EAU Guidelines on

Testicular Cancer

M.P. Laguna (Chair), P. Albers, W. Albrecht, F. Algaba, C. Bokemeyer, J.L. Boormans, G. Cohn-Cedermark, K. Fizazi, H. Gremmels (Patient advocate), A. Horwich, D. Nichol, N. Nicolai, J. Oldenburg

Guidelines Associates: J. Mayor de Castro, Ch. Fankhauser

European Association of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

1.1 Aim and objectives

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients with cancer of the testis. Testicular cancer (TC) represents 5% of urological tumours affecting mostly younger males. This document addresses germ-cell tumours (GCTs) and sex cord/gonadal stromal tumours.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on Testicular Cancer consists of a multidisciplinary group of clinicians including, urologists, oncologists, radiotherapists and a pathologist. Members of this Panel have been selected, based on their expertise, to represent the professionals treating patients suspected of having testis cancer. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/testicular-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU Testicular Cancer Guidelines. All documents are accessible through the EAU website: http://www.uroweb.org/guideline/testicular-cancer/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The European Association of Urology (EAU) published the first guidelines on Testicular Cancer in 2001. Since 2008, the Testicular Cancer Guidelines contains a separate chapter on testicular stromal tumours. This document presents a limited update of the 2018 publication. Review papers have been published in the society's scientific journal European Urology, the latest version dating to 2015 [1].

*1.4.2 **Summary of changes***

For the 2019 Testicular Cancer Guidelines, new references have been added throughout the document. Key changes in this publication include:

- Additional remarks on pathology examination and description have been added to the text for the 2019 print. This relates, in particular, to the definition and morphological description of Rete Testis Invasion and Vascular Invasion;
- Citations relating to a number of low quality papers (SEER [The Surveillance, Epidemiology and End Results programme of the National Cncer Institute] database on stromal tumours incidence and retrospective biased FDG-PET [fluorodeoxyglucose-positron emission tomography] scan) have been removed from the text. However, a decision has been made to include some small phase II studies in the relevant text section on second relapse since there are few publications addressing this rare clinical scenario;
- A number of minor semantic modifications have been corrected in the text and the tables for 2019.

2. METHODS

For the Germ Cell Tumour section, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. The search was limited to studies representing high levels of evidence (i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies) published in the English language. The search was restricted to articles published between November 8th 2017 and June 13th 2018. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 1,230 unique records were identified, retrieved and

screened for relevance. Thirty new papers have been included in the 2019 print. A detailed search strategy is available online: http://uroweb.org/guideline/testicular-cancer/?type=appendices-publications.

For testicular stromal tumours additional literature has been added. Two scoping searches covering the time frame between Jan 1st, 2014 and Aug 26th, 2018 were performed. After deduplication, a total of 159 unique records were identified, retrieved and screened for relevance. Conference abstracts, editorials, letter to the editor and case reports were excluded from the searches.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [2, 3]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.1 Review

This document was subjected to peer review prior to publication in 2015.

2.2 Future goals

- A new chapter on "Incidentally diagnosed testicular masses" will be included in the 2020 major revision of the Guidelines.
- Chapter 8. Follow-up after curative therapy will be revisited, including the engagement of patients in the update of this topic.
- Chapter 9. Testicular stromal tumours will be updated, to include recommendations.
- A systematic review on the topic of "Quality of care of testicular cancer" will be undertaken by the panel. The main research question will investigate the quality of care for patients undergoing post-chemotherapy retroperitoneal lymph node dissection.
- The panel aim to produce an Individual Patient Data (IPD) prognostic factor study on the value of pathological factors in clinical stage I seminoma testis patients under active surveillance.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Testicular cancer represents 1% of male neoplasms and 5% of urological tumours, with three to ten new cases occurring per 100,000 males/per year in Western societies [6]. Its incidence has been increasing during the last decades especially in industrialised countries [7, 8]. Data from the Surveillance Epidemiology and End Results programme (1992 to 2012) show a continuing increased risk among Caucasian and Hispanic men in the USA with further increasing incidence forecast for the next decade [9, 10].

At diagnosis, 1-2% of cases are bilateral and the predominant histology is GCT (90-95% of cases) [6]. Peak incidence is in the third decade of life for non-seminoma, and in the fourth decade for pure seminoma.

Testicular cancers show excellent cure rates based on their chemosensitivity, especially to cisplatin based chemotherapy [11], careful staging at diagnosis, adequate early treatment based on a multidisciplinary approach, and strict follow-up and salvage therapies. A decrease in the meantime of delay to diagnosis and treatment has been observed. Although early stages can be successfully treated in a non-reference centre, the relapse rate is higher than in reference centres [12, 13]. In poor prognosis non-seminomatous germ cell tumours (NSGCT), overall survival (OS) within a clinical trial depends on the number of patients treated at the participating centre (worse if < five patients enrolled) [14]. In the same context, the frequency of post-chemotherapy residual tumour resection is associated with peri-operative mortality and OS [15, 16]. Establishment of second-opinion clinics for TC patients may prevent over- and under-treatment [17].

Genetic changes have been described in patients with TC. A specific genetic marker – an isochromosome of the short arm of chromosome 12 (12p) has been described in all histological types of GCTs [18] and in germ cell neoplasia *in situ* (GCNIS). Alterations in the p53 locus have been identified in 66% of cases of GCNIS [19] and an association between genetic polymorphism in the PTEN tumour suppressor gene and the risk of testicular germ cell tumours (TGCT) has been recently described [20]. A deregulation in the pluripotent programme of foetal germ cells (identified by specific markers, *M2A, C-KIT and OCT4/NANOG*) is likely responsible for the development of GCNIS and germ cell neoplasia. In line with this, genome-wide association studies (GWAS) have revealed several single nucleotide polymorphisms (SNPs) associated with an increased risk of developing TGCT, in particular at 15q21.3 [21]. That said, current genomic studies do not find evidence for a major single high-penetrance TGCT susceptibility gene [22]. There is overlap in the development to seminoma and embryonal carcinoma, as shown by genome-wide expression analysis and detection of alphafetoprotein (AFP) mRNA in some atypical seminomas [23, 24].

Epidemiological risk factors for the development of testicular tumours are components of testicular dysgenesis syndrome (i.e. cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility) [25, 26], familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or GCNIS [18, 25, 27-31]. A recent systematic review confirmed the association between body height and TGCT with an odds ratio (OR) of 1.13 per 5 cm increase in body height [32].

3.2 Pathological classification

The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification [33]:

1. **Germ cell tumours**
   - Germ cell neoplasia *in situ* (GCNIS)
2. **Derived from germ cell neoplasia *in situ***
   - Seminoma
   - Embryonal carcinoma
   - Yolk sac tumour, post-pubertal type
   - Trophoblastic tumours
   - Teratoma, post-pubertal type
   - Teratoma with somatic-type malignancies
   - Mixed germ cell tumours
3. **Germ cell tumours unrelated to GCNIS**
   - Spermatocytic tumour
   - Yolk sac tumour, pre-pubertal type
   - Mixed germ cell tumour, pre-pubertal type
4. **Sex cord/stromal tumours**
   - Leydig cell tumour
     - Malignant Leydig cell tumour
   - Sertoli cell tumour
     - Malignant Sertoli cell tumour
     - Large cell calcifying Sertoli cell tumour
     - Intratubular large cell hyalinising Sertoli cell neoplasia
   - Granulosa cell tumour
     - Adult type
     - Juvenile type

- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
  - Mixed
  - Unclassified
- Tumours containing both germ cell and sex cord/gonadal stromal
  - Gonadoblastoma

5. Miscellaneous non-specific stromal tumours

- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
  - Adenoma
  - Carcinoma
- Tumours of paratesticular structures
  - Adenomatoid tumour
  - Mesothelioma (epithelioid, biphasic)
  - Epididymal tumours
- Cystadenoma of the epididymis
- Papillary cystadenoma
- Adenocarcinoma of the epididymis
- Mesenchymal tumours of the spermatic cord and testicular adnexae

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Diagnostic tools

To determine the presence of macroscopic or occult metastatic disease the half-life kinetics of serum tumour markers, as well as the presence of nodal or visceral metastases, need to be assessed. Consequently, it is mandatory to assess:

- the pre- and post-orchiectomy half-life kinetics of serum tumour markers;
- the status of retroperitoneal and supraclavicular lymph nodes, bone and liver;
- the presence or absence of mediastinal nodal involvement and lung metastases;
- the status of brain and bone in cases of suspicious symptoms or high-risk disease, e.g. poor International Germ Cell Cancer Collaborative Group (IGCCCG) risk group, high human chorionic gonadotropin (hCG) and/or multiple pulmonary metastases.

The minimum mandatory tests are:

- serial blood sampling;
- abdominopelvic and chest computed tomography (CT).

4.2 Serum tumour markers: post-orchiectomy half-life kinetics

The mean serum half-life of AFP and hCG is five to seven days and two to three days, respectively [34]. Tumour markers need to be re-evaluated after orchiectomy to determine half-life kinetics. Marker decline in patients with clinical stage (CS) I disease should be assessed until normalisation has occurred. Markers before the start of chemotherapy are important to classify the patient according to the IGCCCG risk classification [35]. The persistence of elevated serum tumour markers after orchiectomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalisation of marker levels after orchiectomy does not rule out the presence of tumour metastases. During chemotherapy, the markers should decline; persistence has an adverse prognostic value [36, 37]. Slow marker decline in patients with poor prognosis during the first cycle of standard bleomycin, etoposide and cisplatin (BEP) chemotherapy can be used as an indication for early chemotherapy dose intensification [38].

4.3 Retroperitoneal, mediastinal and supraclavicular lymph nodes and viscera

Retroperitoneal and mediastinal lymph nodes are best assessed by CT. The supraclavicular nodes are best assessed by physical examination followed by CT in cases of suspicion.

Abdominopelvic CT offers a sensitivity of 70-80% in determining the state of the retroperitoneal nodes. Its accuracy depends on the size and shape of the nodes; sensitivity and the negative predictive value (NPV) increase using a 3 mm threshold to define metastatic nodes in the landing zones [39]. Those figures decrease slightly in stages I and II [40, 41], with a rate of understaging of 25-30% [42].

Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal

nodal enlargement [43, 44]. Again, the main objections to its routine use are its high cost and limited availability. Nevertheless, MRI can be helpful when abdominopelvic CT or ultrasound (US) are inconclusive [43], when CT is contraindicated because of allergy to contrast media containing iodine, or when the physician or the patient are concerned about radiation dose. Magnetic resonance imaging is an optional test, and there are currently no indications for its systematic use in the staging of TC.

A chest CT is the most sensitive way to evaluate the thorax and mediastinal nodes. This exploration is recommended in all patients with TC as up to 10% of cases can present with small subpleural nodes that are not visible on an X-ray [45]. A CT has high sensitivity, but low specificity [45].

There is no evidence to support the use of FDG-PET in the staging of testis cancer [46, 47]. It is recommended in the follow-up of patients with seminoma with a residual mass larger than 3 cm but should not be performed until eight weeks after completion of the last cycle of chemotherapy, in order to decide on watchful waiting or active treatment [48, 49]. Fluorodeoxyglucose-PET is not recommended in the re-staging of patients with NSGCT after chemotherapy [50].

Other examinations, such as brain or spinal CT, bone scan or liver US, should be performed if there is suspicion of metastases to these organs. A CT or MRI of the brain is advisable in patients with NSGCT, multiple lung metastases and poor-prognosis IGCCG risk group (e.g. high β-hCG values). Table 4.1 shows the recommended tests at staging.

Table 4.1: Recommended tests for staging at diagnosis

Test	Recommendation	Strength rating
Serum tumour markers	Alpha-fetoprotein Human chorionic gonadotrophin (hCG) Lactate dehydrogenase	Strong
Abdominopelvic computed tomography (CT)	All patients	Strong
Chest CT	All patients	Strong
Testis ultrasound (bilateral)	All patients	Strong
Bone scan or magnetic resonance imaging (MRI) columna	In case of symptoms	Strong
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases or high β-hCG values.	Strong
Further investigations		
Fertility investigations: • Total testosterone • Luteinising hormone • Follicle-stimulating hormone • Semen analysis		Weak

4.4 Staging and prognostic classifications

The staging system recommended in these guidelines is the 2016 Tumour, Node, Metastasis (TNM) of the International Union Against Cancer (UICC) (Table 4.2) [33]. This includes:

- determination of the anatomical extent of disease;
- assessment of serum tumour markers, including nadir values of hCG, AFP and lactate dehydrogenase (LDH) after orchiectomy (S category);
- definition of regional nodes;
- N-category modifications related to node size.

Table 4.2: TNM classification for testicular cancer (UICC, 2016, 8th edn. [33]**)**

pT - Primary Tumour[1]			
pTX	Primary tumour cannot be assessed (see note 1)		
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		
N - Regional Lymph Nodes – Clinical			
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 more than 5 nodes positive, none more than 5 cm; or greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour		
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
pN - Regional Lymph Nodes – Pathological			
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 and 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 greatest dimension; or more than 5 nodes positive, none more than 5 cm; or extension of tumour evidence or extranodal extension of tumour		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M - Distant Metastasis			
MX	Distant metastasis cannot be assessed		
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		
S - Serum Tumour Markers			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay.
LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

**AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension [51].*
*** AJCC eighth edition considers the hilar soft tissue invasion as pT2, while the discontinuous tumour in spermatic cord as pM1 [51].*

[1] Except for pTis and 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.

According to the 2009 TNM classification, stage I TC includes the following substages:

Stage grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1-3
Stage II	Any patient/TX	N1-N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0
	Any patient/TX	N1	M0	S1
Stage IIB	Any patient/TX	N2	M0	S0
	Any patient/TX	N2	M0	S1
Stage II	Any patient/TX	N3	M0	S0
	Any patient/TX	N3	M0	S1
Stage III	Any patient/TX	Any N	M1a	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0
	Any patient/TX	Any N	M1a	S1
Stage IIIB	Any patient/TX	N1-N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1-N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S

Stage IA: patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchiectomy serum tumour marker levels within normal limits. Marker decline in patients with CS I disease should be assessed until normalisation.

Stage IB: patients have a more locally invasive primary tumour, but no sign of metastatic disease.

Stage IS: patients have persistently elevated (and usually increasing) serum tumour marker levels after orchiectomy, indicating subclinical metastatic disease (or possibly a second germ cell tumour in the remaining testis).

In large population-based patient series, 75-80% of seminoma patients, and about 55% of patients with NSGCT cancer have stage I disease at diagnosis [52]. True stage IS (persistently elevated or increasing serum marker levels after orchiectomy) is found in about 5% of non-seminoma patients.

In 1997, the IGCCCG defined a prognostic factor-based staging system for metastatic testis tumours based on identification of clinically independent adverse factors. This staging system has been incorporated into the TNM Classification and uses histology, location of the primary tumour, location of metastases and pre-chemotherapy marker levels in serum as prognostic factors to categorise patients into ‘good’, ‘intermediate’ or ‘poor’ prognosis (Table 4.3) [35].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer
(International Germ Cell Cancer Collaborative Group [35])*

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	*All of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma (28% of cases) 5-year PFS 75% 5-year survival 80%	*Any of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as poor prognosis

** Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).*
PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

5. DIAGNOSTIC EVALUATION

5.1 Clinical examination

Testicular cancer usually presents as a painless, unilateral testicular scrotal mass, as a casual US finding, or is revealed by a scrotal trauma [53]. Scrotal pain may be the first symptom in 20% of cases and it is present in up to 27% of patients with TC [53, 54]. Gynaecomastia appears in 7% of cases (more common in non-seminomatous tumours). Back and flank pain due to metastasis is present in about 11% of cases [54].

Diagnosis is delayed in around 10% of cases of TC that mimic orchioepididymitis [54], physical examination reveals the features of the mass and must always be carried out together with a general examination to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. Ultrasound must be performed in any doubtful case. A correct diagnosis must be established in all patients with an intrascrotal mass [55].

5.2 Imaging of the testis

Currently, US is used to confirm the presence of a testicular mass and explore the contralateral testis. Ultrasound sensitivity is almost 100%, and US has an important role in determining whether a mass is intra- or extra-testicular [55]. Ultrasound is an inexpensive test and should be performed even in the presence of clinically evident TC [56].

Ultrasound of the testis should be performed in young men with retroperitoneal or visceral masses and/or elevated serum hCG or AFP, and/or consulting for fertility problems and without a palpable testicular mass [57, 58].

Magnetic resonance imaging of the scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis [59, 60].

5.3 Serum tumour markers at diagnosis

Serum tumour markers are prognostic factors and contribute to diagnosis and staging [61]. The following markers should be determined before, and five to seven days after, orchiectomy:

- alpha-fetoprotein (produced by yolk sac cells);
- hCG (expression of trophoblasts);
- LDH.

Tumour markers are of value for diagnosis (before orchiectomy) as well as for prognosis (after orchiectomy). They are increased in approximately every second patient with TC [53, 62]. Alpha-fetoprotein and hCG are increased in 50-70% and in 40-60% of patients with NSGCT, respectively. About 90% of NSGCT present with a rise in one or both of the markers. Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease [34].

Lactase dehydrogenase is a less specific marker, its concentration being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced TC [34]. Of note, negative marker levels do not exclude the diagnosis of a GCT. Placental alkaline phosphatase (PLAP), is an optional marker in monitoring patients with pure seminoma, but is not recommended in smokers [63].

Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research. There is preliminary evidence that micro-RNAs from two clusters (*miR-371-373* and *miR-302-367*), or a composite panel display, offer higher accuracy in the diagnosis of residual and recurrent GCT than conventional markers. They may be useful in diagnostic, monitoring and prognostication in the future [64, 65].

5.4 Inguinal exploration and orchiectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorisation of the testis within its tunics. Orchiectomy with division of the spermatic cord at the internal inguinal ring must be performed if a malignant tumour is found. If the diagnosis is not clear, a testicular biopsy (and enucleation of the intraparenchymal tumour) is taken for frozen (fresh tissue) section histological examination. Even though only limited data are available, it has been shown that during orchiectomy, a testicular prosthesis can be inserted without increased infectious complications or rejection rates [66].

In cases of life-threatening disseminated disease, life-saving chemotherapy should be given up-front, especially when the clinical picture is very likely TC, and/or tumour markers are increased. Orchiectomy may be delayed until clinical stabilisation occurs or in combination with resection of residual lesions.

5.5 Organ-sparing surgery

Although organ-sparing surgery is not indicated in the presence of non-tumoural contralateral testis, it can be attempted in special cases with all the necessary precautions. In synchronous bilateral TCs, metachronous contralateral tumours, or in a tumour in a solitary testis with normal pre-operative testosterone levels, organ preserving surgery can be performed when tumour volume is less than approximately 30% of the testicular volume and surgical rules are respected. In those cases, the rate of associated GCNIS is high (at least up to 82%) (see Section 5.7).

In cases of undetermined testicular masses (< 1 cm, non-palpable, multiple or of unusual presentation), frozen section examination (FSE) has proven reliable and highly concordant with final histopathology. Frozen section examination may be considered as a selection tool for organ-sparing surgery [67].

5.6 Pathological examination of the testis

Mandatory pathological requirements:

- macroscopic features: side, testis size, maximum tumour size, and macroscopic features of the epididymis, spermatic cord, and tunica vaginalis;

- sampling: a 1 cm^2 section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspected areas;
- at least one proximal and one distal section of spermatic cord plus any suspected area;
- microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2016 [68]:
  - presence or absence of peri-tumoural venous and/or lymphatic invasion;
  - presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion; presence or absence of GCNIS in non-tumour parenchyma;
  - in cases of rete testis invasion (RTI), attention should be paid to distinguishing between pagetoid involvement and stromal invasion [69];
- pT category according to TNM 2016 [33];
- Immunohistochemical studies: in seminoma and mixed GCT, AFP and hCG.

Advisable immunohistochemical markers, in cases of doubt, are:
- in seminoma: cytokeratins (CAM 5.2), PLAP, c-kit;
- in ITGCN: PLAP, c-kit;
- other advisable markers: chromogranin A (Cg A), Ki-67 (MIB-1).

5.7 Germ cell tumours histological markers

Marker	GCNIS	Seminoma	Post-puberal yolk sac tumour	Embryonal Carcinoma	Tropho-blastic Cyto	Tropho-blastic Syncytio	Sperma-tocytic tumour	Pre-puberal yolk sac tumour	Sex cord gonadal stromal tumours
OCT3/4	100%	100%	-	90%	-	-	-	-	-
SALL 4	90%	100%	90%	90%	+	-	50-90% (weak)	100%	-
Glypican3	-	-	100%	8%	100% (irregular)	100% (irregular)	-	-	-
CD30	-	< 10%	< 10%	100%	-	-	-	-	-
AFP	-	-	80%	33%	-	-	-	-	-
β-hCG	-	-	-	-	-	100%	-	-	-
CD117	100%	90/100%	60% (focal)	-	-	-	+/- (Weak)	-	-
PLAP	100%	86/95%	53%	86%	+/-	100%	-	-	-
α-inhibin	-	-	-	-	-	+/-	-	+	Sertoli; 30-50% Leydig; 100%
Calretinin	-	-	-	-	-	-	-	-	100%
AE1/AE3	-	20/36%	+ (focal)	95% (weak)	+/-	+/-	-	-	Sertoli; 64% Leydig; 42%
EMA	-	2%	5%	2%	-	46%	-	-	+/-
CEA	-	-	11%	-	-	25%	-	-	-
GATA 3	-	-	100%	40% (focal)	+	100%	-	-	-
hPL	-	-	-	-	-	+	-	-	-
CgA	-	-	-	-	-	-	-	-	Sertoli; 82% Leydig; 92%
Synapto	-	-	-	-	-	-	-	-	Sertoli; 45% Leydig; 70%
p63	-	-	-	-	+	-	-	-	-

OCT3/4 = homeodomain transcription factor of the POU family; SALL 4 = transcription factor encoded by a member of the Spalt-like (SALL) gene family; Glypican 3 (GPC3) = a membrane-bound heparin sulphate proteoglycan; CD30 = immunohistochemical marker; AFP = alpha-fetoprotein; hCG = human chorionic

gonadotrophin; CD117(c-KIT) = immunohistochemical marker; PLAP = placental alkaline phosphatase; α-inhibin = peptide hormone; Calretinin = 29 kD calcium-binding protein; AE1/AE3 = cytokeratins; EMA = epithelial membrane antigen; CEA = carcinoembryonic antigen; GATA 3 = transcription factor; hPL = human placenta lactogen; CgA = Chromogranin A; Synapto = neuroendocrine markers; p63 = transformation-related protein 63.

5.8 Diagnosis and treatment of germ cell neoplasia *in situ* (GCNIS)

Contralateral biopsy has been advocated to rule out the presence of GCNIS [70]. Although routine policy in some countries [71], the low incidence of GCNIS and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) [72, 73], the morbidity of GCNIS treatment, and the fact that most metachronous tumours are at a low stage at presentation, make it controversial to recommend a systematic contralateral biopsy in all patients [74, 75].

It is still difficult to reach a consensus on whether the existence of contralateral GCNIS must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk for contralateral GCNIS, i.e. testicular volume < 12 mL, a history of cryptorchidism or poor spermatogenesis (Johnson Score 1-3). A contralateral biopsy is not necessary in patients older than 40 years without risk factors [39, 76-79]. A double biopsy increases sensitivity [78]. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy [80].

Once GCNIS is diagnosed, local radiotherapy (RT) (16-20 Gy in fractions of 2 Gy) is the treatment of choice in the case of a solitary testis. Testicular RT in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [74, 81, 82]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [78]. Chemotherapy is significantly less effective and the cure rates are dose-dependent [83].

If GCNIS is diagnosed and the contralateral testis is healthy, the options for management are orchiectomy or close observation (with a five-year risk of developing TC of 50%) [84].

