

# GUIDELINES ON TESTICULAR CANCER

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## Introduction

Compared with other types of cancer, testicular cancer is relatively rare accounting for approximately 1-1.5% of all cancers in men.

A steady increase in incidence has been seen over the past decades in the industrialised countries. The majority of these tumours are derived from germ cells (seminoma and non-seminoma germ cell testicular cancer) and more than 70% of patients are diagnosed with stage I disease. Nowadays testicular tumours show excellent cure rates, mainly due to early diagnosis and their extreme chemo- and radiosensitivity.

**Table 1: Prognostic risk factors for the development of tumours**

### **Epidemiological risk factors**

History of cryptorchidism

Klinefelter's syndrome

Familial history of testis cancer in first-grade relatives

Presence of contralateral tumour

Tin or infertility

**Pathological prognostic risk factors for occult metastatic disease (for stage I)**

For seminoma (not prospectively evaluated)

- Tumour size  $\geq$  4 cm
- Invasion of the rete testis

For non-seminoma

- Vascular/lymphatic invasion or peri-tumoural invasion
- Proliferation rate (MIB-1) > 70%
- Percentage embryonal carcinoma > 50%

**Clinical (for metastatic disease)**

Primary location

Elevation of tumour marker levels

Presence of non-pulmonary visceral metastasis

## Classification

Testicular epithelial cancer is classified into three categories:

- germ cell tumours;
- sex cord stromal tumours;
- miscellaneous germ cell/sex cord stromal tumours.

Germ cell tumours account for 90-95% of cases of testicular cancer according to the WHO classification system.

**Table 2: The recommended pathological classification**  
(modified World Health Organization 2004)

**1. Germ cell tumours**

Intratubular germ cell neoplasia

Seminoma (including cases with syncytiotrophoblastic cells)

Spermatocytic seminoma (mention if there is a sarcomatous component)

Embryonal carcinoma

Yolk sac tumour

Choriocarcinoma

|   |
|---|
| Teratoma (mature, immature, with malignant component)                             |
| Tumours with more than one histological type (specify % of individual components) |
| <b>2. Sex cord/gonadal stromal tumours</b>  |
| Leydig cell tumour  |
| Malignant Leydig cell tumour  |
| Sertoli cell tumour (lipid-rich variant, sclerosing, large cell calcifying)       |
| Malignant Sertoli cell tumour   |
| Granulosa (adult and juvenile)  |
| Thecoma/fibroma group of tumours  |
| Other sex cord/gonadal stromal tumours (incompletely differentiated, mixed)       |
| Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)        |
| <b>3. Miscellaneous non-specific stromal tumours</b>                              |
| Ovarian epithelial tumours  |
| Tumours of the collecting ducts and rete testis                                   |
| Tumours (benign and malignant) of non-specific stroma                             |

## Diagnosis of testicular cancer

The diagnosis of testicular cancer is based on:

*Clinical examination* of the testis and general examination to rule out enlarged nodes or abdominal masses.

*Ultrasound (US) of both testes* should be performed whenever a testicular tumour is suspected. An additional US of the retroperitoneum is recommended to screen for extensive retroperitoneal metastasis. Ultrasound of both testes should also be performed in patients with a retroperitoneal mass and/or elevated tumour serum markers without a palpable scrotal mass.

*Serum tumour markers*, both before, and 5-7 days after orchiectomy (AFP and hCG) and LDH. The latter is mandatory in advanced tumours.

*Inguinal exploration and orchiectomy* with en bloc removal of testis, tunica albuginea, and spermatic cord. If the diagnosis is not clear, a testicular biopsy (tumour enucleation) is to be taken for histopathological frozen section.

Organ-sparing surgery can be attempted in special cases (bilateral tumour or solitary testes). Routine contralateral biopsy for diagnosis of carcinoma *in situ* should be discussed with the patient and is recommended in “high risk” patients (testicular volume < 12 mL, a history of cryptorchidism and age under 40 years).

## Diagnosis and treatment of Tin

Biopsy should be offered to patients with high risk for contralateral Tin (testicular volume < 12 mL, history of cryptorchidism or poor spermatogenesis). If performed, a double biopsy is preferred. In case of Tin, local radiotherapy is indicated following counselling on impaired testosterone production and infertility.

