



European Association of Urology

# GUIDELINES ON TESTICULAR CANCER

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# 1 BACKGROUND

Testicular cancer represents between 1% and 1.5% of male neoplasms and 5% of urological tumours in general, with 3-6 new cases/occurring per 100,000 males/per year in Western society (1,2). An increase in the incidence of testicular cancer was detected during the 1970's and 1980's, particularly in Northern European countries and a recent review shows a clear trend toward an increased Testicular Cancer incidence in the last 30 years in the majority of the industrialized countries in North America, Europe and Oceania but surprising differences in incidence rates are seen between neighbouring countries (3). Incidence data from the Surveillance Epidemiology and End Results Program for the years 1973 to 1998 show a continuing increased risk among white men in the USA only for seminoma (4).

Only 1-2% of cases are bilateral. The histological type varies, although there is a clear predominance (90-95%) of germ cell tumours (1). Peak incidence is in the third decade of life for non-seminoma and in the fourth decade for pure seminoma. Familial clustering has been observed, particularly among siblings (5). Genetic changes have been described in patients with testicular cancer. 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 (5). Intratubular germ cell neoplasia (testicular intraepithelial neoplasia, Tin) shows the same chromosomal changes, and recently alterations in the p53 locus have been found in 66% of cases of testicular Tin (6). Epidemiological risk factors for the development of testicular tumours are: a history of cryptorchidism or undescended testis, Klinefelter's syndrome, familial history of testicular tumours among first grade relatives (father/brothers), the presence of a contralateral tumour or Tin and infertility (7-12). Above average height (>185 cm) was associated with risk of germ cell cancer in a recent study (13) although further confirmation is needed.

Currently, testicular tumours show excellent cure rates. The main factors contributing to this are: careful staging at the time of diagnosis; adequate early treatment based on chemotherapeutic combinations, with or without radiotherapy and surgery; and very strict follow-up and salvage therapies. In the last decade, a decrease in the mean time delay to diagnosis and treatment has been observed (14). For the treatment of Testicular Cancer the choice of the treatment Centre is of paramount importance. Although early stages can be successfully treated in a non-reference Centre, the relapse rate is higher, suggesting that the high survival rate is due to chemo- and radiosensitivity of the early stages rather than the compliance achieved in a non-reference Centre (15). In poor prognosis non seminomatous germ cell tumours it has been shown that overall survival within a clinical trial depended on the number of patients treated at the participating centre (worse < 5 patients enrolled) (16).

## 1.1 Methods

The present Guidelines represent a compilation of previously published texts; the latest EAU guideline text was formally published in 2001 (17) and an update has been distributed among EAU members in March 2004. In addition to the 2004 version which was updated, this edition contains a separate chapter on testicular stromal tumours. A multidisciplinary team of urologists, medical oncologists, radiotherapists and a pathologist were involved in producing the present text which is based on a non-structured review of the literature through 2005 for both the germ cell tumour and the non-germ cell tumour sections. Also data from Meta-analysis studies, Cochrane evidence and the recommendations of the European Germ Cell Cancer Collaborative Group (EGCCCG), as well as other available guidelines have been included (18-25).

Whenever possible, references have been labelled according to the principles of Evidence Based Medicine (EBM) (26). The nature of the recommendations in the present guidelines is labelled according to grade of evidence (26).

# 2 PATHOLOGY AND NATURAL HISTORY

In seminoma Stage I the tumour size and the invasion of the rete testis are independent predictors of relapse. Molecular markers (like CD30 and cytokeratins) are not useful for diagnosis or prognostic evaluation. In the non-seminoma and non-teratoma germ cell tumours, vascular invasion and stage are the most important morphological predictors. The behaviour of teratoma in the two age groups is different; in prepuberal individuals testis teratoma is benign while in the postpuberal group metastases can appear in 27-33% of cases.

The recommended pathological classification (modified from the 2004 version of the World Health Organization) is shown below (27).

1. **Germ cell tumours**
  - Intratubular germ cell neoplasia
  - Seminoma (including cases with syncytiotrophoblastic cells)
  - Spermatocytic seminoma (mention if there is sarcomatous component)
  - Embryonal carcinoma
  - Yolk sac tumour
  - Reticular, solid and polyvesicular patterns
  - Parietal, intestinal, hepatoid and mesenchymal differentiation
  - Choriocarcinoma
  - Teratoma (mature, immature, with malignant component)
  - Tumours with more than one histological type (specify % 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

## 3 DIAGNOSIS

### 3.1 Clinical Examination

Testicular cancer generally affects young men in the third or fourth decade of life. It normally appears as a painless, unilateral mass in the scrotum or the casual finding of an intrascrotal mass (28). In approximately 20% of cases the first symptom is scrotal pain and up to 27% of patients with testicular cancer have local pain (1). Occasionally, trauma to the scrotum may reveal the presence of a testicular mass. Gynaecomastia appears in 7% of cases and is more common in non-seminomatous tumours. Back and flank pain are present in about 11% of cases (14). Reduction in testis size can precede a testicular tumour (29).

In about 10% of cases, a testicular tumour can mimic an orchioepididymitis, with consequent delay of the correct diagnosis (1,2). Ultrasound must be performed in any doubtful case. Physical examination reveals the features of the mass and must always be carried out in conjunction with a general examination in order to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. A correct diagnosis must be established in all patients with an intrascrotal mass (30).

### 3.2 Imaging of the testis

Currently, diagnostic ultrasound serves to confirm the presence of a testicular mass and to explore the contralateral testis. Its sensitivity in detecting a testicular tumour is almost 100%, and it has an important role in determining whether a mass is intra- or extratesticular (31). Ultrasound is an inexpensive test, but it is unnecessary when the presence of a testicular tumour is clinically evident (32). Ultrasound of the testis has to be performed in young men without a palpable testicular mass who have retroperitoneal or visceral masses or elevated serum beta-human chorionic gonadotrophin (beta-hCG) or alpha-fetoprotein (AFP) (33-36). The main uses of ultrasound are as a screening test of the contralateral testis in the follow-up of patients at risk (37).

Magnetic Resonance Imaging (MRI) offers higher sensitivity and specificity than ultrasound for diagnosing tumours (38-40) and may be able to differentiate seminomatous from non-seminomatous tumours.

MRI of the scrotum offers a sensitivity of 100% and a specificity of 95-100% (41), but its high cost does not justify its use for diagnosis.

### 3.3 Serum tumour markers at diagnostic

Serum tumour markers are prognostic factors and contribute to diagnosis and staging (42). The following markers should be determined:

- AFP (produced by yolk sac cells)
- Beta-hCG ( $\beta$ -hCG) (expression of trophoblasts)
- Lactate Dehydrogenase (LDH)

Globally, there is an increase in these markers in 51% of cases of testicular cancer (14). Alpha-Fetoprotein (AFP) increases in 50-70% of patients with non-seminomatous germ cell tumour (NSGCT) and a rise in beta human chorionic gonadotrophin ( $\beta$ -hCG) is seen in 40-60% of patients with NSGCT (28). About 90% of non-seminomatous tumours present with a rise in one or two of the markers. Up to 30% of seminomas can present or develop an elevated beta-hCG level during the course of the disease (43,44). Lactate Dehydrogenase (LDH) is a less specific marker, and its concentration is proportional to tumour volume. Its level may be elevated in 80% of patients with advanced testicular cancer (43). It should be noted that negative marker levels do not exclude the diagnosis of a germ cell tumour. Other markers studied include neuro-specific enolase (NSE) and placental alkaline phosphatase (PLAP). NSE and/or PLAP may be of limited value in monitoring patients with pure seminoma. Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research studies. Measurement of serum AFP, beta-hCG and LDH is mandatory. NSE and PLAP are optional.

### 3.4 Inguinal exploration and orchiectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunica, and immediate orchiectomy with division of the spermatic cord at the internal inguinal ring has to be performed if a tumour is found. The spermatic cord is isolated at the external ring and the testis is then exteriorized with its tunics. The surgical field is protected with surgical sponges, the tunica vaginalis is opened, and the testis is carefully inspected and palpated. If the diagnosis is not clear, a testicular biopsy is taken for frozen section histological examination. Once the diagnosis of testicular tumour has been established, the testis is enveloped into the sponges that protect the surgical field, gloves are changed, the inguinal channel is opened and the spermatic cord is divided at the level of the internal ring. The specimen is sent for definitive histology.

In case of disseminated disease and life-threatening metastases, up-front chemotherapy can be started and orchiectomy delayed until clinical stabilisation.

### 3.5 Organ sparing surgery

Although organ sparing surgery is not indicated 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 preoperative testosterone levels, organ preserving surgery can be performed when the 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 (up to 82%) and all patients have to be treated with adjuvant radiotherapy (20 Gy) (45). Infertility will result after radiotherapy. The option has to be carefully discussed with the patient and surgery performed in a centre with experience (46,47).

### 3.6 Pathological examination of the testis

After surgical ablation of the testis, pathological assessment is mandatory and determination of serum tumour markers is advisable.

Mandatory pathological requirements

- Macroscopic features: side, testis size, tumoral maximum size and macroscopic features of epididymis, spermatic cord and tunica vaginalis.
- Sampling: 1 cm<sup>2</sup> section for every cm of maximal tumoral diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis 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):
  - Presence or absence of peri-tumoral venous and/or lymphatic invasion.
  - Presence or absence of albuginea, tunica vaginalis, epididymis or spermatic cord invasion.
  - Presence or absence of intratubular germinal neoplasia (Tin) in non-tumoral parenchyma.

- pT category according to TNM 2002.
- Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and beta-hCG.

