mediastinal germ cell tumors n=4 seminomas n=7 non-seminomas median age: 20 ys (range 16–47 ys)	first line treatment: n=9 cisplatin-based chemotherapy n=8 (BEP) n=1 (EP) n=1 with seminoma: radiation (30 Gy in 15 fractions) after first lien treatment: n=10 surgery n=5 Postoperative chemotherapy (EP, BEP, 2-3 courses)	no controls	median follow-up: 56 mo (range 16–200 mo) mean observation period: 61.8 mo non-seminoma 106 mo seminoma	overall survival OS	3-yr-OS: seminoma: 100% non-seminoma 83 %		no coi funding not reported	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
Liu TZ 2011	single arm retrospective cohort study n=55 (52 male, 3 female) China 1988 - 2010	primary mediastinal germ cell tumor median age: 25 ys mean age: 23.67 ys in men 41.67 ys in women n=17 (30.9%) seminomatous tumors n=38 (69.1%)	Triple-modality therapy (surgery followed by chemotherapy and radiotherapy) n=6 (chemotherapy followed by surgery and radiotherapy) n=5 (chemotherapy plus radiotherapy) n=12 (surgery followed by chemotherapy) n=7 (chemotherapy followed by surgery) n=5 Chemotherapy alone: n=16	no controls	median follow-up: 31.4 months (0.43–172.6 months)	overall survival OS	5-yr survival rate: 52% Five-yr survival rate: pure seminomatous: 87% nonseminomatous: 33% p = 0.018		no coi funding not reported	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
		nonseminomatous tumors	surgery alone n=2 not receive any treatment owing to the poor performance status: n=2 n=51 chemotherapy 1 to 14 courses of chemotherapy given at 3-week intervals (mean of 4.92 courses) Initial chemotherapy regimens: doxorubicin plus vincristine plus bleomycin							

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			cyclophosphamide plus cisplatin plus doxorubicin cyclophosphamide plus etoposide plus cisplatin bleomycin plus etoposide plus cisplatin etoposide plus ifosfamide plus cisplatin							
Liu Y 2014	single arm retrospective cohort study n=54 (47 males, 7 females) China	Primary malignant mediastinal germ cell tumor average age: male 27 ys	surgical resections n=52 chemoradiotherapy n=2	no controls	no information about mean follow-up time	3-yr-OS 5 yr-OS	overall 5-year survival rate: mediastinal seminoma: 87.7%. overall 3 yr survival rates non-seminomatous 47.4%		no competing interests	LoE 2b SIGN RoB (-) unacceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
	1990 - 2009	female 28.6 ys n=18 seminoma n=36 non-seminomatous	basic treatment cisplatin-based chemotherapy n=22/52 n=6 preoperative radiotherapy After operation: n=42 patients cisplatin-based chemotherapy followed by radiotherapy n=14 n=5 radiotherapy only patients with seminomas: radiotherapy doses from 40 Gy to 50 Gy,				5- yr survival rates NSGCT: 23.0%			

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			patients with NSGCT: radiotherapy doses from 50 Gy to 54 Gy							
Makino T 2016	single arm retrospective cohort study n=14 (all male) Japan 1992 - 2014	extragonadal germ cell tumors (EGCT) n=9 mediastinum n=5 retro-peritoneum n=7 pure seminomas n=7 non-seminomatous	n=14 cisplatin-based combination chemotherapeutic regimens followed by a multimodal strategy that included high-dose chemotherapy (HDCT), aggressive surgery, and early salvage chemotherapy All patients received three to four courses of standard bleomycin, etoposide, cisplatin (BEP) regimen n=7	no controls	median follow-up duration: 30 mo (range=3-67 mo)	5 yr overall survival OS	5-yr OS: seminomatous EGCT: 100% non-seminomatous EGCT: 44%, (p=0.29) 5-yr OS: good- or intermediate-risk: 100% poor-risk group: 40% (p=0.18)		no information about conflicts of interest no information about funding	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
		primary tumor sites: n=9 mediastinum n=5 retroperitoneum Median age 27.5 ys (18-49)	underwent surgical resection after chemotherapy							
Nicolai N 2015	single center retrospective cohort study n=67 December 1982 - January 2013 Italy	n=55 (82.1%) Leydig cell tumor n=11 (16.4%) Sertoli cell tumor median age (IQR)	Testis Sparing Surgery TSS n=31	Radical Orchiectomy n=36	median follow-up: 37.4 mo (IQR, 12.6-82.9 mo)	relapse-free survival (RFS) cancer-specific survival (CSS)	total cohort: 5-year RFS: 89.4% (95% CI, 75.9%-95.5%) 5-yr-CSS: 90.3% (95% CI, 72.7%-96.7%) TSS 5-yr-RFS: 100%		no relevant financial interests no information about funding	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
		44 (32-50) yrs					5-yr-CSS: 100% Orchiectomy: 5-yr-RFS: 82.9 (95% CI 63.7-92.6) 5-yr-CSS: 86.2 (95% CI 62.9-95.4)			
Radaideh SM 2010	single arm retrospective cohort study n=158 PMNSGCT USA 1982 - 2007	primary mediastinal non-seminomatous germ-cell tumors with rising serum tumor markers (STM) following standard platinum-based chemotherapy	cisplatin-based chemotherapy or randomly assignment to an ongoing protocol Surgery to remove residual disease was carried out in all patients no further details about chemotherapy schedule and dose is reported	no controls	median follow-up: 64 mo	overall survival time relapse free survival	median OS time: 11.5 mo (range 2-220 mo) median overall relapse-free survival time: 3 mo (range 1-220 mo) median OS time for patients with viable tumor: 13.5 mo nonviable tumor: 12 mo		no conflict of interest no information about funding	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
		All patients had elevated STM [either alpha-fetoprotein (AFP) or human chorionic gonadotropin (hCG)] at the time of diagnosis n=35 (34 males, 1 female) median age: 27 ys (range 19–44 ys) n=24 (69%) with								

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		viable nonseminomatous germ-cell tumors (NSGCT) n=8 teratoma n=3 necrotic tissue								
Rodney AJ 2012	single arm retrospective cohort study n=34 (all men) USA 1998 - 2005	mediastinal extragonadal germ-cell tumors n=27 nonseminoma n=7 pure seminoma nonseminoma	as the first treatment regimen: n=27 (all) with mediastinal NSGCT: cisplatin-based chemotherapy thereof: n=17 (63%) BEP or etoposide plus cisplatin (EP) n=24 at least 1 course of	no control	median follow-up: 51.3 mo (range 22–110 mo)	overall survival	pure seminoma patients: all alive (100% OS) all free of disease at their last assessment (100% CSS) patients with second-line or salvage therapy: 3-year overall survival rate: 23%		Funding: National Cancer Institute at the National Institutes of Health [core grant CA16672) no information about coi	LoE 4 SIGN RoB (+) acceptable

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		Median age 30 ys (20–53) seminoma Median age: 32ys (20–60)	preoperative chemotherapy n=3 had undergone surgical resection or debulking initially n=11 (41%) with NSGCT: more than 4 courses of preoperative chemotherapy. n=19 (70%) with NSGCT: postchemotherapy resection of a residual mediastinal mass Salvage chemotherapy n= 18 with mediastinal NSGCT at primary treatment			Progression-free survival (PFS) Time to progression (TTP)	long-term PFS for newly diagnosed mediastinal NSGCT: 54% median TTP: Patients with high β-hCG concentrations: 10.8 mo			

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			mediastinal seminoma: BEP n = 1 EP n =5 Radiotherapy n = 1 n=1/7 with seminoma postchemotherapy resection of a residual mediastinal mass							
Rusner C 2013	9 federal cancer registries from Germany n=16.883 malignant GCTs Germany 1998-2008	male: gonadal germ cell tumors: n=10.549	no intervention	no control	1998-2008	Age-standardized incidence rates (cases per 1 million ASR: Age-standardized rate	GCT: n=10.549 annual percentage change (APC): 2.0% (95%CI 1.2 - 2.8) ASR: 54.4 extragonadal germ cell tumors		(DFG) [grant-number RU 1659/1-1]. Dr. Trabert was supported by the intramural research program of the National	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
							n=157 ASR: 0,9		Cancer Institute, NIH, DHHS	
Sarkaria IS 2011	single arm retrospective cohort study n=57 (one female, 56 male) USA July 1980 -April 2008	Primary mediastinal nonseminomatous germ cell tumors PMNGCT median age: 30 ys (range 18–50 ys)	n=54 preoperative chemotherapy with a combination of bleomycin, etoposide, and cis-platinum or etoposide, ifosfamide, and cis-platinum n=57 primary resection for PMNGCT	no control	median postoperative follow-up time : 5.3 ys (range 0–14 ys)	progression free survival (PFS) overall survival (OS)	2 yr PFS: 46% 2 yr OS: 56%		no conflicts of interest no information about funding	LoE 4 SIGN RoB (+) acceptable

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Stang A 2013	retrospective data base analysis 11 cancer registries of Germany U.S. (SEER-13 database) n=11,508 and 10,774 newly diagnosed cases 1997–2006 Germany USA	testicular germ cell cancer patients	no intervention	no control	2002-2006	5-year relative survival (5-year- RS) by histology and age	5-yr-RS for testicular germ cell tumors: 96.7% Germany 96.3% U.S. 5-yr-RS for spermatocytic seminoma: close to 100% in both countries 5-yr-RS: Germany: nonseminoma 93.3% classical seminoma 97.6% 5-yr-RS: U.S. nonseminoma 91.0% classical seminoma 98.2%		in part by a grant from the German Cancer Aid (Deutsche Krebshilfe), no. 108257 no information about coi	LoE 4 SIGN RoB (+) acceptable
Suleiman Y 2013	single-arm retrospective cohort study n=12	Primary Mediastinal Nonseminomatous Germ Cell Tumors	2 consecutive courses of HDCT: carboplatin 700 mg per square meter plus etoposide 750 mg per square meter,	no control	no information about median or mean follow up time	DFS time	median time from first relapse to institution of PBSCT: 7.5 mo (4-20 mo)		no conflict of interest	LoE 4 SIGN RoB (+)

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	USA 2006-2008	Median age: 29 ys (18-44 ys)	each for 3 consecutive days. Both carboplatin and etoposide were given i.v. 5, 4, and 3 days before the infusion of peripheral-blood stem cells. second cycle of HDCT was given 3 to 4 weeks after initiation of the first course Patients with a resectable residual mass after HDCT were offered surgery. Salvage surgery (Resection of mediastinal mass) (before HDCT) n=8 (67%) followed by an infusion of autologous				Median progression-free survival from first day of HDCT: 4 mo (range, 0-50 mo) median survival: 11 mo (range, 5-52 mo)		no information about funding	acceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
			peripheral-blood hematopoietic stem cells with a second course 3 to 4 weeks later							
Wang JL 2012	single arm retrospective cohort study n=39 China 1991 - 2007.	Primary malignant germ cell tumors of mediastinum median age: 27 ys n=18 patients (46.2%) Seminoma n=21 (53.8%) nonseminomatous germ cell tumors	five types of chemotherapy: BEP: n=15 (38.5%) VIP: n=10 (25.6%) EPn=11 (28.2%) CE: n= 2 (5.1%) CAPn=1 (2.6%) median cycles of chemotherapy: n=4 (range 2 to 6) Radiation treatment: Co-60 or linear accelerator with a dose range of between 20 Gy and 61	no controls	median follow-up: 5.2 ys average follow-up period: 12 ys	5 yr-OS PFS	all patients: 5-yr overall survival (OS): 60.2% progression-free survival (PFS): 57.7% 5-yr OS: Seminoma: 87.4% NSGCTs: 36.7% P=0.0004 5-yr PFS rate: Seminoma: 87.4% NSGCTs:31.6% P=0.003		no information about funding no coi	LoE 4 SIGN RoB (-) unacceptable

Referenz (Autor, Jahr)	Studientyp Gesamt-Fallzahl n, Land, Zeitraum der Datenerhebung	Patienten merkmale	Intervention Pro Arm: Anzahl der Patienten in der Interventions-gruppe Anzahl der Patienten in der Kontrollgruppe	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemerkungen Besonderheiten aus der RoB-Bewertung	Finanzierung COI	Evidenzstufe LOE RoB
			Gy Median dose of 41 Gy, at 1.8–2.0 Gy per fraction per day, 5 days per week. Median dose of 36 Gy and 50 Gy were given in patients with seminoma and NSGCTs, respectively. Seminoma: 17/18 patients chemotherapy followed by radiotherapy Nonseminoma: 15/21 patients surgical resection and 6 patients initially received chemotherapy							

9.4.11. Kapitel 11: Diagnosestudien

Referenz (Autor, Jahr)	Studientyp	Patientenmerkmale	potentieller prognostischer Faktor Definition/ Beschreibung Messung	Endpunkt	statistische Analyse univariat multivariat	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemer-kungen	Finanzierung COI	Evidenzstufe LOE RoB
Alanee SR 2014	retrospective database study (SEER-database) n= 37.283 USA 1973-2008	n=17.715 nonseminomatous n=19.568 seminomas n= 824 (2%) mediastinal GCTs n= 1.469 (4%) nonmediastinal extragonadal tumors (94%) with gonadal GCTs	risk for cardiovascular, hematopoietic malignancies, and solid cancer-related causes of death	hematopoietic malignancies, and solid cancer	univariate analysis Multivariate analysis	Mediastinal Hematopoietic malignancies HR 8.84 95% CI 3.14–24.73 p<0.0001 Cardiovascular disorders HR 4.49 95% CI 2.52–8.02 p<0.0001 Solid cancers HR 1.46 95% CI 0.36–5.90 p=0.59 Nonmediastinal extragonadal Hematopoietic malignancies HR 0.93		no coi Supported by the Sidney Kimmel Center for Prostate and Urologic Cancers	LoE 4 low risk of bias (Quips-Tool)

Referenz (Autor, Jahr)	Studientyp	Patientenmerkmale	potentieller prognostischer Faktor Definition/ Beschreibung Messung	Endpunkt	statistische Analyse univariat multivariat	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemer-kungen	Finanzierung COI	Evidenzstufe LOE RoB
						95% CI 0.13-6.84 p=0.94 Cardiovascular disorders HR 2.75 955 CI 1.67-2.51 p<0.0001 Solid cancers HR 1.85 95% CI 0.68-5.01 (p=0.23)			
Buchler T 2012	single-arm retrospective cohort study n=36 Czech Republic 1994-2010	Primary extragonadal germ cell tumors Median age at diagnosis: 35 ys (range 18-66 ys)	baseline characteristics: age, presence/absence of constitutional symptoms, mediastinal versus non-mediastinal primary, seminoma versus nonseminoma, presence/ /absence of choriocarcinoma histology, LDH elevation, AFP elevation, HCG elevation, S stage, bulky tumor, lung	positive FGD-PET as predictor for survival (OS)	Kaplan Meier curves cox proportional hazards model	None of the patients who had positive FDG-PET findings after 1st line chemotherapy survived at three years after diagnosis OS=0% Negative FDG-PET after completion of treatment: 3-ys-OS: 100% 5-ys-OS: 89%		Supported by grant G9005 (NS10420-3/2009) from the Department of Health, the Czech Republic. no coi	LoE 4 moderate Risk of Bias Quips-Tool

Referenz (Autor, Jahr)	Studientyp	Patientenmerkmale	potentieller prognostischer Faktor Definition/ Beschreibung Messung	Endpunkt	statistische Analyse univariat multivariat	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemer-kungen	Finanzierung COI	Evidenzstufe LOE RoB
			involvement, liver involvement, and presence/absence of residual mass resection. post-treatment results: FDG-PET response after first-line of therapy, FDG-PET response after completion of therapy, marker response after first-line of therapy, marker response after the completion of therapy, retroperitoneal nodal dissection as a part of treatment.			no HR reported			
Necchi A 2015	single arm retrospective cohort study n=86	Primary mediastinal germ cell tumors mean age: 29.8 ys (range, 15-63)	Patient, disease, and outcome characteristics: histologic subtype, type of elevated marker at diagnosis, presence of a mediastinal syndrome	overall survival (OS)	Cox proportional hazards regression analysis	final multivariate model for OS: presence of lung metastases (HR, 3.03; 95% CI, 1.12-8.15; P = 0.028) combination of surgery with histology		no coi no information about funding	LoE 4 high risk of bias

Referenz (Autor, Jahr)	Studientyp	Patientenmerkmale	potentieller prognostischer Faktor Definition/ Beschreibung Messung	Endpunkt	statistische Analyse univariat multivariat	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemer-kungen	Finanzierung COI	Evidenzstufe LOE RoB
	1985 -2012 Italy		(discernible only for cases with face or arm swelling reported on charts) and site of distant metastases, if present.	HR (95% CI)		viable cancer vs. necrosis and/or Teratoma: (HR 6.17; 95% CI 1.31-29.00; p= 0.021) necrosis and/or teratoma No versus yes: (HR 11.06; 95% CI 2.28-53.56; p=0.003) 5-yr-OS: No Surgery and Presence of Lung Metastases 25.0% (95% CI 7.5-83.0) No Surgery and Absence of Lung Metastases 37.5% (95% CI 19.0-73.8) Surgery, Viable Cancer and Presence of Lung Metastases 25.4% (95% CI 7.7-83.8)			Probast-Tool

Referenz (Autor, Jahr)	Studientyp	Patientenmerkmale	potentieller prognostischer Faktor Definition/ Beschreibung Messung	Endpunkt	statistische Analyse univariat multivariat	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemer-kungen	Finanzierung COI	Evidenzstufe LOE RoB
						Surgery, Viable Cancer and Absence of Lung Metastases 60.6% (95% CI 36.8-99.8) Surgery, necrosis and/or teratoma and Presence of Lung Metastases 75.0% (95% CI 42.6-100.0) Surgery, necrosis and/or teratoma and Absence of Lung Metastases 87.5% (95% CI 67.3-100.0)			
Rivera C 2010	single arm retrospective cohort study n=31 (2 female) 1986-2009 France	primary mediastinal germ cell tumors median age: 28 ys (range: 16–60 years)	age, sex, tumor histological type, extent of disease at diagnosis, tumor markers concentrations at diagnosis (bHCG), tumor marker grouping , normalization of markers after first-line chemotherapy, surgical resection of the tumor, pathological evidence of persistent viable	5-yr-OS	Univariate analysis Multivariate analysis	multivariate analysis 5-yr-OS: surgical resection of the tumor OR 5.10; 95% CI 1.49–17.45; P=0.009 HR not reported		no information about coi and funding	LoE 4 low risk of bias: Quips Tool

Referenz (Autor, Jahr)	Studientyp	Patientenmerkmale	potentieller prognostischer Faktor Definition/ Beschreibung Messung	Endpunkt	statistische Analyse univariat multivariat	Effekte inkl. Richtung des Effektes pro Outcome dargestellt und Unerwünschte Wirkungen	Bemer-kungen	Finanzierung COI	Evidenzstufe LOE RoB
			cancer in resected tumor			5-yr-OS: surgical treatment: 65.6% no surgical treatment 25%			

9.4.12. Kapitel 12

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
Aparicio J 2014	retrospective cohort study n=744 1994 and 2008 Spain	CS I Seminoma	Low-risk: surveillance	high-risk: two courses of adjuvant carboplatin	Median follow-up time from orchiectomy: 80 mo (range, 24–204 months)	relapse Cause-specific disease-free survival (DFS) incidence of contralateral germ-cell tumors	relapse: on active surveillance n=51/396 (14.8%) after adjuvant carboplatin n=12/348 (3.2%) Actuarial overall DFS 5 yrs 92.3% Actuarial overall DFS 10 yrs 90.7% Median time to relapse: 14 mo predictive factors for relapse: rete testis invasion (P < 0.001) tumor size (P = 0.052)	no coi no information about coi	LoE 2b SIGN RoB (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
Chung P. 2015	prospective multi center cohort study 1998 - 2005 n=658 DK CA	stage I seminoma n=685 median age: 36 yrs (range = 16–82) median tumor size: 3 cm (range = 0.2–13)	surveillance	no control	median follow-up: 3.85 yrs (range = 0.1–10.29)	time to relapse relapse free survival	actuarial relapse-free rate: 3 years: 86.3% 5 years: 85% Median time to relapse: 12 mo (range = 3.7–116 mo) multivariable analysis: risk of relapse: primary tumor size ≥3 cm: HR 1.87 (95% [CI] 1.15–3.06) P = 0.01 rete testis invasion: HR 1.36 (95% CI 0.81–2.28) P = 0.25	No funding information provided no coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
De La Pena, HA 2017	descriptive database analysis n=1447 with a confirmed diagnosis of testicular cancer (886 seminomas, 561 non-seminomas) 2003 – 2015 n=164 confirmed relapses United Kingdom UK	Median age at diagnosis: 34 yrs (11-86)	no intervention	no control	2003-2015	Modality of relapse detection	Modality of relapse detection. **CT scan** Seminomas 84% (n=70) Non-seminomas 62% (n=47) **Tumour markers** Seminomas 15% (n=12) Non-seminomas 38% (n=29) **CXR** Seminomas 0% (n=0) Non-seminomas 0% (n=0) **MRI** Seminomas 1% (n=1) Non-seminomas 0% (n =0)	nop coi no information about funding	LoE 4