## Staging of testicular tumours

For an accurate staging the following steps are necessary:

### *Postorchiectomy half-life kinetics of serum tumour markers.*

The persistence of elevated serum tumour markers after orchiectomy may indicate the presence of disease, while its normalisation does not necessarily mean absence of tumour. Tumour markers should be assessed until they are normal, as long as they follow their half-life kinetics and no metastases are revealed.

### *Assessment of retroperitoneal and mediastinal nodes and*

viscera by abdominal CT and thoracic CT/plain radiography chest. Supraclavicular nodes are to be assessed by physical examination. MRI is helpful only when the above are inconclusive or in patients with an allergy to contrast agents. Other examinations such as brain or spinal CT, bone scan or liver US should be performed if metastases are suspected.

In patients diagnosed with testicular seminoma and a positive abdominopelvic CT, a chest CT is recommended.

A chest CT scan should be routinely performed in patients diagnosed with non-seminomatous germ cell tumours (NSGCT) because in up to 10% of cases, small subpleural nodes may be present that are not visible radiologically.

### Staging system

The Tumour, Node, Metastasis (TNM 2009) staging system is endorsed.

**Table 3: TNM classification for testicular cancer**

**pT - Primary tumour<sup>1</sup>**

|      |   |
|------|---|
| pTX  | Primary tumour cannot be assessed   |
| pT0  | No evidence of primary tumour (e.g. histologic scar in testis)  |
| pTis | Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)   |
| pT1  | Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis                    |
| pT2  | Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis |
| pT3  | Tumour invades spermatic cord with or without vascular/lymphatic invasion   |
| pT4  | Tumour invades scrotum with or without vascular/lymphatic invasion  |

**N - Regional lymph nodes clinical**

|    |  |
|----|--|
| NX | Regional lymph nodes cannot be assessed  |
| N0 | No regional lymph node metastasis  |
| N1 | Metastasis with a lymph node mass $\leq 2$ cm in greatest dimension, or multiple lymph nodes, none $> 2$ cm in greatest dimension                                      |
| N2 | Metastasis with a lymph node mass $> 2$ cm but $\leq 5$ cm in greatest dimension, or multiple lymph nodes, any one mass $> 2$ cm but $\leq 5$ cm in greatest dimension |
| N3 | Metastasis with a lymph node mass $> 5$ cm in greatest dimension   |

**pN - Pathological regional lymph nodes**

|     |  |
|-----|--|
| pNX | Regional lymph nodes cannot be assessed  |
| pN0 | No regional lymph node metastasis  |
| pN1 | Metastasis with a lymph node mass $\leq 2$ cm in greatest dimension and 5 or fewer positive nodes, none $> 2$ cm in greatest dimension                               |
| pN2 | Metastasis with a lymph node mass $> 2$ cm but $< 5$ cm in greatest dimension; or $> 5$ nodes positive, none $> 5$ cm; or evidence of extranodal extension of tumour |
| pN3 | Metastasis with a lymph node mass $> 5$ cm in greatest dimension   |

**M - Distant metastasis**

|     |                                       |
|-----|---------------------------------------|
| MX  | Distant metastasis cannot be assessed |
| M0  | No distant metastasis                 |
| M1  | Distant metastasis                    |
| M1a | Non-regional lymph node(s) or lung    |
| M1b | Other sites                           |

**pM - Pathological distant metastasis**

The pM category corresponds to the M category

### S - Serum tumour markers

|    |  |                 |              |
|----|--|-----------------|--------------|
| Sx | Serum markers studies not available or not performed |                 |              |
| S0 | Serum marker study levels within normal limits       |                 |              |
|    | LDH (U/L)  | hCG (mIU/mL)    | AFP (ng/mL)  |
| S1 | < 1.5 x N and  | < 5,000 and     | < 1,000      |
| S2 | 1.5-10 x N or  | 5,000-50,000 or | 1,000-10,000 |
| S3 | > 10 x N or  | > 50,000 or     | > 10,000     |

<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.

The International Germ Cell Cancer Collaborative Group (IGCCCG) defined a prognostic factor-based staging system for metastatic germ cell cancer that includes good and intermediate prognosis seminoma and good, intermediate, and poor prognosis NSGCT.