Advisable immunohistochemical markers

- In seminoma: cytokeratins (CAM 5.2), PLAP
- In intratubular germ cell neoplasia: PLAP
- Other advisable markers: Chromogranine A (Cg A), Ki 1, and NSE

### 3.7 Diagnosis and treatment of carcinoma in situ (Tin)

Contralateral biopsy has been advocated to rule out the presence of Tin (48). Although this is routine policy in some countries, the low incidence of Tin and contralateral asynchronous testicular tumours, up to 5% and approximately 2.5% respectively, (29,49-53), the morbidity of Tin treatment and the fact that most of these asynchronous tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy (53,55). It is still difficult to reach a consensus whether the existence of contralateral Tin has to be identified in all cases. However biopsy of the contralateral testis should be offered to high-risk patients for contralateral Tin, which are patients with a testicular volume less than 12 ml, a history of cryptorchidism and younger than 30 years of age (50,56).

Once Tin is diagnosed, local Radiotherapy (20 Gy in single fractions of 2 Gy) is the treatment of choice. Because this may produce infertility, the patient must be carefully counselled before treatment commences (50,54). In addition to infertility, Leydig cell function and testosterone production may be impaired for an extended period of time after radiotherapy of Tin (74).

## 4 STAGING

Staging represents the cornerstone on which testicular cancer treatment is based. After diagnostic and determination of the histological type, staging is mandatory. To determine the presence of metastatic or occult disease half-life kinetics of serum tumour markers has to be assessed, the nodal pathway has to be screened and the presence of visceral metastases ruled out.

Consequently, it is mandatory to assess:

- Post-orchietomy half-life kinetics of serum tumour markers
- Status of abdominal and supraclavicular nodes, and the liver
- Presence or absence of mediastinal nodal involvement and lung metastases
- Status of brain and bone if any suspicious symptoms are present

### 4.1 Diagnostic tools

The currently available tests include: serial blood sampling, chest X-ray, abdominal and thoracic CT scan, abdomen ultrasound, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) scan and other specific examinations depending on clinical suspicion.

### 4.2 Serum tumour markers. Postorchietomy half-life kinetics

The mean serum half-life of AFP is 5-7 days and that of beta-hCG approximately 2-3 days (43). Tumour markers have to be re-evaluated after orchietomy to determine half-life kinetics. The persistence of elevated serum tumour markers 3 weeks after orchietomy indicates the presence of metastatic disease (macro- or microscopically) while normalization of marker levels after treatment does not necessarily mean the absence of a tumour. During chemotherapy the markers decline or persistence has a prognostic value.

### 4.3 Abdominal, mediastinal, supraclavicular nodes and viscera

Abdominal and mediastinal nodes are best assessed by means of CT scan. The supraclavicular nodes are best assessed by physical examination.

CT scanning has clear advantages over lymphography in assessing retroperitoneal metastatic disease. It offers a sensitivity of 70-80% in the determination of the state of the retroperitoneal nodes. Its accuracy depends on the size of the nodes; sensitivity and negative predictive value increase using a 3-mm threshold to define metastatic nodes in the landing zones (57). Those figures decrease slightly in stages I and II (58,59), with a rate of understaging of 25-30% (60). New generations of CT scans do not seem to improve the sensitivity.

MRI produces similar results to CT scanning in the detection of retroperitoneal nodal enlargement (61). Again, the main objections to its routine use are high cost and limited access. Nevertheless, MRI can be very

helpful when abdominal CT or ultrasound are inconclusive (61), when CT scan 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 testicular cancer.

Chest X-ray is the routine thorax examination. An antero-posterior and lateral chest X-ray could be considered the only thoracic examination in seminoma when retroperitoneal and pelvic CT scans are negative (62). A chest CT scan is the most sensitive way to evaluate the thorax and mediastinal nodes. This exploration has to be recommended in patients with NSGCT because up to 10% of cases can present with small subpleural nodes that are not visible radiologically (1). The CT scan has high sensitivity but low specificity (61). A chest CT is mandatory in all patients with NSGCT and in those with seminoma and positive abdominal CT scan (62).

There is not enough evidence to support the use of the fluorodeoxyglucose-positron-emission tomography (FDG-PET) scan in early testis tumour stages, it can nevertheless be recommended in the follow-up of seminoma post-chemotherapy residual masses bigger than 3 cm in order to decide Watchful Waiting (WW) or active treatment therapy (63-66).

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. CT scan or MRI of the skull are advisable in patients with NSGCT and widespread lung metastases. Table I shows the recommended test at staging.

**Table 1: Recommended tests for staging at diagnosis**

Test	Recommendation grade B	Recommendation grade C
Serum tumour markers	Alpha – fetoprotein β – hCG LDH	
Abdomen CT scan	All patients	Slim adolescent
Chest X-ray	Seminoma (a)	
Chest CT scan	NSGCT	
Testis ultrasound	Clinical suspicion and normal scrotum at palpation	
MRI	When abdominal CT is inconclusive	All cases
PET scan (b)	Follow-up residual masses in seminoma	
Other	If clinical suspicion	

(a) If negative abdominal computed tomography (CT) scan.  
(b) There is currently no indication for PET scan at diagnosis.

#### 4.4 Staging and prognostic classifications

There are multiple staging systems, generally based on the quantity of tumoral volume at diagnosis taking known risk factors into account. Among them the tumour, node, visceral metastasis (TNM) system, the Peckham classification (Royal Marsden Hospital), the Walter Reed Hospital classification and staging systems from the European Organization for Research and Treatment of Cancer (EORTC), Memorial Sloan Kettering (MMSK) and Indiana University Hospital.

It appears that each group working in the field of testicular cancer has its own staging system. The most commonly systems used in Europe are the TNM and the Peckham classification. The staging system recommended in these guidelines is the 2002 TNM of the UICC (International Union Against Cancer) (Table 2) (67). This includes: determination of the anatomical extent of disease; assessment of serum tumour markers: including nadir values of beta-human chorionic gonadotrophin (beta-hCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) after orchiectomy (S category); clear definition of regional nodes; and some N category modifications related to the node size.

**Table 2: TNM classification for testicular cancer (UICC, 2002 Sixth Edition)**

<b>pT Primary Tumour<sup>1</sup></b>				
pTX	Primary tumour cannot be assessed (see 1, T-Primary tumour)			
pT0	No evidence of primary tumour (e.g. histologic scar in testis)			
pTis	Intratubular germ cell neoplasia (carcinoma in situ)			
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis			
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis			
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion			
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion			
<b>N Regional Lymph Nodes clinical</b>				
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			
<b>pN Pathological</b>				
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 of extranodal extension of tumour			
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension			
<b>M Distant Metastasis</b>				
MX	Distant metastasis cannot be assessed			
M0	No distant metastasis			
M1	Distant metastasis			
M1a	Non-regional lymph node(s) or lung			
M1b	Other sites			
<b>S Serum Tumour Markers</b>				
SX	Serum marker studies not available or not performed			
S0	Serum marker study levels within normal limits			
	<b>LDH (U/L)</b>	<b>hCG (mIU/ml)</b>	<b>AFP (ng/ml)</b>	
	S1 < 1.5 x N and	< 5,000 and	< 1,000	
	S2 1.5– 10 x N or	5,000–50,000 or	1,000–10,000	
	S3 > 10 x N or	>50,000 or	>10,000	
N Indicates the upper limit of normal for the LDH assay.				

<sup>1</sup> Except for PTis and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchiectomy; see pT. In other circumstances, TX is used if no radical orchiectomy has been performed.

According to the 2002 TNM classification, stage I testicular cancer includes the following substages:

Stage IA	pT1	N0	M0	S0
Stage IB	pT2, pT3 or pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3

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. 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, which is evidence of subclinical metastatic disease (or possibly a second germ cell tumour in the remaining testis). If serum tumour marker levels are declining according to the expected half-time decay after orchiectomy, the patient is usually followed up until normalization.

In large, population-based patient series, 75-80% of seminoma patients and about 55% of patients with non-seminomatous germ cell testicular cancer (NSGCT) have stage I disease at diagnosis (68,69). True stage IS (persistently elevated or increasing serum marker levels after orchiectomy) is found in about 5% of non-seminoma patients. If a staging retroperitoneal lymph nodes dissection (RPLND) is performed in stage IS patients, nearly all patients have pathological stage II disease (pN+) (1,2,5,68).

In 1997 the International Germ Cell Cancer Collaborative Group (IGCCCG), defined a prognostic-factor based staging system for metastatic testis tumour based on identification of some clinical 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 markers levels in serum as prognostic factors to categorize patients into "good", "intermediate" or "poor" prognosis (70) (Table 3).