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
Fischer S 2017	retrospective multi center cohort study n=185 31 centers/groups from 20 countries 1987 – 2013	CSI seminoma and a relapse after one or two cycles of adjuvant carboplatin Median age (range), 38 yrs (19-68)	adjuvant carboplatin: One cycle: 147 of 183 (80%)	adjuvant carbo Two cycles: 36 of 183 (20%)	median follow-up: 53 months (95% CI, 48 - 60 months)	Primary end points: overall survival (OS) disease-free survival (DFS) Secondary outcomes: time to relapse, stage at relapse, management strategies chosen, rates of subsequent relapses	5-yr disease-free survival: 82% (95% CI, 77% to 89%), 5-yr overall survival: 98% (95% CI, 95% - 100%) median time from orchiectomy to relapse: 19 mo (95% CI, 17 - 23 mo) relapses after 3 yrs: 15% (95% CI, 10% - 21%)	Supported by the Swiss Cancer Foundation. AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST: Matthew Wheater: Honoraria: Bristol-Myers Squibb, MSD, Pfizer, GlaxoSmithKline, Novartis Consulting or Advisory Role: Roche, Novartis, MSD, Pfizer Research Funding: Roche, GlaxoSmithKline, Novartis	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
								Travel, Accommodations, Expenses: MSD, Bayer AG Emilio Porfiri Consulting or Advisory Role: Novartis, Bristol-Myers Squibb, Pfizer Speakers' Bureau: Novartis, Bristol-Myers Squibb, Pfizer Research Funding: Novartis, GlaxoSmithKline (Inst) Travel, Accommodations, Expenses: Astellas Pharma Aude Fl´echon Honoraria: Sanofi, Pfizer, AstraZeneca, Janssen Pharmaceuticals, Astellas	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
								Pharma, Novartis Travel, Accommodations, Expenses: Novartis, Pfizer, Sanofi, Janssen Pharmaceuticals, Astellas Pharma, MSD Umberto Basso Consulting or Advisory Role: Pfizer, Sanofi, Novartis Travel, Accommodations, Expenses: Pfizer, Sanofi, Janssen Pharmaceuticals, Bristol-Myers Squibb Jonathan Shamash Research Funding: Chugai	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
								Pharmaceutical Travel, Accommodations, Expenses: Bayer AG Anja Lorch Honoraria: Astellas Pharma Travel, Accommodations, Expenses: Novartis Edurne Arriola Honoraria: Eli Lilly Patents, Royalties, Other Intellectual Property: European patent office Travel, Accommodations, Expenses: AstraZeneca Kalena Marti Travel, Accommodatio	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
								ns, Expenses: Servier, Pharmacyclics Brigitte Laguerre Honoraria: Novartis, Pfizer Travel, Accommodations, Expenses: Pfizer, Novartis Silke Gillessen Honoraria: Janssen Pharmaceuticals (Inst), Novartis (Inst) Consulting or Advisory Role: AAA International (Inst), Active Biotech AB (Inst), Astellas Pharma (Inst), Bayer, Bristol-Myers Squibb (Inst), Curevac	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
								(Inst), Dendreon Corporation, Ferring (Inst), MaxiVAX SA, Millennium Pharmaceuticals, Orion, Roche (Inst), Sanofi Patents, Royalties, Other Intellectual Property: Patent application for a method for biomarker WO 2009138392A1	
Janssen-Heijnen MLG 2010	retrospective database study n=8693 (Testicular cancer patients) 1985-2004	testicular patients localized regional metastasized	all therapies		5 yrs after diagnosis 10 yrs after diagnosis	conditional relative survival at 5 yrs at 10 yrs	**at 5 yrs:** age:15-29 100% (95% CI 99 – 100) age: 30-44 99% (95% CI 99 – 100)	grant from the Muntendam Award (2005) of the Dutch Cancer Society (J.-W.W.C.), by the German	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
	Europe						age:45-54 98% (95% CI 96 – 101) age:55-64 98% (95% CI 93 – 102) **at 10 yrs:** age:15-29 99% (95% CI 98 – 100) age: 30-44 100% (95% CI 99 – 100) age:45-54 97% (95% CI 94 – 100) age:55-64 98% (95% CI 90 – 107) Although patients with metastasized disease had a significantly poorer survival at	Cancer Aid (H.B.), and by the European Commission (Directorate General for Health and Consumer Affairs, Luxemburg) for the European Network for Indicators on Cancer (EUNICE) no coi	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
							diagnosis compared with those with localized or regional disease, **this difference disappeared after having survived for 3 years**		
Ko JJ 2016	retrospective database study N=942 1990-2012 5 centres: CA, USA, AUS	Testicular cancer patients with CS II ,CSIII Median age: 31 (range, 4 -89) yrs IGCCCG: Favourable: n=602 (64%) Intermediate: n=181 (19%) Poor: n=154 (16%) Unknown: n=5 (<1)	n= 879 first-line chemotherapy 85% received bleomycin, etoposide, and cisplatin VIP: 3% VeIP: 1% EP: 10% Others: 1%	n=54 either primary or additional radiation therapy	Median follow-up time still alive: 99 months (interquartile range, 57 to 141 months)	2-year conditional overall survival (COS), 2-year conditional disease-free survival (CDFS) time points at 0, 6, 12, 18, 24, 30, 36 months	**2-yr COS:** Time Since Diagnosis (months) 36 mo: All: 99% (95% CI 98 -99) Favourable: 99% (95% CI 98 -100) Intermediate 99% (95% CI 97- 100) Poor 97% (95% CI 93 – 99)	Christopher J. Sweeney: Stock or Other Ownership: Leuchemix, BIND Biosciences Consulting or Advisory Role: Sanofi, Janssen Biotech, Astellas Pharma, Bayer, BIND Biosciences, Genentech, AstraZeneca Research Funding: Janssen Biotech (Inst), Exelixis (Inst), Astellas Pharma	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
							p=0,19 **2-yr CDFS:** Time Since Diagnosis (mo) 36 mo: All: 98% (95% CI 97 – 99) Favourable: 98% (95% CI 97- 99) Intermediate: 98% (95% CI 96 -100) Poor: 99% (95% CI 96 -100) p=0,97	(Inst) Patents, Royalties, Other Intellectual Property: Leuchemix, Parthenolide, Dimethylaminoparthenolide. Exelixis: Abiraterone plus cabozantinib combination Philippe L. Bedard Daniel Y.C. Heng: Consulting or Advisory Role: Pfizer, Novartis, Bristol-Myers Squibb, Janssen Pharmaceuticals, Astellas Pharma	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
								all other authors: no coi no information about funding	
Mortensen MS 2014	retrospective, population-based study n = 1954 1984 - 2008 DK	CS I Seminoma Age, yr, median (range) 37 (16–82) Tumor size, cm, median (range) 3.5 (0.1–15)	surveillance	no control	Median follow-up time: 15.1 yr (range: 0.6–28.7 yr)	Disease-specific survival (DSS), overall survival, relapse rates, time to relapse, detection of relapse, prognostic factors	relapse rate: 18.9% after a median 13.7 mo relapses first 2 yr after orchiectomy: 73.4% (271 of 369) relapse between years 3 and 5: 22.2% (82 of 369) relapse>5 yr after orchiectomy 4.3% (16 of 369) 5 yr OS: 98.1% 10 yr OS: 95.5% 15 yr OS: 91.6%	grants from the Danish Cancer Society, The Danish Cancer Research Foundation, and the Preben & Anna Simonsen Foundation no coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
							5 yr DSS: 99.6% 10 yr DSS: 99.4% 15 yr DSS: 99.3% prognostic factor: tumor size: HR 1.59 (95% [CI] 1.31–1.92)		
Nayan M 2017	single arm retrospective cohort study n=1239 1980 – 2014 CA	**CS I testicular cancer patients** **CSI NSGCT** n=464 n=74 (15,9%) pure Embryonal Carcinoma (EC) on orchiectomy pathology n=121 (26,1%) CSI B disease	all managed with surveillance		**CSI NSGCT:** Median follow-up among those without relapse was 60.6 mo (interquartile range 34.1–99.1) **CSI SGCT** Median follow-up among those without relapse: 88.4 mo (interquartile	**2-yr-cRR** **conditional risk of relapse**: **5-yr-cRR** **conditional risk of relapse**: **CSI NSGCT** stratified by clinical stage at presentation and pure EC on orchiectomy pathology	**2-yr-cRR** **conditional risk of relapse**: **CSI NSGCT** without relapse at 60 mo: CSI A without pure EC 0,0% CSI A with pure EC: 8,0% CSI B without pure EC: 5,0%	no coi no funding	LOE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
		CSI SGCT n = 775			range 52.1–122.1)	**CSI SGCT** stratified by tumour size on orchiectomy pathology	CSI B with pure EC: 0,0% **5-yr-cRR** **conditional risk of relapse**: **CSI NSGCT** CSI A without pure EC 0,0% CSI A with pure EC: 8,0% CSI B without pure EC: 5,0% CSI B with pure EC: 0,0% **2-yr-cRR** **conditional risk of relapse**: **CSI SGCT:**		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
							Time without relapse after orchiectomy 60 mo Tumor size >3 cm 1,6% Tumor size < 3 cm 0,0% **5-yr-cRR** **conditional risk of relapse**: **CSI SGCT** Time without relapse after orchiectomy 60 mo Tumor size >3 cm 2,7% Tumor size < 3 cm		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
							0,0%		
Shinn EH 2010	cross sectional study n=162 TCS n=74 age-matched male relative controls n ranged from 1.123 to 9.775 an age-, sex-, education-, and income-matched population-based control group January 2000 - June 2002 USA, FL	Mean age 37.2 Mean age 38.5 (controls) Time since treatment: 4.5yrs Type Seminomatous n=53 (33%) Nonseminomatous n=109 (67%) Stage at diagnosis I n=50 (31%) II (A/B/C) n=58 (36%) III n=15 (9%)	no intervention measuring health behaviour	measuring health behaviour	time of data collection: 2 to 10 years postdiagnosis	health behaviour	Survivors Versus Age-Matched Relative Controls Check cholesterol in past year OR1.31 (95% CI 0.66 to 2.62) Smoker *v* former/never smoker OR 0.97 (95% CI 0.24 to 1.70) At least one problem drinking episode *v* none OR 0.89 (95% CI 0.0018 to 1.79) **Physical activity (dichotomized)** **OR 1.98 (95% CI 1.08 to 3.63)** 5 or more fruits and vegetables a day	Financial support: Karen M. Basen-Engquist Honoraria: Philippe E. Spiess, UpToDate Research Funding: None	LoE 3b

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
							OR 1.111 (95% CI 0.0277 to 1.77) Drink in the past month? (yes/no) OR 1.41 (95% CI 0.32 to 2.51) Log (average number of drinks); restricted to those who drink OR 0.059 (95% CI 0.33 to 0.45) Survivors Versus CDC Controls: Check cholesterol in past year OR 1.54 (95% CI 0.88 to 2.21) Smoker *v* former/never smoker OR 0.817 (95% CI 0.45 to 1.18) **At least one problem drinking** **episode versus none** **OR 2.05 (95% CI 1.27 to 2.83)**		

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patienten-merkmale	Intervention	Kontrolle	Beobachtungs zeitraum	Endpunkt	Effekte	Finanzierung COI	Evidenzstufe LOE RoB
							Physical activity (dichotomized) OR 1.00 (95% CI 0.67 to 1.33) **5 or more fruits and vegetables a day** **OR 0.48 (95% CI 0.23 to 0.73)** Drink in the past month? (yes/no) OR 1.35 (95% CI 0.84 to 1.86) Log (average number of drinks); restricted to those who drink OR 0.34 (95% CI 0.12 to 0.56)		

9.4.13. Kapitel 13

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
Bamias A 2011	single-arm retrospective cohort study n=142 October 1994 – December 2004 Greece	NSGCT I high risk inclusion criteria: at least 1 of the following risk factors: LVI in the tumour specimen, embryonal carcinoma >50% of the tumour, invasion of tunica vaginalis, spermatic cord, rete testis, or scrotal wall	2 cycles bleomycin/etoposide/cisplatin n=142	without control group	median follow-up time: 79 months (range 2-155)	relapse mortality toxicity	Relapse n=1 CSS:n=0 Grade 3 toxicities n/% Anemia 1 (0.6%) Thrombocytopenia 3 (2%) Neutropenia 8 (6%) Nausea/vomiting 10 (7%) Alopecia 77 (54%) Infection 3 (2%) Grade 4 toxicities n/% Neutropenia 7 (5%)		no information about funding no information to COI	LOE 4 RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
Chau C 2015	single arm retrospective Cohort study n=517 1996-2013 UK	Seminom CSI Median age at diagnosis: 38 years (range 18–73 years)	Carboplatin single dose of adjuvant AUC7 dose was calculated on radioisotope measured glomerular filtration rate (GFR) uncorrected for body surface area using the Calvert formula		Hospital median follow-up: 3.9 years (range 0–17.8 years). Virtual median follow-up: 6.5 years (range 0.3–17.8 years)	RFS (5 yr) OS CSS incidence of contralateral GCT incidence of secondary malignancies	5 yrs relapse free survival (RFS) 95.0% (95%CI 92.8% - 97.3%) CSS: 100% 5 ys OS: 99% (n=511 von 517) metachronous CTGCT: n =17/517 (3.3%) (9 seminoma, 8 non-seminoma) during follow-up median time to CTGCT of 8.8 years (range 0.8–22 years) secondary malignancy n= 6/517 (1.2%) (plasmacytoma, renal cell carcinoma, GIST, rectal cancer,		no conflicts of interest no information about Funding source	LOE 4 RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
							malignant melanoma, mantle cell lymphoma)			
de Haas EC 2013	retrospective two arm single center cohort study n = 439 n=1085 controls 1977 - 2004 NL	disseminated nonseminomatous TC Age at start chemotherapy (years) Median (range) study I: 28 (16–64) study II: 28 (16–52)	platinum-based chemotherapy < April 2004 n=370 study I n=173 study II	PREVEND-study-participants n=1085	Follow-up duration (years) Median (range) study I: 12 (3–29) study II: 5 (3–20)	cardiovascular risk factors metabolic syndrome	prevalence of risk factors: BMI >27.8 kg/m2 85/359 (24%, new in 15% of the patients compared with prechemotherapy), hypercholesterolemia 87/361 (24%, new in 14%), hypertension 106/359 (30%, new in 23%) Median time for development of BMI >27.8 kg/m2 is 1.7 years (range 0.2–28.4),		Dutch Cancer Society (grant RUG 2004–3157). no coi	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
		Age at end follow-up (years) Median (range) study I: 42 (19–73) study II: 37 (19–59)					for hypercholesterolemia 0.9 years (range 0.2–22.4), for hypertension 5.1 years (range 0.2–21.2) median follow-up: 5 years (range 3–20) age: 37 yrs (range 19–59), prevalence of the MS: 44/173 (25%) component of MS: (59%), low HDL cholesterol (44%), high triglycerides (29%), central obesity (17%), high glucose levels (14%)			

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
							increased risk of MS of TC survivors compared with general population OR 2.2 [95% CI 1.5–3.3]			
Domont J 2013	two-arm-retrospective cohort study 1980-2001 n=67 France	CS IIA Seminoma CS IIB Seminoma CS IIC Seminoma mean age: 40 (23-64)	radiation n=37 CS IIA, CSIIB: n=33 CS IIA n=5 CS IIB <3cm n=19 CSIIB >3cm n=9 CSIIC n=4 megavoltage radiation (4 to 20 MV) with antero-posterior parallel	chemotherapy n=30 but: CSIIA and CSIIB: n=3 CSIIB<3cm: n=1 CSIIB>3cm: n=2 CSIIC: n=27	median follow-up: 9.4 yrs	relapse rate time to relapse 5-yr-Overall Survival (OS) toxicity second neoplasms	relapse rate: radiotherapy 30% chemotherapy 27% median time to relapse: 13,5 months (3-51) 5-yr OS: chemotherapy 88% (CI 95%: 53–98) radiotherapy 82% (CI 95%: 52–95)	no different analysis for tumour stages	no information about coi no information about funding	LOE 2b RoB SIGN (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
			opposed fields, at a dose of 2 Gy per fraction per day over 5 days per week only the ipsilateral pelvic lymph nodes with a “dog-leg” technique and the para-aortic nodes up to the T9-T10 vertebral level. total dose of 20 Gy was delivered over 2 weeks to the para-aortic and pelvic lymph nodes, with a boost dose of 16 Gy in 8 fractions to involved para-aortic				P= 0.83 immediate toxicity radiation Grade 1, 2, and 3 nausea: 46%, 46%, 8% Grade –2 diarrhoea: 51% late toxicity: chemotherapy: Fertility disorders (n=2) pulmonary fibrosis (n=1) mild elevation of serum creatinine (between 120 and 140 µmol/l) (n=2)			

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
			lymph nodes. Prophylactic mediastinal or supraclavicular radiotherapy (20 Gy over 2 weeks) was delivered for stage IIB and IIC (22 patients, 59%) until 1992.				second tumor, after follow-up of 5, 9, 20 yrs second cancers radiotherapy n=3 for stage II seminoma, (colorectal carcinoma, duodenal cancer, medullary thyroid carcinoma) second cancers: chemotherapy n=2 (colorectal and esophageal carcinoma)			
Fung C 2013	population based cohort study n=12.691	Median age at diagnosis: 28.8 yrs 94.2% white	Initial Surgery Only (no RT) n=6.678	no control	1980 - 2008	second cancer risk	SIR: 0.93; 95% CI, 0.76 - 1.14; n=99 solid cancers followed management with surgery		no coi	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
	USA 1980 – 2008		n=6.013 chemotherapy			SIR standardized incidence ratio	SIR: 1.43; 95% CI, 1.18 - 1.73; n=111 solid cancers occurred after chemotherapy nonseminoma with chemotherapy kidney (SIR, 3.37; 95% CI, 1.79 to 5.77), thyroid (SIR, 4.40; 95% CI, 2.19 to 7.88), soft tissue (SIR, 7.49; 95% CI, 3.59 to 13.78) site-specific risks of solid cancers after surgery: kidney cancer (SIR, 2.14; 95% CI, 1.07 to 3.84)		Financial support: Chunkit Fung	

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							site-specific risks of solid cancers after chemotherapy: bladder (SIR, 4.01;95%CI, 1.61 - 8.26;n=7) kidney (SIR, 4.52;95%CI, 1.81 to 9.31; n=7) occurred at 10-19 ys			
Gilbert ES 2017	pooled analysis study n=327 cases n=678 controls Hodgkin lymphoma, testicular cancer, cervical cancer Denmark, Sweden,	testicular cancer n=86 cases n=174 controls mean age of 5-yr-survivors: 39,4 ys (18,3-71,8)	external beam radiotherapy mean radiation dose: 24,7 Gy (0,39-59,1) treatment time of radiation: 1953-1992		mean time between first cancer and stomach cancer: 17,9 ys	risk for radiation related stomach cancer Excess Odds Ratio (EOR)	dose-response relationship: EOR/Gy 0.27 95% CI 0.054–1.44		supported in part by the intramural research program of the NIH and the NCI	LoE 3a Moderate RoB

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	Norway, Finland, Canada, USA, Netherlands									
Gizzy 2016	retrospective four arm cohort study n=204 2001-2014 France	GCT seminoma or non seminoma with first line chemotherapy (BEP and EP regimes)	n=146 with risk factor elevated LDH and/or BSA>1,9 low molecular weight heparin LMWH or no prevention	n=58 without risk factors low molecular weight heparin LMWH or no prevention	from the first day of chemotherapy to 6 months after the last cycle of chemotherapy	TEE thrombo embolic event deep or superficial venous thrombosis, or any arterial thromboembolic complication	TEE: DVT or arterial thrombosis: n=26 (13.0%) of patients with risk factors n=2 (2.5%) of pts with no risk factors (p = 0.01) incidence of TEE: (9.2% in at risk patients receiving LMWH versus 16.6% in at risk patients not receiving LMWH, (p = 0.23), OR 0.50 (0.22; 1.13;		none declared no information about funding	LOE 2b RoB SIGN (+) acceptable

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							p =0.09)			
Hallemeier CL 2013	single arm retrospective cohort study n=52 1974-2007 USA	CS II Seminoma median age at diagnosis: 36 ys (22-71)	radiation Megavoltage external beam RT para-aortic lymph nodes ± pelvic lymph nodes with anterior- posterior (AP) and posterior-anterior (PA) fields median infradiaphragmatic RT dose 30.7 Gy	no control group	median follow up: 19 ys (0.4 – 37)	Overall survival (OS), relapse-free survival (RFS), cause-specific survival (CSS) second malignancy (SM)	10 ys-OS 94% 20 ys-OS 83% 10 ys- OS: IIA: 96% IIB: 83%, IIC: 94% II NOS: 100% (log-rank P=0.46) 10-ys-RFS IIA: 83% IIB: 54%		no information about coi no information about funding	LOE 4 RoB SIGN (+) acceptable

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							IIC: 81% II NOS:100%, P=0,21 10 ys-CSS 96% 20 ys CSS 96% 10 ys CSS IIA: 100% IIB: 83% IIC: 94% II NOS: 100% Major cardiac event (MCE) n=10 19% at a median of 18 years (range 7–30) after RT.			

