clinical practice guidelines

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Testicular seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

The incidence of testicular cancer in Europe is rising, with doubling every 20 years. The current incidence is 6.3/100 000/year, with the highest rate in Northern European countries (6.8/100 000/year). The death rate is very low (0.38 cases/100 000/year). Of testicular tumours, 40% are seminomas and 60% non-seminomas.

Invasive testicular cancer develops from carcinoma *in situ* (CIS)/testicular intraepithelial neoplasia (TIN), often found in the residual non-malignant testicular tissue. In a random biopsy, 2%–5% of testicular cancer patients have CIS in the contralateral testis. This is in accordance with a 2%–3% rate of synchronous contralateral or metachronous testicular cancer.

diagnosis

The diagnosis is based on histology of the testicular mass removed by inguinal orchiectomy or by testis-conserving surgery [IV, B].

Biopsy or, instead, high β-human chorionic gonadotropin (β-HCG) without biopsy in patients presenting with extragonadal tumour syndrome (patients with HCG >200 should be regarded as non-seminoma) [IV, B].

In advanced and rapidly progressive disease requiring urgent chemotherapy, diagnosis may be based on typical clinical picture and possible marker elevation alone.

Germ cell tumour may present extragonadally in the retroperitoneum or mediastinum in a minority of cases. In one-third of these patients there is CIS in the testis and one-third has scar tissue ('burned out tumour'), leaving one-third of the patients having definitive primary extragonadal germ cell tumour without affecting the testicle. These patients present with undifferentiated (adeno)carcinoma of unknown origin, mostly with typical marker elevation and/or elevated copy number of chromosome i12p, which is specific for germ cell tumours.

staging and risk assessment

Full blood count, creatinine, electrolytes and liver enzymes should be obtained. Tumour markers [α-fetoprotein (AFP), β-HCG and lactate dehydrogenase (LDH)] are needed for confirmation of pure seminoma and for risk assessment according to UICC/IGCCCG stage and prognostic index.

Markers are taken before orchiectomy and repeated a minimum of 7 days after orchiectomy. Pure classical seminoma does not secrete AFP; however, in some cases elevated levels of HCG may be present.

Patients with raised AFP should be managed as for non-seminoma, even if histology is pure seminoma.

Testicular sonography (7.5 MHz transducer) should be conducted, also noting the size of the contralateral testis. Thoracic CT scan (not mandatory for seminoma stage I), abdomen and pelvis [III, B]. MRI of the central nervous system is needed only in advanced stages or with symptoms. Bone scan should be conducted in case of indirect indicators for involvement (e.g. symptoms).

PET scanning does not contribute in early stages of seminoma [I, B], but is a possible option for stages II/III, in particular for defining treatment strategy in case of residual tumour.

If fertility is an issue, the following is recommended: determination of total testosterone, lutenizing hormone (LH) and follicle-stimulating hormone (FSH) (determined before operation), semen analysis and sperm banking (before operation or chemotherapy).

In case of a borderline lymph node size in imaging (normal <1 cm), CT scan should be repeated 6 weeks later before defining definitive treatment strategy. If imaging is normal, tumour marker decline should be monitored until normalization in order to discriminate stage I and disseminated disease.

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Definition of stage and risk classification must be done according to the UICC/American Joint Committee on Cancer (AJCC) and IGCCCG classification (Table 1).

For histology, the World Health Organization (WHO) classification must be used and the report must specify the tumour localization, size, multiplicity, extension of tumour (e.g. in rete testis or other tissue), pT category (UICC), histopathological type (WHO) and presence of syncytiotrophoblasts. In pluriform tumours, each individual component should be described, with percentage presence or absence of vascular invasion (venous or lymphatic) and presence of TIN.

treatment of primary tumour

Orchiectomy is standard of care and partial orchiectomy may be performed in specific indications [II, B].

Surgery of the primary should be performed before any further treatment, unless there is life-threatening metastatic disease and clear clinical diagnosis of germ cell tumour by marker elevation which requires immediate chemotherapy.

Tumour marker analysis should be performed before surgery and, if elevated, 7 days after surgery to determine the half-life kinetics. Tumour markers should be monitored until normalization. Markers should be taken after surgery, even if normal.

radical orchiectomy

Radical orchiectomy is performed through an inguinal incision [II, A]. Any scrotal violation for biopsy or open surgery should be strongly avoided. Tumour-bearing testis is resected with the spermatic cord at the level of the internal inguinal ring.

A frozen section is recommended in doubtful cases (of small tumours) before definitive surgery [II, B], to allow organ-sparing surgery.

organ-preserving surgery/partial orchiectomy

Radical orchiectomy may be avoided and replaced by organ preserving surgery; however, only in highly experienced centres and, in particular, in the case of synchronous bilateral testicular tumours, metachronous contralateral (second) testicular tumour, tumour in a solitary testis and sufficient endocrine function, and contralateral atrophic testis.