**Table 3: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)**

<b>Good prognosis group</b>	
<i>Non-seminoma</i>	
56% of cases	<i>All of the following criteria:</i>
5-year PFS 89%	
5-year survival 92%	
	<ul style="list-style-type: none"> <li>• Testis/retroperitoneal primary</li> <li>• No non-pulmonary visceral metastases</li> <li>• AFP &lt; 1,000 ng/ml</li> <li>• <math>\beta</math>-hCG &lt; 5,000 mIU/L (1,000 ng/ml)</li> <li>• LDH &lt; 1.5 x ULN</li> </ul>
<i>Seminoma</i>	
90% of cases	<i>All of the following criteria:</i>
5-year PFS 82%	
5-year survival 86%	
	<ul style="list-style-type: none"> <li>• Any primary site</li> <li>• No non-pulmonary visceral metastases</li> <li>• Normal AFP</li> <li>• Any <math>\beta</math>-hCG</li> <li>• Any LDH</li> </ul>
<b>Intermediate prognosis group</b>	
<i>Non-seminoma</i>	
28% of cases	<i>All of the following criteria:</i>
5 years PFS 75%	
5-year survival 80%	
	<ul style="list-style-type: none"> <li>• Testis/retroperitoneal primary</li> <li>• No non-pulmonary visceral metastases</li> <li>• AFP &gt; 1,000 and &lt; 10,000 ng/ml or</li> <li>• <math>\beta</math>-hCG &gt; 5,000 and &lt; 50,000 mIU/L</li> </ul> or <ul style="list-style-type: none"> <li>• LDH &gt; 1.5 and &lt; 10 x ULN</li> </ul>
<i>Seminoma</i>	
10% of cases	<i>Any of the following criteria:</i>
5-year PFS 67%	
5-year survival 72%	
	<ul style="list-style-type: none"> <li>• Any primary site</li> <li>• Non-pulmonary visceral metastases</li> <li>• Normal AFP</li> <li>• Any <math>\beta</math>-hCG</li> <li>• Any LDH</li> </ul>
<b>Poor prognosis group</b>	
<i>Non-seminoma</i>	
16% of cases	<i>Any of the following criteria:</i>
5-year PFS 41%	
5-year survival 48%	
	<ul style="list-style-type: none"> <li>• Mediastinal primary</li> <li>• Non-pulmonary visceral metastases</li> <li>• AFP &gt; 10,000 ng/ml or</li> <li>• <math>\beta</math>-hCG &gt; 50,000 mIU/L (10,000 ng/ml)</li> </ul> or <ul style="list-style-type: none"> <li>• LDH &gt; 10 x ULN</li> </ul>

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### *Seminoma*

No patients classified as poor prognosis

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*PFS = progression-free survival;*

*AFP = alpha-fetoprotein;*

*β-hCG = beta-human chorionic gonadotrophin;*

*LDH = lactate dehydrogenase*

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## **4.5 Prognostic risk factors**

A series of pathological risk factors have been identified in all staging systems, which consequently have a bearing on the prognosis. (11-16).

For seminoma stage I, tumour size ( $\geq 4$  cm) and invasion of the rete testis have been identified as the most important predictors for relapse in multivariate analysis (19). However, in seminoma the risk factors have only been identified in retrospective series.

For non-seminoma stage I, vascular invasion of the primary tumour in blood or lymphatic vessels is the most important predictor of occult metastatic disease. The proliferation rate, as well as the percentage of embryonal carcinoma are additional predictors that improve on the positive predictive value of vascular invasion (71,72). The significant prognostic pathological risk factors for stage I and clinical risk factors for metastatic disease are listed in table 4.

**Table 4: Prognostic factors for occult metastatic disease in testicular cancer**

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### **Pathological (for stage I)**

- Histopathological type
- For seminoma
  - Tumour size ( $\geq 4$  cm)
  - Invasion of the rete testis
- For Non-seminoma
  - Vascular/lymphatic in or peri-tumoral invasion
  - Proliferation rate > 70%
  - Percentage of embryonal carcinoma > 50%

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### **Clinical (for metastatic disease)**

- Primary location
- Elevation of tumour marker levels
- Presence of non-pulmonary visceral metastasis<sup>a</sup>

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<sup>a</sup> Only clinical predictive factor for metastatic disease in seminoma

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## **5 IMPACT ON FERTILITY AND FERTILITY ASSOCIATED ISSUES**

Sperm abnormalities are not infrequent in patients with Testis Tumours. Furthermore chemotherapy treatment can also impair fertility. In patients in the reproductive age, pre-treatment fertility assessment (Testosterone, Luteinizing Hormone (LH) and FSH levels) and sperm analysis should be performed and cryopreservation offered if desired.

Cryopreservation should be performed before or after orchiectomy, but in any case prior to chemotherapy treatment (73-80).

In case of bilateral orchiectomy or low testosterone levels after treatment of Tin, long-life testosterone supplementation is recommended (81). For more detailed information the reader is referred to the EAU Male Infertility Guidelines.

## 6 GUIDELINES FOR DIAGNOSIS AND STAGING OF TESTICULAR CANCER

1. Physical examination may be sufficient for the diagnosis of testicular cancer (grade B recommendation).
2. Testicular ultrasound is mandatory when a tumour is clinically suspected but the examination of the scrotum is normal, or if there is any doubt about the clinical findings in the scrotum (grade B recommendation).
3. Orchiectomy and pathological examination of the testis is necessary to confirm the diagnosis and define the local extension (pT category) (grade B recommendation). Nevertheless, in an emergency clinical situation chemotherapy can be started before orchiectomy.
4. Serum determination of tumour markers (AFP, beta-hCG, LDH) must be performed before and after orchiectomy for staging and prognostic reasons (grade B recommendation).
5. Retroperitoneal, mediastinal and supraclavicular nodes and visceral state have to be assessed in testicular cancer. In seminoma, a chest CT scan is not necessary if abdominal nodes are negative (grade B recommendation).

## 7 TREATMENT: STAGE I GERM CELL TUMOURS

### 7.1 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 (82).

#### 7.1.1 Adjuvant radiotherapy

Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy to a para-aortic (PA) field or to a hockey stick field (para-aortic and ipsilateral iliacal nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to only 1-3% (83-86). After modern radiotherapy nearly all relapses will first occur outside the irradiated field (supradiaphragmatic lymph nodes or in the lungs) (83,86). Based on the results of a large randomized Medical Research Council (MRC) trial, Fossa et al. (83,84) recommended radiotherapy to a para-aortic field as standard treatment for patients with testicular seminoma stage I, T1-T3 and with undisturbed lymphatic drainage. The acute toxicity was reduced and the sperm count within the first 18 months was significantly higher after para-aortic irradiation than after irradiation of the traditional dog-leg field. On the other hand, the relapse rate in the iliac lymph nodes was about 2% (all of them on the right side) after para-aortic and 0% after dog-leg irradiation. Another possible site of failure is in the left renal hilum. Para-aortic irradiation should be tailored according to the site of the primary tumour. Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

Concerning the dose of irradiation, the MRC recently finished a large randomized trial of 20 Gy versus 30 Gy para-aortic radiation in stage I seminoma that showed equivalence for both doses regarding recurrence rates. (84). 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% (83). The main concern surrounding adjuvant radiotherapy is the potentially increased risk of radiation-induced secondary non-germ-cell malignancies (87-89). A scrotal shield can be of benefit during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis (90), but this is not needed for a para-aortic field. At this point in time it is difficult to evaluate the long-term risks after adjuvant radiotherapy for stage I seminoma since former treatment procedures included larger fields, higher doses of radiotherapy and/or the use of alkylating chemotherapy.

#### 7.1.2 Surveillance

Several prospective non-randomized studies of surveillance have been conducted during the last decade, several of which comprised more than 100 patients. A meta-analysis from the 4 largest studies shows an actuarial 5 years relapse-free rate of 82.3%. On multivariate analysis tumour size (> or = 4 cm) and invasion of the rete testis remained the most important predictors for relapse (19). 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 (82,91-93). About 70% of the patients relapsing after surveillance qualify for treatment with radiotherapy alone. Only about 20% of these patients relapse after salvage radiotherapy and need salvage chemotherapy. The overall cancer-specific survival rate reported by experienced centres is 97-100% for seminoma stage I

after surveillance (92,93). A pooled (multivariate) analysis based on the three largest studies of testicular seminoma stage I managed by surveillance indicates that a primary tumour of over 4 cm in size and invasion of the rete testis are important prognostic factors for relapse, with hazard ratios of 1.9 and 2.0, respectively (19). The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes, for at least 5 years after orchiectomy. This compares with the very low risk of subdiaphragmatic relapse after adjuvant radiotherapy.

About 20% of the relapses seen after surveillance occur more than 4 years after orchiectomy (92). Cost analyses of surveillance compared with radiotherapy indicate that it is more expensive (94), but estimates vary depending on the follow-up schedules (95,96).

#### 7.1.3 Adjuvant chemotherapy

A joint MRC and EORTC trial (MRC TE 19 trial) comparing one cycle of carboplatin (AUC 7) to adjuvant radiotherapy recently finished. Single agent carboplatin therapy showed no significant difference to radiotherapy concerning recurrence rate, time to recurrence and survival after a median follow-up of 3 years (97).

Therefore, adjuvant carboplatin therapy is an alternative to radiotherapy or surveillance in stage I seminoma (93,97). Two courses of adjuvant carboplatin seem to further reduce the relapse rate in the order of 1-3% (93,98,99), but further experience and long-term observations are needed (93).

#### 7.1.4 Retroperitoneal Lymph Node Dissection (RPLND)

In a prospective, non-randomized 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 this policy should not be recommended in stage I seminoma (98).

#### 7.1.5 Risk adapted treatment

Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided in a low and high risk group of occult metastatic disease. However, these risk factors have only been evaluated in a meta-analysis of retrospective trials (19). Patients with and without both risk factors have a risk of developing occult disease of 32% and 12%, respectively. Because of the retrospective analysis and the weak discriminative power of these risk factors they are currently not frequently used in clinical decision making, but may be used in the setting of clinical trials.

## 7.2 GUIDELINES FOR THE TREATMENT OF SEMINOMA STAGE 1

1. Adjuvant radiotherapy to a para-aortic or a hockey stick field, with a total dose of 20 Gy. (grade A recommendation)
2. Surveillance (if facilities are available). (grade B recommendation)
3. Carboplatin based chemotherapy (one course at AUC 7) can be recommended as alternative to radiotherapy and surveillance. (grade A recommendation)

## 7.3 NSGCT stage I

If stage IS cases are excluded, up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is adopted after orchiectomy.

#### 7.3.1 RPLND

If RPLND is performed, about 30% of patients are found to have retroperitoneal lymph node metastases, which corresponds to pathological stage II (PS2) disease (99-101). If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites (72,102-105).

The main predictor of relapse in CS1 NSGCT managed by surveillance, both for having PS2 disease and for relapse in PS1 after RPLND, is histopathological evidence of vascular invasion by tumour cells in, or near, the primary tumour in the testis (72,103,105-107). The presence of vascular invasion seems to be a very robust parameter, and is clinically usable even without centralized review by an expert panel (105,108).

