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

H.-J. Schmoll¹, K. Jordan¹, R. Huddart², M. P. Laguna Pes³, A. Horwich², K. Fizazi⁴ & V. Kataja⁵
On behalf of the ESMO Guidelines Working Group*

¹Department of Oncology/Haematology/Haemostaseology, University Hospital Halle, Halle, Germany; ²Department of Academic Radiotherapy, Institute of Cancer Research, Royal Marsden Hospital, Sutton Hospital, UK; ³Department of Urology, AMC University Hospital, Amsterdam, The Netherlands; ⁴Department of Medicine, Institute Gustave Roussy, Villejuif, France; ⁵Department of Oncology, Kuopio University Hospital, Kuopio and Vaasa Central Hospital, Vaasa, Finland

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.

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. This is in accordance with a 2%–3% rate of synchronous contralateral or metachronous testicular cancer.
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...

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

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>TNM (UICC/AJCC)</th>
<th>Serum tumor markers (S) to be determined after orchiectomy</th>
<th>Clinical prognostic classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>pTis intratubular germ cell neoplasia</td>
<td>N0 M0</td>
<td>S0</td>
</tr>
<tr>
<td>IA T1</td>
<td>limited to testis and epididymis, without vascular/lymphatic invasion or tumour may invade into the tunica albuginea but not the tunica vaginalis</td>
<td>N0 M0</td>
<td>S0</td>
</tr>
<tr>
<td>IB T2</td>
<td>limited to testis and epididymis, with vascular/lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis</td>
<td>N0 M0</td>
<td>S0</td>
</tr>
<tr>
<td>IB T2</td>
<td>limited to testis and epididymis, with vascular/lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis</td>
<td>N0 M0</td>
<td>S0</td>
</tr>
<tr>
<td>IB T3</td>
<td>invasion of spermatic cord</td>
<td>N0 M0</td>
<td>S0</td>
</tr>
<tr>
<td>IS Tany N0 M0</td>
<td>S1 &lt;1.5xN and &lt;5000 and &lt;1000</td>
<td>good</td>
<td></td>
</tr>
<tr>
<td>IS Tany N0 M0</td>
<td>S2 1.5-10xN or 5000-50 000 or 1000-10 000</td>
<td>intermediate</td>
<td></td>
</tr>
<tr>
<td>IS Tany N0 M0</td>
<td>S3 &gt;10xN or &gt;50 000 or &gt;10 000</td>
<td>poor</td>
<td></td>
</tr>
<tr>
<td>II A Tany N1 (≤2 cm) M0</td>
<td>S0 normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>II A Tany N2 (&gt;2-5 cm) M0</td>
<td>S0 normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>II B Tany N3 (&gt;5 cm) M0</td>
<td>S0 normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>II A Tany Nany M1a (non-regional nodal and/or pulmonary metastases)</td>
<td>S0 normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>II B Tany N1-3 M0</td>
<td>S2 1.5-10xN or 5000-60 000 or 1000-10 000</td>
<td>intermediate</td>
<td></td>
</tr>
<tr>
<td>II C Tany Nany M1a</td>
<td>S3 &gt;10xN or &gt;50 000 or &gt;10 000</td>
<td>poor</td>
<td></td>
</tr>
<tr>
<td>III C mediastinal primary Nany Many Sany</td>
<td>any level</td>
<td>any level</td>
<td>any level</td>
</tr>
</tbody>
</table>
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 tests.

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 tests with the highest risk (234%) with testicular atrophy (volume <12 ml) and age <40 years, and in patients with extragonadal germ cell tumour prior chemotherapy (233%), but only in 10% post-chemotherapy. If untreated, invasive testicular tumour develops in 70% of the TIN-positive tests 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
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 [1, 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 x 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 [1, 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.
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.
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. 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.

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. 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.

