Wetenschappelijke ondersteuning van het College voor Oncologie: een update van de nationale richtlijn voor testiskanker

KCE reports 142A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2010

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VOORWOORD

Het nationale kankerplan heeft als één van zijn doelstellingen om voor alle vormen van kanker klinische praktijkrichtlijnen uit te werken en up-to-date te houden. Het operationaliseren van deze doelstelling werd toevertrouwd aan het KCE, in overleg met het College voor Oncologie. De werkwijze is welbekend, het verzamelen en kritisch evalueren van de wetenschappelijke gegevens, deze daarna aan een multidisciplinaire discussie onderwerpen om tenslotte te komen tot wetenschappelijk gefundeerde aanbevelingen met een gedegen draagvlak.

Logischerwijze richt het KCE in eerste instantie de aandacht op de meest frequente kankers (zoals borstkanker) of de kankers met een belangrijke sterfte (zoals pancreaskanker). Toch verdienen daarnaast ook de meer zeldzame kankers, waarvoor ook minder wetenschappelijk informatie voorhanden is, onze aandacht. Een voorbeeld hiervan is testiskanker, waarover reeds in 2006 een KCE-rapport werd gepubliceerd. Wat vandaag voorligt is dus een actualisering van deze richtlijn.

Tegen eind 2010 zal ter aanvulling van deze richtlijn een tweede rapport verschijnen. Hierin zal men een aantal indicatoren terugvinden aan de hand waarvan men kan meten in welke mate deze richtlijn ook effectief wordt opgevolgd en of ze daadwerkelijk bijdraagt tot het uiteindelijke doel: het verbeteren van de kwaliteit van de zorg. Des te zeldzamer een aandoening, en dus onvermijdelijk ook de ervaring ermee, des te groter het belang van een goede praktijkrichtlijn.

Ten slotte wensen wij alle experten en clinici te bedanken die hun kennis en ervaring hebben gedeeld en zo hebben bijgedragen tot het realiseren van deze richtlijn.

Jean Pierre CLOSON
Adjunct algemeen directeur

Raf MERTENS
Algemeen directeur

Samenvatting

INLEIDING

Dit document bevat een update van de klinische praktijkrichtlijn over teelbalkanker, gepubliceerd in 2006. De richtlijn behandelt een ruim gamma van onderwerpen, gaande van de diagnose tot de opvolging. De richtlijn heeft voornamelijk betrekking op mannen met testiculaire kiemceltumoren. Mannen met primaire extragonadale kiemceltumoren of testiculaire niet-kiemcel-tumoren maken geen deel uit van deze richtlijn. Alle aanbevelingen zijn gebaseerd op overwegingen van klinische doeltreffendheid; er werd geen kosteneffectiviteitsanalyse uitgevoerd. De richtlijn richt zich op alle zorgverleners die bij de zorg voor deze patiënten betrokken zijn.

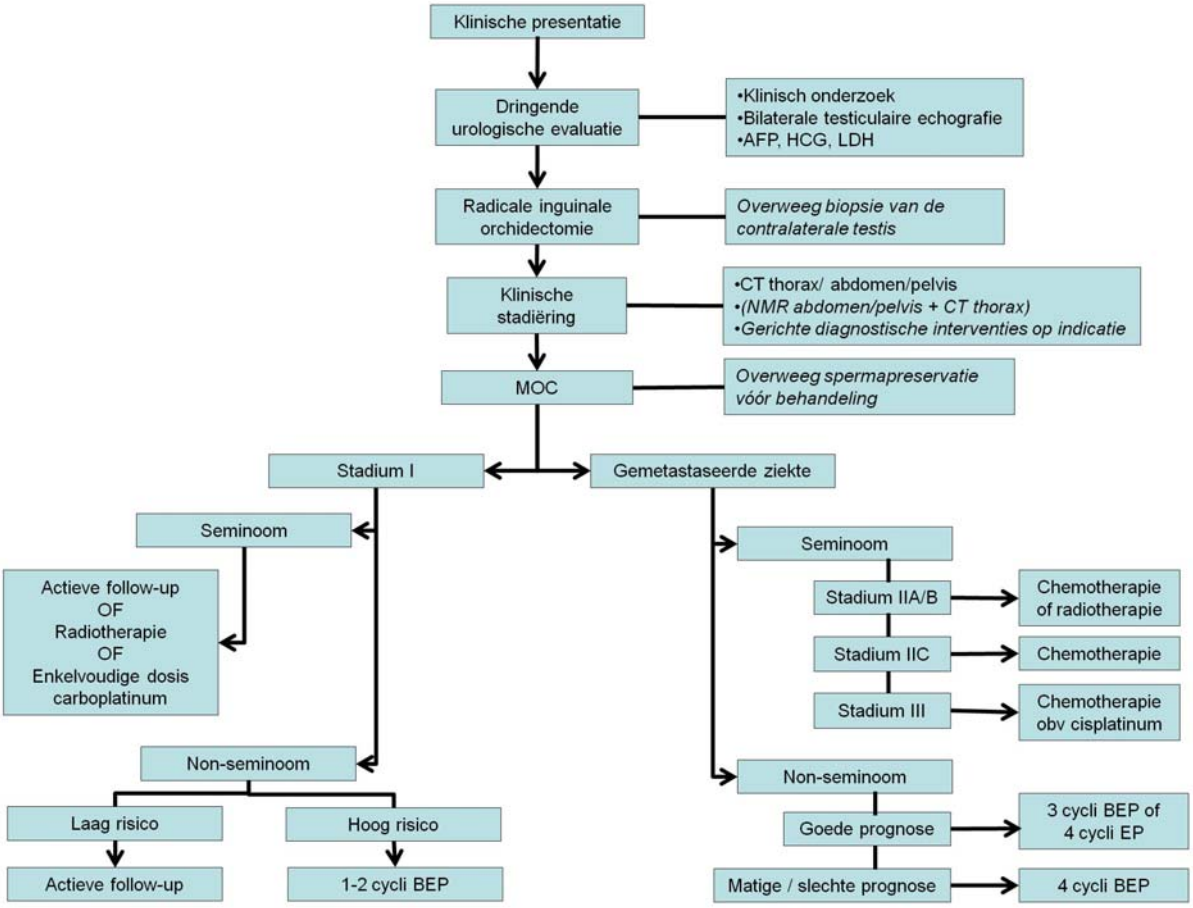
METHODOLOGIE

Er werd gebruik gemaakt van de ADAPTE-methodologie waarbij (inter)nationale richtlijnen aan de Belgische context werden aangepast. Bestaande (inter)nationale richtlijnen werden gezocht in Medline, de National Guideline Clearinghouse en websites van richtlijnorganisaties en oncologische organisaties. De 20 gevonden richtlijnen werden op hun kwaliteit beoordeeld met het AGREE-instrument door twee onafhankelijke onderzoekers en in- of uitgesloten op basis van hun algemene kwaliteit. Daarna werden de 5 geselecteerde richtlijnen voor elke klinische vraag bijgewerkt met aanvullend bewijsmateriaal in Medline en in de Cochrane Database of Systematic Reviews. Een niveau van bewijskracht werd toegekend aan elke oorspronkelijke aanbeveling en aanvullende studie met behulp van het GRADE-systeem.

Op basis van het gevonden bewijsmateriaal stelde een multidisciplinaire richtlijngroep de aanbevelingen op. Een review van deze aanbevelingen werd uitgevoerd door externe experts door middel van een formele procedure. Belangenconflicten werden genoteerd.

DEFINITIEVE AANBEVELINGEN

De details van de richtlijn bevinden zich in het wetenschappelijke rapport na deze samenvatting. Hieronder wordt het algemene algoritme voorgesteld. De tabel bevat alle aanbevelingen geordend per hoofdstuk.



AFP: alfafoetoproteïne; BEP: bleomycine + etoposide + cisplatinum; CT: computed tomography; EP: etoposide + bleomycine; HCG: humaan chorion gonadotrofine; LDH: lactaat dehydrogenase; MOC: multidisciplinair oncologisch consult; NMR: nucleaire magnetische resonantie.

DIAGNOSE, INITIËLE BEHANDELING EN STADIËRING VAN TEELBALKANKER

Diagnose

Aanbeveling	**Niveau van bewijskracht**
Patiënten met een klinisch vermoeden van een maligniteit van de teelbal moeten dringend een urologische evaluatie ondergaan, incluis een klinisch onderzoek en een echografie van de beide teelballen	1C

Initiële behandeling

Aanbevelingen	**Niveau van bewijskracht**
Een preoperatieve evaluatie van tumormerkers (AFP, HCG, LDH) wordt aanbevolen om het postoperatieve beleid van patiënten met teelbalkanker te kunnen bepalen	Mening van deskundigen
Bij patiënten met een sterk vermoeden van teelbalkanker na urologische evaluatie is radicale orchidectomie via inguïnale weg aangewezen	Mening van deskundigen

Stadiëring

Aanbevelingen	**Niveau van bewijskracht**
Een CT met contrast van thorax, abdomen en bekken is aangewezen bij patiënten met bewezen teelbalkanker voor de opsporing van (klier en andere) metastasen	2C
Indien een CT met contrast tegenaangewezen is, kan een nucleaire magnetische resonantie scan (NMR) een alternatief zijn voor de opsporing van abdominale metastasen bij patiënten met bewezen teelbalkanker	Mening van deskundigen
Het bewijsmateriaal voor het gebruik van andere stadiëringstechnieken is te zwak om een routinematig gebruik ervan aan te bevelen voor de stadiëring van teelbalkanker	1C
Bij geselecteerde patiënten zijn gerichte diagnostische interventies aangewezen	Mening van deskundigen
De behandelingsopties voor patiënten met teelbalkanker moeten worden besproken tijdens het multidisciplinaire teamoverleg	Mening van deskundigen

Vruchtbaarheid

Aanbeveling	**Niveau van bewijskracht**
Vóór een behandeling met chemo- of radiotherapie moet spermapreservatie aangeboden worden	Mening van deskundigen

HISTOPATHOLOGISCH ONDERZOEK

Aanbevelingen	**Niveau van bewijskracht**
De distale rand moet worden ingesneden vóór incisie van de teelbal om contaminatie van de zaadstreng met tumorcellen te voorkomen	Mening van deskundigen
Als de tumor wordt geclassificeerd als een gemengd type kiemceltumor, moet de patholoog de hoeveelheid van elke component (als een percentage) schatten	1C

BEHANDELING VAN STADIUM I ZIEKTE

Seminoom

Aanbevelingen	**Niveau van bewijskracht**
Bij patiënten met een stadium I seminoom kan actieve follow-up na orchidectomie worden beschouwd als een behandelingsoptie	2B
Bij patiënten met een stadium I seminoom kan radiotherapie na orchidectomie worden beschouwd als een behandelingsoptie	2B
Bij patiënten met een stadium I seminoom kan een enkelvoudige dosis carboplatinum na orchidectomie worden beschouwd als een behandelingsoptie	2B

Non-seminoom

Aanbeveling	**Niveau van bewijskracht**
Primaire follow-up na orchidectomie is aangewezen bij patiënten met een stadium I non-seminoom (zonder vasculaire of lymfatische invasie en zonder predominante embryonale component), met behandeling bij recidief	2B

BEHANDELING VAN GEMETASTASEERDE ZIEKTE

Stadium II en III seminoom

Aanbevelingen	**Niveau van bewijskracht**
Patiënten met een stadium IIA of IIB seminoom moeten worden behandeld met chemotherapie of radiotherapie	2C
Bij patiënten met een stadium IIC seminoom is chemotherapie de eerste keuze behandeling	2C
Bij patiënten met een stadium III seminoom is chemotherapie op basis van cisplatinum aangewezen	1B

Stadium II, III en IV non-seminoom

Aanbevelingen	**Niveau van bewijskracht**
Patiënten met een gemetastaseerd non-seminoom en een goede prognose moeten worden behandeld met 3 cycli van eerstelijns BEP-chemotherapie of 4 cycli van eerstelijns EP-chemotherapie	1A
Patiënten met een gemetastaseerd non-seminoom en een matige of slechte prognose moeten 4 cycli eerstelijns BEP-chemotherapie krijgen	2A
Patiënten met een gemetastaseerd non-seminoom en een matige of slechte prognose moeten worden geïncludeerd in klinische studies indien ze beschikbaar zijn	Mening van deskundigen

RESIDUELE ZIEKTE

Beeldvorming

Aanbevelingen	**Niveau van bewijskracht**
Een CT met contrast wordt aanbevolen voor de evaluatie van residuele massa's na systemische behandeling van teelbalkanker	Mening van deskundigen
PET-scan wordt niet routinematig aanbevolen voor de evaluatie van residuele massa's, maar kan nuttig zijn bij een gemetastaseerd seminoma	2C

Behandeling van residueel non-seminoom

Aanbevelingen	**Niveau van bewijskracht**
Bij patiënten met een non-seminoom die residuele retroperitoneale massa's hebben na chemotherapie en bij wie de tumormerkers genormaliseerd zijn, moeten de residuele massa's chirurgisch verwijderd worden	Mening van deskundigen
Bij patiënten met een non-seminoom en niet-retroperitoneale massa's na chemotherapie is metastasectomie aanbevolen indien mogelijk	Mening van deskundigen
Indien de primaire teelbaltumor nog niet werd verwijderd, moet een orchidectomie worden uitgevoerd op hetzelfde ogenblik als de excisie van de residuele massa	Mening van deskundigen

Behandeling van residueel seminoom

Aanbevelingen	**Niveau van bewijskracht**
Bij patiënten met een seminoom die residuele massa's hebben van ≤ 3 cm is follow-up aangewezen	Mening van deskundigen
Bij patiënten met een seminoom die eerder werden behandeld met chemotherapie, en die een residuele massa hebben van > 3 cm en/of positieve PET-bevindingen, kan radiotherapie worden overwogen	Mening van deskundigen
Bij patiënten met een seminoom die hervallen na eerstelijns radiotherapie, of bij wie de waarden van de tumormerkers positief worden, is salvage chemotherapie aangewezen	Mening van deskundigen
Bij patiënten met een seminoom die residuele massa's hebben na chemotherapie of radiotherapie, wordt chirurgische verwijdering van de massa's niet aanbevolen	Mening van deskundigen

FOLLOW-UP

Primaire follow-up na orchidectomie

Stadium I seminoom

Aanbevelingen	**Niveau van bewijskracht**
Bij patiënten met een stadium I seminoom onder primaire follow-up moeten elke 3 maanden tijdens het eerste en het tweede jaar, en elke 6 maanden tijdens het derde, vierde en vijfde jaar, een lichamelijk onderzoek en tumormerkers (AFP, HCG, LDH) worden uitgevoerd	Mening van deskundigen
Hoewel er onvoldoende bewijsmateriaal is om een standaardschema voor CT follow-up voor te stellen bij patiënten met een stadium I seminoom onder primaire follow-up, is het wenselijk om elke 6 maanden gedurende de eerste 2 jaar na de orchidectomie minstens een CT van het abdomen en bekken te maken	Mening van deskundigen

Stadium I non-seminoom

Aanbevelingen	**Niveau van bewijskracht**
Bij patiënten met een stadium I non-seminoom onder primaire follow-up moeten elke maand tijdens het eerste jaar, elke twee maanden tijdens het tweede jaar, elke drie maanden tijdens het derde jaar, en elke zes maanden tijdens het vierde en vijfde jaar, een lichamelijk onderzoek en tumormerkers (AFP, HCG, LDH) worden uitgevoerd	Mening van deskundigen
Hoewel er onvoldoende bewijsmateriaal is om een standaardschema voor CT follow-up voor te stellen bij patiënten met een stadium I non-seminoom onder primaire follow-up, is het aanbevolen om minstens een CT van het abdomen en bekken te maken na 3 en na 12 maanden	2B

Follow-up na systemische behandeling of radiotherapie

Aanbevelingen	**Niveau van bewijskracht**
Bij patiënten die werden behandeld met chemotherapie of radiotherapie na de orchidectomie of als primaire behandeling moeten elke 3 maanden tijdens het eerste en het tweede jaar, en elke zes maanden tijdens het derde, vierde en vijfde jaar, een lichamelijk onderzoek en tumormerkers (AFP, HCG, LDH) worden uitgevoerd	Mening van deskundigen
Er is onvoldoende bewijsmateriaal om een standaardschema voor CT follow-up voor te stellen bij patiënten met kiemceltumoren van de teelbal in een gevorderd stadium	Mening van deskundigen

Follow-up van de contralaterale teelbal

Aanbeveling	**Niveau van bewijskracht**
Echografie van de contralaterale teelbal kan worden overwogen tijdens de follow-up van patiënten met kiemceltumoren van de teelbal	Mening van deskundigen

BEHANDELING VAN RECIDIVERENDE OF REFRACTAIRE AANDOENING

Aanbevelingen	**Niveau van bewijskracht**
Patiënten met recidiverende of refractaire kiemceltumoren van de teelbal moeten worden geïncludeerd in klinische studies indien ze beschikbaar zijn	Mening van deskundigen
Bij patiënten met een recidief van een kiemceltumor van de teelbal na eerstelijns chemotherapie gebaseerd op cisplatinum is hoog-gedoseerde chemotherapie met autologe beenmergtransplantatie niet aanbevolen buiten een klinische studie	1A

IMPLEMENTATIE, EVALUATIE EN UPDATE

IMPLEMENTATIE

De implementatie van de huidige richtlijn zal worden geleid door het College voor Oncologie. Een online implementatiehulpmiddel, vergelijkbaar met de hulpmiddelen die de vorige richtlijnen vergezelden, zal worden ontwikkeld.

KWALITEITSCONTROLE

Op basis van deze richtlijn werden kwaliteitsindicatoren ontwikkeld om de implementatie ervan te evalueren. De resultaten van de piloottest van deze indicatoren zullen worden gerapporteerd in een volgend rapport.

BIJWERKING RICHTLIJN

Gezien de veranderende wetenschappelijke literatuur, en op basis van een voorafgaande beoordeling van de literatuur, moet deze richtlijn na 5 jaar volledig worden bijgewerkt. Ondertussen zal belangrijke literatuur die beschikbaar komt vermeld worden op de website van het College voor Oncologie.

Scientific summary

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ABBREVIATIONS

95%CI	95 percent confidence interval
ACCC	Association of Comprehensive Cancer Centres
ACR	American College of Radiology
ACS	American College of Surgeons
ADASP	Association of Directors of Anatomic and Surgical Pathology
AFP	Alphafoetoprotein
AFU	Association Française d'Urologie
AHFMR	Alberta Heritage Foundation for Medical Research
ASCO	American Society of Clinical Oncology
BCR	Belgian Cancer Registry
BEP	Bleomycin, etoposide, cisplatin
CCO	Cancer Care Ontario
CE-CT	Contrast-enhanced CT
CoCanCPG	Coordination of Cancer Clinical Practice Guidelines in Europe
CPG	Clinical practice guideline
CT	Computerized tomography
EAU	European Association of Urology
EGCCCG	European Germ Cell Cancer Consensus Group
EP	Etoposide, cisplatin
ESMO	European Society for Medical Oncology
FDG	Fluorodeoxy-glucose
FNAC	Fine-needle aspiration cytology
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
GCT	Germ cell tumour
GIN	Guidelines International Network
GP	General Practitioner
Gy	Gray
HAS	Haute Authorité de Santé
HCG	Human chorionic gonadotrophin
HDCT	High-dose chemotherapy
HR	Hazard ratio
HTA	Health technology assessment
ICSI	Institute for Clinical Systems Improvement
IGCCC	International Germ Cell Consensus Classification
IGCN	Intratubular germ cell neoplasia
IGCNU	IGCN of the unclassified type
IGG	Italian Germ cell cancer Group
KCE	Belgian Healthcare Knowledge Centre

LDH	Lactate dehydrogenase
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NACB	National Academy of Clinical Biochemistry
NCCN	National Comprehensive Cancer Network
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NPV	Negative predictive value
NS	Not significant
NSGCT	Non-seminoma germ cell tumour
NZGG	New Zealand Guidelines Group
OR	Odds ratio
PET	Positron emission tomography
PLAP	Placental Alkaline Phosphatase
PPV	Positive predictive value
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
RPLND	Retroperitoneal lymph node dissection
RT	Radiotherapy
Se	Sensitivity
SGCT	Seminoma germ cell tumour
SIGN	Scottish Intercollegiate Guidelines Network
SIR	Standardized Incidence Rate
SMR	Standardized Mortality Rate
Sp	Specificity
UICC	Union Against Cancer Classification
US	Ultrasonography
US	United States
USPSTF	US Preventive Services Task Force
WHO	World Health Organization

1 INTRODUCTION

1.1 SCOPE

In the present report, the clinical practice guideline (CPG) on testicular cancer, published in 2006, is updated [1]. The previous guideline was mainly based on an adaptation of published guidelines with an additional search for systematic reviews. However, some of the included CPGs were of low quality. Above this, in a domain such as testicular cancer with few systematic reviews available, a search for recent primary studies seems necessary to dispose of the entire evidence base. In order to have a full evidence-based CPG, it was decided to perform a complete update of the previous version, with a search for guidelines, systematic reviews and primary studies.

This guideline is the result of a collaboration between the College of Oncology and the KCE. The CPG will cover a broad range of topics: diagnosis, staging, treatment and follow-up. It is restricted to men presenting with testicular germ cell tumours and does not address primary extragonadal germ cell cancer or non-germ cell testicular cancers (e.g. Leydig cell tumours, lymphoma, sarcoma, metastatic disease). The CPG is intended to be used by all care providers involved in the care for these men.

1.2 EPIDEMIOLOGY

In Belgium, 269 new testicular cancers were diagnosed in 2006, with a crude incidence rate of 5.2/100 000 person years (source: Belgian Cancer Registry). Since 2003, the crude incidence rate slightly increased (4.7/100 000 person years), although it should be noted that the coverage of the cancer registration markedly improved since then. Testicular cancer typically is a cancer of young men, with a peak age-standardised incidence rate of 20.9/100 000 person years in the age category 25-30 years in 2006. In males aged 15-44 years, testicular cancer was the most frequent cancer in the period 2004-2005.

The Belgian crude incidence rate is comparable to that in the US (age-adjusted incidence rate 5.1/100 000 person years in 2004) [2], but lower than that in Germany (crude incidence rate 10.6/100 000 person years in 2005-2006) [3] and Luxembourg (age-adjusted incidence rate 7.7/100 000 person years in 2000-2004) [4].

