EAU Guidelines on
Testicular Cancer

P. Albers (Chair), W. Albrecht, F. Algaba,
C. Bokemeyer, G. Cohn-Cedermark, K. Fizazi,
A. Horwich, M.P. Laguna, N. Nicolai, J. Oldenburg

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**European
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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 represents 5% of urological tumours affecting mostly younger males. This document addresses germ-cell tumours 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.

1.2   Panel composition
The EAU Guidelines Panel on Testicular Cancer consists of a multidisciplinary group of clinicians including, urologists, a pathologist, oncologists and radiotherapists. Members of this panel have been selected, based on their expertise, to represent the professionals treating patients suspected of harbouring 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, the Pocket guidelines, is available, both in print and in a number of versions for mobile 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 can be viewed on 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 contain a separate chapter on testicular stromal tumours. This document presents a limited update of the 2015 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 2016 Testicular Cancer Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. For this 2016 print, updates include:
*   A new flowchart (Figure 2) on Treatment options in patients with seminoma clinical state IIA and IIB.
*   A new section on Quality of life and long-term toxicities after cure for testicular cancer (Section 8.6).

Conclusions and recommendations have been rephrased and added to throughout the current document. Changed or new conclusions and recommendations can be found in sections:

5.9   Guideline for the Diagnosis and staging of testicular cancer

Recommendation	GR
Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralateral TIN.	A

TIN = testicular intraepithelial neoplasia.

7.2.2   Guideline for the treatment of stage I seminoma

Recommendation	GR
If carboplatin-based adjuvant chemotherapy is considered, offer one course at AUC 7	A

AUC = area under curve.

7.5.6 **Guideline for the treatment of metastatic germ cell tumours**

Recommendation	LE	GR
In seminoma stage CS IIA/B, offer chemotherapy (3 x BEP or 4 x EP, in good prognosis) as an alternative to radiotherapy.	1	A

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

7.3.6 **Guidelines for the treatment of NSGCT stage I**

CS1B (pT2-pT4): high risk	LE	GR
Recommend primary chemotherapy with one course of BEP.	2a	A*
Inform patients about the advantages and disadvantages of two courses of BEP.	2a	A*

BEP = cisplatin, etoposide, and bleomycin.

* Upgraded following panel consensus

Table 8.1: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma

Procedure	Year			
	1	2	3	4-5
Physical examination	4 times	4 times	4 times	Once/year
Tumour markers	4 times	4 times	4 times	Once/year
Plain radiography chest	Twice	Twice	Twice	Twice
Abdominopelvic CT	Twice at 3 and 12 months	Once at 24 months	Once at 36 months	

CT = computed tomography.

Table 8.2: Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma

Procedure	Year				
	1	2	3	4-5	6-10
Physical examination	4 times	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice	Twice		
Abdominopelvic CT	Once	Once	Once	Once/year	

CT = computed tomography.

Table 8.3: Recommended minimum follow-up schedule for post-orchiectomy surveillance, radiotherapy or chemotherapy: stage I seminoma

Procedure	Year		
	1	2	3-5
Physical examination	3 times	3 times	Once/year
Tumour markers	3 times	3 times	Once/year
Plain radiography chest	Twice	Twice	
Abdominopelvic CT	Twice	Twice	at 36 and 60 months

CT = computed tomography.

Table 8.4: Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

Procedure	Year			
	1	2	3-5	Thereafter
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Plain radiography chest	4 times	4 times	Twice/year	Once/year
Abdominopelvic CT*†	Twice	Twice	Once/year	As indicated
Chest CT†‡	Once/year	Once/year	Once/year	As indicated
Brain CT§	Once/year	Once/year	Once/year	As indicated

CT = computed tomography.

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

† If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.

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

§ In patients with headaches, focal neurological findings, or any central nervous system symptoms.

2. METHODS

For the Germ-cell tumour Section, the literature has been assessed and updated throughout the document. For the Testicular Stromal tumours a scoping search as of Jan 1st, 2009 until October 13th, 2014 has been carried out. No restrictions on data level were applied. The search identified 758 unique records, of which 18 references were included in the manuscript.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [2]. Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/. 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. The decision for re-review is made based on the extent of the revision. A major revision resulting in significant changes to the clinical recommendations presented in the text will warrant re-review.

2.2 Future goals
The results of ongoing and new systematic reviews will be included in the 2017 update of the Testicular Cancer Guidelines. These reviews are performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Ongoing systematic review:
• Risk factors for relapse in Seminoma Stage I in Active Surveillance.

Topics selected for subsequent systematic reviews:
• What is the cure rate of patients with germ cell tumours undergoing salvage chemotherapy (including high-dose)?
• What is the rate of long-term toxicities (>10 yrs) after chemotherapy and radiotherapy of metastatic germ cell tumours?

3.   EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1   Epidemiology

Testicular cancer represents 1% of male neoplasms and 5% of urological tumours, with 3-10 new cases occurring per 100,000 males/per year in Western society [3, 4]. Its incidence has been increasing during the last decades especially in industrialised countries [5, 6]. Data from the Surveillance Epidemiology and End Results programme (1992 to 2011) show a continuing increased risk among Caucasian men in the USA for seminoma [7].

At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumour (90-95% of cases) [3]. Peak incidence is in the third decade of life for non-seminoma, and in the fourth decade for pure seminoma.

Testicular cancers (TC) show excellent cure rates based on, their chemosensitivity especially to cisplatin-based chemotherapy [8], 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 [9, 10]. 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 < 5 patients enrolled) [11]. In the same context, the frequency of post-chemotherapy residual tumour resection is associated with perioperative mortality and OS [12, 13].

Genetic changes have been described in patients with TC. A specific genetic marker (an isochromosome of the short arm of chromosome 12 - i(12p) - has been described in all histological types of germ cell tumours [14] and in testicular intraepithelial neoplasia (TIN). Alterations in the p53 locus have been identified in 66% of cases of testicular TIN [15]. 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 TIN and germ cell neoplasia. There is overlap in the development to seminoma and embryonal carcinoma as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma [16, 17].

Epidemiological risk factors for the development of testicular tumours are components of the testicular dysgenesis syndrome (i.e. cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility) [18, 19], familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or TIN [14, 18, 20-22]. Very tall men seem to have a higher risk of GCT (OR 3.35), while short stature is protective [23, 24], although further confirmation is needed.

3.2   Pathological classification

The recommended pathological classification (modified from the 2004 version of the World Health Organization [WHO] guidance) is shown below [25]. In 2016, an update of the WHO pathological classification was published. The findings of this classification will be published in the 2017 update of the Testicular Cancer Guidelines.

1. **Germ cell tumours**
    - Intratubular germ cell neoplasia (IGCNU), unclassified type
    - Seminoma (including cases with syncytiotrophoblastic cells)
    - Spermatocytic seminoma (mention if there is a sarcomatous component)
    - Embryonal carcinoma
    - Yolk sac tumour
    - Choriocarcinoma
    - Teratoma (mature, immature, with malignant component)
    - Tumours with more than one histological type (specify percentage of individual components).
2. **Sex cord/gonadal stromal tumours**
    - Leydig cell tumour
    - Malignant Leydig cell tumour
    - Sertoli cell tumour
        - lipid-rich variant
        - sclerosing
        - large cell calcifying
    - Malignant Sertoli cell tumour

- Granulosa cell tumour
  - adult type
  - juvenile type
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
  - incompletely differentiated
  - mixed
- Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma).
3. **Miscellaneous non-specific stromal tumours**
- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
- Tumours (benign and malignant) of non-specific stroma.

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 5-7 days and 2-3 days, respectively [26]. Tumour markers need to be re-evaluated after orchiectomy to determine half-life kinetics. Marker decline in patients with clinical stage 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 [27]. 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 [28, 29]. Slow marker decline in patients with poor prognosis during the first cycle of standard BEP chemotherapy can be used as an indication for early chemotherapy dose intensification [30].

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.

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 increase using a 3 mm threshold to define metastatic nodes in the landing zones [31]. Those figures decrease slightly in stages I and II [32, 33], with a rate of understaging of 25-30% [34]. New generations of CT devices do not seem to improve the sensitivity.

Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal nodal enlargement [35, 36]. 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 [35], when CT is contraindicated because of allergy to contrast media, or when the physician or the patient are concerned about radiation dose. MRI 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 has to be

recommended in all patients with TC as up to 10% of cases can present with small subpleural nodes that are not visible radiologically [37]. A CT has high sensitivity, but low specificity [35].

There is no evidence to support the use of fluorodeoxyglucose-PET (FDG-PET) in the staging of testis cancer [38, 39]. It is recommended in the follow-up of patients with seminoma with any residual mass at least 6 weeks after the end of the last cycle of chemotherapy in order to decide on watchful waiting or active treatment [40, 41]. Fluorodeoxyglucose-PET is not recommended in the re-staging of patients with NSGCT after chemotherapy [42, 43].

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

Table 4.1: Recommended tests for staging at diagnosis

For staging purposes recommendations are:		
Test	**Recommendation**	**GR**
Serum tumour markers	AFP hCG LDH	A
Abdominopelvic CT	All patients	A
Chest CT	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan or MRI columna	In case of symptoms	
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases and/or high beta-hCG values.	
Further investigations		
Fertility investigations: Total testosterone LH FSH Semen analysis		B
Discuss sperm banking with all men prior to to starting treatment for testicular cancer.		A

hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; CT = computed tomography;
LH = luteinising hormone; FSH = follicle-stimulating hormone ; AFP = alpha fetoprotein.

4.4 Staging and prognostic classifications

The staging system recommended in these guidelines is the 2009 TNM of the International Union Against Cancer (UICC) (Table 4.2) [44]. This includes:
- determination of the anatomical extent of disease;
- assessment of serum tumour markers, including nadir values of hCG, AFP and 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, 2009, 7th edn. [44])

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 (testicular intraepithelial neoplasia)
	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 multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
	N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pn		**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 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
		M1b Other sites
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	S1 < 1.5 x N and	< 5,000 and	< 1,000
S2	S2 1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	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.
[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 testicular cancer includes the following substages:

Stage grouping

Stage 0	pTis	N0	M0	S0, SX
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patientTX	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 IIC	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 clinical stage 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 [45, 46]. 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) [27].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group [47])*

Good-prognosis group	
Non-seminoma (56% of cases)	*All of the following criteria:*
5-year PFS 89%	• Testis/retroperitoneal primary
5-year survival 92%	• 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%	All of the following criteria: • Testis/retroperitoneal 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 presents as a painless, unilateral testicular scrotal mass, as a casual US finding or is revealed by a scrotal trauma [48]. Scrotal pain may be the first symptom in 20% of cases and it is present in up to 27% of patients with TC [48, 49]. 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 [49].

Diagnosis is delayed in around 10% of cases of testicular tumour that mimic orchioepididymitis [49], physical examination reveals the features of the mass and must always be carried out together with a general examination to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. US must be performed in any doubtful case. A correct diagnosis must be established in all patients with an intrascrotal mass [50].

5.2   Imaging of the testis
Currently, US serves to confirm the presence of a testicular mass and to explore the contralateral testis. US sensitivity is almost 100%, and US has an important role in determining whether a mass is intra- or extratesticular [51]. US is an inexpensive test and should be performed even in the presence of clinically evident testicular tumour [52].

US 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 [53, 54].

MRI of the scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis [51, 55].

5.3   Serum tumour markers at diagnosis

Serum tumour markers are prognostic factors and contribute to diagnosis and staging [56]. The following markers should be determined before, and 5-7 days after, orchiectomy:

* AFP (produced by yolk sac cells);
* hCG (expression of trophoblasts);
* LDH (lactate dehydrogenase).

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 [48, 57]. AFP 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 [26].

Lactase dehydrogenase (LDH) is a less specific marker, its concentration being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced TC [26]. Of note, negative marker levels do not exclude the diagnosis of a germ cell tumour. Placental alkaline phosphatase (PLAP), is an optional marker in monitoring patients with pure seminoma, but not recommended in smokers [58].

Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research.

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.

In cases of life threatening disseminated disease, lifesaving chemotherapy should be given up-front, especially when the clinical picture is very likely testicular cancer 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 testicular tumours, 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 30% of the testicular volume and surgical rules are respected. In those cases, the rate of associated TIN is high (at least up to 82%) (see Section 5.7.)

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 2004 [25]:
    - 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 (TIN/ITGCN) in non-tumour parenchyma.
* pT category according to TNM 2009 [44].
* Immunohistochemical studies: in seminoma and mixed germ cell tumour, 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 Diagnosis and treatment of testicular intraepithelial neoplasia (TIN)

Contralateral biopsy has been advocated to rule out the presence of TIN [59]. Although routine policy in some countries, the low incidence of TIN and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) [60, 61], the morbidity of TIN treatment, and the fact that most of metachronous tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy in all patients [62, 63].

It is still difficult to reach a consensus on whether the existence of contralateral TIN must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk for contralateral TIN, 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 [31, 46, 64-66]. A double biopsy increases sensitivity [65]. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy [67].

Once TIN is diagnosed, local radiotherapy (16-20 Gy in fractions of 2 Gy) is the treatment of choice in the case of a solitary testis. Testicular radiotherapy in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [32, 62, 68, 69]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [65].

If TIN is diagnosed and the contralateral testis is healthy, the options for management are orchiectomy or close observation (with a 5-year risk of developing TC of 50%) [70].

5.8 Screening

There are no high level evidence studies proving the advantages of screening programmes, but it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, self-physical examination by the affected individual is advisable.

5.9 Guidelines for the diagnosis and staging of testicular cancer

Recommendations	GR
Perform testicular US in all patients with suspicion of testicular cancer.	A
Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralaterial TIN,	A
Perform orchiectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, start chemotherapy before orchiectomy.	A
Perform serum determination of tumour markers (AFP, hCG, and LDH), both before and 5-7 days after orchiectomy for staging and prognostic reasons.	A
Assess the state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera in testicular cancer.	A

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase;
TIN = testicular intraepithelial neoplasia.

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in NSGCT clinical stage I

Retrospectively, for seminoma stage I, tumour size (> 4 cm) and invasion of the rete testis have been identified as predictors for relapse in a pooled analysis [71]. However, these risk factors have not been validated in a prospective setting except that the absence of both factors indicated a low recurrence rate (6%) [72]. 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, as well as the percentage of embryonal carcinoma, are additional predictors that improve upon the positive and negative predictive value of vascular invasion [73]. 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 [74].

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

	For seminoma	For non-seminoma
Pathological (for stage I)		
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 are frequently found in patients with testis tumours. Furthermore, chemotherapy and radiation treatment can also impair fertility. In patients in the reproductive age group, pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) should be performed, and semen analysis and cryopreservation should be offered. If cryopreservation is desired, it should preferably be performed before orchiectomy, but in any case prior to chemotherapy treatment [68, 75-77]. In cases of bilateral orchiectomy or low testosterone levels after treatment of TIN, life-long testosterone supplementation is necessary [78]. Patients with unilateral or bilateral orchiectomy should be offered a testicular prosthesis [79]. For more detailed information, the reader is referred to the EAU Male Infertility Guidelines [80].

7.2 Stage I Germ cell tumours

7.2.1 Stage I seminoma

After modern staging procedures, about 15-20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone.

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 [81]. Previous analyses from four studies showed an actuarial 5-year relapse-free rate of 82.3%. The Princess Margaret Hospital series (n = 1559) showed an overall relapse rate in unselected patients of 16.8%. The actuarial relapse rate is in the order of 15-20% at 5 years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes [82].

In patients with low risk (tumour size ≤ 4 cm and no rete testis invasion), the recurrence under surveillance is as low as 6% [83]. 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 radiotherapy alone because of small volume disease at the time of recurrence. Patients who relapse after salvage radiotherapy can be effectively treated with chemotherapy [84]. The combination of carboplatin chemotherapy and modern radiotherapy 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 [82, 84]. 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 AUC 7 with adjuvant radiotherapy, did not show a significant difference with regard to recurrence rate, time to recurrence and survival after a median follow-up of 4 years [85-87]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma [82, 85-87]. Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1-3% [72, 88], but additional experience and long-term observation is needed.