After local resection the spared testicular tissue always contains TIN, which can be destroyed by adjuvant radiotherapy. This can and should be delayed in patients who wish to father children, but for a period as short as possible.

contralateral biopsy for diagnosis of TIN

Some 3%–5% of testicular cancer patients have TIN in the contralateral testis with the highest risk (≥34%) with testicular atrophy (volume <12 ml) and age <40 years, and in patients with extragonadal germ cell tumour prior chemotherapy (≥33%), but only in 10% post-chemotherapy. If untreated, invasive testicular tumour develops in 70% of the TIN-positive testis within 7 years.

The sensitivity and specificity of one random biopsy for the detection of TIN is very high. Therefore, patients should be informed about the potential risk of TIN and a contralateral biopsy should be offered. However, patients themselves should be given the opportunity to decide whether a biopsy should be done or only monitoring performed—assuming the same high level of survival (nearly 100%) whatever strategy is chosen.

If the patient has had chemotherapy a biopsy should not be taken <2 years from treatment.

treatment of TIN

If TIN has been diagnosed the options include immediate definitive treatment, surveillance with delayed active treatment or no treatment. The strategy should be chosen by the patient depending on the individual needs, in particular if fertility is an issue. However, fertility potential is often very low in this group of patients. If fertility has to be maintained, definitive treatment should be delayed and substituted by active surveillance until conception followed by either active treatment or further surveillance. If fertility is not relevant, irradiation with 16–20 Gy (2 Gy fraction, five·times per week) [III] should be performed (the strongest evidence is for 20 Gy).

In patients with TIN and no gonadal tumour (incidental diagnosis, e.g. by biopsy for infertility or extragonadal germ cell tumours) orchiectomy is preferred over irradiation, because of potential damage to the contralateral, non-affected testis by scattered radiation.

For TIN in patients receiving chemotherapy, chemotherapy eradicates TIN in two-thirds of patients. Therefore, treatment for TIN is only indicated if re-biopsy after chemotherapy is considered; however, not earlier than 2 years after chemotherapy. Instead of definitive treatment for TIN, it is strongly suggested to follow up the patient by monitoring alone, including the possibility of a (re)biopsy.

treatment of stage I

Some 75% of patients with seminoma have stage I disease, with a survival of >99% independent of the chosen strategy. Most important is to minimize the burden of treatment as much as possible. Active (adjuvant) treatment should be avoided and substituted by active surveillance independent of the individual risk for relapse (Table 2).

The relapse rate at 5 years is 12%, 16% and 32% in patients without risk factors, with one risk factor and with two risk factors (tumour size ≥4 cm; invasion of the rete testis), respectively [II, B]. In 97%, relapse occurs in the retroperitoneal or high iliac lymph nodes. Late relapse is possible even after 10 years in very rare cases.

A risk-adapted strategy with selection of adjuvant treatment according to the individual risk is currently being investigated and still experimental.

With surveillance strategy as standard approach, up to 88% of the standard patient population does not need any treatment after the local tumour ablation. Only if surveillance is not applicable, the equally effective alternatives are either adjuvant carboplatin (one cycle, area under the curve 7) [I, A] or adjuvant radiotherapy (20 Gy in 2 Gy fractions; para-aortic fields) (for field description see Table 3).

Table 1. Staging of seminoma according to UICC/AJCC and IGCCCG classification

Clinical Stage	TNM (UICC/AJC) catgory					Serum tumor markers (S)			IGCCCG prognostic group[c]
	T		N	M	S	LDH[a]	ßHCG (mIU/ml)[b]	AFP (ng/ml)	
0	pTis	intratubular germ cell neoplasia	N0	M0	-	-	-	-	n.a.
IA	pT1	limited to testis and epididymis, **without** vascular/ lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis	N0	M0	S_{any}	any level	any level	normal	n.a.
IB	pT2	limited to testis and epididymis, **with** vascular/ lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis	N0	M0	S_{any}	any level	any level	normal	n.a.
	pT3	invasion of spermatic cord							
	pT4	invasion of scrotum							
IIA	T_{any}		N1 (≤ 2 cm)	M0	S_{any}	any level	any level	normal	n.a.
IIB	T_{any}		N2 (>2-5 cm)	M0	S_{any}	any level	any level	normal	n.a.
IIC	T_{any}		N3 (>5 cm)	M0	S_{any}	any level	any level	normal	good
IIIA/B/C	T_{any}		N_{any}	M1a (non-regional nodal and/or pulmonary metastases)	S_{any}	any level	any level	normal	good
IIIC	T_{any}		N_{any}	M1b (liver, bone, CNS or other visceral metastases, e.g. intestinum or skin; ± pulmonary metastases)	S_{any}	any level	any level	normal	intermediate
IIIC	mediastinal primary		N_{any}	M_{any}	S_{any}	any level	any level	normal	intermediate