No published mortality or survival data specifically for testicular cancer are available for Belgium. However, in the period 2000-2001, the relative 5-year survival for testicular cancer was 95% in Flanders [5]. These data are in line with those reported in the literature for other countries and regions. For example, in England and Wales, the relative 5-year survival rose from 91% between 1986-1990 to 97% between 1996-1999[6]. In the southern of the Netherlands, the relative 5-year survival was 99% and 96% for patients with seminoma and non-seminoma germ cell cancer respectively [7].

2 METHODOLOGY

2.1 GENERAL APPROACH

As for the previous CPGs developed within the collaboration between the College and the KCE, the present CPG was developed by adapting (inter)national CPGs to the Belgian context (www.kce.fgov.be). This approach was recently structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers [8]. The ADAPTE methodology generally consists of three major phases (www.adapte.org):

1. **Set-up Phase:** Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).
2. **Adaptation Phase**: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.
3. **Finalization Phase**: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

2.2 INTERNATIONAL COLLABORATION

The KCE is involved in a European cancer network, CoCanCPG (Coordination of Cancer Clinical Practice Guidelines in Europe), aiming to develop a sustainable international collaboration for the joint management of mutually relevant priorities in CPG development and research to reduce the existing duplication and fragmentation of efforts, skills and information between programmes (www.cocancpg.eu).

Within this network, annual programmes are being exchanged to allow the identification of common projects and to highlight opportunities for collaboration. Since both the Scottish Intercollegiate Guidelines Network (SIGN) and the KCE planned the update of their CPG on testicular cancer, it was decided to use this guideline for a preliminary collaboration. One KCE expert took part of the guideline development group for the SIGN guideline, while two Belgian urologists of the KCE guideline development group served as external reviewer of the SIGN guideline. On the other hand, the KCE was able to use the preliminary documents of SIGN to feed the content of the KCE guideline. It is important to mention that, at the time of this writing, the SIGN guideline still is in the process of external review and consultation.

2.3 CLINICAL QUESTIONS

The CPG addresses the following clinical questions:

1. What diagnostic tests are the most effective to confirm the diagnosis of testicular cancer?
2. What diagnostic tests are necessary to investigate the extent of testicular cancer? What is the place of tumour markers in the diagnosis, staging and prognosis?
3. Which treatments are the most effective for primary management of testicular cancer?
4. What is the work-up for the contralateral testis in case of testicular cancer?
5. What histopathological tests are needed to assess the extent and prognosis of testicular cancer? What parameters need to be reported in the histopathological report?

6. What is the most effective treatment for stage I testicular cancer?
7. What is the most effective treatment for metastatic testicular cancer?
8. What diagnostic tests are needed to evaluate residual disease? What is the most effective treatment of residual testicular cancer?
9. What is the most effective follow-up strategy after treatment for testicular cancer?
10. What is the most effective treatment of relapsing or refractory testicular cancer?

2.4 LITERATURE SEARCHES

2.4.1 Search strategy

To identify published clinical practice guidelines (CPG) on testicular cancer, OVID Medline, the National Guideline Clearinghouse and specific websites (Table 1) were searched. Both national and international CPGs were searched. A language (English, Dutch, French) and date restriction (2000 – 2009) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

Table 1. Searched guideline websites and websites of oncologic organisations.

Alberta Heritage Foundation For Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
American Society of Clinical Oncology (ASCO)	http://www.asco.org/
American College of Surgeons (ACS)	http://www.facs.org/cancer/coc/
Cancer Care Ontario	http://www.cancercare.on.ca/english/home/
CMA Infobase	http://mdm.ca/cpgsnew/cpgs/index.asp
Guidelines International Network (GIN)	http://www.g-i-n.net/
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/
National Cancer Institute	http://www.cancer.gov/
Haute Autorité de Santé (HAS)	http://bfes.has-sante.fr/HTML/indexBFES_HAS.html
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/

The search for peer-reviewed articles included a search in OVID Medline and the Cochrane Database of Systematic Reviews (see appendix for search strings). The search was limited to articles published in English, French and Dutch. No date limit was set. For therapeutic questions, only systematic reviews and randomized controlled trials (RCT) were included. For diagnostic questions, the search was limited to systematic reviews, RCTs and diagnostic accuracy studies. Exclusion criteria for the diagnostic studies were: sample size < 20 patients (< 50 patients for histopathology), inability to reconstruct the contingency table(s), partial verification, absence of reference standard, absence of patient-based analysis, case-control design. Finally, for prognostic questions, systematic reviews and cohort studies were included. Exclusion criteria for prognostic studies were: sample size < 150 patients, absence of multivariate analysis, use of the index test to modify the management. In general, systematic reviews not reporting the search strategy and/or the quality appraisal of the included studies were excluded.

All searches were run between January and December 2009, and updated in January 2010.

The identified studies were selected based on title and abstract. For all eligible studies, the full-text was retrieved. In case no full-text was available, the study was not taken into account for the final recommendations.

2.4.2 Quality appraisal

2.4.2.1 Clinical practice guidelines

The AGREE instrument [9] was used to evaluate the methodological quality of the identified CPGs. Each of the 20 identified CPGs was scored by two independent researchers (JV and SS) and discussed in case of disagreement (see appendix for an overview of the scores). Based on an overall assessment – taking into account the AGREE scores – 5 high-quality CPGs were finally selected. In general, CPGs with an aggregated domain score of 66% or less on the domain 'Rigour of development' were not included (see appendix 3).

2.4.2.2 Peer-reviewed articles

The quality of the retrieved systematic reviews, RCTs and prognostic studies was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl). The methodological quality of the diagnostic accuracy studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist [10]. All critical appraisals were done by a single KCE expert.

2.5 DATA EXTRACTION AND SUMMARY

For each included CPG the following data were extracted: search date & publication year, searched databases, availability of evidence tables, recommendations and referenced evidence.

For each systematic review, the search date, publication year, included studies and main results were extracted. For primary studies, the following data were extracted: publication year, study population, study intervention, and outcomes.

For each clinical question, the recommendations from the identified CPGs and the additional evidence were summarized in evidence tables. A level of evidence was assigned to each recommendation and additional study using the GRADE system (see appendix 2).

2.6 FORMULATION OF RECOMMENDATIONS

Based on the retrieved evidence, a first draft of recommendations was prepared by a KCE expert (JV). This draft together with the evidence tables were circulated to the guideline development group (Table 2) prior to each face-to-face meeting. The guideline development group met on two occasions (September 16th 2009 and January 26th 2010) to discuss the first draft. Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared.

A grade of recommendation was assigned to each recommendation using the GRADE system (see appendix 2). The second draft was once more circulated to the guideline development group for final approval.

Table 2. Composition of guideline development group.

Expert	Field of expertise
Gert De Meerleer	Radiation oncology
Thierry Gil	Medical Oncology
Laurette Renard	Radiation oncology
Sandrine Rorive	Pathology
Sylvie Rottey	Medical oncology
Isabelle Salmon	Pathology
Dirk Schrijvers	Medical oncology
Bertrand Tombal (president)	Urology
Geert Villeirs	Radiology

2.7 EXTERNAL EXPERT MEETING

External experts received the recommendations 10 days prior to the expert meeting. As a preparation of the meeting all invited experts were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the experts were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case an expert disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. All scores were then anonymized and summarized into a median score, minimum score, maximum score and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion (see appendix 3). The recommendations were then discussed during a face-to-face meeting on September 14th 2010. Based on this discussion a final draft of the recommendations was prepared. In appendix 3, an overview is provided of how the comments of the external experts were taken into account.

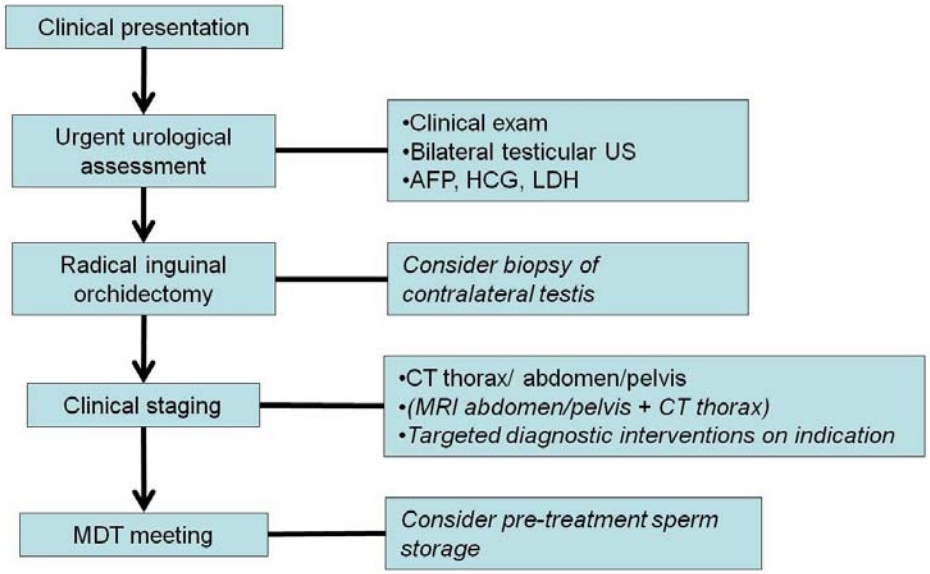
2.8 DEFINITIONS

Germ cell tumours (GCT) are classified as seminomas and non-seminomas. Seminomas develop from the sperm-producing germ cells of the testicle. The 2 main subtypes of these tumours are classical (or typical) seminomas and spermatocytic seminomas. The latter is a rare type of seminoma that tends to occur in older men. Spermatocytic tumours tend to grow more slowly and are less likely to spread to other parts of the body than classical seminomas. Non-seminomas include multiple cell types, such as embryonal cell carcinoma, choriocarcinoma, yolk sac tumour and teratoma. Teratomas are considered to be either mature or immature, depending on whether adult-type differential cell types or partial somatic differentiation is found. When both elements of a seminoma and non-seminoma are present (including an increased alpha-fetoprotein [AFP], a serum tumour marker produced by non-seminomatous cells and not by seminomatous cells), management follows that for a non-seminoma, since this is the more clinically aggressive tumour.

Accepted histological precursors of testicular germ cell cancers include carcinoma in situ or intratubular germ cell neoplasia (IGCN).

3 DIAGNOSIS, PRIMARY MANAGEMENT AND STAGING OF TESTICULAR CANCER

3.1 ALGORITHM



3.2 DIAGNOSIS

Patients with primary testicular cancer usually present with a testicular lump, swelling, pain, or sensation of scrotal heaviness. Seldom, the clinical presentation is extragonadal (retroperitoneal or mediastinal), with symptoms related to metastatic disease (e.g. back pain due to retroperitoneal lymph node metastasis, dyspnoea due to lung metastasis, neurological problems due to brain metastasis). Patients presenting with these testicular symptoms should be examined carefully and an attempt made to distinguish between lumps arising from the body of the testis and other intrascrotal swellings [11].

Patients with a clinical suspicion of testicular malignancy should undergo urgent urological assessment (within 2 weeks) [11], including clinical exam and scrotal ultrasonography, evaluating both testicles and annexes. Overall, ultrasonography was found to have a good sensitivity ranging between 90 and 100% and a low to moderate specificity ranging between 44 and 99% for the diagnosis of testicular malignancy [12-17]. However, the overall quality of these studies was low.

Recommendation

- **Patients with a clinical suspicion of testicular malignancy should undergo urgent urological assessment, including clinical exam and bilateral testicular ultrasonography (1C).**

3.3 PRIMARY MANAGEMENT

Orchidectomy remains the primary treatment for patients with testicular cancer. It is an important diagnostic procedure and in many cases a definitive curative treatment. Staging investigations can be deferred until after inguinal orchidectomy. However, AFP, human chorionic gonadotrophin (HCG) and lactate dehydrogenase (LDH) should be measured preoperatively to indicate prognosis and to guide postoperative management [18]. ASCO recently issued new guidelines on the use of tumour markers in patients with GCT [19]. These guidelines were published after the literature search for this report, and are therefore no part of the evidence tables in appendix. According to these guidelines, AFP and HCG should be measured before orchidectomy for all patients suspected of having a testicular GCT to help establish the diagnosis and interpret postorchidectomy levels. Clearly, it is not recommended to use the results of tumour marker assessment to guide decision making on the need for an orchidectomy. In patients with testicular non-seminoma GCT (NSGCT), ASCO recommends measuring serum AFP, HCG, and LDH shortly after orchidectomy and before any subsequent treatment. The magnitude of postorchidectomy tumour marker elevations is used to stratify risk and select treatment. In patients with testicular seminoma GCT (SGCT), ASCO recommends measuring postorchidectomy serum concentrations of HCG and/or LDH in case of preorchidectomy elevations. However, ASCO recommends against using postorchidectomy serum concentrations of either HCG or LDH to stage or predict prognosis of patients with involved nodes and/or metastasis. ASCO also recommends against using tumour marker levels to guide treatment decisions for seminoma [19].

Every patient with a suspect testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunics. Immediate radical orchidectomy with division of the spermatic cord at the internal inguinal ring should be performed if a tumour is found. If the diagnosis is not clear, a testicular biopsy should be taken for frozen section histological examination. Two retrospective studies found a good sensitivity (94% and 100%) and a moderate to good specificity (89% and 100%) for the diagnosis of malignancy with frozen section analysis [20, 21].

Once the diagnosis of testicular malignancy is confirmed, the testis is enveloped into the sponges which protected the surgical field, gloves are changed, the inguinal channel is opened and the spermatic cord is divided at the level of the internal ring. The specimen is sent for definitive histology (see chapter 4).

In case of disseminated disease and life-threatening metastases, it is current practice to start with up-front chemotherapy, and orchidectomy may be delayed until clinical stabilisation has occurred.

Organ-sparing surgery (tumorectomy) is contraindicated in the presence of a normal contralateral testis. It can be discussed if the tumour volume is less than 30% of the testicular volume in case of synchronous bilateral testicular tumours, metachronous contralateral tumours, or a tumour in a solitary testis with normal preoperative testosterone levels. The absence of long-term data should be explained to the patient, and in particular the very high rate of carcinoma in situ (at least up to 82%), requiring adjuvant radiotherapy [22].

Recommendations

- **Preoperative assessment of tumour markers (AFP, HCG, LDH) is recommended for postoperative management of patients with testicular cancer (expert opinion).**
- **In patients with a high suspicion of testicular malignancy after urological assessment, radical orchidectomy through inguinal approach is indicated (expert opinion).**

3.4 CONTRALATERAL TESTIS

In a large retrospective population-based cohort study involving 29 515 men with testicular cancer diagnosed before age 55 years (1973 – 2001), 175 men (0.6%) were found to have synchronous contralateral testicular cancer [23]. According to a prospective study involving 2 318 patients with testicular germ cell tumours (GCT), about 5% of men with testicular cancer have carcinoma in situ of the contralateral testis [24]. Patients with the highest risk of contralateral testicular carcinoma in situ are those with known infertility, an atrophic testis (i.e. < 12 ml [25]) and a history of cryptorchidism [24, 26-29]. In these patients, a biopsy of the contralateral testis at the time of primary orchidectomy should be considered. A large prospective cohort study involving 1 954 men with testicular germ cell cancer found a sensitivity of 95% (95%CI 89-98%) and a specificity of 100% (95%CI 100-100%) for the detection of testicular intraepithelial neoplasia with contralateral testicular biopsy.

The literature about treatment of testicular carcinoma in situ is limited to small observational studies. Low-dose radiotherapy (18 – 20 Gy) seems to offer the best treatment results [30-33]. Chemotherapy has been shown to be of only little effect in eradicating testicular carcinoma in situ [34]. In some centres, watchful waiting is offered to patients with a carcinoma in situ of the contralateral testis.

3.5 STAGING

Contrast-enhanced CT of the thorax, abdomen and pelvis is the imaging technique of first choice for the detection of retroperitoneal and mediastinal lymph nodes and pulmonary and hepatic metastases in patients with histopathologically confirmed testicular cancer [11, 18]. Data on the diagnostic accuracy of CT are conflicting and limited to small and old studies, with a sensitivity ranging from 41% to 91% and a specificity ranging from 50 to 95% [35-39].

Importantly, CT is a high radiation-dose examination, and every effort should be made to avoid unnecessary radiation, particularly in young patients [40]. Furthermore, adequate precautions should be taken in order to avoid iodine allergy or and to minimize nephrotoxicity. For patients with suspected iodine allergy or chronic renal failure, magnetic resonance imaging (MRI) of the abdomen (combined with a non-contrast-enhanced chest CT) could be an alternative staging technique. However, the literature on the use of MRI is limited to small low-quality studies [41]. Prospective studies comparing CT and MRI for the staging and follow-up of patients with germ cell cancer are needed.

For the evaluation of hepatic metastases, abdominal ultrasonography is often used. For nodal staging, two low-quality studies showed a sensitivity of 87% and 95% and a specificity of 100% and 50% respectively [37, 42].

Recently, the KCE published an evidence report on PET scan [43]. For the staging of testicular cancer, the evidence was found to be inconclusive (sensitivity 66-70%, specificity 97-100%).

In patients with symptomatic metastatic disease, targeted diagnostic interventions are indicated. When symptoms and signs are suggestive of brain metastases (e.g. focal epilepsy, presence of multiple lung metastases, HCG > 10000 IU/l), MRI or CT scanning of the brain should be considered [11]. Bone scintigraphy and targeted imaging of metastatic lesions are indicated in case of symptoms suggestive of bone metastases (e.g. pain, pathologic fracture).

Recommendations

- **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 contrast-enhanced 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).**
- **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)**

3.6 FERTILITY ISSUES

Due to recent advances in in-vitro fertilisation technology and sperm banking procedures, even men with extremely reduced sperm count and motility are candidates for sperm cryopreservation [44]. It is strongly recommended that sperm be collected before initiation of cancer therapy, because the quality of the sample and sperm DNA integrity may be compromised even after a single treatment session. In addition, in patients with testicular cancer, sperm quality may be poor even in patients who have not yet started treatment [11]. Many patients have to start chemotherapy immediately or soon after diagnosis, limiting the potential number of ejaculates to one or two samples. Even in these instances, it is reasonable to make every effort to bank sperm, since recent progress in andrology laboratories and in the use of assisted reproductive techniques, particularly the technique of intracytoplasmic sperm injection, allows the successful freezing and future use of a very limited amount of sperm.

Recommendation

- **Pre-treatment sperm storage should be offered to men who may require chemotherapy or radiotherapy (expert opinion).**

4 HISTOPATHOLOGIC EXAMINATION

4.1 CLASSIFICATION

The recommended *histological classification* of testicular tumours is that of the World Health Organization (WHO) Classification of Tumours [45].

The *pathological staging* of testicular tumours follows the International Union Against Cancer Classification (UICC) TNM classification [46] (see appendix). For metastatic germ cell tumours, the International Germ Cell Consensus Classification (IGCCC) prognostic grouping is now widely used (Table 3).

Table 3. IGCCC prognostic grouping [47].

Non-seminoma	Seminoma
Good prognosis	
All of the following criteria: • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1000 ng/mL • HCG < 5000 IU/L (1000 ng/mL) • LDH < 1.5 x upper limit of normal	All of the following criteria: • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any HCG • Any LDH
Intermediate prognosis	
All of the following criteria: • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP ≥ 1000 and ≤ 10000 ng/mL or • HCG ≥ 5000 and ≤ 50000 IU/L or • LDH ≥ 1.5 and ≤ 10 x upper limit of normal	Any of the following criteria: • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any HCG • Any LDH
Poor prognosis	
Any of the following criteria: • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10000 ng/mL or • HCG > 50000 IU/L (10000 ng/mL) or • LDH > 10 x upper limit of normal	No patients classified as poor prognosis

4.2 MACROSCOPIC EXAMINATION

4.2.1 Description

The macroscopic description of the surgical resection specimen should include the following items:

- Radical orchidectomy vs. tumorectomy
- Side of tumour
- Testis size
- Tumour size (3 measures) and description [48-51]
- Size (3 measures) and description of:
  - Epididymis
  - Spermatic cord
  - Tunica vaginalis (note the presence of intratunical fluid)
  - Albuginea

4.2.2 Sampling of the resection specimen

A sample of the following structures needs to be taken:

- Tumour: 1 cm^2 section for each cm of maximum tumour diameter;
- Normal macroscopic testis tissue: scar area if present;
- Albuginea nearby the tumour;
- Epididymis;
- Proximal and distal (surgical margin) sections of spermatic cord. The distal margin has to be cut prior to incision of the testis [52];
- If any suspected area is found, extensive sampling has to be done.

4.3 MICROSCOPIC EXAMINATION

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) [23, 48, 53-57].

The presence or absence of IGCN in non-tumoural parenchyma needs to be described.

The pathological TNM Staging needs to be done with specific attention to:

- Presence or absence of vascular and/or lymphatic invasion [48, 50, 53, 54];
- Presence or absence of invasion or extension through tunica albuginea, tunica vaginalis, rete testis [51], epididymis or spermatic cord invasion.

4.4 IMMUNOHISTOCHEMISTRY

4.4.1 Diagnosis of IGCN

The evidence on the use of immunohistochemical staining for the diagnosis of IGCN is limited to low-quality observational studies. Tavolini et al. reported a very low sensitivity of 0% and a moderate specificity of 89% for the detection of non-invasive testicular cancer with bilateral testicular FNAC and immunohistochemical staining for Placental Alkaline Phosphatase (PLAP) in cryptorchid patients who underwent orchidopexy [58]. Nevertheless, PLAP can be demonstrated in a high percentage of IGCN of the unclassified type (IGCNU) [45].

CD-117 (or c-kit proto-oncogene) is also widely expressed in IGCN [59]. Above this, nuclear reactivity of OCT3/4 can be useful to identify early forms of IGCNU [60]. However, good diagnostic accuracy studies or prognostic studies investigating their diagnostic potential are lacking.

4.4.2 Distinction between seminoma and non-seminoma

PLAP [61, 62] and CD-117 [59, 63] are widely expressed in classical seminoma. However, in a low-quality retrospective study, Heidenreich et al. found a moderate sensitivity of 79% and a low specificity of 45% for the distinction of seminoma from non-seminoma with PLAP immunohistochemical staining [61].

In case of differential diagnosis between seminoma and embryonal carcinoma, CD-117, CD-30 and pancytokeratins may be helpful [62, 63]. Again, good diagnostic accuracy studies or prognostic studies investigating their diagnostic potential are lacking.