7.2.1.3   Adjuvant radiotherapy and risk-adapted treatment

Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy 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% [89-91]. Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

With regard to the irradiation dose, a large MRC randomised trial of 20 Gy vs. 30 Gy PA radiation in stage I seminoma showed equivalence for both doses in terms of recurrence rates [90]. 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% [89]. The main concern surrounding adjuvant radiotherapy is the increased risk of radiation-induced second non-germ cell malignancies [92-94].

A scrotal shield should be considered during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis [92].

7.2.1.4   Risk-adapted treatment

Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided into a low-and high-risk group of occult metastatic disease. Patients with and without both risk factors have a 32% and 12% risk of occult disease respectively. These risk factors were introduced through an analysis of retrospective trials [71]. A prospective trial based on no risk factors, surveillance, both risk factors and two courses of carboplatin AUC 7 showed the feasibility of a risk-adapted approach. Early data with limited follow-up indicate that patients without either risk factor have a very low risk, 6.0% - 14.8%, of relapse at 5 years. Patients in the high-risk group treated with carboplatin experienced a 1.4% - 3.2% relapse rate at mean follow-up of 34 months [83, 95].

7.2.1.5   Retroperitoneal lymph node dissection (RPLND)

In a prospective, non-randomised study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment. Therefore, RPLND is not recommended in stage I seminoma [93].

7.2.2   **Guidelines for the treatment of stage I seminoma**

Recommendations	GR
Offer surveillance as a management option if facilities are available and the patient is compliant.	A*
Offer one course at AUC 7, if carboplatin-based chemotherapy is considered.	A
Do not perform adjuvant treatment in patients at very low risk.	A
Do not perform radiotherapy as adjuvant treatment.	A

AUC = area under curve.
*Upgraded following panel consensus.

7.3   NSGCT clinical stage I

Up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy. 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.

7.3.1   **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 only close surveillance 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 12 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 [96, 97]. Approximately 35% of relapsing patients have normal levels of serum tumour markers at relapse, with 60% of relapses occuring 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 RPLND [98] 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 clinical stage I non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [99, 100].

7.3.2 Adjuvant chemotherapy

Patients with CS1 NSGCT have a 14-48% risk of recurrence within 2 years after orchiectomy. Adjuvant chemotherapy with two courses of cisplatin, etoposide, and bleomycin (BEP) was introduced in 1996 by a prospective MRC trial [101]. Subsequently, adjuvant chemotherapy was mainly given in high risk patients (vascular invasion present) [101-103]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [101], 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 [104]. However, the very-long term (> 20 years) side effects of adjuvant chemotherapy in this setting are currently unknown, especially the long-term cardio-vascular effects of chemotherapy [105]. This should be taken into consideration during decision-making.

In 2008, the German Testicular Study Group reported a randomised trial of nerve-sparing RPLND or one course of BEP as adjuvant treatment in CS 1 NSGCT without risk-adaption. Adjuvant chemotherapy significantly increased the 2-year recurrence-free survival rate to 99.41% (CI: 95.87%, 99.92%) as opposed to surgery, which had a 2-year recurrence-free survival rate of 92.37% (CI: 87.21%, 95.50%). The difference was 7.04%, (CI: 2.52%, 11.56%) and, therefore, the main endpoint of the trial was reached. The hazard ratio to experience a tumour recurrence with surgery as opposed to chemotherapy was 7.937, (CI: 1.808, 34.48). Of the 174 patients having received one course of BEP, 43% had high risk features (> pT1) [106].

In a community-based prospective study, SWENOTECA recommended one course of BEP in LVI+ patients., while patients with LVI- chose between surveillance and BEP x 1 [107]. The relapse-rate of the 490 patients who received BEP x 1 at 5 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 [108]. 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 improves the risk-benefit ratio of adjuvant chemotherapy considerably.

In addition, it is important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy [109]. Until now, only a limited number of patients with long-term follow-up and toxicity data have been reported on [110].

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 [111]. 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 [112].

7.3.3 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, as several studies have reported similar survival rates and a final cure rate close to 100% with all available treatment options using the risk-stratifying approach [101-103, 107, 108, 113-115].

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 recommended as adjuvant chemotherapy in patients with vascular invasion.

In cases of relapse after BEP x 1, three courses of BEP are recommended. However, there is not a large body of evidence to support any one specific salvage regimen.

7.3.4 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 of the German Testicular Cancer Study group 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 [106].

When RPLND is performed in a multicentre setting, higher rates of in-field recurrences and complications were reported [106, 116]. 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 [116, 117]. If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites [73, 117]. If metastases are present and not treated with adjuvant chemotherapy, recurrence will occur in 31% of patients [117].

The presence of vascular invasion, predominant embryonal carcinoma, pT category as well as a high number of extranodal extension in metastatic nodes may be associated with an increased risk of recurrence in PS2 cases without adjuvant chemotherapy. As yet, the clinical significance of these further parameters remains limited and not applicable in clinical practice [117, 118].

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 [119]. 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 [120].

7.3.5 Guidelines for the treatment of stage 1 NSGCT

Recommendations	LE	GR
Inform patients with stage 1 NSGCT about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and RPLND) including treatment-specific recurrence rates as well as acute and long-term side effects.	2a	A*
In patients with stage 1 NSGCT, offer surveillance or risk-adapted treatment based on vascular invasion (see below).	2a	A*
If patients are not willing to undergo surveillance, offer one course of BEP as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	1b	A*
In patients with marker-positive recurrent and/or progressing lesion during surveillance, perform salvage treatment consisting of three or four courses of BEP chemotherapy according to the IGCCCG classification, followed by post-chemotherapy retroperitoneal lymph node dissection if necessary.	2a	A

*Upgraded following panel consensus.
NSGCT = non-seminomatous germ cell tumou; RPLND = retroperitoneal lymph node dissection;
BEP = cisplatin, eposide, bleomycin; IGCCCG = International Germ Cell Cancer Collaborative Group.

7.3.6 Risk-adapted treatment for clinical stage 1 based on vascular invasion

Stage 1A (pT1, no vascular invasion): low risk	LE	GR
Offer surveillance if the patient is willing and able to comply.	2a	A
In low-risk patients not willing (or suitable) to undergo surveillance, offer adjuvant chemotherapy with one course of BEP.	2a	A*
Stage 1B (pT2-pT4): high risk		
Offer primary chemotherapy with one course of BEP.	2a	A*
Inform patients having adjuvant chemotherapy about the advantages and disadvantages of one vs. two cycles of BEP.	2a	A*
Offer surveillance or nerve-sparing RPLND in high-risk patients not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, discuss further chemotherapy as well as observation with the patient.		A*

*Upgraded following panel consensus.
BEP = cisplatin, eposide, bleomycin; IGCCCG = International Germ Cell Cancer Collaborative Group;
NSGCT = non-seminomatous germ cell tumour; RPLND = retroperitoneal lymph node dissection.

