EAU GUIDELINES ON TESTICULAR CANCER

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Epidemiology , aetiology and pathology

Compared with other types of cancer, testicular cancer (TC) is relatively rare accounting for approximately 1-1.5% of all cancers in men. At diagnosis, 1-2% are bilateral and the predominant histology is Germ Cell Tumour (GCT). Peak incidence is in the third decade of life for non-seminoma and mixed GCTs, and fourth decade for pure seminoma. Epidemiological risk factors for the development of TC are components of testicular dysgenesis syndrome, which encompasses cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility, familial history of testicular tumours among first-grade relatives, and the presence of a contralateral tumour, or germ cell neoplasia *in situ* (GCNIS).

Histological classification

The recommended pathological classification is the 2016 update of the World Health Organization (WHO).

Staging and Classification systems

Staging systems

The 2016 Tumour, Node, Metastasis (TNM) classification of the International Union Against Cancer (UICC) is recommended to assess the anatomical extent of the disease (Table 2).

Table 1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.)

T - Primary Tumour[1]	
pTX	Primary tumour cannot be assessed (see note 1)
pT0	No evidence of primary tumour (e.g. histological scar in testis)
pTIS	Intratubular germ cell neoplasia (carcinoma *in situ*)
pT1	Tumour limited to testis and epididymis[2] without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis*
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica lbuginea with involvement of tunica vaginalis**
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion**
pT4	Tumour invades scrotum with or without vascular/ lymphatic invasion
N - Regional Lymph Nodes - Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension 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 more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour		
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Pn - Regional Lymph Nodes - Pathological			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M - Distant Metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis**		
	M1a Non-regional lymph node(s) or lung metastasis		
	M1b Distant metastasis other than non-regional lymph nodes and lung		
S - Serum tumour markers (Pre-chemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay. LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

** AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension.*

*** AJCC eight edition considers the hilar soft tissue invasion as pT2, while the discontinuous involvement of then spermatic cord is considered as pM1.*

[1] Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

[2] The current "carcinoma in situ" nomenclature is replaced by GCNIS

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 non-seminomatous germ cell tumour (NSGCT) (Table 2).

The IGCCG for metastatic Testicular Cancer

A prognostic factor-based staging system is widely used for metastatic TC based on identification of clinically independent adverse factors.

Table 2: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG)*

Good-prognosis group	
Non-seminoma *(56% of cases* 5-year PFS 89% 5-year survival 92%	*All of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma *(28% of cases)* 5-year PFS 75% 5-year survival 80%	*Any of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN

Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as poor prognosis

** Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).*

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

Diagnostic evaluation

The diagnosis of TC is based on:

1. ***Physical examination***
   Testicular cancer usually presents as a unilateral testicular scrotal mass detected by the patient, or as an incidental ultrasound (US) finding. Around 1% of patients presenting with gynecomastia have a germ cell or sex cord/gonadal tumour of the testes and 11% present with back and flank

pain. When there is suspicion of TC, physical exploration must include abdominal and supraclavicular exploration.

2. Imaging

a. Ultrasound

High frequency (>10 MHz) testicular US should be used to confirm a testicular tumour even in the presence of clinically evident testicular lesion. Testicular US is also recommended for all men with retroperitoneal or visceral masses and/or without elevated serum human chorionic gonadotropin (hCG) or alpha-fetoprotein (AFP) in the absence of a palpable testicular mass.

b. Computerised tomography

Contrast enhanced computerised tomography (CECT) is the most sensitive means to evaluate the thorax, abdomen and pelvis for TC staging. Contrast enhanced computerised tomography is recommended in all patients for staging before orchidectomy, but may be postponed until histopathological confirmation of malignancy. Brain imaging by CECT is recommended in patients with NSGCT, multiple lung metastases and poor-prognosis IGCCCG risk group (for patients with hCG values >5,000 UI/L), or if clinical symptoms are present.

c. Magnetic resonance imaging

Magnetic resonance imaging (MRI) has similar accuracy to CECT in the detection of retroperitoneal nodal enlargement. However, there are no indications for routine use of MRI for TC staging unless CT is contraindicated because of allergy to iodine contrast media.