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							median age at time of MCE: 53 years (range, 34 – 76) First MCE: myocardial infarction (n=7), valve replacement (n=2), coronary artery stent placement (n=1) second malignancies (SM): SM n=5 (10%) at a median of 27 years (range 20–34) after RT SM: esophageal adenocarcinoma (n=2), periampullary adenocarcinoma (n=1),			

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							retroperitoneal undifferentiated neoplasm (n=1), papillary thyroid cancer (n=1)			
Haugnes HS 2012	three-arm- prospective cohort study n=882 1995-2007 Sweden, Norway	poor prognosis patients n=138 median age poor responders: 29 ys (18-56) A) patients with poor response to treatment intensification step 1 (slow marker decline,	poor response to treatment: n=29 with slow marker decline slow tumor marker decline (HCG $T_{1/2}$ >3 days, AFP $T_{1/2}$ >7 days) after two BEP high dose chemotherapy: first HDCT cycle:		Median follow-up 7.5 years (range 0 – 14).	overall survival (OS), failure-free survival (FFS) observation time acute toxicity	group slow marker decline: OS (after median 7.2 ys) 76% failure free survival: 69% progression after high dose: 14% relapse after high dose: 14%		The Swedish Cancer Society, Gunnar Nilsson Foundation for Cancer Research, Nordic Cancer Union no coi	LOE 2b RoB SIGN (-) not acceptable

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		n=29; progressive disease, n=7; in total n=36); B) patients with vital cancer at surgery after intensified chemotherapy (n=7); and C) relapses as specified above (n=12)	daily carboplatin 7x(GFR +25) mg Day 1 – 4, cyclofosfamide 1500 mg/m 2 Day 1 – 4 and etoposide 440 mg/m 2 Day 1 – 4. second HDCT cycle: etoposide was substituted by tiotepa 120 mg/m 2 Day 1 – 4				toxiocity grade 4 Nephrotoxicity n=3 (8.3%) Bleeding n=3 (8.3%) Neurotoxicity n=1 (2.8%) Diarrhea/obstipation n=1 (2.8%)			
Hauptmann M 2016	population-based case control study n=23 982 5-yr survivors	median age at diagnosis of pancreatic cancer 61 yrs; range, 41–81 yrs	n=80 with pancreatic cancer surgery and radiotherapy (81% cases, 74%	two controls per case controls: who survived TC without a second cancer at least as	second primary invasive pancreatic cancer diagnosed during	second primary invasive pancreatic cancer incidence	cumulative incidence: 15 yrs after TC diagnosis 0.14% (95% CI 0.07–0.20%)		no coi no information about funding	LoE 3b low RoB

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	Sweden, Denmark, Norway, Ontario (Canada), Finland, Iowa (USA) NL TC diagnosis: 1947-1991	48% occurred >20 years after TC diagnosis (median, 20 years; range, 6–38 years), 69% located in pancreas head	controls); surgery, radiotherapy, and chemotherapy (8% cases, 6% controls); surgery only (6% cases, 15% controls); or surgery and chemotherapy (4% cases, 6% controls)	long as the corresponding case n=145 controls for n= 80 cases	1965–2004		30 yrs after TC diagnosis 1.08% (95% CI 0.83–1.34%)			
Hauptmann M 2015	population based case-control study Denmark (1943–1999), Finland (1953–2002), Iowa, USA (1973–2001), Ontario, Canada (1964–2003), Sweden	Median age at TC diagnosis: 38 yrs (range, 18–71) 67% seminoma 92% stage I or II disease (at TC diagnosis) Median age at stomach cancer diagnosis:	n=92 patients who developed stomach cancer Treatment for TC included surgery and radiotherapy only (80% cases and 78% controls);	n=180 matched controls	second stomach cancer diagnosed during 1975–2004	second stomach cancer incidence	cumulative incidence of second primary invasive stomach cancer: 0.30% (95% CI 0.20– 0.39%) at 15 years 1.45% (95% CI 1.15–1.74%) at 30 years after TC diagnosis radiotherapy (87 (95%) cases,		no coi no information about funding	LoE 3b low Risk of Bias

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	(1958–2002) Norway (1953–2000). 2003–2009 n=22 269 5-year survivors of histologically confirmed TC TC diagnosis 1959–1987	58 yrs; (range, 31–80) 37% occurred ≥20 years after TC diagnosis (median, 17; range, 7–39)	surgery, radiotherapy and chemotherapy (14% cases and 6% controls); surgery only (3% cases and 9% controls); and surgery and chemotherapy only (1% cases and 7% controls).				151 (84%) controls) had a 5.9-fold (95% confidence interval (CI) 1.7–20.7) increased risk of stomach cancer. Risk increased with increasing stomach dose (P-trend <0.001), OR 20.5 (3.7–114.3) for ≥50.0 Gy compared with <10 Gy. Radiation-related risks remained elevated ≥20 years after exposure (P<0.001). Risk after any chemotherapy: OR=1.1; 95% CI 0.5–2.5; 14 cases and 23 controls			

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Hemminki K 2010	retrospective data base study n=5533 1980 – 2006 Sweden	survivors of testicular cancer n=3001 seminomas n=2532 nonseminomas	treatment for TC	no control	1980 - 2006	Second incidence cancer standardised incidence ratio (SIR)	n=370 second cancers SIR 6.7% Second testicular cancer: SIR n=29 after seminoma SIR n=13 after nonseminoma Seminoma SIR after 1-9 yrs: Skin: SIR 3.22 (95% CI 1.18–7.00) Skin, squamous cell: SIR 3.98 (95% CI 1.46–8.67) SIR after 10-19 yrs: Esophagus: SIR 6.24 (95% CI 1.29–18.25) Stomach: SIR 5.18 (95% CI 1.68–12.10) Colorectum: SIR 2.66		funding: Deutsche Krebshilfe; Swedish Cancer Society; Swedish Council for Working Life and Social Research no coi	LoE 4 SIGN RoB (+) accepatable

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							(95% CI 1.33–4.75) Testis: SIR 14.10 (95% CI 5.17–30.69) SIR after 20 yrs Colorectum: SIR 7.78 (95% CI 3.13–16.04) Pancreas: SIR 12.05 (95% CI 1.46–43.53) Nonseminoma SIR after 10-19 yrs: Colorectum: SIR 4.16 (95% CI 1.67–8.58) Prostate: SIR 2.73 (95% CI 1.36–4.88) Testis: SIR 12.02 (95% CI 5.19–23.68) Skin: SIR 5.25 (95% CI 1.08–15.34) SIR after 1-9 yrs:			

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							Kidney: SIR 5.97 (95% CI 1.23–17.43) Urinary bladder: SIR 4.48 (95% CI 1.22–11.48) Connective tissue: SIR 8.62 (95% CI 1.01–31.15) Leukemia: SIR 7.51 (95% CI 2.44–17.53)			
Horwich A 2014	retrospective database study n=2629 1960 - 1992 UK, NO	n=2629 seminoma pat treated with radiotherapy Median age at diagnosis: 37.2 yrs (interquartile range 31.3–44.7)	radiotherapy 30 Gy, or 35/36 or 40 Gy given over 3–4 weeks	no control	from the date of diagnosis to death censored at 31 December 2007 median overall follow-up: 21.8 yrs (interquartile	mortality standardised incidence ratio (SIR)	SMR for all cancers other than testis cancer: 1.46 (95% CI: 1.30–1.65) n=468 second cancers (excluding non-melanoma skin cancers (NMSCs)) in n=403 men SIR for second cancer incidence (excluding NMSC):		no information about coi no information about funding	LoE 4 SIGN RoB (+) accepatable

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					range 17.5–27.5 yrs)		1.61 (95% CI: 1.47–1.76, Po0.0001) bladder cancer (SIR 2.46, 95% CI: 1.86–3.26), pancreatic cancer (SIR 3.14, 95% CI: 2.13–4.60) stomach cancer (SIR 1.93, 95% CI: 1.31–2.83). For abdominal pelvic sites combined, SIR 1.62 (95% CI: 1.43–1.83)			
Kerns SL 2018	multicenter retrospective four arm cohort study n=1214 USA	testicular cancer survivors Median age at evaluation: 37 ys (range, 18 to 74 ys)	cisplatin-based chemotherapy 3xBEP or 4x BEP or 4xEP or		median time since chemotherapy completion: 4.2 years (range,	Cumulative Burden of Morbidity (CMB)	CBM score: high 14.8% very high 3.8% severe 0.1% score very low 8.6% low 37.7% medium 29.7%		Stock or Other Ownership: Consulting or Advisory Role: Research Funding Employment Travel, Accommodations, Expenses	LoE 2b SIGN RoB (+) accepatable

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			4xVIP		1 to 30 yrs)		associated with higher CBM score: older attained age (OR, 1.18 per 5 years), BEP x4 (OR, 1.44 v BEPx3), VIPx4 (OR, 1.96 v BEP x3) less than a college-level education (OR, 1.44), current disability leave (OR, 3.53) former or current smoking status (OR, 1.28)		for 10 of 20 authors Financial support: Lois B. Travis (author)	
Lauritsen J 2015	retrospective Danish DaTeCa database cohort study n= 1206	disseminated GCC BEP-treated patients (n= 1206)	BEP (three cycles or more) in standard doses [bleomycin 15 000 IU/m2/day i.v.	no control	median follow-up: 15.2 yrs (IQR: 9.3–21.5)	Renal function: glomerular filtration rate (GFR)	Overall median GFR before treatment: 109 ml/min/1.73 m2 (IQR: 99–121) After treatment median GFR:		Danish Cancer Society (grant number R97-A6466-14-S23); and Preben and Anna Simonsens Foundation	LoE 4 SIGN RoB (+) accepatable

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	DK diagnosed 1984–2007	median age: 31.6 yrs [interquartile range (IQR): 25.9–39.1]	day 1, 8, 15, etoposide (VP-16) 100 mg/m2/day day1–5 and cisplatin (CDDP) 20 mg/m2/day day 1–5 every 3 weeks] or double-dose cisplatin.				94 ml/ min/1.73 m2 (IQR: 83–105), 406 (36.5%) in CKD stage II and 42 (3.8%) in stage III GFR changed (ΔGFR) −11.3%, −15.4% and −25.9% after three, four and five+ cycles of BEP GFR had no influence on risk of late toxicity [death: hazard ratio (HR) 1.06, P = 0.50; CVD: HR 0.97, P = 0.61]		(no grant number) no coi	
Lauritsen J. 2016	single arm single center retrospective cohort study n=565 1984 – 2007	all patients with germ cell cancer (GCC) age > 15 years who received treatment with BEP from 1984 to 2007 at Rigshospitalet	BEP, which consisted of bleomycin 15 IU/m2 once per week, etoposide 100 mg/m2 days 1 to 5 every 3 weeks, cisplatin	no control	before, during, and after treatment with BEP for 5 years of follow-up	diffusing capacity of the lungs for carbon monoxide (DLCO), forced expiratory volume in 1 second, and	Overall Pulmonary Function According to Time: long-term restrictive disease 4.1%; (95% CI, 1.8% - 6.3%)		Conflict of interest: Frederik Birkebæk Thomsen Honoraria: Astellas Pharma Travel, Accommodati	LoE 4 SIGN RoB (+) accepatable

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	DK		20mg/m2 days 1 to 5 every 3 weeks			forced vital capacity	obstructive disease 2.7%; (95% CI, 0.8% - 4.6%) Diffusion capacity abnormality: 15.6% (95% CI, 11.3% - 19.9%) at 5 yrs follow-up compared with 20.7% (95% CI, 16.6% - 24.8%) pretreatment Post-treatment DLCOc decreased significantly, with a rebound during follow-up. Forced expiratory volume in 1 second and forced vital capacity remained unchanged after BEP but increased significantly to levels above pretreatment during follow-up.		ons, Expenses: Ipsen all others: no coi Financial support: Gedske Daugaard	

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Pühse G 2010	cross sectional single center study n=539 Germany	mean age at the time of orchiectomy: 35.2 ± 9.3 yrs (range: 11–79) n=238	testicular cancer treatment	no control	mean latency between orchiectomy and completing the questionnaire: 3.5 ± 1.3 yrs (range: 0.5–10 yrs)	phantom testis syndrom	prevalence of phantom testis pain: 25% Quality of post-operative phantom pain: lancinating or stabbing 56.7% (n = 34), dull in 30% (n = 18), burning in 8.3% (n = 5) pulsating in 5% (n = 3) mean postoperative phantom pain intensity: 36 ± 21 mm (on visual analogue pain scale from 1 to 100 mm) Phantom pain: permanent in 28.3% (n = 17),		no information about coi no information about funding	LoE 3b

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							more than once per week in 28.3% (n = 17) more than once per month in 43.3% (n = 26) Phantom pain started on an average of 76 days after radical inguinal orchiectomy			
Pühse G. 2011	single center single arm prospective cohort study n=376 TGCC Germany since 2004	All patients treated for testicular cancer n=160	Seminoma Surgery (wait and see + RPLND) Radiotherapy Chemotherapy (carboplatin) Chemotherapy (PEB/PEI) Nonseminoma Surgery (wait and see + RPLND)	no control	follow-up: 4.8 ± 2.7 yrs; mean ± SD	Testosterone deficiency before, during and after therapy	At primary diagnosis: no significant difference in mean testosterone levels of all patients within the seminoma or the non-seminoma group ($p < 0.05$). Patients with or without TD did not differ in age. With regard to the different treatment modalities, rates of		no information about coi no information about funding	LoE 4 SIGN RoB (-) unacceptable

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			Chemotherapy (PEB/PEI ± RTR)				persistent TD range from 11.1% to 25.0% in the subgroup undergoing surgery alone and from 18.8% to 26.4% in polychemotherapy subgroups. seminoma treatment: TD was evident in: up to 24.0% of patients after carboplatin monotherapy up to 33.3% after retroperitoneal radiotherapy			
Pühse G 2012	cross sectional single center study n=539 Germany	treated for testicular cancer between 1997 and 2007 Mean age at time of orchiectomy:	testicular cancer treatment	no control	mean latency between orchiectomy and completing the questionnaire:	sexual dysfunction testicular pain	Erectile dysfunction (P= .003), inability to maintain an erection (P = .02), reduced intensity of orgasm (P <, .001), ejaculation disorders (P = .01) occur significantly more often in patients		no information about coi no information about funding	LoE 3b

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		35.2 6 9.3 yrs (range, 19–69 yrs) n=238			3.5 ± 1.3 yrs (range, 0.5– 10 yrs)		experiencing chronic pain			
Shinn EH 2010	retrospective single center case control study n=414 USA FL January 2000 - June 2002	diagnosed with seminomatous or nonseminomatous germ-cell testis cancer	n=162 testis cancer survivors	Age-Matched Relative Controls n=74 CDC Controls income-matched population-based control group (n ranged from 1,123 to 9,775)	Time since treatment: 4.5 yrs	health behaviour	Smoking 18% of TCS at the time of the interview After controlling for demographic variables, survivors were not more likely to be current smokers compared with their matched relative controls nor when compared with their CDC controls Alcohol 75.9% of TCS at least one drinking occasion in the past month Regarding problem drinking:		Supported by National Cancer Institute Grants No. R03-CA-3348, K07-CA- 093512, and K07-CA-113641 and a Lance Armstrong Foundation Survivorship Quality of Life Grant. Honoraria: Philippe E. Spiess, UpToDate	LoE 3b

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							32.7% of TCS reported at least one occasion of five or more drinks in the past month. Survivors were not more likely to report problem drinking compared with their matched relative controls (31.1%) Physical activity 54% of the TCS engaged in physical activity at least 3 times a week or more. Survivors were twice as likely to engage in regular physical activity compared with their age-matched relative controls (39%) But when compared with CDC controls (55%), TCS were not statistically more likely to engage in		all other authors: no coi	

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							regular activity (P=0,74) Fruit and vegetable consumption: 11% of the TCS reported having at least five servings of fruits and vegetables per day. No difference was found between TCS and their relative-matched controls (12%). Compared with the CDC controls (21%), the survivors were half as likely to have had at least five fruits and vegetables per day (OR, 0.48) cholesterol screening No difference was found between TCS' rate of cholesterol screening within the past year (45%) compared with their relative matched controls (54%), nor			

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
							with their CDC controls			
Sprauten M 2012	prospective cohort studies n=1,814 Survey I (1998-2002) Survey II (2007-2008) NO	Median age at TC diagnosis 28.7 yrs at Survey I 40.8 yrs nonseminomatous tumors (81.1%) and metastatic disease (82.8%)	Participated in both surveys, had complete SCIN data and remaining blood samples (n = 127) restricted to TCSs treated at Norwegian Radium Hospital (NRH) Primary chemotherapy: CVB (40.8%) standard BEP	no control group	median of 20.0 yrs (range, 13.0 to 27.0 yrs)	Cisplatin-induced neurotoxicity and ototoxicity (NTX)	Survey I multivariate analysis: Cumulative dose of cisplatin and SCIN score or individual symptoms: OR 1.10; 95% CI 0.88-1.39 highest compared with lowest serum platinum quartile associated with total SCIN score: OR 4.69; 95% CI 1.82-12.08 highest compared with lowest platinum quartile for paresthesias in hands:		Supported by Grants No. 1 UL1 RR024160-01 (L.B.T.) from the National Center for Research Resources of the National Institutes of Health, No. 5U56CA118635 (T.H.D., R.E.H., and C.B.) from the National Institutes of Health, and No. 39247 (M.S.) from the South-Eastern Norway Regional	LoE 4 SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
			(39.1%)				OR, 2.87; 95% CI, 1.08 -7.62) paresthesias in feet (OR 2.83; 95% CI, 1.09-7.40) Raynaud's phenomenon in hands: OR 4.15; 95% CI 1.60-10.76 Raynaud's phenomenon in feet (OR 4.46; 95% CI 1.70-11.71) Survey II multivariate analysis: Cumulative dose of cisplatin and total SCIN score or with any of the individual symptoms: OR 1.01; 95% CI 0.78 -1.30		Health Authority. no coi	

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
							total SCIN score and highest compared with lowest serum platinum quartile: OR 4.28;95%CI 1.36 - 13.48 highest quartile of serum platinum: paresthesias in hands OR 4.08;95%CI 1.29 - 12.93) paresthesias in feet: OR 4.63; 95% CI 1.45 14.76) Raynaud's phenomenon in hands: OR 3.11; 95% CI 0.97 -9.94) Raynaud's phenomenon in feet: OR 2.80; 95% CI 0.90 -8.71)			

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
							tinnitus OR 3.44; 95% CI 1.03 - 11.54			
Sprauten M 2014	prospective cohort single center study n=917 1998 to 2002 (Survey I) 2007 to 2008 (Survey II) NO	n=307 TCSs n= 233 men (76%) stage I disease. n=74 TCSs metastatic disease (seminoma, n=19; nonseminoma, n=55)	surgery, radiotherapy (RT), or chemotherapy (CT)	Nordic population-based study n=599 healthy participants from the Nordic Reference Interval Project (NORIP)	Survey I: median of 9 years after diagnosis (range, 5 to 21 yrs) Survey II: median of 18 yrs (range, 13 to 28 yrs)	testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH)	Risk of lower testosterone and higher LH and FSH levels was significantly increased for TCSs at all time points after RT or CT. Survey II: OR: 3.3 (95% CI, 2.3 - 4.7) for lower testosterone categories OR 5.2 (95% CI, 3.5 to 7.9) for RT and CT LH OR 4.4 (95% CI, 3.1-6.5) FSH OR 18.9 (95% CI, 11.0 - 32.6) for RT		Supported by Grant No. 39247 from the South-Eastern Norway Regional Health Authority (M.S.) no coi	LoE 2b SIGN RoB (+) acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
							LH OR 3.6 (95% CI, 2.4 to 5.3) FSH OR 14.2 (95% CI, 8.3 to 24.4) for CT			
Vidal AD, 2015	single-arm-prospective phase-II-study 1995-1999 n =44 Switzerland	NSGCT CS I high risk with VI and/or EC >50% n=40	CT within 4 weeks after orchiectomy 1 modified-BEP cycle daily dose of 20 mg/m2 of bleomycin (given as a continuous i.v. infusion over 24 h to decrease the risk of pulmonary side-effects), 120 mg/m2 of etoposide and 40 mg/m2 of cisplatin	no control	Median follow-up: 186 (10–224) months	Primary end point: rate of relapse after adjuvant chemotherapy, with or without elevation of tumour markers Secondary end points: rates of metachronous testicular tumours, secondary neoplasia, late postchemot	relapse rate after 15 ys: n=1 (2,5%) rate of metachronous tumour: n=3 (7,5%) secondary neoplasia: n=3 (7,5%) (leukemia, colorectal cancer) chemotherapy-side-effects:	small sample size	no information about funding no coi	LOE 4 RoB SIGN (-) not acceptable

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
			administered i.v. on days 1–3			herapy toxicity Intervals to relapse, death, or secondary malignancies were calculated from the date of orchiectomy	n=1 (grade 2 peripheral polyneuropathy) Intermittent grade 1 tinnitus: n=2 (5%) Intermittent grade 2 tinnitus n=1 (2.5%) glomerular filtration rate of 53 ml/min/1.73 m2 and non-ST elevation myocardial infarction (210 months of follow-up) n=1 No overt nephrotoxicity, cardiotoxicity, or pulmonary toxicity registered in other patients			

