COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Testicular Cancer

Version 1.2004

Continue

Testicular Cancer
Guidelines Development Group Members

Prof. dr. Alexandre Zlotta
Mount Sinai Hospital,
Toronto (Canada)

Dr. Margareta Haelterman
Federal public service
Health, food chain safety and environment

Prof. dr. Jacques De Grève
Universitair Ziekenhuis Brussel

Prof. dr. Dirk Ramaekers
Belgian Health Care Knowledge Centre

Prof. dr. Simon Van Belle
University Hospital Ghent

Dr. Guy Dargent
Belgian Health Care Knowledge Centre

The following institutions have participated in the elaboration or reviewing process of the guidelines:

- **College of Oncology**
- **Belgian Society of Medical Oncology (BSMO)**
- **Belgian Association of Urology (BAU) Working Group Oncology**
- **College of Medical Imaging**
- **Belgian Society for Radiotherapy-Oncology (BVRO-ABRO)**

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Reference: Peeters M, Zlotta A, Roucoux F, De Greve J, Van Belle S, Haelterman M, Ramaekers D, Dargent G. Nationale Richtlijnen van het College voor oncologie: A. algemeen kader oncologish kwaliteitshandboek. B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. Reports vol. 29A. Brussel: Federaal Kenniscentrum voor de gezondheidszorg (KCE) ; April 2006. KCERef. D/2006/10.273/12.

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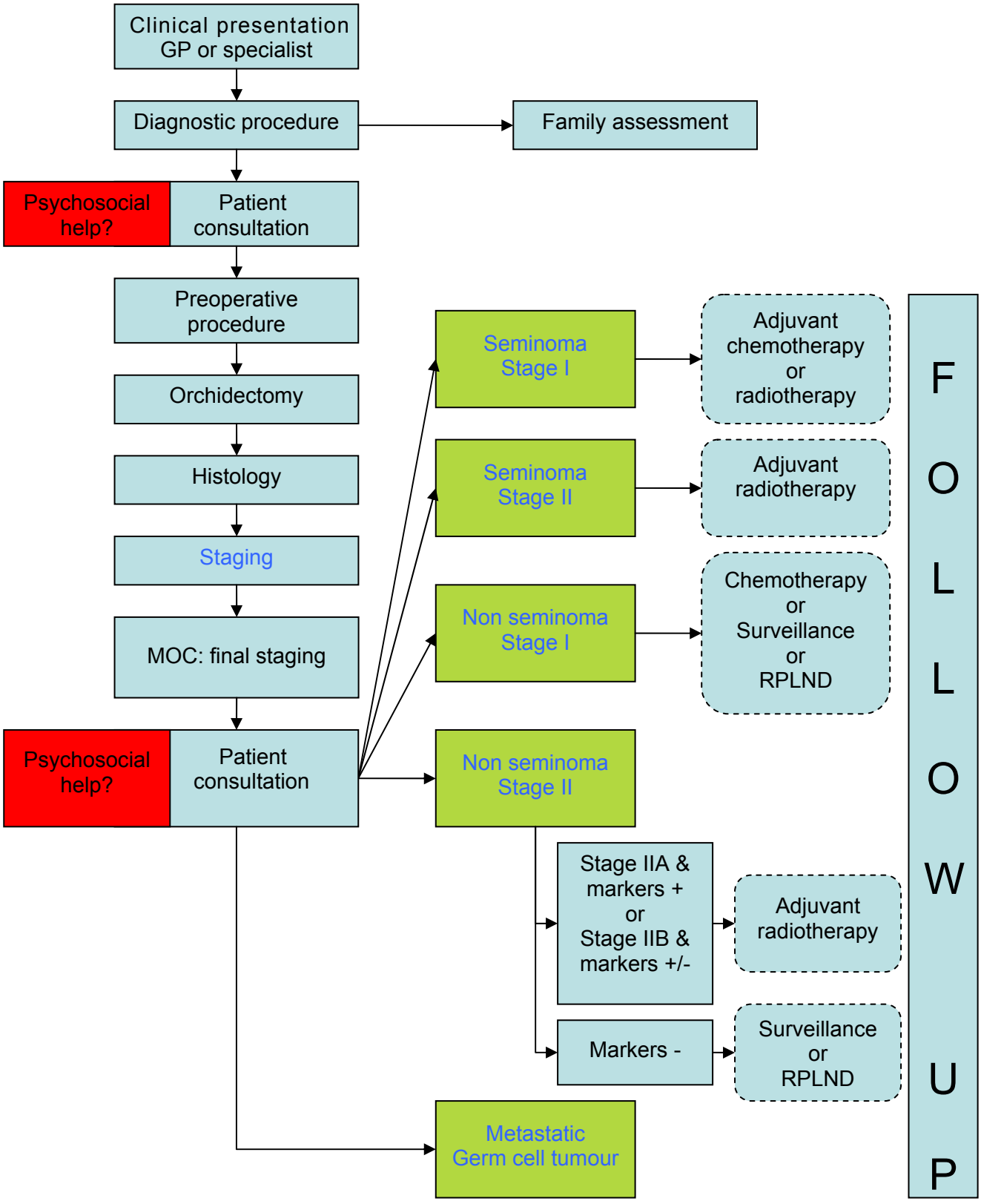
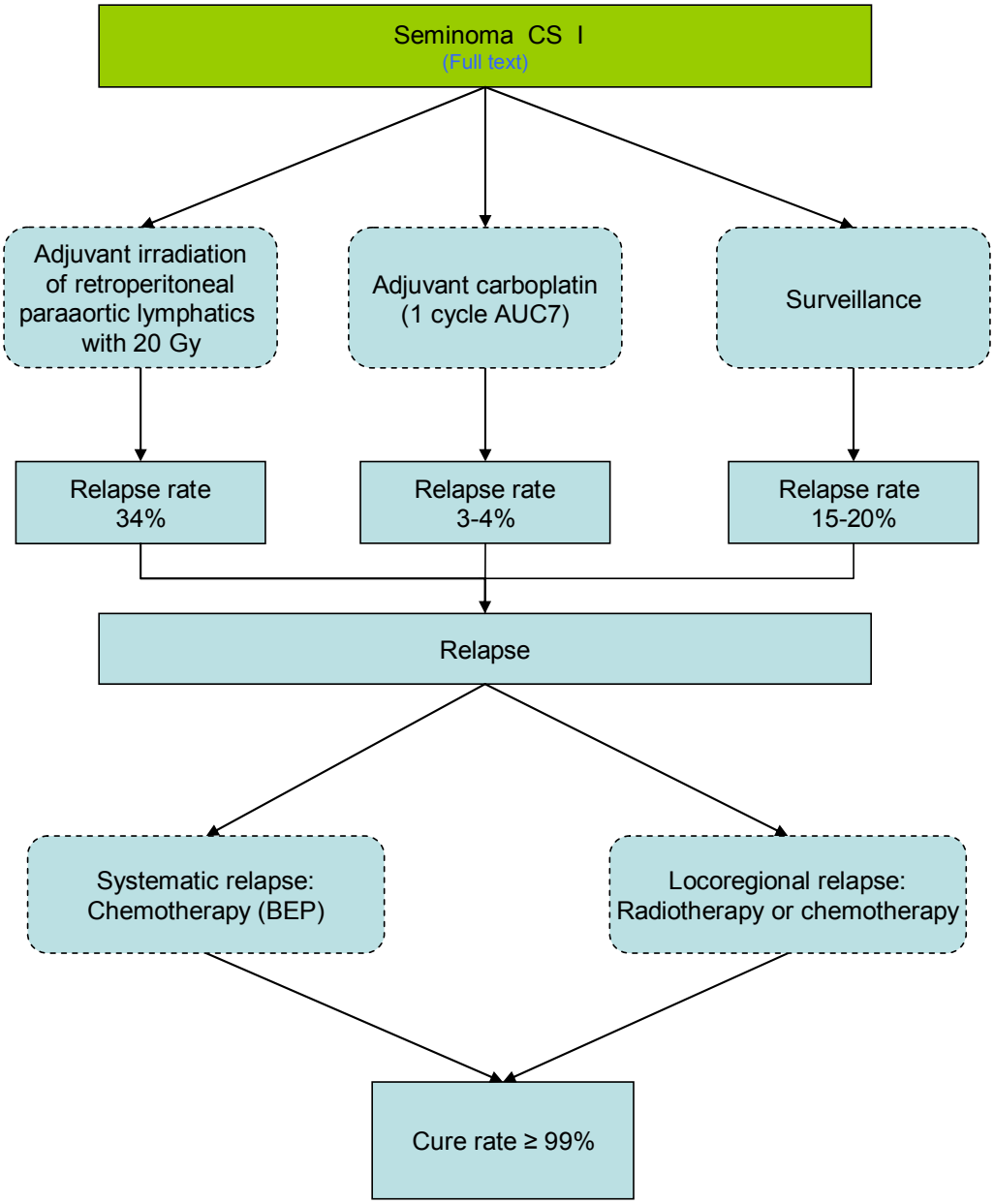
General algorithm