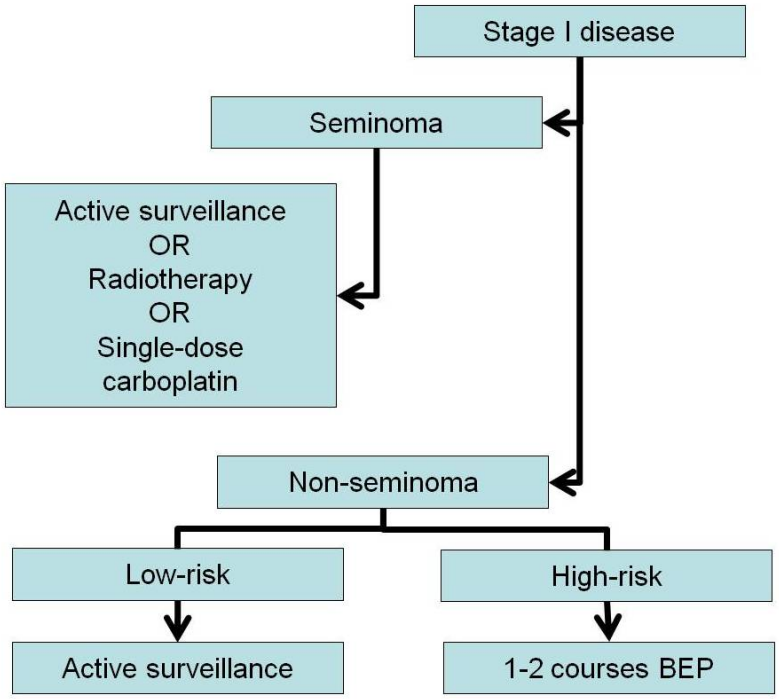
In case of differential diagnosis between seminoma and Yolk sac tumour, teratoma or choriocarcinoma, OCT4, AFP and beta-HCG may be helpful [61, 64-66]. Sensitivity of immunohistochemical staining with AFP for the distinction between non-seminoma and seminoma was found to be low in 2 retrospective studies (20-67%) [61, 64]. Specificity was high (100%) in both studies. Bosman et al. found a sensitivity of 74% and a specificity of 93% for the distinction between non-seminoma and seminoma with beta-HCG immunohistochemical staining [64]. In the study of Heidenreich et al. no positive HCG staining was found [61]. Importantly, both studies potentially suffered from selection bias. Two other retrospective studies, also potentially suffering from selection bias, found a high sensitivity (100%) and a low specificity (63-66%) for the distinction between seminoma and non-seminoma with OCT4 immunohistochemical staining [65, 66].

Recommendations

- **The distal margin has to be cut prior to incision of the testis to avoid tumour cell contamination of the spermatic cord (expert opinion).**
- **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) (1C).**

5 TREATMENT OF STAGE I DISEASE

5.1 ALGORITHM



5.2 STAGE I SEMINOMA

Inguinal orchidectomy is the standard treatment for stage I seminoma (see above).

Canadian Cancer Ontario (CCO) performed a high-quality systematic review as a basis for their guideline on the treatment of stage I seminoma patients [67]. Based on the retrieved evidence, postoperative surveillance was recommended as the preferred treatment option, while adjuvant radiotherapy or chemotherapy were considered as valuable alternatives. However, only one moderate-quality RCT directly compared two of these treatment options [68]. Above this, until now surveillance was never studied in a randomised controlled trial. For this reason, the Association Française d'Urologie (AFU) considered the 3 treatment options as equally effective.

In 1 477 patients with stage I (pT1-T3) seminoma and normal post-orchidectomy tumour markers, radiotherapy (para-aortic strip or dog-leg field) and single-dose carboplatin (AUC 7) were found to be equally effective in terms of relapse-free survival (at 2 years: 96.7% vs. 97.7%; at 3 years: 95.9% vs. 94.8%) [68]. In this RCT, a trend toward more secondary tumours was found with radiotherapy. However, these findings have not been confirmed so far. In 2 other moderate-quality RCTs, different radiotherapy regimens were compared. In 625 patients with stage I (pT1-T3) seminoma and normal post-orchidectomy tumour markers, radiotherapy (para-aortic or dog-leg field) 20 Gy in 10 fractions over 2 weeks and 30 Gy in 15 fractions over 3 weeks were found to be equally effective in terms of relapse-free survival (at 2 years: 97.0% vs. 97.7%; at 5 years: 96.4% vs. 97.0%) [69]. Significantly more pronounced leukopenia was found in the 30 Gy group. In 478 patients with stage I (pT1-T3) seminoma and normal post-orchidectomy tumour markers, para-aortic strip and dog-leg radiotherapy were equally effective in terms of relapse-free survival (at 3 years: 96.0% vs. 96.6%) [70]. Significantly less pronounced leukopenia was found in the para-aortic strip group. Para-aortic strip radiotherapy is therefore considered to be the standard-of-care radiotherapy in stage I seminoma.

Recently, Groll et al. pooled the results of 14 observational studies involving 2 060 patients [71]. Cause-specific survival was found to be 99.7%. Overall, 356 relapses (17%) were found, of which 23 (2%) were late relapses.

Recommendations

- **In patients with stage I seminoma post-orchidectomy, active surveillance can be considered as a management option (2B).**
- **In patients with stage I seminoma post-orchidectomy, radiotherapy can be considered as a management option (2B).**
- **In patients with stage I seminoma post-orchidectomy, single-dose carboplatin can be considered as a management option (2B).**

5.3 STAGE I NON-SEMINOMA

Inguinal orchidectomy is the standard treatment for stage I non-seminoma (see above).

Based on a systematic review of the literature, CCO recommended primary surveillance after inguinal orchidectomy for all patients with clinical stage I non-seminoma, with treatment at relapse [72]. On the contrary, the AFU recommended to take into account the relapse risk for determining the optimal treatment strategy [18]. For patients with low risk (defined by the AFU as no vascular or lymphatic invasion), the AFU offers the choice between surveillance and retroperitoneal lymph node dissection (RPLND). For high-risk patients (defined by the AFU as vascular or lymphatic invasion), the choice is offered between surveillance and chemotherapy [18].

One RCT compared surveillance to adjuvant radiotherapy in 156 patients with clinical stage I non-seminoma [73]. In the first year after orchidectomy, no significant difference in relapse rate was found (radiotherapy 23% vs. surveillance 14%). However, radiotherapy completely prevented retroperitoneal relapse. Importantly, all relapsing patients in the surveillance group were without evidence of disease with a median observation time of 67 months after salvage chemotherapy.

A more recent RCT compared one cycle of BEP (bleomycin + etoposide + cisplatin) to RPLND with 2 cycles of BEP in case of retroperitoneal metastases in 382 patients with clinical stage I non-seminoma [74]. Less recurrences were observed in the BEP group compared to the RPLND group (2 vs. 15, p=0.0011). Recurrence-free survival was significantly better in the BEP group (at 2 years: 99.5% vs. 91.9%; HR 7.937, 95%CI 1.808-34.48).

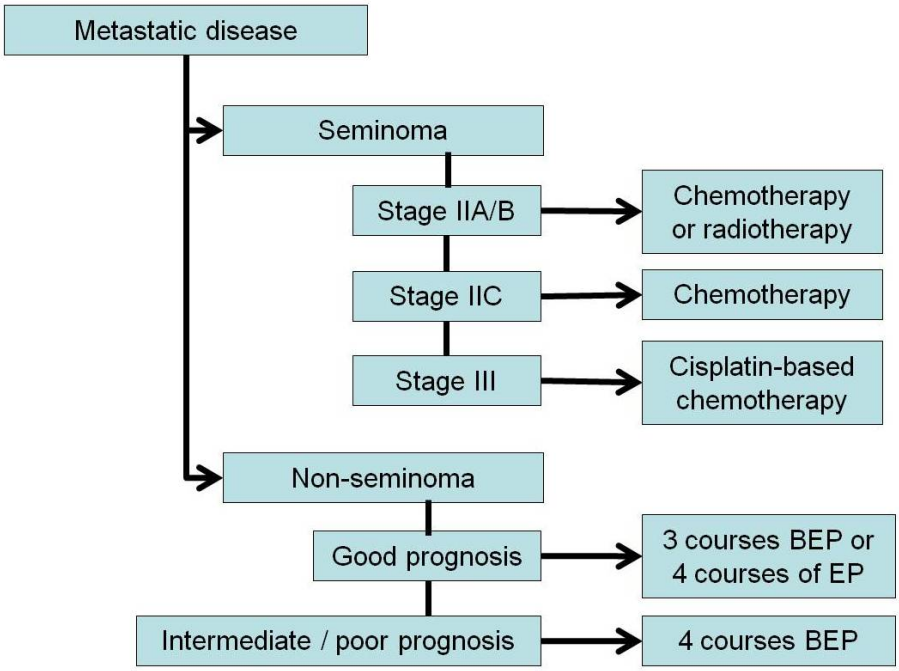
Groll et al. pooled the results of 31 studies (including the RCT of Rorth et al.) [71]. The cause-specific survival was found to be 98.6%. Overall, 1 025 relapses (28%) were identified, of which 55 (2%) were late relapses. The following predictors of relapse were identified: vascular invasion of the primary tumour, predominantly embryonal carcinoma histology (i.e. >50%), T stage and absence of yolk sac tumour in the primary specimen [71]. In stage I non-seminoma patients with these risk factors, treatment with 1 or 2 courses of BEP should be considered [18, 75].

Recommendations

- **Primary surveillance is recommended for patients with stage I non-seminoma (without vascular or lymphatic invasion and without predominant embryonal component) post-orchidectomy, with treatment at relapse (2B).**

6 TREATMENT OF METASTATIC DISEASE

6.1 ALGORITHM



6.2 STAGE II AND III SEMINOMA

Inguinal orchidectomy is an integral part of the standard treatment for stage II and III seminoma (see above).

Two systematic reviews discussed the medical treatment of patients with advanced testicular cancer [76, 77]. Both reviews based their treatment recommendations on risk stratification (good, intermediate or poor prognosis). Two regimens were recommended for good-prognosis GCT: 4 cycles of EP or 3 cycles of BEP. For intermediate- and poor-prognosis GCT, 4 cycles of BEP were recommended [76].

No randomised trials exclusively including patients with stage IIA or IIB seminoma were found. In the SIGN 2010 guideline, one comparative observational study is cited [11]. Thirty-three patients with stage IIA/B seminoma treated with carboplatin and radiotherapy were compared to 80 historical controls treated with radiotherapy alone [78]. A trend towards better relapse-free survival was found in favour of combination therapy. The treatment effect was more pronounced for stage IIB patients. Based on another retrospective study, the AFU considered radiotherapy as the standard treatment for patients with stage IIA or IIB seminoma [18]. However, in the subgroup of 37 patients with stage IIB disease included in this retrospective study, no significant differences were found between chemotherapy and radiotherapy [79].

In the same retrospective study, chemotherapy was associated with an inferior 5-year recurrence-free survival compared to radiotherapy in the subgroup of 39 patients with stage IIC disease [79]. However, these results were not supported by data from three series, in which the relapse rate was 35% when treated with radiotherapy alone [11].

Two randomised trials compared single-agent carboplatin with cisplatin-based chemotherapy in patients with advanced metastatic seminoma [80, 81]. Both studies were also included in a pooled analysis [82], and in the systematic reviews of Feldman et al. [76] and Shelley et al. [77].

Horwich et al. randomised 130 patients with relapsing (after radiotherapy) or newly diagnosed advanced seminoma (stage IIC, III or IV) to single agent carboplatin or cisplatin and etoposide [81]. The majority of the included patients had testicular seminoma (85%). No significant differences were found in terms of overall survival (HR 0.85; 95%CI 0.35-2.10), progression-free survival (HR 0.64; 95%CI 0.32-1.28) and failure-free survival (HR 0.56; 95%CI 0.28-1.09) at three years. In the second study, which is only available as an abstract, 280 patients with advanced metastatic seminoma were randomised to single agent carboplatin or cisplatin, etoposide and ifosfamide [80]. Again, no significant difference was found in terms of overall survival (87% vs. 95%, no p-value provided). However, relapse-free survival was significantly better with cisplatin-based chemotherapy (74% vs. 95%, p<0.01). Cisplatin-based chemotherapy was associated with more grade 3/4 leuko- and thrombopenia (8% vs. 72%). Individual patient data (n=361) from these two trials were pooled [82]. Patients treated with single agent carboplatin had an inferior 5-year overall (89 vs. 94%; p=0.09) and progression-free survival rate (72 vs. 92%; p<0.0001) compared with patients receiving cisplatin-based combinations. Based on these observations, the AFU recommended cisplatin-based chemotherapy (3 courses of BEP or 4 courses of EP) as standard treatment for patients with stage IIC or III seminoma [18].

Recommendations

- **Patients with stage IIA or IIB seminoma should be treated with chemotherapy or radiotherapy (2C).**
- **In patients with stage IIC seminoma chemotherapy is the treatment of choice (2C).**
- **In patients with stage III seminoma cisplatin-based chemotherapy is recommended (1B).**

6.3 STAGE II, III AND IV NON-SEMINOMA

The systematic review of Feldman et al. included 11 RCTs of different first-line chemotherapy regimens in patients with good-prognosis metastatic NSGCT [76]. Four of these studies exclusively included patients with NSGCT [83-86]. Two studies compared 3 vs. 4 cycles of BEP and found equal efficacy, but less toxicity with 3 cycles [87, 88]. In another trial, 3 cycles of BEP were found to be more effective than 3 cycles of EP (overall survival: 95% vs. 86%, p=0.01; failure-free survival: 86% vs. 69%, p=0.01) [89]. However, in a more recent trial, 4 cycles of EP were found to be equivalent to 3 cycles of BEP based on equal efficacy (4-year overall survival: HR 0.42, 95%CI 0.15-1.20) and balanced toxicity [83]. Based on this evidence, the authors recommended two regimens for patients with good-prognosis GCT (both seminoma and non-seminoma): 3 cycles of BEP or 4 cycles of EP (e.g. in case of contraindications for bleomycin). These conclusions are in line with the recommendations of the AFU [18].

Feldman et al. included 8 RCTs of first-line chemotherapy regimens in patients with intermediate- or poor-prognosis metastatic NSGCT [76]. Four of these studies exclusively included patients with NSGCT [90-93]. In all trials that compared 4 cycles of BEP with another regimen, BEP was found to be equally or more effective, but less toxic [91-97]. Based on this evidence, the authors recommended 4 cycles of BEP for intermediate- and poor-prognosis GCT. These conclusions are again in line with the recommendations of the AFU [18].

One more recent RCT compared 4-6 cycles of CISCA/VB to 4 cycles of first-line BEP in 188 patients with intermediate- or poor-prognosis metastatic NSGCT [98]. Five-year event-free (HR 0.76, 95%CI 0.52-1.11) and overall survival (HR 0.73, 95%CI 0.46-1.18) did not differ significantly between the two treatment groups. However, CISCA/VB was associated with more significant haematological and mucous toxicities.

Finally, a recent RCT, presented as an abstract, demonstrated no improved outcomes with high-dose chemotherapy plus autologous stem cell support given as part of first-line therapy in patients with poor-prognosis GCT [99].

Recommendations

- **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).**

7 RESIDUAL DISEASE

7.1 IMAGING

Very few diagnostic accuracy studies evaluated the use of different diagnostic tests for the assessment of residual masses. Pfannenberg et al. compared the diagnostic accuracy of FDG-PET and CT/MRI for the assessment of the viability of 60 residual masses in 28 patients with metastatic GCT treated with high-dose chemotherapy [100]. In this study, MRI was used in patients with iodine allergy, and thus no comparison was made between CT and MRI. No significant differences were found for sensitivity (PET: 62%; CT/MRI: 62%) or specificity (PET: 83%; CT/MRI: 72%). In another study, the diagnostic accuracy of FDG-PET and CT was compared in 54 patients with metastatic seminoma and a CT-documented mass after chemotherapy [101]. For the diagnosis of viability of residual masses, PET scan was found to have a significantly better sensitivity (80% vs. 73%) and specificity (100% vs. 73%) than CT. However, both studies suffered from methodological weaknesses (small sample size, per-lesion-analysis, differential verification, possible incorporation bias).

Finally, Oechsle et al. prospectively evaluated the diagnostic accuracy of FDG-PET in 121 patients with NSGCT and a residual mass on conventional imaging (i.e. CT) after cisplatin-based chemotherapy [102]. Reference standard was histology in all patients. For the evaluation of viability of the residual mass, sensitivity was 70% and specificity 39%.

Despite this poor evidence, CT is the most commonly used diagnostic test for the assessment of residual masses. The evidence discussed above is insufficient to alter current practice. Therefore, CE-CT scan remains recommended for the imaging of residual masses after systemic treatment of testicular cancer. In case of contra-indications (iodine allergy, renal function impairment), MRI can be an alternative diagnostic technique. In view of the inconsistent results for FDG-PET, it cannot be routinely recommended for the evaluation of residual masses, although it may be useful in metastatic seminoma (residual lesions > 3 cm).

Recommendations

- **CE-CT scan is recommended for the imaging of residual masses after systemic treatment of testicular cancer (expert opinion).**
- **PET scan is not routinely recommended for the evaluation of residual masses, but may be useful in metastatic seminoma (2C).**

7.2 TREATMENT OF RESIDUAL NSGCT

The evidence on the treatment of residual NSGCT is limited to observational studies. Therefore, the optimal management of a residual mass following treatment for NSGCT is a subject of ongoing debate. Nevertheless, there is considerable consensus concerning the need for surgical resection in patients with NSGCT who have residual retroperitoneal masses (i.e. > 1 cm) after chemotherapy and whose markers have normalised [103]. The decision on the extent of resection should take into account the postoperative morbidity and risk for residual disease or relapse.

In patients with NSGCT and non-peritoneal masses (e.g. pulmonary or hepatic masses) after chemotherapy, metastasectomy can be safely performed [104-106].

If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time as excision of the residual mass [107].

Recommendations

- **In patients with NSGCT who have residual retroperitoneal masses after chemotherapy and whose markers have normalised, the residual masses should be removed (expert opinion).**
- **In patients with NSGCT and non-retroperitoneal masses after chemotherapy, metastatectomy is recommended if feasible (expert opinion).**
- **If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time as excision of the residual mass (expert opinion).**

7.3 TREATMENT OF RESIDUAL SGCT

In patients with seminoma who have residual masses following chemotherapy or radiotherapy, surgery is not routinely indicated. Indeed, surgical resection of residual seminomatous elements is technically challenging owing to the severe desmoplastic reaction between the regressing mass and the adjacent vascular and visceral structures [103].

According to the consensus-based guidelines of the EGCCCG [108] and the EAU [75], FDG-PET should direct treatment in patients with residual masses of > 3 cm in size after treatment for seminoma. This recommendation is based on the results of the SEMPET trial, in which the sensitivity and specificity of FDG-PET for the prediction of viable residual tumour in patients with residual masses > 3 cm were 80% (95%CI 44-95%) and 100% (95%CI 92-100%) respectively [101]. However, these findings are insufficient to recommend a routine use of PET scan to guide treatment decisions in these patients.

No resection or any other treatment modality is necessary in patients with a mass ≤ 3 cm, and surveillance is recommended in these cases. No clinical data are available to support active treatment in these cases.

In patients with seminoma previously treated with chemotherapy, and who have a residual mass > 3 cm and/or positive PET findings, radiotherapy is recommended. Although this is not studied prospectively, one retrospective series supports this recommendation [109]. Patients who relapse after first-line radiotherapy have a cure rate of > 90% and should be treated with cisplatin-based chemotherapy [108]. In patients with seminoma whose tumour markers become positive, salvage chemotherapy is also indicated.

Recommendations

- **In patients with seminoma who have residual masses ≤ 3 cm, surveillance is recommended (expert opinion).**
- **In patients with seminoma previously treated with chemotherapy, and who have a residual mass > 3 cm and/or positive PET findings, radiotherapy can be considered (expert opinion).**
- **In patients with seminoma relapsing after first-line radiotherapy or whose tumour markers become positive, salvage chemotherapy is indicated (expert opinion).**
- **In patients with seminoma who have residual masses following chemotherapy or radiotherapy, extirpative surgery is not recommended (expert opinion).**

8 FOLLOW-UP

In general, follow-up is intended to [11]:

- Detect relapse at a stage where therapy has the best chance of being effective;
- Monitor and treat treatment-related toxicity;
- Detect metachronous cancers, in particular contralateral testicular cancers.

8.1 PRIMARY SURVEILLANCE POST-ORCHIDECTOMY

Few studies evaluated the use of diagnostic tests for follow-up and the frequency of this follow-up in patients with stage I GCT under primary surveillance after orchidectomy.

One RCT compared surveillance with two CT scans over 1 year (at 3 and 12 months post-orchidectomy) to surveillance with five CT scans over 2 years (at 3, 6, 9, 12 and 24 months post-orchidectomy) in 414 patients with *stage I NSGCT* [110]. Relapse rate was comparable in both groups (15% vs. 20%), no patients had poor prognosis at relapse. Based on observational data, two published guidelines of sufficient quality included recommendations on the follow-up of stage I NSGCT patients [18, 111]. Furthermore, the new SIGN guideline also contains valuable information on this topic [11].

Most guidelines agree on the frequency of follow-up visits that include a clinical examination, blood serum marker tests (AFP, HCG and LDH) and a chest X-ray. These follow-up visits should be conducted every month in the first year, every two months in the second year, every three months in the third year, and every six months in the fourth and fifth years.

On the frequency of post-orchidectomy thoraco-abdomino-pelvic CT scans there is less agreement. Both CCO and AFU recommended a CT scan every three months in the first year, every four to six months in the second year and every six months in the third year [18, 111]. In the fourth and fifth year, the AFU recommended a CT every 6 months [18], while the CCO recommended an annual CT [111]. On the contrary, the SIGN guideline took into account the results of Rustin et al. (2007) [110], and recommended a post-orchidectomy CT scan at 3 and 12 months [11].

On the follow-up of *stage I seminomas* there is less information available. The AFU recommended blood serum marker tests and a CT scan every 6 months in the first five years post-orchidectomy [18]. SIGN proposed a 3-monthly follow-up visit in the first two years and a 6-monthly visit in the third and fourth year [11]. A CT is recommended every 6 months during the first two years and annually during the third and fourth year.

In view of the absence of a consensus on the frequency of CT examinations during primary surveillance, no standard scheme can be proposed. However, at least an abdomino-pelvic CT every 6 months during the 2 first years post-orchidectomy is desirable for stage I seminomas. For patients with stage I non-seminoma under primary surveilance, at least an abdomino-pelvic CT at 3 and 12 months is recommended.

