Management of adult testicular germ cell tumours

A national clinical guideline

March 2011
KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 - Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High quality systematic reviews of case control or cohort studies
     High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytic studies, eg case reports, case series
4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A
At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B
A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+
C
A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++
D
Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

GOOD PRACTICE POINTS

☑ Recommended best practice based on the clinical experience of the guideline development group

NHS Evidence has accredited the process used by Scottish Intercollegiate Guidelines Network to produce guidelines. Accreditation is valid for three years from 2009 and is applicable to guidance produced using the processes described in SIGN 50: a guideline developer’s handbook, 2008 edition (www.sign.ac.uk/guidelines/fulltext/50/index.html). More information on accreditation can be viewed at www.evidence.nhs.uk

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity and assesses all its publications for likely impact on the six equality groups defined by age, disability, gender, race, religion/belief and sexual orientation.

SIGN guidelines are produced using a standard methodology that has been equality impact assessed to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/guidelines/fulltext/50/index.html. The EQIA assessment of the manual can be seen at www.sign.ac.uk/pdf/sign50eqia.pdf. The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our web site www.sign.ac.uk.
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1 Introduction

1.1 BACKGROUND

Testicular germ cell tumours are relatively rare. In 2008, 203 new cases were diagnosed in Scotland with a crude incidence of 8.1 cases per 100,000 of the male population, making it the 15th most common cancer in men in Scotland.\(^1\)

It takes on a greater significance than numbers alone might suggest as it is one of the few curable solid cancers even when it has metastasised, with a crude overall five-year survival rate in Scotland of 95.8\%.\(^1\) Although the cure rate is high, the toxicity of therapy is significant with treatment-related deaths and long term effects being documented. Potential effects on employment and fertility are of particular importance in the affected age group.

Testicular germ cell tumours can be subdivided into seminoma and non-seminomatous germ cell tumours (NSGCTs) both of which must always be considered as malignant neoplasms. Seminomas consist of sheets and cords of relatively uniform cells which resemble primitive germ cells whereas NSGCTs exhibit a wide variety of appearances reflecting the potential of the tumour stem cell to differentiate along embryonic and extra-embryonic lines analogous to the fertilised ovum.

NSGCTs and seminomas have different clinical outcomes\(^2\) and require different clinical management, although in some instances it may be difficult to distinguish between poorly differentiated seminomas and NSGCTs.\(^3\)

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the management of testicular cancer. It excludes the management of germ cell testicular tumours in children, germ cell tumours in women and extragonadal tumours.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of particular interest to patients, oncologists, urologists, radiologists, clinical nurse specialists, general practitioners, pathologists, and all healthcare professionals involved in the management of men with testicular germ cell tumours.

1.3 UPDATING THE EVIDENCE

Since the publication of the first SIGN guideline on adult testicular germ cell tumours (SIGN 28) in 1998 treatments for testicular disease have evolved rapidly and some of the recommendations from SIGN 28 are now out of date. This guideline updates SIGN 28 to reflect the most recent evidence on testicular germ cell tumours.

Where no new evidence was identified to support an update, text and recommendations are reproduced from SIGN 28. The original supporting evidence was not re-appraised by the current guideline development group. The key questions used to develop this guideline can be found in Annex 1.

The sections have been re-sequenced to follow the patient pathway. Throughout the guideline the pathology classification has been changed to incorporate the World Health Organisation (WHO) classification in addition to the British Testicular Tumour Panel and Registry (BTTP&R) classification to reflect current practice.
1.3.1 SUMMARY OF UPDATES TO THE GUIDELINE

<table>
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<tr>
<th>Section</th>
<th>Update Type</th>
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</thead>
<tbody>
<tr>
<td>1. Introduction</td>
<td>Minor update</td>
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<td>Annex 1 Key questions addressed in this update</td>
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<td>Annex 2 Pathology of testicular germ cell tumours</td>
<td>Minor update</td>
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<td>Annex 3 CNS metastases in germ cell tumours</td>
<td>New</td>
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1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

1.4.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (product licence). This is known as ‘off label’ use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

Medicines may be prescribed outwith their product licence in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose.
“Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers’ professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.”

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken.

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).

1.4.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

No relevant SMC advice or NICE MTAs were identified.
2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the evidence is based. It does not reflect the clinical importance of the recommendation.

2.1 TUMOUR MARKERS

☑ Serum markers should be checked pre-orchidectomy, 24 hours after orchidectomy and weekly thereafter until normal.

2.2 PRIMARY MANAGEMENT

☑ Clinical specialist nurse involvement is recommended as early as possible in the management of patients with testicular germ cell tumours.

2.3 MANAGEMENT OF STAGE I DISEASE

SEMINOMA

A In patients with stage I seminoma who are to receive adjuvant 'dog-leg' or para-aortic strip radiotherapy, a dose of 20 Gy in ten fractions over two weeks should be prescribed to the International Commission on Radiation Units (ICRU) reference point.