Vascular invasion was the most predictive of stage in a multifactorial analysis. The absence of vascular invasion has a negative predictive value of 77%, thus allowing for surveillance in low-risk compliant patients (72).

Patients without vascular invasion constitute about 50-70% of the CS1 population, and these patients only have a 15-20% risk of relapse on surveillance, compared with a 50% relapse rate in patients with vascular invasion. The risk of relapse for PS1 patients is less than 10% for those without vascular invasion and about 30% for those with vascular invasion (105,108-110). If CS1 patients with PS2 are only followed up after RPLND, about 30% relapse, mainly at sites outside the abdomen and pelvis. The risk of relapse depends on the amount of retroperitoneal disease resected (111-113). If two (or more) courses of cisplatin-based

chemotherapy are given adjuvant to RPLND in the PS2 cases, the relapse rate is reduced to less than 2%, including teratoma relapse (103,106,114). The risk of retroperitoneal relapse after a properly performed nerve-sparing RPLND is very low (less than 2%), as is the risk of ejaculatory disturbance or other significant side-effects (106,111,112). The follow-up after RPLND is much simpler and less costly than that carried out during post-orchietomy surveillance due to the reduced need for abdominal CT scans (106). A laparoscopic RPLND may become a good alternative to an open RPLND, but can currently not be recommended as standard treatment (115-118).

### 7.3.2 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 orchietomy in CS1 NSGCT patients. The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of the 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 (107,119,120). About 35% of relapsing patients have normal levels of serum tumour markers at relapse. About 60% of the relapses are 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 (103) can be explained by the fact that some patients (presumably at risk) are excluded once surveillance is advised.

### 7.3.3 Primary chemotherapy

Data from several studies involving two courses of chemotherapy with bleomycin, etoposide and cisplatin, (BEP) as primary treatment for high-risk patients (having approximately 50% risk of relapse) have become available (121-125). In these series, involving more than 200 patients, some with a median follow-up of nearly 8 years (121), 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 (126). It is important to be aware of the risk of slow-growing retroperitoneal teratomas after primary chemotherapy and of the risk of chemoresistant cancer relapse. The need for repeated and long-term follow-up with imaging (CT or ultrasound) of the retroperitoneum after primary chemotherapy is not yet clear. 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. Overall costs for the different treatment options for CS1 may be of the same order of magnitude although a unique cost-benefit analysis shows that adjuvant chemotherapy is the cheaper option per life saved (94-96,127).

### 7.3.4 Risk-adapted treatment

Risk adapted treatment is currently based on the risk factor vascular invasion. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is a rational option since 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 (108,121-124,128). Therefore, risk adapted treatment is the treatment of choice in CS1 NSGCT. Patients with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of BEP and patients without vascular invasion are recommended to undergo surveillance. Only if patients or doctors are not willing to accept the appropriate risk adapted treatment or if there are conditions precluding the risk adapted treatment option, the remaining treatments should be considered. Therefore, the treatment decision should 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 and/or the treatment centre.

## 7.4 CS1S with (persistently) elevated serum tumour markers

Serum tumour markers should be followed closely until it is clear whether or not levels are falling according to the expected half-time values for AFP and beta-hCG. If the marker level increases after orchietomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum (129). An ultrasound examination of the contralateral testicle must be performed, if this has not been done initially.

The treatment of true CS1S patients is still controversial. They may be treated with either three courses of primary BEP chemotherapy, with follow-up as for CS1B (high risk; see below) patients after primary chemotherapy (130), or by RPLND (127). The presence of vascular invasion may strengthen the indication for primary chemotherapy as most CS1S with vascular invasion will need chemotherapy sooner or later anyway.

## 7.5 GUIDELINES FOR THE TREATMENT OF NSGCT STAGE I

CS1A (pT1, no vascular invasion); low risk

1. If the patient is willing and able to comply with a surveillance policy and long-term (at least 5 years) close follow-up should be recommended (grade B recommendation)
2. Adjuvant chemotherapy or nerve-sparing RPLND in low risk patients remain options for those not willing to undergo surveillance. If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of BEP should be considered (grade A recommendation)

CS1B (pT2-pT4); high risk

1. Primary chemotherapy with two courses of BEP (grade B recommendation) should be recommended
2. Surveillance or nerve-sparing RPLND in high risk patients remain options for those not willing to undergo adjuvant chemotherapy. If pathological Stage II is revealed at RPLND further chemotherapy should be considered (grade A recommendation)

# 8 TREATMENT: METASTATIC GERM CELL TUMOURS

Treatment of metastatic germ cell tumours depends on:

- Histology of the primary tumour
- Prognostic groups as they have been defined by the International Germ Cell Cancer Collaborative Group (IGCCCG) based on 5,202 non-seminoma and 660 seminoma cases (Table 3) (131).

## 8.1 Low volume metastatic disease (Stage II A/B)

### 8.1.1 Stage II A/B seminoma

The standard treatment of stage II A/B seminoma is radiotherapy. The radiation dose delivered in stage IIA and IIB is 30 Gy and 36 Gy, respectively. The standard radiation field compared to stage I will be extended from the para-aortic region to the ipsilateral iliac field ("hockey-stick"). 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 after 6 years for stage IIA and IIB of 95% and 89%, respectively. Overall survival is almost 100% (132,133).

In stage IIB chemotherapy with 3 cycles BEP ("good prognosis") is an alternative for patients not willing to undergo radiotherapy.

### 8.1.2 Stage II A/B non-seminoma

There is general consensus that treatment should start with initial chemotherapy in all advanced cases of NSGCT except for stage II NSGCT disease without elevated tumour markers, which alternatively can be treated with primary RPLND or surveillance (134,135). These rare cases of Stage IIA/B without marker elevation may represent metastatic differentiated teratoma. Stage II A/B non-seminoma with elevated markers will be treated according to IGCCCG "good prognosis" NSGCT (3 cycles BEP, followed by residual tumour resection). About 30% of patients will not achieve a complete remission after chemotherapy and will need a residual tumour resection.

Patients not willing to undergo primary chemotherapy have the option of primary nerve-sparing RPLND with adjuvant chemotherapy (2 cycles BEP) in case of metastatic disease (pII A/B). 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 (136). The cure rate with either approach will be close to 98% (137, 235, 258, 264, 265, 268, 269).

## 8.2 Advanced metastatic disease

### 8.2.1 Primary chemotherapy

The primary treatment of choice for advanced disease is three or four courses of BEP (or PEB) combination chemotherapy depending on the IGCCCG risk classification (Table 5). These regimens have proven superiority to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease (20,138,139).

**Table 5: British BEP and PEB regimens (every 3 (4) weeks)**

Drug	BEP	PEB
Cisplatin	20 mg/m <sup>2</sup> , days 1–5 <sup>a</sup>	
Etoposide	120 mg/m <sup>2</sup> , days 1, 3, 5	100 mg/m <sup>2</sup> , days 1–5
Bleomycin	30 mg, days 2, 9, 16	

*BEP = bleomycin, etoposide and cisplatin; PEB = cisplatin, etoposide and bleomycin.*  
<sup>a</sup> Plus hydration.

According to the IGCCCG (131) for patients with a 'good prognosis' standard treatment consists of three cycles of PEB, or in case of contraindication against bleomycin, of four cycles of PE (131,140-143). Therapy should be given without reduction of the doses in 22-day intervals; delaying the following chemotherapy cycle is justified only in case of fever with granulocytopenia < 1,000/mm<sup>3</sup> or thrombopenia < 100,000/ul. There is no indication for prophylactic application of hematopoietic growth factors as for example G-CSF. However, if infectious complications have occurred under chemotherapy, prophylactic administration of G-CSF is recommended for the following cycles (142,144).

With the 'intermediate prognosis' group in the IGCCCG a group of patients has been defined which reaches a 5-year survival rate of about 80%. The available data support four cycles of PEB as standard treatment (131,145). Due to the generally less favourable prognosis of this patient group, in comparison to patients with 'good prognosis', they may be treated in prospective trials like for example the EORTC GU Group trial with PEB vs PEB+Paclitaxel (145).

For patients with 'poor prognosis' standard treatment consists of four cycles of PEB; four cycles of PEI (Cisplatin, Etoposide, Ifosfamide) will have the same effect but are more toxic (146,147). The 5-year progression-free survival is between 45 and 50%. It has not yet been proven that high-dose chemotherapy increases the survival rate (148,149). Since a matched-pair analysis resulted in a better survival rate (149,150), these patients should be treated in an ongoing prospective randomized trial, investigating the value of high-dose chemotherapy. Patients meeting 'poor-prognosis' criteria should therefore be transferred to a reference centre. Any general recommendations for treatment modifications for patients with a poor general condition (Karnofsky <50%), extended liver infiltration (>50%) and extended pulmonary infiltration do not exist.

## 8.2.2 Restaging and further treatment

### 8.2.2.1 Restaging

After termination of two courses of chemotherapy, re-evaluation is performed by imaging investigations and determination of tumour markers. At marker decline and stable or regressive tumour manifestation chemotherapy will be completed (three or four cycles depending on the initial stage) (131,151,152). In case of marker decline, but growing metastases, resection of the tumour is obligatory after termination of induction therapy, unless in case of emergency according to local tumour growth (153).

Only with documented marker growth after 2 courses of chemotherapy an early crossover of therapy is indicated. These patients are usually candidates for new drugs trials (149,154). Patients with a low-level marker plateau post treatment will be observed whether or not complete normalisation occurs. Salvage chemotherapy is indicated for documented marker rise only (155,156).

