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. Nevertheless, testis cancer is the most common cancer affecting young men in their third and fourth decades of life.

A steady increase in incidence has been seen over the past decades. 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, pathological and clinical risk factors are well established. Nowadays testicular tumours show excellent cure rates with the standard treatments available, mainly due to their extreme chemo- and radiosensitivity.

Table 1: Prognostic risk factors for testicular cancer

Pathological (for stage I)

- Histopathological type
- For seminoma
  Tumour size (> 4 cm)
  Invasion of the rete testis
- For non-seminoma
  Vascular/lymphatic invasion or peri-tumoural invasion

Percentage embryonal carcinoma > 50%
Proliferation rate (MIB-1) > 70%

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) mixed 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 stromal tumours**
   - Leydig cell tumour
   - Sertoli cell tumour (typical, sclerozing, large cell calcifying)
   - Granulosa (adult and juvenile)
   - Mixed
   - Unclassified
3. **Mixed germ cell/sex cord stromal tumours**

Diagnosis of Testicular Cancer

The diagnostis of testicular cancer is based on:
Clinical examination of the testis and general examination to rule out enlarged nodes or abdominal masses.
Imaging of the testis if necessary to confirm testicular mass and always in a young man with a retroperitoneal mass.
Serum tumour markers before orchiectomy (AFP, hCG and LDH).
Inguinal exploration and orchiectomy and 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

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 an 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 abdominal and mediastinal nodes and viscera (CT scan) and *supraclavicular nodes* (physical examination)
Other examinations such as brain or spinal CT, bone scan or liver ultrasound should be performed if metastases are suspected. Patients diagnosed with testicular seminoma who have a positive abdominal CT scan are recommended to have a chest CT scan. A chest CT scan should be routinely performed in patients diagnosed with non-seminomatous germ cell tumours (NSGCT) because in 10% of cases small subpleural nodes are 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		
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

[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%	All of the following criteria: Testis/retroperitoneal primary No non-pulmonary visceral

5-year survival 80%	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) A physical examination may be sufficient to diagnose testicular cancer (grade B recommendation).
(2) A testis ultrasound is necessary 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 B recommendation).
(3) A pathological examination of the testis is necessary to determine the diagnosis and local extension (pT category) (grade B recommendation).
(4) Serum determination of the tumour markers AFP, hCG and LDH must be performed before and after surgery for staging and prognostic purposes (grade B recommendation).
(5) Retroperitoneal, mediastinal and supraclavicular nodes and the visceral state have to be assessed in testicular cancer; in testicular seminoma, a chest CT scan is not necessary if the abdominal nodes are negative (grade B recommendation).

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, tumour size and macroscopic features of the epididymis, spermatic cord and tunica vaginalis.
(2) Sampling: a 1 cm^2 section for every centimetre of maximal tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis 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: AFP and hCG in seminoma and mixed germ cell tumours.

Table 5: Guidelines for the treatment of testicular cancer

Stage I Seminoma

(1) Prophylactic radiotherapy to a para-aortic field with a total dose of 20 Gy (grade A recommendation).

(2) Surveillance if facilities are available and patient willing and able to comply with a surveillance policy (grade B recommendation).

(3) Carboplatin-based chemotherapy (one course, AUC 7) is an alternative to radiotherapy (grade A recommendation).

Stage I NSGCT

Clinical stage IA (pT1, no vascular invasion). Low risk

(1) If the patient is able and willing to comply with a surveillance policy and long-term (at least 5 years) close follow-up is feasible, surveillance is recommended. In patients not willing to undergo surveillance or

if a surveillance strategy is not feasible, nerve-sparing RPLND or primary chemotherapy are equally effective (grade B recommendation).

(2) If RPLND reveals PN+ (lymph node disease), adjuvant chemotherapy with two courses of BEP should be considered (grade A recommendation).

Clinical stage IB (pT2-pT4, vascular invasion). High risk.
Active treatment is recommended:

(1) Primary adjuvant chemotherapy with two courses of BEP is recommended (grade B recommendation).

(2) If the patient is not willing to undergo chemotherapy or if chemotherapy is not feasible, nerve-sparing RPLND or surveillance with treatment at relapse (in about 50% of patients) are alternative options.

Metastatic germ cell tumours

(1) Standard treatment of low-volume stage IIA seminoma is radiotherapy with 30 Gy in an ipsilaterally extended field compared to stage I ("hockey stick"); and 36 Gy for stage IIB. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding IGCCCG prognostic groups for NSGCT (grade A recommendation).

(2) High-volume stage IIC seminoma is treated as "good prognosis" metastatic tumour with three cycles of BEP. Residual tumour resection is usally not necessary in these patients (grade A recommendation).

(3) Low-volume stage II NSGCT with elevated tumour markers should be treated as metastatic tumours (three cycles of BEP). Only low-volume stage II NSGCT with-

out marker elevation should undergo surveillance or nerve-sparing RPLND first in order to avoid chemotherapy in patients with pure teratoma. In terms of long-term recurrence-free survival, patients with low-volume stage II NSGCT can be treated either by RPLND (eventually followed by two cycles of chemotherapy) or by primary chemotherapy (grade A recommendation).

(4) Three courses of BEP chemotherapy is the primary treatment of choice for patients with good-prognosis metastatic NSGCT (grade A recommendation).

(5) Four courses of BEP chemotherapy is the primary treatment of choice for patients with intermediate- and poor-prognosis metastatic NSGCT (grade A recommendation).

(6) Surgical resection of residual masses after chemotherapy in NSGCT is indicated in cases of a residual mass > 1 cm and when tumour marker levels are normal or normalizing (grade B recommendation).