**Table 4: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG)**

| <b>Good-prognosis group</b>           |   |
|---------------------------------------|---|
| <i>Non-seminoma (56% of cases)</i>    | <i>All of the following criteria:</i>   |
| 5-year PFS 89%<br>5-year survival 92% | Testis/retroperitoneal primary<br>No non-pulmonary visceral metastases<br>AFP < 1,000 ng/mL<br>hCG < 5,000 IU/L (1,000 ng/mL)<br>LDH < 1.5 x ULN          |
| <i>Seminoma (90% of cases)</i>        | <i>All of the following criteria:</i>   |
| 5-year PFS 82%<br>5-year survival 86% | Any primary site<br>No non-pulmonary visceral metastases<br>Normal AFP<br>Any hCG<br>Any LDH  |
| <b>Intermediate-prognosis group</b>   |   |
| <i>Non-seminoma (28% of cases)</i>    | <i>All of the following criteria:</i>   |
| 5-year PFS 75%<br>5-year survival 80% | Testis/retroperitoneal primary<br>No non-pulmonary visceral metastases<br>AFP 1,000 - 10,000 ng/mL or<br>hCG 5,000 - 50,000 IU/L or<br>LDH 1.5 - 10 x ULN |
| <i>Seminoma (10% of cases)</i>        | <i>All of the following criteria:</i>   |



|                                       |   |
|---------------------------------------|---|
| 5-year PFS 67%<br>5-year survival 72% | Any primary site<br>Non-pulmonary visceral metastases<br>Normal AFP<br>Any hCG<br>Any LDH   |
| <b>Poor-prognosis group</b>           |   |
| <i>Non-seminoma</i><br>(16% of cases) | <i>Any of the following criteria:</i>   |
| 5-year PFS 41%<br>5-year survival 48% | Mediastinal primary<br>Non-pulmonary visceral metastases<br>AFP > 10,000 ng/mL or<br>hCG > 50,000 IU/L<br>(10,000 ng/mL) or<br>LDH > 10 x ULN |
| <i>Seminoma</i>                       | No patients classified as poor prognosis  |

*PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = beta-human chorionic gonadotrophin; LDH = lactate dehydrogenase; ULN = upper limit of normal range.*

| <b>Guidelines for the diagnosis and staging of testicular cancer</b>  | <b>GR</b> |
|---|-----------|
| Testicular US is mandatory.   | A         |
| Orchidectomy and pathological examination of the testis is necessary to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, chemotherapy has to be started before orchidectomy. | A         |

|   |   |
|---|---|
| Serum determination of tumour markers (AFP, hCG, and LDH) must be performed before and after orchidectomy for staging and prognostic reasons. | A |
| The state of the retroperitoneal, mediastinal, and supraclavicular nodes and visceral state must be assessed in testicular cancer.            | A |

*AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; US = ultrasound.*

### Pathological examination of the testis

Following orchidectomy, the pathological examination of the testis should include a number of investigations.

1. Macroscopic features: side, testis size, maximum tumour size and macroscopic features of epididymis, spermatic cord and tunica vaginalis.
2. Sampling: 1 cm<sup>2</sup> section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis with selection of suspected areas. At least one proximal and one distal section of the spermatic cord plus any suspected area.
3. Microscopic features and diagnosis:
  - histological type (specify individual components and estimate amount as a percentage);
  - presence or absence of peri-tumoural venous and/or lymphatic invasion;
  - presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion, and;
  - presence or absence of intratubular germinal neoplasia (Tin) in non-tumoural parenchyma intratubular germ cell neoplasia.
4. pT category according to TNM 2009.
5. Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

| <b>Guidelines for the treatment of testicular cancer</b>   |           |
|--|-----------|
| <b>Seminoma stage I</b>  | <b>GR</b> |
| Surveillance is the recommended management option (if facilities available and patient compliant). | A         |
| Carboplatin-based chemotherapy (one course at AUC 7) can be recommended.                           | B         |
| Adjuvant treatment is not recommended for patients at low risk.                                    | A         |
| Radiotherapy is not recommended as adjuvant treatment.   | A         |

| <b>NSGCT stage I</b>  | <b>GR</b> |
|---|-----------|
| CS1 risk-adapted treatments based on vascular invasion or surveillance without using risk factors are recommended treatment options.  | A         |
| <b>Risk-adapted treatments for CS1 based on vascular invasion</b>   |           |
| <b>CS1A (pT1, no vascular invasion): low risk</b>   |           |
| 1. If the patient is willing and able to comply with a surveillance policy, long-term (at least 5 years) close follow-up should be recommended.   | A         |
| 2. In low-risk patients not willing (or suitable) to undergo surveillance, adjuvant chemotherapy or nerve-sparing RPLND are treatment options<br>If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of PEB should be considered. | A         |
| <b>CS1B (pT2-pT4): high risk</b>  |           |
| 1. Primary chemotherapy with two courses of PEB should be recommended (one course of PEB within a clinical trial or registry).  | A         |