### 8.2.2.2 Residual tumour resection

A residual mass of seminoma will not be resected, irrespective of the size, but controlled by imaging investigations and tumour markers (157-163). PET scan in metastatic seminoma after chemotherapy is a valid tool to detect vital residual tumour (164). On progression, salvage chemotherapy will be given, if necessary including surgery and radiotherapy (165-169). In case of non-seminoma and complete remission after chemotherapy, residual tumour resection is not indicated (170-175). In case of residual mass (greater than 1 cm in diameter) and marker normalisation, surgical resection is indicated (170,176-183). Overall, following BEP induction chemotherapy, only 10% of residual masses contain viable cancer, 50% contain mature teratoma and 40% contain necrotic-fibrotic tissue. As yet no imaging investigation including PET or prognosis model are able to predict histological differentiation of the non-seminomatous residual tumour. Thus, residual tumour resection is mandatory (171-173,184-192).

The extent of surgery should be based on the risk of relapse of an individual patient and in quality of life issues (177). If possible, all the masses have to be resected because a complete resection, in the setting of viable malignant cells, is more critical than recourse to postoperative chemotherapy (193). Histology in different organ sites may diverge (185).

### 8.2.2.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or mature teratoma no further treatment is required. In case of complete resection of vital carcinoma or immature teratoma two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e. g. "poor prognosis" patients, 193) (cave: cumulative doses of bleomycine). The prognosis will definitely deteriorate if vital carcinoma is found in resection specimens after second and third line chemotherapy. In this latter situation postoperative chemotherapy is not indicated and unable to improve the prognosis (181,186).

Two courses of cisplatin, vinblastine and bleomycine (PVB), vinblastine, adriamycin and, bleomycine (VAB) or BEP given post-operatively following lymphadenectomy for 'radically' resected retroperitoneal metastases containing viable cancer have been followed by nearly no relapses (194-198). This adjuvant treatment has been questioned by some authors (195-199), who reported equivalent results in 60 radically resected patients with, or without, such treatment. Furthermore, it has been demonstrated in a co-operative retrospective study (193) that the major success factors in these patients are complete surgical resection and percentage of viable cancer in the residual mass, with the effect of adjuvant chemotherapy being borderline. Nevertheless, the results with adjuvant chemotherapy are not statistically superior to those resulting from very careful observation and deferred treatment in case of relapse (200).

## 8.3 Systemic salvage treatment for relapse or refractory disease

### 8.3.1 Seminoma

Cisplatin based combination salvage chemotherapy will result in long-term remissions in approximately 50% of patients who relapse after first-line chemotherapy (201). Regimens of choice are: four cycles of PEI/VIP or four cycles of VeIP. 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 attempted (202). Therefore treatment of these rare patients within clinical trials and at experienced centres is of the utmost importance.

### 8.3.2 Non-seminoma

Standard salvage treatment after first-line chemotherapy consists of either four cycles of PEI/VIP or four cycles of VeIP, respectively (Table 6). Conventionally dosed salvage chemotherapy may achieve long-term remissions in 15 to 40% of patients, depending on individual risk factors (156,203). Prognostic indicators of response to salvage therapy are: location and histology of the primary tumour, response to first line treatment, duration of remissions and level of AFP and  $\beta$ -hCG at relapse (156,203-205). Salvage therapy with VeIP is probably not superior to other conventionally dosed cisplatin based combination regimens (202-204). The use of conventionally dosed combination regimens with more than three agents will increase toxicity without improving treatment outcome (206). Depending on the presence of adverse prognostic factors, the results of salvage therapy after first-line cisplatin based treatment are unsatisfactory (156,207). Although some Phase II trials indicate a 10% improvement in survival with early intensification of first salvage treatment using high-dose chemotherapy, others fail to demonstrate such improvement (208-210). Recently, Taxol and Gemcitabine have proven to be active in the treatment of refractory germ cell tumours; both drugs are synergistic with Cisplatin (211-213). However, all of these patients should be entered into ongoing multicentre studies to define the optimal approach to salvage treatment and should be referred to centers experienced in caring for relapse and/or refractory patients (202).

**Table 6: Standard PEI/VIP (VeIP)**

Drug	PEI/VIP(VeIP)
Cisplatin	20 mg/m <sup>2</sup> days 1–5 <sup>a</sup>
Etoposide (vinblastine)	75 mg/m <sup>2</sup> , days 1–5 (0.11 mg/kg, days 1, 2)
Ifosfamide	1.2 g/m <sup>2</sup> , days 1–5

*PEI/VIP = etoposide, ifosfamide and cisplatin; VeIP = vinblastin, ifosfamide and cisplatin;*

<sup>a</sup> Plus hydration.

## 8.4 Salvage surgery

Residual tumours after salvage chemotherapy should be resected within four to six weeks after marker normalisation or when a marker plateau is reached. In case of marker progression after salvage treatment and lack of other chemotherapeutic options, resection of residual tumours ('desperation surgery') should be considered if complete resection of all tumour seems feasible (about 25% long-term survival may be achieved) (156,179,187,190,215-224).

## 8.5 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 metastasis at initial diagnostic is poor (30-40%), but even poorer is the development of brain metastases as a recurrent disease (five year survival 2-5%) (225,226).

Chemotherapy is the initial treatment in this case and some data support the use of consolidation radiotherapy even in case of a total response after chemotherapy (227). Surgery can be considered in case of a persistent solitary metastasis depending on the systemic state, the histology of the primary tumour and the location of the metastasis.

### 8.6 GUIDELINES FOR THE TREATMENT OF METASTATIC GERM CELL TUMOURS

1. Low volume NSGCT stage IIA/B with elevated markers should be treated like "good prognosis" advanced NSGCT with 3 cycles of BEP. Stage II without marker elevation can be treated either by RPLND or close surveillance
2. In metastatic NSGCT (> stage IIC) with a good prognosis, three courses of BEP is the primary treatment of choice (grade A recommendation)
3. In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard BEP (grade A recommendation)
4. Surgical resection of residual masses after chemotherapy in NSGCT is indicated in case of a residual mass > 1cm and when serum levels of tumour markers are normal or normalizing (grade B recommendation)
5. Metastatic seminoma with less than N3M1 disease can be treated initially with radiotherapy. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT (grade A recommendation)
6. Advanced seminoma (N3 or M1) should be treated with primary chemotherapy according to the same principles used for NSGCT (grade A recommendation).

## 9 FOLLOW-UP AFTER CURATIVE THERAPY

### 9.1 General considerations

In spite of the fact that relatively limited information exists on the value of follow-up testing of asymptomatic patients after potentially curative therapy, testis cancer, the most curable human tumour is an excellent model for post curative therapy surveillance.

The selection of the tests to be performed in follow-up should adhere to the following principles (228):

- A *The interval between examinations and duration of testing should be consistent with the time of maximal risk of recurrence and the natural history of the tumour*
- B *The tests should be directed at the most likely sites of recurrence and should have a high predictive value, both positive and negative*
- C *Therapy should be available that will result in cure of the recurrence, significant prolongation of life or palliation symptoms. The initiation of earlier therapy should improve the outcome compared with therapy given when the patient becomes symptomatic from the tumour recurrence*
- D *The increased risk of second malignancy, both at the primary site and in other tissues that may have been exposed to the same carcinogens or in which there is epidemiologic evidence of increased risk, should also guide the ordering tests. Malignant and non-malignant complications of therapy must also be considered. Such testing should also be performed with a frequency and duration consistent with the nature of the risk and include only tests with high positive and negative predictive values*

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 two years; consequently surveillance should be most frequent and intensive during this time.
- Late relapses can occur beyond 5 years therefore yearly follow-up for life may be advocated.
- After RPLND relapse in the retroperitoneum is rare, the most likely site of recurrence being the chest.

- The value of chest X-ray has been recently questioned in the follow-up of patients with disseminated disease after complete remission (229).
- CT of the chest has a higher predictive value than chest X-ray (230).
- The results of therapy depend on the bulk of the disease, thus an intensive strategy to detect presymptomatic disease may be justifiable.
- After chemotherapy or radiotherapy a small long-term risk for secondary malignancies development exists.

In testis tumour the aims of follow-up are:

- to detect relapse as early as possible in all stages,
- to detect an asynchronous contralateral carcinoma of the testis in an early phase,
- to avoid unnecessary treatment in Stage I.

Since different treatment policies are available for Stage I and low-volume metastatic disease (resulting in the same survival but different recurrence rate), in those stages the intensity of the follow-up should be determined by the rate and timing of relapse. The site of relapse for each one of the policies should dictate the tests to be performed during follow-up.

Whether in early or advanced stages, the tests to be performed during follow-up are:

- Physical examination (search for neck and abdominal masses, gynecomastia, examination of groins, superficial nodes and the remaining testis),
- Serum Tumour Markers determination (AFP, beta-hCG and LDH),
- Chest X-ray and/or Chest CT, Abdominal and pelvic CT or abdominal ultrasound,
- and Brain CT in case of neurological symptoms, and Bone scan in case of bone pain.

Currently, insufficient evidence is available in the literature to provide strict recommendations on timing and testing during follow-up. The nature of the recommendations on follow-up is grade B or C with a consistent lack of randomized studies. Therefore, the authors wish to emphasize that the following recommendations represent the minimum standard of follow-up. Any other tests (e.g., hormonal determinations, spermograms, neurological examinations) or more frequent schedules of evaluation may be performed on the basis of a clinical protocol or for investigational purposes.

## 9.2 Follow-up stage I non-seminoma

Approximately 5% of patients with clinical stage I NSGCT present with elevated levels of tumour markers after orchiectomy and up to 25-30% relapse during the first 2 years (5,105,121,135,231-235). The follow-up schedule will differ depending on which of the three possible treatment strategies was chosen: surveillance, nerve-sparing retroperitoneal lymphadenectomy (RLND) or primary chemotherapy.