5.9 Screening

There are no high level evidence studies proving the advantages of screening programmes [85], but it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, and especially in patients with a family history of testis cancer, family members and the patient should be informed about the importance of physical self-examination [86].

5.10 Recommendations for the diagnosis and staging of testicular cancer

Recommendations	Strength rating
Discuss sperm banking with all men prior to starting treatment for testicular cancer (See chapter 7.1.).	Strong
Perform testicular ultrasound in all patients with suspicion of testicular cancer.	Strong
Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralateral germ cell neoplasia *in situ*.	Strong
Perform orchiectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, start chemotherapy before orchiectomy.	Strong
Perform serum determination of tumour markers (alpha-fetoprotein, human chorionic gonadotrophin, and lactate dehydrogenase), before, five to seven days after orchiectomy, and until normalised, for staging and prognostic reasons.	Strong
Assess the state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera in testicular cancer.	Strong
Advise patients with a familiar history of testis cancer, as well as their family members, to perform regular testicular self-examination.	Strong

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in clinical stage I

Retrospectively, for seminoma stage I, tumour size (> 4 cm) and stromal invasion of the rete testis have been identified as predictors for relapse in a pooled analysis [87]. The absence of both factors indicated a low recurrence rate (6%) [88]. Although the original model was not found to apply in a further retrospective report [89], some prospective series [90-92] sustain the prognostic importance of tumour size and stromal invasion of the rete testis. Two systematic reviews assessed the prognostic value of these risk factors [93, 94]. While tumour size (continuous or dichotomised) and rete testis invasion are associated with a higher risk of relapse, both systematic reviews stress the low quality of the studies included and that the level of evidence is too low to advocate the use of these pathological risk factors to drive the choice of treatment [93, 94]. With modern imaging, CS I patients with seminoma face a risk of occult metastasis, independent of risk factors, of < 15% in all recently published series.

For non-seminoma stage I, vascular invasion of the primary tumour in blood or lymphatic vessels is the most important predictor of occult metastatic disease. The proliferation rate and the percentage of embryonal carcinoma are additional predictors that improve upon the positive- and negative predictive value of vascular invasion [95]. Whether the absence of teratoma (as qualitative data, as opposed to the more subjective assessment of percentage of embryonal carcinoma) can independently complement vascular invasion as a predictive factor of relapse requires validation [96].

The significant prognostic pathological risk factors for stage I TC are listed in Table 6.1.

Table 6.1: Risk factors for occult metastatic disease in stage I testicular cancer

Pathological (for stage I)		
	For seminoma	**For non-seminoma**
Histopathological type	• Tumour size (> 4 cm) • Invasion of the rete testis	• Vascular/lymphatic in or peri-tumoural invasion • Proliferation rate > 70% • Percentage of embryonal carcinoma > 50%

7. DISEASE MANAGEMENT

7.1 Impact on fertility and fertility-associated issues

Sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TCs prior to orchiectomy [97]. Furthermore, chemotherapy and RT can additionally impair fertility; however, long-term infertility is rare after RT and dose-cumulative-dependant after chemotherapy [98, 99]. In patients in the reproductive age group, pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) should be performed, and semen analysis and cryopreservation should be offered as this is the most cost-effective strategy for fertility preservation when several assisted reproductive techniques are compared [100] (Table 5.10). If cryopreservation is desired, it should preferably be performed before orchiectomy, but in any case prior to chemotherapy or RT [81, 98-102]. In cases of bilateral orchiectomy or low testosterone levels after treatment of GCNIS, life-long testosterone supplementation is necessary [103].

Patients with unilateral or bilateral orchiectomy should be offered a testicular prosthesis [104]. For more detailed information, the reader is referred to the EAU Male Infertility Guidelines [105].

7.2 Stage I Germ cell tumours

7.2.1 Seminoma Stage I

After modern staging procedures, less than 15% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone [89, 92, 106, 107].

The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.2.1.1 Surveillance

Several prospective non-randomised surveillance studies have been conducted during the past decade, the largest study from Canada with > 1,500 patients [108]. Previous analyses from four studies showed an actuarial five-year relapse-free rate of 82.3%. The Princess Margaret Hospital series (n = 1,559) showed an overall relapse rate in unselected patients of 16.8%. The actuarial relapse rate is in the order of 15-20% at five years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes [109].

In patients with low risk (tumour size < 4 cm and no stromal rete testis invasion), the recurrence under surveillance is as low as 6% [91]. Chemotherapy, according to the IGCCCG classification, is a possible treatment for seminoma relapse under surveillance. However, 70% of patients with relapse are suitable for treatment with RT alone because of small volume disease at the time of recurrence. Patients who relapse after salvage RT can be effectively treated with chemotherapy [110]. The combination of carboplatin chemotherapy and modern RT for treatment of low-stage seminoma relapse (IIA/IIB) is under investigation.

The overall cancer-specific survival (CSS) rate, reported under surveillance performed by experienced centres, is 97-100% for seminoma stage I [109, 110]. The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes.

7.2.1.2 Adjuvant chemotherapy

A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC), which compared one cycle of carboplatin area under curve (AUC) 7 with adjuvant RT, did not show a significant difference with regard to recurrence rate, time to recurrence and survival after a median follow-up of four years [111-113]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to RT or surveillance in stage I seminoma [109, 111-113]. Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1-3% [88, 114]. Long-term data report the recurrence rate after three years following adjuvant carboplatin as 15%. Not all of these patients were cured [115].

7.2.1.3 Adjuvant radiotherapy and risk-adapted treatment

Seminoma cells are extremely radiosensitive. Adjuvant RT to a para-aortic (PA) field or to a PA and ipsilateral field (PA and ipsilateral iliac nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to 1-3% [116-118]. Adjuvant irradiation of supra-diaphragmatic lymph nodes is not indicated.

With regard to the irradiation dose, a large MRC RCT of 20 Gy vs. 30 Gy PA radiation in stage I seminoma showed non-inferiority in terms of recurrence rates [117]. The rate of severe radiation induced long-term toxicity is less than 2%. Moderate chronic gastrointestinal (GI) side-effects are seen in about 5% of patients, and moderate acute GI toxicity in about 60% [116]. The main concern surrounding adjuvant RT is the increased risk of radiation-induced second non-germ cell malignancies [119-122].

A scrotal shield should be considered during adjuvant RT in order to prevent scattered radiation toxicity in the contralateral testis [119].

7.2.1.4 Risk-adapted treatment

Using tumour size > 4 cm and stromal rete testis invasion, patients with seminoma stage I may be subdivided into low- and high-risk groups for occult metastatic disease. Patients with and without both risk factors have a 32% and 12% risk of occult disease, respectively. These risk factors were introduced through an analysis of retrospective trials [87], and then confirmed in prospective studies [91, 92, 123]. A prospective trial based on one or no risk factors, showed the feasibility of a risk-adapted approach; the group without risk factors were managed with surveillance, whilst the group with both risk factors received two courses of carboplatin, AUC 7 [123]. In patients with two risk factors, adjuvant carboplatin reduces the risk of relapse by about 60% [92]. Early data with limited follow-up indicated that patients without either risk factor have a very low risk, 6-15%, of relapse at five years. Patients in the high-risk group treated with two courses of carboplatin experienced a 1.4%-3.2% relapse rate at mean follow-up of 34 months [94, 123]. The level of evidence supporting risk-adapted treatment based on the existence of pathological risk factors is low [93].

7.2.1.5 *Recommendations for the treatment of stage I seminoma*

Recommendations	Strength rating
Fully inform the patient about all available management options, including surveillance or adjuvant chemotherapy after orchiectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance as a management option if facilities are available and the patient is compliant.	Strong
Offer one course at area under curve 7 (AUC), if carboplatin chemotherapy is considered.	Strong
Do not perform adjuvant treatment in patients at very low risk (no risk factors).	Strong
Do not perform radiotherapy as adjuvant treatment.	Strong

7.2.2 ***NSGCT clinical stage I***

Up to 30% of NSGCT patients with CS1 disease have subclinical metastases and will relapse during surveillance. The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.2.2.1 *Surveillance*

Improvements in clinical staging and follow-up methods, and the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of close surveillance only after orchiectomy in CS1 NSGCT patients. The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of relapses occurring during the first twelve months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later [124, 125]. Approximately 35% of relapsing patients have normal levels of serum tumour markers at relapse, with 60% of relapses occurring in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

The somewhat lower relapse rates reported from surveillance studies compared with some series of patients staged by retroperitoneal lymph node dissection (RPLND) [126] can be explained by the fact that some patients (presumably at higher risk) are excluded once surveillance is advised. Based on the overall CSS data, surveillance within an experienced surveillance programme can safely be offered to patients with non-risk stratified CS1 non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [127, 128].

7.2.2.2 *Adjuvant chemotherapy*

Patients with CS1 NSGCT have a 14-48% risk of recurrence within two years after orchiectomy. Adjuvant chemotherapy with two courses of BEP was introduced in 1996 by a prospective MRC trial [129]. Subsequently, adjuvant chemotherapy was mainly given in high-risk patients (vascular invasion present) [129-131]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [129], a relapse rate of only 2.7% was reported, with very little long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity [132]. However, the very-long term (> 20 years) side effects of adjuvant chemotherapy in this setting are currently unknown, especially the long-term cardiovascular effects of chemotherapy [133]. This should be taken into consideration during decision-making.

In 2008, a RCT of nerve-sparing RPLND or one course of BEP as adjuvant treatment in CS1 NSGCT without risk-adaption reported that adjuvant chemotherapy significantly increased the two-year recurrence-free survival rate to 99.41% (CI: 95.87%, 99.92%) as opposed to surgery, which had a two-year recurrence-free survival rate of 92.37% (CI: 87.21%, 95.5%) [134]. The difference was 7.04%, (CI: 2.52%, 11.56%) and, therefore, the main endpoint of the trial was reached. The hazard ratio (HR) to experience a tumour recurrence with surgery as opposed to chemotherapy was 7.937, (CI: 1.808, 34.48). Of the 174 patients who received one course of BEP, 43% had high-risk features (> pT1) [134].

A community-based prospective study recommended one course of BEP in lymphovascular invasion (LVI)+ patients, while LVI-patients chose between surveillance and BEP x 1 [135]. The relapse-rate of the 490 patients who received BEP x 1 at five years was 3.2% for LVI+ patients and 1.6% for LVI- patients. After a median follow-up of 8.1 years the relapse rate was 2.3%, 3.4% and 1.3% for all, LVI+, and LVI-, respectively [136]. These numbers imply that > 90% of relapses were prevented by adjuvant chemotherapy and, importantly, no

relapses were observed later than 3.3 years. Reduction from two to one cycle of BEP considerably improves the risk-benefit ratio of adjuvant chemotherapy.

In addition, it is important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy [137]. Until now, only a limited number of patients with long-term follow-up and toxicity data have been reported on [138].

The results of cost analyses comparing surveillance, RPLND and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity and costs related to follow-up procedures [139]. With low frequency follow-up CTs (a surveillance strategy which has been proven to be effective in non-seminoma CS1), the costs of follow-up can be considerably reduced [140].

7.2.2.3 Risk-adapted treatment

Risk-adapted treatment is an alternative to surveillance for all patients with CS1 NSGCT. Risk-adapted treatment is based on the risk factor of vascular invasion. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is a rational option. Similar survival rates and a final cure rate close to 100%, with all available treatment options using the risk-stratifying approach, have been reported by several studies [129-131, 135, 136, 141-143].

If the risk-adapted policy is applied, patients with vascular invasion are recommended to undergo adjuvant chemotherapy and patients with absent vascular invasion are recommended a surveillance strategy. In the past, two cycles of BEP have been recommended for adjuvant treatment. In view of the low rates of recurrence (2-3%) and equivalent CSS rates, including salvage strategies in large prospective trials with sufficient follow-up, one cycle of BEP is now recommended as adjuvant chemotherapy in patients with vascular invasion.

In cases of relapse after BEP x 1 in marker negative patients, RPLND should be considered as the relapse may be teratoma. If markers are positive three courses of BEP are recommended. However, only limited evidence exists, which does not support a specific salvage regimen.

7.2.2.4 Retroperitoneal lymph node dissection

In view of the high CSS rates of surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary diagnostic RPLND has diminished. A randomised phase III trial compared RPLND to BEP x 1 as adjuvant treatment, with a 7% difference in favour of chemotherapy. One course of BEP showed a significantly lower recurrence rate as compared to surgery [134]. No clinically relevant differences in quality of life (QoL) were detected [144].

When RPLND is performed in a multicentre setting, higher rates of in-field recurrences and complications were reported [134, 145]. Therefore, nerve-sparing RPLND, if indicated, should be performed by an experienced surgeon in specialised centres.

About 18-30% of patients are found to have retroperitoneal lymph node metastases on RPLND, corresponding to pathological stage II (PS2) disease [145, 146]. If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of patients relapse at distant sites [95, 146] with recent series reporting lower figures in the rate of pN+ cases and of relapses [147]. If metastases are present and not treated with adjuvant chemotherapy, recurrence will occur in approximately 31% of patients [146].

The presence of vascular invasion, predominant embryonal carcinoma, pT category as well as a high number of extranodal extensions in metastatic nodes may be associated with an increased risk of recurrence in PS2 cases without adjuvant chemotherapy. As yet, the clinical significance of these further parameters remains limited and not applicable in clinical practice [146, 148].

The follow-up after RPLND is simpler and less costly than that carried out during post-orchiectomy surveillance because of the reduced need for abdominal CT scans [149]. If there is an indication to perform a staging RPLND, a laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimal-invasive approach cannot be recommended as the standard approach outside of a specialised laparoscopic centre [147].

7.2.2.5 Recommendations for the treatment of stage I non-seminomatous germ cell tumour

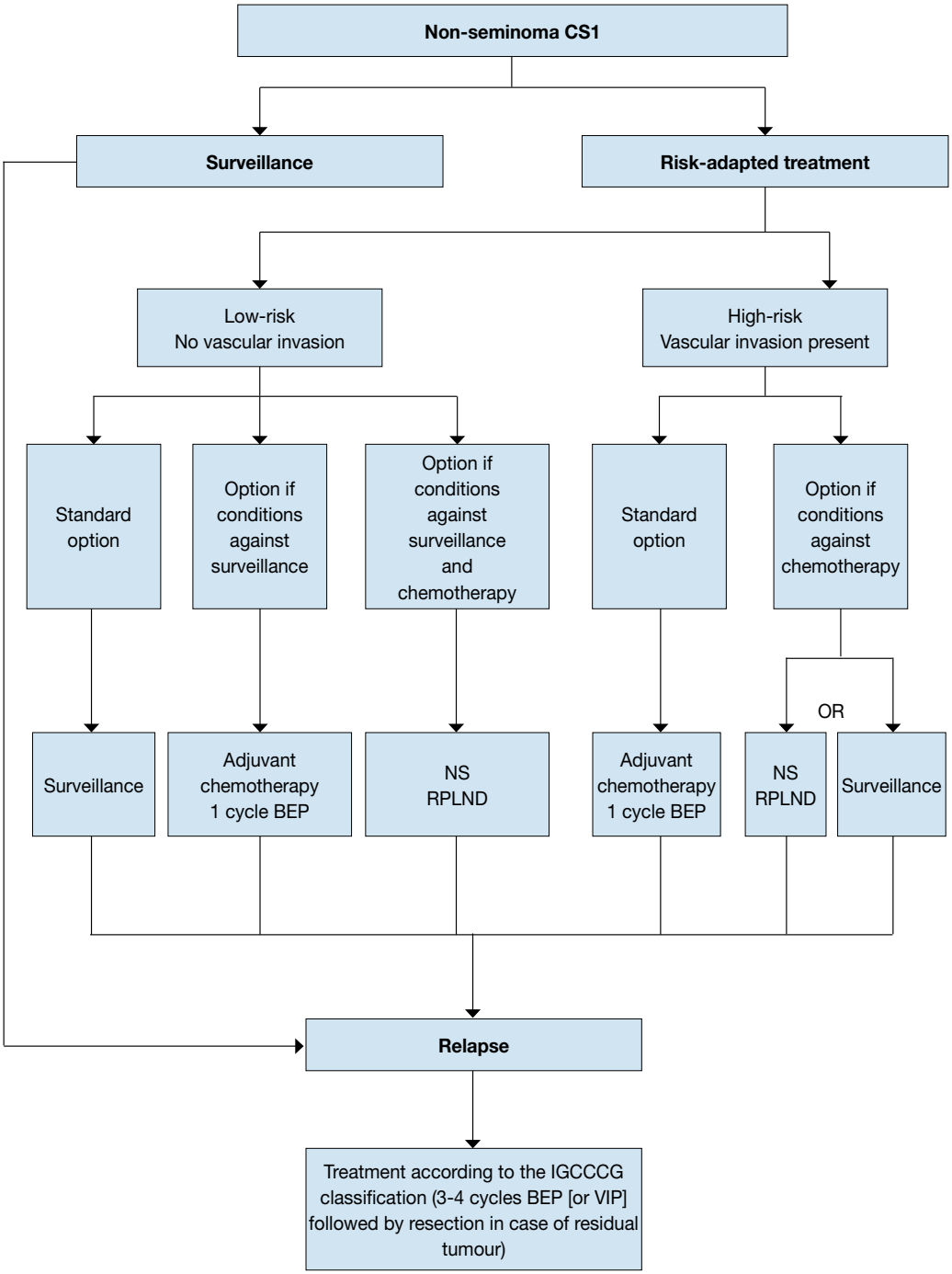
Recommendations	Strength rating
Inform patients with stage I non-seminomatous germ cell tumour (NSGCT) about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection [RPLND]) including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
In patients with stage I NSGCT, offer surveillance or risk-adapted treatment based on vascular invasion (see 7.2.2.6. below).	Strong
If patients are not willing to undergo surveillance, offer one course of cisplatin, etoposide, bleomycin (BEP) as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	Strong
In patients with marker-positive recurrent and/or progressing lesion during surveillance, perform salvage treatment consisting of three or four courses of BEP chemotherapy according to the International Germ Cell Cancer Collaborative Group classification, followed by post-chemotherapy RPLND, if necessary.	Strong

7.2.2.6 Risk-adapted treatment for clinical stage I based on vascular invasion

Recommendations	Strength rating
Stage IA (pT1, no vascular invasion): low risk	
Offer surveillance if the patient is willing and able to comply.	Strong
In low-risk patients not willing (or unsuitable) to undergo surveillance, offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP).	Strong
Stage IB (pT2-pT4): high risk	
Offer primary chemotherapy with one course of BEP, or surveillance.	Strong
Inform patients having adjuvant chemotherapy about the advantages and disadvantages of one vs. two cycles of BEP.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong
Offer nerve-sparing retroperitoneal lymph node dissection to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong

Figure 1 provides a treatment algorithm for patients with NSGCT stage I.

Figure 1: Risk-adapted treatment in patients with CS1 non-seminoma NSGCT [150]*



**Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.*
BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; NS = nerve-sparing; NSGCT = non-seminomatous germ cell tumour; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

7.3 Metastatic germ cell tumours

The first-line treatment of metastatic GCTs depends on:

- the histology of the primary tumour;
- prognostic groups as defined by the IGCCCG based on 5,202 non-seminoma and 660 seminoma cases (Table 4.3) [35];
- marker decline during the first cycle of chemotherapy in “poor-prognosis” patients.

In relapsed patients a new prognostic score has been developed including response to first-line therapy which can be used to estimate patient outcome following salvage chemotherapy (see 7.3.3.).

7.3.1 ***CS1S with (persistently) elevated serum tumour markers***

Serum tumour markers should be followed closely until levels fall into the reference values according to the expected half-life values for AFP and hCG. The clinical significance of persistently elevated LDH after orchiectomy in stage I disease is unclear. If the marker level for AFP or HCG increases after orchiectomy, the patient has residual disease. An US examination of the contralateral testicle must be performed. In case of NSGCT where RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum [151]. The treatment of true CS1S NSGT patients is still controversial. They may be treated with chemotherapy and with follow-up as for CS1B patients (high risk, see below) after primary chemotherapy [152], or by RPLND [140].

A population-based study reported on persistently elevated LDH or β-hCG in 19% and 15% of stage I seminoma patients, respectively. These patients frequently had a more advanced T stage, but both CSS and OS did not differ from stage IA/B patients, independent of treatment [153].

In all patients with GCTs and rising markers only after orchidectomy, repeated imaging to detect metastasis is justified in order to individually tailor treatment.

7.3.2 ***Metastatic disease (stage IIA/B)***

7.3.2.1 Stage IIA/B seminoma

Slightly enlarged retroperitoneal lymph nodes < 2 cm in patients without elevated tumour markers offer a diagnostic problem. These lymph nodes may be benign or represent metastases. An observation period of eight weeks with a second staging is recommended unless a biopsy verifies metastatic disease. Treatment should not be initiated unless metastatic disease is unequivocal, (e.g. growth or positive biopsy).

Specific trials (e.g. including RPLND or involved field radiation combined with a single course of carboplatin chemotherapy) are addressing the role of treatment options with potentially lower toxicity compared to either RT or chemotherapy with three cycles of BEP.

Until recently, the standard treatment for stage IIA/B seminoma has been RT with reported relapse rates of 9-24% [154, 155]. Accumulating data on long-term morbidity, such as increased risk of cardiovascular events and increased risk of second malignancies following RT has led to concern. One study with a follow-up of nineteen years reported sevenfold higher all-cause mortality rates than mortality due to seminoma. [156]. Most reports refer to patients irradiated with larger target volumes and higher doses but there are also more recent studies reporting on patients treated with more modern RT [157]. The radiation dose recommended in stage IIA and IIB is 30 Gy and 36 Gy, respectively. The standard radiation field compared with stage I is extended from the PA region to the ipsilateral iliac field. In stage IIB, the lateral borders should include the metastatic lymph nodes with a safety margin of 1.0-1.5 cm. This technique yields relapse-free survival rates in stage IIA and IIB of 92% and 90%, respectively [154, 155]. Conversely, dose reduction to 27 Gy has been associated with 11% of relapses in stage IIA patients [110, 157].

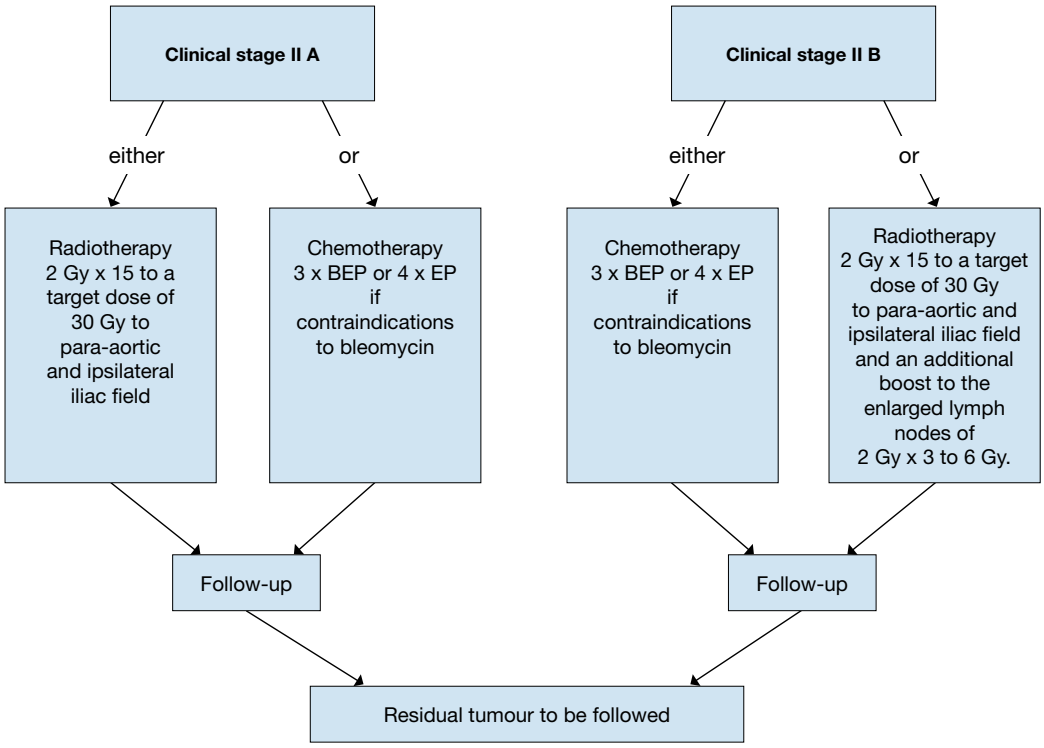
In patients with stage IIA/B seminoma, chemotherapy is an alternative to RT. In this case three courses of BEP or four courses of etoposide and cisplatin (EP), in case of contraindications to bleomycin, should be administered. There are no randomised studies comparing RT vs. chemotherapy. A population based study from the USA, showed that RT is associated with a significant lower all-cause mortality than chemotherapy in stage IIA seminoma (HR 13.3; $p < .01$) [158].

