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 industrialized 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. Epidemiological risk factors for testicular cancer as well as pathological and clinical risk factors in Stage I and in metastatic disease are well established. Nowadays testicular tumours show excellent cure rates, mainly due to early diagnosis and their extreme chemo- and radio-sensitivity.

Three levels of recommendations are used:
The principal recommendations are marked in three grades (A-C), depending on the evidence source upon which a recommendation is based. Page 3 of this publication may be consulted for reference.

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)

- Histopathological type
- For seminoma
  - 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[a]

[a] *Only clinical predictive factor for metastatic disease in seminoma.*

Classification

Testicular epithelial cancer is classified into three categories: (a) germ cell tumours; (b) sex cord stromal tumours; and (c) 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 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
   - Sertoli cell tumour (lipid-rich variant, sclerosing, large cell calcifying)
   - Malignant Sertoli cell tumour
   - Granulosa (adult and juvenile
   - Thecoma/ fibroma group of tumors
   - Other sex cord/gonadal stromal tumors (incompletely differentiated, mixed)
   - Tumours containing germ cell and sex cord/gonadal

stromal (gonadoblastoma)

3. **Miscellaneous non-specific stromal tumours**
   - Ovarian epithelial tumors
   - 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 of the testis to confirm testicular mass and always in a young man with a retroperitoneal mass or elevated tumour serum markers and without a palpable scrotal mass.

Serum tumour markers before orchiectomy (AFP and hCG) and LDH if metastatic disease.

Inguinal exploration and orchiectomy with en bloc removal of testis, tunica albuginea, and spermatic cord.

Organ-sparing surgery can be attempted in special cases (bilateral tumour or solitary testes) in centres of reference.
Routine contralateral biopsy for diagnosis of carcinoma *in situ* should not be performed as a standard assessment but is recommended in "high risk" patients (testicular volume < 12 mL, a history of cryptorchidism and age under 30 years).

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 3 weeks after orchiectomy may indicate the presence of disease, while its normalization 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
(Abdominopelvic CT scan and thoracic CT scan/X-ray Thorax) and *supraclavicular nodes* (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 ultrasound should be performed if metastases are suspected.

In patients diagnosed with testicular seminoma and a positive abdominopelvic CT scan a chest CT scan 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 2002) staging system is endorsed.

TNM classification for testicular cancer (UICC, 2002 Sixth Edition)

pT - Primary Tumour[1]

pTX	Primary tumour cannot be assessed
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

N Regional Lymph Nodes Clinical

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension, or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension

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

pN Pathological Regional Lymph Nodes

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Metastasis with a lymph node mass 2 cm or less in greatest dimension 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

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 Tumor Markers

Sx Serum markers studies not available or not performed

S0 Serum marker study levels within normal limits

	LDH (U/L)		hCG (mlU/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

[1] *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 3: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG)

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

	Any hCG Any LDH
Intermediate-prognosis group	
Non-seminoma (28% of cases) 5-year PFS 75% 5-year survival 80%	All of the following criteria: Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP > 1,000 and < 10,000 ng/mL or hCG > 5,000 and < 50,000 IU/L or LDH > 1.5 and < 10 x ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	Any of the following criteria: Any primary site Non-pulmonary visceral metastases Normal AFP Any hCG Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	Any of the following criteria: Mediastinal primary Non-pulmonary visceral metastases AFP > 10,000 ng/mL or hCG > 50,000 IU/L (10,000 ng/mL) or LDH > 10 x ULN

Seminoma	
No patients classified as poor prognosis	

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

Table 4: Guidelines for the diagnosis and staging of testicular cancer

(1) 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 of the scrotum (Grade of recommendation: B).

(2) Orchiectomy and pathological examination of the testis is necessary to confirm the diagnosis and to define local extension (PT category) (Grade of recommendation: B). In a life-threatening situation due to extensive metastasis chemotherapy has to be started before orchiectomy.

(3) Serum determination of tumour markers (AFP, hCG and LDH in metastatic disease) must be performed before and after ochiectomy for staging and prognostic reasons (Grade of recommendation: B).

(4) 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 of recommendation: B).

Pathological Examination of the Testis

Following orchiectomy, 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^2 section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis with selection of suspected areas. At least one proximal and one distal section of 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 in non-tumoural parenchyma.

