COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Testicular Cancer

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Continue

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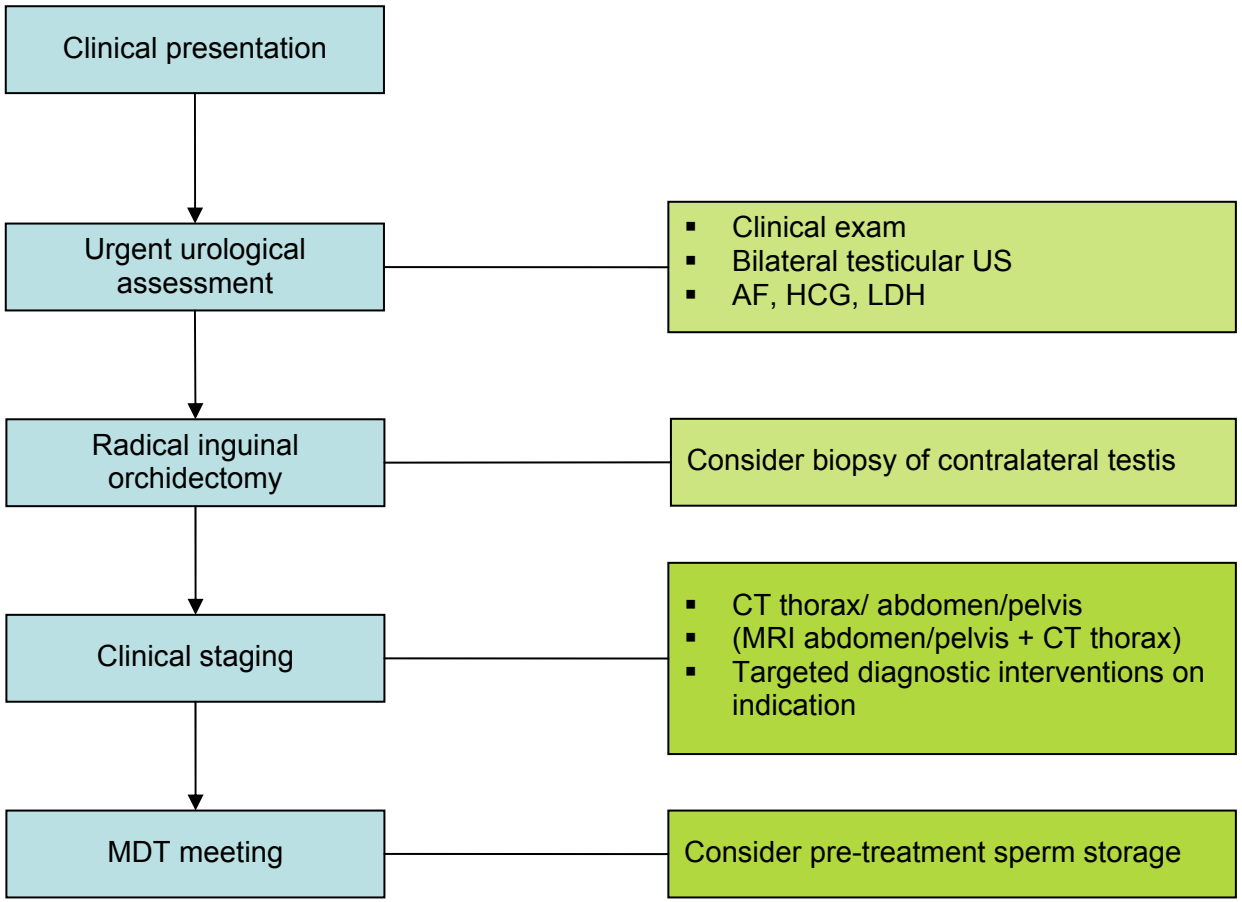
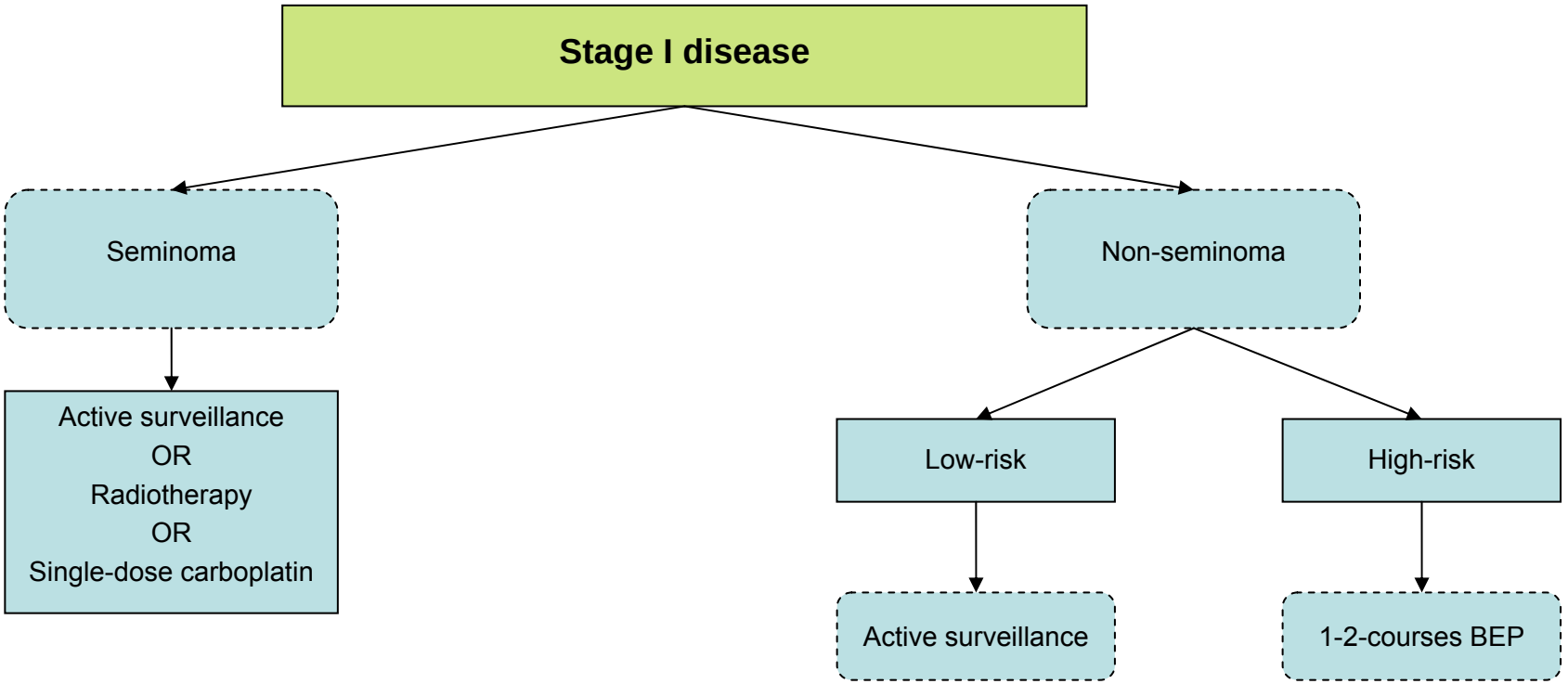
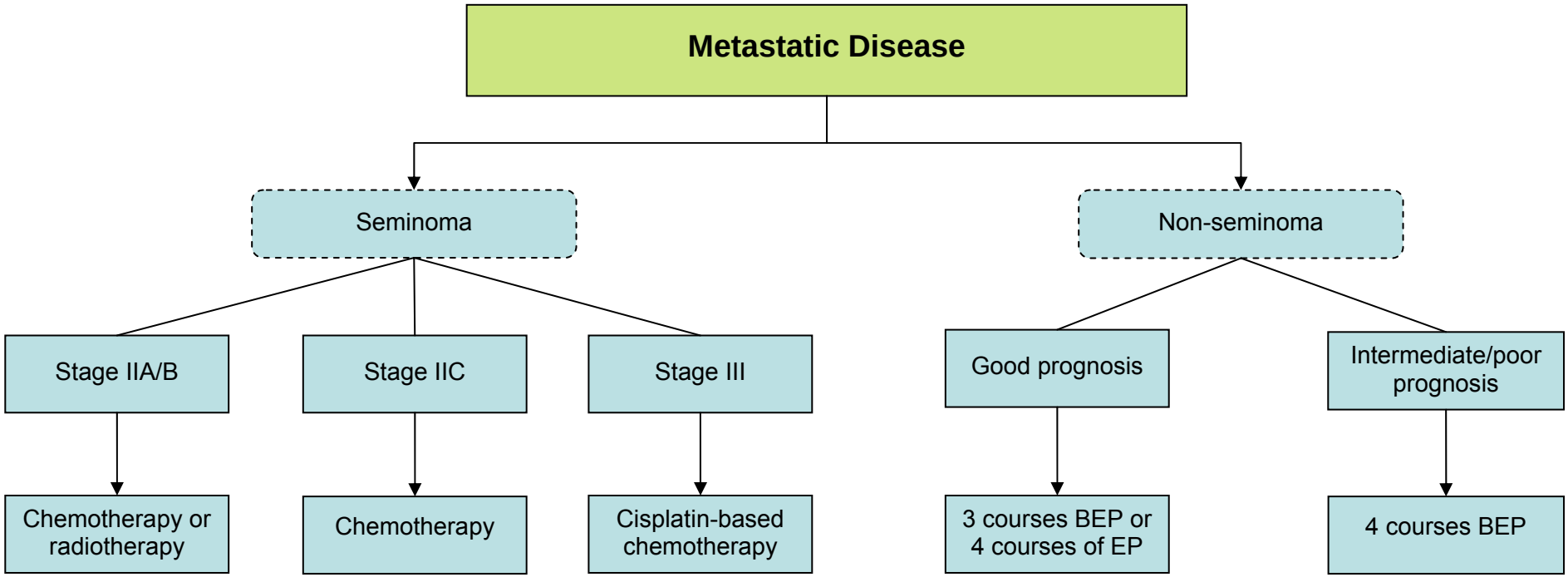
TESTICULAR CANCER