However, a recent meta-analysis of thirteen high-quality studies comparing efficacy and toxicity of RT and chemotherapy in stage IIA and IIB patients [159] shows that RT and chemotherapy appeared to be similarly effective in both stages, with a non-significant trend toward a greater efficacy of chemotherapy (HR: 2.17) in stage IIB seminoma.

Acute toxicity was almost exclusively reported following chemotherapy, while long-term toxicity was more frequent following RT, mainly represented by bowel toxicity and by a higher occurrence of second cancers, almost all occurring in the irradiated field. A recent population-based study [122] did not show a significantly increased risk of second malignancies in stage IIA seminoma patients undergoing RT.

Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease [160].

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B



BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.3.2.2 Stage IIA/B non-seminoma

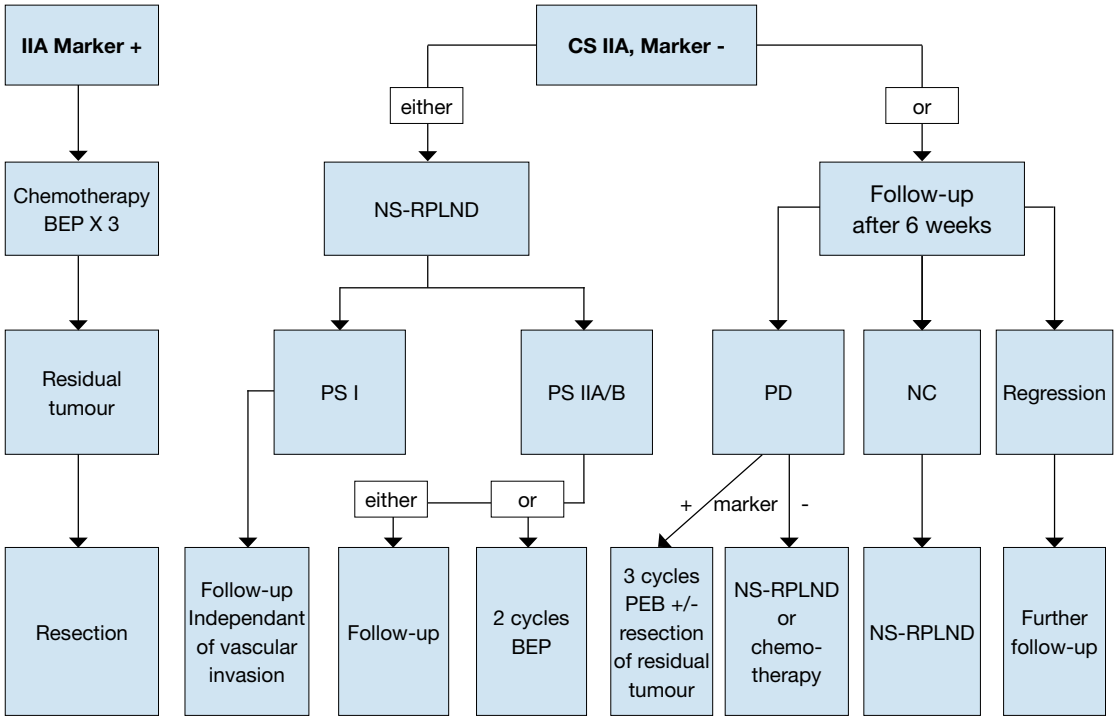
There is a general consensus that treatment should start with initial chemotherapy in all advanced cases of NSGCT except for stage IIA NSGCT disease and pure teratoma without elevated tumour markers, which can be managed by primary RPLND or surveillance to clarify stage [139, 161].

If surveillance is chosen, one follow-up evaluation after six weeks is indicated to document whether the lesion is growing, remaining stable or shrinking. A shrinking lesion is probably non-malignant in origin and should be observed further. A stable or growing lesion indicates either teratoma or an undifferentiated malignant tumour. If the lesion is growing without a corresponding increase in the tumour markers AFP or β-hCG, teratoma is suspected. In such cases "nerve-sparing" RPLND represents the first treatment option which should be performed by an experienced surgeon [161]. Patients with a growing lesion and a concomitant increase in the tumour markers AFP or β-hCG require primary chemotherapy according to the treatment algorithm for patients with metastatic disease and the IGCCCG recommendations (Figure 2). A CT- or US-guided biopsy, if technically possible, may represent an alternative to surveillance strategy in stage IIA non-seminoma patients.

When a marker negative stage IIA/B relapse is diagnosed two or more years following initial diagnosis, a CT- or US-guided biopsy should be carried out to confirm the diagnosis of GCT relapse. There is insufficient published data on PET scans in this situation to provide recommendations.

Primary chemotherapy and primary 'nerve-sparing' RPLND are comparable options in terms of outcome, but early and long-term side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice [162]. In case of PS-IIA or B, patients can be followed or receive two cycles of BEP. The cure rate with either approach will be close to 98% [163-165].

Figure 3: Treatment options in patients with non-seminoma clinical stage IIA



BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

*7.3.3 **Metastatic disease (stage IIC and III)***

7.3.3.1 Primary chemotherapy

7.3.3.1.1 Good prognosis risk group - seminomatous germ cell tumour

For metastatic seminoma, only very limited data are available from RCTs and they indicate that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [166]. Recent data indicate that EP x 4 results in cure in almost all cases of good-prognosis SGCTs [167]. Standard treatment in good-prognosis seminoma should therefore be, BEP x 3 or EP x 4. In the case of contraindications to bleomycin, EP x 4 should be given [168]. Post-chemotherapy masses should be managed as described in Section 7.5.2.

7.3.3.1.2 Intermediate prognosis risk group - seminomatous germ cell tumour

For patients with intermediate-risk seminoma, BEP x 4 or etoposide, cisplatin, ifosfamide (VIP) (in the case of contraindications to bleomycin) are recommended options, although no RCT has focused specifically on this group of rare patients [169]. A risk-adapted approach with EP x 4 for patients with good prognosis and VIP x 4 for patients with intermediate-prognosis metastatic seminoma yielded an OS of 99% and 87% for good- and intermediate-prognosis patients, respectively [167].

7.3.3.1.3 Good prognosis risk group - non-seminomatous germ cell tumour

For non-seminoma, the primary treatment of choice for metastatic disease in patients with good-prognosis disease, according to the IGCCCG risk classification, is BEP x 3 (Table 7.1). This regimen was proven superior to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease [170, 171]. While data support a three-day regimen of administering combination chemotherapy to be equally effective as a five-day regimen, this is associated with increased toxicity when four cycles are used [172], thus the five-day BEP regimen is recommended.

Table 7.1: cisplatin, etoposide, bleomycin (BEP) regimen (interval 21 days)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m^2	Days 1-5*
Etoposide	100 mg/m^2	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

**Plus hydration.*

In selected cases where bleomycin is contraindicated, EP x 4 can be given [171]. A RCT from the French Groupe d'Etude des Tumeurs Genito-Urinaires (GETUG) suggested that when BEP is used in this setting the mortality rate was half that of EP, although the difference did not reach statistical significance [173]. Furthermore, the incidence of active cancer in the retroperitoneal specimen at post-chemotherapy RPLND was significantly higher in patients who received EP x 4 as compared to BEP x 3 (31.9% vs. 7.8%, p. < 0.0.01) [174, 175]. The risk of requiring post-RPLND adjuvant chemotherapy could be higher after EP x 4 which could therefore offset the hoped-for less toxic treatment.

Higher age is an adverse factor for the efficacy of BEP x 3 [176]. A randomised study using 72H-infusional versus bolus bleomycin in order to reduce pulmonary toxicity did not show any significant difference in efficacy or in pulmonary side effects [177].

Therapy should be given without reduction of the doses at 21-day intervals; delaying the following chemotherapy cycle is justified only in cases of fever with granulocytopenia < 1,000/mm^3 or thrombocytopenia < 100,000/IU. Neutropenia without fever is not by itself a reason to delay the next cycle. As GCS-F (Granulocyte colony-stimulating factor) lowers the risk of neutropenic sepsis, one may consider giving it up-front. However, GCS-F should at least be given if infectious complications have occurred during or after chemotherapy, or if treatment interval was delayed due to myelotoxicity [178].

7.3.3.1.4 Intermediate prognosis risk group - non-seminomatous germ cell tumour

The 'intermediate-prognosis' group in the IGCCCG has been defined as patients with a five-year survival rate of about 80%. The available data support BEP x 4 as standard treatment [179, 180]. A RCT comparing BEP x 4 to BEP x 4 with the addition of paclitaxel (T-BEP) showed no significant improvement in OS [181]. The overall toxicity with T-BEP was higher than with BEP; therefore, it cannot be recommended as a standard approach.

Patients with intermediate prognosis treated in recent years (after 1997) are more likely to reach a five year survival of close to 90% [182].

7.3.3.1.5 Poor prognosis risk group - non-seminomatous germ cell tumour

For patients with a 'poor-prognosis' non-seminoma as defined by the IGCCCG, standard treatment consists of BEP x 4. Four cycles of cisplatin, etoposide and ifosfamide (PEI) have the same effect, but are more myelotoxic [183, 184]. The five-year PFS is between 45% and 50%. Four RCTs have shown no advantage in OS for high-dose chemotherapy in the overall 'poor-prognosis' patients group [36, 185-187]. However, patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [36, 37]. An online calculator is available at https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html. Recently, an international randomised phase III trial (GETUG 13) conducted in 263 patients with IGCCCG poor-risk NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS, but not OS in patients with an early unfavourable tumour marker decline [38]. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 should be switched to a more intensive chemotherapy regimen [188, 189]. Further prospective trials/registries are planned to validate this approach.

Additional patient groups that may benefit form up-front dose intensification are those with mediastinal primary non-seminoma and patients with brain metastases at initial diagnosis [190, 191].

Since a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [37, 192], poor-prognosis patients should still be treated in ongoing prospective trials or registries, whenever possible. Patients meeting 'poor-prognosis' criteria should be transferred to a reference centre as a better outcome was reported for intermediate- and poor-prognosis patients who had been treated within a clinical trial in a high volume centre [14, 167]. There are no general recommendations for treatment modifications for patients with a poor general condition (Karnofsky < 50%) or extended liver infiltration (> 50%), but two small reports indicate that a first cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcome. However, the number of subsequent cycles of full-dose therapy should not be reduced after a first low-dose induction cycle [193, 194].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome:

adapting the doses of the BEP regimen in the first cycle of chemotherapy (only three days of EP without bleomycin) has been suggested to reduce the risk of early death in this setting [193]. Management of patients with advanced disease in high-volume centres is associated with improved survival and is consequently recommended [195].

7.4 Restaging and further treatment

*7.4.1 **Restaging***

Restaging is performed by imaging investigations and re-evaluation of tumour markers. Upon marker decline and stable or regressive tumour manifestation, chemotherapy will be completed (three or four cycles, depending on the initial stage) [179, 196, 197]. In the case of marker decline, but growing metastases, resection of the tumour is obligatory after termination of induction therapy, other than in an emergency, according to local tumour growth [198].

Patients with clear upfront progression (primary cisplatin refractory) should be switched to experimental new drug trials [199]. Patients with slow marker decline after the first one to two cycles of chemotherapy are candidates for dose intensification (see section 7.4.4.). Patients with a low-level hCG marker plateau post-treatment should be observed to see whether complete normalisation occurs. In patients with a low plateau serum AFP level after chemotherapy, surgery of residual masses should be performed, with post-surgery AFP monitoring. Salvage chemotherapy is indicated for documented marker rise only [200, 201].

*7.4.2 **Residual tumour resection***

7.4.2.1 Seminoma

A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers [202-205].

Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled > two months after chemotherapy. In patients with residuals of > 3 cm, FDG-PET should be performed in order to gain more information on the viability of these residuals. In patients with residuals of < 3 cm, the use of FDG-PET is optional [48].

In the case of a post-chemotherapy mass that is still positive at reclassification FDG-PET with no volume increase, a second FDG-PET should be performed six weeks later. Alternatively, a biopsy should be taken to ascertain persistent disease. In these cases, as well as in those with progressive disease (i.e. a growing mass which up-takes contrast medium at CT scans or radionuclide tracer at FDG-PET), salvage therapy is indicated (usually chemotherapy or RT) [206-208]. However, a recent publication shows a low PPV for vital tumours in residual lesions (most of them > 3 cm) after chemotherapy in metastatic seminoma (11 to 38% depending on subgroups). Thus, at present, caution is recommended when positive PET lesions alone are driving clinical decisions [209].

Patients with persistent and progressing hCG elevation after first-line chemotherapy should immediately proceed with salvage chemotherapy. Progressing patients without hCG progression should undergo histological verification (e.g. by biopsy or mini-invasive or open surgery) before salvage chemotherapy is given.

Retroperitoneal lymph node dissection is rarely indicated. In cases in which RPLND is indicated, this should be performed in referral centres, as residuals from seminoma may be difficult to remove due to intense fibrosis [207]. Ejaculation may be preserved in these cases [210].

7.4.2.2 Non-seminoma

Following first-line BEP chemotherapy, only 6-10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue [211]. Fluorodeoxyglucose-positron emission tomography is not indicated to re-stage patients after chemotherapy. In cases of complete remission after first-line chemotherapy (no visible tumour), tumour resection is not indicated [212, 213]. So far no diagnostic or risk-calculator can definitely predict histology of residual masses. External validation of new models is still pending [214]. Residual tumour resection is mandatory in all patients with a residual mass > 1 cm at cross-sectional CT imaging [215-218].

The role of surgery is debated in patients with retroperitoneal. Residual lesions < 1 cm. There is still a risk of residual cancer or teratoma, although the vast majority of patients (> 70%) harbour fibro-necrotic tissue [219]. Proponents of post-chemotherapy RPLND for all patients refer to the fact that both teratoma and vital malignant GCTs are still found after radiologic complete remission in lesions < 10 mm [220]. The alternative is to put patients with residual disease < 1 cm on an observation protocol based on recurrence data of 6-9% depending on the time of follow-up [212, 213]. In the series with a longer observation of 15.5 years, twelve of

141 patients (9%) relapsed after having achieved a complete response after primary treatment [213], but eight of the twelve relapsing patients were cured. Therefore, patients treated with first-line chemotherapy should be informed about this life-long risk of recurrence in the order of 10% before consenting to observe residual lesions < 1 cm. Patients after salvage chemotherapy or high-dose chemotherapy in first or subsequent salvage situations harbour vital tumour at a much higher rate [221]. Therefore, there is an indication to perform surgery in salvage patients even with residual disease < 1 cm [212, 213].

When surgery is indicated, all areas of primary metastatic sites must be completely resected within two to six weeks of completion of chemotherapy. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that template resections with unilateral preservation of nerves in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients. The mere resection of the residual tumour (so called lumpectomy) should not be performed [213, 219, 222-225].

Laparoscopic RPLND may yield comparable outcomes to the open procedure in elected cases with low residual disease and in very experienced hands, but it is not recommended outside a specialised laparoscopic centre with specific expertise in TC. In that setting, up to 30% of post-chemotherapy RPLND may be performed via a laparoscopic approach [226-228].

*7.4.3 **Timing of surgery in the case of multiple sites***

In general, residual surgery should start at the location with the highest volume of residual disease. The histology may diverge in different organ sites [215]. In cases of retroperitoneal and lung residual masses, the presence of fibro-necrotic tissue in the retroperitoneum is associated with a probability as high as 90% that lung masses contain the same histology [229].

Resection of contralateral pulmonary lesions is not mandatory in cases where pathologic examination of the lesions from the first lung show complete necrosis. However, disconcordant histology between both lungs may occur in up to 20% of patients [230, 231].

7.4.3.1 Quality and intensity of surgery

Post-chemotherapy surgery is always demanding. Most of the time, post-chemotherapy RPLND does not require further interventions on abdominal or retroperitoneal organs. However, about a third of patients may require a planned intervention where removal of organs affected by the disease (for example kidney, psoas muscle or gross vessels) is performed and followed by *ad hoc* reconstructive surgery (e.g. vascular interventions such as vena cava or aortic prostheses). Patients undergoing adjunct complex surgeries benefit from disease control but have a greater risk of complications than from standard procedures [232, 233]. In patients with intermediate- or poor-risk and residual disease > 5 cm the probability of vascular procedures is as high as 20% [234]. This surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment, the median number of RPLNDs performed per surgeon/year in the U.K. is six [235]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6% to 0.8% [15]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [16].

7.4.3.2 Salvage and desperation surgery.

Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy was improved 70% at 10 years, following taxane-containing regimens [236]. Also, in the case of extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [237, 238].

Desperation surgery refers to resection of non-responsive or progressive (e.g. rising markers) disease following salvage chemotherapy. When the disease is resectable, a significant proportion of these patients can be rendered disease-free in the long-term [239].

7.4.3.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or post-pubertal teratoma, no further treatment is required. In cases of incomplete resection of viable cancer, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g. ‘poor-prognosis’ patients) [223] (caution: cumulative doses of bleomycin). After complete resection of ‘vital’ tumour < 10% of the total volume, especially in patients in an initially good-prognosis group according to IGCCCG, the relapse rate is very low and adjuvant chemotherapy is not beneficial for preventing further relapse [240]. The prognosis will definitely deteriorate if viable malignant neoplasm is found in resection specimens after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated and is unable to improve the prognosis [241].

*7.4.4 **Systemic salvage treatment for relapse or refractory disease***

Cisplatin-based combination salvage chemotherapy will result in long-term remissions in about 50% of the patients who relapse after first-line chemotherapy, but the results are highly dependent on several prognostic factors [242]. The regimens of choice are four cycles of a triplet regimen including cisplatin and ifosfamide plus a third agent: etoposide (PEI/VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7.2) [243]. No RCT has compared these regimens. Due to their potentially lethal risk of haematological toxicity, these regimens should be used with G-CSF support and by well-trained oncologists.

The only available RCT comparing standard-dose vs. high-dose chemotherapy plus transplant in the salvage setting showed no benefit in OS in patients treated with three cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus one cycle of consolidation high-dose chemotherapy, compared with VeIP x 4 [244]. Due to several methodological reasons this trial design can no longer be considered state of the art.

There is clear evidence from large retrospective analyses that there are different prognostic groups in the case of relapse after first-line chemotherapy [245, 246], and the Lorch-Beyer score has resulted in five prognostic subgroups (Table 7.3). Several recent trials have confirmed this score [247, 248]. As in first-line therapy, the prognostic impact of tumour marker decline has also been demonstrated in the salvage setting [249]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [250].

A second large analysis in this cohort of 1,600 patients showed an improvement of about 10-15% in OS in patients from all prognostic subgroups when treated with high-dose salvage therapy compared to standard-dose therapy. To prospectively confirm this finding, an international RCT of high-dose vs. conventional-dose chemotherapy in patients with first-line relapse has started (Tiger trial). If high-dose chemotherapy is used as a salvage treatment, sequential treatment cycles of high-dose carboplatin and etoposide (HD-CE) should be preferred to a single high-dose regimen because the former is associated with less toxicity-related deaths [251]. A recent systematic review confirmed the superiority of using at least two high-dose cycles in the salvage setting over a single high-dose cycle [252].

It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at experienced centres.

Table 7.2: Standard PEI/VIP, TIP and GIP chemotherapy (interval 21 days)

Regimen	Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP	Cisplatin*	20 mg/m^2	Days 1-5
	Etoposide	75-100 mg/m^2	Days 1-5
	Ifosfamide†	1.2 g/m^2	Days 1-5
TIP	Paclitaxel	250 mg/m^2 [xx]	24 hour continuous infusion day 1
	Ifosfamide†	1.5 g/ m^2	Days 2-5
	Cisplatin*	25 mg/m^2	Days 2-5
	Alternative schedule		
	Paclitaxel	175 mg/m^2	Day 1, 3 hour infusion
	Ifosfamide†	1.2 g/m^2	Days 1-5
	Cisplatin*	20 mg/m^2	Days 1-5
GIP	Gemcitabine	1000 mg/m^2	Day 1 + 5
	Ifosfamide	1200 mg/m^2	Days 1-5
	Cisplatin	20 mg/m^2	Days 1-5

** Plus hydration.*

† Plus mesna protection.

[xx] An MRC schedule uses paclitaxel at 175 mg/m^2 in a three hour infusion [253].

The International Prognostic Factors Study Group score, comprised of seven important factors, is listed in Table 7.3. Using these factors, five risk groups (very low risk = -1 points; low risk = 0 points; intermediate-risk = 1-2 points; high risk = 3-4 points; and very high risk > 5 points) were identified with significant differences in PFS and OS. Table 4.3 illustrates the five risk groups and the corresponding two-year PFS and three-year OS rates [254].

Table 7.3: The International Prognostic Factors Study Group Score Construction [246]

Points	-1	0	1	2	3
Variable					
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	< 3 months		
AFP salvage		Normal	< 1000	1000	
hCG salvage		< 1000	1000		
LBB		No	Yes		

AFP = alpha-fetoprotein; CR = complete remission; PRm- = partial remission, negative markers; PRm+ = partial remission, positive markers; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases; PD = progressive disease; PFI = progression-free interval; SD = stable disease.

Table 7.4: PFS and OS estimates for all patients according to IGCCCG-2 prognostic score [246]

Score (n = 1,435)	N	%	HR	2-years PFS	3-year OS
Very Low	76	5.30	1	75.1	77.0
Low	257	17.9	2.07	52.6	69.0
Intermediate	646	45.0	2.88	42.8	57.3
High	351	24.5	4.81	26.4	31.7
Very High	105	7.3	8.95	11.5	14.7
Missing	159	-	-	-	-

HR = hazard ratio; PFS = progression-free survival; n = number of patients; OS = overall survival.

*7.4.5 **Second relapse***

There are no RCTs for patients with second relapse; however, conventional therapy does not appear to be very effective. For patients having received two series of conventionally-dosed therapy (first-line and first-salvage), HD chemotherapy with autologous stem cell support should be used [246]. Even with HD-therapy the chance of cure is only 20-25%.

Refractory disease: Patients relapsing within four to eight weeks after platinum-based therapy, or who are progressing despite platinum-based therapy, as well as those relapsing shortly after HD chemotherapy, are considered cisplatin refractory. For these patients, combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45%. Targeted agents have mostly failed with limited responses for Brentuximab Vedotin in CD30-expressing germ cell tumours [255-260]. Cisplatin re-challenge in association with gemcitabine and paclitaxel could be considered in patients with good renal function [261]. For patients with a second relapse not responding to the combination of oxaliplatin and gemcitabine or the triple combination, inclusion in clinical trials should be encouraged.

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [237, 262]. Immunotherapy with PD1-checkpoint inhibitors is currently being studied due a substantial expression of PDL1 in GCTs; in most series about 50% of tumour cells or tumour infiltration cells express PDL1.