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

Figure 1: Risk-adapted treatment in patients with clinical stage 1 non-seminoma NSGCT CS1 [121]*
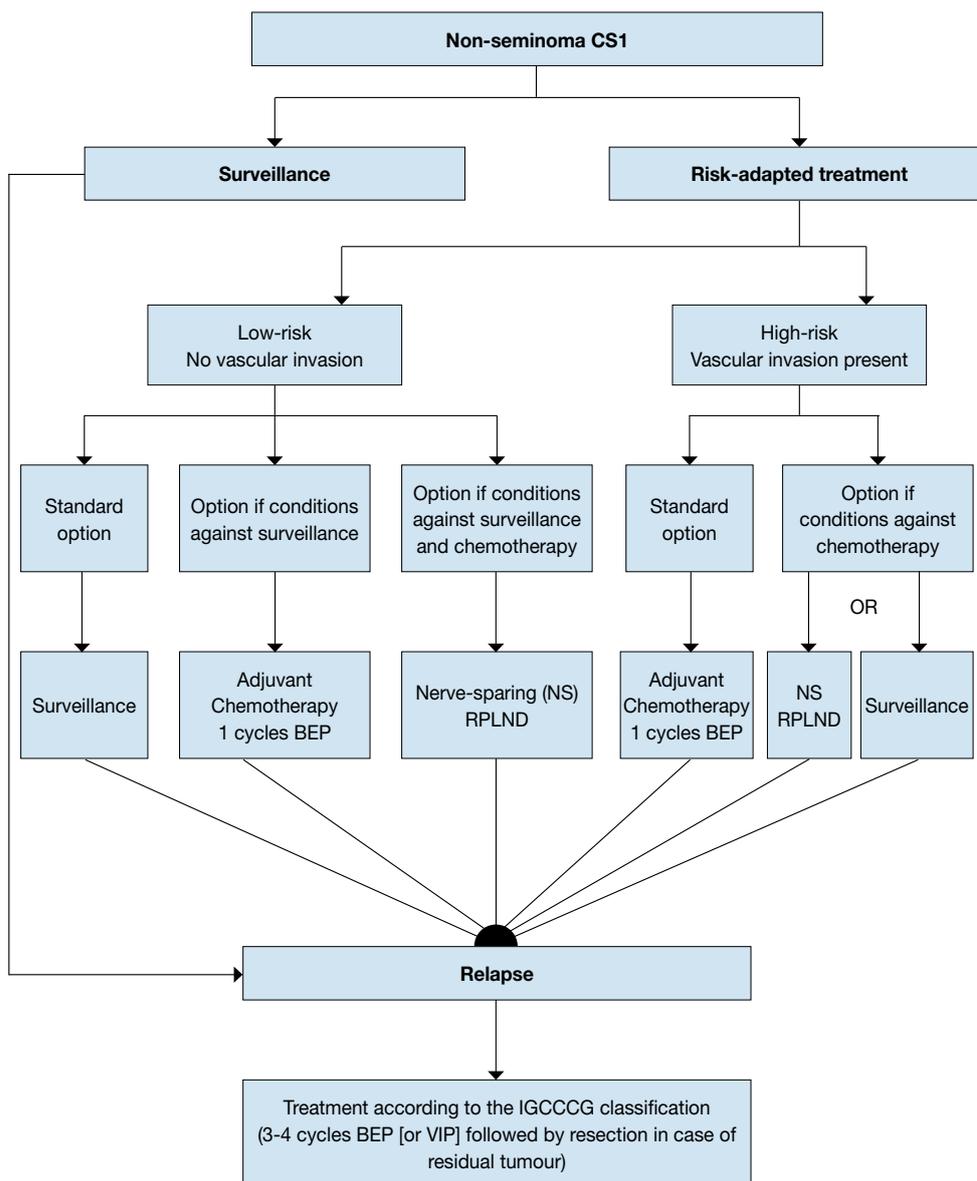
*All treatment options will need discussing with individual patients, to allow for them to make an informed decision as to their further care.
BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

7.4   Metastatic germ cell tumours
The first-line treatment of metastatic germ cell tumours 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) [27].

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.

7.4.1   *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. If the marker level increases after orchiectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum [122]. An US examination of the contralateral testicle must be performed, if this was not done initially.

The treatment of true CS1S patients is still controversial. They may be treated with BEP x 3 chemotherapy and with follow-up as for CS1B patients (high risk, see below) after primary chemotherapy [123], or by RPLND [112].

### 7.4.2 Metastatic disease (stage IIA/B)

7.4.2.1 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 8 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).

So far, the standard treatment for stage IIA/B seminoma has been radiotherapy with reported relapse rates of 9-24% [124, 125]. Accumulating data on long-term morbidity, such as increased risk of cardiovascular events and increased risk of second malignancies following radiotherapy has led to concern. 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 radiotherapy [126]. The radiation dose delivered in stage IIA and IIB is approximately 30 Gy and 36 Gy, respectively. The standard radiation field compared with stage I will be 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 a relapse-free survival in stage IIA and IIB of 92% and 90%, respectively. Overall survival is almost 100% [124, 125]. Conversely, dose reduction to 27 Gy has been associated with 11% of relapses [84, 126].

In stage IIA/B cases, chemotherapy with 3 courses of BEP or 4 courses of etoposide and cisplatin (EP), in cases with contraindications to bleomycin, is an alternative to radiotherapy. There are no randomised studies comparing radiotherapy vs. chemotherapy. Although more toxic in the short term, BEP x 3 or EP x 4 achieve a similar level of disease control [127]. One population-based study with 67 stage IIB patients reported a relapse free-survival of 100% after a median follow-up of 5.5 years [84]. Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease [128]. In CS IIA patients with seminoma, enrollment in clinical trials offering treatment options with potentially lower toxicity as compared to either radiotherapy or chemotherapy with 3 cycles BEP is recommended.

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B
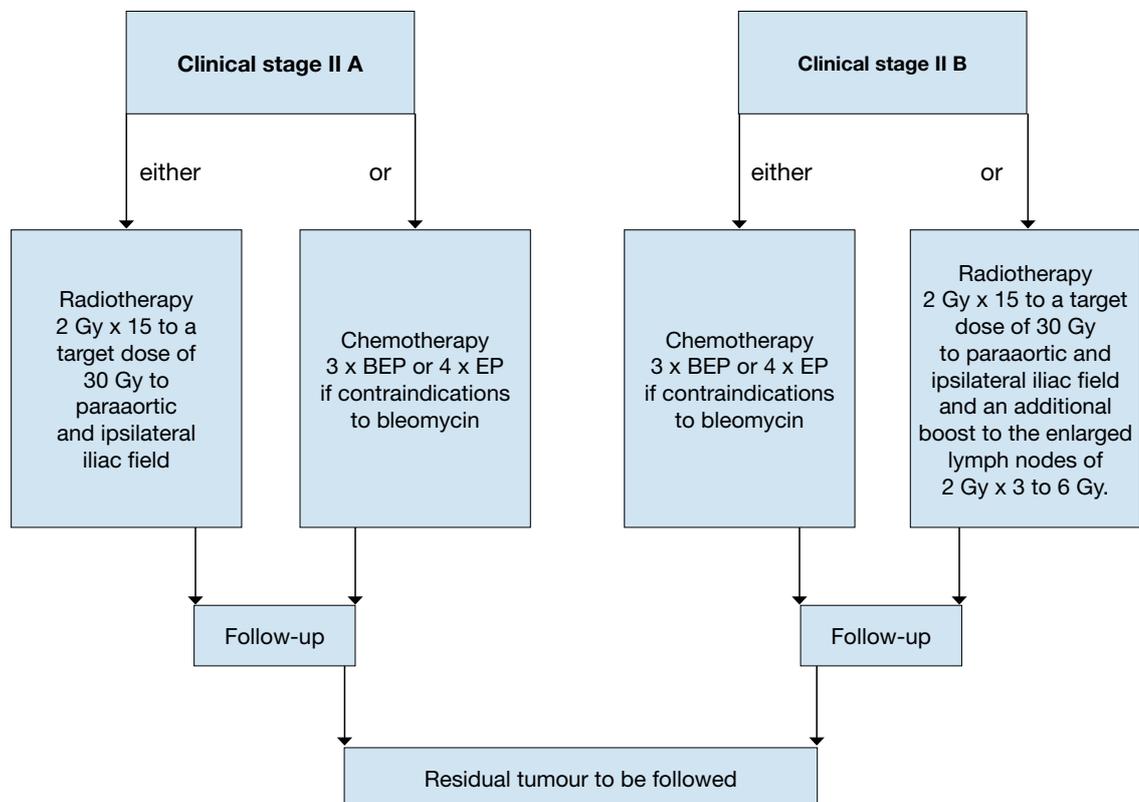
BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.4.2.2   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 [111, 129].