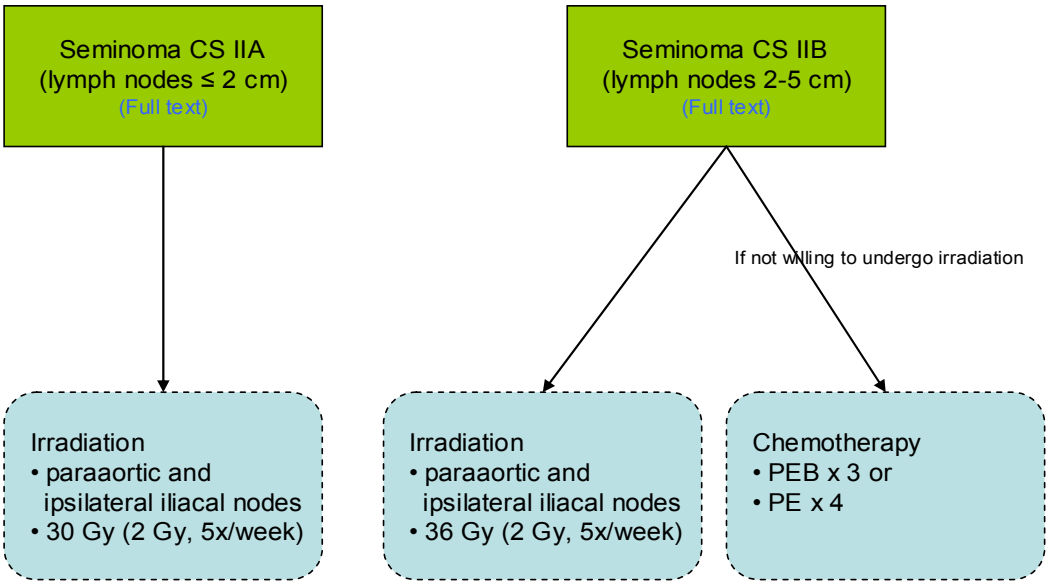


Treatment in seminoma CS I after orchiectomy *



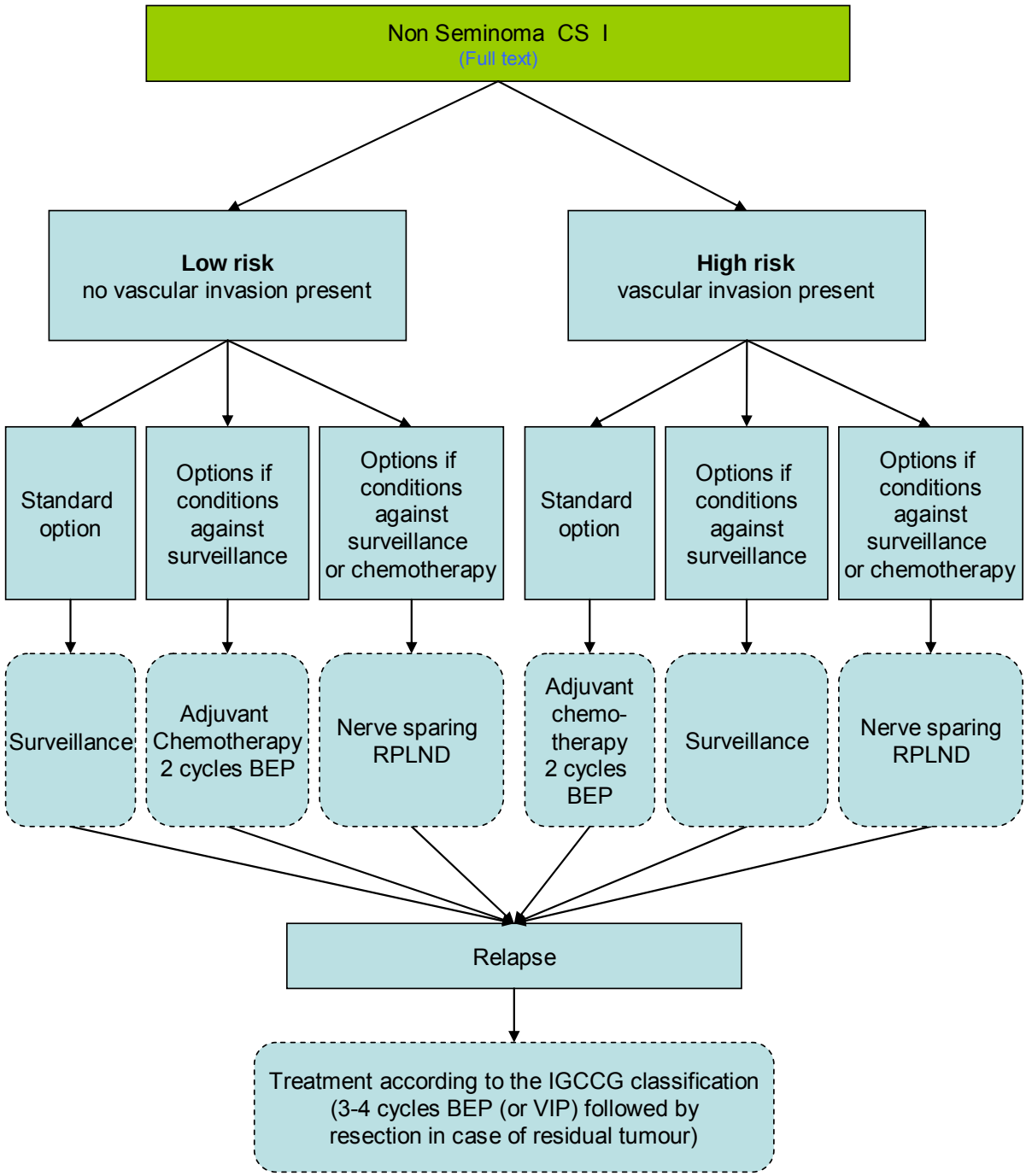
* Taken from EGCCCG guideline

Treatment in seminoma CS IIA &B *



* Taken from EGCCCG guideline

Treatment in non seminoma CS I after orchiectomy *



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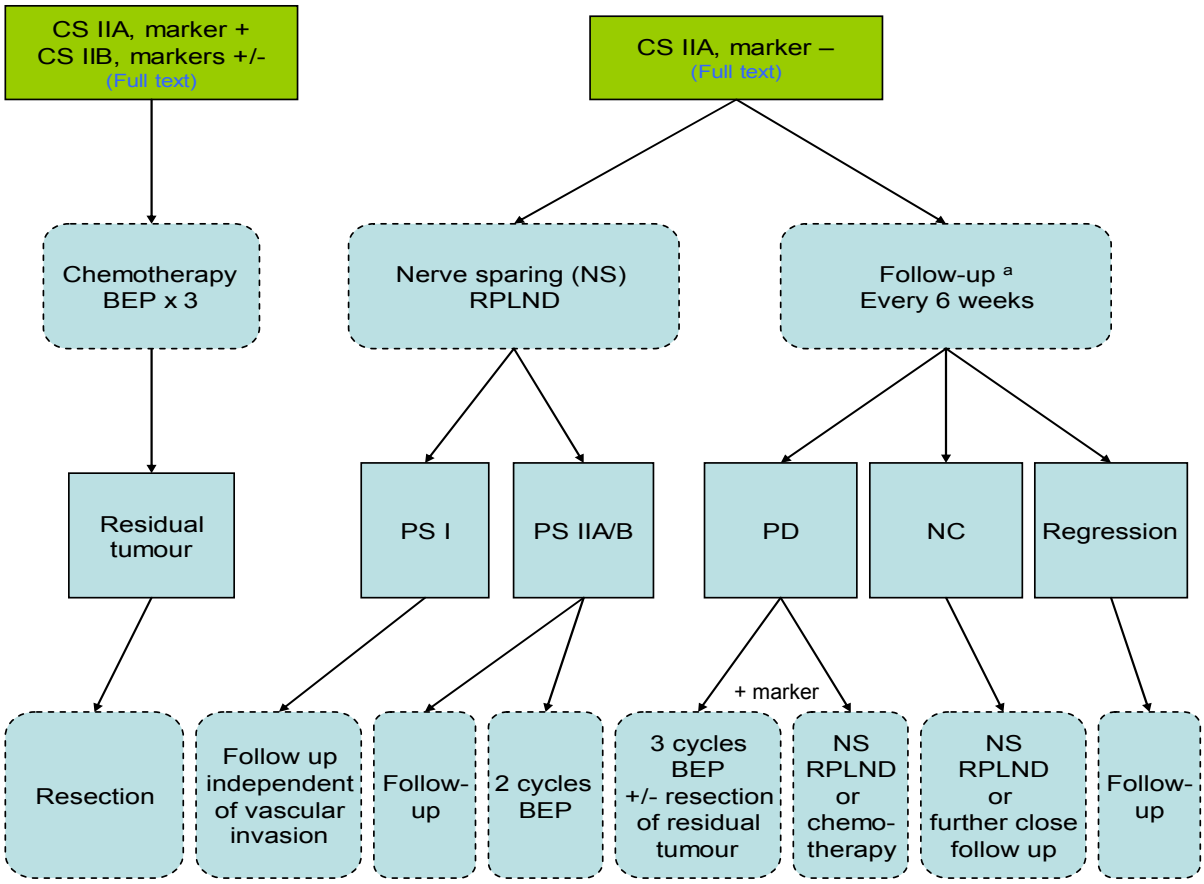
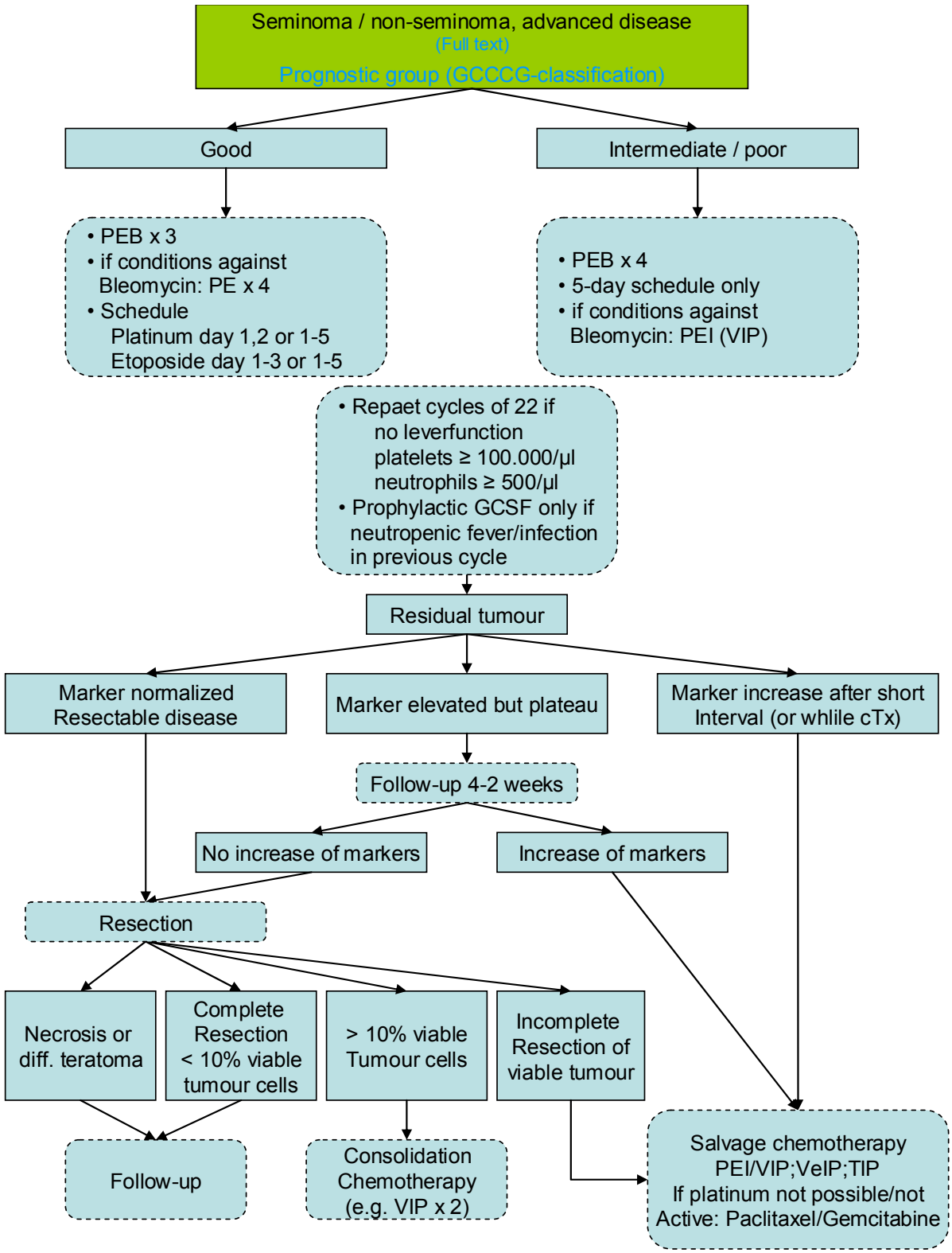
Treatment in non seminoma CS IIA & B *



[a] Follow-up if close surveillance is guaranteed with determination of tumour markers (every 6 weeks) and CT in short intervals.

* Taken from EGCCCG guideline

Treatment in advanced disease *



* Taken from EGCCCG guideline

Staging

TNM classification for testicular cancer (UICC, 2002 Sixth Edition) [1,5]

pT Primary Tumour	
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
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 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

* Taken from EGCCCG guideline

