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. 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 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 - Tumour size (≥ 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:
(a) germ cell tumours;
(b) sex cord stromal tumours;
(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 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)
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 (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)
3. Miscellaneous non-specific stromal tumours
Ovarian epithelial tumours
Tumours of the collecting ducts and rete testis

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. Currently, testicular ultrasound should be performed even in the presence of clinically evident tumour.

Serum tumour markers before 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

Although the diagnosis of Tin remains controversial, a 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 the treatment after 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 3 weeks 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. (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 2009) staging system is endorsed.

Table 3: TNM classification for testicular cancer

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 (testicular intraepithelial neoplasia)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N - Regional lymph nodes clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

N1	Metastasis with a lymph node mass ≤ 2 cm in greatest dimension, or multiple lymph nodes, none > 2 cm in greatest dimension
N2	Metastasis with a lymph node mass > 2 cm but ≤ 5 cm in greatest dimension, or multiple lymph nodes, any one mass > 2 cm but ≤ 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 ≤ 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 (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 4: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG)	
Good-prognosis group	
Non-seminoma (56% of cases)	*All of the following criteria:*
5-year PFS 89% 5-year survival 92%	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)	*All of the following criteria:*
5-year PFS 82% 5-year survival 86%	Any primary site No non-pulmonary visceral metastases Normal AFP Any hCG Any LDH
Intermediate-prognosis group	
Non-seminoma (28% of cases)	*All of the following criteria:*
5-year PFS 75% 5-year survival 80%	Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP 1,000 - 10,000 ng/mL or hCG 5,000 - 50,000 IU/L or LDH 1.5 - 10 x ULN

Seminoma (10% of cases)	*Any of the following criteria:*
5-year PFS 67% 5-year survival 72%	Any primary site Non-pulmonary visceral metastases Normal AFP Any hCG Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases)	*Any of the following criteria:*
5-year PFS 41% 5-year survival 48%	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.

Guidelines for the diagnosis and staging of testicular cancer	GR
Testicular ultrasound 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.

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 (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.

Guidelines for the treatment of testicular cancer	
Seminoma stage I	**GR**
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

NSGCT stage I	GR
CS1 risk-adapted treatments based on vascular invasion or surveillance without using risk factors are recommended treatment options.	
Risk-adapted treatments for CS1 based on vascular invasion	
CS1A (pT1, no vascular invasion): low risk	
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 If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of PEB should be considered.	A
CS1B (pT2-pT4): high risk	
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

Guidelines for the treatment of metastatic germ cell tumours	GR
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 recur-

rence 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 ordering 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.
Chest X-ray	Twice	Twice		
Abdominopelvic CT scan	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.
Chest X-ray	Twice	Twice		
Abdominopelvic CT scan	Once	Once		

CT = computed tomography.

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

Procedure	Year 1	Year 2	Year 3	Year 4-5
Physical examination	3 times	3 times	Once/yr.	Once/yr.
Tumour markers	3 times	3 times	Once/yr.	Once/yr.
Chest X-ray	Twice	Twice		
Abdominopelvic CT scan	Twice	Twice		

CT = computed tomography.

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

Procedure	Year 1	Year 2	Year 3-5	thereafter
Physical examination	4 times	4 times	Twice/yr.	Once/yr.
Tumour markers	4 times	4 times	Twice/yr.	Once/yr.
Chest X-ray	4 times	4 times	Twice/yr.	Once/yr.
Abdominopelvic CT scan*†	Twice	Twice	As indicated	As indicated
Chest CT scan†‡	As indicated	As indicated	As indicated	As indicated
Brain CT scan§	As indicated	As indicated	As indicated	As indicated

* Abdominal CT scanning 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 scan should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET scanning can be performed.

‡ A chest CT scan is indicated if abnormality is detected on chest X-ray and after pulmonary resection.

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

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