GUIDELINES ON TESTICULAR CANCER

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P. Albers (Chair), W. Albrecht, F. Algaba, C. Bokemeyer, G. Cohn-Cedermark, K. Fizazi, A. Horwich, M.P. Laguna, N. Nicolai, J. Oldenburg

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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 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.

Recommended tests for staging at diagnosis		
Test	**Recommendation**	**GR**
Serum tumour markers hCG LDH	Alpha-fetoprotein	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
Sperm banking	should be offered.	A

GR = grade of recommendation; CT = computed tomography; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; LH = luteinising hormone; MRI = magnetic resonance imaging.

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
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 (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

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)	*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)	*All 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	

**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 intratubular germinal neoplasia (TIN) in non-tumoural parenchyma intratubular germ cell neoplasia.

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
Testicular US is a mandatory assessment	A
Biopsy of the contralateral testis can be offered (and its consequences discussed) to patients at high risk for contralateral TIN.	A
Orchiectomy and pathological examination of the testis are necessary to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, chemotherapy must be started before orchiectomy.	A
Serum determination of tumour markers (AFP, hCG, and LDH) must be performed, both before and 5-7 days after, orchiectomy, for staging and prognostic reasons.	A
The state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera must be assessed 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 testicular cancer Seminoma stage I	GR
Surveillance is a recommended management option (if facilities available and patient compliant).	A*
Carboplatin-based chemotherapy (one course at AUC 7) is recommended.	B
Adjuvant treatment is not recommended for patients at very low risk.	A
Radiotherapy is not recommended as adjuvant treatment.	A

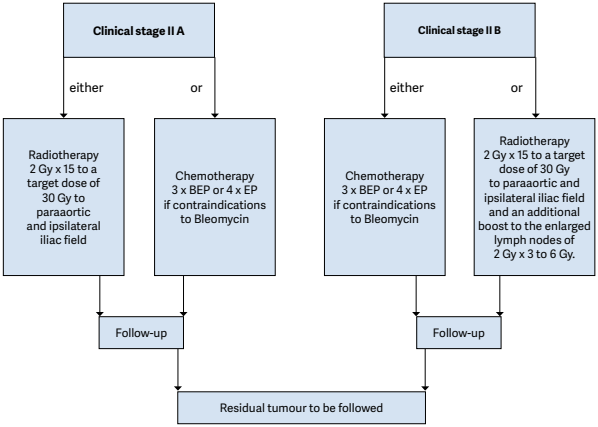
**Upgraded following panel consensus.*
GR = grade of recommendation.

Guidelines for the treatment of NSGCT stage I	LE	GR
NSGCT clinical stage 1 (CS 1)		
Patients with CS 1 NSGCT should be informed 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*
Surveillance or risk-adapted treatment based on vascular invasion (see below) are recommended treatment options.	2a	A*
If patients are not willing to undergo a surveillance strategy, one course of BEP as adjuvant treatment has been proven to be superior to RPLND in terms of recurrence rate in a community based study.	1b	A*
Salvage treatment of patients with recurrence during surveillance consists of three or four courses of BEP chemotherapy according to the IGCCCG classification, followed by post-chemotherapy retroperitoneal lymph node dissection, if necessary.	2a	A
Risk-adapted treatments for CS1 based on vascular invasion		
CS1A (pT1, no vascular invasion): low risk		
Surveillance is recommended if the patient is willing and able to comply.	2a	A
In low-risk patients not willing (or suitable) to undergo surveillance, adjuvant chemotherapy with one course of BEP is recommended.	2a	A*

CS1B (pT2-pT4): high risk		
Primary chemotherapy with one course of BEP is recommended. Patients should be informed about the advantages and disadvantages of two courses of BEP.	2a	A*
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, as well as observation, should be discussed with each patient.		A*

**Upgraded following panel consensus.*
BEP = cisplatin, eposide, bleomycin; GR = grade of recommendation; LE = level of evidence; 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
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 BEP.	2	A
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.	3	B
In metastatic NSGCT (> stage IIC) with a good prognosis, three courses of BEP is the primary treatment of choice.	1	A

In metastatic NSGCT with an intermediate prognosis, the primary treatment of choice is four courses of standard BEP.	1	A
In metastatic NSGCT with a poor prognosis, the primary treatment of choice is one cycle of BEP, followed by tumour marker assessment after 3 weeks. • In case of an unfavourable decline, chemotherapy intensification should be initiated. • In case of a favourable decline, BEP should be continued up to a total of four cycles.	1	A
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.	2	A
Seminoma CSII A/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.	2	B
In seminoma stage CS IIA/B, chemotherapy (3 x BEP or 4 x EP, in good prognosis) is an alternative to radiotherapy. It appears that 3 x BEP or 4 x EP achieve a similar level of disease control.	3	B
Seminoma stage IIC and higher should be treated with primary chemotherapy according to the same principles used for NSGCT.	1	A

EP = eposide, cisplatin; GR = grade of recommendation; LE = level of evidence; NSGCT = non-seminomatous germ cell tumour; BEP = 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

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	
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 978-90-79754-80-9), available to all members of the European Association of Urology at their website, http://www.uroweb.org.