Follow-up of Patients with Testicular Cancer

Regular follow-up is vital for patients with testicular cancer, and they should be watched closely for several years. Follow-up schedules depend on the histology, stage and post-orchiectomy treatment option chosen. The aim is to detect relapse as early as possible, to avoid unnecessary treatment and to detect asynchronous tumour in the contralateral testis.

Table 6: Recommended follow-up for stage I seminoma after radiotherapy or chemotherapy

Procedure	Year 1	Year 2
Physical examination	6 times	4 times
Chest X-ray	6 times	4 times
Tumour markers	6 times	4 times
Abdominal CT scan	once	once
Abdominal ultrasound	once[a]	once[a]

[a] *Alternating with abdominal CT scan.*

Table 7: Recommended follow-up for stage I seminoma on surveillance

Procedure	Year 1	Year 2
Physical examination	6 times	4 times
Tumour markers	6 times	4 times
Chest X-ray	6 times	4 times
Abdominal CT scan	4 times	4 times
Abdominal ultrasound	NN	NN

NN = Not necessary.

[a] *Alternating with abdominal CT scan.*

Year 3	Year 4-5
3 times	twice/year
3 times	twice/year
3 times	twice/year
if indicated	if indicated
once	if indicated

Year 3	Year 4-5	Year 6-10
3 times	twice/year	once/year
3 times	twice/year	once/year
3 times	twice/year	once/year
twice	once/year	if indicated
twice[a]	once/year[a]	if indicated

Table 8: Recommended follow-up for patients with stage I NSGCT on surveillance

Procedure	Year 1	Year 2
Physical examination	12 times	4-6 times
Tumour markers	9-12 times[a]	4-6 times
Chest X-ray	9-12 times[a]	4-6 times
Abdominal CT scan	3-4 times	twice

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

Table 9: Recommended follow-up for stage I NSGCT after RPLND or adjuvant chemotherapy

Procedure	Year 1	Year 2
Physical examination	6 times	3 times
Tumour markers	6 times	3 times
Chest X-ray	6 times	3 times
Abdominal CT scan	twice	once
Abdominal ultrasound	twice[b]	twice[b]

[a] *Due to a risk of late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy.*

[b] *Alternating with abdominal CT scan.*

Year 3-5	Year 6-10
twice/year	once/year
twice/year	once/year
twice/year	once/year
once/year	if indicated

Year 3-5	Year 6-10
twice/ year	once/year
twice/year	once/year
twice/year	once/year
if indicated[a]	if indicated
twice/year	once/year

Table 10: Recommended follow-up for stage IIa-IIb seminoma after radiotherapy

Procedure	Year 1	Year 2
Physical examination	6 times	4 times
Tumour markers	6 times	4 times
Chest X-ray	6 times	4 times
CT abdomen and pelvis[a]	if indicated	if indicated
CT chest[b]	if indicated	if indicated

[a] *Baseline CT of the abdomen/pelvis after treatment and repeated only if indicated.*

[b] *Only if there is an abnormal chest X-ray or if clinical symptoms indicate.*

Table 11: Recommended follow-up stage IIa-IIb NSCGCT after RPLND plus chemotherapy or primary chemotherapy

Procedure	Year 1	Year 2
Physical examination	bimonthly	4 times
Tumour markers	bimonthly	4 times
Chest X-ray	bimonthly	4 times
Abdominal CT[a, b]	baseline, then as indicated	as indicated
Abdominal ultrasound	twice	twice

Patients treated with RPLND followed by surveillance can follow this schedule, but the tests should be performed more frequently: monthly during the 1st year, bimonthly during the 2nd year, every 3 months during the 3rd year, every 4 months during the 4th year, twice in the 5th year and annually thereafter.

Year 3	Year 4	Year 5	Thereafter
3 times	twice	twice	once/year
3 times	twice	twice	once/year
3 times	twice	twice	once/year
if indicated	if indicated	if indicated	if indicated
if indicated	if indicated	if indicated	if indicated

Year 3	Year 4	Year 5	Thereafter
twice	twice	twice	once/year
twice	twice	twice	once/year
twice	twice	twice	once/year
if indicated	if indicated	if indicated	if indicated
if indicated	if indicated	if indicated	if indicated

[a] *After RPLND, a baseline CT scan of the abdomen and pelvis should be obtained and repeated if clinically indicated thereafter.*

[b] *After primary chemotherapy, the retroperitoneum has to be monitored by means of CT at least twice during the first 2 years.*

Table 12: Recommended follow-up for advanced seminoma and NSGCT

Procedure	Year 1	Year 2
Physical examination	monthly	bimonthly
Tumour markers	monthly	bimonthly
Chest X-ray	monthly	bimonthly
Abdominal CT[ab]	as indicated	as indicated
Chest CT[bc]	as indicated	as indicated
Brain CT[d]	as indicated	as indicated

[a] *Abdominal CT scanning has to be performed at least annually if teratoma is found in the retroperitoneum.*

[b] *If the post-chemotherapy evaluation 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.*

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 are tailored to initial staging and treatment.

Year 3	Year 4	Year 5	Thereafter
4 times	3 times	twice	once/year
4 times	3 times	twice	once/year
4 times	3 times	twice	once/year
as indicated	as indicated	as indicated	as indicated
as indicated	as indicated	as indicated	as indicated
as indicated	as indicated	as indicated	as indicated

[c] *A chest CT is indicated if abnormality is detected on chest X-ray and after pulmonary resection.*

[d] *In patients with headaches, focal neurological findings or any central nervous system symptom.*

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 90-70244-19-5), available to all members of the European Association of Urology at their website - http:// www.uroweb.org.