EAU 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. Nowadays, testicular tumours show excellent cure rates, mainly due to early diagnosis and their extreme chemo- and radiosensitivity.

Staging and Classification

Staging

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 their 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.

A chest computed tomography (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.

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

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

Staging system

The Tumour, Node, Metastasis (TNM 2009) staging system is endorsed (Table 1).

Table 1: TNM classification for testicular cancer	
pT	**Primary tumour[1]**
pTX	Primary tumour cannot be assessed (see note 1)
pT0	No evidence of primary tumour (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade unica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N	**Regional lymph nodes clinical**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pn	Pathological		
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M	**Distant metastasis**		
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis M1a Non-regional lymph node(s) or lung M1b Other sites		
S	**Serum tumour markers**		
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	S1 < 1.5 x N and	< 5,000 and	< 1,000
S2	S2 1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	S3 > 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay.

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

[1]Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

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 2).

Table 2: 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 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN

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

** Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day). PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.*

Diagnostic evaluation

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 < 40 years).

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 (TIN/IGCNU) in non-tumour parenchyma.

4. pT category according to the TNM 2009.
5. Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

Diagnosis and treatment of testicular intraepithelial neoplasia (TIN)

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

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

AFP = alpha-fetoprotein; GR = grade of recommendation; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; TIN = testicular intraepithelial neoplasia; US = ultrasound.

Prognosis

Risk factors for occult metastatic disease in stage I testicular cancer		
Pathological (for stage I)	**For seminoma**	**For non-seminoma**
Histopathological type	• Tumour size (> 4 cm) • Invasion of the rete testis	• Vascular/lymphatic or peri-tumoural invasion • Proliferation rate > 70% • Percentage of embryonal carcinoma > 50%

Disease management

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

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

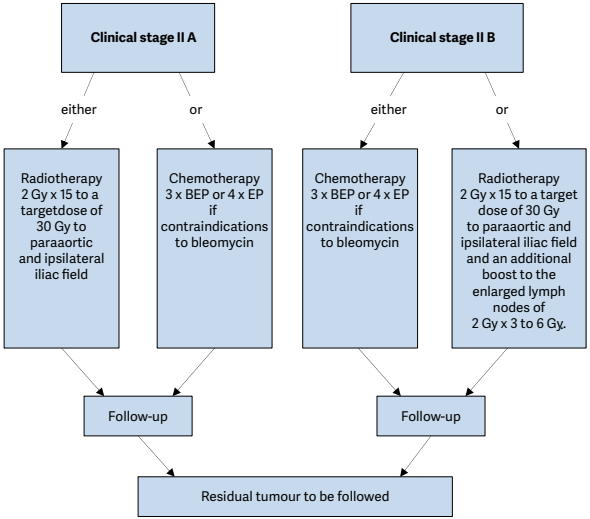
Guidelines for the treatment of stage I NSGCT	LE	GR
Inform patients with stage 1 NSGCT about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and RPLND) including treatment-specific recurrence rates as well as acute and long-term side effects.	2a	A*
In patients with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

** Upgraded following panel consensus.*
BEP = cisplatin, eposide, bleomycin; RPLND = retroperitoneal lymph node dissection; IGCCCG = International Germ Cell Cancer Collaborative Group.

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

** Upgraded following panel consensus.*
BEP = cisplatin, eposide, bleomycin; RPLND = retroperitoneal lymph node dissection.

Figure 1: Treatment options in patients with seminoma clinical stage IIA and B



Guidelines for the treatment of metastatic germ cell tumours	LE	GR
Treat low volume NSGCT stage IIA/B with elevated markers like 'good or intermediate prognosis' advanced NSGCT, with three or four cycles of BEP.	2	A
In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either RPLND or biopsy. If not possible, repeat staging after 6 weeks of surveillance before making a final decision on further treatment.	3	B

In metastatic NSGCT (≥ stage IIC) with good prognosis, treat with three courses of BEP.	1	A
In metastatic NSGCT with an intermediate prognosis, treat with four courses of standard BEP.	1	A
In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, followed by tumour marker assessment after 3 weeks: in the case of an unfavourable decline, initiate chemotherapy intensification; in the case of a favourable decline, continue BEP up to a total of four cycles.	1	A
Perform surgical resection of residual masses after chemotherapy in NSGCT in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.	2	A
Treat seminoma CSII A/B initially with radiotherapy. When necessary, use chemotherapy as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.	2	B
In seminoma stage CS IIA/B, offer chemotherapy (3 x BEP or 4 x EP, in good prognosis) as an alternative to radiotherapy.	1	A
Treat seminoma stage IIC and higher with primary chemotherapy according to the same principles used for NSGCT.	1	A

EP = etoposide, cisplatin; NSGCT = non-seminomatous germ cell tumour; BEP = cisplatin, etoposide, 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/

PRM- 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

The aim of 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 (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 3: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma

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

CT = computed tomography.

Table 4: Recommended minimum follow-up schedule after RPLND or adjuvant chemotherapy: stage I non-seminoma

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

CT = computed tomography.

Table 5: Recommended minimum follow-up schedule for post-orchidectomy surveillance, radiotherapy or chemotherapy: stage I seminoma

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

CT = computed tomography.

Table 6: Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

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

CT = computed tomography.

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

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

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

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

Quality of life and long-term toxicities after cure

Patients diagnosed with TC are usually between 18 and 40 years at diagnosis and life expectancy after cure extends over several decades. Before any treatment is planned, patients should be informed of common long-term toxicities.

Testicular stromal tumours

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

Leydig cell tumours

Approximately 10% of Leydig tumours 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 US 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. In patients with symptoms of gynaecomastia or hormonal disorders or typical imaging on US, until final histology is available, a partial orchiectomy (+ frozen section) should be considered. In the case of histological signs of malignancy, orchiectomy and RPLND are the treatment of choice.

Sertoli cell tumours

Sertoli cell tumours 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 US

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 the case of histological signs of malignancy, orchiectomy and RPLND are the treatment of choice.

Conclusions

Most testis tumours are diagnosed at an early stage. Staging is the cornerstone. 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.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-98-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org.