7.4.5.1 Late relapse (> two years after end of first-line treatment)

Late relapse is defined as recurrence more than two years following cure after chemotherapy for metastatic TC, with, or without, residual tumour surgery and occurs, according to a pooled analysis, in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [263, 264]. If feasible, all lesions of late-relapsing non-seminoma patients should be removed by radical surgery.

Patients with rapidly rising hCG may benefit from induction salvage chemotherapy before complete resection, but in most patients, surgery should be performed irrespective of the level of their tumour markers in order to completely resect all undifferentiated GCT and/or mature teratoma with or without somatic transformation [137, 222, 265].

Survival strongly depends on the histology of the removed lesions rather than on the initial germ cell cancer. Interestingly, in a population-based study all late-relapsing seminoma patients had viable GCT, whereas teratoma or necrosis was found in half of the patients with initial non-seminoma [266].

If the lesions are not completely resectable, biopsies should be obtained for histological

assessment, and salvage chemotherapy should be initiated according to the histological results. In these cases, consultation of an experienced pathologist is required to avoid misinterpretation of the therapeutic morphological changes in the germ cell neoplasms [267]. If the patient responds to salvage chemotherapy, secondary surgery should be conducted, whenever possible. In the case of unresectable, but localised, refractory disease, stereotactic or conventional RT may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [268].

7.4.5.2 Treatment of brain metastases

Brain metastases occur in the frame of the initial diagnosis of metastatic disease or a systemic relapse and rarely as an isolated relapse. The long-term survival of patients presenting with brain metastases at initial diagnosis is poor (30-50%), but it is even poorer when brain metastasis develops as recurrent disease (the five-year survival-rate is 2-5%) [269, 270]. A large international database comprising 523 patients reported 48% three-year OS rates in patients with brain metastases at initial diagnoses and 27% three-year OS rates for patients with brain metastases at relapse [271]. Chemotherapy was the initial treatment in this case, which proved particularly effective in a first-line setting (potentially even as dose-intensified therapy upfront) while data support the use of multimodal treatment particularly in relapsed patients [271]. Consolidation RT, even in the case of a total response after chemotherapy, should thus be used in patients with brain metastases at relapse, but this option must be carefully discussed in a first-line setting [272]. Surgery can be considered in the case of a persistent solitary metastasis, depending on the systemic state, the histology of the primary tumour and the location of the metastasis.

*7.4.6 **Recommendations for the treatment of metastatic germ cell tumours***

Recommendations	Strength rating
Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like 'good- or intermediate-prognosis' advanced NSGCT, with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong
In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either retroperitoneal lymph node dissection (RPLND) or biopsy. If not possible, repeat staging after six weeks of surveillance before making a final decision on further treatment.	Strong
In metastatic NSGCT with an intermediate prognosis, treat with four courses of standard BEP.	Strong
In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, or cisplatin, etoposide and ifosfamide (PEI), in case of poor lung function, followed by tumour marker assessment after three weeks. In case of a favourable marker decline, continue BEP (or PEI) up to a total of four cycles. In case of an unfavourable decline, initiate chemotherapy intensification.	Strong
Perform surgical resection of residual masses after chemotherapy in NSGCT in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.	Strong
In CS IIA seminoma, offer radiotherapy or chemotherapy and inform the patient of possible undesirable long-term side effects of both management options.	Strong
Initially offer chemotherapy in seminoma stage CS IIB (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	Strong
Treat seminoma stage IIC and higher, with primary chemotherapy according to the same principles used for NSGCT.	Strong

8. FOLLOW-UP AFTER CURATIVE THERAPY

8.1 Rationale for follow-up

The primary aim of follow-up in the first five years is the timely diagnosis of recurrent disease in order to be able to treat the patient with curative intent with the least aggressive therapy [263]. An adequate follow-up relies on profound knowledge about TC with regards to histology, stage, primary treatment and treatment success. Follow-up has to be tailored to each individual patient and the schedule has to be acceptable to the patient, the physician, and the health care system. The interval of follow-up visits and the clinical investigations

to be performed at each visit should depend on the risk of relapse, in general, and on the likely site of relapse in an individual patient [273]. Only one RCT was published addressing the implication of different follow-up schedules and the use of imaging and tumour markers [140]. Several recent publications have added valuable information and recommendations [90, 92, 107, 111, 113, 136, 274-277] contributing to the development of consensus recommendations by the European Society for Medical Oncology Testicular Cancer Consensus Committee [278].

In recognition of the ionising radiation exposure risks associated with repeated CT scanning [279] a reduction in the number of follow-up CT scans advised has been seen in the past years [1, 280]. Looking at the different risks of relapse depending on diagnosis and initial treatment three major follow-up groups can be defined:

1. patients with seminoma stage I;
2. patients with non-seminoma stage I on active surveillance;
3. all patients having received either adjuvant treatment or curative chemotherapy for good- and intermediate-prognosis metastatic disease (according to the IGCCCG) achieving a complete remission with, or without, surgery (for seminoma this includes residual lesions < 3 cm, or residual lesions > 3 cm that are PET-negative).

It is important to note that patients not achieving a complete remission or presenting with poor-prognosis disease should be followed up individually in specialised centres.

Tables 8.1-8.3 show the minimal recommendations for follow-up of the three different groups based on recommendations developed at the ESMO Testicular seminoma and non-seminoma consensus conference [278].

Generally, MRI of the abdomen can be used instead of CT in experienced centres. Regarding the use of US of the contralateral testis, the majority of the consensus meeting participants voted against repeat US investigation, both in case of negative biopsy (21/31) and also if no contralateral biopsy has been performed (17/32).

Follow-up for relapse beyond five years is generally not recommended. A very late relapse (VLR) after five years is a rare event occurring in approximately 0.5% of patients according to a population-based analysis [266]. The aim of follow-up beyond five years therefore shifts to detection of late side effects of treatment.

Most patients with VLR are diagnosed due to symptoms; however, in up to 50% elevated tumour markers can be found in both seminomatous and non-seminomatous GCTs [266, 281]. Patient education about relapse symptoms and physician awareness is a very important part of survivorship management. The early use of imaging and tumour markers in case of suspicion of relapse is encouraged.

Table 8.1: Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	Once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography/magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

Table 8.2: Recommended minimal follow-up for non-seminoma stage I on active surveillance

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times**	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic computed tomography/magnetic resonance imaging	2 times	At 24 months***	Once at 36 months*	Once at 60 months*	

* *Recommended by 50% of the consensus group members.*

** *In case of high risk (LVI+) a minority of the consensus group members recommended six times.*

*** *In case of high risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.*

Table 8.3: Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	*	*	*	*	

* *Same time points as abdominopelvic CT/MRI in case of pulmonary metastases at diagnosis.*

** *In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.*

8.2 Quality of life and long-term toxicities after cure of testicular cancer

The vast majority of patients will be cured and five-year relative survival rates are approximately 95% in Western Europe. Furthermore, TC patients are usually between 18 and 40 years of age at diagnosis and life expectancy after cure extends over several decades [282]. Patients should be informed before treatment of common long-term toxicities, which are probably best avoided by adherence to international guidelines.

Treatment of stage I TC is controversial, with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy [128], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with long-term toxicities as quite appealing [283]. Unfortunately, it is not known which treatment spares most patients long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy [130, 138, 284].

During follow-up, patients should be screened and treated for known risk factors such as high blood pressure, hyperlipidaemia and testosterone deficiency. When follow-up by the TC expert is discontinued, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up might be helpful [263, 285]. The following overview is not complete and interested readers are referred to review articles on this topic [282, 285, 286].

*8.2.1 **Second malignant neoplasms (SMN)***

Treatment-induced SMN usually occurs after the first ten years [285]. The risk for solid SMN increases with younger age at RT or chemotherapy and remains significantly elevated for at least 35 years [120, 287-289]. Radiotherapy-related SMNs are primarily localised within or close to the RT field (colon, stomach, pancreas, bladder and the urinary tract) [120, 121, 288-291]. Hauptmann *et al.* could demonstrate a remarkably clear radiation-dose relationship to gastric- and pancreatic-cancer [292]. Fung *et al.* demonstrated that modern cisplatin-based chemotherapy was associated with a 40% increased risk of a solid SMN [293].

The European Society for Blood and Marrow Transplantation (EBMT) reported SMN in 59 of the 5,295 TC patients registered after receiving high-dose chemotherapy within a median follow-up of 3.8 years. Of them, 39% developed a hematologic SMN and 57.6% a solid SMN. Twenty year cumulative incidence of solid and hematologic SMN was 4.2% and 1.4%, respectively, with median OS shorter after diagnosis of hematologic vs. solid SMN (8.6 vs. 34.4. months). Age ≥ 40 years at the time of high-dose chemotherapy was significantly associated with hematologic, but not with solid SMNs [294].

8.2.2 ***Leukaemia***

In a series of 40,576 TC survivors, the observed ratio for developing leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemia was 2.6 [295]. The risk of AML seems to be both related to the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m^2 have been shown to increase the subsequent risk of AML [296]. It is important to keep in mind that the majority of TC patients receive much lower doses of etoposide so that the absolute risk of AML after three to four courses of BEP is very low, and in patients requiring high-dose chemotherapy with cumulative etoposide doses exceeding this threshold, less than 1.5% have been reported to suffer from AML. There is a cumulative dose-disease relationship regarding cisplatin and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first ten years after treatment for TC and has a very poor prognosis [297].

8.2.3 ***Infections***

Chemotherapy-treated TC survivors (TCSs) have a higher risk of dying from infections than the general population (standard mortality ratio 2.48, 95% CI: 1.70-3.5) [298]. This is possibly due to long-term depression of bone-marrow, but also complications of subsequent salvage treatment (which was not reliably registered). Alternatively, extensive or subsequent surgical treatment might contribute to these numbers. Furthermore, asymptomatic pulmonary fibrosis by mediastinal RT and/or bleomycin may render TCSs vulnerable to potentially deadly pneumonias many years after treatment.

8.2.4 ***Pulmonary complications***

Chemotherapy exposed TCSs have a nearly three-fold increased risk of dying of pulmonary diseases than the normal population [298]. Bleomycin-induced lung toxicity may affect 7-21% of patients in the long-term, resulting in death in 1-3% [299]. Chemotherapy-treated TC survivors treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured by surgery alone [300]. Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin dose and not with the dose of bleomycin [300]. The data contrast with a meta-analysis on chemotherapy for TC including 6,498 patients showing a significant effect of bleomycin administration on all-grade pulmonary toxicity [301]. In a Danish cohort of 565 TC survivors, pulmonary function recovered during repeated assessments over five years in almost all patients [302]. Of note, an association with risk factors such as reduced renal function, age, tobacco-smoking, and cumulative chemotherapy, were not associated with pulmonary function, but with pulmonary embolism, lung surgery, and poor IGCCCG risk group [302].

8.2.5 ***Cardiovascular toxicity***

Thromboembolic events (mostly venous) occur more frequently in patients with GCT receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [303]. Low-dose heparins used during the course of chemotherapy may prevent the onset of thromboembolic events [304], though level 1 evidence is lacking. Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population (OR 5) [298, 305, 306]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [133, 307]. Metabolic syndrome, which is a risk factor for CVD and its components, hypertension, obesity and hypercholesterolaemia, increases with treatment intensity (OR 9.8) [306, 308, 309]. Hypogonadism increases the risk of insulin resistance, a proxy for metabolic syndrome, and an inherent risk of CVD. Bogefors *et al.* showed, however, that most associations between TC treatment and metabolic parameters became statistically non-significant after adjustment for hypogonadism, indicating that hypogonadism might be the mediator of several toxicities which are usually attributed to the applied TC treatment [310]. Circulating residual serum platinum might exert endothelial stress and thereby possibly lead to hypertension [311, 312]. Furthermore, exposure to circulating platinum has been shown to be associated with paraesthesia, hypogonadism, and hypercholesterolaemia [312]. Cisplatin-based chemotherapy also causes acute CVD as is shown by a 0.24% incidence of major vascular events [303].

Physical activity reduces the risk of metabolic syndrome and CVD. High-intensity aerobic interval training (HIIT) for twelve weeks improved the cardiorespiratory fitness, multiple pathways of CVD risk, and surrogate markers of mortality in TC survivors as compared to standard care, i.e. no supervised training [313]. However, HIIT during cisplatin-based chemotherapy might be harmful as a planned study on 94 patients closed early after recruiting nineteen patients and the finding of severe CVD complications among three out of nine patients undergoing HIIT [314]. Two patients developed a pulmonary embolism (at days seven and nine of BEP cycle 2, respectively) and the remainder a myocardial infarction (at day seven of BEP cycle 3). It is difficult to draw firm conclusions from such small patient numbers, but the observed CVD was well above the expected 5% risk of thromboembolic complications during, or shortly after, cisplatin-based chemotherapy such that the authors discourage HIIT during cisplatin-based chemotherapy for TC.

Office-based Framingham risk scores to predict the 10-year CVD morbidity after diagnosis can be applied to TC survivors who received chemotherapy. In a population of almost 800 TC survivors, less educated and less vigorously active patients had higher risk scores of 10-year CVD morbidity [315].

8.2.6 ***Raynaud-like phenomena***

Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually ascribed to the application of bleomycin [316, 317]. Cisplatin is believed to contribute to cold-induced vasospasms. Vogelzang *et al.* reported that the incidence of Raynaud's phenomenon was higher after treatment with CVB than after only vinblastine and bleomycin, 41% vs. 21%, respectively [318].

8.2.7 ***Neurotoxicity***

Cisplatin induces a symmetric dose-dependent sensory, distal, length-dependent glove and stocking paraesthesias, affecting 29% of TCSs who received cisplatin-based chemotherapy as opposed to 10% after orchiectomy alone [306, 319]. Treatment with five or more cycles increases the frequency of this symptom to 46%. Paclitaxel-induced acute neuropathy consists of an acute pain syndrome, which usually develops within three days to a week following paclitaxel administration. Platinum is measurable in the serum of TCSs many years after its application and the intensity of paraesthesias is more strongly associated with platinum serum level than with the cumulative dose of applied cisplatin [311]. Patients who experience a larger decline in circulating residual serum platinum during follow-up are at reduced risk of worsening of tinnitus or of paraesthesias in hands [320].

8.2.8 ***Cognitive function***

There are concerns that chemotherapy may reduce the cognitive function leading to "chemo-brain". Amidi *et al.* could show an alteration of brain structural networks after cisplatin-based chemotherapy for TC [321]. Impaired brain networks may underlie poorer performance over time on both specific and nonspecific cognitive functions in TC survivors following chemotherapy.

8.2.9 ***Ototoxicity***

Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4,000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [306, 322-324]. Both hearing impairment and tinnitus are considerably increased after application of 50 mg/m^2 cisplatin over two days as compared to 20 mg/m^2 over five days (OR 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [319]. A significant association between glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [325, 326]. Hopefully, increasing insight into the pathogenesis of and vulnerability for this complication will lead to more individualised treatment in the future.

8.2.10 ***Nephrotoxicity***

Cisplatin-based chemotherapy may lead to long-term renal function impairment in 20-30% of TCSs [319, 322-324]. In TC patients, reduced renal elimination of cisplatin and bleomycin might increase the risk of other toxicities, e.g. bleomycin-related pneumonitis [327, 328]. However, a comprehensive assessment of 1,206 Danish TCSs did not reveal a significant association between chemotherapy-induced impaired renal function and other toxicities [304]. Renal recovery was poor after five or more cycles of BEP as compared to after BEP x 3 [329].

8.2.11 ***Hypogonadism***

Testicular endocrine dysfunction comprises insufficient testosterone production and/or compensatory increased LH levels. Subnormal testosterone levels have been reported in TCSs treated with chemotherapy, when compared to those treated with surgery only or the general population [284, 306, 329, 330].

Hypogonadism increases the risk of insulin resistance and hence of the metabolic syndrome, which, in turn, might lead to CVD in the long-term [310]. Wiechno *et al.* could show a decline in testosterone and an increase in LH and FSH within one year after treatment for unilateral TC [331]. Although there are clear indications of hypogonadism-related complications, and despite an established association between low testosterone and metabolic syndrome, no clear association between Leydig cell dysfunction and the risk of metabolic syndrome during a median ten-year follow-up could be established [332]. Furthermore, the clinical benefits of testosterone substitution are not well established. An ongoing Danish RCT might yield level 1 evidence [333].

Erectile dysfunction (OR 4.2) has been significantly associated with chemotherapy in a recent multicentric study [306].

*8.2.12 **Fatigue***

Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest, and persists for more than six months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [334]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of twelve years after treatment for TC when compared with the age-matched Norwegian population (10%) [335]. Of note, the prevalence of CF increased from 15% to 27% during a ten year period in long-term TCSs [336].

*8.2.13 **Quality of life***

Quality of life is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social- and physical function [335]. When comparing three or four cycles of BEP in good-risk patients, all outcomes favour treatment with three courses [172]. After one and two years, one-third of patients reported an improvement in global QoL after chemotherapy, while one-fifth of patients reported deterioration, with no difference between treatment groups. After adjuvant treatment of non-seminoma stage I patients, there was no difference in short- or long-term (five years) QoL between RPLND, or one course of BEP [337]. Anxiety, depression, fear of cancer recurrence, and distress may impair the health-related quality of life (HRQoL) in TCSs. A recent review by Smith *et al.* from the Australian TC group identified a considerable variation in both severity and prevalence of each of these issues, probably due to use of different questionnaires and also cultural variations [338]. Clinically significant anxiety is reported in approximately 1 out of 5 TCSs and distress in 1 out of 7, and is therefore more frequent among TCSs than in the general population. Depression was not uniformly found to be more frequent, whereas every third TCSs reported fearing recurrence. Importantly, poorer psychological outcomes were more common among single, unemployed TCSs with a low socio-economic status and co-morbidities, as well as those experiencing worse symptoms/side effects, and those using passive coping strategies. These findings are mostly in-line with an earlier reported survivorship study on HRQoL among 486 TCSs revealing a greater prevalence of moderate-to extremely severe anxiety (19%) and depression (20%); and significant deficits to mostly mental aspects of HRQoL. The authors found that, again, helpless/hopeless coping style was correlated with psychological distress and impaired generic HRQoL [339].

A German study found clinically significant anxiety in 6.1% and depression in 7.9% of TC patients, with both a higher number of physical symptoms and having children relating to higher levels of anxiety and depression [340].

For a subset of approximately 11% of TSCc, the diagnosis of TC was traumatic. This subset was found to suffer from post-traumatic stress disorder in the long-term, which resulted in significant QoL reduction [341]. The authors recommend that healthcare professionals explore stress symptoms at follow-up visits in order to timely identify TSCs requiring support.

9. TESTICULAR STROMAL TUMOURS

9.1 Classification

Non-germ-cell tumours of the testicle include sex cord/gonadal stromal tumours and miscellaneous nonspecific stromal tumours. The different histological subtypes of testicular tumours are defined according to the 2016 WHO classification (adapted) [33].

*9.1.1 **Epidemiology and prognosis***

Sex cord stromal tumours comprise less than 5% of testicular neoplasms. Recent population-based registries in the US (National Cancer Data Base and Surveillance Epidemiology and End Results) show that 0.39 to 0.59% of all testis neoplasm patients are diagnosed with a primary malignant Leydig or Sertoli cell tumour. Of these, between 71% and 79% present with a malignant Leydig cell tumour and 21% to 29% with malignant Sertoli cell tumours [342, 343].

Median ages at diagnostic are 39 and 47 years for malignant Sertoli and Leydig cell tumours, respectively. At diagnostic 98.5% of the Leydig cell tumours are CSI, whilst 35% of Sertoli cell tumours are CS II/III [343].

Overall survival at one and five years for CS I Leydig cell tumours is 22-35% (95% CI: 96-100) and 91% (95% CI: 85-96), respectively, and for CSI Sertoli cell tumours OS is 93% (95% CI: 83-100) and 77% (95% CI: 62-95), respectively ($p = 0.015$). Overall, five-year survival estimates of stage I Leydig and Sertoli cell tumours are

significantly lower compared to those of stage I GCTs, with Sertoli cell tumours significantly worse than Leydig cell tumours [342]. Presentation with metastatic disease is the only variable associated with worse CSS [344].

Only limited evidence is available for local and systemic treatment of testicular stromal tumours. After testis sparing surgery, local recurrence rates up to 9.5% have been reported [345].

A systematic review [312] analysing the impact of previously identified pathologic risk factors on harbouring occult metastatic disease (OMD) in patients with CS I testicular stromal tumours showed an increased risk of OMD for each additional risk factor ($p < .001$). Five-year OMD-free survival was 98.1% for those with < 2 risk factors vs. 44.9% for those with ≥ 2 risk factors ($p < 0.001$). Whilst the existing literature does not support making firm recommendations, testis sparing surgery instead of radical orchiectomy might be offered in patients with localised disease and risk stratification might improve clinical decision-making regarding adjuvant treatment options [346].

These data support the importance of large databases to evaluate the efficacy of treatment in rare neoplasms.

9.2 Leydig cell tumours

*9.2.1 **Epidemiology***

Leydig cell tumours constitute about 1-3% of adult testicular tumours [347, 348] and 3% of testicular tumours in infants and children [348]. These tumours are most common in the third to sixth decade in adults, with a similar incidence observed in each decade. Another peak incidence is seen in children aged between three and nine years. Only 3% of Leydig cell tumours are bilateral [347]. These tumours occur in about 8% of patients with Klinefelter's syndrome [348].

*9.2.2 **Pathology of Leydig cell tumours***

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well delineated and usually up to 5 cm in diameter. They are solid, yellow to tan in colour, with haemorrhage and/or necrosis in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm and occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S-100, steroid hormones, calretinin and cytokeratin (focally) [68].

Approximately 10% of Leydig cell tumours are malignant and present with the following parameters [349, 350]:

- large size (> 5 cm);
- older age;
- increased mitotic activity (> 3 per 10 high-power field [HPF]);
- vascular invasion;
- cytological atypia;
- increased MIB-1 expression;
- necrosis;
- infiltrative margins;
- extension beyond the testicular parenchyma;
- DNA aneuploidy.

*9.2.3 **Diagnosis***

Patients either present with a painless enlarged testis or the tumour is found incidentally on US. In up to 80% of cases, hormonal disorders with high oestrogen and oestradiol levels, low testosterone, and increased levels of LH and FSH are reported [351, 352], while negative results are always obtained for the testicular GCT-markers AFP, hCG, LDH and PLAP. Up to 10% of adult patients present with gynaecomastia [352, 353].

Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes, and CT of chest and abdomen. On US, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularisation; however, the appearance is variable and is indistinguishable from GCTs [354]. Contrast-enhanced US [355] or contrast-enhanced MRI [356] may improve the diagnosis. The proportion of metastatic tumours in all published case reports is less than 10%. In three old series with long follow-up, eighteen metastatic tumours were found in a total of 83 cases (21.7%) [347, 349, 357], while five recently published studies with long follow-up reported only two metastatic tumours in 156 patients (1.3%) [342, 352, 353, 358, 359].

9.3 Sertoli cell tumours

*9.3.1 **Epidemiology***

Sertoli cell tumours account for fewer than 1% of testicular tumours, and the mean age at diagnosis is around 45 years, with sporadic cases under 20 years of age [360, 361]. On rare occasions, these tumours may develop in patients with androgen insensitivity syndrome and Peutz-Jeghers syndrome.

*9.3.2 **Pathology of Sertoli cell tumours***

These tumours are well circumscribed, yellow, tan or white in colour, with an average diameter of 3.5 cm [360]. Microscopically, the cells are eosinophilic to pale with a vacuolated cytoplasm. The nuclei are regular with grooves, and inclusions may be present. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible. The stroma is fine with capillaries, but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) [360]. The rate of malignancy ranges between 10% and 22%. Signs of a malignant Sertoli tumour are [362, 363]:

- large size (> 5 cm);
- increased mitotic activity (> 5 per 10 HPF);
- pleomorphic nuclei with nucleoli;
- necrosis;
- vascular invasion.