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	M1	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

* Taken from EGCCCG guideline

Prognosis table *

Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaboration Group)		
Good prognosis group	*Non-seminoma* 56% of cases 5-year PFS 89% 5-year survival 92%	All of the following criteria: • Testis/retropeitoneal primary • No non-pulmonary visceral metatases • AFP < 1.000 ng/ml • ß-hCG < 5.000 mIU/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 metatases • Normal AFP • Any ß-hCG • Any LDH
Intermediate prognosis group	*Non-seminoma* 28% of cases 5-year PFS 75% 5-year survival 80%	All of the following criteria: • Testis/retropeitoneal primary • No non-pulmonary visceral metatases • AFP > 1.000 and < 10.000 ng/ml or • ß-hCG > 5.000 and <50.000 mIU/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 metatases • Normal AFP • Any ß-hCG • Any LDH
Poor prognosis group	*Non-seminoma* 16% of cases 5-year PFS 41% 5-year survival 48%	Any of the following criteria: • Any primary site • Non-pulmonary visceral metatases • AFP > 10.000 ng/ml or • ß-hCG > 50.000 mIU/L (10.000 ng/ml) or • LDH > 10 x ULN
	Seminoma No patients classified as poor prognosis	

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

* Taken from EGCCCG guideline

Chemotherapy protocol for advanced disease *

	Cisplatin, mg/m² (30 min.-inf.)	Etoposide, mg/m² (30-60 min.-inf.)	Ifosfamide*, mg/m² (1h-inf.)	Bleomycin, mg/m² (IV bolus)	q day	No. Of cycles/prognosis	
						Good	Intermediate/ poor
BEP.PEB "5 DAYS"	20d 1-5	100d 1-5	-	d 1,8,15	22	3	4
BEP.PEB "3 DAYS"	50d 1,2	165d 1,2,3	-	d 1,8,15	22	3	-
PE	20d 1-5	100d 1-5	-	-	22	4	-
PEI, VIP**	20d 1-5	75d 1-5	1200d 1-5	-	22-29	-	4

General algorithm

* Taken from EGCCCG guideline

National Guideline

Testicular Cancer

INTRODUCTION

The guidelines presented covers diagnosis, treatment and follow up of testicular cancer. It is based on the existing international guidelines which have been critically appraised (appendix 1) and on the consensus of national societies.