If surveillance is chosen, one follow-up evaluation after 6 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 beta-hCG, RPLND represents the first treatment option and should be performed by an experienced surgeon because of suspected viable disease or teratoma [129]. Patients with a growing lesion and a concomitant increase in the tumour markers AFP or beta-hCG require primary chemotherapy with BEP according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations (Figure 2). An alternative to the surveillance strategy in marker-negative II A/B non-seminoma with suspicion of an undifferentiated malignant tumour is a CT-guided biopsy, if technically possible. There is insufficient published data on PET scans in this situation.

When primary chemotherapy is refused by the patient or when it has some contraindications, primary nerve-sparing RPLND represents a viable option.

Primary chemotherapy and primary RPLND are comparable options in terms of outcome, but side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice [130]. The cure rate with either approach will be close to 98% [131-133].

In patients with marker negative CS IIA follow up is only recommended, if teratoma is more likely than marker negative embryonal carcinoma. If possible, a biopsy is recommended to exclude marker negative embryonal carcinoma.

Figure 3 presents the treatment options for patients with NSGCT CS IIA.

Figure 3: Treatment options in patients with non-seminoma clinical stage IIA
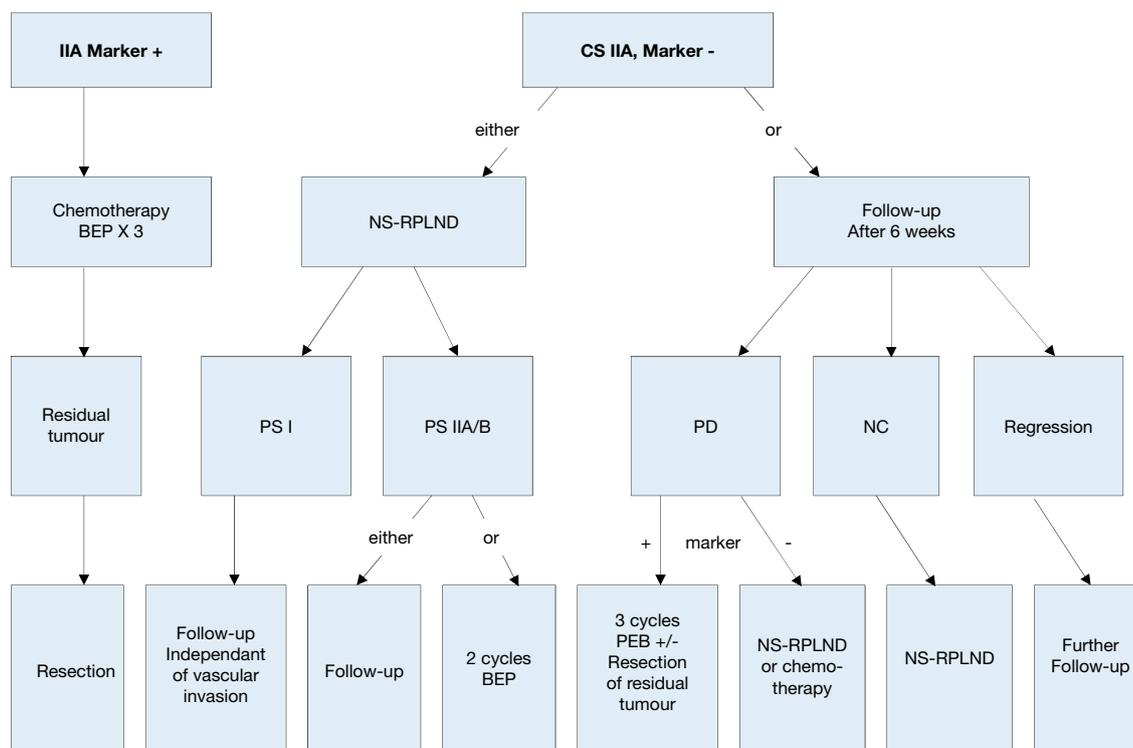
BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

7.4.3 Metastatic disease (stage IIC and III)

7.4.3.1 Primary chemotherapy

7.4.3.1.1 Good prognosis risk group - SGCT

For metastatic seminoma, only very limited data are available from randomised trials and they indicate that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [134]. Recent data indicate that EP x 4 results in cure in almost all cases of good-prognosis seminomatous germ cell cancers [135]. 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 [136]. Post-chemotherapy masses should be managed as described in Section 7.5.2.

7.4.3.1.2 Intermediate prognosis risk group - SGCT

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 randomised trial has focused specifically on this group of rare patients [137].

7.4.3.1.3 Good prognosis risk group - NSGCT

For non-seminoma, the primary treatment of choice for metastatic disease in patients with good prognosis risk 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 [138, 139]. While data support a 3-day regimen of administering combination chemotherapy to be equally effective as a 5-day regimen, this is associated with increased toxicity when four cycles are used [140], thus the 5-day BEP regimen is recommended.

Table 7.1: 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.

BEP = cisplatin, etoposide, bleomycin.

In selected cases where bleomycin is contraindicated, EP x 4 can be given [27, 139]. A randomised trial from the French Groupe d'Etude des Tumeurs Genito-Urinaires (GETUG) suggested that when the BEP is used in this setting the mortality rate was half that of EP, although the difference did not reach statistical significance [141].

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 < 1000/mm^3 or thrombocytopaenia < 100,000/IU. There is no indication for prophylactic application of haematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF). However, if infectious complications have occurred during chemotherapy or the treatment interval was delayed due to myelotoxicity, prophylactic administration of G-CSF is recommended for the following cycles [142].

7.4.3.1.4 Intermediate prognosis risk group - NSGCT

The 'intermediate prognosis' group in the IGCCCG has been defined as patients with a 5-year survival rate of about 80%. The available data support BEP x 4 as standard treatment [27, 143]. A randomised trial compared BEP x 4 to BEP x 4 with the addition of paclitaxel (T-BEP) with no significant improvement in OS [144]. The overall toxicity with T-BEP was higher than with BEP, therefore it cannot be recommended as a standard approach.

7.4.3.1.5 Poor prognosis risk group - NSGCT

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 [145, 146]. The 5-year progression-free survival is between 45% and 50%. Three randomised trials have shown no advantage in OS for high-dose chemotherapy in the overall 'poor prognosis' patients group [147-149]. However, patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [29, 147]. An online calculator is available for free at www.igr.fr/calculation-tumor/NSGCT. xls. 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 [30]. 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 [150]. Further prospective trials /registries are planned to validate this approach further.

Since a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [29, 151], 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 [11, 152]. 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 [153, 154].

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 3 days of EP without bleomycin) was suggested to reduce the risk of early death in this setting [153].

7.5 Restaging and further treatment

7.5.1 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) [27, 155, 156]. 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 [157].

Only with documented marker increase after two courses of chemotherapy is an early crossover of therapy to a completely new regimen indicated. These patients are usually candidates for new drug trials [158]. 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 [159, 160].

7.5.2 Residual tumour resection

7.5.2.1 Seminoma

A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers [161-164].

FDG-PET has a high negative predictive value in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled > 2 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 [40].

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 6 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 radiotherapy) [165-167]. 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.

When RPLND is indicated, this should be performed in referral centres, as residuals from seminoma may be difficult to remove due to intense fibrosis [166]. Ejaculation may be preserved in these cases [168].

7.5.2.2 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 [169]. FDG-PET is not indicated to re-stage patients after chemotherapy [42]. In cases of complete remission after first line chemotherapy (no visible tumour), tumour resection is not indicated [170, 171]. Residual tumour resection is mandatory in all patients with a residual mass > 1 cm in the short axis at cross-sectional CT imaging [172-175].

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 [176].

Proponents of PC-RPLND for all patients refer to the fact that both teratoma and vital malignant germ cell tumours are still found after radiologic complete remission in lesions < 10 mm [177]. 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 [170, 171]. In the series with a longer observation of 15.5 years, 12 of 141 patients (9%) relapsed after having achieved a complete response after primary treatment [171], but eight of the 12 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 [178]. Therefore, there is an indication to perform surgery in salvage patients even with residual disease < 1 cm [170, 171].

If residual surgery is indicated, all areas of primary metastatic sites must be completely resected within 2-6 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 [171, 176, 179-182].