Table of contents







National Guidelines Testicular Cancer

INTRODUCTION

This document presents the updated clinical practice guidelines on testicular cancer which was first published in 2006 [1]. It covers a broad range of topics: diagnosis, staging, treatment, and follow-up. The guidelines primarily concern men presenting with testicular germ cell tumours and does not address primary extragonadal germ cell cancer or non-germ cell testicular cancers (e.g. Leydig cell tumours, lymphoma, sarcoma, metastatic disease). For more in-depth information and the scientific background, we would like to ask the readers to consult the full scientific report at www.kce.fgov.be.

The guidelines are developed by a panel of experts (see 'expert panel') comprising clinicians of different specialties and were reviewed by relevant professional associations (see 'external reviewers and validators').

SEARCH FOR EVIDENCE

Sources

The present guidelines were developed by adapting (inter)national clinical practice guidelines to the Belgian context using the ADAPTE methodology [2].

To identify published clinical practice guidelines on testicular cancer, OVID Medline, the National Guideline Clearinghouse and specific websites were searched. Both national and international clinical practice guidelines were searched. A language (English, Dutch, French) and date restriction (2000–2009) were used. Clinical practice guidelines without references were excluded, as were clinical practice guidelines without clear recommendations.

The search for peer-reviewed articles included a search in OVID Medline and the Cochrane Database of Systematic Reviews. The search was limited to articles published in English, French and Dutch. No date limit was set. For therapeutic questions, only systematic reviews and randomized controlled trials were included. For diagnostic questions, the search was limited to systematic reviews, randomized controlled trials and diagnostic accuracy studies. Finally, for prognostic questions, systematic reviews and cohort studies were included.

The methodological quality of the identified clinical practice guidelines was assessed using the AGREE instrument [3]. The quality of the systematic reviews, randomized controlled trials and prognostic studies was critically appraised using the checklists of the Dutch Cochrane Centre. The methodological quality of the diagnostic accuracy studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies checklist [4].

Grade of recommendation

A grade of recommendation was assigned to each recommendation using the GRADE system (appendix 1).

EXTERNAL REVIEW

The guidelines prepared by the expert panel were circulated to the relevant professional associations (see 'external reviewers'). Each association was asked to assign two key persons to discuss the recommendations during an open meeting. As a preparation of the meeting all invited experts were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the experts were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case an expert disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. All scores were then anonymized and summarized into a median score, minimum score, maximum score and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion. The recommendations were then discussed during a face-to-face meeting on September 14th 2010. Based on this discussion a final draft of the recommendations was prepared.