We will go through the following topics:

- diagnosis
- clinical staging
- first multidisciplinary team meeting
- surgical procedure
- histological procedure
- final staging (2d MDT meeting)
- treatment
- follow up

The grade of recommendation is stated in the text as follow:

GR A = Evidence derived from RCT or meta-analysis or systematic review of RCT
GR B = Evidence from non-randomised controlled trials or observational studies
GR C = Professional consensus, or case reports or case series

The key to evidence statements and grade of recommendations are presented in appendix 2.

CLINICAL QUESTIONS

The clinical questions of this guideline are the following:

- What is the evidence for testicular cancer diagnosis management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for testicular cancer therapy management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for testicular cancer follow up management?

SEARCH FOR EVIDENCE

The keywords used for testicular cancer were “testicular with cancer and neoplasm”. The National guideline Clearinghouse (1 reference) and Pubmed (11 references, limit: practice guidelines) were searched in December 2004 without date limit or language restriction. The

websites of known agencies were systematically searched (Europe: ESMO, European Association of Urology, The Netherlands: Oncoline, UK: NICE, Scotland: SIGN, CANADA: Ontario Cancer care, USA: NCCN, NIC, ASCO, France: ANAES, FNCLCC. Two search engines were also searched (Google and Journalservice for medics) with the same keywords than mentioned earlier.

Finally a search for systematic reviews in the Cochrane database and in DARE (4 references) was performed.

DIAGNOSIS

Patient's history

A *personal history* has to be taken.

The diagnostic procedure is generally indicated for patients with the following symptoms: swelling, pain, sensation of scrotal heaviness [1] **(GR B)**. The clinical presentation is typically a young man with testicular mass and/or pain in the back [2] ***(GR C)***. In a minority of patients, the clinical presentation is extra gonadal (retroperitoneal or mediastinal) [1-5] ***(GR C)***.

The following elements have to be detected: undescended testis, early age of puberty and sedentary life style 4, and contralateral testis tumour [1-5] **(GR B)**.

A *family history* has to be taken: testicular tumour in any first grade relative? [2,4,5] **(GR B)**.

Examination: palpation [2]. Physical examination may be sufficient for the diagnosis of testicular cancer [5] **(GR B)**.

Markers: α Feto-Protein and HCG for distinction between seminoma and non seminoma [1,2,4,5] **(GR B**) and for the follow up of patients with teratoma [1] **(GR B)**. In case of advanced disease: LDH in addition, as prognostic factor [1,5] **(GR B)**.

Imaging: Testicular sonography (7.5 MHz transducer) [1,2,5] **(GR B)** except if clinically evident [1] **(GR B)**.

Biopsy: in case of symptoms with no elevation of markers [1,5] and for contralateral testis (open or needle biopsy) [1,2] **(GR B)**.
The biopsy must give answers to the following questions:

- Presence or absence of Carcinoma in situ ***(GR C)***
- Degree of spermatogenesis ***(GR C)***
- Evidence of atrophy of seminiferous tubules [1] **(GR B)**.

CLINICAL STAGING

To detect metastases, the following examinations are recommended:

Imaging

- CT scan of abdomen and pelvis [1,4] **(GR B)**
- Chest CT scan except for seminoma stage I [1,4,5] **(GR B)**
- MRI of chest and abdomen if CT contraindicated, ***(GR C)***
- CT scan or preferably MRI of CNS: only in advanced disease with intermediate or poor prognosis, or if symptoms ***(GR C)***
- PET scan: cfr HTA report of KCE (http://www.kenniscentrum.fgov.be/documents/D20051027330.pdf):

Staging: Due to the difficulties for classical imaging techniques to evaluate small volume metastasis, every patient receives chemotherapy or radiotherapy (or retroperitoneal lymph nodes resection) but this is not needed in 70% of patients with non germ cell tumour and in 80% of patients with germ cell tumour. Nevertheless, the sensitivity of PET between 70% and 90% with specificity between 94% and 100% is not high enough to diminish the value of adjuvant therapies in case of negative results. Indeed the risk of a false negative result for nodes smaller than 1 cm is too high.

cTNM
Pre-treatment clinical classification, based on clinical examination, imaging, biopsy, (TNM classification for testicular cancer UICC, 2002 Sixth Edition) [5].

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

FIRST MULTIDISCIPLINARY TEAM MEETING (MOC)

The objective of this first meeting is to decide if the cancer is metastatic or not and to decide on the related therapeutic options ***(GR C)***.

If possible, the general practitioner of the patient should attend this meeting. If not, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient ***(GR C)***.

Patients should be given clear information about the potential risks and benefits of treatment in order that they can understand adequately the therapeutic decision [1] **(GR B)**.

The fertility issues must be discussed with the patient: sperm banking, testosterone replacement and contraception [1] **(GR B)**.

Information about local support services should be made available to both the patient and their relatives. Healthcare professionals should respect patients' wishes to be involved when making plans about their own management ***(GR C)***.

The need for a psychosocial help must be evaluated and, if required, the help has to be started [1] ***(GR C)***.

SURGICAL PROCEDURE

The patient is always oriented to surgery (inguinal orchidectomy) which remains the only curative option [1,2,4,5] **(GR B)**. There is no need for emergency surgery [2] ***(GR C)***.

A preoperative risk assessment should be performed according to the appropriate guidelines (http://www.kenniscentrum.fgov.be/fr/Publications.html).

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunics, and immediate orchidectomy with division of the spermatic cord at the internal inguinal ring has to be performed if a tumour is found [1,2,4,5] **(GR B)**.