As mentioned above, CT is a high radiation-dose examination, and every effort should be made to avoid unnecessary radiation, particularly in young patients [40]. Furthermore, adequate precautions should be taken in order to avoid iodine allergy or nephrotoxicity. For these patients, MRI could be an alternative follow-up technique.

Recommendations

- **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 surveilance, at least an abdomino-pelvic CT every 6 months during the 2 first years post-orchidectomy 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, every three months in the third year, and every six months in the 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 non-seminoma under primary surveilance, at least an abdomino-pelvic CT at 3 and 12 months is recommended (2B).**

8.2 FOLLOW-UP AFTER SYSTEMIC TREATMENT OR RADIOTHERAPY

Useful information on the follow-up of patients with GCT treated with systemic treatment or radiotherapy is scarce. SIGN recommended a follow-up visit every three months during the first two years and every 6 months in the third, fourth and fifth year [11]. For patients with NSGCT, the recommended frequency of follow-up visits is higher during the first year. For stage I seminomas not treated with primary surveillance, SIGN recommended an annual CT during the first three years. For all other patients treated with systemic treatment or radiotherapy, SIGN recommended to stop routine follow-up CT scans if the post-treatment CT is normal [11].

However, in view of the absence of a consensus on the frequency of CT examinations during primary surveillance, no standard scheme can be proposed.

Recommendations

- **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 (expert opinion).**
- **There is insufficient evidence to define a standard scheme for CT follow-up in patients with advanced stage testicular germ cell cancer (expert opinion).**

8.3 FOLLOW-UP OF THE CONTRALATERAL TESTIS

Observational studies suggest a role of US for the follow-up of the contralateral testis in patients with testicular germ cell cancer. In a recent small retrospective study (n = 16), testicular tumours detected through US were significantly smaller than those diagnosed by palpation only [112]. Above this, the rate of organ preservation was higher in tumours detected through US. Therefore, US of the contralateral testis can be considered during the follow-up of patients with testicular germ cell cancer.

Recommendation

- **Ultrasonography of the contralateral testis can be considered during the follow-up of patients with testicular germ cell cancer (expert opinion).**

8.4 FOLLOW-UP FOR LATE TOXICITY

For the present guideline, no specific systematic search was done addressing late toxicity after treatment for testicular cancer. Therefore, no separate recommendations were formulated addressing this issue. Nevertheless, the 2010 SIGN guideline specifically addressed this topic and was therefore consulted to write the paragraph below [11].

Besides the well-known short, medium and long-term toxicities, such as neurotoxicity, nephrotoxicity, pulmonary toxicity and androgen deficiency, SIGN identified two specific types of very late toxicity associated with testicular cancer therapy with an increasing body of evidence: cardiovascular events and second cancers.

SIGN identified several studies showing an increased standardized mortality rate (SMR) and standardized incidence rate (SIR) for cardiovascular disease in patients treated for germ cell cancer. Inconsistent evidence was found for an increased frequency of cardiovascular risk factors in survivors of testicular cancer. SIGN recommended that oncologists should advise survivors of testicular cancer and their general practitioners (GPs) of the increased risk of cardiovascular disease and its risk factors at the time of discharge from the hospital or at around five years after diagnosis if maintained on long term follow up [11].

In addition, observational studies showed an increased SMR and SIR for second non-germ cell cancer [11]. Elevated SIRs are reported for a wide range of solid and haematological cacners. Based on this evidence, SIGN recommended that oncologists should advise patients and their GPs of the increased risk of non-germ cell second malignancies (at the time of initial diagnosis, following initial therapy and at discharge from follow up by oncology clinics). The risks are greatest for those treated before the age of 30 years. Increased risks continue beyond 15 years following treatment. SIGN also stated that there should be increased awareness of the risk of haematological malignancies especially after chemotherapy and solid malignancies in or near 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 [11].

9 TREATMENT OF RELAPSING OR REFRACTORY DISEASE

The evidence on the treatment of relapsing or refractory disease is mainly limited to observational studies. Two RCTs evaluated the efficacy of high-dose chemotherapy in patients with relapsed or refractory GCT after cisplatin-based chemotherapy. Pico et al. compared 4 cycles of PEI (ifosfamide, cisplatin and etoposide) or VeIP (ifosfamide, cisplatin and vinblastine) with 3 cycles of these regimens followed by CarboPEC (high-dose carboplatin, etoposide and cyclophosphamide) and haematopoietic stem cell support [113]. Three-year event-free survival did not differ significantly between the two treatment arms (35% vs. 42%, p=0.16), while the 3-year disease-free survival in patients achieving complete response was better in the group treated with high-dose chemotherapy (55% vs. 75%, p=0.04). However, high-dose chemotherapy was associated with significantly more adverse events. Lorch et al. compared two regimens of high-dose chemotherapy (1 cycle of VIP and 3 cycles of high-dose carboplatin and etoposide [VIP/CE] vs. 3 cycles of VIP and 1 cycle of high-dose carboplatin, etoposide and cyclophosphamide [VIP/CEC]) [114]. Both regimens were found to be equally effective, but were associated with different toxicity patterns. The trial was prematurely stopped as a result of excess treatment-related mortality after VIP/CEC. Based on this evidence, SIGN did not routinely recommend high-dose chemotherapy as a salvage therapy for patients with GCT who relapse after standard cisplatin-based chemotherapy [11].

No randomised trials were found comparing different regimens of standard-dose salvage chemotherapy. Therefore, patients with relapsing or refractory GCT should be enrolled in clinical trials.

Recommendations

- **Patients with relapsing or refractory GCT should be enrolled in clinical trials when available (expert opinion).**
- **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 (1A).**

10 IMPLEMENTATION AND UPDATE OF THE GUIDELINE

10.1 IMPLEMENTATION

The implementation of the present guideline will be led by the College of Oncology. An online implementation tool – similar to the tools accompanying previous guidelines (https://portal.health.fgov.be/portal/page?_pageid=56,10338450&_dad=portal&_schema=PORTAL) – will be developed. The tool will be based on the algorithms of this guideline.

10.2 QUALITY CONTROL

Based on this guideline, quality indicators were developed to evaluate its implementation. The results of the pilot test of these indicators will be reported in a subsequent report.

10.3 GUIDELINE UPDATE

In view of the changing evidence, and based on a pre-assessment of the literature, this guideline should be fully updated in 5 years. In the meanwhile, when important evidence becomes available, this will be mentioned on the website of the College of Oncology.

11 APPENDICES

APPENDIX 1: SEARCH STRATEGIES

TESTICULAR CANCER

1	Testicular Neoplasms/
2	Seminoma/
3	Teratoma/
4	((testis or testicular or testes) adj5 (neoplasm$ or cancer$ or carcinoma$ or tumo$ or malign$ or metasta$)).tw.
5	or/1-4

DIAGNOSTIC TESTS (DIAGNOSIS, STAGING, FOLLOW-UP)

1	tomography scanners, x-ray computed/ or tomography, x-ray computed/ or magnetic resonance imaging/ or positron-emission tomography/ or tomography, spiral computed/ or tomography/
2	Ultrasonography/
3	Neoplasm Staging/
4	Biopsy/ or Biopsy, Needle/ or Biopsy, Fine-Needle/
5	Biological Markers/ or Tumor Markers, Biological/
6	Testicular Neoplasms/us, ra, di, pa, ri [Ultrasonography, Radiography, Diagnosis, Pathology, Radionuclide Imaging]
7	Seminoma/ra, us, pa, di, ri [Radiography, Ultrasonography, Pathology, Diagnosis, Radionuclide Imaging]
8	Teratoma/us, pa, ra, di, ri [Ultrasonography, Pathology, Radiography, Diagnosis, Radionuclide Imaging]
9	or/1-8

HISTOPATHOLOGY

1	pathology.mp. or Pathology/ or Pathology, Clinical/ or Pathology, Surgical/
2	Lymph Nodes/
3	(resection adj margin$).mp.
4	Neoplasm Invasiveness/
5	Neoplasm Staging/ or TNM.mp.
6	Neoplasm Recurrence, Local/
7	R0.mp.
8	R1.mp.
9	Frozen Sections/
10	Histology/
11	histopathology.mp.
12	Microscopy/ or Microscopy, Fluorescence/
13	morphology.mp.
14	Biopsy/ or Biopsy, Fine-Needle/ or Biopsy, Needle/
15	cytopathology.mp.
16	or/1-15

SEARCH FILTER DIAGNOSTIC ACCURACY STUDIES

1	exp "Sensitivity and Specificity"/
2	sensitivity.tw.
3	specificity.tw.
4	((pre-test or pretest) adj probability).tw.
5	post-test probability.tw.
6	predictive value$.tw.
7	likelihood ratio$.tw.
8	or/1-7

SEARCH FILTER SYSTEMATIC REVIEWS

1	meta-analysis.pt,ti,ab,sh.
2	1 or (meta anal$ or metaanal$).ti,ab,sh.
3	(methodol$ or systematic$ or quantitativ$).ti,ab,sh.
4	((methodol$ or systematic$ or quantitativ$) adj (review$ or overview$ or survey$)).ti,ab,sh.
5	(medline or embase or index medicus).ti,ab.
6	((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
7	or/3-6
8	7 and review.pt,sh.
9	2 or 8

SEARCH FILTER RANDOMISED CONTROLLED TRIALS

1	Randomized controlled trials/
2	Randomized controlled trial.pt.
3	Random allocation/
4	Double blind method/
5	Single blind method/
6	Clinical trial.pt.
7	exp clinical trials/
8	or/1-7
9	(clinic$ adj trial$1).tw.
10	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
11	Placebos/
12	Placebo$.tw.
13	Randomly allocated.tw.
14	(allocated adj2 random).tw.
15	or/9-14
16	8 or 15
17	Case report.tw.
18	Letter.pt.
19	Historical article.pt.
20	Review of reported cases.pt.
21	Review, multicase.pt.
22	or/17-21
23	16 not 22
24	8 or 23

SEARCH FILTER PROGNOSTIC STUDIES

1	"prognos*".ti,ab.
2	first.ti,ab.
3	episode.ti,ab.
4	3 and 2
5	cohort.ti,ab.
6	5 or 1 or 4

APPENDIX 2: GRADE SYSTEM

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

APPENDIX 3: AGREE SCORES OF IDENTIFIED GUIDELINES

Source	Title	Standardised Methodology Score	Final Appraisal
NICE 2002 [115]	Improving outcomes in urological cancers	54.8%	Not recommended (no guideline)
EAU 2008 [75]	Guidelines on testicular cancer	33.3%	Not recommended
EGCCCG 2008 [108]	European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group	35.7%	Not recommended
NCCN 2009 [116]	Testicular cancer	45.2%	Not recommended
CCO 2001 [111]	Surveillance programs for early stage non-seminomatous testicular cancer. Practice Guideline Report No. 3-5	92.9%	Recommended with provisos
ACCC 2002 [117]	Testiscarcinoom. Landelijke richtlijn versie 1.1	14.3%	Not recommended
ACR 2007 [118]	ACR appropriateness criteria for staging of testicular malignancy	28.6%	Not recommended
ADASP 2000 [119]	Protocol for malignant and potentially malignant neoplasms of the testis and paratestis	4.8%	Not recommended
CCO 2008a [67]	Management of stage I seminoma: guideline recommendations	71.4%	Recommended with provisos
CCO 2008b [72]	Management of stage I nonseminomatous testicular cancer: guideline recommendations	71.4%	Recommended with provisos
ESMO 2008 [120]	Mixed or non-seminomatous germ-cell tumors: ESMO Clinical Recommendations for diagnosis, treatment and follow-up	16.7%	Not recommended
ESMO 2008 [121]	Testicular seminoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up	16.7%	Not recommended
NACB 2008 [122]	National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian Cancers	35.7%	Not recommended
USPSTF 2004 [123]	Screening for testicular cancer	81.0%	Not recommended (out of scope)
AFU 2007 [18]	Tumeurs du testicule	66.7%	Recommended with provisos
IGG 2008 [124]	IGG practice guidelines on germ cell tumor in adult male patients	26.2%	Not recommended
Martin et al. 2007 [125]	Evidence-based guidelines for following stage I seminoma	38.1%	Not recommended
van As et al. 2008 [126]	Evidence-based pragmatic guidelines for the follow-up of testicular cancer: optimising the detection of relapse	31.0%	Not recommended

Source	Title	Standardised Methodology Score	Final Appraisal
FNCLCC 2007 [127]	Recommandations pour la pratique clinique: utilisation de la TEP-FDG dans les cancers du rein, de la prostate, du testicule et de la vessie	88.1%	Recommended with provisos
Anonymous 2000 [119]	Protocol for malignant and potentially malignant neoplasms of the testis and paratestis	4.8%	Not recommended
ASCO 2006 [44]	American Society of Clinical Oncology recommendations on fertility preservation in cancer patients	69%	Recommended with provisos

APPENDIX 4: RESULTS OF EXTERNAL EXPERT MEETING

Item	Recommendation(s)	GOR	LoE	MED	MIN	MAX	% 4 or 5	Comments	Decision
Diagnosis, primary management and staging	Patients with a clinical suspicion of testicular malignancy should undergo urgent urological assessment, including clinical exam and bilateral testicular ultrasonography	1	C	5	5	5	100%		No change
	Preoperative assessment of tumour markers (AFP, HCG, LDH) is recommended for postoperative management of patients with testicular cancer	Expert opinion		5	2	5	75%		No change
	In patients with a high suspicion of testicular malignancy after urological assessment, radical orchidectomy through inguinal approach is indicated	Expert opinion		5	5	5	100%		No change
	Biopsy of the contralateral testis should be considered in patients with testicular cancer and infertility, an atrophic testis (i.e. < 12 ml) or a history of cryptorchidism	1	C	3	3	4	25%		Remove recommendation because of disagreement; discussion in text is sufficient
	In patients with carcinoma in situ of the contralateral testis, irradiation of the testis should be considered	2	C	3	2	5	25%	E2: Insufficient data that this is superior to strict follow-up E3: when family planning completed	Remove recommendation because of disagreement; discussion in text is sufficient
	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	2	C	5	4	5	100%		No change
	In patients with confirmed testicular cancer, magnetic resonance imaging is an alternative for the detection of metastatic disease	Expert opinion		4	3	5	80%	E5: ...if CE-CT is contra indicated	Adaptation of recommendation
	The evidence supporting other staging techniques is too weak to recommend their routine use for the staging of testicular cancer	1	C	5	4	5	100%		No change
	In selected patients, targeted diagnostic interventions are indicated	Expert opinion		5	4	5	100%		No change
	Treatment options for patients with testicular cancer should be discussed at the multidisciplinary team meeting	Expert opinion		5	4	5	100%		No change
	Pre-treatment sperm storage should be offered to men who may require chemotherapy or radiotherapy	Expert opinion		3.5	3	5	50%		No change
Pathology	The distal margin has to be cut prior to incision of the testis to avoid tumour cell contamination of the spermatic cord	Expert opinion		4	4	4	100%		No change
	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)	1	C	4	3	4	67%		No change
Stage I disease	In patients with stage I seminoma post-orchidectomy, active surveillance can be considered as a management option	2	B	5	3	5	75%	E5: Active surveillance should be recommended if a pericentimeter lymphnode is detected in order to avoid under or over treatment	No change
	In patients with stage I seminoma post-orchidectomy, radiotherapy can be considered as a management option	2	B	5	2	5	75%	E2: Lancet 2005; manuscript attached	No change, but remark of secondary tumours after RT added in text
	In patients with stage I seminoma post-orchidectomy, single-dose carboplatin can be considered as a management option	2	B	5	4	5	100%		No change
	Primary surveillance is recommended for patients with stage I non-seminoma (without vascular or lymphatic invasion) post-orchidectomy, with treatment at relapse	2	B	5	4	5	100%	E3: if no embryonal component	Adaptation of recommendation

Item	Recommendation(s)	GOR	LoE	MED	MIN	MAX	% 4 or 5	Comments	Decision
Metastatic disease	Patients with stage IIA or IIB seminoma should be treated with chemotherapy or radiotherapy	2	C	5	4	5	100%		No change
	In patients with stage IIC seminoma chemotherapy is the treatment of choice	2	C	5	4	5	100%		No change
	In patients with stage III seminoma cisplatin-based chemotherapy is recommended	1	B	5	4	5	100%		No change
	Patients with good prognosis metastatic NSGCT should be treated with 3 cycles of first-line BEP chemotherapy	1	A	5	4	5	100%	E3: or 4 x EP	Adaptation of recommendation
	Outside a clinical trial, patients with intermediate prognosis metastatic NSGCT should receive first-line BEP chemotherapy in 4 cycles	2	A	5	4	5	100%		No change
	Outside a clinical trial, patients with poor prognosis metastatic NSGCT should be treated with first-line BEP chemotherapy in 4 cycles	2	A	5	4	5	100%		No change
	Patients with intermediate and poor prognosis metastatic NSGCT should be enrolled in clinical trials	Expert opinion		4	3	4	75%	E3: whenever available	Adaptation of recommendation
Residual disease	CE-CT scan is recommended for the imaging of residual masses after systemic treatment of testicular cancer	Expert opinion		5	4	5	100%		No change
	PET scan is not routinely recommended for the evaluation of residual masses, but may be useful in metastatic seminoma	2	C	4	4	5	100%		No change
	Patients with NSGCT who have residual retroperitoneal masses after chemotherapy and whose markers have normalised should be treated with (template) retroperitoneal lymph node dissection	Expert opinion		4,5	3	5	75%		Adaptation of recommendation: no disagreement on extent of resection
	In patients with NSGCT and non-retroperitoneal masses after chemotherapy, metastasectomy is recommended	Expert opinion		4,5	3	5	75%		No change
	If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time as excision of the residual mass	Expert opinion		5	4	5	100%		No change
	In patients with seminoma who have residual masses ≤ 3 cm and negative PET findings, surveillance is recommended	Expert opinion		4,5	4	5	100%	E3: PET not really necessary	Adaptation of recommendation: remove part on PET scan
	In patients with seminoma previously treated with chemotherapy, and who have a residual mass > 3 cm and positive PET findings, or who have a histologically confirmed recurrence, radiotherapy is recommended	Expert opinion		4	3	5	75%	E3: in case of recurrence, chemo can be an option	Adaptation of recommendation: remove part on recurrence (chapter is on residual disease)
	In patients with seminoma relapsing after first-line radiotherapy or whose tumour markers become positive, salvage chemotherapy is indicated	Expert opinion		5	5	5	100%		No change
	In patients with seminoma who have residual masses following chemotherapy or radiotherapy, extirpative surgery is not recommended	Expert opinion		5	4	5	100%		No change

Item	Recommendation(s)	GOR	LoE	MED	MIN	MAX	% 4 or 5	Comments	Decision
Follow-up	In patients with stage I non-seminoma under primary surveillance, physical examination and blood serum marker tests (AFP, HCG) should be conducted every month in the first year, every two months in the second year, every three months in the third year, and every six months in the fourth and fifth years	Expert opinion		4,5	4	5	100%		Add LDH
	In patients with stage I non-seminoma under primary surveillance, abdomino-pelvic CT at 3 and 12 months post-orchidectomy is recommended (2B). If the post-treatment abdomino-pelvic CT at 12 months is normal, no further routine CT scans are indicated	Expert opinion		4	3	5	80%	E4: thoraco-abdomino-pelvic CT E5: If the abdomino-pelvic CT at 12 months is normal, no further routine CT scans are indicated	Adaptation of recommendation: stress fact that evidence is lacking. However, the GDG would like to recommend a minimal requirement of CT
	In patients with stage I seminoma under primary surveillance, physical examination and blood serum marker tests (AFP, HCG) 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		4	3	5	75%		Add LDH
	In patients with stage I seminoma under primary surveillance, abdomino-pelvic CT is recommended every 6 months during the 2 first years post-orchidectomy and annually during the 2 following years	Expert opinion		4	3	5	80%	E4: thoraco-abdomino-pelvic CT E5: In case of a 1 cm lymphnode is detected at diagnosis, a CE CT should be done every 3 months for the first year..... and annually durinf the 3 following years	Adaptation of recommendation: stress fact that evidence is lacking. However, the GDG would like to recommend a minimal requirement of CT
	In patients treated with chemotherapy or radiotherapy post-orchidectomy or as primary treatment, physical examination and blood serum marker tests (AFP, HCG) 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		4	3	5	75%		Add LDH; recommendation on US of contralateral testis will be added
	If a post-treatment abdomino-pelvic CT is normal, no further routine CT scans are indicated	Expert opinion		3	2	5	40%	E4: Routine US of the contralateral testis is recommended	Adaptation of recommendation: lack of evidence should be stressed
Relapsing or refractory disease	Patients with relapsing or refractory GCT should be enrolled in clinical trials	Expert opinion		4	3	5	75%	E3: when available	Adaptation of recommendation
	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	1	A	4,5	4	5	100%		No change

APPENDIX 5: EVIDENCE TABLES

DIAGNOSTIC TESTS

Guidelines

CPG ID	Ref	Search date	Recommendation(s)	Supporting evidence	Level of evidence
AFU 2007 [128]		August 2007	Le minimum requis : - L'examen clinique - Les marqueurs tumoraux (niveau IIa) - La TDM thoraco-abdomino-pelvienne - L'échographie scrotale Les examens optionnels : - L'IRM - L'échographie abdominale - L'IRM cérébrale - La TEP scan	Albers 2007 (consensus guideline) Schmoll 2004 (consensus guideline)	Very low

Ultrasonography

Diagnosis: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Kennedy 1999 [13]	Patients with intratesticular lesion identified by US (n=44)	**Ultrasonography** Standard: Pathology of clinical follow-up	Differentiation between malignancy and benignity (n=41)	*Sensitivity*: 95% (74-100%) *Specificity*: 59% (36-79%)	Retrospective study. Consecutive patients. Differential verification. No definition provided of clinical follow-up. Three patients excluded from analysis. Two patients with lymphoma included in the group with malignancy.
Lenz 1996 [129]	Patients with unilateral testicular cancer (n=78)	**Ultrasonography** (of contralateral testis) Standard: Histology (open biopsy)	Diagnosis of carcinoma in situ (n=78)	*Sensitivity*: 89% (52-100%) *Specificity*: 59% (47-71%)	Unclear design.
Coret 1995 [12]	Patients referred to the hospital because of pain, tenderness, appearance of a mass in the scrotum or swelling of the scrotum after trauma (n=39)	**Ultrasonography** Standard: Surgical findings or follow-up (including US)	Diagnosis of malignancy (n=39)	*Sensitivity*: 97% (83-100%) *Specificity*: 44% (14-79%)	Unclear design. Differential verification. Incorporation bias.
Van Dijk 1994 [17]	Patients referred for scrotal ultrasonography (why?) (n=411)	**Ultrasonography** Standard: Surgical findings, pathology or clinical follow-up	Diagnosis of malignancy (n=411)	*Sensitivity*: 100% (81-100%) *Specificity*: 99% (97-100%)	Unclear design. Patients selected from group of 483 consecutive patients. 72 patients were not included because of lost-to-follow-up or unavailability of clinical data or US examination. Differential verification. No information on test included in clinical follow-up.

