EAU GUIDELINES ON TESTICULAR CANCER

(Limited text update March 2018)

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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

Postorchiectomy half-life kinetics of serum tumour markers

For an accurate staging the following steps are necessary (see Table 1):

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.

Table 1: Recommended tests for staging at diagnosis

Tests	Recommendations	Strength rating
Serum tumour markers	- Alpha-fetoprotein - human chorionic gonadotrophin (hCG) - Lactate dehydrogenase	Strong
Abdominopelvic computed tomography (CT)	All patients	Strong
Chest CT	All patients	Strong
Testis ultrasound (bilateral)	All patients	Strong
Bone scan or magnetic resonance imaging (MRI) columna	In case of symptoms	Strong
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases and/ or high beta-hCG values.	Strong
Further investigations		
Fertility investigations: • total testosterone • luteinising hormone • follicle-stimulating hormone • semen analysis		Weak
Discuss sperm banking with all men prior to starting treatment for testicular cancer.		Strong

Staging system

The Tumour, Node, Metastasis (TNM 2017) staging system is endorsed (Table 2).

Table 2: 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 (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 lbuginea 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 and 5 or fewer positive 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 more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour

N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Pn - Regional Lymph Nodes - 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 metastasis	
	M1b	Distant metastasis other than non-regional lymph nodes and lung	
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	< 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

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 3).

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/retro-peritoneal 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%	*Any of the following criteria:* • Testis/retro-peritoneal 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 five to seven 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 the epididymis, spermatic cord, and tunica vaginalis;

2. sampling: a 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;
3. at least one proximal and one distal section of spermatic cord plus any suspected area;
4. microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2004;
5. presence or absence of peri-tumoural venous and/or lymphatic invasion;
6. presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion; presence or absence of germ cell neoplasia *in situ* (GCNIS) in non-tumour parenchyma;
7. pT category according to TNM 2016;
8. immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

Diagnosis and treatment of testicular intraepithelial neoplasia

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.

Recommendations for the diagnosis and staging of testicular cancer	Strength rating
Perform testicular ultrasound in all patients with suspicion of testicular cancer.	Strong
Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralateral germ cell neoplasia *in situ*.	Strong
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.	Strong
Perform serum determination of tumour markers (alpha-fetoprotein, human chorionic gonadotrophin, and lactate dehydrogenase), both before, and five to seven days after orchiectomy, for staging and prognostic reasons.	Strong
Assess the state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera in testicular cancer.	Strong
Advise patients with a familiar history of testis cancer, as well as their family members, to perform regular testicular self-examination.	Strong

Prognosis

Risk factors for occult metastatic disease in stage I testicular cancer		
	For seminoma	**For non-seminoma**
Pathological (for stage I)		
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

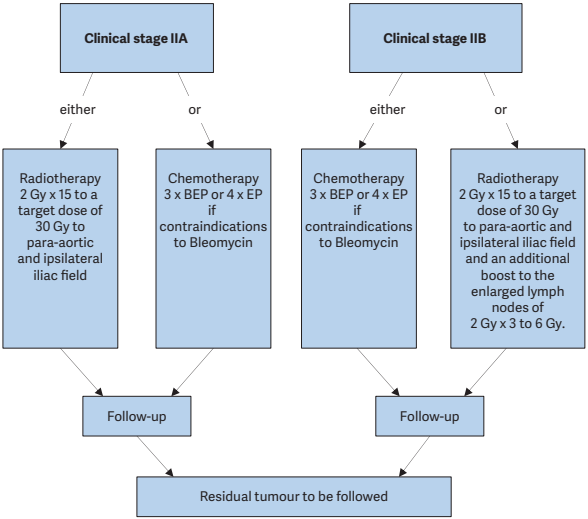
Recommendations for the treatment of stage I seminoma	Strength rating
Fully inform the patient about all available management options, including surveillance or adjuvant chemotherapy after orchiectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance as a management option if facilities are available and the patient is compliant.	Strong
Offer one course at area under curve (AUC) 7, if carboplatin chemotherapy is considered.	Strong
Do not perform adjuvant treatment in patients at very low risk (no risk factors).	Strong

Do not perform radiotherapy as adjuvant treatment.	Strong

Recommendations for the treatment of stage 1 non-seminomatous germ cell tumour	**Strength rating**
Inform patients with stage 1 non-seminomatous germ cell tumour (NSGCT) about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection [RPLND]) including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
In patients with stage 1 NSGCT, offer surveillance or risk-adapted treatment based on vascular invasion (see below).	Strong
If patients are not willing to undergo surveillance, offer one course of cisplatin, etoposide, bleomycin (BEP) as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	Strong
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 International Germ Cell Cancer Collaborative Group classification, followed by post-chemotherapy RPLND, if necessary.	Strong

Recommendations for risk-adapted treatment for clinical stage 1 based on vascular invasion	Strength rating
Stage IA (pT1, no vascular invasion): low risk	
Offer surveillance if the patient is willing and able to comply.	Strong
In low-risk patients not willing (or unsuitable) to undergo surveillance, offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP).	Strong
Stage IB (pT2-pT4): high risk	
Offer primary chemotherapy with one course of BEP, or surveillance.	Strong
Inform patients having adjuvant chemotherapy about the advantages and disadvantages of one vs. two cycles of BEP.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong
Offer nerve-sparing retroperitoneal lymph node dissection to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong

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



BEP = cisplatin, etoposide, bleomycin; EP = etoposide and cisplatin.

Recommendations for the treatment of metastatic germ cell tumours	Strength rating
Treat low volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like 'good- or intermediate-prognosis' advanced NSGCT, with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong

In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either retroperitoneal lymph node dissection (RPLND) or biopsy. If not possible, repeat staging after six weeks of surveillance before making a final decision on further treatment.	Strong
In metastatic NSGCT with an intermediate prognosis, treat with four courses of standard BEP.	Strong
In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, or cisplatin, etoposide and ifosfamide (PEI) in case of poor lung function, followed by tumour marker assessment after three weeks. In case of a favourable marker decline, continue BEP (or PEI) up to a total of four cycles. In case of an unfavourable decline, initiate chemotherapy intensification.	Strong
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.	Strong
In CS IIA seminoma, offer radiotherapy or chemotherapy and inform the patient of possible undesirable long-term side effects of both management options.	Strong
Initially offer chemotherapy in seminoma stage CS IIB (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	Strong

Treat seminoma stage IIC and higher, with primary chemotherapy according to the same principles used for NSGCT.	Strong

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) four 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 primary aim of follow-up in the first five years is the timely diagnosis of recurrent disease in order to be able to treat the patient with curative intent with the least aggressive therapy.

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 4: Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography/ magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

Table 5: Recommended minimal follow-up for non-seminoma stage I on active surveillance

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times**	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic computed tomography/magnetic resonance imaging	2 times	At 24 months ***	Once at 36 months*	Once at 60 months*	

**Recommended by 50% of the consensus group members.*

***In case of high risk (LVI+) a minority of the consensus group members recommended six times.*

****In case of high risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.*

Table 6: Recommended minimal follow up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography/ magnetic resonance imaging	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	*	*	*	*	

**Same time points as abdomino-pelvic CT/MRI in case of pulmonary metastases at diagnosis.*

***In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.*

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.

During follow-up, patients should be screened and treated for known risk factors such as high blood pressure, hyperlipidaemia and testosterone deficiency. When follow up by the clinical expert is discontinued, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up might be helpful.

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.

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 (978-94-92671-01-1), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.