If the diagnosis is not clear, a testicular biopsy is taken for frozen section histological examination. Once the diagnosis of testicular tumour has been established, the testis is enveloped into the sponges which protected the surgical field, gloves are changed, the inguinal channel is opened and the spermatic cord is divided at the level of the internal ring. The specimen is sent for definitive histology [1,2,4,5] **(GR B)**.

It must be explained to patients preoperatively that this procedure is being done to exclude any cancer in a situation where there is high index of suspicion and that following such a bivalving procedure in those situations where malignancy is not confirmed and where the testis is replaced there may be moderate to severe testicular damage [1] ***(GR C)***.

It is said that in case of disseminated disease and life-threatening metastases, up-front chemotherapy can be started and orchidectomy delayed until clinical stabilisation [5] ***(GR C)***.

From time to time a scrotal exploration is performed for what is thought to be an inflammatory non malignant condition but tumour is found and it is necessary to proceed to orchidectomy. In this situation there is no need to perform secondary wound excision and the postoperative management should continue in exactly the same way as if the operation had been performed through the conventional inguinal approach [1] **(GR B)**.

A testicular prosthesis should be offered to all patients [1] **(GR B)**.

HISTOLOGICAL PROCEDURE

After surgical ablation of the testis, pathological assessment is mandatory and determination of serum tumour markers is advisable [5] **(GR B)**.

Mandatory pathological requirements 2 ***(GR C)****:*

- Macroscopic features: side, testis size, tumoural maximum size and macroscopic features of epididymis, spermatic cord and tunica vaginalis 1 ***(GR C)****.*
- Sampling: 1 cm2 section for every cm of maximal tumoural diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis selection of suspected areas. At least one proximal and one distal section of spermatic cord plus any suspected area ***(GR C)****.*
- Microscopic features and diagnosis 1: histological type (specify individual components and estimate amount as percentage) ***(GR C)****.*
- Presence or absence of peri-tumoral venous and/or lymphatic invasion 3 **(GR B)**.
- Presence or absence of albuginea, tunica vaginalis, epididymis or spermatic cord invasion ***(GR C)****.*
- Presence or absence of intratubular germinal neoplasia (Tin) in non-tumoral parenchyma ***(GR C)***.
- Category pT category according to TNM 2002.
- Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and beta-hCG 3 **(GR B)**.
- Advisable immunohistochemical markers
- In seminoma: cytokeratins (CAM 5.2), PLAP
- In intratubular germ cell neoplasia: PLAP
- Other advisable markers: Chromogranine A (Cg A), Ki 1, and NSE 5 ***(GR C)***

The histological report must contain the following items:

- Localisation
- Multiplicity
- Gross Description: Size of Testis, Size of Tumour,
- Features: Haemorrhage, Necrosis, Cysts
- Number of blocks of tumour taken
- Germ Cell Tumour Components (WHO descriptive terms)

Seminoma (presence of syncitiotrophoblasts), NSGCT (Differentiated somatic elements, Embryonal Carcinoma, Syncytiotrophoblast, Yolk Sac Tumour, Choriocarcinoma, Other)

- Other tumour type
- Invasion: Vascular space invasion, cut end of cord, confined to testis, invades rete, invades tunica albuginea, invades epididymis, present in cord, invades scrotum
- Other features: areas of scarring only, biopsy of contralateral testis? Intra Tubular Germ Cell Neoplasia present?
- Summary (BTTP diagnosis): Seminoma, Spermatocytic Seminoma, Combined Tumour, Other, TD, MTI, MTU, MTT (NHS National minimum dataset Testicular cancer histopathology report) ***(GR C)***.

The tumour must be classified according to the WHO 2 ***(GR C)***.

WHO classification of germ cell tumours of the testis:

Tumours of one histological type

- Seminoma
- Spermatocytic seminoma
- Embryonal carcinoma
- Polyembryoma
- Teratoma: Mature, immature, with malignant transformation
- Yolk sac tumour (endodemal sinus tumour)
- Choriocarcinoma

Tumours of more than one histological type

- Embryonal carcinoma with teratoma (teratocarcinoma)
- Choriocarcinoma and any other types (specify)
- Other combinations (specify)

FINAL STAGING

Testicular cancers should be staged using the TNM staging system: pTNM: post-surgical histopathological classification (see 'Staging').

The staging is done during the second multidisciplinary meeting (MOC) on the basis of all results and reports ***(GR C)***.

If possible, the general practitioner of the patient should attend this meeting. If not, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient ***(GR C)***.

Depending on tumour stage, the further treatment options are decided. The adjuvant chemotherapy regimen is decided during the multidisciplinary team meeting. A written report with staging and treatment options is mandatory for each patient ***(GR C)***.

TREATMENT

A desicion tree of the treatment in general is presented here.

Seminoma CS I

There are three main options to treat a Seminoma stage I.

The decision must be based on a discussion with the patient, taking into account the benefits and disadvantages of each strategy as well as the individual situation ***(GR C)***.

Adjuvant radiotherapy of retroperitoneal para-aortic lymphatic field with a total target volume of 20 Gy with modern radiotherapy (linear accelerator) [1,2,5] **(GR B)**. This is the standard treatment for Stage I T1 to T3 patients with undisturbed lymphatic drainage [5] ***(GR C)***. The dose is applied in single doses of 2 Gy, five fractions per week [1,2] **(GR B)**. The upper field margin is defined by D11 and the lower field margin by L5. The lateral field should include the ipsilateral renal hilum and the contralateral processus transversus of the lumbar vertebrae [1,2] **(GR A)**.

Surveillance is also an option due to the fact that 20 % of patients only relapse after orchidectomy, and due to the potential risk of subsequent cancer following radiotherapy [2, 5] ***(GR C)***. This strategy is not valid in case of doubt about patient's compliance [1] **(GR B)** and must take into account the greater psychological stress due to higher risk of relapse [2] ***(GR C)***. On the contrary this strategy may be recommended for patients with horseshoe or pelvic kidney, inflammatory bowel disease or prior radiotherapy [6] ***(GR C)***.