[a] N indicates the upper limit of normal for the LDH assay, [b] Cave: ßHCG levels are given in mIU/ml; to convert in ng/ml divide by factor 5

[c] poor prognosis is not applicable in seminoma

n.a.: not applicable

Table 2. Treatment algorithm for seminoma

Clinical stage	Standard treatment	Only, if standard is not applicable	Status after treatment	Further management	Management at relapse/ progression
I	**Surveillance**	**Adjuvant treatment** - Carboplatin, 1cycle AUC 7 or - Radiotherapy*		• Follow up	Chemotherapy as stage IIC/III
IIA (1-2 cm) IIB "borderline" (2-2.5 cm)	**Radiotherapy***	**Chemotherapy** - PEB x 3 cycles - If arguments against bleomycin: PE x 4 cycles	• CR	• Follow up	If previous radiotherapy: chemotherapy as stage IIC/III
			• Residual tumour	• Follow up	
IIB (2.5-5 cm)	**Chemotherapy** • PEB x 3 cycles • If arguments against bleomycin: PE x 4 cycles	**Radiotherapy***	• CR	• Follow up	If previous chemotherapy: salvage chemotherapy; consider radiotherapy for localized relapse
IIC/III	**Chemotherapy** • Good prognosis (IGCCCG): PEB x 3 cycles (3 or 5 d)	**Chemotherapy** Good prognosis: - PE x 4 cycles	• CR	• Follow up	• Relapse from CR/NED: - Standard salvage chemotherapy • Small localized relapse: - consider radiotherapy • Progression under follow up, residual, non resected disease - salvage chemotherapy - exceptional: local (re-)irradiation
			• Residual tumour: < 3 cm: PET optional	• no PET done: follow up • PET done and negative: follow up • PET done and positive: • consider resection or alternatively • follow up	
	• Intermediate prognosis (IGCCCG): PEB x 4 cycles (5 d)	Intermediate prognosis: - PEI/ ≈ VIP x 4 cycles	• Residual tumour: > 3 cm: PET recommended	• no PET done: follow up or resection • PET done and negative: follow up • PET done and positive: consider resection	

* see table 3 radiotherapy

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Table 3. Radiation doses and fields for early stage seminoma

Clinical stage	Radiation field	Dose/ fraction/ time
I	**Paraaortic field** upper border of Th 11 lower border of L 5 lateral extension: ipsilateral to renal hilium contralateral: processus transversus of the lumbar vertebrae	20 Gy/ 10 fractions/ 2 weeks
IIA "IIB border line"	**Paraaortic + ipsilateral iliac field** upper border of Th 11 lower border of ipsilateral acetabulum lateral extensions see stage I	30 Gy/ 15 fractions/ 3 weeks
IIB	**Paraaortic + ipsilateral iliac field** upper border of Th 11 lower border of ipsilateral acetabulum lateral extensions: individually modified according to extension of lymph nodes + additional safety margin of 1-1.5 cm	36 Gy/ 18 fractions/ 3.5 weeks

Both options deliver the burden of active systemic or local treatment to 100% of the patients and, in addition, full PEB chemotherapy to 3%–5% of the patients because of relapse after adjuvant treatment. Since with any modality (surveillance only or adjuvant carboplatin or radiation) the survival is ≥98%. Surveillance offers the lowest burden of overall treatment.

treatment of stage IIA (lymph nodes 1–2 cm)/borderline IIB (lymph nodes 2–2.5 cm)

Clinical stage IIA seminoma should be verified beyond standard imaging, e.g. by fine-needle biopsy, before initiation of systemic chemotherapy.

Standard treatment is para-aortic and ipsilateral iliac radiotherapy to 30 Gy in 2 Gy fractions (Table 3).

Chemotherapy (PEB for three cycles or PE for four cycles, if there are arguments against bleomycin) is an equivalent option with different and more acute toxicities, but probably less risk for secondary cancer.

treatment of stage IIB (lymph nodes 2.5–5 cm)

PEB for three cycles is standard (3- or 5-day schedule). If there are arguments against bleomycin [reduction in lung capacity, emphysema, severe (ex)smokers, etc.] then four cycles of PE are used (Table 2).

For patients refusing or otherwise non-candidates for chemotherapy, para-aortic and ipsilateral iliac field radiotherapy to 36 Gy in 2 Gy fractions is standard (Table 3).

treatment of advanced seminoma stage IIC/III

Chemotherapy with PEB is standard treatment (Table 2): three cycles for good prognosis patients (3- or 5-day schedule) and four cycles for intermediate prognosis patients (5-day schedule) (see below).