MRI has a primary role in the detection of brain metastasis because it is more sensitive than CECT.

d. *Fluorodeoxyglucose- positron emission tomography*
There is no evidence to support the use of fluorodeoxy-glucose-positron emission tomography (FDG-PET) for initial staging and routine follow-up of TC.

e. *Bone scan*
There is no evidence to support the use of bone scan for staging of TC.

3. Serum tumour markers

Serum tumour markers (AFP, β-hCG and LDH,) should be determined before, and after orchidectomy until normalisation. Normal serum markers levels do not exclude the presence of TC, whilst persistence, or increase of elevated serum tumour markers following orchidectomy indicates the likely presence of metastatic disease. Tumour markers should be routinely used for follow-up.

4. Inguinal exploration and initial management

Orchidectomy including division of the spermatic cord at the internal inguinal ring represents the standard of care in patients with TC.

- Testis sparing surgery (TSS) may be attempted in patients with a solitary testis to preserve fertility and hormonal function. It should only be offered together with frozen section examination (FSE).
- Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchidectomy.
- Routine contralateral biopsy for diagnosis of GCNIS should be discussed with the patient and is recommended in 'high-risk' patients (testicular volume < 12 mL, a history of cryptorchidism and age < 40 years).

5. Pathological examination of the testis

Following orchidectomy, the pathological examination of the testis should include a number of investigations:

1. macroscopic features: side, testis size, maximum tumour size, and macroscopic features of the epididymis, spermatic cord, and tunica vaginalis;
2. sampling: a 1 cm^2 section for every cm^2 of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspected areas;
3. at least one proximal and one distal section of spermatic cord plus any suspected area;
4. microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2016;
    - 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;
    - presence or absence of GCNIS in non-tumour parenchyma;
    - in cases of rete testis invasion, attention should be paid to distinguishing between the pagetoid involvement and stromal invasion;
5. pT category according to TNM 2016;
6. immunohistochemical studies: in seminoma and mixed GCT, AFP and hCG.

6. Screening

There are no high-level evidence studies supporting screening programs. In the presence of clinical risk factors, and a family history of TC, family members and the patient should be informed about the importance of physical self-examination.

7. Impact on fertility and fertility-associated issues

Sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TCs prior to orchidectomy. Furthermore, treatment for TC, including orchidectomy, may have a negative impact on reproductive function. As such, all patients should be offered semen preservation

Recommendations for diagnosis and staging of testicular cancer	**Strength rating**
Discuss sperm banking with all men prior to starting treatment for testicular cancer (TC).	Strong
Perform bilateral testicular ultrasound (US) in all patients with suspicion of TC.	Strong
Perform physical examination including clavicular, cervical, axillary and inguinal lymph nodes, breast and testicles.	Strong
Measure serum determination of tumour markers both before and after orchidectomy taking into account half-life kinetics.	Strong
Perform orchidectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, start chemotherapy before orchidectomy.	Strong
Perform contrast enhanced computerised tomography scan (chest, abdomen and pelvis) in patients with diagnosis of TC. If iodine allergy or other limiting factors, perform abdominal and pelvic magnetic resonance imaging (MRI).	Strong

Perform MRI of the brain if facilities available (or brain CECT if not available) in patients with multiple lung metastases or high β-hCG values or those in the poor-prognosis IGCCCG risk group.	Strong
Do not use positron-emission tomography CT or bone scan for staging.	Strong
Encourage patients with testicular germ cell cancers to perform self-examination and to inform first-degree male relatives of the need for self-examination.	Strong
Discuss testis-sparing surgery with frozen section examination in patients with a high-likelihood of having a benign testicular tumour and which are suitable for enucleation.	Strong
Offer biopsy of the contralateral testis and discuss its consequences with patients at high-risk for contralateral germ cell neoplasia *in situ*.	Strong

Prognosis

Table 3: Pathological risk-factors for occult metastatic disease in Stage I TC

Histological type	Seminoma	Non seminoma
Pathological risk-factors	• Tumour size • Invasion of the rete testis	• Lympho-vascular invasion in peri-tumoural tissue

Disease management

1. Stage I Germ cell Tumours

GCNIS, when diagnosed, can be treated by local radiotheray (18-20 Gy in fractions of 2 Gy) or orchidectomy.