### 9.2.1 Follow-up after surveillance

The results of a surveillance policy depend on a careful pre-operative staging procedure and follow-up management. Half of the relapses will occur in the first 6 months; however, recurrent disease has been detected as late as 6 years after orchiectomy. 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 (range 1-62 months), but relapses after 3-5 years, and even later, may still occur, with an annual rate of 4% (119,120). Relapse occurs mainly in the retroperitoneum; approximately 20% of patients have evident metastases in the retroperitoneum and 10% in the mediastinum and lungs (236). Sometimes the only indication is an elevated level of tumour markers.

Careful observation during the first 6 -12 months after orchiectomy is mandatory; thereafter, the interval may be longer. Surveillance should continue for a minimum of 6 years and indefinite yearly follow-up is advocated by some. There is no universally accepted protocol for surveillance. A recommended follow-up schedule is shown in Table 7. It is particularly difficult to establish recommendations for those patients with negative pre-operative tumour markers levels.

**Table 7: Recommended follow-up schedule in a surveillance policy: – stage I non-seminoma**

Procedure	Year			
	1	2	3–5	6–10
Physical examination	Monthly	4- 6 times	Twice/year	Once/year
Tumour markers	9-12 times (Monthly the first 6 months)	4-6 times	Twice/year	Once/year
Chest X-ray	9-12 times (Monthly for the first 6 months)	4-6 times	Twice/year	Once/year
Abdominal CT scan	3-4 times	Twice	Once/year	If indicated

### 9.2.2 Follow-up after nerve-sparing RLND

Retroperitoneal relapse after a properly performed nerve-sparing RLND is extremely rare. RLND should eliminate the retroperitoneal nodes as a site of relapse, and thus the need for repeated abdominal CT scans. The USA Intergroup data show retroperitoneal relapse in 7/264 patients with pathological stage I disease (and 20 pulmonary relapses); four of these seven had no marker elevation (237). In the Indiana series, only one relapse in 559 cases was reported (238). 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 RLND (69,239). The recommended follow-up schedule is shown in Table 8.

**Table 8: Recommended follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy - stage I non-seminoma**

Procedure	Year			
	1	2	3–5	5–10
Physical examination	6 times	3 times	2 per year	Once/year <sup>a</sup>
Tumour markers	6 times	3 times	2 per year	Once/year <sup>a</sup>
Chest X-ray	6 times	3 times	2 per year	Once/year <sup>a</sup>
Abdominal computed tomography scan	Twice	Once	If indicated <sup>b</sup>	If indicated
Abdominal ultrasound	Twice <sup>c</sup>	Twice <sup>c</sup>	Twice/year	Once/year

<sup>a</sup> Grade C recommendation

<sup>b</sup> Due to a risk of late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy once a year.

<sup>c</sup> Alternating with abdominal CT scan.

### 9.2.3 Follow-up after adjuvant chemotherapy

Although the number of patients treated using adjuvant chemotherapy is still small, some prospective reports with long-term follow-up show a very low relapse rate (121,122,231,232) of about 3%. The need for repeated and long-term assessment of the retroperitoneum is still not clear. Primary chemotherapy in the treatment of NSGCT cannot be regarded as investigational, but still has to be offered in the setting of clinical trials. The follow-up schedule will depend on the results of these studies, but will probably be similar to that recommended for RPLND (Table 8). Owing to the risk of developing a late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy, an abdominal CT or an ultrasound examination should also be performed (at least) annually during the third to fifth year.

## 9.3 Follow-up stage I seminoma

The majority of patients with seminoma (70-80%) present with clinical stage I disease at diagnosis (92). 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 (92). The relapse rate varies between 1% and 20%, depending on the post-orchietomy therapy chosen. Only up to 30% of seminomas present with elevation of beta-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 (240). The treatment options post-orchietomy in stage I seminoma are

retroperitoneal radiotherapy, surveillance and adjuvant chemotherapy. Due to extreme radio- and chemosensitivity, high cure rates of almost 100% are reached with each of the approaches, even in case of relapse. The costs of the different therapies vary, as do the expected side-effects (94,241,242).

The optimal schedule of follow-up has yet to be defined and will vary depending on the treatment chosen. Different tests have to be performed according to the relapse time and pattern of relapse.

### 9.3.1 Follow-up after radiotherapy

Low doses of radiotherapy (20-24 Gy) limited to the retroperitoneal or the hockey stick field achieve an overall survival rate of approximately 99% at 5-10 years (83-85,243,244). The rate of relapse is 1- 2% and the most common time of presentation is within 18 months after treatment (83,86,242,245,246), although late relapses have also been described (247). 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 (92). The side-effects of radiotherapy include impaired spermatogenesis, gastrointestinal symptoms (peptic ulceration) and induction of second malignancies (242,248,249). Up to 50% of patients can develop moderate toxicity Grade I-II (243). The schedule of follow-up is described in Table 9.

**Table 9: Follow-up for post-orchietomy radiotherapy or chemotherapy – stage I seminoma**

Procedure	Year			
	1	2	3	4-5
Physical examination	6 times	4 times	3 times	2/year
Chest X-ray	6 times	4 times	3 times	2/year
Tumour markers	6 times	4 times	3 times	2/year
Abdominal CT scan	Once	Once	If indicated	If indicated
Abdominal ultrasound	Once <sup>a</sup>	Once <sup>a</sup>	Once	If indicated

<sup>a</sup> Alternating with abdominal computed tomography scan.

### 9.3.2 Follow-up after surveillance

It must be recognized that there is a somewhat higher need for salvage chemotherapy if prophylactic radiotherapy is omitted. Alternatively, at least 80% of patients will receive unnecessary radiotherapy if this is given prophylactically to all those with seminoma stage I. There are already prospective, but not randomized, studies of surveillance showing that the actuarial risk of relapse at 5 years ranges between 15% and 20% (250-254). Nevertheless, 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 (92). 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 (92). Due to the high and often late rate of relapse, close and active follow-up is mandatory for at least 5 years. The major disadvantages of this policy are lack of long-term follow-up data, high costs and patient compliance. The schedule of follow-up is described in Table 10.

**Table 10: Follow-up in surveillance policy**

Procedure	Year				
	1	2	3	4-5	6-10
Physical examination	Six times	Four times	Three times	Twice/year	Once/year
Tumour markers	Six times	Four times	Three times	Twice/year	Once/year
Chest X-ray	Six times	Four times	Three times	Twice/year	Once/year
Abdominal computed tomography scan	Four times	Four times	Twice	Once/year	If indicated
Abdominal ultrasound	<sup>a</sup>	<sup>a</sup>	Twice <sup>b</sup>	Once/year <sup>b</sup>	If indicated

<sup>a</sup> Not required.

<sup>b</sup> Alternating with abdominal computed tomography scan

### 9.3.3 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 less than 2%, but the number of patients treated in a prospective setting is still low and the length of follow-up is also limited in most studies. In general, this treatment is well tolerated, with only mild, acute and intermediate-term toxicity (255,256). As the relapse rate is low, the follow-up schedule may be the same as the one proposed for post-orchietomy radiotherapy (Table 9).

## 9.4 Follow-up of stage II and advanced (metastatic) disease

The more advanced the nodal stage of the disease, the higher the likelihood of recurrence (114). In general, the primary tumour bulk governs the outcome for patients with NSGCT (257). 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 (134,135,258).

In advanced metastatic germ cell tumours, the extent of the disease is correlated with the response to therapy and with survival. The combination of cisplatin-based chemotherapy and surgery (aggressive multi-modality) achieves cure rates between 65% and 85%, depending on the initial extent of disease (257,259). Complete response rates to chemotherapy are in the order of 50-60% (257); another 20-30% of patients could be rendered disease-free with post-chemotherapy surgery (260).

The main reasons for failure of therapy in advanced NSGCT are (257,261,262):

- The presence of bulky disease not responding completely to chemotherapy
- Unresectable residual teratoma after chemotherapy
- Presence or development of chemoresistant non-germ cell elements, which account for 8.2% of cases

There is a lack of randomized trial results from which to plan evidence-based follow-up, and the different schedules used by various centres have a higher variability and are more individualized than for stage IA.

### 9.4.1 Clinical and pathological stage II NSGCT

As previously stated in this guideline low-volume stage II NSGCT can be treated by primary RPLND or primary chemotherapy.

#### 9.4.1.1 Relapse after primary RPLND

Two different situations can occur:

1. About 23-28% of clinical stage II patients will have pathological stage I disease and should be followed up accordingly (see follow-up for NSGCT stage I) (263,264).
2. Between 72% and 77% of clinical stage II patients will be pathological stage II, having a different relapse rate depending on the type of treatment. Whatever the treatment policy chosen, the majority of relapses occur within the first 2 years and outside the surgical field.

#### *Relapse after primary RPLND followed by two immediate cycles of chemotherapy*

The relapse rate for this group is 6% at 4 years (114,259). In non-randomized series, with a mean follow-up ranging from 30-72 months, this treatment policy results in a high overall disease-free survival rate of 98-100% (134,265).

The main disadvantage of adjuvant chemotherapy is that it represents an overtreatment in approximately 50% of patients with stage II disease.

#### *Relapse after primary RPLND followed by surveillance*

The average relapse rate in this group is 35% (range 8-49%) at a mean of 4 years (114,266,267).

Nevertheless, the relapse rate depends on pathological stage; pathological stage IIa presents a risk of relapse of less than 50%, while pathological stage IIb presents a risk of relapse of at least 50% (114,134,259,268).

Following primary RPLND the retroperitoneal CT scan can be replaced by a less expensive abdominal ultrasound, although a baseline post-RPLND CT scan is recommended (Table 11). When primary RPLND is followed by surveillance (generally in cases of low-volume lymph node involvement or pathological stage IIa), a stricter schedule of follow-up is needed than with adjuvant chemotherapy. A physical examination, tumour marker assessment and chest X-ray are performed more frequently than in the former treatment policy.