(4) pT category according to TNM 2002.

(5) Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

Table 5: Guidelines for the treatment of testicular cancer

Stage I Seminoma

(1) Surveillance (if available facilities and patient compliance) (Grade of recommendation: B).

(2) Carboplatin-based chemotherapy (one course at AUC 7) can be recommended as alternative to radiotherapy and surveillance (Grade of recommendation: A).

(3) Adjuvant radiotherapy to a para-aortic field, with a total dose of 20 Gy (Grade of recommendation: A).

Stage I NSGCT

CS 1

Risk adapted treatment based on vascular invasion or surveillance are recommended treatment options (Grade of recommendation: B).

CS 1A (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, surveillance should be recommended (Grade of recommendation: B).
(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 PEB should be considered (Grade of recommendation: A).

CS 1B (pT2-pT4, vascular invasion). High risk.

(1) Primary chemotherapy with two courses of PEB should be recommended (Grade of recommendation: B).
(2) Surveillance or nerve-sparing RPLND remain options for those not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, further chemotherapy should be considered (Grade of recommendation: A).

Metastatic germ cell tumours

(1) Low volume NSGCT Stage IIA/B with elevated mark-

ers should be treated like "good or intermediate prognosis' advanced NSGCT with 3 or 4 cycles of PEB. Stage II A/B without marker elevation can bet treated either by RPLND or close surveillance.

(2) In metastatic NSGCT (≥ stage IIC) with a good prognosis, three courses of PEB is the primary treatment of choice (Grade of recommendation: A).
(3) In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard PEB (Grade of recommendation: A).
(4) Surgical resection of residual masses after chemotherapy in NSGCT is indicated in case of visible residual masses and when serum levels of tumour markers are normal or normalizing (Grade of recommendation: B).
(5) Metastatic seminoma with less than N3MI 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 of recommendation: A).
(6) Advanced seminoma (N3 or M1) should be treated with primary chemotherapy according to the same principles used for NSGCT (Grade of recommendation: A).

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) an increased long-term risk for secondary malignancies exists after radiotherapy or chemotherapy.

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.

Table 6: Recommended minimum follow-up schedule or stage I NSGCT in a surveillance policy

Procedure	Year 1	Year 2
Physical examination	3-monthly	3-monthly
Tumour markers	3-monthly	3-monthly
Chest X-ray	Twice/year	Twice/year
Abdominopelvic CT scan	Twice/year (3 and 12 months)	

Table 7: Recommended minimum follow-up for stage I NSGCT after RPLND or adjuvant chemotherapy seminoma on surveillance

Procedure	Year 1	Year 2
Physical examination	3-monthly	3-monthly
Tumour markers	3-monthly	3-monthly
Chest X-ray	Twice/year	Twice/year
Abdominopelvic CT scan	Once/year	Once/year

Table 8: Recommended minimum follow-up for patients with stage I Seminoma post orchiectomy surveillance, radiotherapy or chemotherapy

Procedure	Year 1	Year 2
Physical examination	3-monthly	3-monthly
Tumour markers	3-monthly	3-monthly
Chest X-ray	Twice/year	Twice/year
Abdominopelvic CT scan	Twice/year	Twice/year

[a] *Monthly for the first 6 months.*

Year 3-5	Year 6-10
Twice/year	Once/year
Twice/year	Once/year

Year 3-5	Year 6-10
Twice/year	Once/year
Twice/year	Once/year

Year 3	Year 4-5
Twice/year	Once/year
Twice/year	Once/year
Once/year	Once/year
Once/year	Once/year

Table 9: Recommended minimum follow-up of advanced NSGCT and Seminoma

Procedure	Year 1	Year 2
Physical examination	3-monthly	3-monthly
Tumour markers	3-monthly	3-monthly
Chest X-ray	3-monthly	3-monthly
Abdominopelvic CT scan	Twice/year	Twice/year

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 gynecomastia.

These tumours are often treated by inguinal orchiectomy because they are misinterpreted as germ cell tumours.

Year 3-5	thereafter
Twice/year	Once/year
Twice/year	Once/year
Twice/year	Once/year
Once/year	Once/year

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 can be 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 usu-

ally 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 2002 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 978-90-70244-91-0), available to all members of the European Association of Urology at their website - http://www.uroweb.org.