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

Recommendations for the treatment of stage I non-seminomatous germ cell tumour	Strength rating
Inform patients with stage I non-seminomatous germ cell tumour (NSGCT) about all adjuvant treatment options after orchidectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection [RPLND]) including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
In patients with stage I NSGCT, offer surveillance or risk-adapted treatment based on lymphovascular invasion.	Strong
If patients are not willing to undergo surveillance, offer one course of cisplatin, etoposide, bleomycin (BEP) as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	Strong

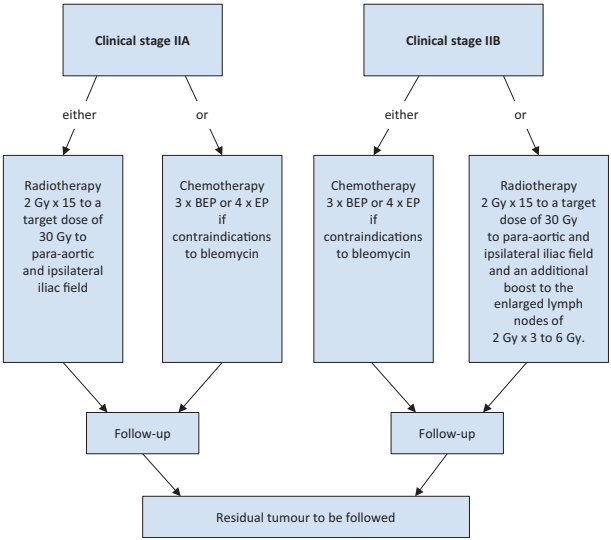
Recommendations for risk-adapted treatment for clinical stage I based on vascular invasion	Strength rating
Stage IA (pT1, no vascular invasion): low risk	
Offer surveillance if the patient is willing and able to comply.	Strong
In low-risk patients not willing (or unsuitable) to undergo surveillance, offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP).	Strong

Stage IB (pT2-pT4): high risk	
Offer primary chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong
Offer nerve-sparing retroperitoneal lymph node dissection to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong
Primary retroperitoneal lymph node dissection should be advised in men with teratoma with somatic-type malignancy.	Weak

2. Metastatic Germ cell Tumours

Clinical S1 (CS1) stage patients with peristently elevated serum tumours markers require repeated imaging including US examination of contralateral testis and abdominal and extrabdominal sites. They should be treated according to IGCCCG prognostic groups.

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



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

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

In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either retroperitoneal lymph node dissection or biopsy. If not possible, repeat staging after six weeks of surveillance before making a final decision on further treatment.	Strong
In metastatic NSGCT with an "intermediate prognosis", treat with four cycles of standard BEP.	Strong
In metastatic NSGCT with a "poor prognosis", treat with one cycle of BEP, (or cisplatin, etoposide and ifosfamide [PEI] in case of poor lung function), followed by tumour marker assessment after three weeks. In case of a favourable marker decline, continue BEP (or PEI) up to a total of four cycles. In case of an unfavourable decline, initiate chemotherapy intensification.	Weak
Perform surgical resection of residual masses after chemotherapy in NSGCT in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.	Strong
In Clinical stage IIA seminoma, offer radiotherapy or chemotherapy and inform the patient of potential long-term side effects of both treatment options.	Strong
Offer initial chemotherapy in seminoma stage IIB (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	Strong

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

Relapse after chemotherapy

The treatment of relapsed GCT after chemotherapy is typically salvage chemotherapy. For patients at first relapse with good prognostic features (initial achievement of complete response/partial remission negative markers [CR/PRm] and gonadal primary tumour) four cycles of standard-dose salvage chemotherapy are proposed. For patients with poor prognostic factors (extragonadal primary and/or incomplete response to first-line chemotherapy) and for all patients with subsequent (second or more) relapse, high-dose chemotherapy with autologous stem cell support is recommended.