The follow-up outlined in Table 11 can be used, but the tests have to be performed:

- Monthly during the first year
- Bimonthly during the second year
- Quarterly during the third year
- Every 4 months during the fourth year

- Twice in the fifth year
- Yearly thereafter

**Table 11: Follow-up of NSGCT stage IIa–IIb after RPLND plus chemotherapy or primary chemotherapy**

Procedure	Year					
	1	2	3	4	5	Thereafter
Physical examination	Bimonthly	Four times	Twice	Twice	Twice	Once/year
Tumour markers	Bimonthly	Four times	Twice	Twice	Twice	Once/year
Chest X-ray	Bimonthly	Four times	Twice	Twice	Twice	Once/year
Abdominal CT <sup>ab</sup>	Baseline, then as Indicated	As indicated	If indicated	If indicated	If indicated	If indicated
Abdominal ultrasound	Twice	Twice	If indicated	If indicated	If indicated	If indicated

*CT = computed tomography.*

<sup>a</sup> After RPLND, a baseline CT scan of the abdomen and pelvis is obtained, and repeated if clinically indicated thereafter.

<sup>b</sup> After primary chemotherapy, the retroperitoneum has to be monitored by means of CT scan at least twice during the first 2 years

#### 9.4.1.2 Relapse after primary chemotherapy

Between 68% and 78% of patients (average 75%) will reach a complete clinical response (235,258,269). The relapse rate is around 5%, and most relapses occur in the first 8 months after chemotherapy, continuing up to 2 years. Nevertheless, later relapses in the range 2-5% may occur depending on several prognostic factors (e.g. whether the metastasis is: > 3 cm or < 3 cm in size, histology of the primary tumour/teratoid elements). Mature teratomas have been described at 5-8 years of follow-up (134). Generally, the relapse rate at a median follow-up of 5.5 years is approximately 8%. The progression-free survival rate is approximately 92% and the overall survival rate is 97% (258).

Although this treatment policy avoids RPLND in 68-78% of patients, depending on whether the clinical stage is IIa or IIb (190,258,269), it requires extended follow-up. After primary chemotherapy, retroperitoneal CT scans cannot be omitted from the follow-up schedule. The follow-up schedule is basically the same as that for primary RPLND plus adjuvant chemotherapy, although after primary chemotherapy an abdominal and pelvic CT scan has to be performed at least twice during the first 2 years (Table 11).

#### 9.4.2 Clinical stage II seminoma

Relapse rates following radiotherapy for clinical stages IIa and IIb are in the range 5-15%. Most relapses occur within the first 2 years and present with a supraclavicular or mediastinal mass, while relapses in the irradiated field are rare (259). The recommend follow-up schedule is outlined in Table 12.

**Table 12: Follow-up of seminoma stage IIa–IIb after radiotherapy**

Procedure	Year					
	1	2	3	4	5	> 5
Physical examination	Six times	Four times	Three times	Twice	Twice	Once/year
Tumour markers	Six times	Four times	Three times	Twice	Twice	Once/year
Chest X-ray	Six times	Four times	Three times	Twice	Twice	Once/year
CT abdomen and pelvis <sup>a</sup>	If indicated					
CT chest <sup>b</sup>	If indicated					

*CT = computed tomography.*

<sup>a</sup> Baseline CT of the abdomen/pelvis post-treatment and repeated only if indicated.

<sup>b</sup> Only if there is an abnormal chest X-ray or if clinical symptoms indicate.

### 9.4.3 Clinical stage IIc and III seminoma and non-seminoma

In advanced disease following the IGCCCG classification, the overall survival rate is in the order of 92% for patients in the good prognostic category, 80% for those in the intermediate category and 48% for those in the poor prognostic category (131). Stage IIc is generally grouped in the subset of patients with good prognosis (134).

After chemotherapy, careful follow-up is recommended if there is a decrease of at least 90% in the volume of retroperitoneal masses, provided there is no evidence of teratomatous elements in the primary tumour. Nevertheless, to date there are no reliable CT scan criteria to distinguish tumour or teratoma from necrotic debris in the post-chemotherapy setting; false-negative CT scan rates range from 8-37% (261). In advanced NSGCT, despite statistical correlation with a variety of factors (e.g., degree of shrinkage, size of residual mass, pre-chemotherapy tumour marker levels, teratomatous components in orchiectomy specimen), the risk of a false-negative prediction based on a CT scan is currently still approximately 20% (261). In advanced seminoma, the rate of 'in-site' failure is 3% when the CT scan is normal or shows a residual abnormality less than 3 cm in diameter (157,161-163). The follow-up schedule for advanced disease (seminoma and non-seminoma) is presented in Table 13.

In advanced disease routine estimation of serum tumour markers ( $\beta$ -hCG and AFP) seems to be the single most important follow-up procedure followed by physical examination and clinical history (229-230), some recent studies question the value of routine chest X-ray (230).

A brain CT has to be performed during follow-up if neurological symptoms are present, because up to 5% of patients with advanced disease present with or develop brain metastases (259). An abdominal CT scan has to be performed at least annually, because of the ominous significance of teratoma, if found in the retroperitoneum.

**Table 13: Follow-up of advanced NSGCT and seminoma**

Procedure	Year					
	1	2	3	4	5	Thereafter
Physical examination	Monthly	Bimonthly	Four times	Three times	Twice	Once/year
Tumour markers	Monthly	Bimonthly	Four times	Three times	Twice	Once/year
Chest X-ray	Monthly	Bimonthly	Four times	Three times	Twice	Once/year
Abdominal CT <sup>ab</sup>	As indicated					
Chest CT <sup>bc</sup>	As indicated					
Brain CT <sup>d</sup>	As indicated					

CT = computed tomography.

<sup>a</sup> Abdominal CT scan has to be performed at least annually if teratoma is found in retroperitoneum.

<sup>b</sup> If the post-chemotherapy evaluation shows any mass > 3 cm, the appropriate CT scan should be repeated 2 and 4 months later to ensure that the mass is continuing to regress.

<sup>c</sup> Chest CT is indicated if abnormality is detected on chest X-ray and after pulmonary resection.

<sup>d</sup> In patients with headaches, focal neurological findings or any CNS symptom.

## 10 TESTICULAR STROMAL TUMOURS

### 10.1 Background

Testicular stromal tumours are rare and account for only 2-4% of adult testicular tumours. However, only Leydig cell and Sertoli cell tumours are of clinical relevance. As no general recommendations are published to date, the Testicular Cancer Working Group of the European Association of Urology (EAU) has decided to include these tumours in the EAU Germ Cell Tumour Guidelines. Recommendations for diagnosis and treatment are given only for Leydig and Sertoli cell tumours.

### 10.2 Methods

A Medline search for Leydig cell tumours (synonym: interstitial cell tumour) and Sertoli cell tumours (synonym: androblastoma) was performed. Approximately 850 papers were found. After excluding pure laboratory work without clinical data, female and paediatric tumours and animal cases, 371 papers and abstracts were reviewed. Double publications and papers with unclear histology or missing data on clinical course were excluded. The majority of the remaining 285 publications are case reports, with only a few papers

reporting series of more than 10 cases, most of them published in the pathology literature. The true incidence of stromal tumours remains therefore uncertain and the proportion of metastatic tumours can only be given approximately.

Nevertheless, the symptoms for preoperative suspicion of testicular stromal tumours and the characteristics of tumours at high risk for metastases are sufficiently well established (EBM IIA and EBM IIB) to enable recommendations to be made regarding diagnosis and surgical approach. However, no recommendations for appropriate follow-up can be given due to the absence of follow-up data in most reported cases and the fatal outcome of metastatic tumours, irrespective of the therapy chosen.

The individual publications have been rated according to evidence-based medicine (EBM) categories (*see above*).

The literature research for clinical data on **Leydig cell tumours** resulted in 193 publications dealing with more than 480 tumours in adults, including three publications (1-3) reporting larger series on a total of 90 patients. Follow-up data of more than 2 years are available for about 80 patients.

The literature research for clinical data on **Sertoli cell tumours** resulted in 93 publications dealing with more than 260 tumours in adults, including three publications (from the same group) (4-6) reporting on a total of 80 patients. Follow-up data of more than 2 years are available in less than 40 patients.

### 10.3 Classification

The non-germ cell tumours of the testicle include the sex cord/gonadal stromal tumours and the miscellaneous non-specific stromal tumours.

The different histological subtypes of testicular tumours are defined according to the WHO classification 2004 (adapted) (7).

### 10.4 Leydig cell tumours

#### 10.4.1 Epidemiology

Leydig cell tumours constitute about 1-3% of adult testicular tumours (2,8) and 3% of testicular tumours in infants and children (8). The tumour is most common in the third to sixth decade in adults with a similar incidence observed in every decade. Another peak incidence is seen in children between 3 and 9 years. 3% of Leydig cell tumours are bilateral (2). Occasionally, they occur in patients with Klinefelter's syndrome (8).

#### 10.4.2 Pathology of Leydig cell tumours

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well outlined and usually up to 5 cm in diameter. They are also solid, coloured yellow to tan, with haemorrhage and/or necrosis present in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm with occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S100, steroid hormones, calretinin and cytokeratin (focally) (7).

About 10% of Leydig cell tumours are malignant tumours, which present with the following parameters:

- Large size (> 5 cm)
- Cytologic atypia
- Increased mitotic activity (> 3 per 10 high-power field [HPF])
- Increased MIB-1 expression (18.6% vs 1.2% in benign)
- Necrosis
- Vascular invasion (9)
- Infiltrative margins
- Extension beyond the testicular parenchyma
- DNA aneuploidy (1,10).