The risk factors for relapse are a tumour size > 4 cms and invasion of rete testis. Surveillance requires a prolonged and more intensive follow-up (repeated imaging examination of the retroperitoneal nodes for at least 5 years after orchidectomy) [2,5] **(GR B).** In case of relapse, a more intensive treatment is needed 2 but with equivalent results to the adjuvant radiotherapy [2,5] ***(GR C)***.

Adjuvant carboplatin chemotherapy with one cycle of carboplatin AUC7 (7X [glomerular filtration rate + 25] mg). This strategy may reduce the occurrence of second primary testicular germ-cell tumours following radiotherapy. However, the findings need to be confirmed [7] ***(GR C)***.

The relapse rate is the same for chemotherapy and for radiation therapy but with other localisation (more retroperitoneal lymph node relapse with chemotherapy >< more pelvic lymph node relapse with irradiation) [2,5] **(GR A)**.

A decision tree is presented here.

Seminoma CS II A and B

The standard treatment is radiotherapy [1] **(GR B)**. Target volume includes the paraaortal and ipsilateral iliacal lymphatics [1,2] **(GR B)**.

- Upper field margin: upper border of D11 [1,2] **(GR B)**
- Lower field margin: upper border of the acetabulum [1] **(GR B)**
- Lateral field: for CS IIA: the same as for CSI [1] **(GR B)**;
  for CS IIB: lateral field margins are individually modified according to the extension of the lymph nodes with a safety margin of 1 – 1.5 cm [2] **(GR B)**
- Radiation doses: 30 Gy for CSIIA and 36 Gy for CSIIB, homogeneously with single dose of 2 Gy at five fractions per week [2] ***(GR C)***.

- Shielding of the remaining testicle is mandatory 2 ***(GR C)***.

Three months after radiation therapy, abdominal and pelvic CT should be performed (basis for follow up) [2] **(GR B)**.

An alternative strategy for patients not willing radiotherapy is 3 cycles BEP or 4 cycles PE [2,5] **(GR B)**.

BEP and PE regimens (every 3(4) weeks)

- BEP: Cisplatin 20mg/m2, days 1-5 and hydratation
- Etoposide : 120mg/m2, days 1,3,5
- Bleomycin : 30mg, days 2,9,16
- PE: etoposide 100mg/m2, days 1-5

Availability and reimbursement policy of the chemotherapy regimens in Belgium may be checked at: (http://www.cbip.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm) (http://www.bcfi.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm)

A decision tree is presented here.

Non Seminoma CS I

The most important prognosis factor for relapse is vascular invasion.

In case of low risk (no vascular invasion), the standard treatment is follow up1 2 **(GR B)**. In case of relapse, a chemotherapy treatment will result in a cure rate close to 100% [1,2] **(GR B)**.

In case of high risk (vascular invasion), the standard treatment is 2 cycles of BEP. For several reasons like patient choice, surveillance only may be an option, with a cure rate > 98% in case of relapse cured by chemotherapy [1,2] **(GR B)**.

In both cases, a third option is possible: nerve sparing lymph-adenectomy, with a risk of recurrence or relapse of +/- 10% [2] ***(GR C***).

A decision tree is presented here.

Non Seminoma CS II A & B

Patients with abnormal serum tumour markers AFP/HCG and/or LDH are treated depending of the prognosis (see prognosis table of the IGCCCG in appendix ?????).

In case of good prognosis, 3 cycles of BEP and if Bleomycin is contraindicated, 4 cycles of Carboplatin and Etoposide (PE) can be given [2] **(GR A)**.

Patients with retro-peritoneal lymph nodes (1-2 cms) suspected to be CS IIA without tumour markers: either:

Staging and nerve sparing Retro Peritoneal Lymph Nodes Dissection 2 ***(GR C***). If pathology stage is I, surveillance is recommended 2 (GR B). If pathology stage is II A or B, surveillance or 2 cycles BEP [2] **(GR A)**

or

Surveillance with a follow up at short intervals (6 weeks) 2 ***(GR C):*** if regression of the tumour, surveillance 2 ***(GR C);*** if no change or progression of the disease with negative markers RPLND or surveillance 2 ***(GR C);*** if progression of the disease with positive markers, 3 cycles BEP and resection of the residual tumour [1,2] **(GR B**).

A decision tree is presented in here.

Advanced disease

For patients with advanced disease, treatment is based on the prognosis evaluation, according to IGCCCG criteria (Table 1).

For patients with good prognosis disease, standard treatment is 3 cycles of BEP. In case of contraindication of bleomycin, 4 cycles of cisplatin and etoposide(PE) [2] **(GR A)**.

For intermediate and poor prognosis patients, the 5 day BEP regimen for four cycles is the standard treatment [2] **(GR A)**.
For intermediate prognosis patients, the treatment is given in prospective trials to design more effective treatments [2] ***(GR C)***.

For brain metastases, resection if the metastases are accessible, followed by curative or palliative radiotherapy [1] **(GR C)** in addition to systemic chemotherapy [2] **(GR C)**.

Patients with seminoma who have residual masses following chemotherapy can generally be managed by surveillance. Surgery is not routinely indicated [1,2] **(GR B)**.

Cisplatin based salvage chemotherapy is indicated after first line therapy with BEP: 4 cycles of Cisplatin, etoposide and ifosfamide (PEI), etoposide, ifosfamide and cisplatin (VIP) or vinblastine, ifosfamide and cisplatin (VEIP) or paclitaxel, ifosfamide and cisplatin (TIP) [2] **(GR B)**.

For the treatment of late relapse, surgery should be considered [1] **(GR B)**.

A decision tree is presented here. The chemotherapy regimens are presented in Table 2.

Management of unresectable metastases

Each patient should receive an evaluation for first and second line chemotherapy. The most important parameter therefore is the health performance status ***(GR C)***. The patient assessment and decision about treatment options should be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed ***(GR C)***.

The need for a psychosocial help must be evaluated and, if required, the help has to be started ***(GR C)***.

Patients with advanced cancer may benefit both from treatment of the cancer and from palliative care. These are concomitant approaches to management ***(GR C)***. Palliative care specialists should be members of, and integrated with, cancer multi-disciplinary teams; their role includes the provision of education and advice for other health professionals and direct patient management ***(GR C)***.

A patient in good health status and progressing despite standard therapy should be proposed a clinical trial protocol ***(GR C)***.