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Polak 1990 [16]	Patients with suspected testicular tumour (based on palpation) (n=56)	**Ultrasonography** Standard: Surgical findings or pathology	Diagnosis of malignancy (n=56)	*Sensitivity*: 95% (82-99%) *Specificity*: 58% (33-80%)	Prospective study. Differential verification.
London 1989 [15]	Patients with scrotal symptoms or signs (n=109, of which 57 men with increase in scrotal size)	**Ultrasonography** Standard: Surgical findings or follow-up	Diagnosis of malignancy (n=57)	*Sensitivity*: 100% (54-100%) *Specificity*: 98% (90-100%)	Prospective study. Differential verification. For some patients, US was part of follow-up (incorporation bias).
Kromann-Andersen 1988 [14]	Patients with suspected scrotal disease (how?) (n=166)	**Ultrasonography** Standard: Surgical findings, histopathology or follow-up (including US)	Diagnosis of malignancy (n=166)	*Sensitivity*: 90% (55-100%) *Specificity*: 95% (90-98%)	Prospective study. Consecutive patients. Differential verification. Incorporation bias.

Staging: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Schwerk 1987 [42]	Patients with histologically confirmed testicular neoplasms or tumour-like lesions (n=54)	**Ultrasonography** Standard: Histology (n=12) or clinical and US follow-up (n=42)	Nodal staging	*Sensitivity*: 87% (60-98%) *Specificity*: 100% (91-100%)	Prospective study. Differential verification. Incorporation bias. Lymphangiography performed in only 32 patients.
Frick 1979 [37]	Patients with a proven primary testicular tumour (n=24)	**Ultrasonography** Comparator: CT Standard: Explorative laparotomy	Nodal staging	**Discordant data in article!** US: *Sensitivity*: 95% (77-100%) *Specificity*: 50% (1-99%) CT: *Sensitivity*: 91% (71-99%) *Specificity*: 50% (1-99%)	Unclear design.

Lymphangiography

Staging: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Tesoro-Tess 1985 [130]	Patients with pStage I and II testicular carcinoma treated with radical orchidectomy and radical retroperitoneal lymphadenectomy (n=167)	**Lymphangiography** Standard: Histology	Nodal staging	*Sensitivity*: 74% (64-83%) *Specificity*: 78% (67-86%)	Retrospective study. Consecutive patients. Possible selection bias. Only 35 patients underwent CT (results therefore not presented).
Thomas 1981 [39]	Patients with histopathologically confirmed testicular carcinoma (n=27)	**CT** Comparator: Lymphangiography Standard: Histology	Nodal staging	CT: *Sensitivity*: 90% (70-99%) *Specificity*: 83% (36-100%) Lymphangiography: *Sensitivity*: 71% (48-89%) *Specificity*: 67% (22-96%)	Retrospective study. Possible selection bias (selection based on reference standard).

CT scan

Staging: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Cremerius 1999 [35]	Patients with germ cell cancer (n=50)	**FDG-PET** Comparator: CT Standard: Sum of all available clinical data, including the results of the follow-up examinations (histopathology: n=12)	Staging (detection of metastatic disease)	PET: *Sensitivity*: 87% (60-98%) *Specificity*: 94% (81-99%) CT: *Sensitivity*: 73% (45-92%) *Specificity*: 94% (81-99%)	Unclear design. Differential verification. Incorporation bias.
Richie 1982 [38]	Patients with primary non-seminomatous testicular tumour treated with radical orchidectomy (n=30)	**CT** Standard: Histology (retroperitoneal lymphadenectomy)	Nodal staging (retroperitoneal)	*Sensitivity*: 65% (41-85%) *Specificity*: 90% (55-100%)	Prospective study.
Thomas 1981 [39]	Patients with histopathologically confirmed testicular carcinoma (n=27)	**CT** Comparator: Lymphangiography Standard: Histology	Nodal staging	CT: *Sensitivity*: 90% (70-99%) *Specificity*: 83% (36-100%) Lymphangiography: *Sensitivity*: 71% (48-89%) *Specificity*: 67% (22-96%)	Retrospective study. Possible selection bias (selection based on reference standard).
Frick 1979 [37]	See above: Ultrasonography – staging.				
Sohaib 2009 [131]	See below: MRI – staging.				

MRI

Diagnosis: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Schultz-Lampel 1991 [132]	Patients with scrotal pathology (n=205), of which 88 had clinical suspicion of malignancy	**MRI** Standard: Histology	Detection of malignancy	*Sensitivity*: 100% (95-100%) *Specificity*: 100% (84-100%)	Retrospective study. Unclear on what the clinical suspicion was based.

Staging: systematic reviews

Study ID	Population	Index test	Results	Comments
Hansen 2009 [41]	Patients with stage I testicular cancer	**MRI** Comparator: Multislice CT	Two primary studies selected: - Harisinghani 2005 (identified by our search, but excluded because no per-patient analysis): n=18 (early stage testicular cancer), 42 node samples; reference standard = histopathology; Se 88%, Sp 92%. - Pfannenberg 2004 (see PET scan): n=28 (metastatic germ cell tumours), 60 residual tumour masses; reference standard = histopathology or follow-up; Se 62%, Sp 72% for CT/MRI.	Search date: October 2008. Searched databases: PubMed, EMBASE, ISI Web of Science. No clear quality appraisal.

Staging: primary studies

Study ID	Population	Index test	Outcome	Results	Comments
Sohaib 2009 [131]	Patients with testicular germ cell tumours (n=53)	**MRI** **CT** Standard: Combination of CT, MRI and follow-up imaging	Detection of retroperitoneal disease	MRI: (3 readers) Se 78 – 96% Sp 91_100% CT: (3 readers) Se 82-100% Sp 96-100%	Exclusion of 12 patients from original sample of 65 patients because of inability to schedule for CT and MRI within a 6-week period. Differential verification. Incorporation bias.

PET scan

Diagnosis: systematic reviews

Study ID	Population	Index test	Results	Comments
Bourguet 2007 [127]	Patients with testicular cancer	**FDG-PET**	No new primary studies found since the previous FNCLCC report (FNCLCC 2003).	Moderate-quality SR, as a basis for a CPG (update of earlier report, that was included in the previous KCE report) *Search date*: August 2006

Staging: HTA reports and systematic reviews

Study ID	Population	Index test	Results	Comments
HTA reports				
AHRQ 2008 [133]	Patients with testicular cancer	**FDG-PET**	One primary study identified (Lassen 2003). Forty-six patients included having undergone orchidectomy and negative postoperative conventional staging (abdominopelvic CT, chest X-ray, αFP and □HCG). Sensitivity 70%, specificity 100%, PPV 100%, NPV 92% and diagnostic accuracy 93%. Better diagnostic performance than conventional imaging, although not statistically significant (p<0.06).	Good-quality HTA *Search date*: 2003 - March 2008 *Databases*: Medline, EMBASE, Central, Scopus *Meta-analysis* using the DerSimonian and Laird random effects method. Software: RevMan software version 5.0.
Systematic reviews				
Bourguet 2007 [127]	Patients with testicular cancer	**FDG-PET**	One new primary study (Lassen 2003) found since the previous FNCLCC report: see AHRQ 2008.	See above

Staging: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
de Wit 2008 [36]	Patients with non-seminomatous germ cell tumours at an early stage (I and II) undergoing primary retroperitoneal lymph node dissection (n=72)	**FDG-PET** Comparator: CT Standard: Histology (RPLND)	Nodal staging	FDG-PET vs. CT: *Sensitivity* 66% (47-81%) vs. 41% (24-59%) (p=0.038) *Specificity* 97% (87-100%) vs. 95% (83-99%) (NS) *PPV* 95% vs. 87% (NS) *NPV* 78% vs. 67% (p=0.05)	Prospective study Of the 87 enrolled patients, 15 were excluded: 14 because of observation without RPLND Consecutive patients?

Detection of recurrence: HTA reports and systematic reviews

Study ID	Population	Index test	Results	Comments
HTA reports				
AHRQ 2008 [133]	Patients with testicular cancer	**FDG-PET**	Two primary studies identified. Hinz 2008 (n=20): Se 100% (95%CI 29%–100%), Sp 47% (95%CI 23–72%) Karapetis 2003 (n=15) : Se 100%, Sp 72%	See above
Systematic reviews				
Bourguet 2007 [127]	Patients with testicular cancer	**FDG-PET**	No new primary studies found since the previous FNCLCC report (FNCLCC 2003).	See above

Evaluation of residual mass: HTA reports and systematic reviews

Study ID	Population	Index test	Results	Comments
HTA reports				
AHRQ 2008 [133]	Patients with testicular cancer	**FDG-PET**	One primary study identified. Becherer 2005 (n=48): per-lesion analysis.	See above
Systematic review				
Bourguet 2007 [127]	Patients with testicular cancer	**FDG-PET**	Two new primary studies (Becherer 2005, Pfannenberg 2004) identified since previous FNCLCC report (in total 76 patients included). Better sensitivity (80% vs. 73%) and specificity (100% vs. 73%, p<0.001) for PET compared to CT in one study (for diagnosis of viability of residual masses; per-lesion analysis), but comparable sensitivity (62% vs. 62%) and specificity (83% vs. 72%) for PET and CT/MRI in other study.	See above

Evaluation of residual mass: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Oechsle 2008 [102]	Patients with NSGCT and a primary or metastatic retroperitoneal tumour of at least 5 cm or with distant metastases at the time of primary diagnosis or first relapse (n=121)	**FDG-PET** Standard: Histology (resection specimen)	Evaluation of residual mass	*Sensitivity* 70% (58-81%) *Specificity* 39% (26-53%) *PPV* 59% (vs. 55% for CT) *NPV* 51%	Prospective study No information on blinding Consecutive patients?

Tumour markers

Diagnosis of recurrence: primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Venkitaraman 2007 [134]	Patients with testicular germ cell tumours with no clinical evidence of disease after a complete response to treatment or on surveillance for stage I disease (n=499)	**LDH** Standard: Elevated serum markers AFP, hCG or LDH, with radiological or pathological evidence of persistence or progression of TGCT	Detection of recurrent disease	*Sensitivity*: 40% (16-68%) *Specificity*: 91% (87-93%)	Retrospective study. Differential verification. Incorporation bias.

Prognosis: primary studies

Study ID	Population	Index test	Outcome	Results	Comments
Von Eyben 1992 [135]	Patients with metastatic testicular germ cell tumours treated with cisplatin-based chemotherapy (n=44)	**LDH isoenzyme 1** before first course of chemotherapy	Treatment response Overall survival	In multivariate analysis regarding response, only tumour volume classified according to the Royal Marsden system (p=0.0036) and S-LDH-1 (p=0.0069) yielded information. Regarding survival, S-LDH-1 (p=0.0141) and an estimate of total tumour mass (p=0.0171) had most impact with additional information from S-hCG only (p=0.0536).	Unclear design.

Frozen section analysis

Primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Connolly 2006 [20]	Patients with a painless testicular mass of unclear etiology (n=80)	**Frozen section analysis** Standard: Histology and/or follow-up	Detection of malignancy	*Sensitivity*: 94% (84-99%) *Specificity*: 89% (72-98%)	Retrospective study. Differential verification.
Elert 2002 [21]	Patients with testicular tumour (n=354)	**Frozen section analysis** Standard: Histology	Detection of malignancy	*Sensitivity*: 100% (99-100%) *Specificity*: 100% (91-100%)	Retrospective study.
Herr 1997 [136]	Patients with non-seminomatous germ cell tumour of the testis treated with chemotherapy (n=62)	**Frozen section analysis** Standard: Histology	Evaluation of resection margins (positive if viable germ cell tumour or teratoma)	*Sensitivity*: 86% (68-96%) *Specificity*: 100% (89-100%)	Prospective study. Consecutive patients.

Biopsy

Primary studies

Study ID	Population	Index test	Outcome	Results (95%CI)	Comments
Dieckmann 1999 [137]	Patients with testicular germ cell cancer (n=1954)	**Contralateral testicular biopsy** Standard: Histology or follow-up	Detection of testicular intraepithelial neoplasia	*Sensitivity*: 95% (89-98%) *Specificity*: 100% (100-100%)	Prospective study. Consecutive patients.

PATHOLOGY

Diagnostic accuracy studies

Study ID	Study Description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
Bosman FT 1980 [64]	Retrospective cohort study N=73	Patients with testicular germ cell tumours (GCT) Cases were orchidectomy specimens with available embedded tissue blocks 46 seminomas (S), 27 non-seminomas (NS)	Index tests: Immunohistochemical staining for AFP and HCG Reference standard: Histology	Differentiation NS from S: *AFP* Se 67% (18/27) (95%CI 46-83%) Sp 100% (46/46) (92-100%) *HCG* Se 74% (20/27) (54-89%) Sp 93% (43/46) (82-99%)	Possible selection bias. Independent evaluation of immunohistochemical staining.	Low
Dimov ND 2007 [138]	Retrospective cohort study N=109	Patients with primary testicular GCTs. 57 seminomas, 52 mixed GCTs. In total, 181 GCT foci examined.	Index tests: Immunohistochemical staining for Topoisomerase II alpha Reference standard:	Distinction between teratomas and other GCT foci: Se 91% (85-95%) Sp 64% (45-80%)	Possible selection bias. No information on blinding. Positive cases = positive + focally positive	Very low

Study ID	Study Description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
			Histology			
Eid H 1999 [139]	Cohort study, unclear design N=81	Patients with testicular GCTs. 26 seminomas, 55 non-seminomas. TNM c Stage I: n=37; c Stage II: n=18; c Stage III: 0=26.	Index tests: mdm-2 immunostaining Reference standard: Histology	Distinction between NS and S: Se 55% (41-68%) Sp 85% (65-96%)	Possible selection bias. Unclear if blinding.	Very low
Heidenreich A 1998 [61]	Retrospective cohort study N=51	Patients with testicular GCTs. 31 seminomas, 20 non-seminomas. pStage I: n=10; pStage II: n=41.	Index tests: Immunohistochemical staining for 43-9F, AFP, HCG, PLAP Reference standard: Histology	Distinction of embryonal carcinoma (EC) from other malignant GCT foci: *43-9F* Se 100% (83-100%) Sp 36% (26-47%) Distinction S from NS: *PLAP* Se 79% (58-93%) Sp 45% (34-56%) Distinction NS from S: *AFP* Se 20% (12-30%) Sp 100% (86-100%) No positive HCG staining.	Possible selection bias. No information on blinding.	Very low
Jones TD 2004 [66]	Retrospective cohort study N=91	Patients with testicular neoplasms. 64 adult mixed GCTs, 5 spermatocytic seminomas, 8 Leydig cell tumours, 6 Sertoli cell tumours, 4 unclassified sex cord-stromal tumours, 2 adenomatoid tumours, 1 testicular tumour of the adrenogenital syndrome,and 1 granulosa cell tumour. In total, 209 tumoral foci examined.	Index test: Immunohistochemical staining for OCT4 Reference standard: Histology	Distinction between Sand NS foci: Se 100% (93-100%) Sp 66% (59-74%)	Possible selection bias. No information on blinding.	Very low
Santagata S 2007 [65]	Retrospective cohort study N=84	Patients with primary and metastatic GCTs. 21 pure GCTs (14 seminomas, 3 embryonal carcinomas, 4 teratomas), 20 mixed GCTs, 43 metastatic GCTs In total, 68 foci of primary testicular GCTs.	Index test: Immunohistochemical staining for NANOG, OCT3/4, SOX2 Reference standard: Histology	Distinction between Sand NS foci: *NANOG* Se 100% (83-100%) Sp 63%(47-76%) *OCT3/4* Se 100% (83-100%) Sp 63% (47-76%) Distinction between NS and S foci:	Possible selection bias. No information on blinding.	Very low

Study ID	Study Description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
				SOX2 Se 73% (58-85%) Sp 100% (83-100%)		
Tavolini IM 2006 [58]	Prospective cohort study N=68	Cryptorchid patients who underwent orchidopexy	Index test: Bilateral testicular FNAC with cytology and immunohistochemical staining for PLAP Reference standard: Andrological clinical evaluation and testicular ultrasonography (repeated after 8 years); yearly clinical and andrological evaluation in the meantime, and continued afterwards for PLAP-positive patients	Detection of non-invasive testicular cancer: Se 0% (0-97%) Sp 89% (78-96%)	Differential verification. 11 patients excluded from the study (reasons provided in article).	Low
Yu H 2007 [140]	Retrospective cohort study N=76	Patients with malignancies 43 primary GCTs (14 seminomas, 4 teratomas, 2 embryonal carcinomas, 23 mixed GCTs), 33 metastatic GCTs.	Index test: Immunohistochemical staining for D2-40 Reference standard: Histology	Distinction between Sand NS foci (primary GCTs): Se 100% (85-100%) Sp 32% (19-47%)	Possible selection bias. No information on blinding.	Very low

Prognostic studies

Study ID	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
Aass N 1991 [141]	Cohort study, unclear Design N=200 Median observation time for surviving patients: 75 months	Patients with advanced non-seminomatous testicular cancer (stage IIB or higher)	Outcome(s): Survival Pathology parameters: Post-chemotherapy histology (1st operation)	Multivariate analysis: Significant prognostic factors: - High-volume metastatic burden - Age >35 years - Pre-chemotherapy AFP > 500mg/L and/or HCG > 1000 U/L - Interval between orchidectomy and start of chemotherapy < 3 weeks	Unselected patient group. No information on blinding. 193 assessable patients Multivariate analysis with Cox regression proportional hazards model.	Low
Albers P 2003 [48]	Prospective cohort study N=165 Median follow-up ranging between 24.9 and 34.5 months	Patients with cStage I non-seminomatous testicular GCTs	Outcome(s): Relapse or pStage II Pathology parameters: Histology of primary tumour, MIB-1 score, vascular invasion, flow cytometry	Multivariate analysis: Significant prognostic factors: - Vascular invasion (OR 3.7143, 95%CI 1.8501-7.4566) - MIB-1 score, cut-off 70% (OR 3.1774, 95%CI 1.5189-6.6465) - Embryonal carcinoma, cut-off 50% (OR 1.8646, 95%CI 0.9286-3.7440)	No information on blinding. Stepwise logistic regression analysis.	Low
Bosl GJ 1983 [142]	Retrospective cohort Study	Patients with metastatic testicular cancer	Outcome(s): Treatment response (complete remission)	The variables achieving statistical significance were the logarithm of the serum values of LDH (p <	No information on blinding Logistic regression to create mathematic model for the	Low

Study ID	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
	N=171		Pathology parameters: Presence of choriocarcinoma, embryonal carcinoma, teratocarcinoma	0.001) and HCG ($p < 0.001$), and the total number of sites of metastasis ($p < 0.001$). The model was tested against 49 patients with metastatic testicular cancer, and it correctly predicted 86% of complete remissions and 84% of all outcomes.	prediction of complete remission. Validation by independent dataset.	
de Haas EC 2008 [143]	Retrospective cohort Study N=304	Patients with non-seminomatous testicular cancer who have been treated with bleomycin- and platinum-containing chemotherapy	Outcome(s): Testicular cancer related survival Pathology parameters: Royal Marsden stage BLMH genotype	Multivariate analysis: Significant prognostic factors: - Prognosis group according to IGCCC - BLMH genotype: adjusted for IGCCC, patients with the G/G genotype showed a significantly increased risk for TC-related death (HR 4.97; 95%CI 2.17-11.39; p=0.0001) and disease progression (HR 3.10; 95%CI 1.50-6.44; p=0.002) compared with the A/A group.	No information on blinding. Cox regression model.	Very low
Fossa SD 1999 [144]	Retrospective cohort study N=164 Median follow-up of living patients: 8.5 years	Patients with advanced GCTs progressing during or after cisplatin-based induction chemotherapy	Outcome(s): Survival from date of Progression Pathology parameters: Response to induction therapy	Multivariate analysis: - Progression-free interval - Response to induction treatment - Tumour marker levels	No information on blinding. Cox proportional hazards regression model. Validation of prognostic model with independent dataset of 66 patients.	Low
Fossa SD 2005 [23]	Retrospective population-based cohort study (US) N=29515	Patients who were diagnosed with testicular GCT as their first malignancy	Outcome(s): Contralateral testicular Cancer Pathology parameters: Histology, tumour size, extent of disease	Multivariate analysis: Only non-seminomatous histology of the first testicular cancer was associated with a statistically significantly decreased risk of metachronous contralateral testicular cancer (HR 0.60; 95%CI 0.46-0.79; p<0.001).	No information on blinding. Cox proportional hazards analysis	Low
Geller NL 1989 [145]	Retrospective cohort Study N=216 Median follow-up 4.5 years	Patients with metastatic GCTs	Outcome(s): Time to relapse, Survival Pathology parameters: Pathologic stage, presence/absence of choriocarcinoma, teratocarcinoma, embryonal carcinoma or pure seminoma	Multivariate analysis: Significant prognostic factors: - Surgery for residual tumour after chemotherapy - LDH and HCG at the time of initial chemotherapy	No information on blinding. Cox proportional hazards model.	Very low

