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Testicular non-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 nonmalignant 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 testicular mass removed by inguinal orchiectomy or by testis-conserving surgery [IV, B].

Biopsy or, instead, high α-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG) (without biopsy) in patients presenting with extragonadal tumour syndrome [IV, B].

In advanced and rapidly progressive disease requiring urgent chemotherapy, diagnosis may be based on typical clinical picture and marker elevation alone, without orchiectomy.

Germ cell tumour may present extragonadally in the retroperitoneum or mediastinum in a minority of cases.

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staging and risk assessment

Full blood count, creatinine, electrolytes and liver enzymes should be obtained. Tumour markers [AFP, β-HCG and lactate dehydrogenase (LDH)] are needed for risk assessment according to UICC/IGCCCG stage and prognostic index. Markers are determined before orchiectomy and repeated a minimum of 7 days after orchiectomy (for differentiation of stage and IGCCCG prognostic group). HCG must be followed until normalization.

Testicular sonography (7.5 MHz transducer) should be conducted, also noting the size of the contralateral testis. CT scan of chest, 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 the case of indicators of involvement (e.g. symptoms). PET scanning does not contribute and routine use is not recommended [I, B].

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

In the 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.

Early consultation of an oncologist is mandatory. 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.

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

Clinical Stage	TNM (UICC/AJC)				Serum tumor markers (S) to be determined after orchiectomy				Clinical prognostic classification
	T		N	M	S	LDH[a]	ßHCG	AFP (ng/ml)	
0	pTis	intratubular germ cell neoplasia	N0	M0	S0[c]/ SX[d]	normal	normal	normal	
IA	T1	limited to testis and epididymis, **without** vascular/ lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis	N0	M0	S0	normal	normal	normal	low risk (≤20%)
IB	T2	limited to testis and epididymis, **with** vascular/ lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis	N0	M0	S0	normal	normal	normal	high risk (≥50%)
IB	T2	limited to testis and epididymis, **with** vascular/ lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis	N0	M0	S0	normal	normal	normal	IGCCCG prognostic group
	T3	invasion of spermatic cord							
	T4	invasion of scrotum							
IS	Tany		N0	M0	S1	<1.5xN and	<5000 and	<1000	good
					S2	1.5-10xN or	5000-50 000 or	1000-10 000	intermediate
					S3	>10xN or	>50 000 or	>10 000	poor
IIA	Tany		N1 (≤ 2 cm)	M0	S0	normal	normal	normal	
					S1	<1.5xN and	<5000 and	<1000	
IIB	Tany		N2 (>2-5 cm)	M0	S0	normal	normal	normal	good
					S1	<1.5xN and	<5000 and	<1000	
IIC	Tany		N3 (>5 cm)	M0	S0	normal	normal	normal	good
					S1	<1.5xN and	<5000 and	<1000	
IIIA	Tany		N_{any}	M1a (non-regional nodal and/or pulmonary metastases)	S0	normal	normal	normal	good
					S1	<1.5xN and	<5000 and	<1000	
IIIB	Tany		N1-3	M0	S2	1.5-10xN or	5000-50 000 or	1000-10 000	intermediate
			N_{any}	M1a					
IIIC	Tany		N1-3	M0	S3	> 10xN or	>50 000 or	>10 000	poor
				M1a	S3	> 10xN or	>50 000 or	>10 000	poor
			N_{any}	M1b (liver, bone, CNS or other visceral metastases, e.g. intestinum or skin; ± pulmonary metastases)	S_{any}	any level	any level	any level	poor
IIIC	mediastinal primary		N_{any}	M_{any}	S_{any}	any level	any level	any level	poor

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

[c] S0: no raised markers, [d] SX: marker not available/or not performed

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 cases 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 *per se* 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.

post-operative treatment

Patients should be treated by oncologists with experience in the management of testicular cancer. In early stage non-seminoma there are several treatment options with different treatment burden and toxicities. The patient must be well informed about the different treatment modalities, their acute and late toxicities, and the overall outcome.