FOLLOW UP

Large differences exist in the risk of recurrence or progression for patients with germ cell cancer due to differences in stage at initial presentation and individual management decisions. The intensity of the follow up depends on these factors. There is limited information about the optimal follow up procedure [2] ***(GR C)***.

Early identification of therapeutic failure in Non seminomatous Germ cell tumours by assessing serum tumour markers decline during chemotherapy is still not ready for routine clinical use [8].

For residual mass evaluation, there is evidence of diagnosis accuracy, but no evidence that PET scan results change the patient management. For therapeutic response and detection of occult recurrence, there is a lack of evidence for the use of PET.

PET scan: cfr HTA report of KCE
(http://www.kenniscentrum.fgov.be/documents/D20051027330.pdf)

APPENDICES

Appendix 1

Evidence table testicular guidelines

Title	Country	Year	Scope	AGREE overall assessment
SIGN: Management of adult testicular germ cell tumours [1]	UK Scotland	1998 & update 2005	Testicular germ cell tumours	Strongly recommend
NICE: Improving outcomes in urological cancers [3]	UK	2002	Urological cancers	Recommend (with provisos or alterations)
The Royal College of radiologists COIN guidelines: Testicular Germ cell Tumours [4]	UK	1998	Testicular germ cell tumours	Recommend (with provisos or alterations)
European Association of Urology: Guidelines on Testicular Cancer [5]	Europe	2004	Testicular germ cell tumours	Recommend (with provisos or alterations)
European Consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group [2]	Europe	2004	Testicular germ cell tumours	Recommend (with provisos or alterations)
NCCN: Testicular cancer [6]		2005	Testicular germ cell tumours	Recommend (with provisos or alterations)
National Cancer Institute: Testicular cancer Treatment [9]	USA	2003	Testicular germ cell tumours	Recommend (with provisos or alterations)
Cancercare Ontario Program: Surveillance programs for early stage non-seminomatous testicular cancer [10]	Canada	2001	Non seminomatous testicular cancer	Recommend (with provisos or alterations)
Vereniging van Integrale Kankercentra: Testiscarcinoom [1]1	The Netherlands	2002	Testicular germ cell tumours	Not recommend

The assessment of the guidelines was made with the AGREE instrument. All details can be found on the AGREE collaboration website: http://www.agreecollaboration.org/
The AGREE instrument can be found on:
http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf

AGREE scores

Key items	SIGN	NICE	NCCN	NCI	COIN	EAU	Cancer Care Ontario	EGCCCG	Oncoline
Scope and purpose									
1	4	4	4	4	4	4	4	4	4
2	4	4	4	4	4	4	4	4	4
3	4	4	4	4	4	4	4	4	4
Stakeholder involvment									
4	4	4	4	1	4	3	3	2	2
5	3	4	1	3	3	3	3	1	1
6	4	4	3	4	4	3	3	3	4
7	2	2	2	2	2	2	2	2	2
Rigour of development									
8	4	4	2	2	4	3	4	4	1
9	4	4	4	4	4	2	4	4	1
10	4	4	4	4	4	2	4	4	1
11	4	4	4	4	4	4	4	4	1
12	4	2	4	4	4	4	4	4	1
13	4	4	2	2	4	2	4	2	1
14	4	3	3	1	1	1	4	1	1
Clarity and presentation									
15	4	3	4	4	4	4	4	2	4
16	4	4	4	4	4	4	4	4	4
17	4	2	4	4	4	4	3	2	4
18	4	1	4	4	1	1	1	1	1
Applicability									
19	2	1	1	1	1	1	1	1	1
20	1	3	1	1	1	1	1	1	1
21	4	4	1	1	4	1	1	1	1
Editorial independance									
22	4	4	4	2	4	4	4	4	4
23	4	4	2	2	1	1	1	1	1
Overall assessment	SR	R	R	R	R	R	R	R	NR

Appendix 2: Key to evidence statements and grades of recommendations testicular cancer guideline

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN) [1]

Levels of evidence

1++ High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias

1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

2++ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non analytic studies, e.g. case reports, case series

4 Expert opinion

Grades of recommendation

A At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or
body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ , directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE)

A Evidence derived from randomised controlled trials or systematic reviews of randomised trials

B Evidence from non-randomised controlled trials or observational studies

C professional consensus

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Level

I Meta-analysis of multiple well designed, controlled studies; randomised trials with low falsepositive and low false-negative errors (high power)

II At least one well designed experimental study; randomised trials with high false-positive or high false-negative errors or both (low power)

III Well designed, quasi-experimental studies, such as nonrandomised controlled, single-group, preoperative-postoperative comparison, cohort, time, or matched case-control series
IV Well designed, non experimental studies such as comparative and correlational descriptive and case studies
V Case reports and clinical examples

Grade

A Evidence of type I or consistent findings from multiple studies of type II, III or IV
B Evidence of type II, III or IV and generally consistent findings
C Evidence of type II, III or IV but inconsistent findings
D Little or no systematic empirical evidence

NATIONAL CANCER INSTITUTE (NCI)

Strenght of study design

- Randomised controlled clinical trials
- Double-blinded
- Non blinded (allocation schema or treatment delivery)
- Non randomised controlled clinical trials
- Case series
- Population-based, consecutive series
- Consecutive cases (not population-based)
- Non consecutive cases

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) [6]

Category 1 There is uniform NCCN consensus, based on high level evidence, that the recommendation is appropriate
Category 2A There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate
Category 2B There is non uniform consensus (but no major disagreement), based on lower level evidence including clinical experience, that the recommendation is appropriate
Category 3 There is major NCCN disagreement that the recommendation is appropriate

European Association of Urology (see AHRQ)[61]

European Consensus on diagnosis and treatment of germ cell cancer [58]

Level IA Evidence obtained from meta-analysis of RCT and systematic reviews of RCT
Level IB Evidence obtained from at least one RCT
Level IIA Evidence obtained from at least one well-designed controlled study without randomisation
Level IIB Evidence obtained from at least one other type of well-designed quasiexperimental study
Level III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
Level IV Evidence obtained from expert committee or opinion and/or clinical experience of respected authorities without transparent proof.

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