Study ID	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
Klepp O 1990 [53]	Retrospective cohort Study N=279 Median follow-up 50 months	Patients with cStage I non-seminomatous GCTs	Outcome(s): pStage II, relapse Pathology parameters: Vascular invasion, pT, tumour size, histology	Multivariate analysis: Significant prognostic factors for *pStage II:* - Vascular invasion - Elevated AFP Significant prognostic factors for *relapse* (190 pStage I patients): - Vascular invasion - Interval between orchidectomy and RPLND - Presence of teratoma elements	No information on blinding. Cox proportional hazards regression.	Very low
Mead GM 1992 [55]	Retrospective cohort Study N=795 Median follow-up 45 months	Patients with non-seminomatous GCTs	Outcome(s): Survival Pathology parameters: Histology	Multivariate analysis: Significant prognostic factors (n=520): - Number of lung metastases (HR 4.68; 95%CI 2.56-8.56) - Tumour markers (HR 2.46; 95%CI 1.42-4.25) - Absence of undifferentiated teratoma (HR 2.04; 95%CI 1.19-3.52) - Absence of fibrous tissue (HR 2.13; 95%CI 1.30-3.50) - Size of mediastinal mass (HR 2.89; 1.18-7.04) -Age (HR 1.03; 95%CI1.01-1.05) - Liver, bone or brain M+ (HR 1.97; 95%CI 1.02-3.82)	Blinded review of histopathology. Cox regression analysis.	Low
MRC WG TT 1985 [146]	Prospective cohort study N=458	Patients with advanced testicular GCTs	Outcome(s): Survival Pathology parameters: Para-aortic nodes, histology	Multivariate analysis: Significant prognostic factors: -Age - Histology - Year of first chemotherapy	No information on blinding. Cox regression analysis.	Low
Parker C 2002 [49]	Retrospective cohort study N=150 Median follow-up of 2.4- 16.5 years	Patients with stage I seminoma managed by surveillance	Outcome(s): Time to relapse (from surgery) Pathology parameters: TIL count, tumour diameter <6 vs. >6 cm), lymphatic or vascular invasion, tumour invasion of rete testis, histological type, ploidv status	Multivariate analysis: Significant prognostic factors: - Age <33 vs. >33): HR 4.6 (95%CI 1.7-12.2) - Tumour diameter <6 vs. >6 cm): HR 2.8 (95%CI 1.2-6.5)	No blinding. Cox proportional hazards model.	Very low
Shayegan B 2007 [147]	Retrospective analysis of	Patients with with intermediate- and poor-	Outcome(s): Progression-free	Multivariate analysis: Significant prognostic factors:	No information on blinding. Cox proportional hazards	Very low

Study ID	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
	prospective database N=157 Median follow-up 36 months	risk non-seminomatous GCT	probability, disease-specific survival Pathology parameters: R0 vs. R1 resection, Retroperitoneal histology	- Retroperitoneal histology: teratoma vs. fibrosis (HR 3.34; 95%CI1.43-7.79), viable GCT vs. fibrosis (HR 7.26; 95%CI2.81-18.80) - Resection (incomplete vs. complete): HR 10.42 (95%CI 3.89-27.91) - Mass size after chemotherapy: HR 1.14 (95%CI1.03-1.25)	regression.	
Steyerberg EW 1995 [56] Steyerberg EW 2001 [148] Vergouwe Y 2001 [149] Vergouwe Y 2007 [150]	Retrospective cohort Study N=556 (Steyerberg 1995)	Patients with metastatic GCT	Outcome(s): Histology after chemotherapy Pathology parameters: Primary tumour histology (teratoma or not), pre-chemotherapy and post-chemotherapy mass size	Multivariate analysis: Significant prognostic factors necrosis vs. other (n=544): - Primary tumour histology (teratoma + or -): OR 2.46 (95%CI1.6-3.7) - AFP (normal vs. elevated): OR 2.49 (95%CI 1.6-3.9) - HCG (normal vs. elevated): OR 2.22 (95%CI 1.4-3.5) - LDH ln: OR 2.76 (95%CI 1.8 4.2) - Post-chemotherapy mass size: OR 0.744 (95%CI 0.63-0.87) - Tumour shrinkage: OR 1.17 (95%CI 1.1-1.3) Significant prognostic factors cancer vs. teratoma (n=299): - LDH ln: OR 1.58 (95%CI 0.93-2.7) - Post-chemotherapy mass size: OR 1.17 (95%CI 0.99-1.4) -Tumour shrinkage: OR 1.06 (95%CI 0.95-1.2)	No information on blinding. Logistic regression analysis. Validation and refinement of model in 3 articles: - Steyerberg 2001: independent dataset of 172 patients - Vergouwe 2001: 276 cases - Vergouwe 2007: 1094 cases (including the 544 original cases)	Low
Stoter G 1987 [151] Stoter G 1988 [152]	Prospective cohort study N=163	Patients with disseminated testicular GCTs	Outcome(s): Response (complete response rate) Pathology parameters: Histology of primary tumour, trophoblastic elements in tumour, seminoma elements in tumour, size and number of several M+ sites	Multivariate analysis: Significant prognostic factors: - Trophoblastic elements in tumour - AFP - Lung metastases - Size and number of lung metastases	No information on blinding. Linear logistic regression model.	Low
Stoter G 1993 [153]	Prospective cohort study	Patients with non-seminomatous GCTs	Outcome(s): Complete response	Multivariate analysis: Significant prognostic factors for	No information on blinding. Cox proportional hazards	Low

Study ID	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
			rate, survival Pathology parameters: Primary tumour histology, tumour size	complete response (n=570): - HCG - Size abdominal mass - AFP - Number of lung M+ Significant prognostic factors for survival (n=570): - Number of lung M+ - Size abdominal mass - Supraclavicular metastases - HCG	regression.	
Vaeth M 1984 [154]	Prospective cohort study N=214	Patients with testicular GCTs	Outcome(s): Recurrence-free survival Pathology parameters: Tumour size, necrosis, bleeding, index of local invasion, histology	Multivariate analysis (only for non-seminomatous GCTs): Significant prognostic factors stage I (n=252): - Invasion index - Number of mitoses - Postoperative HCG Significant prognostic factors stage II (n=76): - Invasion index Significant prognostic factors stage III (n=90): - Presence of liver or lung metastases - Postoperative HCG level - Presence of choriocarcinoma or endodermal sinus tumour -Age	No information on blinding. Cox proportional hazards regression.	Low
Warde P 1997 [50]	Retrospective cohort study N=201 Median follow-up 6.1 years	Patients with stage I testicular seminoma treated with surveillance	Outcome(s): Relapse Pathology parameters: Tumour size (6 vs. >6cm), small vessel invasion, mitosis, DNA S phase, ploidy, syncytiotrophoblasts, TIL, LMW keratin on IHC	Multivariate analysis: Significant prognostic factors: - Age - Tumour size	No information on blinding. Cox proportional hazards model.	Very low
Warde P 2002 [51]	Retrospective cohort study N=638 Median follow-up 7	Patients with stage I testicular seminoma treated with surveillance	Outcome(s): Relapse Pathology parameters: Tumour size, small vessel invasion, histology,	Multivariate analysis: Significant prognostic factors: - Tumour size – Rete testis invasion	No information on blinding. Possible overlap with Warde 1997.	Very low

Study ID	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
	years		rete testis invasion			

STAGE I SEMINOMA

Guidelines

CPG ID	Ref	Search date	Recommendation(s)	Supporting evidence	Level of evidence
CCO 2008 (#3-18) [67]		May 2007	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 treatment plan should be developed that includes the patient's preferences and clinical judgement of that specific case.	Fossa 1999 Jones 2005 Oliver 2005 24 non-randomised trials	Low
CCO 2008 (#3-18) [67]		May 2007	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. 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.	Fossa 1999 Jones 2005 Oliver 2005	Moderate
CCO 2008 (#3-18) [67]		May 2007	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.	Oliver 2005	Moderate
AFU 2007 [18]		August 2007	Séminome pur pT1 à pT4, N0, M0: Radiothérapie 20 Gy lombo-aortique exclusif (niveau Ib), OU Surveillance active (marqueurs et TAP/ 6 mois 5 ans, puis annuellement 5 ans) (niveau III-1), OU 1 cycle carboplatine (AUC = 7) (niveau II)	Radiotherapy: Jones 2005 (RCT) Classen 2004 (retrospective study) Chemotherapy: Oliver 2005 (RCT) Aparicio 2005 (prospective cohort study) Surveillance: Choo 2005, Aparicio 2005 (prospective studies) Alomary 2006, Tyldesley 2006 (retrospective studies)	Moderate

Systematic reviews

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Level of evidence
Groll 2007 [71]		Dec 2005	Patients with stage I seminoma	Surveillance	Pooled analysis of 2060 patients (14 studies): - Relapse rate: 17% - Cause-specific survival: 99.7%	No information on quality appraisal. Twenty-three quantitative studies included: 7 cohort studies, 1 pooled analysis, 1 comparative cost analysis and 14 descriptive studies.	Low
Shelley 2002 [77]		May 2002	Patients with stage I seminoma	Treatment in general	Five RCTs included: Fossa 1999 (MRC TE10), Jones 2001 (MRC TE18), Fossa 2002 (MRC TE18), Aass 1997, Khoo 1997. Descriptive presentation of results. Conclusions of authors: The standard treatment for stage I seminomas following orchidectomy is infradiaphragmatic lymph node irradiation with response rates approaching 100%, although surveillance is also a management option.	Search strategy available on request. No information on quality appraisal.	Low – moderate

Randomised controlled trials

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Oliver 2005 [68]		Patients with histologically confirmed SGCT (classic or anaplastic), stage pT1–pT3 (excluding patients with pT4; involvement of the cut end of the spermatic cord); clinical and radiological stage I with normal α-FP concentrations before and after orchidectomy; and normal concentrations of HCG after orchidectomy (n=1477)	Radiotherapy (para-aortic strip or dog-leg field; n=904) Single-dose carboplatin (n=573)	*Relapse-free survival*: - At 2y: RT 96.7% (95%CI 95.3-97.7) vs. carboplatin 97.7% (96.0-98.6) - At 3y: 95.9% (94.4-97.1) vs. 94.8% (92.5-96.4) *Death from any cause*: - 1 cancer-related death after RT - Other causes: 4 after RT, 2 after carboplatin *Second cancer incidence*: - GCT: 10 vs. 2 - Non-GCT: 4 vs. 3	Central randomisation. No blinding of patients, clinicians or assessors. Median follow-up: 4 years. Quality of life measured, but no results presented.	Moderate
Jones 2005 [69]		Patients with histologically confirmed SGCT, stage pT1–pT3 (excluding patients with involvement of the cut end of the spermatic cord [pT4]); clinical and radiological stage I with normal α-FP concentrations before and after orchidectomy; and normal concentrations of HCG after orchidectomy (n=625)	Radiotherapy 20 Gy in 10 fractions over 2 weeks (n=313) Radiotherapy 30 Gy in 15 fractions over 3 weeks (n=312)	*Relapse-free survival*: - At 2y: 30 Gy 97.7% (95%CI 95.2-98.9) vs. 20 Gy 97.0% (94.4-98.4) - At 5y : 97.0% (94.3-98.3) vs. 96.4% (93.5-98.0) *Death from any cause*: - 1 cancer-related death after 20 Gy - Other causes: 2 after 30 Gy, 3 after 20 Gy *Second cancer incidence*: - GCT: 3 after 30 Gy vs. 6 after 20 Gy - 6 non-GCT cancers after 30 Gy *Acute morbidity*: - Trend towards higher grades of nausea & vomiting in 30 Gy group (p=0.06) - More pronounced leukopenia in 30 Gy group (p=0.02)	Central randomisation. Unclear if blinding of patients, clinicians or assessors. Median follow-up: 61 months.	Moderate
Fossa 1999 [70]		Patients with histologically confirmed SGCT, stage pT1–pT3; Royal Marsden stage I with normal α-FP concentrations before and after orchidectomy; and normal concentrations of HCG after orchidectomy (n=478)	Para-aortic strip radiotherapy (PA: n=236) Dog-leg radiotherapy (DL: n=242)	*Relapse-free survival*: - At 3y: PA group 96.0% (95%CI 93.5-98.5) vs. DL group 96.6% (94.2-98.9) *Death from any cause*: - 1 cancer-related death in PA group *Second cancer incidence*: - GCT: 1 in both groups - 1 non-GCT cancer in PA group *Acute morbidity*: - Less pronounced leukopenia in PA group (p<0.0001) *Late toxicity*: - Significantly longer time to first normal sperm count in DL group (37 vs. 24 months, p=0.01)	Unclear randomisation procedure. Unclear if blinding of patients, clinicians or assessors. Median follow-up: 4.5 years.	Moderate

STAGE I NON-SEMINOMA

Guidelines

CPG ID	Ref	Search date	Recommendation(s)	Supporting evidence	Level of evidence
CCO #3-19 [72]		May 2007	Patients should be made aware of all treatment options and the risks and benefits surrounding each of these options.	-	Expert opinion
CCO #3-19 [72]		May 2007	The consensus opinion of the Genitourinary Disease Site Group (GU DSG) is that primary surveillance is recommended for all patients with CS I NSGCT, with treatment at relapse. When a primary surveillance approach is adopted, patients should be informed of their estimated risk of recurrence and the need for frequent ongoing investigations, including blood tumour markers and computerised tomography (CT) scans of the abdomen and pelvis, to monitor for recurrence.	Rustin 2007 Albers 2006 (abstract) 21 non-randomised trials	Low - moderate
CCO #3-19 [72]		May 2007	Patients with CS I NSGCT should be assessed and have management plans developed at multidisciplinary centres with experience in the treatment of testicular cancer.	-	Expert opinion
CCO #3-5 [111]		Dec 2000	A recommended surveillance schedule is as follows: Physical examination, blood serum marker tests (AFP and bHCG) and chest x-rays should be conducted every month in the first year, every two months in the second year, every three months in the third year, and every six months in the fourth and fifth years; CT scans of the abdomen and pelvis should be conducted every three months in the first year, every four to six months in the second year and every six months in the third year. Although the limited data available suggest that beyond two years the frequency of CT scans of the abdomen and pelvis does not influence relapse rate, salvage rate and survival, the current standard of care should be maintained and CT scans of the abdomen and pelvis should be performed at least every six months in the third year and once a year in the fourth and fifth year.	Rorth 1991 Pooled analysis of 13 non-randomised studies	Low - moderate
CCO #3-5 [111]		Dec 2000	Upon relapse, patients should be treated rapidly with the appropriate modality of therapy by a physician experienced in the treatment of non-seminomatous germ cell tumours of the testis.	Rorth 1991 Pooled analysis of 13 non-randomised studies	Low - moderate
AFU 2007 [18]		August 2007	Tumeur non séminomateuse pT1 à pT4, N0, M0 à marqueurs normalisés: Stratégie fonction du risque: Bas risque : absence d'invasion vasculaire ou lymphatique Haut risque : présence d'invasion vasculaire ou lymphatique Modalités techniques : Surveillance : marqueurs / mois pendant 1 an, puis / 2 mois pendant 1 an, puis / 3 mois pendant 1 an, puis / 6 mois pendant 2 ans, et TDM TAP / 3 mois pendant 1 an, puis / 4 mois pendant 1 an, puis / 6 mois pendant 3 ans et échographie scrotale annuelle si haut risque lésion controlatérale (cryptorchidie, microlithiases diffuses, volume testiculaire < 12 ml)) Curage rétropéritonéal : curage modifié homolatéral avec conservation nerveuse. Si plus de 3 à 6 ganglions métastatiques ou si stade pN2 (1 ganglion métastatique de plus de 2 cm) ou si rupture capsulaire : + 2 BEP Chimiothérapie : 2 cycles de BEP (chaque cycle espacé de 21 jours) Indications : Bas risque : surveillance ou curage (niveau IIa-IIb) Haut risque : surveillance ou chimiothérapie (niveau IIb)	Amato 2004, Maroto 2005, Kildahlandersen 2005 (retrospective studies)	Low

Systematic reviews

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Level of evidence
Groll 2007 [71]		Dec 2005	Patients with stage I non-seminoma	Surveillance	Pooled analysis of 3613 patients (31 studies): - Relapse rate: 28% - Cause-specific survival: 98.6%	No information on quality appraisal. Fifty-nine papers included: 1 mixed qualitative-quantitative, 38 descriptive studies, 2 RCTs, 7 cohort studies, 1 before-and-after study, 2 cross-sectional studies and 3 decision analyses.	Low
Shelley 2002 [77]		May 2002	Patients with stage I non-seminoma	Treatment in general	One RCT included: Rorth 1991. Descriptive presentation of results. Conclusions of authors: The majority of early stage non-seminomas are cured by orchidectomy alone.	Search strategy available on request. No information on quality appraisal.	Low – moderate

Randomised controlled trials

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Albers 2008 [74]		Patients with histologically confirmed NSGCT after orchidectomy, clinical and radiological stage I (n=382)	One cycle of bleomycin and etoposide + cisplatin (n=191) Retroperitoneal lymph node dissection (n=191). In case of retroperitoneal M+: 2 cycles of BEP	*Recurrence-free survival*: - At 2y: BEP 99.5% (95%CI 96.2-99.9) vs. RPLND 91.9% (86.9-95.0) ; HR 7.937 (1.808-34.48) *Overall survival*: - 6 deaths *Cancer-specific survival*: - No cancer-specific deaths	Central randomisations using telephone-based block randomisation pattern by center. No blinding of patients, clinicians or assessors. Follow-up of at least 15 months. Median follow-up 4.7 years. Exclusion of 35 patients after randomisation due to protocol violations.	Moderate
Rustin 2007 [110]		Patients with histologically confirmed NSGCT after orchidectomy, clinical and radiological stage I (n=414)	Surveillance with 2 CT scans over 1 year (at 3 and 12 months after orchidectomy; n=247) Surveillance with 5 CT scans over 2 years (at 3, 6, 9, 12 and 24 months; n=167)	*Relapses*: 37 (15%) in the two-scan arm vs. 33 (20%) in the five-scan arm. No patients had poor prognosis at relapse, but two (0.8%) of those relapsing In the two-scan arm had intermediate prognosis compared with 1 (0.6 %) in the five-scan arm, a difference of 0.2% (90% CI, -1.2% to 1.6%). No *deaths* have been reported.	Central randomisation. No blinding of patients, clinicians and assessors. Unclear if intention-to-treat analysis. Median follow-up of 40 months.	Moderate

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Rorth 1991 [73]		Patients with clinical stage I NSGCT (n=156)	Radiotherapy (40 Gy, 25 fractions, para-aortic and ipsilateral pelvic lymph nodes; n= 77) Surveillance (n=79)	*Relapses*: 23 patients in the surveillance group vs. 11 patients in the radiotherapy group. Radiotherapy completely prevented retroperitoneal relapse; 14 retroperitoneal relapses occurred in the surveillance-only group. All relapsing patients in the surveillance-only group are without evidence of disease with a median observation time after chemotherapy of 67 months. *Deaths*: 2 patients with relapse in the radiotherapy group died with disease; the others are alive without evidence of disease, with a median observation time after relapse treatment of 72 months.	Randomisation by central closed envelop system. No blinding of patients, clinicians and assessors. Unclear if intention-to-treat analysis. Median follow-up: 64 months.	Moderate

SEMINOMA: ADVANCED STAGES

Guidelines

CPG ID	Ref	Search date	Recommendation(s)	Supporting evidence	Level of evidence
AFU 2007 [18]		Feb 2007	Stade pT1 à pT4, N1 ou N2, M0: La radiothérapie dans un champ lombo-aortique et iliaque homolatéral est le traitement standard. La dose est de 25 Grays avec un surdosage de 5 à 10 Grays sur les aires ganglionnaires suspectes à la tomodensitométrie (niveau de preuve: III-1).	Chung 2004 (retrospective study)	Low
AFU 2007 [18]		Feb 2007	Stade pT1 à pT4, N3, M1a ou M1b: La chimiothérapie est actuellement le traitement de référence en présence d'un séminome de stade avancé. Sont préconisées 3 cures de BEP, ou 4 cures de EP (Etoposide – Cisplatine) (niveau de preuve: I).	Bokemeyer 2004 : pooled analysis of 2 RCTs (Clemm 2000 [abstract !] and Horwich 2000)	Low – moderate

Systematic reviews

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Level of evidence
Feldman 2008 [76]		Oct 2007	Patients with advanced testicular cancer	Medical treatment in general	**First-line chemotherapy for metastatic GCT** Good-prognosis GCT: (12 RCTs) Two effective regimens: 4 cycles of EP or 3 cycles of BEP (applies to seminoma and non-seminoma) Intermediate- and poor-prognosis: (8 RCTs) Standard regimen: 4 cycles of BEP **Second- and third-line chemotherapy** Standard doses of 3-drug combinations based on ifosfamide and cisplatin or high-dose	Search in Medline and CENTRAL. Jadad scale used for RCTs. Narrative overview of evidence.	Moderate

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Level of evidence
					chemotherapy with autologous stem-cell support.		
Shelley 2002 [77]		May 2002	Patients with metastatic germ cell tumors	Treatment in general	No extra information in addition to Feldman 2008	Search strategy available on request. No information on quality appraisal. Narrative overview of evidence.	Low – moderate

Randomised controlled trials

Seminoma patients only

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Horwich 2000 [81]		Chemo-naive patients with histologically confirmed testicular or extragonadal seminoma who had either relapsed with any stage of disease following previous irradiation, or were newly diagnosed with Royal Marsden stage IIC, III or IV disease (n=130) 85% primary site = testis	Single agent carboplatin (400 mg/m² to be corrected for glomerular filtration rate, day 1 of a 21 day cycle; 4 cycles) (C group, n=64) Etoposide (120 mg/m² on days 1, 2 and 3; 4 cycles of 21 days) + cisplatin (20 mg/m²; days 1, 2, 3, 4 and 5 of each cycle) (EP group, n=66)	*Progression-free survival at 3 years*: HR 0.64 (95%CI 0.32-1.28, p=0.21). 3y-PFS: 71% vs. 81%. *Failure-free survival*: HR 0.56 (95%CI 0.28-1.09, p=0.08), in favour of EP regimen. 3y-FFS: 67% vs. 81% *Overall survival*: HR 0.85 (95%CI 0.35-2.10, p=0.73). 3y-OS 84% vs. 89%. *Toxicity*: Significantly lower WBC count (p<0.0001) in EP group and platelets (p=0.02) in C group.	Central randomisation. No information on blinding of patients or investigators. Unclear if intention-to-treat analysis. Median follow-up: 4.5 years. Low statistical power. Included in Feldman 2008 and Shelley 2002.	Moderate
Clemm 2000 [80]		Patients with advanced metastatic seminoma (n=280)	Arm A: cisplatin 20 mg/m², etoposide 75 mg/m², ifosfamide 1,2 g/m² days 1-5, every 4 weeks Arm B: carboplatin monotherapy (400 mg/m²) every 4 weeks	*Overall survival*: 92%; no statistically significant difference between arm A and B (95% and 87%). *Relapse-free survival*: 95% in arm A vs. 74% in arm B (p<0.01). *Grade 3/4 leuko- and thrombopenia*: 72% in arm A vs. 8% in arm B.	Published as an abstract. Median follow-up: 52 months. Included in Shelley 2002.	Low