If treatment is performed correctly, the cure rate of patients with non-seminoma in stage I is ∼99%, in stage IIA/B 98% and in advanced disease with good prognosis 90%, intermediate prognosis 80% and poor prognosis 60%.

treatment of non-seminoma stage I

Stage I patients are divided into low risk (20% relapse rate) or high risk (40%–50% relapse rate) according to the absence or presence of vascular (lymphatic or venous) invasion. The prognosis is excellent (98%–100%), whichever management option is used. The choice should be made on the basis of acute and late toxicities, overall treatment burden and personal preferences, including fertility issues associated with family planning. Sperm banking should be offered if active treatment is chosen. However, two or even four cycles of PEB are associated with a high level of residual fertility after recovery from chemotherapy-associated damage.

The number of cycles of adjuvant chemotherapy is a current research topic. The option of one cycle of PEB is prospectively compared with the current standard of two cycles of PEB, with preliminary data indicating that one cycle of PEB might be sufficient [IIA].

treatment of low-risk non-seminoma stage I

The standard option for low risk without vascular invasion is surveillance (Table 2). If surveillance is not applicable (e.g. no possibility to follow up by markers and imaging), adjuvant chemotherapy with two cycles of PEB is recommended.

treatment of high-risk non-seminoma stage I

There are two treatment options: adjuvat chemotherapy (two cycles of PEB) or surveillance.

risks and benefits. Both options should be discussed, including detailed information about risks and benefits. The survival is the same (99%) whichever option is used. In detail:

- surveillance. Relapse rate ∼40%–50%; therefore chemotherapy (three cycles of PEB) eventually required for only 50% of the patients.
- adjuvant chemotherapy. Relapse rate ∼3%–4%, but

Table 2. Treatment algorithm for non-seminoma stage I

Clinical stage	Clinical prognostic classification	Treatment		
		1st choice	2nd choice	3rd choice
IA	"Low risk" (no vascular invasion)	Surveillance	Adjuvant chemotherapy (PEB x 2 cycles)	Only for very restricted cases (e.g. if chemotherapy or surveillance declined by the patient): nerve sparing-RPLND
IB	"High risk" (vascular invasion)	2 comparable options with same final outcome (> 98% survival) with different treatment/ follow up burden • adjuvant chemotherapy (PEB x 2 cycles) or • surveillance	• Surveillance or • adjuvant chemotherapy (PEB x 2 cycles)	

chemotherapy (two cycles of PEB) used for 100% of the patients.

role of RPLND in stage I low-/high-risk patients

For very restricted cases, only if surveillance or adjuvant chemotherapy is declined by the patient due to very specific or personal reasons, a nerve-sparing RPLND may be considered. This treatment has the highest treatment burden with the lowest efficacy and should be performed by specialized surgeons only, in order to minimize complications including loss of ejaculation. The risk of relapse is reduced but not eliminated since the risk to develop lung metastases remains.

treatment of non-seminoma stage IIA/B

These stages belong to the IGCCCG good prognosis category.

stage IIA, marker negative

There are two equivalent strategies.

strategy 1. Only follow-up every 6 weeks until either regression/ normalization or progression with treatment accordingly (Table 3).

strategy 2. Active treatment with either biopsy or nerve-sparing RPLND.

Both options have the same overall result. Further management depends on the results of the follow-up or RPLND (Table 4).

stage IIA, marker positive, or stage IIB, marker positive or negative

The standard treatment is chemotherapy with PEB for three cycles (Table 3). PE for four cycles may be used if there are arguments against the use of bleomycin.

In the case of complete response no further treatment is necessary. In the case of residual tumour (>1 cm lymph node diameter) resection of this residual lesion should be performed, followed by routine follow-up (independent of the result of the resection).

treatment of advanced non-seminoma stage [stage Is, IIb, IIc, III]

The treatment options for advanced non-seminoma with good, intermediate and poor prognosis are given in Table 4. This table also gives the individual steps for further management depending on the result of the primary chemotherapy, including secondary surgery after chemotherapy and salvage treatment.

Patients with good prognosis receive three cycles of PEB. PEB can be given as classical 5- or 3-day protocol [I, B]. If there are arguments against the use of bleomycin, e.g. factors predisposing for bleomycin-induced acute or cumulative pneumonitis/fibrosis, PEB can be substituted by PE × 4 cycles.