Referenz (Autor, Jahr)	Studientyp Fallzahl Zeitraum Land	Patientenmerkmale	Intervention Anzahl der Patienten	Vergleich Anzahl der Patienten	Beobachtungs-zeitraum	Endpunkt	Effekte inkl. Richtung des Effektes	Bemerkungen	Finanzierung COI	Evidenz-stufe (LOE) RoB
Wortel RC 2015	single arm prospective cohort study n=238 1999-2013 Netherlands	CS I Seminoma n=145 CS II Seminoma with radiation after orchiectomy n=16 median age: 36 ys (18-70)	radiation 26 Gray (Gy) in 2 Gy fractions to para-aortic region with an additional 10 Gy boost to enlarged nodes visible on computer tomography (CT) scan for stage II		median follow-up time 55 months (range 3–148)	incidence and severity of short-term effects of orchiectomy and radiotherapy on body image and sexual function	fertility concerns: 48% changes in body images: 61%		funding by Dutch Society for Sexual Medicine (NVVS) Fund for Stimulation and Development of Sexology no coi	LOE 4 RoB SIGN (+) acceptable

9.4.14. Kapitel 14

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
Alacacioglu A 2014	case-control-study	testicular cancer survivors (TCS) n=41 healthy men n=38	European Organization for Research on Treatment of Cancer Questionnaires Quality of Life-C30 (EORTC-QoL-C30) Hospital Anxiety and Depression Scale (HADS) Golombok-Rust Inventory of Sexual Satisfaction (GRISS)	In conclusion, because of being curable, even if metastatic, the scores of anxiety, depression and sexual satisfaction of TCSs were similar with normal population. Depression affected all the subscores of QoL except role functioning. In the testicular survivors whose depression scores were high, physical, cognitive, emotional, social functioning and global quality of life subscores of GRISS were found statistically significantly low.	after therapy
Brand S 2015	longitudinal study	21 men commencing active surveillance for stage one germ cell cancer, with (pT2) or without (pT1) lymphovascular invasion	Brief Male Sexual Function Inventory for Urology (BMSFIU)	Men's sexual function is altered at diagnosis and improves by 3 months. At 12 months, whilst not statistically significant, sexual function improves but not to the same level as normative data comparison.	at 3 and 12 mo after diagnosis
Bumbasirevic U 2013	cross-sectional study	Serbian long-term testicular cancer survivors (TCS) n=202 TCS	short form health survey 36-item (SF-36) EORTC QLQ-C30 Beck Depression Inventory (BDI) Sexual function nine-item generic questionnaire containing dichotomy choice questions (yes/no): erectile and ejaculatory function, sexual drive, assessment of sexual life before and after treatment	Sexual problems seriously impaired HRQoL in TCS. Additionally, HRQoL was also affected by age, depression, and fatigue. Serbian TCS achieved high levels of SF-36 scores.	followed up after platinum-based chemotherapy

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
			(not validated)		
Cappuccio F 2018	Systematic Review	n=20.266 pts n=54 included studies	HADS (Hospital depression and sexual Anxiety and Depression Scale), GRISS satisfaction levels of TCSs (Golombok-Rust Inventory of Sexual Satisfaction) and EORTC-30 SWL (Satisfaction with Life Scale) DSFI (Derogatis Sexual Functioning Inventory) UCLA/RAND sexual module and the Groningen sexual questionnaire BSFI (Brief Male Sexual Function Inventory) QLS (Questions on Life Satisfaction) IES (Impact of Events Scale) short form health survey 36-item (SF-36) FQ (Fatigue Questionnaire) EORTC QLQ C-30 + TC module EPQ-18 (Eysenck Personality Questionnaire); BSFI; HSCL (Hopkin Symptom Checklist) PSE (Present State Examination) GHQ-28 (General Health Questionnaire-28). BDI-II (Beck Depression Inventory-II);	CONCLUSIONS: It is necessary to identify TCSs with higher risks of poorer QoL outcomes, to focus interventions on the areas with the greatest impairments. Further researches should consider the effects of testicular cancer on the impaired areas, collecting more data to better identify survivor's needs and consequent interventions, with a special focus on adolescent and young adult TCSs. Other works are requested on therapies, preventive and ameliorative, to reduce chronic side effects of testicular cancer treatment	Up to 11 yrs after therapy

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
			MFI (Multidimensional Fatigue Inventory-20) EORTC QLQ-PR25 SWEDQUAL (Swedish Health Related Quality of Life Questionnaire) GQL (Gothenburg Quality of Life Instrument) EPQ-18; Rosenberg Self-Esteem Scale (RSES) CaSUN (Supportive care needs), DASS21 (Depression Anxiety Stress Scale 21); SF-36v2 EORTC QLQ-TC26 (TC- module HRQoL); MAC (Mental Adjustment to Cancer Scale), DUFSS (Functional Social Support Questionnaire), MMQ (Maudsley Marital Questionnaire) SSL (Social Support List), RSES, IIEF (International Index of Erectile Function) and CES-D (Center for Epidemiological Studies Depression Scale)		
Dahl AA 2005	Systematic Review	23 articles		QOL on the group level was equal to that of men of the same age in the general population. Treatment strategies hardly influenced the QOL. The anxiety level, but not depression, was higher among survivors, while sexual functioning hardly differed from the male population norm. Patients to be treated for testicular cancer should be told about the outlook for good QOL, and the low risk of mental and physical long-term effects.	after treatment

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
Dieckmann KP 2015	retrospective chart analysis	GCT n=475	18 questions no information about validity	More than one quarter of GCT patients wish to have a testicular prosthesis. Over-all satisfaction with implants is high in more than 80% of patients.	having the implant for at least half a year and no longer than 10 years
Flechtner HH 2016	RCT	CSI-NSGCT to receive either one course of BEP or RPLND after orchiectomy n=382	(EORTC) Quality of Life Questionnaire (QLQ-C30) plus additional scales questionnaire (QLQ-C30+)	QoL assessment of this large randomised trial was not able to detect significant differences in QoL scores between patients undergoing RPLND and BEP in a community-based setting	after adjuvant treatment
Grimison PS 2010	multicenter randomized phase III trial	good-prognosis germ cell tumors n=166	Spitzer Quality of Life Index GLQ-8	After the completion of treatment, average GLQ-8 scores for numbness (P = .003) and hair loss (P = .04) and the Spitzer Quality of Life Index (P = .05) favoured 3B90E500P	before random assignment and during and after treatment
Hartung TJ 2016	cross-sectional study	adult male patients with germ cell cancer n=164	Short- Form Health Survey (SF-8)	Survivors of germ cell tumors can expect an overall long-term QoL similar to that of other men of their age	after treatment
Holzner B 2013	Phase I-III-study for questionnaire development qualitative and quantitative designs	Phase I n=62 Phase III n=156	development of the EORTC QLQ-TC26-questionnaire	The newly developed EORTC QLQ-TC26 is now available in several languages to assess QOL in TC patients receiving treatment and in TC survivors. Phase IV of questionnaire development will comprise international field testing, including extensive analysis of psychometric characteristics of the EORTC QLQ-TC26.	not applicable
Jansen F 2015	cross-sectional study	cancer survivors n=212	EQ-5D (EuroQol) and study specific questionnaire	Perceived need for supportive care including healthy lifestyle programs was high, and in general, cancer	after treatment

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
				survivors had a positive attitude towards self-management and eHealth. Need and attitude were associated with sociodemographic and clinical variables and quality of life. Therefore, a tailored approach seems to be warranted to improve and innovate supportive care targeting cancer survivors.	
Kim C 2011	case control study	n=246 TGCT (testicular germ cell tumor) cases n=236 non-testicular cancer controls	short form health survey 36-item (SF-36)	In conclusion, our study suggests that quality of physical health, but not mental health, among TGCT survivors may be lower than that of controls. Additionally, TGCT survivors treated with chemotherapy may have reduced physical health compared to controls, whereas other treatments did not significantly differ. And in particular, physical functioning, role- physical, and general health are strongly affected.	after treatment
O'Carrigan B 2014	prospective cohort study	GCT n=54	(Hospital Anxiety and Depression Scale (HADS),14 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)	Biochemical hypogonadism was found to be common in TCS, but was not correlated with QoL, as reflected in the indices measuring depression, fatigue and functional well-being in this study. Clinicians should be mindful of symptoms of hypogonadism, and consider screening and testosterone replacement to reduce long-term complications.	assessments at 12 mo after surgery or (where relevant) chemotherapy
Pacey A 2013	longitudinal study	good prognoses GCT and haematological cancer	Health-related quality of life (QLQ-C30)	For those men who are uncertain about future reproductive plans, decisions depend more on their HRQoL on diagnosis and satisfaction with clinic	at diagnosis (Time 1 (T1)) and 1 year later (Time 2 (T2))

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
		n=91 bankers and non-bankers in HRQoL at T1 and T2		care. Among this group, those who did not bank were younger, less likely to have had children, more concerned about the health of children born after cancer and less certain about what they should do.	
Pal SK 2013	longitudinal study	survived at least 4 years after HDCT n=48	EORTC QLQ-C30 and the FACT-T questionnaires	HDCT with the TECTIC regimen produces durable remissions in patients with relapsed or refractory GCTs with acceptable QOL in long-term survivors.	after therapy
Pedersen AF 2012	cross sectional study	n=316 TCS	Beck Depression Inventory II (BDI-II) and fear of recurrence with one question	Fear of recurrence is prevalent in long-term TCSs. The observed relationship between FoR and a psychological causal attribution is probably complex and the direction of causality may be twofold: attributing the disease to a factor that is perceived as uncontrollable in nature could induce loss of control, and high levels of FoR may increase the need to gain control over the situation by pointing out factors that could be responsible for the disease such as psychological stress.	after therapy
Quinten C 2014	cross sectional study	cancer patients n=7417 n=318 with testicular cancer	EORTC QLQ-C30	for each cancer site, at least 1 HRQOL domain provided prognostic information that was additive over and above clinical and sociodemographic variables in testis cancer, role functioning was predictive for survival	after treatment

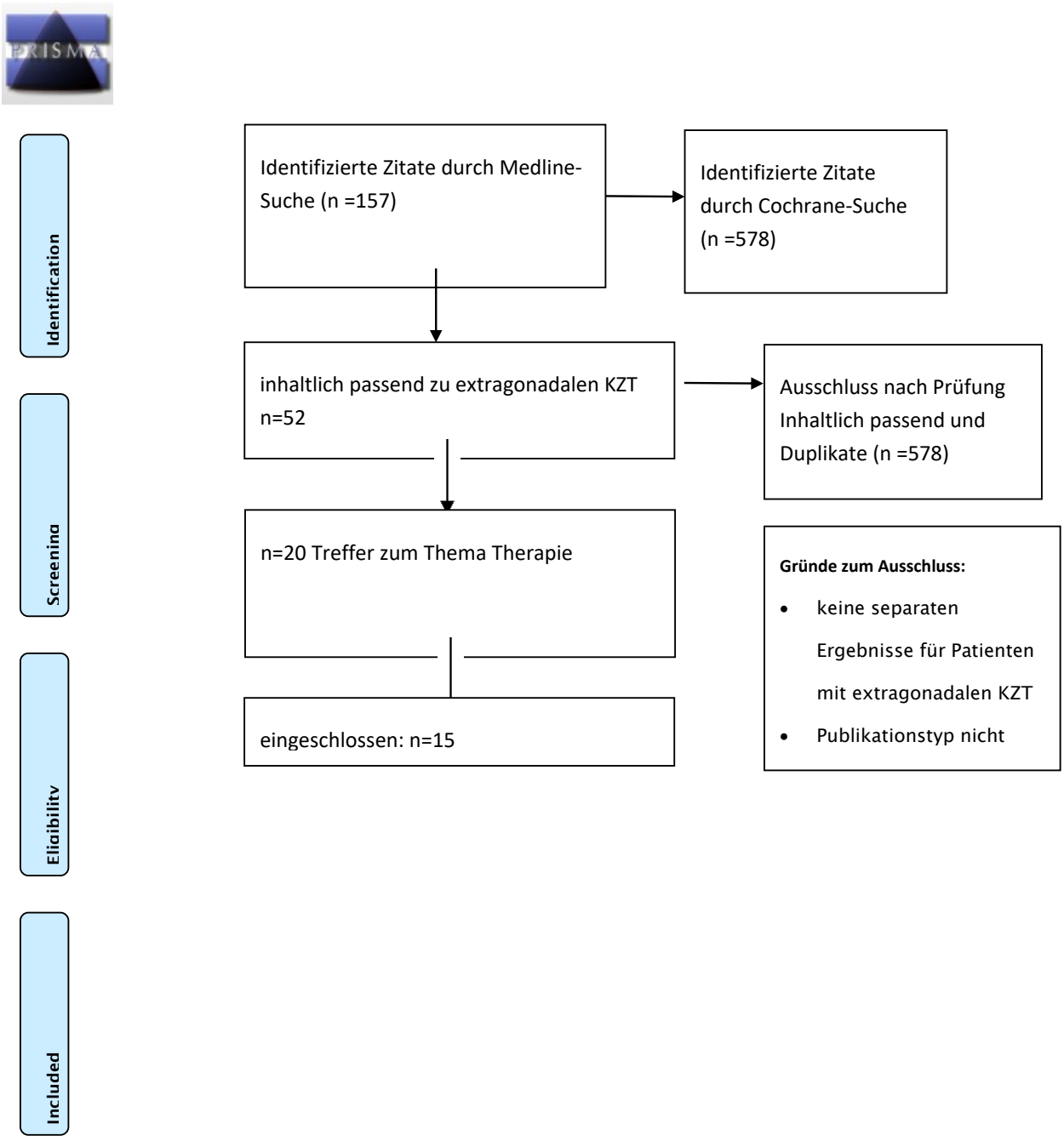
Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
Rutskij R 2010	cross-sectional questionnaire study	n=1326 TCSs	brief approach/avoidance coping questionnaire (BACQ)	We found that TCSs used similar coping patterns as NORM, avoidant coping was associated with significantly more problems than observed among TCSs who used more approach coping.	after treatment
Skaali T 2011	longitudinal study	n=276 chemotherapy patients n=71 radiotherapy patients	QLQ-C30 and a testicular cancer module (TC module)	In patients with testicular cancer with no information or expectation bias, an increased rate of cognitive complaints was observed shortly after chemotherapy, with return to baseline levels at 12 months. Treatment modality (chemotherapy vs. radiotherapy) was not associated with cognitive complaints at any time point after adjustment for relevant QoL variables.	before treatment (baseline), at 3 mo, and at 12 mo
Smith AB 2013	cross sectional study	n=244 TCS	supportive care needs (CaSUN), psychological distress (DASS21) and health-related quality of life (HRQoL; SF36v2	The majority of TC survivors reported one or more unmet needs. Unmet needs regarding existential survivorship issues were frequently reported by TC survivors despite their favourable prognosis. Relationships unmet needs were less prevalent but still more common than in breast and gynaecological cancer survivors. These findings appear to be related to the young age of TC survivors. As a higher number of unmet needs is significantly associated with psychological morbidity and impaired HRQoL, interventions addressing this constellation of issues are needed.	after treatment

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
Smith AB 2016	cross sectional study	n=244 TCS	DASS21, generic health-related quality of life (HRQOL; SF-36v2), TC-specific HRQOL (EORTC QLQ-TC26), coping (MAC), social support (DUFSS), and unmet needs (CaSUN)	TC survivors appear to experience mild psychological distress and HRQOL impairments, while a vulnerable subgroup experience more severe morbidity.	after treatment
Smith AB 2017	Systematic Review	n=66 articles reporting about n=33 studies total number of pts. not reported	BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; CES-D, Centre for Epidemiologic Studies Depression Scale; CG, Comparison Group; CT, Chemotherapy; DASS21, Depression, Anxiety Stress Scale - 21; Dx, Diagnosis; EORTC, European Organisation for the Research and Treatment of Cancer; FCR, Fear of Cancer Recurrence; Gen Pop, General Population; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Anxiety Questionnaire; HARS, Hamilton Anxiety Rating Scale; HRQOL, Health-related Quality of Life; HSCL-25, Hopkins Symptom Checklist; IES, Impact of Event Scale; ITSIS, Impact of Traumatic Stressors Interview Schedule; L, Level; M, Mean; MA, Multivariate Analysis; MADRS, Montgomery-Asberg Depression Rating Scale; Med, Median; MMPI, Minnesota Multiphasic Personality Inventory; NR, Not Reported; OCWA, Overall Current Work Ability; P, Prevalence; POMS, Profile of Mood States; PSS, Perceived Stress Scale; QLQ-TC26, Quality of Life Questionnaire - Testicular Cancer 26; QLS, RPLND, Retroperitoneal Lymph Node Dissection; RRTM, Resection of Residual Tumour Mass; RT, Radiotherapy; SD, Standard Deviation; SDS, Symptom Distress Scale; SSQ, Study-Specific Question; STAI-S, State-Trait Anxiety Inventory - State; STAI-T,	The literature to date suggests that many TC survivors, particularly those with substantial treatment side effects and passive coping styles, grapple with anxiety and FCR and would potentially benefit from intervention. Studies evaluating TC-specific prevention and management interventions targeting issues pertinent to this group are needed.	Only two studies reported time after treatment period (3-12 mo)

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
			State-Trait Anxiety Inventory - Trait; SURG, Surgery; SURV, Surveillance; TC, Testicular Cancer; Tx, Treatment; UA, Univariate Analyses; UCLA, University of California, Los Angeles; UK, United Kingdom; US(A), United States (of America); WAI, Work Ability Index		
Stoehr B 2013	cross sectional study	n=104 TC survivors	EORTC QLQ-TC 26	TC survivors who achieved paternity have a statistically significant better QoL and are more satisfied with their treatment compared with controls. We believe our data clearly underline the important influence of achieved/non-achieved paternity on QoL for TC survivors.	after treatment
Vidrine DJ 2010	longitudinal study	men with newly diagnosed non-seminoma germ cell tumors of the testis n=116	36-Item Short-Form Health Survey (SF 36)	Results from this study indicate that chemotherapy is associated with only a temporary decrease in HRQOL. Other HRQOL domains, including mental functioning, role emotional, and general health perceptions, were not associated with treatment type at any of the assessment times.	before beginning adjuvant chemotherapy or a surveillance regimen. 1 week after the completion of adjuvant chemotherapy, or 3 months after baseline assessment for participants who did not receive adjuvant chemotherapy. 12 mo after the baseline assessment

Referenz	Studiendesign	Fallzahl	Instrument	Schlussfolgerung	Zeitpunkt der Datenerhebung
Wortel RC 2015	longitudinal study	n=161 TGCT	Dutch questionnaire used for evaluation of men with sexual dysfunction	Short-term effects of treatment included fertility concerns and changes in body image. Reported erectile rigidity was significantly decreased after 6 months, as were sexual interest, activity, and pleasure. Disease and treatment had negative effects on sexual life, and changes in body image were associated with sexual dysfunction. Therefore, body image and sexual functioning should be addressed at an early stage in order to offer adequate treatment and counselling.	prior to radiotherapy after 3 and 6 mo

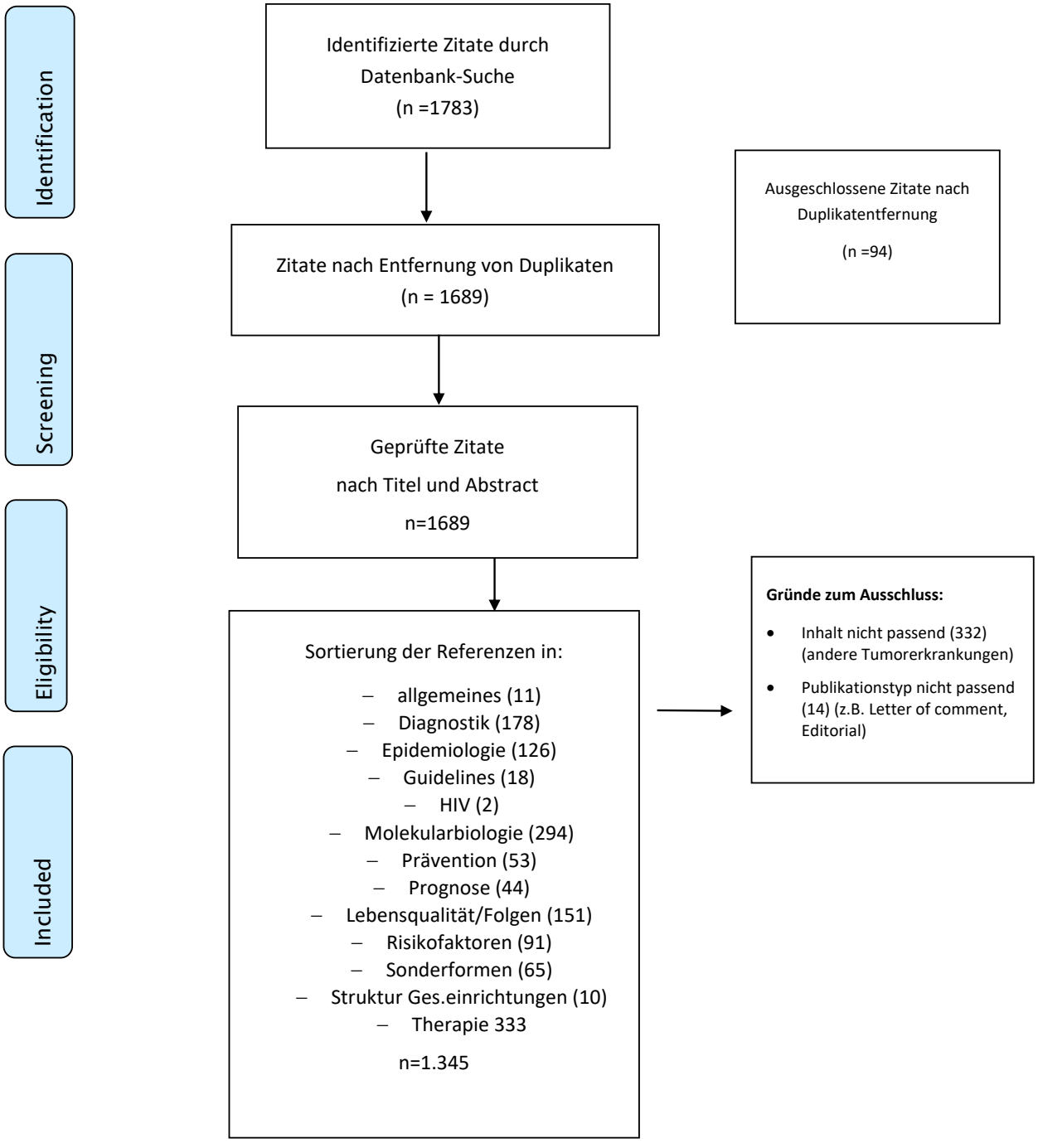
9.5. PRISMA Flowchart Extrasuche zum Kapitel 11 Sonderformen