EPIDEMIOLOGY [5-10]

In Belgium, 269 new testicular cancers were diagnosed in 2006, with a crude incidence rate of 5.2/100 000 person years (source: Belgian Cancer Registry). Since 2003, the crude incidence rate slightly increased (4.7/100 000 person years), although it should be noted that the coverage of the cancer registration markedly improved since then. Testicular cancer typically is a cancer of young men, with a peak age-standardised incidence rate of 20.9/100 000 person years in the age category 25-30 years in 2006. In males aged 15-44 years, testicular cancer was the most frequent cancer in the period 2004-2005.
No published mortality or survival data specifically for testicular cancer are available for Belgium. However, in the period 2000-2001, the relative 5-year survival for testicular cancer was 95% in Flanders [2]. These data are in line with those reported in the literature for other countries and regions.

DEFINITIONS

Germ cell tumours are classified as seminomas and non-seminomas. Seminomas develop from the sperm-producing germ cells of the testicle. The 2 main subtypes of these tumours are classical (or typical) seminomas and spermatocytic seminomas. The latter is a rare type of seminoma that tends to occur in older men. Spermatocytic tumours tend to grow more slowly and are less likely to spread to other parts of the body than classical seminomas. Non-seminomas include multiple cell types, such as embryonal cell carcinoma, choriocarcinoma, yolk sac tumour and teratoma. Teratomas are considered to be either mature or immature, depending on whether adult-type differential cell types or partial somatic differentiation is found. When both elements of a seminoma and non-seminoma are present (including an increased alpha-fetoprotein, a serum tumour marker produced by non-seminomatous cells and not by seminomatous cells), management follows that for a non-seminoma, since this is the more clinically aggressive tumour.
Accepted histological precursors of testicular germ cell cancers include carcinoma in situ or intratubular germ cell neoplasia.

DIAGNOSIS [11-17]

- Patients with a clinical suspicion of testicular malignancy should undergo urgent urological assessment, including clinical exam and bilateral testicular ultrasonography ***(1C recommendation)***.

PRIMARY MANAGEMENT [18-22]

- Preoperative assessment of tumour markers (AFP, HCG, LDH) is recommended for postoperative management of patients with testicular cancer ***(expert opinion)***.
- In patients with a high suspicion of testicular malignancy after urological assessment, radical orchidectomy through inguinal approach is indicated ***(expert opinion)***.

CONTRALATERAL TESTIS [23-34]

- Patients with the highest risk of contralateral testicular carcinoma in situ are those with known infertility, an atrophic testis (i.e. < 12 ml) and a history of cryptorchidis. In these patients, a biopsy of the contralateral testis at the time of primary orchidectomy should be considered.

STAGING [11,18,35-43]

- Contrast-enhanced CT of the thorax, abdomen and pelvis is recommended in patients with confirmed testicular cancer for the detection of (nodal and extranodal) metastatic disease ***(2C recommendation)***.
- In patients with confirmed testicular cancer, magnetic resonance imaging is an alternative for the detection of abdominal metastatic disease if contrast-enhanced CT is contraindicated ***(expert opinion)***.
- The evidence supporting other staging techniques is too weak to recommend their routine use for the staging of testicular cancer ***(1C recommendation)***.
- In selected patients, targeted diagnostic interventions are indicated ***(expert opinion)***.
- Treatment options for patients with testicular cancer should be discusses at the multidisciplinary team meeting ***(expert opinion)***.

FERTILITY ISSUES [11,44]

- Pre-treatment sperm storage should be offered to men who may require chemotherapy or radiotherapy (expert opinion).

HISTOPATHOLOGICAL EXAMINATION [23,45-66]

Classification

- The recommended histological classification of testicular tumours is that of the World Health Organization (WHO) Classification of Tumours.

- The pathological staging of testicular tumours follows the International Union Against Cancer Classification (UICC) TNM classification (appendix 2).
- For metastatic germ cell tumours, the International Germ Cell Consensus Classification (IGCCC) prognostic grouping is now widely used (Table 1).