In intermediate and poor prognosis patients PEB for four cycles is standard, given as 5-day schedule. Since four cycles are given, the 3-day schedule should not be applied [I, B]. PEB can be substituted in the case of factors against the use of bleomycin by PEI for four cycles.

Chemotherapy cycles must be repeated every 3 weeks, independent of leukocyte count but with platelet recovery >100 000 count (at day 22); only in this case and in the case of infection at day 22 should the next cycle be delayed until recovery.

Supportive management with prophylactic use of G-CSF or antibiotics and modern anti-emetic therapy ($5HT_3$ receptor antagonist + steroid ± NK-1 receptor antagonist) are recommended.

High-dose chemotherapy has proved not to be of benefit in three randomized trials.

management after primary chemotherapy

If restaging 4 weeks after the last treatment cycle reveals elevated markers and/or residual tumour, the next steps depend on the individual situation of the patient.

In principal, any residual tumour must be resected if there is no marker increase within the first weeks after termination of chemotherapy.

In the case of a marker plateau, the resection should be delayed since there is a good chance that this represents a 'pseudomarker plateau' resulting from necrotic tumour tissue

Table 3. Treatment algorithm for non-seminoma stage II A/B

Clinical stage	Treatment	Result		Further management
II A marker + II B marker +/-	Chemotherapy • standard: PEB x 3 cycles • option: PE x 4 cycles	• CR	→	Follow up
		• Residual tumor (> 1 cm)	→	Resection and follow up
II A marker -	**Strategy 1*** follow up only q 6 weeks	• PD, and marker ⊕	→	PEB x 3 cycles (or PE x 4 cylces, in case of residual tumour (> 1 cm): resection
		• PD, marker remains ⊖	→	PEB x 3 cycles (or PE x 4 cycles) or* Nerve sparing-RPLND
		• NC	→	Nerve sparing-RPLND
		• Regression	→	Further follow up
	Strategy 2* active treatment: biopsy or nerve sparing-RPLND	• Pathological stage I	→	Surveillance (independent of vascular invasion)
		•Pathological stage II A/B	→	• Follow up or* • PEB x 2 cycles or* • PE x 2 cycles

* equivalent options

which is still resolving and liberating tumour markers into the blood. These patients should be followed up in short intervals until markers have been normalized or the final decision with respect to the resection can be made.

In the case of multiple metastases in several organs or brain or liver, resection is probably not appropriate and the indications and extent of resection should be discussed with experts and treated at specialized centres.

Further management depends on the result of the primary treatment and secondary surgery. In the case of complete response or R0 resection with scar tissue only or differentiated teratoma or viable tumour <10% of the resected specimen, follow-up is recommended, whereas in the case of >10% viable tumour, consolidation chemotherapy with, for example, two cycles of VIP should be considered and seems to be appropriate[III].

In the case of incomplete resection of viable tumour and/or residual tumour, salvage chemotherapy should be applied, as well as in the case of relapse from complete remission (CR) or progression after marker normalization in the case of unresectable residual lesions.

monitoring during and after treatment

Tumour markers must be determined before every cycle. Four weeks after the last cycle, determination of tumour markers as well as imaging (chest X-ray, CT scan or MRI of the initial sites) should be conducted.

A PET scan is regarded as experimental (should not be performed outside of clinical trials).

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 further 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, TIP or VeIP. There is no proven benefit of high-dose chemotherapy either in first- or second-line salvage treatment in any patient subgroup.

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 experimental and should only be performed in clinical trials. Surgery should be part of the strategy, particularly in those patients with localized or late relapse, and with poor response to chemotherapy. Patients should be included in clinical trials and referred to expert centres whenever possible.

