GUIDELINES ON TESTICULAR CANCER

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Introduction

Compared with other types of cancer testicular cancer is relatively rare accounting for about 1 - 1.5% of all cancers in men. Its incidence has been steadily growing during the last decades. Nevertheless, testis cancer is the most common cancer affecting young men in their third and fourth decades of life. The majority of these tumours are derived from germ cells (Seminoma and Non-Seminoma germ cell testicular cancer), and more than 50% 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 standard available treatments and mainly due to its extreme chemo- and radiosensitivity.

Table 1. Prognostic Risk factors for testicular cancer

Pathological (for stage I)

- Histopathological type
- For Seminoma
  - Tumor size (= or > 4 cm)
  - Invasion of the rete testis
- For Non-seminoma
  - Vascular/lymphatic in or peri-tumoral invasion

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) is shown below.

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 diagnostic of testis tumor 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 massa

Serum tumor markers before ochiectomy (AFP, β-hCG and LDH)

Inguinal exploration and orchiectomy with early ligation of the vessels and in bloc removal of testis and tunica albuginea. Organ sparing surgery can be attempted in special ocassions (bilateral tumor or solitary testes) in Centers of reference. Routine contralateral biopsy for diagnosis of carcinoma in situ should not been recommended systematically

Staging of Testicular Tumors

Postorchiectomy half life kinetics of serum tumor markers.

The persistence of elevated serum tumor markers 3 weeks after orchiectomy indicates the presence of disease while its normalization does not necessarily mean absence of tumor.

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 tumors (NSGCT) because in 10% of cases small subpleural nodes are presented 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 (see, T-Primary Tumour above)
- 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 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

[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) has devised 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)

Groups	Non-seminoma	Seminoma
Good prognosis	56% of cases	90% of cases
5-year progression-free survival	89%	82%
5-year survival	92%	86%
With all of	testis/retroperitoneal primary	any primary site
	no non-pulmonary visceral metastases	no non-pulmonary visceral metastases
	AFP <1,000 ng/ml	normal AFP
	hCG <5,000 mIU/l (1,000 ng/ml) and	any hCG
	LDH <1.5x upper limit of normal	any LDH
Intermediate prognosis	28% of cases	10% of cases
5-year progression-free survival	75%	67%
5-year survival	80%	72%
With all of	testis/retroperitoneal primary	any primary site
	no non-pulmonary visceral metastases	non-pulmonary visceral metastases
	AFP > 1,000 and <10,000 ng/ml or	normal AFP

	β-hCG > 5,000 and <50,000 mIU/l	any hCG
	LDH > 1.5 and <10x upper limit of normal	any LDH
Poor prognosis	16% of cases	no patients classified as poor prognosis
5-year progression-free survival	41%	
5-year survival	48%	
With all of	mediastal primary non-pulmonary visceral metastases AFP >10,000 ng/ml or hCG >50,000 mIU/l (10,000 ng/ml) or LDH >10x upper limit of normal	

PFS = progression-free survival; AFP = alpha-fetoprotein; β-hCG = beta-human chorionic gonadotrophin;
LDH = lactate dehydrogenase.

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, β-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 centimeter of maximal tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis selec-

tion 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, 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 β-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 or a hockey stick field to a total dose of 20-24 Gy *(Grade A recommendation)*

(2) Surveillance if available facilities and compliance *(Grade B recommendation)*

(3) Carboplatin-based chemotherapy only in the setting of clinical trials *(Grade B 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 equivalent to nerve-sparing RPLND *(Grade B recommendation)*

(2) If RPLND reveals PN+ (lymph node disease), adjuvant chemotherapy with two courses of PEB should be considered *(Grade A recommendation)*

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

(1) Nerve-sparing RPLND, which must be bilateral if PN+ (regional lymph node disease) is revealed peri-operatively (nerve-sparing on the opposite side). *(Grade A recommendation)*

(2) Primary chemotherapy with two courses of PEB; this option should only be considered in a clinical trial as further long-term results regarding the risk of retroperitoneal relapse are awaited *(Grade B recommendation)*

Metastatic germ cell tumours

(1) Low-volume stage II NSGCT can be treated either by RPLND (eventually followed by surveillance or by two cycles of chemotherapy) or by primary chemotherapy *(Grade A recommendation)*

(2) Three courses of PEB chemotherapy is the primary treatment of choice for patients with good prognosis metastatic NSGCT *(Grade A recommendation)*

(3) Four courses of PEB chemotherapy is the primary treatment of choice for patients with intermediate- and poor-prognosis metastatic NSGCT *(Grade A recommendation)*

(4) Surgical resection of residual masses after chemotherapy in NSGCT is indicated in case of diameter > 1 cm and when tumour marker levels are normal or normalizing *(Grade B recommendation)*

(5) Metastatic seminoma with less than N3M1 disease can be treated first with radiotherapy; when necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic factor groups of NSGCT *(Grade A recommendation)*

(6) Advanced seminoma (N3 or M1) should be treated with primary chemotherapy according to the same principles used for NSGCT *(Grade A 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 tumor in the contralateral testis.

Table 6. Recommended follow-up for stage I seminoma after Radiotherapy or Chemotherapy

Procedure	Year	
	1	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	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.*

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

3	4-5	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	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	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.*

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

Procedure	Year	
	1	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.*

3-5	6-10
twice/year	once/year
twice/year	once/year
twice/year	once/year
once/year	If indicated

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

3	4	5	>5
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

Table 11. Recommended follow-up for stage IIa-IIb NSCGCTa after RPLND and chemotherapy or primary chemotherapy

Procedure	Year	
	1	2
Physical examination	bimonthly	4 times
Tumour markers	bimonthly	4 times
Chest X-ray	bimonthly	4 times
Abdominal CT[a, b, c]	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.

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

Procedure	Year	
	1	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.*

3	4	5	>5
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.*

3	4	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.*

Conclusions

Most of the testis tumors are derived from germ cells and diagnosed in early stages. 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 rate are going to depend on it. In metastasic disease a multidisciplinary therapeutic approach offers an acceptable survival. Follow-up schedules are tailored to initial staging and treatment.

This short booklet 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: www.uroweb.org.