Table 1: IGCCC prognostic grouping

Non-seminoma	**Seminoma**
Good prognosis	
All of the following criteria: • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1000 ng/mL • HCG < 5000 IU/L (1000 ng/mL) • LDH < 1.5 x upper limit of normal	All of the following criteria: • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any HCG • Any LDH
Intermediate prognosis	
All of the following criteria: • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP ≥ 1000 and ≤ 10000 ng/mL or • HCG ≥ 5000 and ≤ 50000 IU/L or • LDH ≥ 1.5 and ≤ 10 x upper limit of normal	All of the following criteria: • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any HCG • Any LDH
Poor prognosis	
Any of the following criteria: • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10000 ng/mL or • HCG > 50000 IU/L (10000 ng/mL) or • LDH > 10 x upper limit of normal	No patients classified as poor prognosis

Macroscopic examination

- The macroscopic description of the surgical resection specimen should include the following items:
  - Radical orchidectomy vs. tumorectomy
  - Side of tumour
  - Testis size
  - Tumour size (3 measures) and description
  - Size (3 measures) and description of:
  - Epididymis
  - Spermatic cord
  - Tunica vaginalis (note the presence of intratunical fluid)
  - Albuginea
- A sample of the following structures needs to be taken:
  - Tumour: 1 cm^2 section for each cm of maximum tumour diameter;
  - Normal macroscopic testis tissue: scar area if present;
  - Albuginea nearby the tumour;
  - Epididymis;
  - Proximal and distal (surgical margin) sections of spermatic cord. The distal margin has to be cut prior to incision of the testis to avoid tumour cell contamination of the spermatic cord ***(expert opinion)***;
  - If any suspected area is found, extensive sampling has to be done.

Microscopic examination

- If the tumour is classified as a mixed type germ cell tumour, the pathologist has to estimate the amount of each component (as a percentage) ***(1C recommendation)***.

- The presence or absence of IGCN in non-tumoural parenchyma needs to be described.
- The pathological TNM Staging needs to be done with specific attention to:
  - Presence or absence of vascular and/or lymphatic invasion;
  - Presence or absence of invasion or extension through tunica albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion.

TREATMENT OF STAGE 1 DISEASE

Stage I seminoma [67-71]

- In patients with stage I seminoma post-orchidectomy, active surveillance can be considered as a management option ***(2B recommendation)***.
- In patients with stage I seminoma post-orchidectomy, radiotherapy can be considered as a management option ***(2B recommendation)***.
- In patients with stage I seminoma post-orchidectomy, single-dose carboplatin can be considered as a management option ***(2B recommendation)***.

Stage I non-seminoma [18,71-75]

- Primary surveillance is recommended for patients with stage I non-seminoma (without vascular or lymphatic invasion and without predominant embryonal component) post-orchidectomy, with treatment at relapse ***(2B recommendation)***.

TREATMENT OF METASTATIC DISEASE

Stage II and III seminoma [11,76-82]

- Patients with stage IIA or IIB seminoma should be treated with chemotherapy or radiotherapy ***(2C recommendation)***.
- In patients with stage IIC seminoma chemotherapy is the treatment of choice ***(2C recommendation)***.
- In patients with stage III seminoma cisplatin-based chemotherapy is recommended ***(1B recommendation)***.

Stage II, III en IV non-seminoma [18,76,83-99]

- Patients with good prognosis metastatic NSGCT should be treated with 3 cycles of first-line BEP chemotherapy or 4 cycles of first-line EP chemotherapy ***(1A recommendation)***.
- Patients with intermediate prognosis metastatic NSGCT should receive first-line BEP chemotherapy in 4 cycles ***(2A recommendation)***.
- Patients with poor prognosis metastatic NSGCT should be treated with first-line BEP chemotherapy in 4 cycles ***(2A recommendation)***.
- Patients with intermediate and poor prognosis metastatic NSGCT should be enrolled in clinical trials when available ***(expert opinion)***.

RESIDUAL DISEASE

Imaging [100-102]

- CE-CT scan is recommended for the imaging of residual masses after systemic treatment of testicular cancer ***(expert opinion)***.
- PET-scan is not routinely recommended for the evaluation of residual masses, but may be useful in metastatic seminoma ***(2C recommendation)***.

Treatment of residual residual NSGCT [103-107]

- In patients with NSGCT who have residual retroperitoneal masses after chemotherapy and whose markers have normalised, the residual masses should be removed ***(expert opinion)***.
- In patients with NSGCT and non-retroperitoneal masses after chemotherapy, metastatectomy is recommended if feasible ***(expert opinion)***.
- If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time as excision of the residual mass ***(expert opinion)***.