|   |   |
|---|---|
| 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. | A |
|---|---|

| <b>Guidelines for the treatment of metastatic germ cell tumours</b>  | <b>GR</b> |
|--|-----------|
| 1. Low volume NSGCT stage IIA/B with elevated markers should be treated like 'good or intermediate prognosis' advanced NSGCT, with three or four cycles of PEB.  | A         |
| 2. In stage IIA/B without marker elevation, histology can be gained by RPLND or biopsy. A repeat staging can be performed after six weeks of surveillance before final decision on further treatment.        | B         |
| 3. In metastatic NSGCT (> stage IIC) with a good prognosis, three courses of PEB is the primary treatment of choice.   | A         |
| 4. In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard PEB and inclusion in clinical trials is strongly recommended.                     | A         |
| 5. Surgical resection of residual masses after chemotherapy in NSGCT is indicated in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.                  | A         |
| 6. Seminoma CS IIA/B can initially be treated with radiotherapy. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT. | A         |

|   |   |
|---|---|
| 7. In seminoma stage CS IIB, chemotherapy (4 x EP or 3 x PEB, in good prognosis) is an alternative to radiotherapy. It appears that 4 x EP or 3 x PEB achieve a similar level of disease control. | B |
| 8. Seminoma stage IIC and higher should be treated with primary chemotherapy according to the same principles used for NSGCT.   | A |

*EP = eposide, cisplatin; NSGCT = non-seminomatous germ cell tumour; PEB = cisplatin, eposide, bleomycin;*

*RPLND = retroperitoneal lymph node dissection.*

### Relapse after chemotherapy

The treatment of relapsed GCT after chemotherapy is typically salvage chemotherapy. For patients at first relapse with good prognostic features (initial achievement of CR/PR M- and gonadal primary tumour) 4 cycles of standard dose salvage chemotherapy are proposed. For patients with poor prognostic factors (extragonadal primary and/or incomplete response to first line chemotherapy) and for all patients with subsequent (> first) relapse, high-dose chemotherapy with autologous stem cell support is recommended.

### Follow-up of patients with testicular cancer

The aim of the follow-up is to detect relapse as early as possible and to monitor the contralateral testis. In the presence of a curative- or life prolongation therapy, the following principles should apply;

- (a) interval between examinations and duration of follow-up should be consistent with the time of maximal risk of recurrence;
- (b) tests should be directed at the most likely sites of recurrence and have a good accuracy;
- (c) the increased risk of second malignancy, both in the primary site and in other tissues that may have been exposed to the same carcinogens, or in which there is

epidemiological evidence of increased risk, should also guide the selection of tests;

- (d) non-malignant complications of therapy must also be considered.

**Table 5: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma**

| Procedure                | Year 1                 | Year 2  | Year 3-5 | Year 6-10 |
|--------------------------|------------------------|---------|----------|-----------|
| Physical examination     | 4 times                | 4 times | Once/yr. | Once/yr.  |
| Tumour markers           | 4 times                | 4 times | Once/yr. | Once/yr.  |
| Plain radio-graphy chest | Twice                  | Twice   |          |           |
| Abdominopelvic CT        | Twice (at 3 and 12 mo) |         |          |           |

CT = computed tomography.

**Table 6: Recommended minimum follow-up schedule after RPLND or adjuvant chemotherapy: stage I non-seminoma**

| Procedure                | Year 1  | Year 2  | Year 3-5 | Year 6-10 |
|--------------------------|---------|---------|----------|-----------|
| Physical examination     | 4 times | 4 times | Once/yr. | Once/yr.  |
| Tumour markers           | 4 times | 4 times | Once/yr. | Once/yr.  |
| Plain radio-graphy chest | Twice   | Twice   |          |           |
| Abdominopelvic CT        | Once    | Once    |          |           |

CT = computed tomography; RPLND = retroperitoneal lymph node dissection.