Seminoma and non-seminoma patients mixed

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Motzer 2007 [97]		Patients with intermediate or poor-risk germ cell cancer (n=219) 7 patients (3%) with intermediate-risk seminoma 68% primary site = testis	Four cycles of bleomycin, etoposide, and cisplatin (BEP alone) (n=111) vs. Two cycles of BEP followed by two cycles of high-dose carboplatin, etoposide, and cyclophosphamide (BEP + HDCT) administered with autologous hematopoietic stem-cell transplantation (n=108)	More severe *toxicity* in BEP + HDCT group (no p-values provided). Ten *deaths* during treatment: 4 in BEP group vs. 6 in BEP + HDCT group. *Complete remission*: - BEP: 55% (95%CI 46-64%) - BEP + HDCT: 56% (47-66%) *Time-to-treatment failure*: 11.3 (BEP) vs. 23.2 months (BEP + HDCT), p=0.40 *Overall survival*: no difference (1-year survival 83% for entire population).	No information on blinding of patients or investigators. Higher median elevated HCG value at baseline in the BEP + HDCT arm. Intention-to-treat analysis. Included in Feldman 2008. Only 83/108 (77%) patients in the BEP + HDCT group were treated with HDCT. One withdrawal in the BEP group. Twelve patients received 2 or fewer cycles.	Moderate
de Wit 2001 [155]		Patients with good-prognosis metastatic germ cell cancer (n=812) 182 patients (22%) with seminoma 97% primary site = testis	3 cycles of BEP (3BEP) for 3 days 3 cycles of BEP for 5 days 3 cycles of BEP and 1 of EP (3BEP-1EP) for 3 days 3 cycles of BEP and 1 of EP for 5 days	<u>Number of cycles</u>: *Toxicity*: - More acute sensory neuropathy in 3BEP-1EP group (37% vs. 24%, p=0.001) - More acute pulmonary toxicity in 3BEP-1EP group (20% vs. 14%, p=0.047) - More late sensory neuropathy in 3BEP-1EP group (36% vs. 28%, p=0.019) No significant differences in *complete remission*. *2-year progression-free survival*: 90.7% (3BEP) vs. 89.1% (3BEP-1EP), HR 0.93 (80%CI 0.71-1.24, p=0.021 for non-inferiority). <u>Number of days</u>: *Toxicity*: - Nausea (all grades): 80% (3d) vs. 72% (5d) (p=0.003) - Ototoxicity: 27% vs. 21% (p=0.056) - Late ototoxicity: 20% vs. 12% (p=0.002) - No other significant differences *Complete response*: 72.7% vs. 71.1% (NS) *2-year progression-free survival*: 89.0% (95%CI 86.3-93.0%) vs. 88.8% (95'%CI 85.3-92.2%), HR 1.05 (80%CI 0.78-1.41,	2x2 factorial design. No information on randomisation procedure (but probably central randomisation). No information on blinding of patients or investigators. Twenty ineligible patients excluded from analysis. Included in Feldman 2008 and Shelley 2002.	Low

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
				p=0.008 for non-inferiority).		
Toner 2001 [88]		Patients with histologically confirmed germ cell tumour (seminoma or non-seminoma) with good prognosis as defined by modified Memorial Sloan-Kettering criteria (n=166) 34 patients with seminoma (20%) 98% primary site = testis	Regimen A: 3 cycles of 20 mg/m^2 cisplatin on days 1–5, 100 mg/m^2 etoposide on days 1–5, and 30 kU bleomycin on days 1, 8, and 15, repeated every 21 days (n=83) Regimen B: 4 cycles of 100 mg/m² cisplatin on day 1, 120 mg/m² etoposide on days 1–3, and 30 kU bleomycin on day 1, repeated every 21 days (n=83)	*Overall survival*: HR 0.22 (95%CI 0.06-0.77, p=0.008) in favour of regimen A. *Failure-free survival*: HR 0.84 (0.43-1.63, p=0.6). *Toxicity*: Nausea/vomiting 57 vs. 74% (p=0.02) in favour of regimen A. No other significant differences.	Central randomisation. No information on blinding of patients or investigators. More patients with intermediate or poor prognosis disease (IGCCC) were assigned regimen B (n=16) than regimen A (n=12). Intention-to-treat analysis. Median follow-up: 33 months. Included in Feldman 2008 and Shelley 2002.	Moderate
Nichols 1998 [96]		Patients with advanced stage disseminated germ cell cancer (n=286) No previous chemotherapy 44 patients with seminoma (15%) 72% primary site = testis	BEP: etoposide 100 mg/m² on day 1-5 + weekly bolus of bleomycin 30 U for 12 weeks + cisplatin 20 mg/m² on day 1-5 vs. VIP: etoposide 75 mg/m² on day 1-5 + ifosfamide 1.2 g/m² on day 1-5 + cisplatin 20 mg/m² on day 1-5 + mesna	*Complete remission*: 31% vs. 37% (NS) *2-year failure-free survival*: 60% vs. 64% (NS) *2-year overall survival*: 71% vs. 74% (NS) More grade 3-4 toxicity after VIP	Randomisation with permuted block strategy with blocks of size 6 for each participating centre. Unclear if allocation concealment. No information on blinding of patients or investigators. Included in Feldman 2008 and Shelley 2002.	Low
Loehrer 1995 [89]		Patients with good-risk testicular or extragonadal germ cell cancer, minimal or moderate stage disease (Indiana University Staging System) (n=178) 23 patients with seminoma (13%) 96% primary site = testis	Cisplatin (20 mg/m² on days 1 to 5) plus etoposide (100 mg/m² on days 1 to 5) with (n=86) or without (n=85) weekly bleomycin (30 IU/wk for 9 consecutive weeks). Following three cycles of chemotherapy over 9 weeks, patients with residual radiographic disease underwent surgical resection. If persistent carcinoma was noted, two additional 3-week courses of chemotherapy were administered.	*Failure-free survival*: 86% vs. 69% (p=0 .01) in favour of bleomycin group. *Overall survival*: 95% vs. 86% (p=0.01) in favour of bleomycin group. *Disease-free status*: 94% vs. 88% (p=0.20) (chemotherapy +/- surgery) *Toxicity*: Grade 4 myelosuppression: 14% vs. 5% (p=0.06) in favour of EP group. No other significant differences.	Central randomisation. No information on blinding of patients or investigators. 7 ineligible patients excluded from analysis. Included in Feldman 2008 and Shelley 2002.	Moderate

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Bosl 1994 [156] Bajorin 1993 [157]		Patients with good-risk germ cell tumours (MSKCC criteria: stage IIC, stage III, or extragonadal seminoma, relapsed seminoma following radiation therapy, or NSGCT of gonadal origin) (n=265) 69 patients with seminoma (26%) 4% primary site = extragonadal	Four cycles of 21 days: Etoposide (100 mg/m² for 5 days) + carboplatin (350-500 mg/m²) (EC: n=131) Etoposide (100 mg/m² for 5 days) + cisplatin (20 mg/m² for 5 days) (EP: n=135)	*Complete response*: 88% (EC) vs. 90% (EP) *Relapse rates*: 12% vs. 3% *Unfavourable outcome events*: 32 vs. 17 (p=0.02) Equivalent *overall survival* (p=0.52). Lower relapse- (p= 0.005) and event-free survival (p=0.02) in EC group. *Toxicity*: significantly more haematological toxicity in the EC arm, including neutropenic fever requiring hospitalisation (p=0.016).	No information on randomisation procedure or blinding of patients and investigators. Included in Feldman 2008 and Shelley 2002.	Low
Levi 1993 [158]		Patients with inoperable histologically confirmed germ cell tumours of good prognosis (n=222) No previous chemotherapy 6% seminomas 2% primary site = extragonadal	Induction chemotherapy with cisplatin 100 mg/m² on day 1 + vinblastine 6 mg/m² on day 1 and 2 with (PVB: n=110) or without (PV: n=112) bleomycin 30 mg IM for a maximum of 12 weeks Two courses of consolidation chemotherapy if complete remission	*Complete remission*: 89% (PV) vs. 94% (PVB) (NS) *Relapse rate*: 7% vs. 5% *Deaths from progressive disease*: 15% vs. 5% (p=0.02) Significant more toxicity with PVB	Central randomisation by random number system. No information on blinding of patients and investigators. Included in Feldman 2008 and Shelley 2002.	Moderate
Nichols 1991 [95]		Patients with poor-risk disseminated germ cell tumours (n=159) No prior chemotherapy with cisplatin, etoposide or bleomycin 21 patients with seminoma (14%) 73% primary site = testis	Etoposide + bleomycin + standard-dose cisplatin (20 mg/m² d1-5) (n=78) vs. high-dose cisplatin (40 mg/m² d1-5) (n=76)	*Complete remission*: 47% vs. 46% (NS) No significant difference in overall survival. Significantly more ototoxicity (0% vs. 24%), neurotoxicity (1% vs. 26%) and gastrointestinal toxicity (4% vs. 26%) in high-dose arm.	Central randomisation, no information on randomisation method. No information on blinding of patients and investigators. Five ineligible patients in high-dose arm (disease extent did not qualify for advanced-disease status). Included in Feldman 2008 and Shelley 2002.	Moderate

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Wozniak 1991 [159]		Patients with disseminated testicular germ cell tumours (n=169) 32 patients with seminoma (20%)	Four cycles of 21 days: Cisplatin (120 mg/m² on day 3), vinblastine (12 mg/m² on day 1), and bleomycin (15 U/m² twice a week) (PVB: n=77) Vinblastine (8 mg/m² on day 1), cisplatin (120 mg/m² on day 3), and etoposide (50 mg/m² day 2-5) (VPV: n=83) Cytoreductive surgery was done post-induction if a chemotherapy CR was not achieved.	No difference in the percentage of patients achieving a *disease-free status* between PVB (77%) and VPV (73%) (p=0.39). No significant survival difference (p=0.19). Mean platelet nadir was significantly lower (p=0.003) in the VPV arm. All bleomycin-related toxicities (pulmonary, mucositis, skin) were avoided in the VPV arm.	Central randomisation. No information on blinding of patients and investigators. 9 patients not included in analysis (reasons provided in full-text). Median follow-up: 3.4 years. Included in Shelley 2002.	Moderate
Motzer 1990 [160] Bosl 1988 [161]		Patients with good-risk germ cell tumours (n=164) 31 patients with seminoma (19%) 4% primary site = extragonadal	VAB-6: vinblastine 4 mg/m² d1; cyclophosphamide 600 mg/m² d1; doctinomycin 1 mg/m² d1; bleomycin 30U d1; bleomycin 20 U/m² d1-3; cisplatin 120 mg/m² d4. Three 3 cycles every 4 weeks, no bleomycin in 3rd week. Surgery considered after 3 cycles (n=82). EP: etoposide 100 mg/m² d1-5; cisplatin 20 U/m² d1-5. Four cycles every 3-4 weeks. Surgery considered after 4 cycles (n=82).	*Complete remission*: 96% vs. 93% *Residual disease at operation*: 20% (11/56) vs. 8% (4/52) *Event-free survival*: not significantly different. *Toxicity*: less toxicity with EP. Significant differences in nadir platelets, emesis volume and nadir magnesium, all in favour of EP.	No information on randomisation procedure or blinding of patients and investigators. Median follow-up: 25 months. Included in Feldman 2008 and Shelley 2002.	Low
Einhorn 1989 [87]		Patients with good-prognosis disseminated germ cell tumours (n=188) No previous chemotherapy No information on number of patients with seminoma or testicular site	$PVB_{16}B$ 4 courses over 12 weeks (n=96) vs. 3 courses over 9 weeks (n=88)	*Disease-free status*: 98% (3 courses) vs. 97% (4 courses) Five relapses in each arm	Central randomisation, unclear randomisation method. No information on blinding of patients and investigators. Included in Feldman 2008 and Shelley 2002.	Moderate

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Levi 1988 [162]		Patients with proven diagnosis of germ cell carcinoma with inoperable stage II or III disease and achieving complete remission after initial chemotherapy with cisplatin, vinblastine, and bleomycin followed by surgical resection of residual masses if possible (n=88) Unclear how many of these had extragonadal or even ovarian disease	Maintenance chemotherapy with vinblastine 10 mg/m² at 28-day intervals for a total of 6 courses (n=43). No maintenance chemotherapy (n=45).	*Relapses*: 26% (11/43) vs. 16% (7/45), p=0.08. Other outcomes are not presented per arm.	Exclusion of 7 patients from analysis: 4 lost-to-follow-up, 2 protocol violations, 1 no germ cell carcinoma. Allocation by a random number system: blinded? No information on blinding of patients and investigators. Median follow-up: 64 months. Included in Shelley 2002.	Low
Kaye 1985 [163]		Patients with advanced testicular cancer (n=203)	First randomisation: High-dose PVB: cisplatin 20 mg/m² days 1-5 every 3 weeks for 4 courses, bleomycin 30 mg weekly for 12 weeks, and vinblastine 0.20 mg/kg on days 1 and 2 every 3 weeks for four courses (n=64). Low-dose PVB: same, but vinblastine 0.15 mg/kg (n=70). Second randomisation (if complete remission): Maintenance chemotherapy: with cisplatin 50 mg/m² every 6 weeks and vinblastine 0.2 mg/kg every 3 weeks (n=37). No further chemotherapy (n=31).	*Complete response*: 71% in both arms of PVB. *Toxicity*: no significant difference in non-haematological side effects. Mucositis: 55% vs. 36%. Significant differences in haematological side effects: - Leucocytopenia <1000/mm²: 30% vs. 13%, p<0.001 - Neutropenic fever: 55% vs. 30% *Relapse after second randomisation*: 3% vs. 6% (NS)	Interim analysis. 69 patients excluded from analysis: insufficient data (n=24), too early to assess response (n=44), non-cancer-related death (n=1). No information on randomisation procedure or blinding of patients and investigators.	Low
Samson 1984 [164]		Patients with advanced, histologically proven germ cell tumour of testicular origin and clearly measurable metastatic disease and/ or elevated serum beta subunit of human chorionic gonadotrophin or alpha-fetoprotein (n=114) 11 patients with seminoma (10%)	Cisplatin 120 mg/m² d3 + vinblastine 12 mg/m² d1 + bleomycin 15 U/m² d1 every 4 weeks, 4 cycles (n=56). vs. Same, but with cisplatin 15 mg/m² d1-5 (n=58). Patients in complete remission received maintenance chemotherapy. Patients in partial remission received cytoreductive surgery + maintenance chemotherapy if disease-free.	*Complete response rate*: 63% vs. 43%, p=0.03 in favour of high-dose. *Relapse rate*: overall, 4 patients relapsed, all randomised to low-dose. Significant survival advantage for high-dose (p=0.0009). Higher frequency of leucopenia, renal, neuromuscular, and mucosal toxicity with high-dose therapy.	Interim analysis. Central randomisation. No information on blinding of patients and investigators. Included in Shelley 2002.	Moderate

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Einhorn 1981 [165]		Patients with disseminated testicular cancer (n=171) 9% seminomas	First randomisation: Remission-induction therapy with cisplatin + vinblastine + bleomycin (n=87) vs. cisplatin + vinblastine + bleomycin + doxorubicin (n=84) Second randomisation: In patients achieving complete remission and disease-free status after surgical resection: maintenance vinblastine (n=58) vs. no further therapy (n=55) Patients with surgical resection of viable carcinoma: 2 postoperative courses of cisplatin combination chemotherapy	Remission-induction regimens: *Complete remission*: 64% vs. 68% (NS) *Disease-free status after chemotherapy and surgery*: 11% in both groups *Relapse*: 4 vs. 5 cases Maintenance therapy: *Relapse rate*: 9% vs. 7% (NS) *Disease-free status at time of evaluation*: 97% vs. 95% (NS)	Central randomisation (using random variable, permuted blocks of 4). No information on blinding of patients and investigators. Included in Shelley 2002.	Moderate
Einhorn 1980 [166]		Patients with disseminated testicular cancer (n=78) 8 patients with seminoma (10%)	Cisplatin 20 mg/m² d1-5 every 3 weeks, 3-4 cycles + Bleomycin 30U weekly for 12 weeks + (1) vinblastine 0.4 mg/kg every 3 weeks for 4 cycles (n=26); or (2) vinblastine 0.3 mg/kg every 3 weeks for 4 cycles (n=27); or (3) vinblastine 0.2 mg/kg plus Adriamycin 50 mg/m² every 3 weeks for 4 cycles (n=25)	*Granulocytopenic fever*: 35% with regimen 1 vs. 15% with regimen 2. *Complete remission*: 69% vs. 63% vs. 72% *Relapses*: 19% vs. 10% vs. 15%	No information on randomisation procedure or blinding of patients and investigators. Median follow-up: 25 months.	Low

NON-SEMINOMA: ADVANCED STAGES

Guidelines

CPG ID	Ref	Search date	Recommendation(s)	Supporting evidence	Level of evidence
AFU 2007 [18]		Feb 2007	Stade pT1 à pT4, N1 à N3 ou M1a, M1b ou N0, M0 à marqueurs non normalisés : Le traitement repose sur la chimiothérapie : bon pronostic: 3 cycles de BEP strictement tous les 21 jours (niveau de preuve: II) pronostic intermédiaire: 4 cycles de BEP strictement tous les 21 jours (niveau de preuve: II) mauvais pronostic: En raison de la rareté et de la gravité de cette situation, il faut inclure ces patients dans un essai clinique (GETUG 13). En cas d'impossibilité absolue d'inclusion, le standard repose sur 4 cycles de BEP strictement tous les 21 jours.	Culine 2007 (RCT) Mezvrishvili 2005, Kondagunta 2004, Kondagunta 2005, Kildahlandersen 2005 (retrospective studies)	Low

Systematic reviews

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Level of evidence
Feldman 2008 [76]		Oct 2007	Patients with advanced testicular cancer	Medical treatment in general	**First-line chemotherapy for metastatic GCT** Good-prognosis GCT: (12 RCTs) Two effective regimens: 4 cycles of EP or 3 cycles of BEP (applies to seminoma and non-seminoma) Intermediate- and poor-prognosis: (8 RCTs) Standard regimen: 4 cycles of BEP **Second- and third-line chemotherapy** Standard doses of 3-drug combinations based on ifosfamide and cisplatin or high-dose chemotherapy with autologous stem-cell support.	Search in Medline and CENTRAL. Jadad scale used for RCTs. Narrative overview of evidence.	Moderate
Shelley 2002 [77]		May 2002	Patients with metastatic germ cell tumors	Treatment in general	No extra information in addition to Feldman 2008	Search strategy available on request. No information on quality appraisal. Narrative overview of evidence.	Low – moderate

Randomised controlled trials

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Culine 2008 [98]		Patients with metastatic NSGCT and intermediate/poor risk according to IGR prognostic model (n=188) No previous chemotherapy 74% testis = primary site 4 patients with pure seminoma but elevated AFP levels	CISCA/VB: cyclophosphamide 400 mg/m² d1-2 + doxorubicin 35 mg/m² d1-2 + cisplatin 100 mg/m² d3 and vinblastine 2.5 mg/m² d1-5 + bleomycin 25 mg/m² d1-5 alternatively delivered every 3 weeks for a total of 4-6 cycles (n=94). BEP: bleomycin 30 mg d1, d8, d15 + etoposide 100 mg/m² d1-5 + cisplatin 20 mg/m² d1-5 every 3 weeks for a total of 4 cycles (n=94).	Surgical resection of residual masses in 60% and 64% (p=0.008). More significant haematological and mucous toxicities after CISCA/VB: - grade 4 neutropenia: 57% vs. 25% of cycles, p<0.0001 - febrile neutropenia: 19.2% vs. 5.3% of cycles, p<0.0001 - blood transfusions: 13.6% vs. 8.8%, p=0.043 - grade 3/4 thrombocytopenia: 13.1% vs. 6.5%, p=0.0033 - mucositis: 17% vs. 10.1%, p=0.002 - dermatologic: 6% vs. 11% of cycles, p=0.0154 *Favourable response*: 56% vs. 65%, NS. *5-year event-free survival*: 37% (95%CI 27-47%) vs. 47% (95%CI 37-57%); HR 0.76, 95%CI 0.52-1.11, p=0.15. *5-year overall survival* : 59% (95%CI 47-67%) vs. 69% (95%CI 58-77%); HR 0.73, 95%CI 0.46-1.18, p=0.24.	GETUG T93MP trial. No information on randomisation procedure or blinding of patients and investigators. 3 patients excluded from analysis in CISCA/VB group due to non-receiving of treatment. Differences in baseline values of AFP and HCG. Median follow-up: 7.8 years. Intention-to-treat analysis.	Low
Culine 2007 [83]		Patients with metastatic NSGCT and good risk according to IGR prognostic model (n=270) No previous chemotherapy 99% testis = primary site	BE500P: bleomycin 30 IU on days 1, 8 and 15 + etoposide 100 mg/m² on days 1-5 + cisplatin 20 mg/m² on days 1-5, repeated every 3 weeks, three cycles (n=131) E500P: etoposide 100 mg/m² on days 1-5 + cisplatin 20 mg/m² on days 1-5, repeated every 3 weeks, four cycles (n=126)	*Favourable response*: 94.7% (90%CI 91.4-97.9%) vs. 96.8% (94.2-99.4%). No statistically significant differences. *4-year event-free survival*: 91% (95%CI 84.5-94.7%) vs. 86% (78.3-90.8%) (HR 0.58, 95%CI 0.29-1.19, p=0.135). *4-year overall survival*: 96% (91.0-98.4%) vs. 92% (85.1-95.8%) (HR 0.42, 95%CI 0.15-1.20, p=0.096). *Toxicity*: - Grade 3-4 neutropenia: more frequently in E500P group (72% vs. 90%, p=0.0002) - No differences in febrile neutropenia - More frequent neurological toxicity (16% vs. 5%, p=0.006) and dermatologic toxicity (29% vs. 8%, p<0.0001) in BE500P group	GETUG T93BP trial. No information on randomisation procedure or blinding of patients and investigators. 13 patients not evaluable for response. Median follow-up: 53 months. Intention-to-treat analysis. Included in Feldman 2008.	Low