In case of an increased risk for bleomycin-induced lung toxicity, three cycles of PEB in good prognosis patients may be substituted by four cycles of PE. In patients with intermediate prognosis the substitution of bleomycin by ifosfamide, without increasing the number of cycles, seems to be an appropriate option [I, B].

Chemotherapy consists of PEB given as a 5- or 3-day schedule for good prognosis patients and as 5-day schedule for intermediate prognosis patients [I, B]. The 5-day schedule is cisplatin 20 mg/m^2 (30–60 min), days 1–5; etoposide 100 mg/m^2 (30–60 min), days 1–5; bleomycin 30 mg (absolute) bolus, days 1, 8 and 15. The 3-day protocol is cisplatin 50 mg/m^2 (30–60 min), days 1–2; etoposide 165 mg/m^2 (30–60 min), days 1–3; bleomycin 30 mg (absolute) bolus, days 1, 8 and 15.

In the case of complete response, follow-up only is required. In cases of residual tumour >3 cm, a PET scan (a minimum of 6 weeks after chemotherapy) is recommended, whereas it is only

Table 4. Follow-up for seminoma

Clinical stage	Strategy		investigations (year)					
			1	2[b]	3	4	5[b]	6 to 10[b]
I	Surveillance	Exam/markers*	4x	4x	3x	2x	2x	1x
		Chest X-ray	2x	2x	1x	1x	1x	-
		CT abdomen	2x	2x	1x	1x	1x	-
	Carboplatin	Exam/markers*	4x	3x	2x	2x	2x	(1x)?[c]
		Chest X-ray	2x	2x	2x	1x	1x	(1x)?[c]
		CT abdomen	2x	2x	1x	-	1x	(1x)?[c]
	Radiotherapy	Exam/markers*	4x	3x	2x	2x	2x	-
		Chest X-ray	2x	2x	2x	1x	1x	-
		CT abdomen/pelvis	2x	2x	1x	-	1x	-
IIA/B	Radiotherapy	Exam/markers*	4x	3x	2x	2x	2x	-
		Chest X-ray	3x	1x	1x	1x	1x	-
	Chemotherapy	CT abdomen/pelvis	2x	1x	-	-	1x	-
IIC/III good	Chemotherapy	Exam/markers*	6x	3x	2x	2x	2x	-
		Chest X-ray	3x	3x	1x	1x	1x	-
IIC/III intermediate		CT abdomen/pelvis	CT 1-4x until CR with or without surgery, than according to chest X-ray plan					

[a] AFP, HCG, LDH

[b] Determination of late effects: Urea and electrolytes, fasting cholesterol (HDL, LDL), triglycerides, fastin glucose, FSH, LH, Testosterone

[c] Policies vary among countries and hospitals and there is no definitive evidence.

optional in residual lesion <3 cm (in lesions <3 cm predictive value is less proven).

If PET scan is positive there is strong evidence for residual active tumour and resection should be considered. If PET scan is negative, follow-up only without active treatment is needed. If no PET is done, lesions >3 cm can be either resected or followed only until resolution or progression.

salvage treatment

relapse after radiation of early stages of seminoma

Chemotherapy is the treatment of choice (standard chemotherapy as in stage IIC/III). In cases with localized, small volume relapse (re)irradiation may be considered instead of chemotherapy, in particular if the interval has been long and it is not a disseminated relapse.

relapse after primary chemotherapy

salvage chemotherapy. Relapse after a longer (>3 months) period following initial favourable response does not always represent a platinum-resistant situation. Cisplatin is part of salvage treatment protocols, preferably together with additional agents that have not been used in the first-line treatment.

After second-line and, in some cases, also after third-line treatment, chemosensitivity may still be present.

Standard first-line salvage chemotherapy is standard dose VIP (etoposide, ifosfamide, cisplatin), TIP or VeIP. There is no proven benefit of high-dose chemotherapy for first- or second-line salvage treatment.

In refractory patients, e.g. those who never reach a marker-negative complete response after first-line treatment or have no favourable response after salvage treatment, no standard treatment can be recommended. Gemcitabine/paclitaxel may be considered as an option. High-dose chemotherapy in this setting is highly experimental and should only be performed in clinical trials. Surgery should be part of the strategy, in particular in those patients with localized or late relapse with poor response to chemotherapy. Patients should be included in clinical trials and referred to expert centres whenever possible.

response evaluation for metastatic disease

The treatment effect must be monitored by appropriate measures (chest X-ray, CT scan and markers) at 1 month after end of treatment [IV, B]. In the case of residual mass a PET scan is recommended [II].

follow-up

The recommended follow-up schedules are very pragmatic and have never been validated. Table 4 gives an exemplary programme.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the consensus conference panel.

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