**Table 7: Recommended minimum follow-up schedule for post-orchidectomy surveillance, radiotherapy or chemotherapy: stage I seminoma**

| <b>Procedure</b>         | <b>Year 1</b> | <b>Year 2</b> | <b>Year 3</b> | <b>Year 4-5</b> |
|--------------------------|---------------|---------------|---------------|-----------------|
| Physical examination     | 3 times       | 3 times       | Once/yr.      | Once/yr.        |
| Tumour markers           | 3 times       | 3 times       | Once/yr.      | Once/yr.        |
| Plain radio-graphy chest | Twice         | Twice         |               |                 |
| Abdominopelvic CT        | Twice         | Twice         |               |                 |

CT = computed tomography.

**Table 8: Recommended minimum follow-up in advanced NSGCT and seminoma**

| <b>Procedure</b>         | <b>Year 1</b> | <b>Year 2</b> | <b>Year 3-5</b> | <b>thereafter</b> |
|--------------------------|---------------|---------------|-----------------|-------------------|
| Physical examination     | 4 times       | 4 times       | Twice/yr.       | Once/yr.          |
| Tumour markers           | 4 times       | 4 times       | Twice/yr.       | Once/yr.          |
| Plain radio-graphy chest | 4 times       | 4 times       | Twice/yr.       | Once/yr.          |
| Abdominopelvic CT*†      | Twice         | Twice         | As indicated    | As indicated      |
| Chest CT                 | As indicated  | As indicated  | As indicated    | As indicated      |
| Brain CT                 | As indicated  | As indicated  | As indicated    | As indicated      |

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

*CT = computed tomography; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography computed tomography.*

## Testicular stromal tumours

Testicular stromal tumours are rare, however, Leydig cell and Sertoli cell tumours are of clinical relevance.

### Leydig cell tumours

Leydig cell tumours constitute 1-3% of adult testicular tumours and 3% of testicular tumours in children. Only about 10% of them are malignant presenting the following features:

- Large size (> 5 cm);
- Cytologic atypia and DNA aneuploidy;
- Increased mitotic activity and increased MIB -1 expression;
- Necrosis;
- Vascular invasion infiltrative margins;
- Extension beyond the testicular parenchyma.

The tumour presents as a painless enlarged testis or as an incidental ultrasound finding accompanied in up to 80% of cases by hormonal disorders. Serum tumour markers are negative and approximately 30% of patients present with gynaecomastia. These tumours are often treated by inguinal



orchiectomy because they are misinterpreted as germ cell tumours.

Especially in patients with symptoms of gynaecomastia or hormonal disorders or typical imaging on ultrasound, until final histology is available, a partial orchiectomy (+ frozen section) should be considered. In case of histological signs of malignancy orchiectomy and RPLND are the treatment of choice.

### **Sertoli cell tumours**

They are even rarer than Leydig cell tumours, and they are malignant in 10-22% of cases. Morphological signs of malignancy are:

- Large size (> 5 cm);
- Pleomorphic nuclei with nucleoli;
- Increased mitotic activity;
- Necrosis and vascular invasion.

They present either as an enlarged testis or as incidental ultrasound finding. Hormonal disorders are infrequent and serum tumour markers are negative.

Ultrasonographically they generally appear as hypoechoic and cannot be safely distinguished from germ-cell tumour except for the subtype large cell calcifying form which is usually associated with genetic syndromes (Carney's complex, Peutz-Jeghers syndrome). Sertoli cell tumours are often interpreted as germ-cell tumours and an orchiectomy is performed.

Organ-sparing surgery should be considered (with caution) but in case of histological signs of malignancy orchiectomy and RPLND are the treatment of choice.

### **Conclusions**

Most testis tumours derive from germ cells and are diagnosed at an early stage. Staging is the cornerstone and the 2009

TNM system is recommended for classification and staging purposes.

The IGCCCG staging system is recommended for metastatic disease. Following orchiectomy, excellent cure rates are achieved for those early stages irrespective of the treatment policy adopted, although pattern and relapse rates are closely linked to the treatment modality chosen. In metastatic disease a multidisciplinary therapeutic approach offers an acceptable survival. Follow-up schedules should be tailored to initial staging and treatment. Testicular stromal tumours are rare and usually benign. When suspected and pathologically confirmed they can be treated by organ sparing surgery. However, in case of malignancy (small percentage) orchiectomy and RPLND are the treatment of choice.

*This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-96-0), available to all members of the European Association of Urology at their website, <http://www.uroweb.org>.*