In persistent larger volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within 2-6 weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed [171, 176, 179]. Laparoscopic RPLND may yield similar outcomes to the open procedure in very selected cases of very low residual disease and in very experienced hands, but it is not recommended outside a specialised laparoscopic centre [183-185].

7.5.3 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 [172]. 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 [186].

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 histologies between both lungs may occur in up to 20% of patients [187, 188].

7.5.3.1 Quality and intensity of surgery

Post-chemotherapy surgery is always demanding. Most of the time, post-chemo RPLND does not require further interventions on abdominal or retroperitoneal organs. 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 preformed and followed by ad hoc reconstructive surgery (e.g. vascular interventions such as vena cava or aortic prostheses) [189, 190]. In patients with intermediate or poor risk and residual disease > 5 cm the probability of vascular procedures is as high as 20% [191]. This surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Patients treated within such centres benefit from a significant reduction in perioperative mortality from 6% to 0.8% [12]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [13].

7.5.3.2 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 [192]. Also, in the case of extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [193, 194].

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 [195].

7.5.3.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or mature/immature 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) [180] (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 [196]. The prognosis will definitely deteriorate if

vital 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 [197].

7.5.4 *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 [198]. 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) [199]. No randomised trial has ever 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 randomised trial comparing standard-dose vs. high-dose chemotherapy plus transplant in the salvage setting showed no benefit in OS in patients treated with 3 cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus 1 cycle of consolidation high-dose chemotherapy, compared with VeIP x 4 [200]. At present, it is impossible to determine whether conventionally dosed cisplatin based combination chemotherapy is sufficient as first-salvage treatment or whether early intensification of first-salvage treatment with high-dose chemotherapy should be used. However, there is evidence from large retrospective analyses that there are different prognostic groups in the case of relapse after first-line chemotherapy [201-203], and the Lorch-Beyer score has resulted in 5 prognostic subgroups (Table 7.3).

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 randomised trial of high-dose vs. conventional dose chemotherapy in patients with first-line relapse is planned (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 [204].

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
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

PEI/VIP = cisplatin, etoposide, ifosfamide; TIP = paclitaxel, ifosfamide, cisplatin; GIP = gemcitabine, ifosfamide, cisplatin
* Plus hydration.
† Plus mesna protection.
xx An MRC schedule uses paclitaxel at 175 mg/m^2 in a 3 hour infusion [205].

The International Prognostic Factors Study Group score comprised of 7 important factors is listed in Table 7.3 (seminoma vs. non-seminoma histology, primary tumour site, response to initial chemotherapy, duration of progression-free interval, AFP marker level at salvage, hCG marker level at salvage, and the presence of liver, bone, or brain metastases at salvage). Using these factors, 5 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 5 risk groups and the corresponding 2-year PFS and 3-year OS rates [206].

Table 7.3: The International Prognostic Factors Study Group Score Construction [202]

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; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases;
PFI = progression-free interval.

Table 7.4: PFS and OS estimates for all patients according to IGCCCG-2 prognostic score [202]

	N	%	HR	2-years PFS	3-year OS
Score n = 1435					
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				

IGCCCG = International Germ Cell Cancer Collaborative Group; OS = overall survival; PSF = progression-free survival.

7.5.5 Second relapse

There are no randomised trials 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), High-dose (HD) chemotherapy with autologous stem cell support should be used [202]. Even with HD-therapy the chance of cure is only 20-25%.

Refractory disease: Patients relapsing within 4-8 weeks after platinum-based therapy or who are progressing despite platinum-based therapy as well as those relapsing shortly after HD chemotherapy are considered cis-platinum refractory. For those patients, combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45%. Cisplatin re-challenge in association with gemcitabine and paclitaxel, could be considered in patients with good renal function [207].

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [193].

7.5.5.1 Late relapse (≥ 2 years after end of first-line treatment)

Late relapse is defined as recurrence more than 2 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% in seminoma and non-seminoma patients, respectively [208, 209]. 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 germ-cell tumour, mature teratoma with or without somatic transformation [109, 210, 211].

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 germ cell tumour, whereas teratoma or necrosis was found in half of the patients with initial non-seminoma [212].

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 [213]. 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 radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [214].

7.5.5.2   Treatment of brain metastases
Brain metastases occur in the frame of 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 5-year survival-rate is 2-5%) [215, 216]. Chemotherapy is the initial treatment in this case, and some data support the use of consolidation radiotherapy, even in the case of a total response after chemotherapy [217]. 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.

*7.5.6   **Guidelines for the treatment of metastatic germ cell tumours***

Recommendations	LE	GR
Treat low volume NSGCT stage IIA/B with elevated markers like 'good or intermediate prognosis' advanced NSGCT, with three or four cycles of BEP.	2	A
In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either RPLND or biopsy. If not possible, repeat staging after 6 weeks of surveillance before making a final decision on further treatment.	3	B
In metastatic NSGCT (≥ stage IIC) with good prognosis, treat with three courses of BEP.	1	A
In metastatic NSGCT with an intermediate prognosis, treat with four courses of standard BEP.	1	A
In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, followed by tumour marker assessment after 3 weeks: in the case of an unfavourable decline, initiate chemotherapy intensification. In the case of a favourable decline, continue BEP up to a total of four cycles.	1	A
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.	2	A
Treat seminoma CSII A/B initially with radiotherapy. When necessary, use chemotherapy as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.	2	B
In seminoma stage CS IIA/B, offer chemotherapy (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	1	A
Treat seminoma stage IIC and higher with primary chemotherapy according to the same principles used for NSGCT.	1	A

EP = eposide, cisplatin; GR = grade of recommendation; NSGCT = non-seminomatous germ cell tumour;
BEP = cisplatin, eposide, bleomycin; RPLND = retroperitoneal lymph node dissection.

8.   FOLLOW-UP AFTER CURATIVE THERAPY

8.1   Follow-up care for cancer patients
There is no consensus on a standardised follow-up of patients treated for germ-cell cancer.

8.2   General considerations
The following considerations apply in a general manner for the selection of an appropriate schedule and testing in the follow-up of all stages of testis tumour.
- Most recurrences after curative therapy will occur in the first 2 years; surveillance should therefore be most frequent and intensive during this time.
- Late relapses can occur beyond 5 years, and therefore yearly life-long follow-up may be advocated.
- After RPLND, relapse in the retroperitoneum is rare, the most likely site of recurrence being the chest.
- The value of a plain radiography chest has been recently questioned in the follow-up of patients with disseminated disease after complete remission [218, 219].
- CT of the chest has a higher predictive value than plain radiography chest [219].
- The results of therapy are dependent on the bulk of disease; therefore, an intensive strategy to detect asymptomatic disease may be justifiable.

- After chemotherapy or radiotherapy, there is a long-term risk of the development of secondary malignancies.
- Exposure to diagnostic X-rays causes second malignancies [220]. Therefore, the frequency of CT scans should generally be reduced and any exposure to X-rays should be well justified in a patient cohort with a very long life-expectancy after successful treatment.
- CT can be substituted by MRI however, MRI is a protocol-dependent method and should be performed in the same institution with a standardised protocol.
- With special expertise, US may be used as a method to screen the retroperitoneum during follow-up. However, the method is very much dependent on the investigator and cannot be recommended as the standard method during follow-up.
- Longer follow-up in patients after radiotherapy and chemotherapy is justified to detect late toxicities (e.g. cardio-vascular, endocrine).

A number of interdisciplinary organisations have presented recommendations for follow-up of TC patients [221-223]. The follow-up tables below (Tables 8.1 through 8.4) present the minimum recommendations based on the expert opinions of the guideline authors.

8.3 Follow-up: stage I non-seminoma

Approximately 5% of patients with CS1 NSGCT present with elevated levels of tumour markers after orchiectomy, and 25-30% relapse during the first 2 years [102, 224-226]. The follow-up schedule will differ depending on which of the three possible treatment strategies was chosen:
- surveillance;
- nerve-sparing RPLND;
- adjuvant chemotherapy.