Follow-up

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

The following factors should be taken into account:

a) Follow-up must be tailored to the individual patient with a schedule acceptable to the patient, the clinician, and the health care system.
b) The interval of follow-up visits and the clinical investigations to be performed at each visit should depend on the risk of relapse, in general, as well as the likely sites of relapse in an individual patient.
c) When possible, an effort should be made to minimise any risks associated with ionising radiation exposure.
d) The increased risk of second malignancy (in the primary site and in other tissues that may have been exposed to the same carcinogens, or in which there is epidemiological evidence of increased risk) should also guide the selection of tests.

Table 4: Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)[1]

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

Table 5: Recommended minimal follow-up for non-seminoma stage I on active surveillance[1]

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

LVI = lymphovascular invasion

[1] Recommendations based upon ESMO Testicular seminoma and non-seminoma consensus meeting outcomes.

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

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

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

Table 6: Recommended minimal follow up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission[1])

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

[1] Recommendations based upon European Society for Medical Oncology (ESMO)Testicular seminoma and non-seminoma consensus meeting outcomes.

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

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

Quality of life and long-term toxicities after cure

Patients diagnosed with TC are usually between 18 and 40 years of age at diagnosis, and life expectancy after cure extends over several decades. Patients should be informed before treatment of common long-term toxicities before any treatment is planned.

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

Included among the long-term toxicity and secondary effects of TC treatment are: second malignant neoplasms, leukemia, infections, pulmonary and cardiovascular complications, Raynaud-like phenomena, neuro- nephro- and ototoxiciy, impaired cognitive function, hypogonadism and fatigue as well as quality of life issues.

Testicular Stromal Tumours

Testicular stromal tumours are rare; however, Leydig cell and Sertoli cell tumours are of clinical relevance.

Leydig cell tumours

Approximately 10% of Leydig tumours are malignant presenting the following features:

- large size (> 5 cm);
- older age;
- cytologic atypia and DNA aneuploidy;
- increased mitotic activity (> 3 per 10 high-power field [HPF]) and increased MIB-1 expression;
- necrosis;
- vascular invasion infiltrative margins;
- extension beyond the testicular parenchyma.

The tumour presents as a painless enlarged testis or as an incidental US finding accompanied in, up to 80% of cases, by hormonal disorders. Serum tumour markers are negative and approximately 30% of patients present with gynaecomastia. These tumours are often treated by inguinal orchidectomy because they are misinterpreted as GCTs. In patients with symptoms of gynaecomastia, hormonal disorders, or atypical imaging on US, a partial orchidectomy (+ frozen section) should be considered until final histology is available. In the case of histological signs of malignancy and orchidectomy. Adjuvant RPLND is not justified in CSI disease without high risk features. Retroperitoneal lymph node dissection is an

option in stage IIA to achieve long term cure.

Sertoli cell tumours

Sertoli cell tumours are malignant in 10 - 22% of cases. Morphological signs of malignancy are:

- large size (> 5 cm);
- increased mitotic activity (> 5 per 10 HPF);
- pleomorphic nuclei with nucleoli;
- necrosis and/or vascular invasion.

Sertoli cell tumours present either as an enlarged testis or as incidental US finding. Hormonal disorders are infrequent and serum tumour markers are negative. Ultrasonographically, they generally appear as hypoechoic and cannot be safely distinguished from germ-cell tumour except for the subtype large cell calcifying form which is usually associated with genetic syndromes (Carney's complex, Peutz-Jeghers syndrome). Sertoli cell tumours are often interpreted as germ-cell tumours and an orchidectomy is performed.

Organ-sparing surgery should be considered (with caution), but in the case of histological signs of malignancy, orchidectomy. Adjuvant RPLND is not justified in CSI disease without high risk features. Retroperitoneal lymph node dissection is an option in stage IIA to achieve long term cure.

Conclusions

Most testis tumours are diagnosed at an early stage. Staging is the cornerstone of treatment. Following orchidectomy, excellent cure rates are achieved for those early stages irrespective of the treatment policy adopted, although pattern and relapse rates are closely linked to the treatment modality chosen. In metastatic disease a multidisciplinary therapeutic approach offers an acceptable survival. Follow-up schedules should be tailored to initial staging and treatment.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-07-3), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.