#### 10.4.3 Diagnosis

Patients either present with a painless enlarged testis or the tumour is an incidental ultrasound finding. In up to 80%, hormonal disorders with high oestrogen and oestradiol levels and low testosterone, increased levels of LH and FSH are reported (11,12), while negative results are always obtained for the testicular germ cell tumour markers, AFP, beta-HCG, LDH and PLAP. Approximately 30% of patients present with gynecomastia (13,14). 3% of tumours are bilateral (2).

Leydig cell tumours must be distinguished from the multinodular tumour-like and often bilaterally occurring lesions of the androgenital syndrome (15). Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH, if not conclusive: additionally oestrogen, oestradiol, progesterone and cortisol), ultrasound of both testes and CT scan of chest and abdomen.

On ultrasound, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularization, but the appearance is variable and is indistinguishable from germ cell tumours (16,17). The proportion of metastatic tumours in all published case reports is only 10%. Within three larger series with

longer follow-up, 18 metastatic tumours were found in a total of 83 cases (21.7%) (1-3). Histopathological signs of malignancy have been listed above (see 4.2) (1,10). In addition, patients of older age have a greater risk of harbouring a tumour of malignant potential.

#### 10.4.4 Treatment

Asymptomatic testicular tumours of small volume are often misinterpreted as germ cell tumours and inguinal orchiectomy is performed. It is highly recommended to perform an organ-sparing procedure in every small intraparenchymal lesion to gain the histological diagnosis. Especially in patients with symptoms of gynaecomastia or hormonal disorders, a non germ-cell tumour should be considered and immediate orchiectomy should be avoided (18). In cases of germ cell tumour in either frozen section or paraffin histology, orchiectomy is recommended as long as a contralateral normal testicle is present.

In stromal tumours with histological signs of malignancy, especially in patients of older age, orchiectomy and retroperitoneal lymphadenectomy is recommended to prevent metastases (19). Without histological signs of malignancy an individualized surveillance strategy after orchiectomy is recommended (CT follow up may be most appropriate since specific tumour-markers are not available).

Tumours that have metastasized to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor (19).

#### 10.4.5 Follow-up

Recommendations for appropriate follow-up cannot be given because of the lack of follow-up data in most reported cases and the lethal outcome of metastatic tumours, irrespective of the therapy chosen.

### 10.5 Sertoli cell tumour

#### 10.5.1 Epidemiology

Sertoli cell tumours account for less than 1% of testicular tumours, the mean age at diagnosis is around 45 years with rare cases under the age of 20 (4,20). On rare occasions, these tumours may develop in patients with the androgen insensitivity syndrome and Peutz-Jeghers syndrome.

#### 10.5.2 Pathology of Sertoli cell tumours

The tumour is well circumscribed, yellow, tan or white, with an average diameter of 3.5 cm (4). Microscopically, the cells are eosinophilic to pale with vacuolated cytoplasm. The nuclei are regular with grooves and there may be inclusions. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible. The stroma is fine and capillary but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) (4).

The rate of malignant tumours ranges between 10 and 22% and less than 50 cases are reported (23-25). Signs of a malignant Sertoli tumour are:

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

#### 10.5.2.1 Classification

Three subtypes have been described (20):

- the classic Sertoli cell tumour (4)
- the large cell calcifying form with characteristic calcifications (5,21)
- the rare sclerosing form (6,22).

#### 10.5.3 Diagnosis

Patients present either with an enlarged testis or the tumour is an incidental ultrasound finding (26). Most classic Sertoli tumours are unilateral and unifocal. Hormonal disorders are infrequent, though gynaecomastia is sometimes seen (4). The testicular tumour-markers, AFP, Beta-HCG, LDH and PLAP are always negative.

Diagnostic work-up has to include tumour markers, hormones (at least testosterone, LH and FSH, if not conclusive: additionally oestrogen, oestradiol, progesterone and cortisol, ultrasound of both testes and CT scan of chest and abdomen.

Sertoli cell tumours are generally hypoechoic on ultrasound but they can be of variant appearance and therefore cannot be safely distinguished from germ cell tumours (20). Only the large cell calcifying form has a characteristic image with brightly echogenic foci due to calcification (27,28).

The large cell calcifying form is diagnosed in younger men and is associated with genetic syndromes (Carney's complex (29) and Peutz-Jeghers syndrome (30)) or, in about 40% of cases, endocrine disorders. 44% are bilateral, either synchronous or metachronous, and 28% show multifocality (24).

The characteristics of metastatic tumours have been depicted above (24,25). However, among patients whose tumours have been histopathologically classified as 'malignant' using these or similar characteristics (i.e., 18.8% of tumours in all reported cases), only 7% showed metastatic disease during follow-up.

In the largest series with the longest follow-up, 7.5% of patients had been classified as "malignant" at primary diagnosis and 11.7% showed metastatic disease long-term (4). In general, affected patients are of higher age, tumours are nearly always palpable and show more than one sign of malignancy (4).

Up to 20% of the large cell sclerosing form are malignant. There are some hints that discrimination between an early and late onset type may define a different risk for metastatic disease (5.5% compared with 23%) (20). Metastases in the infrequent sclerosing subtype are rare.

#### 10.5.4 Treatment

Testicular tumours of small volume, otherwise asymptomatic, are often misinterpreted as germ cell tumours and inguinal orchiectomy is performed. It is highly recommended to proceed with an organ-sparing approach in small intraparenchymal testicular lesions until final histology is available. Especially, in patients with symptoms of gynaecomastia or hormonal disorders or typical imaging on ultrasound (calcifications, small circumscribed tumours), organ-sparing surgery should be considered. Secondary orchiectomy can be performed, if final pathology reveals a non-stromal (e.g. germ cell) tumour. Organ-sparing surgical approaches are justified as long as the remaining testicular parenchyma is sufficient for endocrine (and in stromal tumours also exocrine) function.

In tumours with histological signs of malignancy, especially in patients of older age, orchiectomy and retroperitoneal lymphadenectomy are recommended to prevent metastases (19). Without signs of malignancy, an individualized surveillance strategy after orchiectomy is recommended (CT scans may be most appropriate since specific tumour-markers are not available). Tumours metastasizing to lymph nodes, lung or bone respond poorly to chemotherapy or radiation and survival is poor.

#### 10.5.5 Follow-up

Recommendations for appropriate follow-up cannot be given because of the lack of follow-up data in most reported cases and the lethal outcome of metastatic tumours, irrespective of the therapy chosen.

### 10.6 Granulosa cell tumour

This is a rare tumour, with two variants – juvenile and adult.

The juvenile type is benign. It is the most frequent congenital testicle tumour and represents 6.6% of all prepubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type (31).

With the adult type, the average age at presentation is 44 years. The typical morphology is of a homogeneous, yellow-grey, tumour, with elongated cells, with grooves in micro-follicular and Call-Exner bodies' arrangement.

Malignant tumours represent around 20% of cases. They are usually > 7 cm diameter. Vascular invasion and necrosis are features suggestive of malignant biology (32).

### 10.7 Thecoma/fibroma group of tumours

These tumours are very rare and benign (7).

### 10.8 Other sex cord/gonadal stromal tumours

Sex cord/gonadal stromal tumours may be incompletely differentiated or mixed forms.

There is limited experience with incompletely differentiated sex cord/gonadal stromal tumours and no cases of reported metastasis (7). In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour is most likely to reflect the predominant pattern or the most aggressive component of the tumour (33)

### 10.9 Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)

If the arrangement of the germ cells are in nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. It is most frequent in gonadal dysgenesis with ambiguous genitalia. Bilateral tumours are present in 40% of cases. The prognosis is correlated with the invasive growth of the germinal component (34).

In 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 (35).

## 10.10 Miscellaneous tumours of the testis

### 10.10.1 Tumours of ovarian epithelial types

These tumours resemble the epithelial tumours of the ovary. Cystic appearance with occasional mucinous material can be observed. Microscopically, the aspect is identical to their ovarian counterparts and their evolution is similar to the different epithelial ovarian subtypes. Some Brenner types can be malignant (7).

### 10.10.2 Tumours of the collecting ducts and rete testis

These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) have been reported, with malignant tumours showing local growth with a mortality rate of 56% (18).

### 10.10.3 Tumours (benign and malignant) of non-specific stroma

These are very uncommon and have a similar criteria, prognosis and treatment as the soft tissue sarcomas.

# 11 REFERENCES

## 11.1 REFERENCES germ cell tumours

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## 12 ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations.*

AFP:	alpha-fetoprotein
BEP:	bleomycin, etoposide & cisplatin
beta-hCG:	beta-human chorionic gonadotrophin
CgA:	Chromogranine A
CT:	computed tomography
EBM:	Evidence Based Medicine
EGCCCG:	European Germ Cell Cancer Collaborative Group
EP:	Etoposide and Cisplatin
EORTC:	European Organization for Research and Treatment of Cancer
FDG-PET:	fluorodeoxyglucose-positron-emission tomography
HPF:	high power field
IGCCCG:	International Germ Cell Cancer Collaborative Group
LH:	luteinizing hormone
LDH:	Lactate Dehydrogenase
MMSK:	Memorial Sloan Kettering
MRC:	Medical Research Council
MRI:	magnetic resonance imaging
NSE:	neuro-specific enolase
NSGCT:	non-seminomatous germ cell tumour
PEB:	Cisplatin, Etoposide and Bleomycin
PEI/VIP:	Cisplatin, Etoposide, Ifosfamide
PET:	positron emission tomography
PVI:	Cisplatin, Vinblastine, Ifosfamide
PLAP:	placental alkaline phosphatase
PVB:	Cisplatin, Vinblastine and Bleomycin
RPLND:	retroperitoneal lymph node dissection
Tin:	intratubular germ cell neoplasia
TNM:	Tumour Node Metastasis
UICC:	International Union Against Cancer
VAB:	Vinblastine, Adriamycin and Bleomycin
VeIP:	Vinblastin, Ifosfamide and Cisplatin