8.3.1 Follow-up investigations during surveillance
The results of a surveillance policy depend upon a careful pre-operative staging procedure and follow-up management. In a 'wait and see' policy, relapses will occur in 30% of cases. Of these relapses, 80% will occur in the first 12 months after orchiectomy, and approximately 12% during the second year. The median time to relapse is 6 months, but relapses after 3-5 years, and even later, can still occur, with an annual rate of 4% [90, 91]. Relapse occurs mainly in the retroperitoneum: approximately 70% of patients have evident metastases in the retroperitoneum, and 10% in the mediastinum and lungs [227]. Sometimes the only indication is an elevated level of tumour markers.

A randomised trial of two vs. five CTs has been published by the MRC, which recommends the reduction of imaging during surveillance in this stage, to one CT scan at 3 months after orchiectomy, and another at 12 months. The trial, with a cohort of 414 patients, was powered to exclude a 3% probability of detecting a patient during surveillance only, with a relapse presenting already-metastatic disease with 'intermediate' or 'poor' prognosis features. Relapses were detected in 15% with two CT, and 20% with five CT; 1.6% of these patients had 'intermediate' or 'poor' prognostic features. Only 10% of patients had high-risk features (vascular invasion). In summary, this first randomised trial yielded level 1 evidence for a minimum follow-up in patients with CS1 non-seminoma [115]. The recommended follow-up schedule (Table 8.1) includes the minimum requirements for imaging, and adds recommendations for other surveillance tests [227].

Table 8.1: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma [227]

Procedure	Year			
	1	2	3	4-5
Physical examination	4 times	4 times	4 times	Once/year
Tumour markers	4 times	4 times	4 times	Once/year
Plain radiography chest	Twice	Twice	Twice	Twice
Abdominopelvic CT	Twice at 3 and 12 months	Once at 24 months	Once at 36 months	

CT = computed tomography.

8.3.2 Follow-up after nerve-sparing RPLND
Retroperitoneal relapse after a properly performed nerve-sparing RPLND is rare. RPLND should eliminate the retroperitoneal nodes as a site of relapse and thus the need for repeated abdominal CTs. The USA Testicular Cancer Intergroup study data showed retroperitoneal relapse in 7/264 patients with pathological stage I disease

and 20 pulmonary relapses. Four of these seven had no marker elevation [228]. In the Indiana series, only one relapse in 559 cases was reported [229]. If a relapse occurs, it is generally in the chest, neck or at the margins of the surgical field.

Pulmonary relapses occur in 10-12% of patients, and more than 90% of those relapses occur within 2 years of RPLND [45, 230]. However, the low rate of retroperitoneal relapse after RPLND can only be achieved by surgery in specialised centres, as shown by the high in-field relapse rate (7/13 relapses) in the German randomised trial of RPLND vs. BEP x 1 [106]. The recommended minimum follow-up schedule is shown in Table 8.2.

Table 8.2: Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma

Procedure	Year				
	1	2	3	4-5	6-10
Physical examination	4 times	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice	Twice		
Abdominopelvic CT	Once	Once	Once	Once/year	

CT = computed tomography.

8.3.3 *Follow-up after adjuvant chemotherapy*
Prospective reports with long-term follow-up after adjuvant chemotherapy have shown a low relapse rate of about 3% [102]. In a randomised trial with one course of BEP vs. RPLND, the relapse rate with adjuvant chemotherapy was 1% (2/174 patients, one with marker relapse, one with mature teratoma in the retroperitoneum) [106]. The need for repeated and long-term assessment of the retroperitoneum is still not clear. Owing to the risk of developing a late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy, an abdominal CT should still be performed (see Table 8.2).

8.4 Follow-up: stage I seminoma
The majority of patients with seminoma (70-80%) present with clinical stage I disease at diagnosis. In 15-20% of cases there is nodal radiological involvement at the level of the retroperitoneum and only 5% of patients present with distant metastasis.

The relapse rate varies between 1% and 20% depending on the post-orchiectomy therapy chosen. Up to 30% of seminomas present with elevation of hCG at diagnosis or in the course of the disease. Consequently, in most cases, measurement of blood markers will not be a reliable test for follow-up [231]. The treatment options post-orchiectomy in stage I seminoma are surveillance or adjuvant carboplatin chemotherapy.

8.4.1 *Follow-up after radiotherapy*
Low doses of radiotherapy (20-24 Gy) limited to the retroperitoneal or the para-aortic and ipsilateral field achieve an OS rate of approximately 99% at 5-10 years [90, 91, 232, 233]. The rate of relapse is 1-2% and the most common time of presentation is within 18 months of treatment [90, 233-235], although late relapses have also been described [210]. The site of relapse is mainly at the supradiaphragmatic lymph nodes, mediastinum, lungs or bones. In a small proportion of cases, the tumour will relapse in the inguinal or external iliac nodes. After para-aortic field RT there is also a pelvic node relapse pattern.

The side-effects of radiotherapy include temporary impaired spermatogenesis, GI symptoms (peptic ulceration), and induction of second malignancies [234, 236, 237]. Up to 50% of patients can develop moderate toxicity grade I-II [231]. The follow-up schedule is described in Table 8.3.

Table 8.3: Recommended minimum follow-up schedule for post-orchiectomy surveillance, radiotherapy or chemotherapy: stage I seminoma [226]

Procedure	Year		
	1	2	3-5
Physical examination	3 times	3 times	Once/year
Tumour markers	3 times	3 times	Once/year
Plain radiography chest	Twice	Twice	
Abdominopelvic CT	Twice	Twice	at 36 and 60 months

CT = computed tomography.

8.4.2   ***Follow-up during surveillance***
The actuarial risk of relapse at 5 years ranges between 6% and 20% [92, 238-242]. There is no increased risk of death. The median time to relapse ranges from 12-18 months, but up to 29% of relapses can develop later than this [81, 243]. The sites of relapse are the PA lymph nodes in up to 82% of cases, the pelvic lymph nodes, inguinal nodes and lungs can also be affected [81, 105, 244-247]. Due to the high and often late rate of relapse, close and active follow-up is mandatory for at least 5 years [238] (see Table 8.3).

8.4.3   ***Follow-up after adjuvant chemotherapy***
One or two courses of carboplatin-based chemotherapy is an effective alternative treatment in stage I seminoma. The relapse rate is 1.9-4.5%. In general, this treatment is well tolerated, with only mild, acute and intermediate-term toxicity [238, 239]. Long-term data on late relapses and survival are missing (see Table 8.3).

8.5   Follow-up: metastatic disease
The more advanced the nodal stage of the disease, the higher the likelihood of recurrence [131]. In general, the primary tumour bulk governs the outcome for patients with NSGCT [243]. In stage II NSGCT, regardless of the treatment policy adopted, excellent survival rates of 97% are reached provided that relapse is identified as soon as possible [111, 132].

In advanced metastatic germ-cell tumours, the extent of the disease correlates with the response to therapy and with survival. The combination of cisplatin-based chemotherapy and surgery (aggressive multimodality) achieves cure rates of between 65% and 85%, depending on the initial extent of disease [241, 242]. Complete response rates to chemotherapy are in the order of 50-60% [241]; another 20-30% of patients could be disease-free with post-chemotherapy surgery [248].

The main reasons for failure of therapy in advanced NSGCT are [27, 240, 249]:
* the presence of bulky disease not responding completely to chemotherapy;
* unresectable residual teratoma after chemotherapy;
* the presence or development of chemoresistant non-germ elements, which account for 8.2% of cases.

Table 8.4 presents the recommended minimum follow-up schedule in advanced NSGCT and seminoma.

Table 8.4: Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

Procedure	Year			
	1	2	3-5	Thereafter
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Plain radiography chest	4 times	4 times	Twice/year	Once/year
Abdominopelvic CT*	Twice	Twice	Once/year	As indicated
Chest CT[†‡]	Once/year	Once/year	Once/year	As indicated
Brain CT[§]	Once/year	Once/year	Once/year	As indicated

CT = computed tomography.
* An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.
† If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.
‡ A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.
§ In patients with headaches, focal neurological findings, or any central nervous system symptoms.