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

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Treatment</th>
<th>Result</th>
<th>Further management</th>
</tr>
</thead>
</table>
| II A marker + | Chemotherapy  
• standard: PEB x 3 cycles  
• option: PE x 4 cycles | CR → | Follow up |
| II B marker +/- | | Residual tumor (> 1 cm) | Resection and follow up |
| II A marker - | | PD, and marker @ | PEB x 3 cycles (or PE x 4 cycles, 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 1*  
follow up only q 6 weeks | | |
| | 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  
• PE x 2 cycles |

* equivalent options
Table 4. Treatment algorithm for advanced non-seminoma stage CS IIC-III

<table>
<thead>
<tr>
<th>IGCCCG-prognosis group</th>
<th>Survival</th>
<th>Treatment</th>
<th>Result</th>
<th>Next step</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>90%</td>
<td>PEB x 3 cycles (3 or 5 d schedule)</td>
<td>Marker normalized and no residual tumour</td>
<td>Follow up</td>
<td>Follow up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If arguments against bleomycin: PE x 4 cycles</td>
<td>Marker normalized and residual, but resectable tumour</td>
<td>Resection</td>
<td>Salvage chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• R1/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• R0, no viable tumour</td>
<td></td>
<td>Follow up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• R0, viable tumour present &lt;10%</td>
<td></td>
<td>Follow up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• R0, teratoma</td>
<td></td>
<td>Follow up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• R0, viable tumour &gt;10%</td>
<td></td>
<td>Consolidation chemotherapy (e.g. VIP 2x cycles)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• R?, unclear resection margins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>80%</td>
<td>PEB x 4 cycles (5 d schedule)</td>
<td>Marker not normalized and residual tumour, but potentially resectable</td>
<td>Follow up q 4-12 w</td>
<td>Resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If arguments against bleomycin: PEIV x VIP x 4 cycles</td>
<td>• markers normalised or plateau</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• markers increased</td>
<td></td>
<td>Salvage chemotherapy$^a$</td>
</tr>
<tr>
<td>Poor</td>
<td>60%</td>
<td></td>
<td>Marker normalized, but irresectable and/or multiple residual tumour$^b$</td>
<td>Follow up q 6 w in case of progression:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &gt;12 w</td>
<td></td>
<td>Salvage chemotherapy$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &lt;12 w</td>
<td></td>
<td>Experimental (high dose chemotherapy)</td>
</tr>
</tbody>
</table>

$^a$ N indicates the upper limit of normal for the LDH assay
$^b$ Cave: E-HCG levels are given in mIU/ml, to convert in ng/ml divided by factor 5
$^c$ consider PFT 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
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.

Acknowledgements

The manuscript is based on the results of an expert panel discussion, organized and financed by an educational grant of the European Society of Medical Oncology (ESMO) in association with the ESMO Symposium on Testicular Cancer, EIS in May 2008 and was performed as a formal expert consensus conference. Members of the consensus conference panel are H.-J. Schmoll (Chair), Germany; M.P. Laguna (Co-chair), The Netherlands; K. Fizazi (Co-chair), France; A. Horwich (Co-chair), UK; P. Albers, Germany; W. Albrecht, Germany; F. Algaba, Spain; A. Bamias, Greece; I. Bodrogi, Hungary; G. Cohn-Cedermark, Sweden; S. Culine, France; M. Cullen, UK; G. Daugaard, Denmark; M. De Santis, Austria; R. De Wit, The Netherlands; G. Derigs, Germany; K. Dieckmann, Germany; J.P. Droz, France; E. Einhorn, USA; A. Flechon, France; S. Fossa, Norway; R.S. Foster, USA; J. Garcia del Muro Solans, Spain; T. Gauler, Germany; L. Géczi, Hungary; J.R. Germa Lluch, Spain; S. Gillessen, Switzerland; M. Gospodorowicz, Canada; M. Hartmann, Germany; R. Huddart, UK; M. Jewett, Canada; J. Joffe, UK; K. Jordan, Germany; V. Kataja, Finland; O. Klepp, Norway; C. Kollmannsberger, Canada; S. Krege, Germany; L. Looijenga, The Netherlands; G.M. Mead, UK; A. Necchi, Italy; C. Nichols, USA; N. Nicolai, Italy; T. Oliver, UK; D. Ondrus; Slovak Republic; W. Osterhuis, The Netherlands; L. Paz-Ares, Spain; T. Powles, UK; T. Pottek, Germany; E. Rajpert-De Meyts, Denmark; G. Rosti, Italy; G. Rustin, UK; R. Salvioni,
Italy; H. Schmidberger, Germany; F. Sedlmayer, Austria; A. Sella, Israel; C. Sippel, Germany; N.E. Skakkebaek, Denmark; A. Sohaib, UK; S. Tjulandin, Russia; A.W. van den Belt-Dusebout, The Netherlands; H. von der Maase, Denmark; P. Warde, Canada; L. Wood, Canada.

**Literature**