9.3.2.1 Classification

Three subtypes have been described [361]:

- classic Sertoli cell tumour [360];
- large cell calcifying form with characteristic calcifications [364, 365];
- sclerosing form [366, 367].

*9.3.3 **Diagnosis***

Patients present either with an enlarged testis, or the tumour is found incidentally on US. Most classic Sertoli cell tumours are unilateral and unifocal. Hormonal disorders are infrequent, although gynaecomastia is sometimes seen [360]. The testicular tumour-markers AFP, hCG, LDH and PLAP are always negative. Diagnostic work-up must include tumour markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes and CT of chest and abdomen. Sertoli cell tumours are generally hypoechoic on US, but they can be of variant appearance and thus cannot be safely distinguished from GCTs [361]. Only the large cell calcifying form has a characteristic image with bright echogenic foci due to calcification [368]. Metastatic disease of 12% in classic Sertoli cell tumour has been reported. In general, affected patients are older, tumours are nearly always palpable, and show more than one sign of malignancy [360].

The large cell calcifying form is diagnosed in younger men and is associated with genetic dysplastic syndromes (Carney's complex [369] and Peutz-Jeghers syndrome [370]) or, in about 40% of cases, endocrine disorders. Forty-four percent of cases are bilateral, either synchronous or metachronous, and 28% show multifocality with good prognosis [365].

Up to 20% of the large cell calcifying forms are malignant. It has been suggested that discrimination between an early and late onset type may define a different risk for metastatic disease (5.5% compared to 23%) [361].

The sclerosing subtype is very rare, unilateral, with a mean age around 40 years and metastases are infrequent [367].

9.4 Treatment of Leydig- and Sertoli cell tumours

Asymptomatic, small volume testicular tumours are often misinterpreted as GCTs, and inguinal orchidectomy is performed. An organ-sparing procedure in every small US-detected, non-palpable intraparenchymal lesion is highly recommended in order to obtain a histological diagnosis. The incidence of benign definitive histology is high at approximately 80% [371]. When a non-GCTI is suggested by frozen section immediate orchidectomy can be avoided. In cases with GCT in either frozen section or paraffin histology, orchidectomy is recommended as long as a contralateral normal testicle is present.

When diagnosed and treated early, long-term favourable outcomes are seen at follow-up in Leydig cell tumours, even with its potential metastatic behaviour. In stromal tumours with histological signs of malignancy, especially in older patients, orchidectomy and early RPLND may be an option to prevent metastases [342, 372] or to achieve long-term cure in stage IIA cases [373]. Prophylactic RPLND is unjustified for patients with CSI disease without high-risk features [374].

Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor [342, 372]. No recommendations are available for the treatment of these patients.

9.5 Granulosa cell tumour

This is a rare tumour with two variants: juvenile and adult. Less than 100 cases are reported with a predominance of the juvenile type.

- The juvenile type is benign. It is the most frequent congenital testicular tumour and represents about 1-5% of all pre-pubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type [375, 376].
- The average age of the adult type at presentation is 45 years. The typical morphology is a homogeneous, yellow-grey tumour, with elongated cells with grooves in microfollicular and Call-Exner body arrangements [377].

Malignant tumours represent around 20% of cases. Lymphovascular invasion, necrosis, infiltrative borders and size > 4 cm may help in identifying cases with aggressive behaviour. Mitotic counts vary and do not appear to be of prognostic significance [378].

9.6 Thecoma/fibroma group of tumours

These tumours are rare with variable histology such as minimal invasion into surrounding testis, high cellularity, and increased mitotic rate. Their immunoprofile is variable and typically not diagnostic. They seem to be uniformly benign [379].

9.7 Other sex cord/gonadal stromal tumours

Sex cord/gonadal stromal tumours may be incompletely differentiated or in mixed forms. There is limited experience with incompletely differentiated sex cord/gonadal stromal tumours and no reported cases of metastasis [40]. In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour most likely reflects the predominant pattern or the most aggressive component of the tumour [380].

9.8 Tumours containing germ cell and sex cord/gonadal stroma (gonadoblastoma)

Some patients with disorders of sex development (DSDs) have abnormal gonadal development with ambiguous genitalia and an increased risk of GCTs. If the arrangement of the germ cells is in a nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. Bilateral tumours are present in 40% of cases. The prognosis correlates with the invasive growth of the germinal component [381, 382].

In the case of a diffuse arrangement of the different components, there are some doubts about the neoplastic nature of the germinal cells and some authors consider them to be entrapped rather than neoplastic [383].

9.9 Miscellaneous tumours of the testis

*9.9.1 **Tumours of ovarian epithelial types***

These tumours resemble epithelial tumours of the ovary. A cystic appearance with occasional mucinous material can be observed. Microscopically, their aspect is identical to their ovarian counterparts, and their evolution is similar to that of the different epithelial ovarian subtypes. Some Brenner types are malignant [68].

*9.9.2 **Tumours of the collecting ducts and rete testis***

These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) variants have been reported, with malignant tumours showing local growth with a mortality rate of 40% within one year [384].

*9.9.3 **Tumours (benign and malignant) of non-specific stroma***

These are very uncommon and have similar criteria, prognosis and treatment to soft tissue sarcomas.

10. REFERENCES

1. Albers, P., *et al.* Guidelines on Testicular Cancer: 2015 Update. Eur Urol, 2015. 68: 1054. https://www.ncbi.nlm.nih.gov/pubmed/26297604
2. Guyatt, G.H., *et al.* What is “quality of evidence” and why is it important to clinicians? BMJ, 2008. 336: 995. https://www.ncbi.nlm.nih.gov/pubmed/18456631

3. Guyatt, G.H., *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 2008. 336: 924.
https://www.ncbi.nlm.nih.gov/pubmed/18436948
4. Phillips B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
5. Guyatt, G.H., *et al.* Going from evidence to recommendations. BMJ, 2008. 336: 1049.
https://www.ncbi.nlm.nih.gov/pubmed/18467413
6. La Vecchia, C., *et al.* Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol, 2010. 21: 1323.
https://www.ncbi.nlm.nih.gov/pubmed/19948741
7. Jemal, A., *et al.* Cancer statistics, 2009. CA Cancer J Clin, 2009. 59: 225.
https://www.ncbi.nlm.nih.gov/pubmed/19474385
8. Nigam, M., *et al.* Increasing incidence of testicular cancer in the United States and Europe between 1992 and 2009. World J Urol, 2014. 33: 623.
https://www.ncbi.nlm.nih.gov/pubmed/25030752
9. Ghazarian, A.A., *et al.* Recent trends in the incidence of testicular germ cell tumors in the United States. Andrology, 2015. 3: 13.
https://www.ncbi.nlm.nih.gov/pubmed/25331158
10. Ghazarian, A.A., *et al.* Future of testicular germ cell tumor incidence in the United States: Forecast through 2026. Cancer, 2017. 123: 2320.
https://www.ncbi.nlm.nih.gov/pubmed/28241106
11. Hoffmann, R., *et al.* Innovations in health care and mortality trends from five cancers in seven European countries between 1970 and 2005. Int J Public Health, 2014. 59: 341.
https://www.ncbi.nlm.nih.gov/pubmed/23989709
12. Zengerling, F., *et al.* German second-opinion network for testicular cancer: sealing the leaky pipe between evidence and clinical practice. Oncol Rep, 2014. 31: 2477.
https://www.ncbi.nlm.nih.gov/pubmed/24788853
13. Jones, A., *et al.* Is surveillance for stage 1 germ cell tumours of the testis appropriate outside a specialist centre? BJU Int, 1999. 84: 79.
https://www.ncbi.nlm.nih.gov/pubmed/10444129
14. Collette, L., *et al.* Impact of the treating institution on survival of patients with “poor-prognosis” metastatic nonseminoma. European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Cancer Working Party. J Natl Cancer Inst, 1999. 91: 839.
https://www.ncbi.nlm.nih.gov/pubmed/10340903
15. Capitanio, U., *et al.* Population-based study of perioperative mortality after retroperitoneal lymphadenectomy for nonseminomatous testicular germ cell tumors. Urology, 2009. 74: 373.
https://www.ncbi.nlm.nih.gov/pubmed/19501893
16. Flechon, A., et al. Long-term oncological outcome after post-chemotherapy retroperitoneal lymph node dissection in men with metastatic nonseminomatous germ cell tumour. BJU Int, 2010. 106: 779.
https://www.ncbi.nlm.nih.gov/pubmed/20089110
17. Schrader, M., *et al.* Burden or relief: do second-opinion centers influence the quality of care delivered to patients with testicular germ cell cancer? Eur Urol, 2010. 57: 867.
https://www.ncbi.nlm.nih.gov/pubmed/19931248
18. Bosl, G.J., *et al.* Testicular germ-cell cancer. N Engl J Med, 1997. 337: 242.
https://www.ncbi.nlm.nih.gov/pubmed/9227931
19. Kuczyk, M.A., *et al.* Alterations of the p53 tumor suppressor gene in carcinoma in situ of the testis. Cancer, 1996. 78: 1958.
https://www.ncbi.nlm.nih.gov/pubmed/8909317
20. Andreassen, K.E., *et al.* Genetic variation in AKT1, PTEN and the 8q24 locus, and the risk of testicular germ cell tumor. Hum Reprod, 2013. 28: 1995.
https://www.ncbi.nlm.nih.gov/pubmed/23639623
21. Loveday, C., *et al.* Validation of loci at 2q14.2 and 15q21.3 as risk factors for testicular cancer. Oncotarget, 2018. 9: 12630.
https://www.ncbi.nlm.nih.gov/pubmed/29560096
22. Litchfield, K., *et al.* Large-scale Sequencing of Testicular Germ Cell Tumour (TGCT) Cases Excludes Major TGCT Predisposition Gene. Eur Urol, 2018. 73: 828.
https://www.ncbi.nlm.nih.gov/pubmed/29433971

23. Looijenga, L.H., *et al.* Relevance of microRNAs in normal and malignant development, including human testicular germ cell tumours. Int J Androl, 2007. 30: 304.
https://www.ncbi.nlm.nih.gov/pubmed/23666239
24. Reuter, V.E. Origins and molecular biology of testicular germ cell tumors. Mod Pathol, 2005. 18 Suppl 2: S51.
https://www.ncbi.nlm.nih.gov/pubmed/15761466
25. Jorgensen, N., *et al.* Testicular dysgenesis syndrome comprises some but not all cases of hypospadias and impaired spermatogenesis. Int J Androl, 2010. 33: 298.
https://www.ncbi.nlm.nih.gov/pubmed/20132348
26. Lip, S.Z., *et al.* A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. Arch Dis Child, 2013. 98: 20.
https://www.ncbi.nlm.nih.gov/pubmed/23193201
27. Peng, X., *et al.* The association risk of male subfertility and testicular cancer: a systematic review. PLoS One, 2009. 4: e5591.
https://www.ncbi.nlm.nih.gov/pubmed/19440348
28. Greene, M.H., *et al.* Familial testicular germ cell tumors in adults: 2010 summary of genetic risk factors and clinical phenotype. Endocr Relat Cancer, 2010. 17: R109.
https://www.ncbi.nlm.nih.gov/pubmed/20228134
29. Lutke Holzik, M.F., *et al.* Genetic predisposition to testicular germ-cell tumours. Lancet Oncol, 2004. 5: 363.
https://www.ncbi.nlm.nih.gov/pubmed/15172357
30. Kharazmi, E., *et al.* Cancer Risk in Relatives of Testicular Cancer Patients by Histology Type and Age at Diagnosis: A Joint Study from Five Nordic Countries. Eur Urol, 2015. 68: 283.
https://www.ncbi.nlm.nih.gov/pubmed/25913387
31. Schaapveld, M., *et al.* Risk and prognostic significance of metachronous contralateral testicular germ cell tumours. Br J Cancer, 2012. 107: 1637.
https://www.ncbi.nlm.nih.gov/pubmed/23059747
32. Lerro, C.C., *et al.* A systematic review and meta-analysis of the relationship between body size and testicular cancer. Br J Cancer, 2010. 103: 1467.
https://www.ncbi.nlm.nih.gov/pubmed/20978513
33. Brierley, J.E., *et al.*, The TNM Classification of Malignant Tumours 8th edition. 2016.
http://www.uicc.org/resources/tnm/publications-resources
34. Peyret, C. Tumeurs du testicule. Synthèse et recommandations en onco-urologie. [Testicular tumours. Summary of onco-urological recommendations] [Article in French]. Prog Urol 1993. 2: 60. [No abstract available].
35. Mead, G.M., et al. The International Germ Cell Consensus Classification: a new prognostic factor-based staging classification for metastatic germ cell tumours. Clin Oncol (R Coll Radiol), 1997. 9: 207.
https://www.ncbi.nlm.nih.gov/pubmed/9315391
36. Motzer, R.J., *et al.* Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol, 2007. 25: 247.
https://www.ncbi.nlm.nih.gov/pubmed/17235042
37. Fizazi, K., *et al.* Early predicted time to normalization of tumor markers predicts outcome in poor-prognosis nonseminomatous germ cell tumors. J Clin Oncol, 2004. 22: 3868.
https://www.ncbi.nlm.nih.gov/pubmed/15302906
38. Fizazi, K., et al. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. Lancet Oncol, 2014. 15: 1442.
https://www.ncbi.nlm.nih.gov/pubmed/25456363
39. Smith, Z.L., *et al.* Testicular Cancer: Epidemiology, Diagnosis, and Management. Med Clin North Am, 2018. 102: 251.
https://www.ncbi.nlm.nih.gov/pubmed/29406056
40. Jing, B., *et al.* Metastases to retroperitoneal and pelvic lymph nodes: computed tomography and lymphangiography. Radiol Clin North Am, 1982. 20: 511.
https://www.ncbi.nlm.nih.gov/pubmed/7051132
41. Husband, J.E., *et al.* Evaluation of computed tomography in the management of testicular teratoma. Br J Urol, 1981. 53: 179.
https://www.ncbi.nlm.nih.gov/pubmed/7237052
42. Swanson, D.A., Role of retroperitoneal lymphadenectomy (RLDN) when patients with nonseminomatous germ cell testicular tumours are at high risk of needing lymph node surgery plus chemotherapy. In: Lymph Node Surgery in Urology. International Society of Urology Reports, D. J.P., Editor. 1996, Isis Medical Media: Oxford, UK.

43. Ellis, J.H., *et al.* Comparison of NMR and CT imaging in the evaluation of metastatic retroperitoneal lymphadenopathy from testicular carcinoma. J Comput Assist Tomogr, 1984. 8: 709. https://www.ncbi.nlm.nih.gov/pubmed/6539790
44. Sohaib, S.A., *et al.* Prospective assessment of MRI for imaging retroperitoneal metastases from testicular germ cell tumours. Clin Radiol, 2009. 64: 362. https://www.ncbi.nlm.nih.gov/pubmed/19264179
45. See, W.A., et al. Chest staging in testis cancer patients: imaging modality selection based upon risk assessment as determined by abdominal computerized tomography scan results. J Urol, 1993. 150: 874. https://www.ncbi.nlm.nih.gov/pubmed/8345604
46. de Wit, M., *et al.* [18F]-FDG-PET in clinical stage I/II non-seminomatous germ cell tumours: results of the German multicentre trial. Ann Oncol, 2008. 19: 1619. https://www.ncbi.nlm.nih.gov/pubmed/18453520
47. Huddart, R.A., *et al.* 18fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC Trial TE22--the NCRI Testis Tumour Clinical Study Group. J Clin Oncol, 2007. 25: 3090. https://www.ncbi.nlm.nih.gov/pubmed/17634488
48. De Santis, M., *et al.* 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. J Clin Oncol, 2004. 22: 1034. https://www.ncbi.nlm.nih.gov/pubmed/15020605
49. Bachner, M., *et al.* 2-(1)(8)fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) for postchemotherapy seminoma residual lesions: a retrospective validation of the SEMPET trial. Ann Oncol, 2012. 23: 59. https://www.ncbi.nlm.nih.gov/pubmed/21460378
50. Oechsle, K., *et al.* [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. J Clin Oncol, 2008. 26: 5930. https://www.ncbi.nlm.nih.gov/pubmed/19018083
51. Amin, M.B. *et al.* AJCC Cancer Staging Manual. 8th ed. AJCC Cancer Staging Manual. 2017. https://www.springer.com/la/book/9783319406176
52. Klepp, O., *et al.* Early clinical stages (CS1, CS1Mk+ and CS2A) of non-seminomatous testis cancer. Value of pre- and post-orchiectomy serum tumor marker information in prediction of retroperitoneal lymph node metastases. Swedish-Norwegian Testicular Cancer Project (SWENOTECA). Ann Oncol, 1990. 1: 281. https://www.ncbi.nlm.nih.gov/pubmed/1702312
53. Germa-Lluch, J.R., *et al.* Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: the experience of the Spanish Germ-Cell Cancer Group (GG). Eur Urol, 2002. 42: 553. https://www.ncbi.nlm.nih.gov/pubmed/12477650
54. Moul, J. Timely diagnosis of testicular cancer. Urol Clin North Am, 2007. 34: 109. https://www.ncbi.nlm.nih.gov/pubmed/17484916
55. Richie, J.P., *et al.* Ultrasonography as a diagnostic adjunct for the evaluation of masses in the scrotum. Surg Gynecol Obstet, 1982. 154: 695. https://www.ncbi.nlm.nih.gov/pubmed/7071705
56. Shaw, J. Diagnosis and treatment of testicular cancer. Am Fam Physician, 2008. 77: 469. https://www.ncbi.nlm.nih.gov/pubmed/18326165
57. Angulo, J.C., *et al.* Clinicopathological study of regressed testicular tumors (apparent extragonadal germ cell neoplasms). J Urol, 2009. 182: 2303. https://www.ncbi.nlm.nih.gov/pubmed/19762049
58. Mancini, M., *et al.* High prevalence of testicular cancer in azoospermic men without spermatogenesis. Hum Reprod, 2007. 22: 1042. https://www.ncbi.nlm.nih.gov/pubmed/17220165
59. Kim, W., *et al.* US MR imaging correlation in pathologic conditions of the scrotum. Radiographics, 2007. 27: 1239. https://www.ncbi.nlm.nih.gov/pubmed/17848688
60. Cassidy, F.H., *et al.* MR imaging of scrotal tumors and pseudotumors. Radiographics, 2010. 30: 665. https://www.ncbi.nlm.nih.gov/pubmed/20462987

61. Gilligan, T.D., *et al.* American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. J Clin Oncol, 2010. 28: 3388. https://www.ncbi.nlm.nih.gov/pubmed/20530278
62. Wanderas, E.H., *et al.* Trends in incidence of testicular cancer in Norway 1955-1992. Eur J Cancer, 1995. 31a: 2044. https://www.ncbi.nlm.nih.gov/pubmed/8562163
63. Koshida, K., *et al.* Significance of placental alkaline phosphatase (PLAP) in the monitoring of patients with seminoma. Br J Urol, 1996. 77: 138. https://www.ncbi.nlm.nih.gov/pubmed/8653285
64. Dieckmann, K.P., *et al.* Serum Levels of MicroRNA miR-371a-3p: A Sensitive and Specific New Biomarker for Germ Cell Tumours. Eur Urol, 2017. 71: 213. https://www.ncbi.nlm.nih.gov/pubmed/27495845
65. Murray, M.J., *et al.* The present and future of serum diagnostic tests for testicular germ cell tumours. Nat Rev Urol, 2016. 13: 715. https://www.ncbi.nlm.nih.gov/pubmed/27754472
66. Robinson, R., *et al.* Is it safe to insert a testicular prosthesis at the time of radical orchidectomy for testis cancer: an audit of 904 men undergoing radical orchidectomy. BJU Int, 2016. 117: 249. https://www.ncbi.nlm.nih.gov/pubmed/25168859
67. Matei, D.V., *et al.* Reliability of Frozen Section Examination in a Large Cohort of Testicular Masses: What Did We Learn? Clin Genitourin Cancer, 2017. 15: e689. https://www.ncbi.nlm.nih.gov/pubmed/28216275
68. Moch, H. *et al.* WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. 2016, Lyon. http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=70&codcch=4008
69. Verrill, C., *et al.* Reporting and Staging of Testicular Germ Cell Tumors: The International Society of Urological Pathology (ISUP) Testicular Cancer Consultation Conference Recommendations. Am J Surg Pathol, 2017. 41: e22. https://www.ncbi.nlm.nih.gov/pubmed/28368923
70. Dieckmann, K.P., *et al.* Prevalence of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasms. J Clin Oncol, 1996. 14: 3126. https://www.ncbi.nlm.nih.gov/pubmed/8955658
71. Ruf, C.G., *et al.* Contralateral biopsies in patients with testicular germ cell tumours: patterns of care in Germany and recent data regarding prevalence and treatment of testicular intra-epithelial neoplasia. Andrology, 2015. 3: 92. https://www.ncbi.nlm.nih.gov/pubmed/25146646
72. Andreassen, K.E., *et al.* Risk of metachronous contralateral testicular germ cell tumors: a population-based study of 7,102 Norwegian patients (1953-2007). Int J Cancer, 2011. 129: 2867. https://www.ncbi.nlm.nih.gov/pubmed/21626506
73. Harland, S.J., *et al.* Intratubular germ cell neoplasia of the contralateral testis in testicular cancer: defining a high risk group. J Urol, 1998. 160: 1353. https://www.ncbi.nlm.nih.gov/pubmed/9751353
74. Tabernero, J., *et al.* Incidence of contralateral germ cell testicular tumors in South Europe: report of the experience at 2 Spanish university hospitals and review of the literature. J Urol, 2004. 171: 164. https://www.ncbi.nlm.nih.gov/pubmed/14665868
75. Albers, P., *et al.* Clinical course and histopathologic risk factor assessment in patients with bilateral testicular germ cell tumors. Urology, 1999. 54: 714. https://www.ncbi.nlm.nih.gov/pubmed/10510934
76. Heidenreich, A., *et al.* Contralateral testicular biopsy procedure in patients with unilateral testis cancer: is it indicated? Semin Urol Oncol, 2002. 20: 234. https://www.ncbi.nlm.nih.gov/pubmed/12489055
77. Giwercman, A., *et al.* Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. J Urol, 1989. 142: 998. https://www.ncbi.nlm.nih.gov/pubmed/2571738
78. Dieckmann, K.P., *et al.* Diagnosis of contralateral testicular intraepithelial neoplasia (TIN) in patients with testicular germ cell cancer: systematic two-site biopsies are more sensitive than a single random biopsy. Eur Urol, 2007. 51: 175. https://www.ncbi.nlm.nih.gov/pubmed/16814456
79. Classen, J., *et al.* Radiotherapy with 16 Gy may fail to eradicate testicular intraepithelial neoplasia: preliminary communication of a dose-reduction trial of the German Testicular Cancer Study Group. Br J Cancer, 2003. 88: 828. https://www.ncbi.nlm.nih.gov/pubmed/12644817