8.6   Quality of life and long-term toxicities after cure for testicular cancer
The vast majority of patients will be cured and 5-year relative survival rates approximate 95% in Western Europe. Furthermore, TC patients are usually between 18 and 40 years at diagnosis such that life expectancy after cure extends over several decades [250]. 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 [100], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with its known long-term toxicities as quite appealing [251]. 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 [102, 110, 252].

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 [208, 253]. The following overview is not complete and interested readers are referred to review articles on this topic [250, 253, 254].

8.6.1 Second malignant neoplasms (SMN)
Treatment-induced SMN usually occur after the first 10 years [253]. The risk for solid SMN increases with younger age at radio- or chemotherapy and remains significantly elevated for at least 35 years [93, 255-257]. RT-related SMN are primarily localised within or close to the RT field (colon, stomach, pancreas, bladder and the urinary tract) [93, 94, 256-259]. Fung *et al.* demonstrated that modern cisplatin-based chemotherapy was associated with a 40% increased risk of a solid SMN [260].

8.6.2 Leukaemia
In a series of 40,576 TC survivors, the observed/expected ratio for developing a leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemia was 2.6 [261]. 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 [262]. It is important to keep in mind that the majority of TC patients do receive much lower doses of etoposide such 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 10 years after treatment for TC and has a very poor prognosis [263].

8.6.3 Infections
Chemotherapy-treated TC survivors (TCSs) have a higher risk of dying from infections than the normal population, (SMR 2.48, 95% CI: 1.70 to 3.50) [264]. This is possibly due to long-term depression of the bone-marrow, but also complications of subsequent salvage treatment (which was not reliably registered) or extensive or subsequent surgical treatment might lie behind these numbers. Furthermore, asymptomatic pulmonary fibrosis by mediastinal radiotherapy and/or bleomycin may render TCSs vulnerable to potentially deadly pneumonias many years after treatment.

8.6.4 Pulmonary complications
Chemotherapy exposed TCSs have a nearly 3-fold increased risk of dying of pulmonary diseases than the normal population [264]. Bleomycin-induced lung toxicity may affect 7% to 21% of patients in the long term, resulting in death in 1%-3% [265]. TCSs treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured by surgery only [266]. Intriguingly, pulmonary complications were associated with the cumulative cisplatin dose and not to the dose of bleomycin.

8.6.5 Cardiovascular toxicity
Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population [264, 267]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [105, 246]. The metabolic syndrome is a strong predictor for CVD and its components, hypertension, obesity and hypercholesterolemia, increase with treatment intensity [247, 268]. Circulating residual serum platinum might exert endothelial stress [269].

8.6.6 Raynaud-like phenomena
Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually ascribed to the application of bleomycin [270, 271]. Cisplatin is believed to contribute to cold-induced vasospasms, as Vogelzang *et al.* reported that the incidence of Raynaud's phenomenon was higher after treatment with CVB than after vinblastine and bleomycin only, 41% vs. 21%, respectively [272].

8.6.7 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 [273]. Application of 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 of paclitaxel administration, or within a week. 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 [269].

8.6.8 Ototoxicity

Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [274-276]. 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 (odds ratio 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [273]. A significant association between glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [277, 278]. Hopefully, increasing insight into the pathogenesis of and vulnerability for this complication will lead to more individualised treatment in the future.

8.6.9 Nephrotoxicity

Cisplatin-based chemotherapy may lead to long-term renal function impairment in 20-30% of TCSs [273-276]. In TC patients, reduced renal elimination of cisplatin and bleomycin might increase the risk of other toxicities, e.g. bleomycin-related pneumonitis [279, 280].

8.6.10 Hypogonadism

Testicular endocrine dysfunction comprises insufficient testosterone (T) production and/or compensatory increased Luteinizing hormone (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 [253, 281].

8.6.11 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 6 months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [282]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of 12 years after treatment for TC when compared with the age-matched Norwegian population (10%) [283]. Of note, the prevalence of CF increased from 15% to 27% during a 10 year period in long-term TCSs [284].

8.6.12 Quality of life

Quality of life (QoL) is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social and physical functions [285]. When comparing three or four cycles of BEP in good risk patients, all outcomes favour treatment with three courses [140]. After one and two years, one third of patients reported an improvement in global QoL after chemotherapy, while one fifth of patients reported deterioration, with no difference between treatment groups. In adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (5 year) QoL between RPLND or one course of BEP [286].

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 WHO classification 2004 (adapted) [25].

9.2 Leydig cell tumours

9.2.1 Epidemiology

Leydig cell tumours constitute about 1-3% of adult testicular tumours [287, 288] and 3% of testicular tumours in infants and children [288]. 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 3 and 9 years. Only 3% of Leydig cell tumours are bilateral [287]. These tumours occur in about 8% of patients with Klinefelter's syndrome [289].

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) [25].

Approximately 10% of Leydig cell tumours are malignant and present with the following parameters [290, 291]:

- 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 [292, 293], while negative results are always obtained for the testicular germ cell tumour-markers AFP, hCG, LDH and PLAP. Up to 10% of adult patients present with gynaecomastia [293, 294]. Only 3% of tumours are bilateral [287].

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 germ-cell tumours [295]. The proportion of metastatic tumours in all published case reports is less than 10%. In three old series with long follow-up, 18 metastatic tumours were found in a total of 83 cases (21.7%) [287, 290, 296], while 5 recently published studies with long follow-up reported only 2 metastatic tumours in 156 patients (1.3%) [293, 294, 297-299].

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 [300, 301]. 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 [300]. Microscopically, the cells are eosinophilic to pale with 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%) [300]. The rate of malignancy ranges between 10% and 22%. Signs of a malignant Sertoli tumour are as follows [302, 303]:

- 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 [301]:

- classic Sertoli cell tumour [300];
- large cell calcifying form with characteristic calcifications [304, 305];
- sclerosing form [306, 307].

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 [300]. 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 germ-cell tumours [301]. Only the large cell calcifying form has a characteristic image with bright echogenic foci due to calcification [308]. 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 [300].

The **large cell calcifying** form is diagnosed in younger men and is associated with genetic dysplastic syndromes (Carney's complex [309] and Peutz-Jeghers syndrome [310] 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 [305].

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%) [301].

The sclerosing subtype is very rare, unilateral, with a mean age around 40 years and metastases are infrequent [307].

9.4 Treatment of Leydig- and Sertoli cell tumours

Asymptomatic, small volume testicular tumours are often misinterpreted as germ-cell tumours, and inguinal orchidectomy is performed. An organ-sparing procedure in every small US-detected, nonpalpable intraparenchymal lesion is highly recommended in order to obtain a histological diagnosis. The incidence of benign definitive histology is high at approximately 80% [311]. In patients with symptoms of gynaecomastia or hormonal disorders, a non-germ-cell tumour should be considered and immediate orchidectomy avoided. In cases with germ-cell tumour 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 retroperitoneal lymphadenectomy may be an option to prevent metastases [312] or to achieve long-term cure in stage IIA cases [313]. Prophylactic RPLND is unjustified for patients with clinical stage I disease without high-risk features [314].

Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor [312]. No recommendations are available for the treatment of these patients.

9.5 Follow-up of Leydig- and Sertoli cell tumours

Without clinical signs of malignancy, an individualised surveillance strategy after orchidectomy is recommended in patients with one, or more, pathological features of malignancy. Follow-up is recommended in all high risk patients; every 3 to 6 months with physical examination, hormone assays, scrotal and abdominal ultrasonography, chest radiography, and CT [293].

9.6 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 prepubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type [315, 316].
- 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 [317].

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 [318].

9.7 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 [319].

9.8 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 [32]. 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 [320].

9.9 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 germ-cell tumours. 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 [321, 322].

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 [323].

9.10 Miscellaneous tumours of the testis

9.10.1 Tumours of ovarian epithelial types

These tumours resemble epithelial tumours of the ovary. A cystic appearance with occasional mucinous material can be observed. Microscopically, the 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 [25].

9.10.2 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 [324].

9.10.3 Tumours (benign and malignant) of non-specific stroma

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

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11.   CONFLICT OF INTEREST