Treatment of residual SGCT [75,101,103,108,109]

- In patients with seminoma who have residual masses ≤ 3 cm, surveillance is recommended ***(expert opinion)***.
- In patients with seminoma previously treated with chemotherapy, and who have a residual mass > 3 cm and/or positive PET findings, radiotherapy can be considered ***(expert opinion)***.
- In patients with seminoma relapsing after first-line radiotherapy or whose tumour markers become positive, salvage chemotherapy is indicated ***(expert opinion)***.
- In patients with seminoma who have residual masses following chemotherapy or radiotherapy, extirpative surgery is not recommended ***(expert opinion)***.

FOLLOW UP

Primary surveillance post-orchidectomy [11,18,40, 110,111]

- In patients with stage I seminoma under primary surveillance, physical examination and blood serum marker tests (AFP, HCG, LDH) should be conducted every 3 months in the first and second years, and every six months in the third, fourth and fifth years ***(expert opinion)***.
- Although the evidence is insufficient to propose a standard scheme for CT follow-up in patients with stage I seminoma under primary surveilance, at least an abdomino-pelvic CT every 6 months during the 2 first years post-orchidectomy is desirable ***(expert opinion)***.
- In patients with stage I non-seminoma under primary surveillance, physical examination and blood serum marker tests (AFP, HCG, LDH) should be conducted every month in the first year, every two months in the second year, every three months in the third year, and every six months in the fourth and fifth years ***(expert opinion)***.
- Although the evidence is insufficient to propose a standard scheme for CT follow-up in patients with stage I non-seminoma under primary

surveilance, at least an abdomino-pelvic CT at 3 and 12 months is recommended ***(2B recommendation)***.

Follow-up after systemic treatment or radiotherapy [11]

- In patients treated with chemotherapy or radiotherapy post-orchidectomy or as primary treatment, physical examination and blood serum marker tests (AFP, HCG, LDH) should be conducted every 3 months in the first and second years, and every six months in the third, fourth and fifth years ***(expert opinion)***.
- There is insufficient evidence to define a standard scheme for CT follow-up in patients with advanced stage testicular germ cell cancer ***(expert opinion)***.

Follow-up of the contralateral testis [112]

- Ultrasonography of the contralateral testis can be considered during the follow-up of patients with testicular germ cell cancer ***(expert opinion)***.

Follow-up for late toxicity [11]

- For the present guideline, no specific systematic search was done addressing late toxicity after treatment for testicular cancer. Therefore, no separate recommendations were formulated addressing this issue.

TREATMENT OF RELAPSING OR REFRACTORY DISEASE [11,113-114]

- Patients with relapsing or refractory GCT should be enrolled in clinical trials when available ***(expert opinion)***.
- In patients with testicular GCT relapsing after cisplatin-based first-line chemotherapy, high-dose chemotherapy with autologous bone marrow support is not recommended outside a clinical trial ***(1A recommendation)***.

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Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

TNM classification for testicular cancer (UICC, 2009 Seventh Edition)

cT Primary Tumour	
	Except for 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.
cN Regional Lymph Nodes	
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 >2cm but <5cm in greatest dimension; or multiple lymph nodes, any one mass >2cm but <5cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
cM Distant Metastasis	
M0	No distant metastasis
M1a	Non-regional lymph node(s) or lungmetastasis
M1b	Distant metastasis other than non-regional lymph nodes and lung

pT Primary Tumour	
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
pN 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 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 >2cm but <5cm in greatest dimension; or >5 nodes positive, none >5cm; or evidence or extranodal extension of tumour
pN3	Metastasis with a lymph node mass >5 cm in greatest dimension
pM Distant Metastasis	
pM1	Distant metastasis microscopically confirmed
S Serum tumour markers	
SX	Serum marker studies not available
S0	Serum marker study levels within normal limits
S1	LDH <1.5 x N and betaHCG < 5000 mIU/ml and AFP < 1000 ng/ml
S2	LDH 1.5-10 x N or betaHCG 5000-50000 mIU/ml or AFP 1000-10000 ng/ml

TNM Stage grouping

Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M1a	S3
	Any pT/TX	Any N	M1b	S3