9.6. Suchstrategie zum Kapitel 11 Sonderformen in Medline über OVID

1	((spermatocyt* or Leydig cell or sertoli cell or sex cord or gonadal stromal or non-germ cell) adj2 (tumor* or tumour*)).tw,mp.
2	(benign testis adj2 (tumor* or tumour*)).tw.
3	benign testis tumour.tw.
4	benign testis tumor.tw.
5	burned out tumour.tw.
6	burned out tumor.tw.
7	(burned out adj2 (tumor* or tumour*)).tw.
8	regressed tumour.tw.
9	regressed tumor.tw.
10	(regressed adj2 (tumor* or tumour*)).tw.
11	(benign testis adj1 (tumor* or tumour*)).tw.
12	(burned out adj1 (tumor* or tumour*)).tw.
13	(regressed adj1 (tumor* or tumour*)).tw.
14	(burned out adj (tumor* or tumour*)).tw.
15	(incidental* adj (tumor* or tumour*)).tw.
16	11 or 13 or 14 or 15
17	limit 16 to yr="2000 -Current"
18	limit 1 to yr="2000 -Current"

9.7. PRISMA Flow Diagramm Literatursuche Hauptsuche



9.8. GRADE-Bewertungen der DeNovo-Recherchen Kapitel 9 und 10

Autor(en): Wilborn für AG Ruf Kapitel 9

Datum: 05.03.2018

Frage: PICO 24, 25: Adjuvante Behandlung nach Risikostratifizierung verglichen mit adjuvante Behandlung ohne Risikostratifizierung bei Patienten mit Nichtseminom CSI

Setting: Klinik

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studien design	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	adjuvante Behandlung nach Risikostratifizierung	adjuvante Behandlung ohne Risikostratifizierung		
Gesamtüberleben 5 und 10 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	adjuvante Behandlung nach Risikostratifizierung	adjuvante Behandlung ohne Risikostratifizierung		
4	Beobachtungsstudien [1,2,3,4]	schwerwiegend [1,2,3,4,a]	nicht schwerwiegend	sehr schwerwiegend [b]	nicht schwerwiegend	keine	n=7887	n=0	**5 yr-OS[1]:** Surveillance 100% **CS IA 5-yr OS[2]:** Surveillance 97.3% (CI 96.3-98.0), RPLND 99.1% (CI 97.6-99.7), Chemo 98.0% (CI 96.2-99.0) **CS IB 5-yr-OS[2]:** Surveillance 96.5% (CI 94.8-97.7), RPLND 97.8% (CI 95.5-99.0), Chemo 96.0% (CI 94.1-97.3) **5 yr OS[3]** total: 99,0 %, Chemo with LVI: 98,7%, Chemo without LVI 99,2% **5 yr OS[4]:** Surveillance low risk group: n=281/ 287 (97.9%) Chemotherapy high risk group: n=166/ 167 (99.4%) **CS IA 10 yr OS[2]** Surveillance 94.2% (CI 91.2-96.2), RPLND 97.5% (CI 93.6-99.1), Chemo 95.1% (CI 89.8-97.7) **10 yr OS[3]** total: 96,9% Chemotherapy with LVI: 96,9%, Chemotherapy without LVI: 96,9%	⨁◯◯◯ SEHR NIEDRIG
Rezidivrate										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	adjuvante Behandlung nach Risikostratifizierung	adjuvante Behandlung ohne Risikostratifizierung		
4	Beobachtungsstudien [1,3,4,6, 8]	schwerwiegend [a]	nicht schwerwiegend	sehr schwerwiegend [b]	nicht schwerwiegend	keine	n=1569	n=0	**Recurrence rate[5]:** NS GCT I low risk: 69,6%, NS GCT I high risk: 1,1% **Recurrence rate[1]:** NS GCT I low risk: n=0 (0%), NS GCT I high risk: n=3 (23%) **Recurrence rate[3]** with LVI: n=8 (3,2%), without LVI: n=4 (1,6%) **Recurrence rate[4]:** low risk : n=48 (16.7%) **Recurrence free rate[6]:** stage Ia: 100%, stage Ib: 84,7%	⨁◯◯◯ SEHR NIEDRIG
Gesamtüberleben 10 Jahre										
1	randomisierte klinische Studie [7]	schwerwiegend [d]	nicht schwerwiegend	schwerwiegend[c]	nicht schwerwiegend	keine	n=232	n=0	**10-yr-OS** Surveillance: n=2/129 (98,5%), CVB-Chemotherapy x2: n=1/55 (98,2%)	⨁⨁◯◯ NIEDRIG
Krankheitsspezifisches Überleben 10 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	adjuvante Behandlung nach Risikostratifizierung	adjuvante Behandlung ohne Risikostratifizierung		
1	randomisierte klinische Studien 7	schwerwiegend d	nicht schwerwiegend	sehr schwerwiegend b	nicht schwerwiegend	keine	n=232	n=0	DSS total =100%	⊕◯◯◯ SEHR NIEDRIG
Krankheitsspezifisches Überleben 5 Jahre										
2	Beobachtungsstudien [4,5]	schwerwiegend [a,d]	nicht schwerwiegend	sehr schwerwiegend [b,c]	nicht schwerwiegend	keine	n=767	n=0		⊕◯◯◯ SEHR NIEDRIG

Explanations

a. Kohortenstudien, Risk of Bias-Bewertung mit dem SIGN-Tool: mittlere oder niedrige Qualität der Studien
b. zweiarmige Kohortenstudien, sie untersuchen jedoch die Risikoadaptierte Therapie (low risk vs high risk), d.h. kein Vergleich passend zur PICO
c. die Studie untersucht die Risikoadaptierte Therapie, d.h. kein Vergleich passend zur PICO
d. das RCT Tanstadt 2010 hat einen LoE of 2b (hohes RoB)

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GRADE-Erläuterungen

⊕⊕⊕⊕ Hohes Vertrauen
Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert

⊕⊕⊕⊖ Moderates Vertrauen
Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.
⊕⊕⊖⊖ Geringes Vertrauen
Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.
⊕⊖⊖⊖ Sehr geringes Vertrauen
Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.

Autor(en): Wilborn für AG Ruf Kapitel 9

Datum: 05.02.2018

Frage: PICO 26: Carboplatin Monotherapie verglichen mit Surveillance bei Seminom-Patienten CS I

Setting: Klinik

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Carboplatin Monotherapie	Surveillance		
Rezidivrate										
3	Beobachtungsstudien [1,2,3]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend [b]	keine	n=458	n=402	**Relapse rate**[1]: Surveillance: n=21 (8,2%), 1x Carbo: n=18 (5%) **Relapse Rate**[2]: Surveillance: 22.3%, Carboplatin: 1,2% **Progression rate**[3] Surveillance: 9.5%, Carboplatin 12.5 %	⨁◯◯◯ SEHR NIEDRIG
Krankheitsspezifisches Überleben 2, 5 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Carboplatin Monotherapie	Surveillance		
4	Beobachtungsstudien [5,6,7]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=689	n=1075	**2 yr CSSI[5]** Observation 100% (95% CI 100-100) Chemotherapy: 100% (95% CI 100-100) **5 yr CSS[6]:** Surveillance: 100%, Carbo 1x: 100% **5 yr CSS[7]:** Surveillance: 99,8%, Carbo 1x: 100%	⨁◯◯◯ SEHR NIEDRIG
Gesamtüberleben 3 und 5 Jahre										
4	Beobachtungsstudien [2,4,6,7]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=764	n=1206	**3 yr OS[4]**: Surveillance: 100%, Carbo: 100% **5 yr OS[2]:** Surveillance: 100%, Carboplatin: 92,3% **5 yr OS[6]:** Surveillance: 99,2%, Carbo 1x: 98,9% **5 yr OS[7]**: Surveillance: 98,4%, Carbo 1x: 99,2%	⨁◯◯◯ SEHR NIEDRIG
Gesamtüberleben 10 und 20 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Carboplatin Monotherapie	Surveillance		
2	Beobachtungsstudien [6,8]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=479	n=655	**10 yr OS[6]:** Surveillance: 96,8%, Carbo 1x: 98,5% **10 yr OS[8]:** Surveillance: 100%, Chemotherapy: 100%	⊕◯◯◯ SEHR NIEDRIG
Zeitdauer bis zum Rezidiv										
5	Beobachtungsstudien [6,7,8,9,10]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=755	n=1553	**Median time to relapse[6]:** Surveillance: 1,3 ys (0,4-5,6), Carbo 1x: 1,7 ys (0,2-6,5) **Median time to relapse[7]:** Surveillance: 1,4 ys, Carboplatin 1x: 1,8 ys **Median time for relapse[8]:** Surveillance: 21.0 mo, Chemotherapy 42.8 mo **Time to relapse for all[9]:** 15 mo (4-93) **Median time to relapse[10]:** Surveillance:14 (3–36) mo, Carboplatin: 20 mo	⊕◯◯◯ SEHR NIEDRIG

Explanations

a. Kohortenstudien, Risk of Bias-Bewertung mit dem SIGN-Tool: mittlere oder niedrige Qualität der Studien

b. Die Konfidenzintervalle der Effektschätzer HR in Dieckmann 2016 und in Tandstad 2011 sind sehr breit, auch wenn die Fallzahlen in den untersuchten Armen jeweils dreistellig hoch sind, nur in den Armen RT und CT bei Dieckmann liegen die TN-Zahlen unter n=100

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GRADE-Erläuterungen
⊕⊕⊕⊕ **Hohes Vertrauen**
Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert
⊕⊕⊕⊖ **Moderates Vertrauen**
Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.
⊕⊕⊖⊖ **Geringes Vertrauen**
Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.
⊕⊖⊖⊖ **Sehr geringes Vertrauen**
Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet

Autor(en): Wilborn für AG Ruf Kapitel 9

Datum: 07.02.2018

Frage: PICO 26b: Carboplatin-Monotherapie verglichen mit Bestrahlung bei Seminom-Patienten CS I

Setting: Klinik

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	**Studiendesign**	**Risiko für Bias**	**Inkonsistenz**	**Indirektheit**	**Fehlende Genauigkeit**	**Andere Faktoren**	**Carboplatin-Monotherapie**	**Bestrahlung**		
Rezidivrate										
2	Beobachtungsstudien [1,2]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=442	n=171	**Relapse Rate[1]:** Carboplatin: 1,2%, Radiotherapy: 7,7% **Relapse rate[2]**: Radiotherapy: n=1 (2,4%), 1x Carbo: n=18 (5%)	⨁◯◯◯ SEHR NIEDRIG
Krankheitsfreies Überleben 5 Jahre										
4	Beobachtungsstudien [1,4]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=183	n=312	**5 yr DFS[1]:** Carboplatin: 97,7%, Radiotherapy: 91,9% **5 yr RFS[4]:** Chemotherapy 94%, Radiotherapy 95%	⨁◯◯◯ SEHR NIEDRIG
Krankheitsfreies Überleben 5 Jahre										
1	randomisierte klinische Studie [6]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=573	n=904	**5 yr CSS for all :** 99.8% (95% CI: 99.6% - 99.9%)	⨁⨁⨁⨁ HOCH

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	**Studiendesign**	**Risiko für Bias**	**Inkonsistenz**	**Indirektheit**	**Fehlende Genauigkeit**	**Andere Faktoren**	**Carboplatin-Monotherapie**	**Bestrahlung**		
Gesamtüberleben 5 Jahre / 10 Jahre										
3	Beobachtungsstudien [1,4,7]	schwerwiegend [a]	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=325	n=793	**5 yr OS[1]:** Carboplatin: 92,3%, Radiotherapy: 97,4% **5 yr OS[7]:** Carbo 1x: 99,2%, Radiation: 98,7% **10 yr OS[4]:** Chemotherapy: 100%, Radiotherapy: 99.4%	⨁◯◯◯ SEHR NIEDRIG

Explanations

a. Kohortenstudien, Risk of Bias-Bewertung mit dem SIGN-Tool: mittlere oder niedrige Qualität der Studien

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GRADE-Erläuterungen

⊕⊕⊕⊕ **Hohes Vertrauen**
Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert
⊕⊕⊕⊖ **Moderates Vertrauen**
Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.
⊕⊕⊖⊖ **Geringes Vertrauen**
Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.
⊕⊖⊖⊖ **Sehr geringes Vertrauen**
Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.

Autor(en): Wilborn für AG Ruf Kapitel 9

Datum: 02.02.2018

Frage: PICO 27: Surveillance verglichen mit Radiatio bei Seminom-Patienten Stadium I

Setting: Klinik

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Surveillance	Bestrahlung		
Rezidivrate										
3	Beobachtungsstudien 1,2,3	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=812	n=451	Relapse rate1: Surveillance: n=21 (8,2%), Radiotherapy: n=1 (2,4%) Relapse rate2: Surveillance: n=72 (15%), Radiation: n= 14 (5%) Relapse rate3: Surveillance: 22,3%, Radiotherapy: 7,7%	⊕◯◯◯ SEHR NIEDRIG
Zeitdauer bis zum Rezidiv										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Surveillance	Bestrahlung		
5	Beobachtungsstudien 2,4,5,6,7	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=1510	n=1125	Median time to relapse2: Surveillance 14 mo, Radiation 15 mo Median time to relapse4: Surveillance14 (3–36) mo, Radiation 9, 14, 15, 25 mo Time to relapse for all5: 15 mo (4-93) Median time for relapse6: Surveillance 21.0 mo, Radiotherapy 37.9 mo Median time to relapse7: Surveillance 1,4 ys, Radiation 1,1 ys	⊕◯◯◯ SEHR NIEDRIG
Krankheitsfreies Überleben 5 Jahre										
5	Beobachtungsstudien 3,6	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=258	n=312	5 yr DFS3: Surveillance 64,2%, Radiotherapy 91,9% 5 yr RFS6: Surveillance 90%, Radiotherapy 95%	⊕◯◯◯ SEHR NIEDRIG
Gesamtüberleben 5 Jahre/10 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Surveillance	Bestrahlung		
5	Beobachtungsstudien 2,3,6,7,10	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=2753	n=6058	5 yr OS2: Surveillance 98.6%, adjuvant RT 97.2% 5 yr OS3: Surveillance 100%, Radiotherapy 97,4% 5 yr OS7: Surveillance 98,4%, Radiation 98,7% 5 yr OS10: Radiation 97,7%, Surveillance 95.0% 10 yr OS10: Surveillance 92.2%, Radiation 94.8% 10 yr OS2: Surveillance 97.7%, Radiation 91.4% 10 yr OS6: Surveillance 100%, Radiotherapy 99.4%	⊕◯◯◯ SEHR NIEDRIG
Krankheitsspezifisches Überleben 5 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Surveillance	Bestrahlung		
4	Beobachtungsstudien 4,7,8,9, 10	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=2459	n=6330	Total DSS4: Surveillance 100%, Radiation 100% 5-yr-DSS8: Surveillance 89%, Radiation: 93% 5 yr CSS9: Surveillance 100%, Radiation 99.3% (95% CI 98.2-100) 5 ys-CSS7: Surveillance 99,8%, Radiation 100% 5y CSS10: Radiation 99.6% (95% CI 99.4-99.8) Surveillance: 98.7% (95% CI 98.1-99.4)	⊕◯◯◯ SEHR NIEDRIG

Explanations

a. Kohortenstudien, Risk of Bias-Bewertung mit dem SIGN-Tool: mittlere oder niedrige Qualität der Studien

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GRADE-Erläuterungen

⊕⊕⊕⊕ Hohes Vertrauen

Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert

⊕⊕⊕⊖ Moderates Vertrauen

Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.

⊕⊕⊖⊖ Geringes Vertrauen

Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.

⊕⊖⊖⊖ Sehr geringes Vertrauen

Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.

Autor(en): Wilborn für AG Heinzelbecker Kapitel 9

Datum: 28.03.2018

Frage: PICO 31: Chemotherapie (PEB 3x / EP 4x) verglichen mit Radiatio bei Seminom IIA/IIB

Setting: Klinik

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Chemotherapie (PEB 3x / EP 4x)	Bestrahlung		
Gesamtüberleben 5 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Chemotherapie (PEB 3x / EP 4x)	Bestrahlung		
6	Beobachtungsstudien 1,2,3,4,5, 6	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=1351	n=1381	CSIIA 5 yr OS1: Chemotherapy 88%, Radiation 96% CSIIA 5 yr OS3:Chemotherapy 91.2%, Radiation 99.4% CSIIA 5 yr OS5:Chemotherapy 100%, Radiation 100% CSIIB 5 yr OS1: Chemotherapy 90%, Radiation 98% CSIIB 5 yr OS3: Chemotherapy 92.8%, Radiation 96.1% CSIIB 5 yr OS5: Chemotherapy 100%, Radiation 100% CSII 5 yr OS2: Chemotherapy 88%, Radiation 82% CSII 5 yr OS4: Chemotherapy 90.7%, Radiation 92.3% CSII 5 yr-OS6 :Chemotherapy: 93%	⊕◯◯◯ SEHR NIEDRIG
Krebsspezifisches Überleben 5 Jahre										

Certainty assessment							№ der Patienten eingeschlossen pro Arm		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Chemotherapie (PEB 3x / EP 4x)	Bestrahlung		
3	Beobachtungsstudien 1,5, 6	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=531	n=165	CSIIA: 5 yr CSS1: Chemotherapy 96%, Radiation 97% CSIIA: 5 yr CSS5: Chemotherapy 100%, Radiation 100% CSIIB: 5 yr CSS1: Chemotherapy 98%, Radiation 98% CSIIB: 5 yr CSS5: Chemotherapy 100%, Radiation 100% CSII: 5-yr-CSS6: Chemotherapy: 95%	⊕◯◯◯ SEHR NIEDRIG
Zeitdauer bis zum Rezidiv										
2	Beobachtungsstudien 2,5	schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=76	n=66	Median time to relapse2: 13,5 mo Median time to relapse5: 2,1 ys	⊕◯◯◯ SEHR NIEDRIG

Explanations

a. Kohortenstudien, Risk of Bias-Bewertung mit dem SIGN-Tool: mittlere oder niedrige Qualität der Studien

References

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GRADE-Erläuterungen

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Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert

⊕⊕⊕⊖ Moderates Vertrauen

Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.

⊕⊕⊖⊖ Geringes Vertrauen

Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.

⊕⊖⊖⊖ Sehr geringes Vertrauen

Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.

Autor(en): Wilborn für AG Heinzelbecker Kapitel 9

Datum: 07.02.2018

Frage: PICO 33b: Standard-Chemotherapie (4xPEI, PEI) verglichen mit intensivierter Therapie (Fizazi-Schema, Hochdosis) bei Patienten der Schlechte-Prognose-Gruppe mit inadäquatem Markerabfall

Setting: Klinik

Certainty assessment							№ der Patienten		Ergebnisse	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Standard-Chemotherapie (4xPEI, PEI)	intensivierte Therapie (Fizazi-Schema, Hochdosis)	aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	
Progressionsfreies Überleben 3 Jahre										
1	randomisierte klinische Studie 1	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	schwerwiegend a	keine	n=98	n=105	3 yr PFS: 59% (95% CI 49–68) in the Unfav-dose-dense group 48% (95% CI 38–59) in the Unfav-BEP group (HR 0·66, 95% CI 0·44–1·00, p=0·05) favours dose dense	⊕⊕⊕◯ MODERAT
Gesamtüberleben 3 Jahre										

Certainty assessment							№ der Patienten		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Standard-Chemotherapie (4xPEI, PEI)	intensivierte Therapie (Fizazi-Schema, Hochdosis)		
1	randomisierte klinische Studien 1	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	schwerwiegend a	keine	n=98	n=105	3 yr OS 73% (95% CI 64–81) in the Unfav-dose dense group 65% (95% CI 55–75) in the Unfav-BEP group (HR 0·78, 95% CI 0·46–1·31, p=0·34) favours dose dense	⊕⊕⊕◯ MODERAT
Gesamtüberleben 10 Jahre										
1	Beobachtungsstudien 2,b	schwerwiegend c	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	keine Angaben	n=88	10 yr OS2: 67.4% (95% CI 56.7 -76.1)	⊕◯◯◯ SEHR NIEDRIG
Progressionsfreies Überleben 10 Jahre										
1	Beobachtungsstudien 2	schwerwiegend c	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	keine Angaben	n=88	10 yr PFS2: 63,8% (95% CI 53.2 -72.6)	⊕◯◯◯ SEHR NIEDRIG
Krebsspezifisches Überleben 10 Jahre										
1	Beobachtungsstudien 2	schwerwiegend c	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	keine Angaben	n=88	10 yr CSS2: 68,5% (95% CI 57.5 - 76.8)	⊕◯◯◯ SEHR NIEDRIG

Explanations

a. weite Konfidenzintervalle in den Survival-Ergebnissen

c. Kohortenstudien, Risk of Bias-Bewertung mit dem SIGN-Tool: mittlere oder niedrige Qualität der Studien

References

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GRADE-Erläuterungen

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⊕⊖⊖⊖ Sehr geringes Vertrauen

Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.