80. Souchon, R., *et al.* Contralateral testicular cancer in spite of TIN-negative double biopsies and interval cisplatin chemotherapy. Strahlenther Onkol, 2006. 182: 289.
https://www.ncbi.nlm.nih.gov/pubmed/16673063
81. Petersen, P.M., *et al.* Effect of graded testicular doses of radiotherapy in patients treated for carcinoma-in-situ in the testis. J Clin Oncol, 2002. 20: 1537.
https://www.ncbi.nlm.nih.gov/pubmed/11896102
82. Heidenreich, A., *et al.* Testis-preserving surgery in bilateral testicular germ cell tumours. Br J Urol, 1997. 79: 253.
https://www.ncbi.nlm.nih.gov/pubmed/9052478
83. Dieckmann, K.P., *et al.* Treatment of testicular intraepithelial neoplasia (intratubular germ cell neoplasia unspecified) with local radiotherapy or with platinum-based chemotherapy: a survey of the German Testicular Cancer Study Group. Ann Oncol, 2013. 24: 1332.
https://www.ncbi.nlm.nih.gov/pubmed/23293116
84. Hoei-Hansen, C.E., *et al.* Carcinoma in situ testis, the progenitor of testicular germ cell tumours: a clinical review. Ann Oncol, 2005. 16: 863.
https://www.ncbi.nlm.nih.gov/pubmed/15821122
85. Screening for testicular cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med, 2011. 154: 483.
https://www.ncbi.nlm.nih.gov/pubmed/21464350
86. Thornton, C.P. Best Practice in Teaching Male Adolescents and Young Men to Perform Testicular Self-Examinations: A Review. J Pediatr Health Care, 2016. 30: 518.
https://www.ncbi.nlm.nih.gov/pubmed/26778347
87. Warde, P., *et al.* Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol, 2002. 20: 4448.
https://www.ncbi.nlm.nih.gov/pubmed/12431967
88. Aparicio, J., *et al.* Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study. J Clin Oncol, 2005. 23: 8717.
https://www.ncbi.nlm.nih.gov/pubmed/16260698
89. Chung, P., *et al.* Evaluation of a prognostic model for risk of relapse in stage I seminoma surveillance. Cancer Med, 2015. 4: 155.
https://www.ncbi.nlm.nih.gov/pubmed/25236854
90. Mortensen, M.S., *et al.* A nationwide cohort study of stage I seminoma patients followed on a surveillance program. Eur Urol, 2014. 66: 1172.
https://www.ncbi.nlm.nih.gov/pubmed/25064686
91. Aparicio, J., *et al.* Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG). Ann Oncol, 2014. 25: 2173.
https://www.ncbi.nlm.nih.gov/pubmed/25210015
92. Tandstad, T., *et al.* Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). Ann Oncol, 2016. 27: 1299.
https://www.ncbi.nlm.nih.gov/pubmed/27052649
93. Boormans, J.L., *et al.* Testicular Tumour Size and Rete Testis Invasion as Prognostic Factors for the Risk of Relapse of Clinical Stage I Seminoma Testis Patients Under Surveillance: a Systematic Review by the Testicular Cancer Guidelines Panel. Eur Urol, 2017.
https://www.ncbi.nlm.nih.gov/pubmed/29100813
94. Zengerling, F., *et al.* Prognostic factors for tumor recurrence in patients with clinical stage I seminoma undergoing surveillance-A systematic review. Urol Oncol, 2017.
https://www.ncbi.nlm.nih.gov/pubmed/28712790
95. Albers, P., *et al.* Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German Testicular Cancer Study Group Trial. J Clin Oncol, 2003. 21: 1505.
https://www.ncbi.nlm.nih.gov/pubmed/12697874
96. Alexandre, J., *et al.* Stage I non-seminomatous germ-cell tumours of the testis: identification of a subgroup of patients with a very low risk of relapse. Eur J Cancer, 2001. 37: 576.
https://www.ncbi.nlm.nih.gov/pubmed/11290432
97. Bandak, M., *et al.* Preorchiectomy Leydig Cell Dysfunction in Patients With Testicular Cancer. Clin Genitourin Cancer, 2017. 15: e37.
https://www.ncbi.nlm.nih.gov/pubmed/27524512
98. Brydoy, M., *et al.* Paternity and testicular function among testicular cancer survivors treated with two to four cycles of cisplatin-based chemotherapy. Eur Urol, 2010. 58: 134.
https://www.ncbi.nlm.nih.gov/pubmed/20395037

99. Brydoy, M., *et al.* Sperm counts and endocrinological markers of spermatogenesis in long-term survivors of testicular cancer. Br J Cancer, 2012. 107: 1833.
https://www.ncbi.nlm.nih.gov/pubmed/23169336
100. Gilbert, K., *et al.* Fertility preservation for men with testicular cancer: Is sperm cryopreservation cost effective in the era of assisted reproductive technology? Urol Oncol, 2018. 36: 92.e1.
https://www.ncbi.nlm.nih.gov/pubmed/29169844
101. Jacobsen, K.D., *et al.* Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. Eur Urol, 2002. 42: 229.
https://www.ncbi.nlm.nih.gov/pubmed/12234507
102. Spermon, J.R., *et al.* Fertility in men with testicular germ cell tumors. Fertil Steril, 2003. 79 Suppl 3: 1543.
https://www.ncbi.nlm.nih.gov/pubmed/12801557
103. Nieschlag E, Pharmacology and clinical use of testosterone, In: Testosterone-Action, Deficiency, Substitution., Nieschlag E., Behre HM., Nieschlag S., Eds. 1999, Springer Verlag Berlin-Heidelberg-New York.
104. Skoogh, J., *et al.* Feelings of loss and uneasiness or shame after removal of a testicle by orchidectomy: a population-based long-term follow-up of testicular cancer survivors. Int J Androl, 2011. 34: 183.
https://www.ncbi.nlm.nih.gov/pubmed/20550599
105. Jungwirth A., *et al.* EAU Guidelines on Male Infertility. Edn presented at the 4th EAU Annual Meeting in Barcelona, in EAU Guidelines, E.G. Office, Editor. 2019, EAU Guidelines Office Arnhem, The Netherlands.
106. Cohn-Cedermark, G., *et al.* Surveillance vs. adjuvant therapy of clinical stage I testicular tumors - a review and the SWENOTECA experience. Andrology, 2015. 3: 102.
https://www.ncbi.nlm.nih.gov/pubmed/25270123
107. Kollmannsberger, C., *et al.* Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. J Clin Oncol, 2015. 33: 51.
https://www.ncbi.nlm.nih.gov/pubmed/25135991
108. Groll, R.J., *et al.* A comprehensive systematic review of testicular germ cell tumor surveillance. Crit Rev Oncol Hematol, 2007. 64: 182.
https://www.ncbi.nlm.nih.gov/pubmed/17644403
109. Aparicio, J., *et al.* Multicenter study evaluating a dual policy of postorchiectomy surveillance and selective adjuvant single-agent carboplatin for patients with clinical stage I seminoma. Ann Oncol, 2003. 14: 867.
https://www.ncbi.nlm.nih.gov/pubmed/12796024
110. Tandstad, T., *et al.* Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish norwegian testicular cancer study group. J Clin Oncol, 2011. 29: 719.
https://www.ncbi.nlm.nih.gov/pubmed/21205748
111. Oliver, R.T., *et al.* Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol, 2011. 29: 957.
https://www.ncbi.nlm.nih.gov/pubmed/21282539
112. Oliver, R.T., *et al.* Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. Lancet, 2005. 366: 293.
https://www.ncbi.nlm.nih.gov/pubmed/16039331
113. Mead, G.M., *et al.* Randomized trials in 2466 patients with stage I seminoma: patterns of relapse and follow-up. J Natl Cancer Inst, 2011. 103: 241.
https://www.ncbi.nlm.nih.gov/pubmed/21212385
114. Schoffski P., *et al.* Health-related quality of life (QoL) in patients with seminoma stage I treated with either adjuvant radiotherapy (RT) or two cycles of carboplatinum chemotherapy (CT): Results of a randomized phase III trial of the German Interdisciplinary Working Party on Testicular Cancer. J Clin Oncol, 2007. 25.
http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.5050
115. Fischer, S., *et al.* Outcome of Men With Relapse After Adjuvant Carboplatin for Clinical Stage I Seminoma. J Clin Oncol, 2017. 35: 194.
https://www.ncbi.nlm.nih.gov/pubmed/27893332
116. Fossa, S.D., *et al.* Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. J Clin Oncol, 1999. 17: 1146.
https://www.ncbi.nlm.nih.gov/pubmed/10561173

117. Jones WG, F.S., Mead GM, *et al.* A randomized trial of two radiotherapy schedules in the adjuvant treatment of stage I seminoma (MRC TE 18). Eur J Cancer 2001. 37: abstr 572. https://www.ejcancer.com/article/S0959-8049(01)81064-9/abstract
118. Melchior, D., *et al.* Long term results and morbidity of paraaortic compared with paraaortic and iliac adjuvant radiation in clinical stage I seminoma. Anticancer Res, 2001. 21: 2989. https://www.ncbi.nlm.nih.gov/pubmed/11712799
119. Bieri, S., *et al.* Seminoma of the testis: is scrotal shielding necessary when radiotherapy is limited to the para-aortic nodes? Radiother Oncol, 1999. 50: 349. https://www.ncbi.nlm.nih.gov/pubmed/10392822
120. van den Belt-Dusebout, A.W., *et al.* Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol, 2007. 25: 4370. https://www.ncbi.nlm.nih.gov/pubmed/17906202
121. Horwich, A., *et al.* Second cancer risk and mortality in men treated with radiotherapy for stage I seminoma. Br J Cancer, 2014. 110: 256. https://www.ncbi.nlm.nih.gov/pubmed/24263066
122. Patel, H.D., *et al.* Radiotherapy for stage I and II testicular seminomas: Secondary malignancies and survival. Urol Oncol, 2017. 35: 606 e1. https://www.ncbi.nlm.nih.gov/pubmed/28712791
123. Aparicio, J., *et al.* Risk-adapted treatment in clinical stage I testicular seminoma: the third Spanish Germ Cell Cancer Group study. J Clin Oncol, 2011. 29: 4677. https://www.ncbi.nlm.nih.gov/pubmed/22042940
124. Freedman, L.S., *et al.* Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. Lancet, 1987. 2: 294. https://www.ncbi.nlm.nih.gov/pubmed/2886764
125. Read, G., *et al.* Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol, 1992. 10: 1762. https://www.ncbi.nlm.nih.gov/pubmed/1403057
126. Klepp, O., *et al.* Prognostic factors in clinical stage I nonseminomatous germ cell tumors of the testis: multivariate analysis of a prospective multicenter study. Swedish-Norwegian Testicular Cancer Group. J Clin Oncol, 1990. 8: 509. https://www.ncbi.nlm.nih.gov/pubmed/1689773
127. Kollmannsberger, C., *et al.* Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. Ann Oncol, 2010. 21: 1296. https://www.ncbi.nlm.nih.gov/pubmed/19875756
128. Nichols, C.R., *et al.* Active surveillance is the preferred approach to clinical stage I testicular cancer. J Clin Oncol, 2013. 31: 3490. https://www.ncbi.nlm.nih.gov/pubmed/24002502
129. Cullen, M.H., *et al.* Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol, 1996. 14: 1106. https://www.ncbi.nlm.nih.gov/pubmed/8648364
130. Pont, J., *et al.* Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol, 1996. 14: 441. https://www.ncbi.nlm.nih.gov/pubmed/8636755
131. Chevreau, C., *et al.* Long-term efficacy of two cycles of BEP regimen in high-risk stage I nonseminomatous testicular germ cell tumors with embryonal carcinoma and/or vascular invasion. Eur Urol, 2004. 46: 209. https://www.ncbi.nlm.nih.gov/pubmed/15245815
132. Bohlen, D., *et al.* Fertility and sexual function following orchiectomy and 2 cycles of chemotherapy for stage I high risk nonseminomatous germ cell cancer. J Urol, 2001. 165: 441. https://www.ncbi.nlm.nih.gov/pubmed/11176393
133. Huddart, R.A., *et al.* Cardiovascular disease as a long-term complication of treatment for testicular cancer. J Clin Oncol, 2003. 21: 1513. https://www.ncbi.nlm.nih.gov/pubmed/12697875
134. Albers, P., *et al.* Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I Nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. J Clin Oncol, 2008. 26: 2966. https://www.ncbi.nlm.nih.gov/pubmed/18458040

135. Tandstad, T., *et al.* Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. J Clin Oncol, 2009. 27: 2122. https://www.ncbi.nlm.nih.gov/pubmed/19307506
136. Tandstad, T., *et al.* One course of adjuvant BEP in clinical stage I nonseminoma mature and expanded results from the SWENOTECA group. Ann Oncol, 2014. 25: 2167. https://www.ncbi.nlm.nih.gov/pubmed/25114021
137. Baniel, J., *et al.* Late relapse of testicular cancer. J Clin Oncol, 1995. 13: 1170. https://www.ncbi.nlm.nih.gov/pubmed/8770308
138. Westermann, D.H., *et al.* Long-term followup results of 1 cycle of adjuvant bleomycin, etoposide and cisplatin chemotherapy for high risk clinical stage I nonseminomatous germ cell tumors of the testis. J Urol, 2008. 179: 163. https://www.ncbi.nlm.nih.gov/pubmed/18001800
139. Baniel, J., *et al.* Cost- and risk-benefit considerations in the management of clinical stage I nonseminomatous testicular tumors. Ann Surg Oncol, 1996. 3: 86. https://www.ncbi.nlm.nih.gov/pubmed/8770308
140. Rustin, G.J., *et al.* Randomized trial of two or five computed tomography scans in the surveillance of patients with stage I nonseminomatous germ cell tumors of the testis: Medical Research Council Trial TE08, ISRCTN56475197--the National Cancer Research Institute Testis Cancer Clinical Studies Group. J Clin Oncol, 2007. 25: 1310. https://www.ncbi.nlm.nih.gov/pubmed/17416851
141. Maroto, P., *et al.* Multicentre risk-adapted management for stage I non-seminomatous germ cell tumours. Ann Oncol, 2005. 16: 1915. https://www.ncbi.nlm.nih.gov/pubmed/16126737
142. Tandstad, T., *et al.* Long-term follow-up after risk-adapted treatment in clinical stage 1 (CS1) nonseminomatous germ-cell testicular cancer (NSGCT) implementing adjuvant CVB chemotherapy. A SWENOTECA study. Ann Oncol, 2010. 21: 1858. https://www.ncbi.nlm.nih.gov/pubmed/20142410
143. Klepp, O., *et al.* Risk-adapted treatment of clinical stage 1 non-seminoma testis cancer. Eur J Cancer, 1997. 33: 1038. https://www.ncbi.nlm.nih.gov/pubmed/9376184
144. Flechtner, H.H., *et al.* Quality-of-Life Analysis of the German Prospective Multicentre Trial of Single-cycle Adjuvant BEP Versus Retroperitoneal Lymph Node Dissection in Clinical Stage I Nonseminomatous Germ Cell Tumours. Eur Urol, 2016. 69: 518. https://www.ncbi.nlm.nih.gov/pubmed/26620368
145. Heidenreich, A., *et al.* Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. J Urol, 2003. 169: 1710. https://www.ncbi.nlm.nih.gov/pubmed/12686815
146. Nicolai, N., *et al.* Retroperitoneal lymph node dissection with no adjuvant chemotherapy in clinical stage I nonseminomatous germ cell tumours: long-term outcome and analysis of risk factors of recurrence. Eur Urol, 2010. 58: 912. https://www.ncbi.nlm.nih.gov/pubmed/20817343
147. Nicolai, N., *et al.* Laparoscopic Retroperitoneal Lymph Node Dissection for Clinical Stage I Nonseminomatous Germ Cell Tumors of the Testis: Safety and Efficacy Analyses at a High Volume Center. J Urol, 2018. 199: 741. https://www.ncbi.nlm.nih.gov/pubmed/28964782
148. Al-Ahmadie, H.A., *et al.* Primary retroperitoneal lymph node dissection in low-stage testicular germ cell tumors: a detailed pathologic study with clinical outcome analysis with special emphasis on patients who did not receive adjuvant therapy. Urology, 2013. 82: 1341. https://www.ncbi.nlm.nih.gov/pubmed/24094656
149. Foster, R.S., *et al.* Clinical stage I nonseminoma: surgery versus surveillance. Semin Oncol, 1998. 25: 145. https://www.ncbi.nlm.nih.gov/pubmed/9562447
150. Krege, S., *et al.* 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 (EGCCCG): part I. Eur Urol, 2008. 53: 478. https://www.ncbi.nlm.nih.gov/pubmed/18191324
151. Pizzocaro G, *et al.* Marker positive clinical stage I non seminomatous germ cell tumours (NSGCT) of the testis: which primary therapy? J Urol 1996. 155(Suppl):328A. [No abstract available].

152. Davis, B.E., *et al.* The management of patients with nonseminomatous germ cell tumors of the testis with serologic disease only after orchiectomy. J Urol, 1994. 152: 111.
https://www.ncbi.nlm.nih.gov/pubmed/7515445
153. Ahmed, K.A., *et al.* Outcomes and treatment patterns as a function of time in stage IS testicular seminoma: a population-based analysis. Cancer Epidemiol, 2014. 38: 124.
https://www.ncbi.nlm.nih.gov/pubmed/24613492
154. Classen, J., *et al.* Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. J Clin Oncol, 2003. 21: 1101.
https://www.ncbi.nlm.nih.gov/pubmed/12637477
155. Chung, P.W., *et al.* Stage II testicular seminoma: patterns of recurrence and outcome of treatment. Eur Urol, 2004. 45: 754.
https://www.ncbi.nlm.nih.gov/pubmed/15149748
156. Hallemeier, C.L., *et al.* Long-term outcomes of radiotherapy for stage II testicular seminoma--the Mayo Clinic experience. Urol Oncol, 2013. 31: 1832.
https://www.ncbi.nlm.nih.gov/pubmed/22537538
157. Horwich, A., *et al.* Neoadjuvant carboplatin before radiotherapy in stage IIA and IIB seminoma. Ann Oncol, 2013. 24: 2104.
https://www.ncbi.nlm.nih.gov/pubmed/23592702
158. Paly, J.J., *et al.* Management and outcomes of clinical stage IIA/B seminoma: Results from the National Cancer Data Base 1998-2012. Pract Radiat Oncol, 2016. 6: e249.
https://www.ncbi.nlm.nih.gov/pubmed/27345128
159. Giannatempo, P., *et al.* Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: a systematic review and meta-analysis of patient outcomes. Ann Oncol, 2015. 26: 657.
https://www.ncbi.nlm.nih.gov/pubmed/23592702
160. Krege, S., *et al.* Single agent carboplatin for CS IIA/B testicular seminoma. A phase II study of the German Testicular Cancer Study Group (GTCSG). Ann Oncol, 2006. 17: 276.
https://www.ncbi.nlm.nih.gov/pubmed/16254023
161. Stephenson, A.J., *et al.* Nonrandomized comparison of primary chemotherapy and retroperitoneal lymph node dissection for clinical stage IIA and IIB nonseminomatous germ cell testicular cancer. J Clin Oncol, 2007. 25: 5597.
https://www.ncbi.nlm.nih.gov/pubmed/18065732
162. Weissbach, L., *et al.* RPLND or primary chemotherapy in clinical stage IIA/B nonseminomatous germ cell tumors? Results of a prospective multicenter trial including quality of life assessment. Eur Urol, 2000. 37: 582.
https://www.ncbi.nlm.nih.gov/pubmed/10765098
163. Williams, S.D., *et al.* Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. N Engl J Med, 1987. 317: 1433.
https://www.ncbi.nlm.nih.gov/pubmed/2446132
164. Horwich, A., *et al.* Primary chemotherapy for stage II nonseminomatous germ cell tumors of the testis. J Urol, 1994. 151: 72.
https://www.ncbi.nlm.nih.gov/pubmed/8254836
165. Donohue, J.P., *et al.* The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). J Urol, 1995. 153: 85.
https://www.ncbi.nlm.nih.gov/pubmed/7966799
166. Bokemeyer, C., *et al.* Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: a pooled analysis of two randomised trials. Br J Cancer, 2004. 91: 683.
https://www.ncbi.nlm.nih.gov/pubmed/15266338
167. Thibault, C., *et al.* Compliance with guidelines and correlation with outcome in patients with advanced germ-cell tumours. Eur J Cancer, 2014. 50: 1284.
https://www.ncbi.nlm.nih.gov/pubmed/24560488
168. de Wit, R. Refining the optimal chemotherapy regimen in good prognosis germ cell cancer: interpretation of the current body of knowledge. J Clin Oncol, 2007. 25: 4346.
https://www.ncbi.nlm.nih.gov/pubmed/17906198
169. Beyer, J., *et al.* [Chemotherapy for germ cell cancer]. Urologe A, 2004. 43: 1507.
https://www.ncbi.nlm.nih.gov/pubmed/15592707
170. de Wit, R., *et al.* Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. J Clin Oncol, 1997. 15: 1837.
https://www.ncbi.nlm.nih.gov/pubmed/9164193

171. Horwich, A., *et al.* Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol, 1997. 15: 1844.
https://www.ncbi.nlm.nih.gov/pubmed/9164194
172. de Wit, R., *et al.* Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol, 2001. 19: 1629.
https://www.ncbi.nlm.nih.gov/pubmed/11250991
173. Grimison, P.S., *et al.* Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: updated analysis of a randomized trial. J Natl Cancer Inst, 2010. 102: 1253.
https://www.ncbi.nlm.nih.gov/pubmed/20631341
174. Cary, K.C., *et al.* The impact of bleomycin on retroperitoneal histology at post-chemotherapy retroperitoneal lymph node dissection of good risk germ cell tumors. J Urol, 2015. 193: 507.
https://www.ncbi.nlm.nih.gov/pubmed/25254937
175. Culine, S., *et al.* Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol, 2007. 18: 917.
https://www.ncbi.nlm.nih.gov/pubmed/17351252
176. Kier, M.G., *et al.* Prognostic Factors and Treatment Results After Bleomycin, Etoposide, and Cisplatin in Germ Cell Cancer: A Population-based Study. Eur Urol, 2017. 71: 290.
https://www.ncbi.nlm.nih.gov/pubmed/27649970
177. Shamash, J., *et al.* A randomized phase III study of 72 h infusional versus bolus bleomycin in BEP (bleomycin, etoposide and cisplatin) chemotherapy to treat IGCCCG good prognosis metastatic germ cell tumours (TE-3). Ann Oncol, 2017. 28: 1333.
https://www.ncbi.nlm.nih.gov/pubmed/28327896
178. Fossa, S.D., *et al.* Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. J Clin Oncol, 1998. 16: 716.
https://www.ncbi.nlm.nih.gov/pubmed/9469362
179. Sheinfeld J, *et al.* Management of postchemotherapy residual masses in advanced germ cell tumours. Urol Clin North Am 1997: 18.
https://www.ncbi.nlm.nih.gov/pubmed/8381994
180. de Wit, R., *et al.* Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. Br J Cancer, 1998. 78: 828.
https://www.ncbi.nlm.nih.gov/pubmed/9743309
181. de Wit, R., *et al.* Randomized phase III study comparing paclitaxel-bleomycin, etoposide, and cisplatin (BEP) to standard BEP in intermediate-prognosis germ-cell cancer: intergroup study EORTC 30983. J Clin Oncol, 2012. 30: 792.
https://www.ncbi.nlm.nih.gov/pubmed/22271474
182. Seidel, C., *et al.* Intermediate prognosis in metastatic germ cell tumours-outcome and prognostic factors. Eur J Cancer, 2018. 94: 16.
https://www.ncbi.nlm.nih.gov/pubmed/29505967
183. de Wit, R., *et al.* Management of intermediate-prognosis germ-cell cancer: results of a phase I/II study of Taxol-BEP. Int J Cancer, 1999. 83: 831.
https://www.ncbi.nlm.nih.gov/pubmed/10597204
184. Nichols, C.R., *et al.* Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol, 1998. 16: 1287.
https://www.ncbi.nlm.nih.gov/pubmed/9552027
185. Droz, J.P., *et al.* Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. Eur Urol, 2007. 51: 739.
https://www.ncbi.nlm.nih.gov/pubmed/17084512