Table 4. Treatment algorithm for advanced non-seminoma stage CS IIC–III

IGCCCG-prognosis group	Survival	Treatment	Result	Next step	Further management
Good - testis/retroperitoneal primary and - no liver/bone/CNS metastases and - good markers: - LDH < 1,5 N[a] and - ßHCG < 5000 mIu/ml[b] and - AFP < 1000 ng/ ml	90%	• PEB x 3 cycles (3 or 5 d schedule) • If arguments against bleomycin: PE x 4 cycles	• Marker normalized and no residual tumour	→ Follow up	→ Follow up
			• Marker normalized and residual, but resectable tumour	→ Resection	
				• R1/2	→ Salvage chemotherapy
				• R0, no viable tumour	→ Follow up
				• R0, viable tumour present <10%	→ Follow up
				• R0, teratoma	→ Follow up
				• R0, viable tumour >10%	→ Consolidation chemotherapy (e.g. VIP 2x cycles)
				• R?, unclear resection margins	
Intermediate - testis/retroperitoneal primary and - non regional nodal and/or pulmonary metastases - intermediate markers: - LDH > 1,5-10 x N and/or - ßHCG > 5000-50000 mIu/ml and/or - AFP > 1000-10000 ng/ ml	80%	• PEB x 4 cycles (5 d schedule) • If arguments against bleomycin: PEI/ ≈ VIP x 4 cycles	• Marker not normalized and residual tumour, but potentially resectable	→ Follow up q 4-12 w	
				• markers normalised or plateau	→ Resection
				• markers increased	→ Salvage chemotherapy[d]
Poor - mediastinal primary and/or - liver/bone/CNS or other visceral metastases ± pulmonary metastases and/or - poor markers - any of: - LDH > 10 x N and/or - ß-HCG > 50000 mIu/ml and/or - AFP > 10000 ng/ ml	60%		• Marker normalized, but irresectable and/or multiple residual tumour[c]	→ Follow up q 8 w in case of progression:	
				• >12 w	→ Salvage chemotherapy[e]
				• <12 w	→ Experimental (high dose chemotherapy)

[a] N indicates the upper limit of normal for the LDH assay

[b] Cave: ß-HCG levels are given in mIU/ml, to convert in ng/ml divided by factor 5

[c] consider PET in individually patients for further planning of prognosis and management

[d] consider experimental chemotherapy in protocols for "refractory patients" (e.g. new drugs)

[e] consider also local radiotherapy, if appropriate/applicable

Table 5. Follow-up for non-seminoma

Clinical stage	Strategy	Relapse rate		Year					
				1	2[b]	3	4	5[b]	6 to 10[b]
I	Surveillance	Low risk: ≤ 20%	exam/ markers[a]	12x	4x	3x	2x	2x	?[c]
			chest X-ray	7x	4x	3x	2x	2x	?[c]
		High risk: ≥ 50%	CT abdomen	2x	1x	-	-	-	?[c]
	Chemotherapy	≤ 3%	exam/ markers[a]	5x	3x	2x	2x	2x	?[c]
			chest X-ray	3x	1x	1x	1x	1x	?[c]
			CT abdomen	1x	-	-	-	-	?[c]
IIA/B, IIC + III	Chemotherapy	Good: 10%	exam/ markers[a]	6x	3x	2x	2x	2x	-
		Intermediate: 20%	chest X-ray	3x	3x	1x	1x	1x	-
		Poor: 40%	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.

late relapse

If technically feasible, radical surgical resection of all lesions should be performed, irrespective of the level of tumour markers, particularly in poor responders to chemotherapy. If the lesions are not completely resectable, at least a biopsy should be obtained for histological assessment. Salvage chemotherapy should be initiated.

Late relapses (when chemotherapy has been used as part of the management) respond less well to new chemotherapy (often yolk sac tumour, AFP-positive, slow-growing teratoma). If the patient responds to salvage chemotherapy, secondary surgery should be conducted whenever possible.

late toxicity

There is a 3% risk of developing contralateral testis tumour during the first 15 years (if TIN has not been diagnosed or diagnosed and treated prophylactically by radiation). There is a risk of secondary cancer, including leukaemia, gastrointestinal carcinoma, genitourinary cancer, lung cancer and sarcoma, particularly in previously irradiated fields.

Chemotherapy-related late toxicity includes cardiovascular disease and metabolic syndrome (hypercholesterolaemia, hypertension and diabetes), hypogonadism, persisting neurotoxicity, Raynaud's syndrome and ototoxicity.

follow-up

Relapses are most commonly detected by marker elevation.

A reduced number of CT scans during follow-up is as effective as a higher frequency [I, B] (evidence level only for stage I).

All other recommendations are not prospectively proved, but may serve as a basis for clinical practice (Table 5). Follow-up beyond 5 years is probably relevant to detect late toxicities or secondary cancer for early intervention.

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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