Autor(en): Wilborn für AG Pfister Kapitel 10

Datum: 28.03.2018, ergänzt 09.05.2018

Frage: PICO 62: TIP-Chemotherapie verglichen mit Hochdosis-Chemotherapie bei Patienten nach RLA und Chemo

Setting: Klinik

assessment							№ der Patienten		Ergebnisse aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Certainty Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	TIP-Chemotherapie (Salvage)	Hochdosis-Chemotherapie		
Komplette Remission										
3	Beobachtungsstudien 1,2, 4	sehr schwerwiegend a, g	nicht schwerwiegend	schwerwiegend b, f	nicht schwerwiegend	keine	n=26	n=21	CR1: n=5/10 CR2: n=1/14 CR4 : n=21/36	⊕◯◯◯ SEHR NIEDRIG
5-Jahres-Gesamtüberleben										
2	Beobachtungsstudien 1, 6	nicht schwerwiegend a	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=10 n=773	n=821	5 yr OS1: 66% 5-yr-OS6 : CDCT 40,8% 5-yr OS 6: HDCT 53,2% HR OS6: 0.65 (95% CI, 0.56 - 0.75), favoring HDCT	⊕⊕◯◯ NIEDRIG
Zeitdauer bis Tod										
1	Beobachtungsstudien 2	sehr schwerwiegend a,b	nicht schwerwiegend	schwerwiegend b	nicht schwerwiegend	keine	n=14	keine Kontrollgruppe	Median overall survival time2: 21,1 mo	⊕◯◯◯ SEHR NIEDRIG
2 Jahres Progressionsfreies Überleben										

assessment							№ der Patienten		Ergebnisse	
									aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Certainty Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	TIP-Chemotherapie (Salvage)	Hochdosis-Chemotherapie		
2	Beobachtungsstudien 4, 6	nicht schwerwiegend c	nicht schwerwiegend	nicht schwerwiegend	nicht schwerwiegend	keine	n=773 + 16=789	n=821 + 21=842	HDCT as initial salvage therapy: 2-yr-PFS4: 33,3,% (95% CI 14,9-53,1) TIP as initial salvage therapy: 2-yr-PFS4: 61,9% (95% CI 33,9-80,8) CDCT6: 27,8% HDCT6: 49,6% HR6 0.44 (95% CI 0.39 - 0.51) favoring HDCT	⊕⊕◯◯ NIEDRIG
2 Jahres Gesamtüberleben										
2	Beobachtungsstudien 3, 4	schwerwiegend c, d	nicht schwerwiegend	schwerwiegend e	nicht schwerwiegend	keine	n=16	n=385	HDCT as second-line: 2-yr OS3: 67% (95% CI, 61% - 72%) HDCT as third-line or later therapy: 2-yr-OS3: 60% (95% CI, 46% - 71%) HDCT as initial salvage therapy4: 2-yr-OS: 47,6% (95% CI 25,7-66,7) TIP as initial salvage therapy4: 2-yr-OS: 75% (95% CI 46,3-89,8)	⊕◯◯◯ SEHR NIEDRIG

assessment							№ der Patienten		Ergebnisse	
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	TIP-Chemotherapie (Salvage)	Hochdosis-Chemotherapie	aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Certainty Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty

Certainty assessment							№ der Patienten		Ergebnisse	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	TIP-Chemotherapie	Hochdosis-Chemotherapie	aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	
5 Jahres Gesamtüberleben										
1	randomisierte klinische Studien [7]	nicht schwerwiegend	nicht schwerwiegend	schwerwiegend	nicht schwerwiegend	keine		n=108 Arm A 1xVIP+3xHD n=103 Arm B 3xVIP+1xHD	5 yr OS: 49% (95% CI, 40% - 59%) in arm A 5 yr OS: 39% (95% CI, 30% - 49%) in arm B HR 1.42; 95% CI, 0.99 - 2.05; p=0,057	⨁⨁⨁◯ MODERAT

Certainty assessment							№ der Patienten		Ergebnisse	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	TIP-Chemotherapie	Hochdosis-Chemotherapie	aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	
5 Jahres Progressionsfreies Überleben										
1	randomisierte klinische Studien [1]	nicht schwerwiegend	nicht schwerwiegend	schwerwiegend [a]	nicht schwerwiegend	keine		n=108 Arm A 1xVIP+3xHD n=103 Arm B 3xVIP+1xHD	5 yr-PFS: 47% (95% CI, 37% - 56%) in arm A 5 yr PFS: 45% (95% CI, 35% - 55%) in arm B HR 1.16; 95% CI, 0.79 - 1.70; p=0,454	⨁⨁⨁◯ MODERAT

Explanations

a. Studie von Kurobe 2015 und Park 2011 sind einarmige Studien, es fehlt somit die Vergleichsgruppe

b. die Studien von Kurobe 2015 und Park 2011 untersuchen jeweils in einem single-Arm Design nur eine Gruppe von Patienten, es fehlt eine Vergleichsgruppe, daher ist die Indirektheit als schwerwiegend einzustufen

d. die Studie von Narayan 2016 ist eine retrospektive single-arm Kohortenstudie und hatte in der SIGN-RoB-Bewertung einen mittleren RoB

e: die Studie von Narayan 2016 untersucht in einem single-Arm Design nur jeweils eine Gruppe von Patienten, es fehlen jeweils eine Vergleichsgruppe, daher ist die Indirektheit als schwerwiegend einzustufen

f: die Studie von Narayan 2016 untersucht in einem single-Arm Design nur jeweils eine Gruppe von Patienten, es fehlt eine Vergleichsgruppe, daher ist die Indirektheit als schwerwiegend einzustufen

g: die Studie von Narayan 2016 ist eine retrospektive single-arm Kohortenstudie und hatte in der SIGN-RoB-Bewertung einen mittleren RoB

h. die Studie von Lorch et al. 2012 vergleicht zwei HD--Regime, daher sind die Ergebnisse nur indirekt zur Beantwortung der PICO geeignet

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GRADE-Erläuterungen

⊕⊕⊕⊕ **Hohes Vertrauen** Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert

⊕⊕⊕⊖ **Moderates Vertrauen** Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.

⊕⊕⊖⊖ **Geringes Vertrauen** Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.

⊕⊖⊖⊖ **Sehr geringes Vertrauen** Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.

Die Studie von Necchi 2017 wurde nicht mit in die GRADE-Bewertung eingeschlossen, da sie nur Seminom-Patienten einschließt, die PICO aber alle Patienten umfasst, die Ergebnisse sind daher nur eingeschränkt aussagekräftig und werden daher nicht mit in die GRADE-Bewertung aufgenommen.

Autor(en): Wilborn für AG Pfister Kapitel 10

Datum: 02.02.2018

Frage: PICO 63: TIP/Hochdosis-Chemotherapie verglichen mit Chemotherapie analog der histologischen Differenzierung bei Patienten mit maligner somatischer Transformation in der RTR

Setting: Klinik

Certainty assessment							№ der Patienten		Ergebnisse	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	TIP/Hochdosis-Chemotherapie	Chemotherapie analog der histologischen Differenzierung	aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	
Krankheitsspezifisches Überleben nach einem Jahr										
1	Beobachtungsstudien 1	sehr schwerwiegend a	nicht schwerwiegend	schwerwiegend b	nicht schwerwiegend	keine	keine Kontrollgruppe	n=12 unresectable PNET-group PNET: Primitive Neuroectodermal Tumor	unresectable PNET-group: 1-y-CSS1: 80%	⊕◯◯◯ SEHR NIEDRIG
Krankheitsspezifisches Überleben nach zwei Jahren										
1	Beobachtungsstudien 1	sehr schwerwiegend a	nicht schwerwiegend	schwerwiegend b	nicht schwerwiegend	keine	keine Kontrollgruppe	n=12 unresectable PNET-group	unresectable PNET-group: 2-yr-CSS1: 50%	⊕◯◯◯ SEHR NIEDRIG
Kein Nachweis der Erkrankung										

Certainty assessment							№ der Patienten		Ergebnisse	Certainty
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	TIP/Hochdosis-Chemotherapie	Chemotherapie analog der histologischen Differenzierung	aufgrund der Ergebnisberichtung in den Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	
2	Beobachtungsstudien 1,2	sehr schwerwiegend c	nicht schwerwiegend	schwerwiegend d	nicht schwerwiegend	keine	keine Kontrollgruppe	n=18	n=1/122 n=6 /61 NED (No Evidence of Disease) nach 33 Monaten	⊕◯◯◯ SEHR NIEDRIG

Explanations

a. die Studie von Al Hader 2015 ist eine retrospektive single-arm Kohortenstudie und hatte in der SIGN-RoB-Bewertung einen hohen RoB

b. die Studie vonAl-Hader 2015 untersucht in einem single-Arm Design nur eine Gruppe von Patienten, es fehlt eine Vergleichsgruppe, daher ist die Indirektheit als schwerwiegend einzustufen

c. die Studien von Al Hader 2015 und Ehrlich 2010 sind jeweils retrospektive single arm Kohortenstudien und hatten beide in der SIGN-RoB-Bewertung einen hohen Risk of Bias

d. die Studien von Al-Hader 2015 und Ehrlich untersuchen beide jeweils in einem single-Arm Design nur eine Gruppe von Patienten, es fehlt eine Vergleichsgruppe, daher ist die Indirektheit als schwerwiegend einzustufen

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1. Al-Hader, A. A.,Jain,A.,Al-Nasrallah,N.,& Einhorn,L. H.. Metastatic malignant transformation of teratoma to primitive neuroectodermal tumor (PNET): results with PNET-based chemotherapy. . American Journal of Clinical Oncology, ; 2015.

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GRADE-Erläuterungen

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⊕⊕⊕⊖ Moderates Vertrauen

Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.

⊕⊕⊖⊖ Geringes Vertrauen

Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.

⊕⊖⊖⊖ Sehr geringes Vertrauen

Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.

Autor(en): Wilborn für AG Pfister Kapitel 10

Datum: 02.02.2018

Frage: PICO 64: Eine Residual-Tumor-Resektion RTR verglichen mit Chemotherapie bei Patienten mit Marker-Positivem Residualtumor

Setting: Klinik

Certainty assessment							№ der Patienten		Ergebnisse	
№ der Studien	Studiendesign	Risiko für Bias	Inkonsistenz	Indirektheit	Fehlende Genauigkeit	Andere Faktoren	Residual-Tumor-Resektion RTR	Chemotherapie	aufgrund des Fehlens von weiteren Einzelstudien ist eine Ergebniszusammenfassung per Metanalyse nicht möglich	Certainty
Gesamtüberleben 5 Jahre										
1	Beobachtungsstudien 1	sehr schwerwiegend a	nicht schwerwiegend	schwerwiegend b	nicht schwerwiegend	keine	n=39	keine Patienten	5 yr-OS: n=15/39	⊕◯◯◯ SEHR NIEDRIG

Explanations

a. Kohortenstudien, Risk of Bias-Bewertung mit dem SIGN-Tool: mittlere oder niedrige Qualität der Studien

b. da der Studie von Cary 2015 die Vergleichsgruppe fehlt, wird die Frage nach der Indirektheit mit schwerwiegend eingestuft

References

1. Cary, C.,Pedrosa,J. A.,Jacob,J.,Beck,S. D.,Rice,K. R.,Einhorn,L. H.,& Foster,R. S.. Outcomes of postchemotherapy retroperitoneal lymph node dissection following high-dose chemotherapy with stem cell transplantation.. Cancer,; (2015).

GRADE-Erläuterungen

⊕⊕⊕⊕ Hohes Vertrauen

Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert

⊕⊕⊕⊖ Moderates Vertrauen

Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.

⊕⊕⊖⊖ Geringes Vertrauen

Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.

⊕⊖⊖⊖ Sehr geringes Vertrauen

Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet

9.9. Recherche nach nationalen und internationalen Qualitätsindikatoren zu den Keimzelltumoren des Hodens

Rechercheauftrag

Die Recherche wurde vom Bereich Infoplattform (Jessica Lobitz und Maike Schäfer) zwischen dem 17.07.2018 und 31.07.2018 durchgeführt.

Als Recherchevokabular wurden folgende Begriffe verwendet:

Population:

Erwachsene Männer mit Keimzelltumoren des Hodens in allen Versorgungssettings (ambulant/stationär).

Hodenkarzinom, Hodenkrebs, Keimzelltumor

Testicular Neoplasms

seminoma OR non-seminoma OR testicular OR testis OR germ cell OR germinomatous OR non-germinomatous OR spermatocyte OR Leydig cell OR sertoli cell OR sex cord OR gonadal stromal

AND (tumor OR tumour OR cancer OR cancers OR carcinoma OR neoplasm OR neoplasms OR neoplasia)

Intervention:

Qualitätsindikator; Qualitätsindikatoren

Quality Indicators, Health Care

quality indicator* OR performance indicator* OR health indicator* OR quality measure* OR performance measure* OR health measure*

Limits:

Bei der Suche erfolgte eine Einschränkung des Suchzeitraums (1.07.2008 bis 17.07.2018).

Weitere Einschränkungen bezüglich spezifischer Subgruppen innerhalb der Zielpopulation erfolgten nicht.

Die Suche wurde in folgenden Quellen durchgeführt:

- Literaturdatenbanken: Medline über https://www.ncbi.nlm.nih.gov/ & Cochrane über http://www.cochranelibrary.com/
- Webseiten von nationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren

- Webseiten von internationaler Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Suchmaschine: www.google.de

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und unter 2 Recherchestrategien dargelegt.

Recherchestrategien

Bibliographische Datenbanken

PubMed

Recherchedatum: 17.07.2018

Search	Query	Items found
#8	Search **(#6 AND #7)** Filters: Publication date from 2008/07/01 to 2018/07/17; Humans; English; German	57
#7	Search **(#3 AND #6)**	123
#6	Search **(#4 OR #5)**	239848
#5	Search **Quality Indicators, Health Care [MeSH Terms]**	18424
#4	Search **(quality[Title/Abstract] OR performance[Title/Abstract]) AND (indicator[Title/Abstract] OR indicators[Title/Abstract] OR measure[Title/Abstract] OR measures[Title/Abstract])**	228497
#3	Search **(#1 OR #2)**	41884
#2	Search **Testicular Neoplasms [MeSH Terms]**	24836
#1	Search **(((seminoma[Title/Abstract] OR non-seminoma[Title/Abstract] OR testicular[Title/Abstract] OR testis[Title/Abstract] OR germ cell[Title/Abstract] OR germinomatous[Title/Abstract] OR non-germinomatous[Title/Abstract] OR spermatocyte[Title/Abstract] OR Leydig cell[Title/Abstract] OR sertoli cell[Title/Abstract] OR sex cord[Title/Abstract] OR gonadal stromal[Title/Abstract])) AND (tumor[Title/Abstract] OR tumour[Title/Abstract] OR cancer[Title/Abstract] OR cancers[Title/Abstract] OR carcinoma[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplasia[Title/Abstract]))**	31821

Cochrane

Recherchedatum: 17.07.2018

Search	Query	Items found
#1	Search **(seminoma OR non-seminoma OR testicular OR testis OR germ cell OR germinomatous OR non-germinomatous OR spermatocyte OR Leydig cell OR sertoli cell OR sex cord OR gonadal stromal) AND (tumor OR tumour OR cancer OR cancers OR carcinoma OR neoplasm OR neoplasms OR neoplasia):ti,ab,kw** (Word variations have been searched)	1118
#2	Search **(quality OR performance OR health) AND (indicator* OR measure*) ti** (Word variations have been searched)	1312
#3	Search **#1 and #2**	1
#5	Search **#1 and #2**; Publikation Year from 2008	0

Nationale Qualitätsindikatorenprojekte/-programme

Recherchedatum: 19.07.2018

Institution	Quelle	Treffer
QISA	QISA – Qualitätsindikatorensystem für die ambulante Versorgung http://www.aok-gesundheitspartner.de/bund/qisa/themen/index.html	0
GKV-Spitzenverband	Qualitätsindikatoren-Thesaurus über https://quinth.gkv-spitzenverband.de/content/suche.php	0
IQTiG	Suchfunktion auf https://iqtig.org	0

Internationale Qualitätsindikatorenprojekte/ -programme

Recherchedatum: 19.07.2018

Institution	Quelle	Treffer
AHRQ (Agency for Health Research and Quality) Quality Indicators	Über http://www.qualityindicators.ahrq.gov/ https://www.ahrq.gov/gam/index.html	0

Institution	Quelle	Treffer
AMA (American Medical Association)	Über https://www.thepcpi.org/	0
ASCO (American Society of Clinical Oncology) Quality Oncology Practice Initiative	http://qopi.asco.org/index.html	0
CIHI (Canadian Institute for Health Information) Health Indicators	https://www.cihi.ca/en/health-indicators	0
CQCO (Cancer Quality Council of Ontario) Cancer System Quality Index – set of indicators	http://www.csqi.on.ca/all_indicators/#.UlJ9iW25OH4	0
ISD Scotland Health Indicators	http://www.isdscotland.org/Health-Topics/Cancer/ http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis/quality_performance_indicators.aspx	10
JCAHO (Joint Commission on Accrediation of Healthcare Organizations)	http://www.jointcommission.org/accountability_measures.aspx	0
NHS (National Health Services) Indicators for Quality Improvement	https://digital.nhs.uk/ https://digital.nhs.uk/data-and-information	0
NQF (National Quality Forum) Performance Measures	http://www.qualityforum.org/QPS/	0
OECD Health Care Quality Indicators	http://www.oecd.org/health/health-systems/hcqi-cancer-care.htm	0
RAND Corporation Quality of Care Assessment Tools (QA Tools)	http://www.rand.org/health/surveys_tools/qatools.html	0
Oncoline (Niederlande)	http://oncoline.nl/index.php	0
KCE (Belgien)	https://kce.fgov.be/	12

Suchmaschine

Recherchedatum: 31.07.2018

Suchmaschine: www.google.de

Suche deutsch: **(Hodenkarzinom OR Hodenkrebs OR Keimzelltumor) AND (Qualitätsindikator OR Qualitätsindikatoren)**

Suche englisch: **((seminoma OR non-seminoma OR testicular OR testis OR germ cell OR germinomatous OR non-germinomatous OR spermatocyte OR Leydig cell OR sertoli cell OR sex cord OR gonadal stromal) (tumor OR tumour OR cancer OR carcinoma OR neoplasm OR neoplasia) (quality OR performance) (indicator OR measure))**

Treffer nach Screening: 0

9.10. Anlage Ergebnis Recherche Qualitätsindikatoren

Rechercheergebnisse

Ausschlussgründe:

A1: Doppelpublikation

A2: andere Entität

A3: kein Qualitätsindikator

Bibliographische Datenbanken

Anzahl der Treffer nach Titel- und Abstractsichtung (Pubmed): 1

Treffer nach Volltextsichtung: 0

Nationale Qualitätsindikatoren

Recherchedatum: 19.07.2018

Treffer: 0

Internationale Qualitätsindikatoren

Recherchedatum: 19.07.2018

ISD Scotland Health Indicators

[2]

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
QPI 1: Radiological Staging: Patients with testicular cancer should be evaluated with appropriate imaging to detect the extent of disease and guide treatment decision making*.	Nein	**7.2** Männer mit neu diagnostiziertem KZT sollen zur Ausbreitungsdiagnostik eine kontrastmittelgestützte Computertomographie (CT) von Abdomen/Becken und Thorax erhalten.