186. Daugaard, G., *et al.* A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). Ann Oncol, 2011. 22: 1054.
https://www.ncbi.nlm.nih.gov/pubmed/21059637
187. Dieckmann, K.P., *et al.* Myocardial infarction and other major vascular events during chemotherapy for testicular cancer. Ann Oncol, 2010. 21: 1607.
https://www.ncbi.nlm.nih.gov/pubmed/20067918
188. Olofsson, S.E., *et al.* Population-based study of treatment guided by tumor marker decline in patients with metastatic nonseminomatous germ cell tumor: a report from the Swedish-Norwegian Testicular Cancer Group. J Clin Oncol, 2011. 29: 2032.
https://www.ncbi.nlm.nih.gov/pubmed/21482994
189. Oldenburg, J., *et al.* Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2013. 24 Suppl 6: vi125.
https://www.ncbi.nlm.nih.gov/pubmed/24078656
190. Bokemeyer, C., *et al.* Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol, 2002. 20: 1864.
https://www.ncbi.nlm.nih.gov/pubmed/11919246
191. Kollmannsberger, C., *et al.* Identification of prognostic subgroups among patients with metastatic 'IGCCCG poor-prognosis' germ-cell cancer: an explorative analysis using cart modeling. Ann Oncol, 2000. 11: 1115.
https://www.ncbi.nlm.nih.gov/pubmed/11061604
192. Bokemeyer, C., *et al.* First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: A multivariate and matched-pair analysis. J Clin Oncol, 1999. 17: 3450.
https://www.ncbi.nlm.nih.gov/pubmed/10550141
193. Massard, C., *et al.* Poor prognosis nonseminomatous germ-cell tumours (NSGCTs): should chemotherapy doses be reduced at first cycle to prevent acute respiratory distress syndrome in patients with multiple lung metastases? Ann Oncol, 2010. 21: 1585.
https://www.ncbi.nlm.nih.gov/pubmed/20181575
194. Gillessen, S., *et al.* Low-dose induction chemotherapy with Baby-BOP in patients with metastatic germ-cell tumours does not compromise outcome: a single-centre experience. Ann Oncol, 2010. 21: 1589.
https://www.ncbi.nlm.nih.gov/pubmed/20164149
195. Woldu, S.L., *et al.* Impact of hospital case volume on testicular cancer outcomes and practice patterns. Urol Oncol, 2018. 36: 14.e7.
https://www.ncbi.nlm.nih.gov/pubmed/28935185
196. Gerl, A., *et al.* Prognostic implications of tumour marker analysis in non-seminomatous germ cell tumours with poor prognosis metastatic disease. Eur J Cancer, 1993. 29A: 961.
https://www.ncbi.nlm.nih.gov/pubmed/7684597
197. Murphy, B.A., *et al.* Serum tumor marker decline is an early predictor of treatment outcome in germ cell tumor patients treated with cisplatin and ifosfamide salvage chemotherapy. Cancer, 1994. 73: 2520.
https://www.ncbi.nlm.nih.gov/pubmed/7513603
198. Andre, F., *et al.* The growing teratoma syndrome: results of therapy and long-term follow-up of 33 patients. Eur J Cancer, 2000. 36: 1389.
https://www.ncbi.nlm.nih.gov/pubmed/10899652
199. de Wit, R., *et al.* Serum alpha-fetoprotein surge after the initiation of chemotherapy for non-seminomatous testicular cancer has an adverse prognostic significance. Br J Cancer, 1998. 78: 1350.
https://www.ncbi.nlm.nih.gov/pubmed/9823978
200. Zon, R.T., *et al.* Management strategies and outcomes of germ cell tumor patients with very high human chorionic gonadotropin levels. J Clin Oncol, 1998. 16: 1294.
https://www.ncbi.nlm.nih.gov/pubmed/9552028
201. Fossa, S.D., *et al.* Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumours. Br J Cancer, 1999. 80: 1392.
https://www.ncbi.nlm.nih.gov/pubmed/10424741
202. Hofmockel, G., *et al.* Chemotherapy in advanced seminoma and the role of postcytostatic retroperitoneal lymph node dissection. Urol Int, 1996. 57: 38.
https://www.ncbi.nlm.nih.gov/pubmed/8840489

203. Kamat, M.R., *et al.* Value of retroperitoneal lymph node dissection in advanced testicular seminoma. J Surg Oncol, 1992. 51: 65.
https://www.ncbi.nlm.nih.gov/pubmed/1381455
204. Loehrer, P.J., Sr., *et al.* Chemotherapy of metastatic seminoma: the Southeastern Cancer Study Group experience. J Clin Oncol, 1987. 5: 1212.
https://www.ncbi.nlm.nih.gov/pubmed/2442317
205. Motzer, R., *et al.* Residual mass: an indication for further therapy in patients with advanced seminoma following systemic chemotherapy. J Clin Oncol, 1987. 5: 1064.
https://www.ncbi.nlm.nih.gov/pubmed/3598610
206. Herr, H.W., *et al.* Surgery for a post-chemotherapy residual mass in seminoma. J Urol, 1997. 157: 860.
https://www.ncbi.nlm.nih.gov/pubmed/9072586
207. Mosharafa, A.A., *et al.* Is post-chemotherapy resection of seminomatous elements associated with higher acute morbidity? J Urol, 2003. 169: 2126.
https://www.ncbi.nlm.nih.gov/pubmed/12771733
208. Puc, H.S., *et al.* Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan-Kettering Cancer Center. J Clin Oncol, 1996. 14: 454.
https://www.ncbi.nlm.nih.gov/pubmed/8636757
209. Cathomas, R., *et al.* Questioning the Value of Fluorodeoxyglucose Positron Emission Tomography for Residual Lesions After Chemotherapy for Metastatic Seminoma: Results of an International Global Germ Cell Cancer Group Registry. J Clin Oncol, 2018. 36: 3381.
https://www.ncbi.nlm.nih.gov/pubmed/30285559
210. Miki, T., *et al.* Post-chemotherapy nerve-sparing retroperitoneal lymph node dissection for advanced germ cell tumor. Int J Urol, 2009. 16: 379.
https://www.ncbi.nlm.nih.gov/pubmed/19191930
211. Carver, B.S., *et al.* Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol, 2007. 25: 5603.
https://www.ncbi.nlm.nih.gov/pubmed/17998544
212. Kollmannsberger, C., *et al.* Management of disseminated nonseminomatous germ cell tumors with risk-based chemotherapy followed by response-guided postchemotherapy surgery. J Clin Oncol, 2010. 28: 537.
https://www.ncbi.nlm.nih.gov/pubmed/20026807
213. Ehrlich, Y., *et al.* Long-term follow-up of Cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? J Clin Oncol, 2010. 28: 531.
https://www.ncbi.nlm.nih.gov/pubmed/20026808
214. Leao, R., *et al.* A New Model to Predict Benign Histology in Residual Retroperitoneal Masses After Chemotherapy in Nonseminoma. Eur Urol Focus, 2018.
https://www.ncbi.nlm.nih.gov/pubmed/29428550
215. Hartmann, J.T., *et al.* Comparison of histological results from the resection of residual masses at different sites after chemotherapy for metastatic non-seminomatous germ cell tumours. Eur J Cancer, 1997. 33: 843.
https://www.ncbi.nlm.nih.gov/pubmed/9291803
216. Hendry, W.F., *et al.* Metastatic nonseminomatous germ cell tumors of the testis: results of elective and salvage surgery for patients with residual retroperitoneal masses. Cancer, 2002. 94: 1668.
https://www.ncbi.nlm.nih.gov/pubmed/11920527
217. Sheinfeld, J. The role of adjunctive postchemotherapy surgery for nonseminomatous germ-cell tumors: current concepts and controversies. Semin Urol Oncol, 2002. 20: 262.
https://www.ncbi.nlm.nih.gov/pubmed/12489059
218. Steyerberg, E.W., *et al.* Prediction models for the histology of residual masses after chemotherapy for metastatic testicular cancer. ReHiT Study Group. Int J Cancer, 1999. 83: 856.
https://www.ncbi.nlm.nih.gov/pubmed/10597211
219. Carver, B.S., *et al.* Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. J Clin Oncol, 2007. 25: 1033.
https://www.ncbi.nlm.nih.gov/pubmed/17261854
220. Oldenburg, J., *et al.* Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. J Clin Oncol, 2003. 21: 3310.
https://www.ncbi.nlm.nih.gov/pubmed/12947067

221. Rick, O., *et al.* Residual tumor resection after high-dose chemotherapy in patients with relapsed or refractory germ cell cancer. J Clin Oncol, 2004. 22: 3713.
https://www.ncbi.nlm.nih.gov/pubmed/15365067

222. Baniel, J., *et al.* Late relapse of clinical stage I testicular cancer. J Urol, 1995. 154: 1370.
https://www.ncbi.nlm.nih.gov/pubmed/7658541

223. Fizazi, K., *et al.* Assessing prognosis and optimizing treatment in patients with postchemotherapy viable nonseminomatous germ-cell tumors (NSGCT): results of the sCR2 international study. Ann Oncol, 2008. 19: 259.
https://www.ncbi.nlm.nih.gov/pubmed/18042838

224. Heidenreich, A., *et al.* Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. Eur Urol, 2009. 55: 217.
https://www.ncbi.nlm.nih.gov/pubmed/18926622

225. Beck, S.D., *et al.* Is full bilateral retroperitoneal lymph node dissection always necessary for postchemotherapy residual tumor? Cancer, 2007. 110: 1235.
https://www.ncbi.nlm.nih.gov/pubmed/17665498

226. Busch, J., *et al.* Laparoscopic and open postchemotherapy retroperitoneal lymph node dissection in patients with advanced testicular cancer--a single center analysis. BMC Urol, 2012. 12: 15.
https://www.ncbi.nlm.nih.gov/pubmed/22651395

227. Arai, Y., *et al.* Extraperitoneal laparoscopic retroperitoneal lymph node dissection after chemotherapy for nonseminomatous testicular germ-cell tumor: surgical and oncological outcomes. Int Urol Nephrol, 2012. 44: 1389.
https://www.ncbi.nlm.nih.gov/pubmed/22648291

228. Nicolai, N., *et al.* Laparoscopic Postchemotherapy Retroperitoneal Lymph-Node Dissection Can Be a Standard Option in Defined Nonseminomatous Germ Cell Tumor Patients. J Endourol, 2016. 30: 1112.
https://www.ncbi.nlm.nih.gov/pubmed/27533924

229. Steyerberg, E.W., *et al.* Residual masses after chemotherapy for metastatic testicular cancer: the clinical implications of the association between retroperitoneal and pulmonary histology. Re-analysis of Histology in Testicular Cancer (ReHiT) Study Group. J Urol, 1997. 158: 474.
https://www.ncbi.nlm.nih.gov/pubmed/9224327

230. Besse, B., *et al.* Nonseminomatous germ cell tumors: assessing the need for postchemotherapy contralateral pulmonary resection in patients with ipsilateral complete necrosis. J Thorac Cardiovasc Surg, 2009. 137: 448.
https://www.ncbi.nlm.nih.gov/pubmed/19185168

231. Schirren, J., *et al.* The role of residual tumor resection in the management of nonseminomatous germ cell cancer of testicular origin. Thorac Cardiovasc Surg, 2012. 60: 405.
https://www.ncbi.nlm.nih.gov/pubmed/22383152

232. Ehrlich, Y., *et al.* Vena caval reconstruction during postchemotherapy retroperitoneal lymph node dissection for metastatic germ cell tumor. Urology, 2009. 73: 442 e17.
https://www.ncbi.nlm.nih.gov/pubmed/18436290

233. Heidenreich, A., *et al.* Surgical management of complex residual masses following systemic chemotherapy for metastatic testicular germ cell tumours. Ann Oncol, 2017. 28: 362.
https://www.ncbi.nlm.nih.gov/pubmed/27831507

234. Winter, C., *et al.* Residual tumor size and IGCCCG risk classification predict additional vascular procedures in patients with germ cell tumors and residual tumor resection: a multicenter analysis of the German Testicular Cancer Study Group. Eur Urol, 2012. 61: 403.
https://www.ncbi.nlm.nih.gov/pubmed/22078334

235. Wells, H., *et al.* Contemporary retroperitoneal lymph node dissection (RPLND) for testis cancer in the UK - a national study. BJU Int, 2017. 119: 91.
https://www.ncbi.nlm.nih.gov/pubmed/27353395

236. Eggener, S.E., *et al.* Pathologic findings and clinical outcome of patients undergoing retroperitoneal lymph node dissection after multiple chemotherapy regimens for metastatic testicular germ cell tumors. Cancer, 2007. 109: 528.
https://www.ncbi.nlm.nih.gov/pubmed/17177200

237. Oechsle, K., *et al.* Long-term survival after treatment with gemcitabine and oxaliplatin with and without paclitaxel plus secondary surgery in patients with cisplatin-refractory and/or multiply relapsed germ cell tumors. Eur Urol, 2011. 60: 850.
https://www.ncbi.nlm.nih.gov/pubmed/21704446

238. Nicolai, N., *et al.* Long-term results of a combination of paclitaxel, cisplatin and gemcitabine for salvage therapy in male germ-cell tumours. BJU Int, 2009. 104: 340.
https://www.ncbi.nlm.nih.gov/pubmed/19239440
239. Beck, S.D., *et al.* Outcome analysis for patients with elevated serum tumor markers at postchemotherapy retroperitoneal lymph node dissection. J Clin Oncol, 2005. 23: 6149.
https://www.ncbi.nlm.nih.gov/pubmed/16135481
240. Fizazi, K., *et al.* Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy--results from an international study group. J Clin Oncol, 2001. 19: 2647.
https://www.ncbi.nlm.nih.gov/pubmed/11352956
241. Stenning, S.P., *et al.* Postchemotherapy residual masses in germ cell tumor patients: content, clinical features, and prognosis. Medical Research Council Testicular Tumour Working Party. Cancer, 1998. 83: 1409.
https://www.ncbi.nlm.nih.gov/pubmed/9762943
242. Miller, K.D., *et al.* Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. J Clin Oncol, 1997. 15: 1427.
https://www.ncbi.nlm.nih.gov/pubmed/9193335
243. Fizazi, K., *et al.* Combining gemcitabine, cisplatin, and ifosfamide (GIP) is active in patients with relapsed metastatic germ-cell tumors (GCT): a prospective multicenter GETUG phase II trial. Ann Oncol, 2014. 25: 987.
https://www.ncbi.nlm.nih.gov/pubmed/24595454
244. Pico, J.L., *et al.* A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol, 2005. 16: 1152.
https://www.ncbi.nlm.nih.gov/pubmed/15928070
245. Lorch, A., *et al.* Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. J Clin Oncol, 2007. 25: 2778.
https://www.ncbi.nlm.nih.gov/pubmed/17602082
246. Oechsle, K., *et al.* Patterns of relapse after chemotherapy in patients with high-risk non-seminomatous germ cell tumor. Oncology, 2010. 78: 47.
https://www.ncbi.nlm.nih.gov/pubmed/20215785
247. Agarwala, A.K., *et al.* Salvage chemotherapy with high-dose carboplatin and etoposide with peripheral blood stem cell transplant in patients with relapsed pure seminoma. Am J Clin Oncol, 2011. 34: 286.
https://www.ncbi.nlm.nih.gov/pubmed/20523207
248. Berger, L.A., *et al.* First salvage treatment in patients with advanced germ cell cancer after cisplatin-based chemotherapy: analysis of a registry of the German Testicular Cancer Study Group (GTCSG). J Cancer Res Clin Oncol, 2014. 140: 1211.
https://www.ncbi.nlm.nih.gov/pubmed/24696231
249. Massard, C., *et al.* Tumor marker kinetics predict outcome in patients with relapsed disseminated non-seminomatous germ-cell tumors. Ann Oncol, 2013. 24: 322.
https://www.ncbi.nlm.nih.gov/pubmed/23104726
250. Necchi, A., *et al.* Prognostic impact of progression to induction chemotherapy and prior paclitaxel therapy in patients with germ cell tumors receiving salvage high-dose chemotherapy in the last 10 years: a study of the European Society for Blood and Marrow Transplantation Solid Tumors Working Party. Bone Marrow Transplant, 2016. 51: 384.
https://www.ncbi.nlm.nih.gov/pubmed/26642334
251. Lorch, A., *et al.* Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: long-term results of a prospective randomized trial. J Clin Oncol, 2012. 30: 800.
https://www.ncbi.nlm.nih.gov/pubmed/22291076
252. Bin Riaz, I., *et al.* Role of one, two and three doses of high-dose chemotherapy with autologous transplantation in the treatment of high-risk or relapsed testicular cancer: a systematic review. Bone Marrow Transplant, 2018. 53: 1242.
https://www.ncbi.nlm.nih.gov/pubmed/29703969
253. Mead, G.M., *et al.* A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial. Br J Cancer, 2005. 93: 178.
https://www.ncbi.nlm.nih.gov/pubmed/15999102

254. Segal, R., *et al.* Surveillance programs for early stage non-seminomatous testicular cancer: a practice guideline. Can J Urol, 2001. 8: 1184.
https://www.ncbi.nlm.nih.gov/pubmed/11268306
255. Jain, A., *et al.* Phase II clinical trial of oxaliplatin and bevacizumab in refractory germ cell tumors. Am J Clin Oncol, 2014. 37: 450.
https://www.ncbi.nlm.nih.gov/pubmed/23388561
256. Mego, M., *et al.* Phase II study of everolimus in refractory testicular germ cell tumors. Urol Oncol, 2016. 34: 122 e17.
https://www.ncbi.nlm.nih.gov/pubmed/26612480
257. Oing, C., *et al.* Investigational targeted therapies for the treatment of testicular germ cell tumors. Expert Opin Investig Drugs, 2016. 25: 1033.
https://www.ncbi.nlm.nih.gov/pubmed/27286362
258. Necchi, A., *et al.* Pazopanib in advanced germ cell tumors after chemotherapy failure: results of the open-label, single-arm, phase 2 Pazotest trial. Ann Oncol, 2017. 28: 1346.
https://www.ncbi.nlm.nih.gov/pubmed/24161525
259. Albany, C., *et al.* Treatment of CD30-Expressing Germ Cell Tumors and Sex Cord Stromal Tumors with Brentuximab Vedotin: Identification and Report of Seven Cases. Oncologist, 2018. 23: 316.
https://www.ncbi.nlm.nih.gov/pubmed/29222199
260. Adra, N., *et al.* Phase II trial of pembrolizumab in patients with platinum refractory germ-cell tumors: a Hoosier Cancer Research Network Study GU14-206. Ann Oncol, 2018. 29: 209.
https://www.ncbi.nlm.nih.gov/pubmed/29045540
261. Necchi, A., *et al.* Combination of paclitaxel, cisplatin, and gemcitabine (TPG) for multiple relapses or platinum-resistant germ cell tumors: long-term outcomes. Clin Genitourin Cancer, 2014. 12: 63.
https://www.ncbi.nlm.nih.gov/pubmed/24161525
262. Mulherin, B.P., *et al.* Long-term survival with paclitaxel and gemcitabine for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. Am J Clin Oncol, 2015. 38: 373.
https://www.ncbi.nlm.nih.gov/pubmed/26214082
263. Beyer, J., *et al.* Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. Ann Oncol, 2013. 24: 878.
https://www.ncbi.nlm.nih.gov/pubmed/23152360
264. Oldenburg, J., *et al.* Late relapses of germ cell malignancies: incidence, management, and prognosis. J Clin Oncol, 2006. 24: 5503.
https://www.ncbi.nlm.nih.gov/pubmed/17158535
265. George, D.W., *et al.* Update on late relapse of germ cell tumor: a clinical and molecular analysis. J Clin Oncol, 2003. 21: 113.
https://www.ncbi.nlm.nih.gov/pubmed/12506179
266. Oldenburg, J., *et al.* Late recurrences of germ cell malignancies: a population-based experience over three decades. Br J Cancer, 2006. 94: 820.
https://www.ncbi.nlm.nih.gov/pubmed/16508636
267. Lee, A.H., *et al.* The value of central histopathological review of testicular tumours before treatment. BJU Int, 1999. 84: 75.
https://www.ncbi.nlm.nih.gov/pubmed/10444128
268. Lipphardt, M.E., *et al.* Late relapse of testicular cancer. World J Urol, 2004. 22: 47.
https://www.ncbi.nlm.nih.gov/pubmed/15064970
269. Fossa, S.D., *et al.* Treatment outcome of patients with brain metastases from malignant germ cell tumors. Cancer, 1999. 85: 988.
https://www.ncbi.nlm.nih.gov/pubmed/10091779
270. Bokemeyer, C., *et al.* Treatment of brain metastases in patients with testicular cancer. J Clin Oncol, 1997. 15: 1449.
https://www.ncbi.nlm.nih.gov/pubmed/9193339
271. Feldman, D.R., *et al.* Brain Metastases in Patients With Germ Cell Tumors: Prognostic Factors and Treatment Options--An Analysis From the Global Germ Cell Cancer Group. J Clin Oncol, 2016. 34: 345.
https://www.ncbi.nlm.nih.gov/pubmed/26460295
272. Hartmann JT., *et al.* Multidiciplinary treatment and prognosis of patients with central nervous metastases (CNS) from testicular germ cell tumour (GCT) origin. Proc Ann Soc Clin Oncol, 2003. 22. [No abstract available].