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Droz 2007 [90] Chevreau 1993 [167]		Patients with previously untreated high-volume metastatic NSGCT of either testicular or extragonadal origin (n=114) 71% testis = primary site High-volume status was determined according to a logistic regression model by using hCG and AFP marker levels.	PVeBV: vinblastine (0.2 mg/kg on day 1) + etoposide (100 mg/m²/d on days 1 through 5) + cisplatin (40 mg/m²/d on days 1 through 5) + bleomycin (30 mg on days 1, 8, and 15); 3 or 4 cycles every 21 d (n=57). ABMT: 2 cycles every 28 d of identical doses of (vinblastine, etoposide, and cisplatin) + bleomycin at a dose of 20 mg/d as a continuous infusion on days 1 through 5, and then at a dose of 15 mg on days 8,15, and 22 by intramuscular injection. The third cycle included etoposide (350 mg/m²/d on days 1 through 5)+ cisplatin (40 mg/m²/d on days 1 through 5) + cyclophosphamide (1600 mg/m²/d on days 2 through 5) + mesna (550 mg/m² by IV bolus every 8 h on days 2 through 5). Autologous bone marrow was reinfused on day 8, 72 h after the last infusion of chemotherapy (n=57).	*Complete response*: 56% vs. 42% (p=0.099). *5-year survival*: 75% vs. 61%. - Intermediate IGCCCG group: 88% vs. 82% (NS) - Poor IGCCCG group: 69% vs. 44% (p=0.045). *Toxicity*: - Grade 2 or worse mucositis:46% vs. 26%, p=0.0023 (cycle 1&2) - Grade 2 or worse neurologic toxicities: 26% vs. 7%, p=0.008 - Neutropenia: 32% vs. 47%, p=0.03 (cycle 1&2) - More haematological toxicities with ABMT in cycle 3&4	Randomisation by a centralised computer program using a stratified block design. No information on blinding of patients and investigators. Intention-to-treat analysis. Median follow-up: 9.7 years. Included in Feldman 2008.	Moderate
Fizazi 2002 [168]		Patients with metastatic (stage II to III-B5) testicular NSGCT and a HCG level < 50000 mIU/ml (n=124) No previous chemotherapy	CISCA/VB: cyclophosphamide 500 mg/m² d1-2 + doxorubicin 45 mg/m² d1-2 + cisplatin 120 mg/m² d3 and vinblastine 3 mg/m² d1-5 + bleomycin 30 mg/m² d1-5 alternatively delivered every 3 weeks for a total of 4-6 cycles (n=65). Low-dose CISCA/VB: cyclophosphamide 400 mg/m² d1-2 + doxorubicin 35 mg/m² d1-2 + cisplatin 100 mg/m² d3 and vinblastine 2.5 mg/m² d1-5 + bleomycin 25 mg/m² d1-5 alternatively delivered every 3 weeks for a total of 4-6 cycles (n=59).	*Complete response*: 82% vs. 90%, p=0.29. *5-year disease-free survival*: 89.1% vs. 89.5%, p=0.87. *5-year overall survival*: 93.7% vs. 94.1%, p=0.88. *Toxicity*: - Febrile neutropenia: 91% vs. 63%, p<0.001 - Grade 4 thrombocytopenia: 28% vs. 10%, p<0.03 - Mucositis grade 4: 15% vs. 1.7%, p<0.01 - Discontinuation because of toxicity: 6 vs. 1	No information on randomisation procedure or blinding of patients and investigators. Median follow-up: 6.8 years. No intention-to-treat analysis. Included in Shelley 2002.	Low
de Wit 1998 [92]		Patients with metastatic testicular NSGCT and intermediate prognosis (i.e. lymph node metastases 5-10 cm	BEP: bleomycin 30 mg on day 1 for 12 weeks + etoposide 120 mg/m² on day 1, 3, 5 every 3 weeks +	*Complete response*: 79% vs. 74%, p=0.62. *Treatment failure*: 20% vs. 15%, HR 0.83	No information on randomisation procedure or blinding of patients and	Low

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
		in diameter, lung metastases > 4 in number or > 3 cm, HCG 5000-50000 IU/l, AFP > 1000 IU/l) (n=84) No previous radiotherapy or chemotherapy	cisplatin 20 mg/m² on days 1-5 every 3 weeks; 4 cycles (n=38) VIP: ifosfamide 1.2 g/m² on days 1-5 every 3 weeks + etoposide 120 mg/m² on day 1, 3, 5 every 3 weeks + cisplatin 20 mg/m² on days 1-5 every 3 weeks; 4 cycles (n=46)	(95%CI 0.30-2.28), p=0.72. *5-year progression-free survival*: 83% vs. 85%. *Toxicity*: - Grade 4 leucocytopenia: 8% vs. 26%, p<0.001 - No other significant differences	investigators. Median follow-up: 7.7 years. Intention-to-treat analysis. Included in Feldman 2008 and Shelley 2002.	
Kaye 1998 [91]		Patients with histologically proven poor-prognosis metastatic NSGCT (n=380) No prior chemotherapy or radiotherapy Primary site testis: 80%	First randomisation: BEP/EP (n=185) vs. BOP/VIP-B (n=186) Second randomisation: BEP/EP without filgrastim vs. BOP/VIP-B without filgrastim vs. BEP/EP with filgrastim vs. BOP/VIP-B with filgastrim	*Complete response*: 57% vs. 54% (NS) *1-year failure-free survival*: 60% vs. 53% (NS) *Toxicity*: - More grade 3-4 myelosuppression, febrile neutropenia and weight loss with BOP/VIP-B - Toxic deaths: 9% vs. 5%	Central randomisation and data collection. No information on blinding of patients and investigators. 9 ineligible patients for response analysis: inappropriate disease stage or histology/tumour type. Included in Feldman 2008 and Shelley 2002.	Moderate
de Wit 1997 [85]		Patients with metastatic testicular NSGCT and good prognosis (i.e. lymph node metastases <5 cm in diameter, lung metastases <4 in number and <2 cm, no haematogenous spread outside the lungs, HCG ≤10000 IU/l, AFP ≤1000 IU/l) (n=395) No previous radiotherapy or chemotherapy	BEP: bleomycin 30 mg on day 1 for 12 weeks + etoposide 120 mg/m² on day 1, 3, 5 every 3 weeks + cisplatin 20 mg/m² on days 1-5 every 3 weeks; 4 cycles (n=200) EP: etoposide 120 mg/m² on day 1, 3, 5 every 3 weeks + cisplatin 20 mg/m² on days 1-5 every 3 weeks; 4 cycles (n=195)	*Complete response*: 92% vs. 85%, p=0.0276. *Time-to-progression*: no significant difference. *Overall survival*: no significant difference. *Toxicity*: - No significant differences in haematological toxicities - Neuropathy grade 1-3: 29% vs. 13%, p<0.001 - Skin toxicity: 39% vs. 5%, p<0.001 - Late toxicities: 24% vs. 10%, p<0.001	No information on randomisation procedure or blinding of patients and investigators. Median follow-up: 7.3 years. Intention-to-treat analysis. Included in Feldman 2008 and Shelley 2002.	Low
Horwich 1997 [84]		Patients with histologically confirmed good-risk testicular NSGCT (n=598)	Four cycles of BEP (etoposide 120 mg/m² d1-3, belomycin 30U d2; cisplatin 20 mg/m² d1-5 or 50 mg/m² d1-2) vs. CEB (etoposide 120 mg/m² d1-3, belomycin 30U d2; carboplatin)	*Complete response*: 94% vs. 87% (p=0.009) *1-year failure free survival*: 91% vs. 77% *Treatment failure*: 30 vs. 79 (p<0.001) *3-year survival*: 97% vs. 90%	Central randomisation. No information on randomisation procedure or blinding of patients and investigators. Included in Feldman 2008 and Shelley 2002.	Moderate
Bokemeyer 1996 [86]		Patients with metastatic testicular NSGCT and good risk (i.e. minimal disease: tumour marker elevation (AFP, HCG) only, cervical or supraclavicular lymph node metastases, abdominal lymph node metastases <10 cm in diameter or <5 pulmonary metastases, all < 2 cm in diameter, or moderate disease: abdominal lymph node metastases	BEP: bleomycin 30 mg on days 1, 8 and 15 + etoposide 100 mg/m² on day 1-5 every 3 weeks + cisplatin 20 mg/m² on days 1-5 every 3 weeks; 3 cycles (n=29) CEB: carboplatin + etoposide 120 mg/m² on day 1-3 + bleomycin 30 mg on days 1, 8 and 15 (cycle 1-3); every 3 weeks, 4 cycles (n=25)	*Complete response*: 81% vs. 76% (NS) *1-year progression-free survival*: 86% vs. 84% *Toxicity*: (no p-values) - nausea/vomiting: 68% vs. 47% - nephrotoxicity: 16% vs. 0% - polyneuropathy: 10% vs. 0%	Interim analysis. No information on randomisation procedure or blinding of patients and investigators. Median follow-up: 33 months. Included in Feldman 2008 and Shelley 2002.	Low

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
		>10 cm without further metastatic disease, 5-10 pulmonary metastases all < 3 cm in diameter, a singular pulmonary metastasis >3 cm or mediastinal lymphatic nodes <50% of the intrathoracic diameter) (n=54) No previous chemotherapy				
de Wit 1995 [93]		Patients with metastatic testicular NSGCT and poor prognosis (lymph node metastases >5 cm, lung metastases >4 in number or >2 cm, haematogenous spread outside the lungs such as in liver or bone, HCG >10000 IU/l or AFP>1000 IU/l) (n=234 eligible) (n=208) No previous radiotherapy or chemotherapy	BEP: bleomycin 30 mg on day 2 every week + etoposide 120 mg/m² on days 1, 3, 5 every 3 weeks + cisplatin 20 mg/m² on days 1-5 every 3 weeks; 4 cycles (n=105 evaluable) Alternating PVB/BEP: PVB = bleomycin 30 mg on day 2 every week + vinblastine 0.15 mg/kg on days 1-2 every 3 weeks + cisplatin 20 mg/m² on days 1-5 every 3 weeks; total of 4 cycles (n=103 evaluable)	*Treatment response*: Complete response (CR): 72% vs. 76%, p=0.58. Relapse rate from CR: 16% vs. 12%, p=0.65. *Time-to-progression*: No exact data provided; p=0.27. *Survival*: No exact data provided, p=0.32. *Toxicity*: Grade 4 leucopenia: 5% vs. 28%, p<0.001. Neutropenic fever: 5% vs. 16%, p=0.006. Grade 4 thrombocytopenia: 1% vs. 10%, p=0.001. Neuropathy: 25% vs. 47%, p<0.001. Mucosal toxicity: 16% vs. 28%, p<0.05.	No information on randomisation procedure or blinding of patients and investigators. Mean follow-up: 6 years. Included in Feldman 2008 and Shelley 2002.	Low
Weissbach 1991 [169]		Patients with testicular NSGCT stage IIB (n=225) No previous radiotherapy or chemotherapy	Cisplatin 20 mg/m² day 1-5 + vinblastine 6 mg/m² day 1-2 or etoposide 100 mg/m² day 1-5 + bleomycin 12 mg/m² day 1-5, 2 cycles (n=114) vs. 4 cycles (n=111)	No significant differences in *side effects*. *Relapse rate*: 5% vs. 1%, p=0.75.	Central randomisation, but no information on exact randomisation procedure. No information on blinding of patients and investigators. Median follow-up: 43 months. Included in Shelley 2002.	Moderate
Ozols 1988 [170]		Patients with poor-prognosis NSGCT (n=52) Extragonadal site: 23%	PVeBV (cisplatin 40 mg/m² d1-5, vinblastine 0.2 mg/kg d1, bleomycin 30U d1, d8 and d15, etoposide 100 mg/m² d1-5) vs. PVeB (cisplatin 20 mg/m² d1-5, vinblastine 0.3 mg/kg d1, bleomycin 30U d1, d8 and d15)	*Complete remission*: 88% vs. 67% (NS) *5-year survival*: 78% vs. 48% (p=0.06) *Disease-free survival*: 68% vs. 33% at the time of analysis (median follow-up 4 years) (p=0.02) *Toxicity*: leukopenia 91% vs. 50% (p<0.05)	Central randomisation, but no information on exact randomisation procedure. No information on blinding of patients and investigators. Included in Shelley 2002.	Moderate
Williams 1987 [94]		Patients with pathological stage II testicular cancer (n=195), all NSGCT	Immediate cisplatin-based adjuvant chemotherapy (PVB) (n=97) vs. monthly observation with treatment at relapse (n=98)	*Recurrence*: 49% vs. 6% No significant difference in overall survival.	Central randomisation (partially by sealed envelopes). Partially blinded assessment. Included in Feldman 2008 and Shelley 2002.	Moderate

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Hartlapp 1987 [171]		Patients with stage IIA/B testicular NSGCT (n=263) No previous radiotherapy or chemotherapy	*Stage IIA*: No adjuvant treatment (n=16) or 2 courses of PVB (n=32): vinblastine 6 mg/m² on d1-2, bleomycin 12 mg/m² on d1-5, cisplatin 20 mg/m² on d1-5 *Stage IIB*: 2 (n=87) vs. 4 courses of PVB (n=75)	*Relapses*: Stage IIA: 1 vs. 0 Stage IIB: 3 vs. 1 *Toxicity*: Discontinuation of treatment: Stage IIA: 3.6% Stage IIB: 3.6% vs. 11% Overall toxicity: nausea 94%, vomiting 86%, alopecia 82%, stomatitis 22%, sepsis 7%.	No information on randomisation procedure or blinding of patients and investigators. Unclear if intention-to-treat analysis, probably not. 210 patients were evaluable. Median follow-up 17-18 months.	Low
Stoter 1986 [172]		Patients with metastatic testicular NSGCT with at least stage IIB (n=214) No previous radiotherapy or chemotherapy	High-dose PVB (vinblastine 0.2 mg/kg on d1-2 every 3 weeks, cisplatin 20 mg/m² on d1-5 every 3 weeks, bleomycin 30 mg on d2 for 12 weeks) (n=98) vs. low-dose PVB (same, but with vinblastine 0.15 mg/kg) (n=116)	*Treatment response*: Complete response: 68% vs. 71% Time-to-progression in complete responders: no significant difference (p=0.08). No significant differences in *survival*. *Toxicity*: Grade 4 leukopenia: 29% vs. 13% (p=0.01). Neutropenic fever: 34% vs. 20% (p=0.13). Mucositis: 53% vs. 37% (p=0.006).	Central randomisation, but no information on exact randomisation procedure. No information on blinding of patients and investigators. Median follow-up: 33 months. No intention-to-treat analysis. Included in Shelley 2002.	Moderate
Rorth 1984 [173]		Patients with stage II testicular NSGCT (n=51)	All patients received 6 courses of PVB (vinblastine 6 mg/m² on d1-2, bleomycin 15 mg/m² on d2, 9 and 16, cisplatin 20 mg/m² on d1-5). Randomisation to radiotherapy (n=19), split course 2x (2.5 Gy x 8) afer 3rd and 4th course; or no radiotherapy (n=32)	Dose reductions in radiotherapy group. No differences in results between 2 groups: results not presented separately. Overall: 75% complete remission after treatment (+ additional 14% after supplementary surgery); 5% toxic deaths; 6% disease-related deaths	Interim analysis of DATECA study. Randomisation with sealed envelop. No information on blinding of patients and investigators. Median follow-up: 20 months.	Low

Study ID	Ref	Population	Intervention(s)	Results	Comments	Level of evidence
Javadpour 1982 [174]		Patients with bulky stage III testicular NSGCT and poor prognosis (palpable retroperitoneal disease, liver involvement, invasion or obstruction of the inferior vena cava, or lung metastases >2 cm in diameter) (n=39) No previous radiotherapy or chemotherapy	Chemotherapy with (n=20) or without (n=19) preceding cytoreductive surgery (removal of as much tumour bulk as safely possible). Different possible chemotherapy regimens.	*Cytoreductive surgery*: 17 patients reached an estimated 70-90% reduction in retroperitoneal tumour volume after surgery. *Response rate*: Overall response (complete + partial): 75% vs. 84%, NS. Complete response: 50% vs. 37%, NS. *Survival*: Trend towards better survival in favour of chemotherapy alone (p=0.055). No exact data provided. *Toxicity*: Surgery: transient lower extremity oedema 32%, thrombophlebitis 11%. Chemotherapy: leukopenia 38%, nausea and vomiting 97%, alopecia 94%.	Randomisation with randomisation decks. No information on blinding of patients and investigators. Unclear if intention-to-treat analysis. Median follow-up: 24 months.	Low
Scheulen 1980 [175]		Patients with NSGCT and measurable metastatic disease (n=40). No prior chemotherapy with drugs under investigation. 98% testis = primary site	Group A: (n=25) 2 courses of regimen A (vinblastine 0.4 mg/kg on d1-2 and bleomycin 30U/d on d1-5) + 2 courses of regimen B (doxorubicin 60 mg/m² on d1-5 + cisplatin 20 mg/m² on d1-5) Group B: (n=15) 2 courses of regimen B + 2 courses of regimen A	*Response*: Complete remission: 68% vs. 67% Complete remission after 2 courses: 40% in both groups. No difference in *survival*. *Toxicity*: No detailed information.	No information on randomisation procedure or blinding of patients and investigators. Unclear if intention-to-treat analysis.	Low
De Wys 1979 [176]		Patients with histologically confirmed stage III NSGCT or recurrent NSGCT after primary surgery or radiotherapy (n=63)	Two cycles of cyclophosphamide + actinomycin D + vinblastine + bleomycin + high-dose cisplatin (n=23) vs. low-dose cisplatin (n=22)	*Complete remission: 35% vs. 36% after 2 cycles (NS)* *No significant differences in toxicity*	No information on randomisation procedure or blinding of patients and investigators. Exclusion of 17 patients because of insufficient data submission, and 1 patient because of uncertainty about histologic diagnosis.	Low

TREATMENT OF RELAPSE

Randomized controlled trials

Study ID	Ref	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
Lorch A 2007 [114]		RCT N=216 Median follow-up = 36 months	Patients with relapsed or refractory germ cell tumours (GCT) after cisplatin-based combination chemotherapy for metastatic GCT (including late relapses). 189 patients with gonadal GCT.	1 cycle of cisplatin 100 mg/m², etoposide 375 mg/m², and ifosfamide 6 g/m² (VIP) plus 3 cycles of high-dose carboplatin 1500 mg/m² and etoposide 1500 mg/m² (CE; arm A) (n=108) 3 cycles of VIP plus 1 cycle of high-dose carboplatin 2200 mg/m², etoposide 1800 mg/m², and cyclophosphamide 6400 mg/m² (CEC; arm B) (n=103) Reinfusion of autologous peripheral blood progenitor cells in both arms.	*Completion of treatment*: Arm A: 70% vs. arm B: 81% *Toxicity*: - Treatment-related deaths: 4% vs. 16% (p<0.01). - Organ failures (p<0.001): Hemodialysis 1% vs. 8% Mechanical ventilation: 19% vs. 18% - Grade 3/4 toxicities: Infections: 82% vs. 57% (p<0.001) Cardiac: 6% vs. 12% (p<0.01) Hepatic: 11% vs. 20% (p<0.01) Neurologic: 3% vs. 6% (p<0.01) *Response*: - Rate of successful resections: 52% vs. 47% (p=0.54) - Complete response: 22% vs. 21% *Survival*: - Event-free survival: 1-year 41% vs. 34% (NS) 3-year 34% vs. 31% (NS) - Progression-free survival: 1-year 55% vs. 51% (NS) 3-year 47% vs. 45% (NS) - Overall survival: 1-year 81% vs. 62% (NS) 3-year 48% vs. 46% (NS)	Central randomisation. No information on blinding of patients or investigators. Intention-to-treat analysis. 5 exclusions because of non-GCT histology. Prematurely stopped as a result of excess treatment-related mortality in arm B.	Moderate

Study ID	Ref	Study description	Patient characteristics	Intervention(s)	Results	Comments	Level of evidence
Pico JL 2005 [113]		RCT N=280 Median follow-up= 45 months	Patients with relapsed GCT after cisplatin-based combination chemotherapy. 220 patients with testicular GCT.	4 cycles of PEI (ifosfamide 1200 mg/m², mesna 400 mg/m² and cisplatin 20 mg/m², days 1–5 + etoposide 75 mg/m², days 1–5) or VeIP (ifosfamide 1200 mg/m², mesna 400 mg/m² and cisplatin 20 mg/m², days 1–5 + vinblastine 0.11 mg/kg, days 1–2) (n=128) 3 cycles of PEI or VeIP followed by CarboPEC (high-dose carboplatin on day 1; etoposide 450 mg/m²/day, cyclophosphamide 1600 mg/m²/day and mesna 3600 mg/m²/day on days 1-4) with haematopoietic stem cell support (n=135)	*Completion of treatment*: 88% received at least 3 cycles of PEI or VeIP. 4 cycles: 80% vs. 73%. *Toxicity*: - Significantly more grade 3+ haematological adverse events during cycles 1-3 in arm A. - Grade 3+ adverse events during all cycles: febrile neutropenia 49% vs. 78% (p<0.001), thrombocytopenia 56% vs. 85% (p<0.001), nausea and vomiting 13% vs. 42% (p<0.001), diarrhoea 2% vs. 14% (p<0.001), mucositis 2% vs. 36% (p<0.001). - Toxic deaths: 4 vs. 9 deaths *Response*: - Complete response after 4 cycles: 27% vs. 26% - Overall complete response: 42% vs. 43% *Survival*: - 3-year event-free survival: 35% vs. 42% (p=0.16) - 3-year disease-free survival in patients achieving complete response: 55% vs. 75% (p=0.04)	Central randomisation. No information on blinding of patients or investigators. Intention-to-treat analysis.	Moderate

APPENDIX 6: TNM CLASSIFICATION

TNM CLINICAL CLASSIFICATION

T – primary tumour

Except for pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

N – regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension

N2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension

N3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

M – distant metastasis

M0 No distant metastasis

M1 Distant metastasis

- M1a Non-regional lymph node(s) or lung metastasis
- M1b Distant metastasis other than non-regional lymph nodes and lung

PTNM PATHOLOGICAL CLASSIFICATION

pT – primary tumour

pTX	Primary tumour cannot be assessed (see T – primary tumour, above)
pT0	No evidence of primary tumour (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion

pN – regional lymph nodes

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

pM – distant metastasis

pM1 Distant metastasis microscopically confirmed

S – serum tumour markers

SX Serum marker studies not available

S0 Serum marker study levels within normal limits

S1 LDH <1.5 x N and betaHCG < 5000 mIU/ml and AFP < 1000 ng/ml

S2 LDH 1.5-10 x N or betaHCG 5000-50000 mIU/ml or AFP 1000-10000 ng/ml

S3 LDH > 10 x N or betaHCG > 50000 mIU/ml or AFP > 10000 ng/ml

STAGE GROUPING

Stage 0	pTis	N0	M0	S0, SX
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2-T4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-S3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

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7. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
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