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Numerator: Number of patients with testicular cancer undergoing CT scanning of the chest, abdomen and pelvis within 3 weeks of orchidectomy. **Denominator:** All patients with testicular cancer undergoing orchidectomy.		Konsensstärke 100% **LoE 5 EG A** Anmerkung: Soll-Empfehlung enthält keine Zeitangabe
QPI 2: Pre-operative Assessment Patients with testicular cancer should have pre-operative assessment of the testicle and Serum Tumour Markers (STMs)†. **Numerator:** Number of patients with testicular cancer undergoing orchidectomy, who undergo a pre-operative assessment of the testicle which, at a minimum, includes: (i) STMs (ii) testicular ultrasound. **Denominator:** All patients with testicular cancer undergoing orchidectomy.	Nein	**7.9** Bei Patienten mit Verdacht auf einen KZT sollen vor Ablatio testis die Serumtumormarker AFP, Beta-hCG und LDH bestimmt werden. Konsensstärke 100% **EK** **7.1** Bei klinischem Verdacht auf einen KZT sollen umgehend eine körperliche Untersuchung sowie eine beidseitige Hodensonographie mit mind. 7.5 MHZ Schallkopf erfolgen. Konsensstärke 100% **LoE 5 EG A**
QPI 3: Primary Orchidectomy Patients with testicular cancer should have primary orchidectomy within 2 weeks of ultrasonographic diagnosis. **Numerator:** Number of patients with testicular cancer undergoing orchidectomy within 2 weeks of ultrasonographic diagnosis. **Denominator:** All patients with testicular cancer undergoing orchidectomy.	Nein	**7.11** Bei Verdacht auf einen KZT sollen eine inguinale Hodenfreilegung und bei Nachweis eines malignen Tumors eine Ablatio testis erfolgen. Konsensstärke 95,8% **LoE 5 EG A** Anmerkung: Soll-Empfehlung enthält keine Zeitangabe
QPI 4: Multi-Disciplinary Team Meeting Patients with testicular cancer should be discussed by a Multi Disciplinary Team (MDT) to agree a definitive	Nein	**4.2** KZT-Patienten mit postchemotherapeutischen Residualtumoren sollen nur nach vorheriger multidisziplinärer Abstimmung sowie an

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
management plan post orchidectomy with staging and pathology. **Numerator:** Number of patients with testicular cancer undergoing orchidectomy who are discussed at the MDT to agree a definitive management plan post orchidectomy. **Denominator:** All patients with testicular cancer undergoing orchidectomy.		Zentren mit hoher Expertise und den Voraussetzungen für multidisziplinäre chirurgische Eingriffe eine Residualtumorresektion erhalten. Konsensstärke 72% **EK**
QPI 5: Pathology Reporting All pathology reports for testicular cancer should contain full pathology information to inform patient management. **Numerator:** Number of patients with testicular cancer undergoing orchidectomy where histological pathology report contains tumour type and size, vascular invasion and rete stromal invasion (based upon the current Royal College of Pathologists dataset). **Denominator:** All patients with testicular cancer undergoing orchidectomy.	Nein	**7.17** Der pathohistologische Befundbericht des Hodenpräparates soll folgende Aussagen beinhalten: Angabe von Seite, Größe des Hodens, maximaler Tumorgröße (in 3 Dimensionen), makroskopische Merkmale des Nebenhodens, Samenstranges und der Tunica vaginalis, Tumor im Absetzungsrand (ja/nein), histologischer Typ mit Spezifizierung individueller Komponenten und prozentualer Bestimmung gemäß WHO 2016, peritumorale venöse und/oder lymphatische Invasion (ja/nein), Invasion der Tunica albuginea (ja/nein), Tunica vaginalis (ja/nein), Rete testis (ja/nein), Weichgewebe des Hilus, des Nebenhodens oder des Samenstranges (ja/nein), Germ cell neoplasia in situ im nicht-tumorösen Parenchym (ja/nein), sowie pT Kategorie gemäß der TNM Klassifikation von 2017. Konsensstärke 96,6% **LoE 2a EG A**
QPI 6: Quality of Adjuvant Treatment Patients with stage I seminoma receiving adjuvant single dose carboplatin should have an AUC‡ of 7mg/ml/min based on ethylene diamine tetra-acetic acid (EDTA) clearance.	Nein	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Numerator: Number of patients with stage I seminoma undergoing adjuvant single dose carboplatin AUC7, based on EDTA clearance, within 8 weeks of orchidectomy. **Denominator:** All patients with stage I seminoma undergoing adjuvant single dose carboplatin AUC7.		
QPI 7: Serum Tumour Markers Patients with metastatic testicular cancer should undergo Serum Tumour Markers (STMs) before starting chemotherapy to determine their correct International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic grouping. **Numerator:** Number of patients with metastatic testicular cancer undergoing chemotherapy who have STMs* checked 2 weeks before starting chemotherapy. **Denominator:** All patients with metastatic testicular cancer undergoing chemotherapy.	Nein	
QPI 8: Systemic Therapy Patients with metastatic testicular cancer who are undergoing systemic therapy should receive Systemic Anti-Cancer Therapy (SACT) within 3 weeks of a MDT decision to treat with SACT§. **Numerator:** Number of patients with metastatic testicular cancer undergoing SACT within 3 weeks of an MDT decision to treat with SACT. **Denominator:** All patients with metastatic testicular cancer undergoing SACT.	Nein	
QPI 9: Computed Tomography scanning for surveillance patients Patients with stage I testicular non-seminomatous (or mixed) germ cell tumour (NSGCT) under surveillance should undergo Computed	Nein	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Tomography (CT) scanning of the abdomen +/- chest and pelvis, as per clinical relevance. **Numerator:** Patients with stage I testicular non-seminomatous (or mixed) germ cell tumour who undergo at least three CT scans of the abdomen +/- chest and pelvis within 14 months of diagnosis. **Denominator:** All patients with stage I testicular non-seminomatous (or mixed) germ cell tumour.		
QPI 10: 30 Day Mortality 30 day mortality following treatment for testicular cancer. **Numerator:** Number of patients with testicular cancer who receive treatment who die within 30 days of treatment. **Denominator:** All patients with testicular cancer undergoing treatment (orchidectomy, chemotherapy, radiotherapy).	Nein	

* This includes CT performed pre-operatively providing this is carried out no longer than 3 weeks prior to surgery.

† AFP – Alpha Feta Protein,
HCG – Human chorionic Gonodotrophin
LDH – Lactate dehydrogenase

§ Patients may also begin treatment up to 3 weeks prior to MDT in order to ensure there are no delays to treatment

KCE (Belgian Health Care Knowledge Centre)

[1]

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Diagnosis and staging TC1: Proportion of patients with testicular cancer undergoing tumour	Ja, siehe auch [1] 2006: 81%	**7.9** Bei Patienten mit Verdacht auf einen KZT sollen vor Ablatio testis die

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
marker assessment before any treatment	2001: 72%	Serumtumormarker AFP, Beta-hCG und LDH bestimmt werden. Konsensstärke 100% **EK**
Diagnosis and staging TC2: Proportion of patients with testicular cancer undergoing contrast-enhanced Computed Tomography (CE-CT) or Magnetic Resonance Imaging (MRI) for primary staging	nein	**7.2** Männer mit neu diagnostiziertem KZT sollen zur Ausbreitungsdiagnostik eine kontrastmittelgestützte Computertomographie (CT) von Abdomen/Becken und Thorax erhalten. Konsensstärke 100% **LoE 5 EG A**
Diagnosis and staging TC3: Proportion of patients with testicular cancer discussed at the multidisciplinary team meeting	Ja, siehe auch [1] 2006: 67% (167/248) 2005: 65% (165/254) 2004: 53% (110/207) 2003: 44% (88/198) 2001: 44%	**4.2** KZT-Patienten mit postchemotherapeutischen Residualtumoren sollen nur nach vorheriger multidisziplinärer Abstimmung sowie an Zentren mit hoher Expertise und den Voraussetzungen für multidisziplinäre chirurgische Eingriffe eine Residualtumorresektion erhalten. Konsensstärke 72% **EK**
Treatment TC4: Number of annually surgically treated patients with testicular cancer per centre	2004 – 2006 >9 Orchidekto-mien: 14/97 Zentren (40% der Operationen) Maximalwert: 50 Operationen	
Treatment TC5: Radiation dose and field in patients with testicular cancer treated with radiotherapy by stage	nein	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Treatment TC6: Proportion of patients with stage I non-seminoma treated with active surveillance	Ja, siehe auch [1] 2006: 20% (12/58) 2005: 23,5% (16/69) 2004: 22% (11/51) 2003: 37% (17/46) 2002: 17,1% (6/36) 2001: 28% (7/26)	**Nichtseminomatöser KZT im nicht metastasierten cSI** **9.15** In der Niedrigrisiko - Situation soll die aktive Überwachung favorisiert werden. Konsensstärke 100% **LoE 2b EG A**
Treatment TC7: Proportion of patients receiving CE-CT or MRI for residual disease assessment at the end of systemic treatment	nein	**9.22** Zwei bis drei Monate nach einer Strahlentherapie soll eine Abdomen-/Becken-CT zur Kontrolle erfolgen. Analog soll nach Chemotherapie verfahren werden. Das Ergebnis dieser Untersuchung ist zugleich Ausgangspunkt für die weitere Nachsorge. Konsensstärke 92,5% **LoE 5 EG A**
Treatment TC8: Degree and duration of active surveillance in patients with stage I non-seminoma or seminoma: mean number of tumour marker assessments during the first year after surgery	Ja, siehe auch [1] Seminoma 2006: 6,8 2001: 5,4 Non-Seminoma 2006: 9,6 2001: 15,9	
Treatment TC9: Proportion of patients with relapsing testicular cancer after curative treatment that are included in a clinical trial	nein	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Generic indicator TC10: Overall 5-year survival by stage	Ja, siehe auch [1] 2006: 94% 2001: 91%	
Generic indicator TC11: Disease-specific 5-year survival by stage	Ja, siehe auch [1] 2006: 95% 2001: 92%	
Generic indicator TC12: Disease-free 5-year survival by stage	nein	

Literaturverzeichnis

1. Belgian Health Care Knowledge Centre (KCE). Kwaliteitsindicatoren in oncologie: teelbalkanker, Brussels: KCE, 2010.
2. Healthcare Improvement Scotland (HIS) and National Health Services Scotland (NHS). Testicular Cancer. Clinical Quality Performance Indicators. Published: October 2014, Updated: June 2016 (V2.0), 2016.

9.11. Kommentare zur Konsultationsfassung (Stand 20.03.2019)

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
	soermatozytisches Seminom	spermatozytischer Tumor	nach WHO 2016	wurde korrigiert
Tabelle 3	Es wird lediglich in AG 8 und 9 das Thema der Arbeitsgruppe erwähnt,	Thema auch bei den anderen AGs zu ergänzen	Übersichtlichkeit	wurde ergänzt; AG 9 Leitung: Änderungen wurden kurzfristig erforderlich
Tabelle 4	bei der Auflistung der Substanzen der Chemotherapieregime wird bei CEC ein "und" eingefügt, bei den anderen nur mit Kommata getrennt	Einheitlich nur Kommata, kein und	Sprachliche Verbesserung	wurde korrigiert
10.1.2.1	nach adjuvanter Therapie mit PEB wird im Rezidiv erneut PEB empfohlen; in einigen Fällen könnte dies zu insgesamt 6# PEB führen (2 adjuvant, 4 im Rezidiv)	hier sollt auf die nicht zu überschreitende Bleomycin-Dosis (400 mg ~4# PEB, s. Kapitel 9.5.3.7.5, S. 99) und ggf. alternative Regime hingewiesen werden	Gefahr des Missverständnisses, Überdosierung Bleomycin	Kapitelverweis wurde ergänzt
Qualitätsindikator 7	Lediglich 3# PEB werden als gültig genannt	als Alternative zu #3 PEB sollte 4# PE genannt werden	Anmerkung unten an der Tabelle ist m.E. nicht deutlich genug	Die Empfehlung in der Anmerkung ist eindeutig. Alternativ müsste die Dopplung des Empfehlungstextes erfolgen, was die Lesbarkeit und Länge der Leitlinie beeinflusst.

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
Qualitätsindikator 8/9/10	Lediglich 4# PEB werden als gültig genannt	als Alternative zu #4 PEB sollte 4# PEI genannt werden	Anmerkung unten an der Tabelle ist m.E. nicht deutlich genug	Die Empfehlung in der Anmerkung ist eindeutig. Alternativ müsste die Dopplung des Empfehlungstextes erfolgen, was die Lesbarkeit und Länge der Leitlinie beeinflusst.
		Allgemeines: - ich habe in Kapitel 9.5.3 mehrere Textabschnitte geschrieben (als Mitglied der AG von Fr. Heinzelbecker) und war be der Konsensukonferenz als Vertreterin der AIO (Vertreterin von H. Bokemeyer) dabei - **ich möchte darum bitten, dies auch zu erwähnen** - an mehreren Stellen wird im Text bei Beschreibung von Studien / -ergebnissen zwischen Zeiten (Präsens / Präteritum) hin- und her gewechselt, Beispiele: - S 86 2./3.. Satz des Textblocks ... behandelt werden.... Monotherapie war das Überleben...., - S 96 / 4. und 5. Textblock, - S 155 2. Textblock		Dr. Dieng wurde als Stellvertreterin ergänzt und in der AG Heinzelbecker gelistet. Sprachliche Vereinheitlichungen wurde durchgeführt.

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
		Sprachlich wäre es schöner, dies zu vereinheitlichen (Präteritum)		
Seite 6	Inhaltverzeichnis 11.2 Extragonadale Keimzelltumore 11.4 .. Keimzelltumoren	Bitte einheitlich „Keimzelltumoren“ verwenden und im Text durchgehend angleichen		wurde korrigiert
Seite 133, 10.21	Bei Patienten mit einer malignen somatischen Transformation im Rezidiv nach Therapie eines KZT soll sich die Chemotherapie nach der Histologie richten.	Bei Patienten mit einer malignen somatischen Transformation im Rezidiv nach Therapie eines KZT soll sich die Chemotherapie nach der Histologie der somatischen Mutation richten.	Klarstellung!	wurde ergänzt
Seite 66, Kapitel 9.3.4.6.		Ergänzung eines Verweises auf Kapitel 13.14.3.	Der Vergleich der Therapieoptionen nur anhand der Effektivität und ohne Berücksichtigung der Toxizitäten ist aus meiner Sicht nicht legitim.	wurde ergänzt
Seite 88, Kapitel 9.5.3.4., Empfehlung 9.38.	„… gegen Bleomycin drei Zyklen PEI-Chemotherapie oder 4 Zyklen EP erhalten.“	„… Bleomycin vier Zyklen EP erhalten.“	Bei good prognosis ist 3x PEI nicht zu empfehlen.	Nach Prüfung des Abstimmungsverlaufes und der zugrunde liegenden Literatur wurde die Empfehlung entsprechend geändert. Hier ist ein Übertragungsfehler unterlaufen und es wurde der Text der ursprünglich

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
				abgestimmten Empfehlung übernommen.
Seite 94, Tabelle 20		Bitte bei HD-PEI Stammzell-Re-Infusion an Tag 7 ergänzen.	Es sollte im Schema deutlich werden, dass diese Chemotherapie nur mit Stammzell-Support möglich ist.	Stammzell-Re-Infusion an Tag 7 wurde ergänzt
Seite 112	Kapitel 9.6.7.	Gehört in Kapitel 10.	Residualtumorresektion nach Salvage-Chemotherapie wird dort thematisiert.	Verweis auf Kapitel 10 wurde ergänzt
Seite 123, Empfehlung 10.12.	„… sollte die Hochdosischemotherapie durchgeführt werden.“	Sprachliche Verbesserung: „… sollte eine Hochdosischemotherapie …“		wurde verbessert
Seite 128, Empfehlung 10.17	„Nach Ansprechen auf eine Therapie mit GOP soll eine Resektion …“	Literaturverweis für diese Empfehlung fehlt bisher.	Oechsle K, Kollmannsberger C, Honecker F, Mayer F, Waller CF, Hartmann JT, Boehlke I, Bokemeyer C; German Testicular Cancer Study Group. Long-term survival after treatment with gemcitabine and oxaliplatin with and without paclitaxel plus secondary surgery in patients with cisplatin-refractory and/or multiply relapsed germ cell tumors. Eur Urol. 2011 Oct;60(4):850-5.	wurde ergänzt

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
Seite 179, Empfehlung 15.1.	„… sollten der Patient und bei Bedarf seine Angehörigen …“	„… sollten der Patient und seine Angehörigen …“	Zugang und Information sollten immer möglich sein, da der Bedarf vom Patienten und seine Angehörigen definiert wird (und nicht primär von den Behandlern).	Der Patient ist der primäre Ansprechpartner des Arztes. Der Kontakt zu Angehörigen erfolgt auf Wunsch.
Literaturverzeichnis		Doppelte Literaturangeben	Souchon et al 2000 ist offensichtlich identisch mit Souchon et al 2002; Strahlenther Onkol, 176(9):388-405. Die Jahreszahl 2000 dürfte stimmen Sedlmayer, F. doppelt aufgeführt, die erste der beiden Eingaben ist zutreffend. Schmoll et .al. 2004c und Schmoll 2004c sind identisch Rick, O. 2016 und Rick 2017 wahrscheinlich identisch, die zweite Eingabe enthält keine Spezifikationen Petersen P.M. ebenfalls doppelt, die zweite von beiden ist die bessere Nayan 2017 Eur. Urol.: Vorname fehlt. Korrekt ist: Nayan, M. in der Eingabe ist auch ein falscher (unschöner) Zeilenumbruch	Literaturstellen wurden korrigiert

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
			Giwercman, A. 1987 „Urol“ gibt es nicht. Hier muß es heißen: „J. Urol.“ 138: Seitenzahlen sind aber richtig ESUR: das ist eine sehr ungünstige Eingabe. Der Artikel wurde von Richenberg als Erstautor publiziert (und auch in PubMed so gelistet) und so sollte der Artikel hier auch zitiert werden. Die Autoren sind alle richtig aufgeführt. Die Quelle lautet: Eur. Radiol. 25(2) 323-330 (2015) Auf S. 56 in der evidenzbasierten, Empfehlung 9.8, kommt mir das Lay out merkwürdig vor mit der Trennung des Wörtchens oder (o-der) mit viel Leerstellen.	
Seite 65	Das krebsspezifische Überleben lag in der Strahlentherapiegruppe nach fünf, zehn und 20 Jahren höher als in der Überwachungsgruppe. Berücksichtigt werden müssen bei dieser Arbeit die unterschiedliche Gruppengröße mit über 5.200 bestrahlten Patienten gegenüber 1.500 Patienten unter Überwachung, dass es keine Angaben über die Strahlendosis und die Bestrahlungsfelder gibt, sowie ein durchschnittlicher	Das krebsspezifische Überleben lag in der Strahlentherapiegruppe nach fünf, zehn und 20 Jahren höher als in der Überwachungsgruppe. Berücksichtigt werden müssen bei dieser Arbeit die unterschiedliche Gruppengröße mit über 5.200 bestrahlten Patienten gegenüber 1.500 Patienten unter Überwachung, dass es keine Angaben über die Strahlendosis und die Bestrahlungsfelder gibt, sowie ein durchschnittlicher Nachbeobachtungszeitraum von 7,6	Dieser gesamte Absatz scheint neu zu sein. Wir haben ihn in der letzten Version nicht gefunden. Die Änderung betrifft den letzten gelbmarkierten Teilsatz. Die Argumentation entspricht der unter 9.3.4.7. SEER Analysen sind aufgrund dieser Datenlücke (keine Dosis, kein Bestrahlungsvolumen) für Sekundärtumoranalysen nach Strahlentherapie nicht geeignet.	Die Prüfung des Dokumentenverlaufs ergab die korrekte Darstellung im finalen Dokument. Nach der Konsensuskonferenz wurde die aktuelle Textpassage durch die AG eingefügt und wird daher beibehalten.