273. Cathomas, R., *et al.* Interdisciplinary evidence-based recommendations for the follow-up of testicular germ cell cancer patients. Onkologie, 2011. 34: 59.
https://www.ncbi.nlm.nih.gov/pubmed/21346388
274. Daugaard, G., *et al.* Surveillance for stage I nonseminoma testicular cancer: outcomes and long-term follow-up in a population-based cohort. J Clin Oncol, 2014. 32: 3817.
https://www.ncbi.nlm.nih.gov/pubmed/25267754
275. Chau, C., *et al.* Treatment outcome and patterns of relapse following adjuvant carboplatin for stage I testicular seminomatous germ-cell tumour: results from a 17-year UK experience. Ann Oncol, 2015. 26: 1865.
https://www.ncbi.nlm.nih.gov/pubmed/26037797
276. Ko, J.J., *et al.* Conditional Survival of Patients With Metastatic Testicular Germ Cell Tumors Treated With First-Line Curative Therapy. J Clin Oncol, 2016. 34: 714.
https://www.ncbi.nlm.nih.gov/pubmed/26786931
277. Lieng, H., *et al.* Recommendations for followup of stage I and II seminoma: The Princess Margaret Cancer Centre approach. Can Urol Assoc J, 2018. 12: 59.
https://www.ncbi.nlm.nih.gov/pubmed/29381453
278. Oldenburg, J., *et al.* Appendix 9: Testicular seminoma and non-seminoma: eUpdate published online 29 June 2017 (www.esmo.org/Guidelines/Genitourinary-Cancers). Ann Oncol, 2017. 28: iv165.
https://www.ncbi.nlm.nih.gov/pubmed/28881930
279. Brenner, D.J., *et al.* Computed tomography--an increasing source of radiation exposure. N Engl J Med, 2007. 357: 2277.
https://www.ncbi.nlm.nih.gov/pubmed/18046031
280. Rathmell, A.J., *et al.* Early detection of relapse after treatment for metastatic germ cell tumour of the testis: an exercise in medical audit. Clin Oncol (R Coll Radiol), 1993. 5: 34.
https://www.ncbi.nlm.nih.gov/pubmed/7678749
281. Mortensen, M.S., *et al.* Late Relapses in Stage I Testicular Cancer Patients on Surveillance. Eur Urol, 2016. 70: 365.
https://www.ncbi.nlm.nih.gov/pubmed/26996661
282. Travis, L.B., *et al.* Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst, 2010. 102: 1114.
https://www.ncbi.nlm.nih.gov/pubmed/20585105
283. Oldenburg, J., *et al.* Personalizing, not patronizing: the case for patient autonomy by unbiased presentation of management options in stage I testicular cancer. Ann Oncol, 2015. 26: 833.
https://www.ncbi.nlm.nih.gov/pubmed/25378299
284. Vidal, A.D., *et al.* Long-term outcome of patients with clinical stage I high-risk nonseminomatous germ-cell tumors 15 years after one adjuvant cycle of bleomycin, etoposide, and cisplatin chemotherapy. Ann Oncol, 2015. 26: 374.
https://www.ncbi.nlm.nih.gov/pubmed/25392157
285. Haugnes, H.S., *et al.* Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. J Clin Oncol, 2012. 30: 3752.
https://www.ncbi.nlm.nih.gov/pubmed/23008318
286. Fossa, S.D., *et al.* Short- and long-term morbidity after treatment for testicular cancer. BJU Int, 2009. 104: 1418.
https://www.ncbi.nlm.nih.gov/pubmed/19840023
287. Hemminki, K., *et al.* Second cancers after testicular cancer diagnosed after 1980 in Sweden. Ann Oncol, 2010. 21: 1546.
https://www.ncbi.nlm.nih.gov/pubmed/20019089
288. Richiardi, L., *et al.* Second malignancies among survivors of germ-cell testicular cancer: a pooled analysis between 13 cancer registries. Int J Cancer, 2007. 120: 623.
https://www.ncbi.nlm.nih.gov/pubmed/17096341
289. Travis, L.B., *et al.* Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst, 2005. 97: 1354.
https://www.ncbi.nlm.nih.gov/pubmed/16174857
290. Wanderas, E.H., *et al.* Risk of subsequent non-germ cell cancer after treatment of germ cell cancer in 2006 Norwegian male patients. Eur J Cancer, 1997. 33: 253.
https://www.ncbi.nlm.nih.gov/pubmed/9135497
291. Bokemeyer, C., *et al.* Treatment of testicular cancer and the development of secondary malignancies. J Clin Oncol, 1995. 13: 283.
https://www.ncbi.nlm.nih.gov/pubmed/7799032

292. Hauptmann, M., *et al.* Increased stomach cancer risk following radiotherapy for testicular cancer. Br J Cancer, 2015. 112: 44.
https://www.ncbi.nlm.nih.gov/pubmed/25349972
293. Fung, C., *et al.* Solid tumors after chemotherapy or surgery for testicular nonseminoma: a population-based study. J Clin Oncol, 2013. 31: 3807.
https://www.ncbi.nlm.nih.gov/pubmed/24043737
294. Necchi, A., *et al.* Secondary malignancies after high-dose chemotherapy in germ cell tumor patients: a 34-year retrospective study of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant, 2018. 53: 722.
https://www.ncbi.nlm.nih.gov/pubmed/29367713
295. Howard, R., *et al.* Risk of leukemia among survivors of testicular cancer: a population-based study of 42,722 patients. Ann Epidemiol, 2008. 18: 416.
https://www.ncbi.nlm.nih.gov/pubmed/18433667
296. Kollmannsberger, C., *et al.* Secondary leukemia following high cumulative doses of etoposide in patients treated for advanced germ cell tumors. J Clin Oncol, 1998. 16: 3386.
https://www.ncbi.nlm.nih.gov/pubmed/9779717
297. Nichols, C.R., *et al.* Secondary leukemia associated with a conventional dose of etoposide: review of serial germ cell tumor protocols. J Natl Cancer Inst, 1993. 85: 36.
https://www.ncbi.nlm.nih.gov/pubmed/7677934
298. Fossa, S.D., *et al.* Noncancer causes of death in survivors of testicular cancer. J Natl Cancer Inst, 2007. 99: 533.
https://www.ncbi.nlm.nih.gov/pubmed/17405998
299. O'Sullivan, J.M., *et al.* Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol, 2003. 14: 91.
https://www.ncbi.nlm.nih.gov/pubmed/12488299
300. Haugnes, H.S., *et al.* Pulmonary function in long-term survivors of testicular cancer. J Clin Oncol, 2009. 27: 2779.
https://www.ncbi.nlm.nih.gov/pubmed/19414680
301. Necchi, A., *et al.* Effect of Bleomycin Administration on the Development of Pulmonary Toxicity in Patients With Metastatic Germ Cell Tumors Receiving First-Line Chemotherapy: A Meta-Analysis of Randomized Studies. Clin Genitourin Cancer, 2017. 15: 213.
https://www.ncbi.nlm.nih.gov/pubmed/27692810
302. Lauritsen, J., *et al.* Pulmonary Function in Patients With Germ Cell Cancer Treated With Bleomycin, Etoposide, and Cisplatin. J Clin Oncol, 2016. 34: 1492.
https://www.ncbi.nlm.nih.gov/pubmed/26903578
303. Piketty, A.C., *et al.* The risk of thrombo-embolic events is increased in patients with germ-cell tumours and can be predicted by serum lactate dehydrogenase and body surface area. Br J Cancer, 2005. 93: 909.
https://www.ncbi.nlm.nih.gov/pubmed/16205699
304. Gizzi, M., *et al.* Predicting and preventing thromboembolic events in patients receiving cisplatin-based chemotherapy for germ cell tumours. Eur J Cancer, 2016. 69: 151.
https://www.ncbi.nlm.nih.gov/pubmed/27821318
305. Fossa, S.D., *et al.* Increased mortality rates in young and middle-aged patients with malignant germ cell tumours. Br J Cancer, 2004. 90: 607.
https://www.ncbi.nlm.nih.gov/pubmed/14760372
306. Kerns, S.L., *et al.* Cumulative Burden of Morbidity Among Testicular Cancer Survivors After Standard Cisplatin-Based Chemotherapy: A Multi-Institutional Study. J Clin Oncol, 2018. 36: 1505.
https://www.ncbi.nlm.nih.gov/pubmed/29617189
307. van den Belt-Dusebout, A.W., *et al.* Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol, 2006. 24: 467.
https://www.ncbi.nlm.nih.gov/pubmed/16421423
308. Haugnes, H.S., *et al.* Components of the metabolic syndrome in long-term survivors of testicular cancer. Ann Oncol, 2007. 18: 241.
https://www.ncbi.nlm.nih.gov/pubmed/17060482
309. Alberti, K.G., *et al.* The metabolic syndrome--a new worldwide definition. Lancet, 2005. 366: 1059.
https://www.ncbi.nlm.nih.gov/pubmed/16182882
310. Bogefors, C., *et al.* Hypogonadism in testicular cancer patients is associated with risk factors of cardiovascular disease and the metabolic syndrome. Andrology, 2017. 5: 711.
https://www.ncbi.nlm.nih.gov/pubmed/28544654

311. Sprauten, M., *et al.* Impact of long-term serum platinum concentrations on neuro- and ototoxicity in Cisplatin-treated survivors of testicular cancer. J Clin Oncol, 2012. 30: 300. https://www.ncbi.nlm.nih.gov/pubmed/22184390
312. Rove, K.O., *et al.* Pathologic Risk Factors for Metastatic Disease in Postpubertal Patients With Clinical Stage I Testicular Stromal Tumors. Urology, 2016. 97: 138. https://www.ncbi.nlm.nih.gov/pubmed/27538802
313. Adams, S.C., *et al.* Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. Cancer, 2017. 123: 4057. https://www.ncbi.nlm.nih.gov/pubmed/28708930
314. Thorsen, L., *et al.* Thromboembolic events after high-intensity training during cisplatin-based chemotherapy for testicular cancer. J Clin Oncol, 2017. 35: 4551. http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.4551
315. Feldman, D.R., *et al.* Predicting Cardiovascular Disease Among Testicular Cancer Survivors After Modern Cisplatin-based Chemotherapy: Application of the Framingham Risk Score. Clin Genitourin Cancer, 2018. 16: e761. https://www.ncbi.nlm.nih.gov/pubmed/29534941
316. Teutsch, C., *et al.* Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. Cancer Treat Rep, 1977. 61: 925. https://www.ncbi.nlm.nih.gov/pubmed/70274
317. Adoue, D., *et al.* Bleomycin and Raynaud's phenomenon. Ann Intern Med, 1984. 100: 770. https://www.ncbi.nlm.nih.gov/pubmed/6201095
318. Vogelzang, N.J., *et al.* Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. Ann Intern Med, 1981. 95: 288. https://www.ncbi.nlm.nih.gov/pubmed/6168223
319. Brydoy, M., *et al.* Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. J Natl Cancer Inst, 2009. 101: 1682. https://www.ncbi.nlm.nih.gov/pubmed/19940282
320. Hjelle, L.V., *et al.* Long-term serum platinum changes and their association with cisplatin-related late effects in testicular cancer survivors. Acta Oncol, 2018. 57: 1392. https://www.ncbi.nlm.nih.gov/pubmed/29775128
321. Amidi, A., *et al.* Changes in cognitive functions and cerebral grey matter and their associations with inflammatory markers, endocrine markers, and APOE genotypes in testicular cancer patients undergoing treatment. Brain Imaging Behav, 2017. 11: 769. https://www.ncbi.nlm.nih.gov/pubmed/27240852
322. Bauer, C.A., *et al.* Cochlear structure and function after round window application of ototoxins. Hear Res, 2005. 201: 121. https://www.ncbi.nlm.nih.gov/pubmed/15721567
323. Bokemeyer, C., *et al.* Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. Br J Cancer, 1998. 77: 1355. https://www.ncbi.nlm.nih.gov/pubmed/9579846
324. Osanto, S., *et al.* Long-term effects of chemotherapy in patients with testicular cancer. J Clin Oncol, 1992. 10: 574. https://www.ncbi.nlm.nih.gov/pubmed/1372350
325. Oldenburg, J., *et al.* Genetic variants associated with cisplatin-induced ototoxicity. Pharmacogenomics, 2008. 9: 1521. https://www.ncbi.nlm.nih.gov/pubmed/18855538
326. Oldenburg, J., *et al.* Cisplatin-induced long-term hearing impairment is associated with specific glutathione s-transferase genotypes in testicular cancer survivors. J Clin Oncol, 2007. 25: 708. https://www.ncbi.nlm.nih.gov/pubmed/17228018
327. Perry, D.J., *et al.* Enhanced bleomycin toxicity during acute renal failure. Cancer Treat Rep, 1982. 66: 592. https://www.ncbi.nlm.nih.gov/pubmed/6174233
328. Bennett, W.M., *et al.* Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. Cancer Treat Rep, 1980. 64: 921. https://www.ncbi.nlm.nih.gov/pubmed/6160913
329. Sprauten, M., *et al.* Longitudinal serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels in a population-based sample of long-term testicular cancer survivors. J Clin Oncol, 2014. 32: 571. https://www.ncbi.nlm.nih.gov/pubmed/24419125

330. Bandak, M., *et al.* Longitudinal Changes in Serum Levels of Testosterone and Luteinizing Hormone in Testicular Cancer Patients after Orchiectomy Alone or Bleomycin, Etoposide, and Cisplatin. Eur Urol Focus, 2016.
https://www.ncbi.nlm.nih.gov/pubmed/28753832
331. Wiechno, P.J., *et al.* Dynamics of hormonal disorders following unilateral orchiectomy for a testicular tumor. Med Oncol, 2017. 34: 84.
https://www.ncbi.nlm.nih.gov/pubmed/28389909
332. Bandak, M., *et al.* Leydig cell dysfunction, systemic inflammation and metabolic syndrome in long-term testicular cancer survivors. Eur J Cancer, 2017. 84: 9.
https://www.ncbi.nlm.nih.gov/pubmed/28772110
333. Bandak, M., *et al.* A randomized double-blind study of testosterone replacement therapy or placebo in testicular cancer survivors with mild Leydig cell insufficiency (Einstein-intervention). BMC Cancer, 2017. 17: 461.
https://www.ncbi.nlm.nih.gov/pubmed/28673265
334. Orre, I.J., *et al.* Chronic cancer-related fatigue in long-term survivors of testicular cancer. J Psychosom Res, 2008. 64: 363.
https://www.ncbi.nlm.nih.gov/pubmed/18374735
335. Fossa, S.D., *et al.* Quality of life in good prognosis patients with metastatic germ cell cancer: a prospective study of the European Organization for Research and Treatment of Cancer Genitourinary Group/Medical Research Council Testicular Cancer Study Group (30941/TE20). J Clin Oncol, 2003. 21: 1107.
https://www.ncbi.nlm.nih.gov/pubmed/12637478
336. Sprauten M, *et al.* Fatigue in relation to treatment and gonadal function in a population-based sample of 796 testicular cancer survivors 12 and 19 years after treatment. J Clin Oncol, 2014. 32.
http://ascopubs.org/doi/abs/10.1200/jco.2014.32.15_suppl.4564
337. Albers P, *et al.* Chemotherapy compared to surgery: Quality-of-life analysis of the German prospective multicenter trial in clinical stage I NSGCT (AUO AH 01/94). J Clin Oncol, 2014. 32: (suppl; abstr 4563).
http://ascopubs.org/doi/abs/10.1200/jco.2014.32.15_suppl.4563
338. Smith, A.B., *et al.* A systematic review of quantitative observational studies investigating psychological distress in testicular cancer survivors. Psycho Oncol, 2018. 27: 1129.
https://www.ncbi.nlm.nih.gov/pubmed/29171109
339. Smith, A.B., *et al.* The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study. J Cancer Surviv, 2016. 10: 223.
https://www.ncbi.nlm.nih.gov/pubmed/26178326
340. Vehling, S., *et al.* Anxiety and depression in long-term testicular germ cell tumor survivors. Gen Hosp Psychiatry, 2016. 38: 21.
https://www.ncbi.nlm.nih.gov/pubmed/26439320
341. Dahl, A.A., *et al.* Aspects of posttraumatic stress disorder in long-term testicular cancer survivors: cross-sectional and longitudinal findings. J Cancer Surviv, 2016. 10: 842.
https://www.ncbi.nlm.nih.gov/pubmed/26920871
342. Banerji, J.S., *et al.* Patterns of Care and Survival Outcomes for Malignant Sex Cord Stromal Testicular Cancer: Results from the National Cancer Data Base. J Urol, 2016. 196: 1117.
https://www.ncbi.nlm.nih.gov/pubmed/27036305
343. Osbun, N., *et al.* Characteristics of Patients With Sertoli and Leydig Cell Testis Neoplasms From a National Population-Based Registry. Clin Genitourin Cancer, 2017. 15: e263.
https://www.ncbi.nlm.nih.gov/pubmed/27594555
344. Yuh, L.M., *et al.* A contemporary population-based study of testicular sex cord stromal tumours: Presentation, treatment patterns, and predictors of outcome. Can Urol Assoc J, 2017. 11: E344.
https://www.ncbi.nlm.nih.gov/pubmed/29382456
345. Laclergerie, F., *et al.* Testicle-sparing surgery versus radical orchiectomy in the management of Leydig cell tumors: results from a multicenter study. World J Urol, 2018. 36: 427.
https://www.ncbi.nlm.nih.gov/pubmed/29230496
346. Bozzini, G., *et al.* Treatment of leydig cell tumours of the testis: Can testis-sparing surgery replace radical orchidectomy? Results of a systematic review. Actas Urol Esp, 2017. 41: 146.
https://www.ncbi.nlm.nih.gov/pubmed/27890492
347. Kim, I., *et al.* Leydig cell tumors of the testis. A clinicopathological analysis of 40 cases and review of the literature. Am J Surg Pathol, 1985. 9: 177.
https://www.ncbi.nlm.nih.gov/pubmed/3993830

348. Ulbright T.M., *et al.* Tumors of the Testis, Adnexa, Spermatic Cord, and Scrotum (Atlas of Tumor Pathology, Third Series, Fascicle 25). 1999. https://onlinelibrary.wiley.com/doi/abs/10.1002/1096-9896%28200010%29192%3A2%3C273%3A%3AAID-PATH683%3E3.0.CO%3B2-0
349. Cheville, J.C., *et al.* Leydig cell tumor of the testis: a clinicopathologic, DNA content, and MIB-1 comparison of nonmetastasizing and metastasizing tumors. Am J Surg Pathol, 1998. 22: 1361. https://www.ncbi.nlm.nih.gov/pubmed/9808128
350. McCluggage, W.G., *et al.* Cellular proliferation and nuclear ploidy assessments augment established prognostic factors in predicting malignancy in testicular Leydig cell tumours. Histopathology, 1998. 33: 361. https://www.ncbi.nlm.nih.gov/pubmed/9822927
351. Reznik, Y., *et al.* Luteinizing hormone regulation by sex steroids in men with germinal and Leydig cell tumours. Clin Endocrinol (Oxf), 1993. 38: 487. https://www.ncbi.nlm.nih.gov/pubmed/8392454
352. Suardi, N., *et al.* Leydig cell tumour of the testis: presentation, therapy, long-term follow-up and the role of organ-sparing surgery in a single-institution experience. BJU Int, 2009. 103: 197. https://www.ncbi.nlm.nih.gov/pubmed/18990169
353. Bozzini, G., *et al.* Long-term follow-up using testicle-sparing surgery for Leydig cell tumor. Clin Genitourin Cancer, 2013. 11: 321. https://www.ncbi.nlm.nih.gov/pubmed/23317518
354. Maizlin, Z.V., *et al.* Leydig cell tumors of the testis: gray scale and color Doppler sonographic appearance. J Ultrasound Med, 2004. 23: 959. https://www.ncbi.nlm.nih.gov/pubmed/15292565
355. Isidori, A.M., *et al.* Differential diagnosis of nonpalpable testicular lesions: qualitative and quantitative contrast-enhanced US of benign and malignant testicular tumors. Radiology, 2014. 273: 606. https://www.ncbi.nlm.nih.gov/pubmed/24968192
356. Manganaro, L., *et al.* A prospective study on contrast-enhanced magnetic resonance imaging of testicular lesions: distinctive features of Leydig cell tumours. Eur Radiol, 2015. 25: 3586. https://www.ncbi.nlm.nih.gov/pubmed/25981218
357. Matveev, B.P., *et al.* [Leydig-cell tumors of the testis]. Urol Nefrol (Mosk), 1997: 34. https://www.ncbi.nlm.nih.gov/pubmed/9381620
358. Di Tonno, F., *et al.* Lessons from 52 patients with leydig cell tumor of the testis: the GUONE (North-Eastern Uro-Oncological Group, Italy) experience. Urol Int, 2009. 82: 152. https://www.ncbi.nlm.nih.gov/pubmed/19322000
359. Leonhartsberger, N., *et al.* Increased incidence of Leydig cell tumours of the testis in the era of improved imaging techniques. BJU Int, 2011. 108: 1603. https://www.ncbi.nlm.nih.gov/pubmed/21631694
360. Young, R.H., *et al.* Sertoli cell tumors of the testis, not otherwise specified: a clinicopathologic analysis of 60 cases. Am J Surg Pathol, 1998. 22: 709. https://www.ncbi.nlm.nih.gov/pubmed/9630178
361. Giglio, M., *et al.* Testicular sertoli cell tumours and relative sub-types. Analysis of clinical and prognostic features. Urol Int, 2003. 70: 205. https://www.ncbi.nlm.nih.gov/pubmed/12660458
362. Kratzer, S.S., *et al.* Large cell calcifying Sertoli cell tumor of the testis: contrasting features of six malignant and six benign tumors and a review of the literature. Am J Surg Pathol, 1997. 21: 1271. https://www.ncbi.nlm.nih.gov/pubmed/9351565
363. Henley, J.D., *et al.* Malignant Sertoli cell tumors of the testis: a study of 13 examples of a neoplasm frequently misinterpreted as seminoma. Am J Surg Pathol, 2002. 26: 541. https://www.ncbi.nlm.nih.gov/pubmed/11979085
364. Proppe, K.H., et al. Large-cell calcifying Sertoli cell tumor of the testis. Am J Clin Pathol, 1980. 74: 607. https://www.ncbi.nlm.nih.gov/pubmed/7446466
365. Plata, C., *et al.* Large cell calcifying Sertoli cell tumour of the testis. Histopathology, 1995. 26: 255. https://www.ncbi.nlm.nih.gov/pubmed/7541015
366. Zukerberg, L.R., *et al.* Sclerosing Sertoli cell tumor of the testis. A report of 10 cases. Am J Surg Pathol, 1991. 15: 829. https://www.ncbi.nlm.nih.gov/pubmed/1719830
367. Kao, C.S., *et al.* Sclerosing Sertoli cell tumor of the testis: a clinicopathologic study of 20 cases. Am J Surg Pathol, 2014. 38: 510. https://www.ncbi.nlm.nih.gov/pubmed/24552667

368. Gierke, C.L., *et al.* Large-cell calcifying Sertoli cell tumor of the testis: appearance at sonography. AJR Am J Roentgenol, 1994. 163: 373.
https://www.ncbi.nlm.nih.gov/pubmed/8037034
369. Washecka, R., *et al.* Testicular tumors in Carney's complex. J Urol, 2002. 167: 1299.
https://www.ncbi.nlm.nih.gov/pubmed/11832717
370. Young, S., *et al.* Feminizing Sertoli cell tumors in boys with Peutz-Jeghers syndrome. Am J Surg Pathol, 1995. 19: 50.
https://www.ncbi.nlm.nih.gov/pubmed/7802138
371. Giannarini, G., *et al.* Organ-sparing surgery for adult testicular tumours: a systematic review of the literature. Eur Urol, 2010. 57: 780.
https://www.ncbi.nlm.nih.gov/pubmed/20116165
372. Mosharafa, A.A., *et al.* Does retroperitoneal lymph node dissection have a curative role for patients with sex cord-stromal testicular tumors? Cancer, 2003. 98: 753.
https://www.ncbi.nlm.nih.gov/pubmed/12910519
373. Silberstein, J.L., *et al.* Clinical outcomes of local and metastatic testicular sex cord-stromal tumors. J Urol, 2014. 192: 415.
https://www.ncbi.nlm.nih.gov/pubmed/24518791
374. Featherstone, J.M., *et al.* Sex cord stromal testicular tumors: a clinical series--uniformly stage I disease. J Urol, 2009. 181: 2090.
https://www.ncbi.nlm.nih.gov/pubmed/19286222
375. Shukla, A.R., *et al.* Juvenile granulosa cell tumor of the testis:: contemporary clinical management and pathological diagnosis. J Urol, 2004. 171: 1900.
https://www.ncbi.nlm.nih.gov/pubmed/15076304
376. Zugor, V., *et al.* Congenital juvenile granulosa cell tumor of the testis in newborns. Anticancer Res, 2010. 30: 1731.
https://www.ncbi.nlm.nih.gov/pubmed/20592370
377. Cornejo, K.M., *et al.* Adult granulosa cell tumors of the testis: a report of 32 cases. Am J Surg Pathol, 2014. 38: 1242.
https://www.ncbi.nlm.nih.gov/pubmed/24705318
378. Miliaras, D., *et al.* Adult type granulosa cell tumor: a very rare case of sex-cord tumor of the testis with review of the literature. Case Rep Pathol, 2013. 2013: 932086.
https://www.ncbi.nlm.nih.gov/pubmed/23762714
379. Zhang, M., *et al.* Testicular fibrothecoma: a morphologic and immunohistochemical study of 16 cases. Am J Surg Pathol, 2013. 37: 1208.
https://www.ncbi.nlm.nih.gov/pubmed/23715159
380. Perito, P.E., *et al.* Sertoli-Leydig cell testicular tumor: case report and review of sex cord/gonadal stromal tumor histogenesis. J Urol, 1992. 148: 883.
https://www.ncbi.nlm.nih.gov/pubmed/1512847
381. Pleskacova, J., *et al.* Tumor risk in disorders of sex development. Sex Dev, 2010. 4: 259.
https://www.ncbi.nlm.nih.gov/pubmed/20558977
382. Ulbright, T.M., *et al.* Gonadoblastoma and selected other aspects of gonadal pathology in young patients with disorders of sex development. Semin Diagn Pathol, 2014. 31: 427.
https://www.ncbi.nlm.nih.gov/pubmed/25129544
383. Ulbright, T.M., *et al.* Sex cord-stromal tumors of the testis with entrapped germ cells: a lesion mimicking unclassified mixed germ cell sex cord-stromal tumors. Am J Surg Pathol, 2000. 24: 535.
https://www.ncbi.nlm.nih.gov/pubmed/10757400
384. Klotz, T., *et al.* [Carcinoma of the rete testis with lymphogenous metastasis: multimodal treatment]. Urologe A, 2012. 51: 409.
https://www.ncbi.nlm.nih.gov/pubmed/22282103

11. CONFLICT OF INTEREST

All members of the Testicular Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines. This guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

12. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Barcelona 2019. ISBN 978-94-92671-04-2.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.