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
	Nachbeobachtungszeitraum von 7,6 Jahren, wobei die Rate an Sekundärmalignomen nach mehr als zehn Jahren steigt [Jones et al. 2013]."	Jahren. Die berichtete gestiegene Sekundärmalignomrate kann ohne Angaben zu Dosis und Bestrahlungsvolumen nicht sinnvoll gewertet werden. Die Rate an Drittmalignomen war gleich [Jones et al. 2013]. Bei Beschränkung der Radiotherapie auf die Paraaortalregion sind Sekundärmalignomraten im Langzeitverlauf (>20 Jahre) nicht erhöht (SIR=0,91) [Horwich et al. 2014](siehe 9.3.4.7.).		
Seite 162	„Darüber hinaus können asymptomatische Lungenfibrosen durch mediastinale Strahlentherapie und/oder Bleomycin Patienten viele Jahre nach der Behandlung anfällig für Pneumonien machen."	„Darüber hinaus können asymptomatische Lungenfibrosen durch Bleomycin Patienten viele Jahre nach der Behandlung anfällig für Pneumonien machen."	Diese Formulierung hatten wir bereits ändern lassen (ist wohl untergegangen). Bei Keimzelltumoren wird nicht mediastinal bestrahlt. Bestrahlungsdosen bei Bronchialkarzinomen sind deutlich höher als bei KZT und daher Adaptationen aus diesem Spektrum mediastinaler Bestrahlungen nicht sinnvoll.	Die Prüfung des Dokumentenverlaufs ergab die korrekte Darstellung im finalen Dokument. Aufgrund der Plausibilität haben wir im aktullen Dokument die unten genannte Textmodifikation angepasst: „Darüber hinaus können asymptomatische Lungenfibrosen durch Bleomycin (oder eine heutzutage nicht mehr indizierte mediastinale Strahlentherapie)

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
				Patienten viele Jahre nach der Behandlung anfällig für Pneumonien machen.“
		Neues Kapitel 4 einfügen: **Patienteninformation und –aufklärung**		Ein neues Kapitel „Patienteninformation“ kann zum jetzigen Projektstand nicht eingefügt werden. Dieser Vorschlag wird bei der Leitlinienaktualisierung diskutiert.
S. 49, Tabelle 11	Stadium IIA: jedes pT/Tx N1 M0 S0 jedes pT/Tx N2 M0 S1	Stadium IIA: Jedes pT/Tx N1 M0 S0 jedes pT/Tx N1 M0 S1	Erst ab Stadium IIB gilt N2 (Kontrolle in aktuell gültiger TNM Klassifikation nach UICC 2017)	wurde geändert
		S3 LL Hodentumoren: Ich würde bei der Tu Nachsorge in allen drei Gruppen zumindest bis zum 5. Jahr ein MRT Abdomen empfehlen		Das ist eine Individualempfehlung und wird nicht durch Evidenz unterlegt. Die derzeitige Empfehlung kann aus diesem Grund nicht geändert werden.
	Stadium IIA: Jedes pT/ Tx N2 M0 S1	Stadium IIA: Jedes pT/ Tx N1 M0 S1	Schreibfehler; Stadium IIA ist immer N1	wurde korrigiert

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
	„Primärprävention“	„Sekundärprävention“	Die genannten Maßnahmen gehören dem Instrumentarium der Sekundärprävention an. Eine Primärprävention von Hodentumoren ist m.E.n. nicht möglich.	Der Titel des Kapitels wurde in „Präventive Maßnahmen“ geändert.
S.81, Empf. 9.26	„..im R0-Status soll..“ „Alternativ kann…“	„…im R0-Status sollte…“	„Soll“ definiert einen Therapiestandard, der zwecks Einheitlichkeit durch die Nennung einer möglichen Alternative nicht aufgeweicht werden sollte. Besser wäre hier daher, das weniger stikte „sollte“ zu verwenden.	Eine abgestimmte Empfehlung werden wir aktuell nicht mehr ändern. Allerdings können wir diese Diskrepanz bei der Aktualisierung versuchen aufzulösen, wenn die Evidenzlage dies dann hergibt.
S. 80, Empf. 9.24	„…alternativ eine diagnostische RLA erfolgen.“	„…alternativ eine diagnostische RLA oder histologische Sicherung mit ggf. anschließender Chemotherapie erfolgen.“	Die Möglichkeit, vergrößerte unklare Lymphknoten beispielsweise mittels roboterassistierter Laparoskopie zu entfernen und in Abhängigkeit vom histologischen Ergebnis (maligne: Chemotherapie, außer bei reifem Teratom, benigne: weitere Kontrollen) wird im gegenwärtigen Leitlinientext nicht ermöglicht. Im Hintergrundtext steht „Eine Entfernung nur der bildmorphologisch auffälligen Lymphknoten ist nicht	Inhaltlich alles nachvollziehbar, aber aufgrund der schlechten Publikationslage wurde weder zur Laparoskopischen noch zur rotobischen LA ein klares Statement abgegeben. Eine diagnostische RLA ist derzeit das einzig abgesicherte und das weitere Vorgehen ist im Text klar angegeben. Die

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
			ausreichend.“ Das ist richtig, aber nur im Zusammenhang mit einer alleinigen operativen Entfernung ohne anschließende Chemotherapie. Wenn im Stadium IIA der unklare Lymphknoten minimalinvasiv entfernt und histologisch gesichert wird, ist hinterher die Therapieplanung einfacher und die Gefahr einer Überbehandlung wird gebannt. Zu dieser Option sollte die Leitlinie zumindest im Hintergrundtext Stellung nehmen. Wenn diese Option als vertretbar angesehen wird, sollte auch die Zahl der nach Entfernung eines kleinen (z. B. 1.9 cm großen) befallenen Lymphknotens erforderlichen Chemotherapiezyklen angegeben werden.	individuelle Bewertung der derzeitgen Möglichkeiten kann leider nicht in der LL berücksichtigt werden.
7.1.4./ S.39	Vorletzter Absatz: „Hodenprothese“	Hodenimplantat	Kein funktioneller, sondern kosmetischer Ersatz	wurde geändert
10.2.3./ 10.12/ S.124	Strahlentherapie sollte „individuell“ erwogen werden	„Individuell“ weglassen oder Kriterien angeben	„Individuell“ ist zu wage formuliert. Woran soll sich der Leser orientieren?	An der individuellen Situation und Beratung des Patienten – das beinhaltet individuell. Bei Wegfall dieses Wortes würde die Strahlentherapie generell

Kapitel/Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Anmerkung des Redaktionsteams
				in Erwägung gezogen. Dies ist nicht intendiert.
11.6./ S.145	Andere nichtgerminale Hodentumore	TART fehlt.	Dieser seltene beidseitige gutartige Hodentumor imponiert bildmorphologisch wie ein Malignom, sollte aber nicht freigelegt werden. Insgesamt fehlt ein Kapitel „Differentialdiagnosen“. S. Hüppe,P et al. Urologe 2014; 53: 196-200	Das ist korrekt und kann gerne bei der Überarbeitung der LL Eingang finden.
12.1./ S.146	Hinweis auf die ESMO-Leitlinie ist veraltet	Neue ESMO-Leitlinie einarbeiten, z.B. die überarbeiteten Empfehlungen zur Nachsorge	ESMO Consensus Conference on testicular germ cell cancer. AnnOncol 2018; 0: 1-29	Die alte Referenz wurde durch die neue Referenz ersetzt.
12.1./ Tab 21/ S.148		Primäre nerverhaltende RLA einfügen	Zwar seltene Indikation, aber nicht ganz auszuschließen	Aktuell kein Änderungsbedarf
12.1./ Tab 23/ S.150	NSCTC Std.I hohes Risiko: 2x PEB	1x PEB	Literatur s. Albers et al., SWENOTECA etc.	Die Inhalte der Tabelle entsprechend geändert.
12.1. / Tabellen 24, 26, 27	Rö-Thorax Untersuchungen	weglassen	Bei nicht durchgeführter Therapie im Retroperitoneum oder Surveillance ist mit einer alleinigen Metastasierung in die Lungen nicht zu rechnen	Aktuell keine Änderung, da abgestimmt.

9.12. Ergebnisse der Interessenkonflikterklärungen

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Einschätzung des Interessenkonfliktes in Bezug zum Leitlinienthema	**MODERAT**	**MODERAT**	**GERING*** *bei <10.000€ PRO JAHR PRO FIRMA; ansonsten MODERAT	**GERING**	**GERING**	**HOCH**	**GERING**	
KOORDINATOREN								
Albers, Prof. Dr. Peter	Nein	Roche, Sanofi	Hexal	Nein	Nein	Nein	DKG, AUA, ASCO, EAU Uro-Onkologie	GERING, da kein thematischer Bezug zur Leitinie
Kliesch, Prof. Dr. Sabine	Nein	Jenapharm, Merck	AMS, Jenapharm, Dr. Kade Besins, Merck	Nein	Dr. Kade-Besins, Galen	Nein	DKG, DGU, DGA, EAA, EAU, ESSM	GERING, da kein thematischer Bezug zur Leitinie
Schmidt, Dr. Stefanie	Nein	Nein	Nein	Nein	Ja	Nein	DNEbM	GERING
Wilborn, Dr. Doris	Nein	Nein	Nein	Nein	Nein	Nein	DGP, hlb, DNEbM, EPUAP	GERING

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
ARBEITSGEMEINSCHAFTEN								
Beintker, Dr. Matthias	Nein	Nein	Nein	Nein	Nein	Nein	DGU, BDU, Thier-Krebsgesellschaft, Uro-Onkologie	GERING
Diemer, PD Dr. Thorsten	Cheplapharm GmbH, Advance Medical (ESP)	Marpinion GmbH	AMS (Boston Scientific), Pfizer, div. Non-Profit-Org. (Wiss. Gesellschaften)	Nein	DFG, Land Hessen	Lilly Deutschland GmbH, Lilly Inc. (USA)	Mitgliedschaften: DGU, DGA, EAU, Akademie LÄK Hessen Stellv. Vorsitzender des AK Andrologie Vorstand Deutsche Gesellschaft für Andrologie(DGA) Vice-Chair EAU Guideline Group „Male Infertility" Assoc. Board Member ESAU (EAU, Urological Andrology)	GERING, da kein thematischer Bezug zur Leitinie
Bokemeyer, Prof. Dr. Carsten	Ja	Lilly, Ipsen, Merck, Serono, Sanofi, Novartis; MSD; Bristol Myers,Astra Zeneca (<	nationale und internationale Vorlesungen/ Fortbildungen unterstützt von verschieden Firmen und	Nein	100 Studien in meiner Abteilung werden durchgeführt Drei dieser Studien	Nein	ASCO, DKG, AIO, Hamburger Krebsgesellschaft, GTCSG, Leiter Hodentumoren, Geschäftsf. Vorsitzender	GERING, da kein thematischer Bezug zur Leitinie

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
		10.000 pro Jahr)	Institutionen (< 10.000 pro Jahr)		schließen Patienten mit KZT ein.		DGHO, 2. Vorsitzender DKH Patientenbehandlung mit systematischer Therapie	
Dieckmann, Prof. Dr. Klaus-Peter	Ja	Nein	Nein	Nein	Nein	MiR detect GmbH	DGU Urologie	HOCH bzgl. Tumormarker miRNA, jedoch aktuell noch nicht Leitlinienrelevant
Hakenberg, Prof. Dr. Oliver	Ja	Astellas	Janssen SKB		Astellas, Sofio, Bayer	Nein	DGU Onkologie	GERING, da kein thematischer Bezug zur Leitinie
Oechsle, Prof. Dr. Karin	Nein	Nein	Nein	Nein	DKG	Nein	ASCO, ESMO, DKG, DGHO, DGP, APM, ASORS Urologische Tumore Palliativmedizin	GERING
Rick, Prof. Dr. Oliver	Nein	Nein	Nein	Nein	Nein	Nein	DKG, DGHO, ASCO	GERING

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
							Rehabilitation, Onkologie	
Rudolph, Dr. Ivonne	Nein	Nein	Nein	Nein	Nein	Nein	AG Prio, DVGS	GERING
Schirren, Prof. Dr. Joachim	Nein	Nein	Nein	Nein	Nein	Nein	DGT, DGCH, DKG, AOT Onkologische Thoraxchirurgie	GERING
Schmidberger, Prof. Dr. Heinz	Nein	Nein	Nein	wiss. Publikationen	Varian, Palo Alto	Nein	DEGRO, DKG, ARO, ASTRO, ESTRO	GERING
Schrader, Prof. Dr. Mark	Ja	Janssen	nationale und internationale Vorlesungen/ Fortbildungen	Nein	Bayer	Bayer, Novartis, Pfizer, Roche	BUG, DGU, AKO, ASCO, EAU, DKG	GERING, da kein thematischer Bezug zur Leitinie
Otto, Prof. Dr. Ullrich	Nein	Farco-Pharma	diverse	diverse	diverse	Patent	Vorsitzender AK Rehabilitation Urologischer und Nephrologischer Erkrankungen (DGU) Fachspezifische urologische Rehabilitation	GERING, da kein thematischer Bezug zur Leitinie

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
De Wit, Prof. Dr. Maike	Pierre Fabre, Novartis, Boehringer	Nein	Roche, Promedicis, NG-Adademie, Ipsen, Janssen, Sanofi, Daiichi	--	Nein	BMS	DGHO, DKG, ASORS, ESMO, ASCO, DGIM	GERING, da kein thematischer Bezug zur Leitinie
Müller, PD Dr. Arndt-Christian	Nein	Siemens	Nein	Ribasepharm	Elekta/Philips, Siemens, AKF-Förderung	Nein	DEGRO, ARO, ASTRO, ESTRO, DKG, GTCSG	GERING, da kein thematischer Bezug zur Leitinie
Heidenreich, Prof. Dr. Axel	Nein	Astellas, Amgen, Bayer, Ipsen	Nein	Nein	Astellas, Senofi	Nein	DGU, EAU, ASCO, ESMO, ESON	GERING, da kein thematischer Bezug zur Leitinie
Zermann, Prof. Dr. Dirk-Henrik	Nein	Nein	Nein	--	Uni Chemnitz	Nein	Nein	GERING
Wittekind, Prof. Dr. Christian	Nein	Zeitschrift Onkologie	DKG	Nein	Nein	Nein	Vorstandsmitglied BVP klinische Pathologie, Tumorklassifikationen speziell TNM	GERING
FACHGESELLSCHAFTEN								

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Aigner, Prof. Dr. Clemens	Ja	Nein	Nein	Nein	Nein	Nein	Präsident Thoraxchirurgie, Vorstand ESTS Regent Onkologische Thoraxchirurgie, LuTX	GERING, da kein thematischer Bezug zur Leitinie
Albrecht, PD Dr. Walter	Ja	European Group on Tumormarkers	AKO (DGU), Astellas, Contag Dresden, ÖGU	EAU	Nein	Nein	Uro-Onkologie	GERING, da kein thematischer Bezug zur Leitinie
Beyersdorff, PD Dr. Dirk	Nein	Bayer Vital GmbH	Bayer Vital, Janssen	wiss. Journal	Nein	Philips, Invivo	DRG, ESUR, DEGUM, ESR Uroradiologie	GERING, da kein thematischer Bezug zur Leitinie
Claßen, Prof. Dr. Johannes	Nein	Nein	Nein	Nein	Nein	Nein	BVDST Mamma-, Bronchial-, HNO-, Urogenitalkarzinome	GERING
Kristiansen, Prof. Dr. Glen	Ja	Nein	Roche	DAKO	Ja, Astellas AR-Forschungspreis 2018	Nein	Leiter ENUP Pathologie	GERING, da kein thematischer Bezug zur Leitinie

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Göckel-Beining, Dr. Bernt	Nein	Nein	Akademie der Urologen, UroAktuell	Nein	Nein	Nein	DGU, AGU, EGU, GDGU, BDUUrologische/Uro-Onkologische Operationen, Medikamentöse Tumortherapien inkl. Polychemotherapien	GERING
Gockel, Dr. Matthias	Nein	Nein	RV Bund, Kaiserin-Friedrich-Stiftung	Nein	Nein	Nein	Vorstandsmitglied Berl.LV d. Dt. Ges. f. Palliativmedizin Klinische stationäre Palliativmedizin	GERING
Hermanns, Dr. Thomas	Nein	Nein	Nein	Nein	Nein	Nein	Uroonkologie inkl. interdisziplinäre Hodentumorsprechstd.	GERING
Kornmann, Prof. Dr. Marko	Nein	Nein	Nein	Nein	Nein	Nein	DGAV, AG Onkologie Gastrointestinale chirurgische Onkologie	GERING
Kotzerke, Prof. Dr. Jörg	Nein	Bayer	Nein	Nein	Nein	Nein	Präsident DGN	GERING, da kein

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
							PET-Tumordiagnostik, Therapie onkologischer Erkrankungen mit offenen Radionukliden, Strahlenbiologie offener Radionuklide	thematischer Bezug zur Leitinie
Krege, Prof. Dr. Susanne	Ja	BMS, Bayer, Hexal, Takeda, Pierre Fabre, BMS, Novartis, Pfizer, Roche	AUO, AKO,	Springer-Medizin	Nein	Nein	DGU, AKO, EAU, AUA, DKG, AUO Uro-Onkologie Plast. Rekonstruktive Urologie	GERING, da kein thematischer Bezug zur Leitinie
Lorch, Prof. Dr. Anja	Nein	Novartis, BMS	Nein	Nein	Studien für Prostata, Blase, Niere	Nein	DGHO, ESMO, EAU, ASCO, LL Hoden Keimzelltumore, Urothel, Prostata, Niere	GERING, da kein thematischer Bezug zur Leitinie
Recken, Heinrich	Nein	Nein	AAL-Akademie	Nein	„Pflegebrille“	Nein	DGP	GERING
Schmelz, Prof. Dr. Hans	Nein	Nein	Dr. Diekmann Congress Consulting	Nein	Nein	Nein	DGU, DGA Uro-Onkologie	GERING

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Schweyer, Prof. Dr. Stefan	Nein	Nein	AUO, Roche <10.000€	Nein	Nein	Nein	DGP, BDP, S1-LL Hodentumoren	GERING
Kaufmann, PD Dr. Sascha	Nein	Nein	Nein	Nein	Nein	Nein	Nein	GERING
Zillmann, Dipl. med. Roger	Janssen-Cilag	Astellas, Sanofi, Novartis	Janssen-Cilag, Sanofi, Pierre Fabre, GSK	Nein	Janssen-Cilag, Novartis	Nein	DGHO, DGU, BDvU, BUG	GERING, da kein thematischer Bezug zur Leitinie
AG-LEITER								
Bedke, Prof. Dr. Jens	Nein	Bayer, BMS, Novartis, Pfizer, Roche, Eusa, Eisou	Nein	Nein	Novartis (2015-2016) Boehringer Ingelheim (2014-2016)	Protaffin Biotechnologie	DGU, EAU, AUA, DKG (AUO, AIO), Deutsche Hodentumor-studiengruppe, BAGN Uro-Onkologie	GERING, da kein thematischer Bezug zur Leitinie
Busch, PD Dr. Jonas	Ja	Pfizer	Pfizer, Novartis, Bayer, BMS	„siehe Pubmed“	BiH	Nein	DGU, AUA, EAU, BUG, AUO/DKG, AG KZT, AG NZK Uro-Onkologie	GERING, da kein thematischer Bezug zur Leitinie
Heinzelbecker, PD Dr. Julia	Nein	Nein	Takeda	Nein	Nein	Nein	Endomiologie	GERING

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Pfister, Prof. Dr. David	Nein	Sanofi	Astellas, Ferring, Teva, Janssen, Ipsen	Nein	Nein	Nein	DGU, EAU, CAU, GeSRU Uro-Onkologie	GERING, da kein thematischer Bezug zur Leitinie
Ruf, PD Dr. Christian	Nein	Janssen	Nein	Nein	Nein	Nein	DGU, EAU, GeSRU Uro-Onkologie, Andrologie, Hodentumor Urologie	GERING, da kein thematischer Bezug zur Leitinie
Winter, Dr. Christian	Nein	Nein	Nein	Nein	Nein	Nein	Nein	GERING
Zengerling, Dr. Friedemann	Nein	Roche, BMS, Novartis	Bayer	Nein	Astellas, Bayer, BMS, Janssen-Cilag, Merck, Novartis, Pfizer, Roche	Nein	GTCSG, Zweitmeinungszentrum Hodentumor Hodenkarzinom, Uro-Onkologie	GERING, da kein thematischer Bezug zur Leitinie
PATIENTENVERTRETER								
Ohloff, Timur	Nein	Nein	Nein	Nein	Nein	Nein	Deutsche Stiftung für junge Erwachsene mit Krebs, Berlin	GERING
EXPERTEN								

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft [1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen) [3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Ost, Dr. Ekkehard	Ja	Nein	KC Onkologie/ MDK Nordrhein weniger als 10.000 € pro Jahr	Nein	Nein	Nein	Fortbildungen für Ärzte des MDK und Mitarbeiter der GKV, DGHO, BDI	GERING, da kein thematischer Bezug zur Leitinie
STELLVERTRETER MIT STIMMRECHT								
Souchon, Prof. Dr. Rainer	Nein	Nein	Nein	Nein	Nein	Nein	Sprecher: German Testicular Cancer Study Group Schwerpunkte: Hodentumore, Mammakarzinome, Radioonkologie	GERING
Müller, PD Dr. Arndt	Nein	Siemens	Nein	Ribosepharm	Elekta/Philips, Siemens, Universität Tübingen	Nein	DEGRO, ARO, ESTRO, ASTRO, DKG, DTSG, Landes-qualitätskonferenz Prostatakarzinom, Urogenitale Tumoren, Imaging, Stereotaxie, Hirntumoren, kindliche Tumoren, Sarkome, Mammakarzinom	GERING da kein thematischer Bezug zur Leitinie

	Bezahlte Berater- bzw. Gutachter-tätigkeit [1]	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungs-tätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungsvorhaben/ Durchführung klinischer Studien [1]	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fach-gesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Oing, Dr. Chritstoph	Nein	Nein	Nein	Nein	Nein	Nein	Nein	GERING

1 = Hier werden entsprechend §139b SGB V finanzielle Beziehungen zu Unternehmen, Institutionen oder Interessenverbänden im Gesundheitswesen erfasst. Folgende Frage wurde beantwortet: Haben Sie oder die Einrichtung, für die Sie tätig sind, innerhalb des laufenden Jahres oder der 3 Kalenderjahre davor Zuwendungen erhalten von Unternehmen der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), industriellen Interessenverbänden, kommerziell orientierten Auftragsinstituten, Versicherungen/Versicherungsträgern, oder von öffentlichen Geldgebern (z.B. Ministerien), Körperschaften/Einrichtungen der Selbstverwaltung, Stiftungen, oder anderen Geldgebern?

2 = Angaben zu Mischfonds waren nicht erforderlich

3 = Hierzu wurden folgende Aspekte abgefragt: Mitgliedschaft /Funktion in Interessenverbänden; Schwerpunkte wissenschaftlicher Tätigkeiten, Publikationen; Schwerpunkte klinischer Tätigkeiten; Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten; Persönliche Beziehungen (als Partner oder Verwandter 1. Grades) zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft; sonstige relevante Interessen

9.13. Anlage AMSTAR-Instrument 2009

AMSTAR: Risk of bias assessment for systematic reviews 1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	YesNoCan't answerNot applicable
2. Was there duplicate study selection and data extraction?There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	YesCan't answerNot applicableNo
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	YesNoCan't answerNot applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	YesNoCan't answerNot applicable
5. Was a list of studies (included and excluded) provided?A list of included and excluded studies should be provided.	YesNoCan't answerNot applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	YesNoCan't answerNot applicable
7. Was the scientific quality of the included studies assessed and documented?'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	YesNoCan't answerNot applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	YesNo Can't answerNot applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	YesNoCan't answerNot applicable

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	YesNoCan't answerNot applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	YesNoCan't answerNot applicable

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Erstveröffentlichung:	05/2019
Nächste Überprüfung geplant:	05/2024