C The potential risk of second malignant neoplasms should be outlined to patients where adjuvant radiotherapy is being considered.

NON-SEMINOMATOUS GERM CELL TUMOURS

☑ Patients on surveillance should be seen in a designated clinic following a strict protocol.

B In low-risk patients under surveillance CT scanning at three and 12 months post-orchidectomy is recommended.

2.4 MANAGEMENT OF METASTATIC DISEASE

A Patients with a good prognosis metastatic non-seminomatous germ cell tumour should receive three cycles of BEP chemotherapy in either a 3-day or 5-day schedule.

2.5 TREATMENT OF RELAPSED DISEASE

D The International Prognostic Factors Study Group’s model should be applied to guide prognostic information for patients who relapse after first line platinum based chemotherapy.
2.6 LATE TOXICITY

- Survivors of testicular cancer should be advised not to smoke.
- Oncologists should advise survivors of testicular cancer and their GPs of the increased risk of cardiovascular disease.
- Patients should remain vigilant of any unusual or alert symptoms, particularly relating to the gastrointestinal, respiratory or urinary tract, and report these promptly to their GPs.
- There should be increased awareness of the risk of haematological malignancies especially after chemotherapy and solid malignancies in or near the fields of radiotherapy. There should be a low threshold for further investigation and appropriate referral to secondary care if any alert symptoms are reported.
3 Presentation and referral

3.1 PRESENTATION

There is evidence to suggest that delay in presentation is more of a problem than delay in referral and this has prompted some authors to suggest that a public education campaign might be helpful.\textsuperscript{5,6} In Scotland, there is recent evidence that patients are presenting with earlier stage disease than previously reported.\textsuperscript{7}

Most general practitioners (GPs) will see a patient with a testicular malignancy only very infrequently, if ever. Most of these patients present with an enlarged testicle or a painless, solid, unilateral mass in the scrotum (lump). A decrease in testicular size may also occur. Scrotal pain is present in around 20\% of patients with tumours at presentation and up to 27\% of patients with testicular cancer may have local pain. Another feature which should heighten suspicion is a dragging sensation in the scrotum. Rare presentations include hydrocoele and gynaecomastia, which appears in around 7\% of cases. Backache is present in about 10\% of patients but is a very common and non-specific symptom.\textsuperscript{8} Reports have not confirmed an association with vasectomy.\textsuperscript{9} A small proportion of patients present following local trauma to the testes, however, it is not thought that the trauma causes the cancer, but rather that it brings an existing tumour to the attention of the patient and physician.

Due to the rarity of testicular malignancy and its variable, complex and potentially toxic treatments, it is imperative that the patient’s general practitioner and other community services are well informed and involved throughout treatment and follow up.

3.2 REFERRAL

Patients with testicular tumours will most often present with a testicular lump. Abnormal masses in the epididymis are a common problem referred for specialist urology assessment but these are unlikely to be testicular tumours and do not represent such an urgent problem. Increasing tumour bulk is associated with advancing stage of disease and correspondingly the need for increasingly toxic therapy and consequently poorer outcomes. It is therefore essential to refer for investigation urgently (within two weeks).

- Patients presenting with a swelling in the scrotum should be examined carefully and an attempt made to distinguish between lumps arising from the body of the testis and other intrascrotal swellings.
- An ultrasound, if available at this stage, should be performed to make a distinction.

Those patients suspected of harbouring a testicular malignancy, ie a lump in the testis, doubtful epididymo-orchitis or orchitis not resolving within two to three weeks, should be referred urgently for urological assessment.
4 Tumour markers

4.1 AFP AND HCG

Management of patients with NSGCTs has improved markedly since immunoassay techniques of high sensitivity and adequate specificity have allowed determination of serum concentrations of alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG). These markers are good detectors of residual NSGCT after orchidectomy. However, neither marker should be regarded as specific for NSGCT and may be raised with a variety of non-germ cell tumour neoplasms. Mild elevations of AFP can be seen after alcohol abuse, and cannabis can similarly raise HCG. However, the combined accuracy and predictive value of HCG and AFP is of a level that a decision to start, continue, modify or resume treatment may be strongly influenced by the finding of rising serum concentrations of either marker.

About 50% of patients with NSGCTs will produce elevated HCG and about 60% elevated AFP. Owing to overlap in positivity the combined sensitivity varies from 60-75%. Serial monitoring of AFP and HCG may enable the biological half-life to be calculated. In the absence of residual disease after orchidectomy this is estimated as 24 hours for HCG and 4-6 days for AFP.\textsuperscript{10}

- Serum markers should be checked pre-orchidectomy, 24 hours after orchidectomy and weekly thereafter until normal.

Measurement of serum AFP and HCG is essential in the follow up of patients with non-seminomatous germ cell tumours.

In patients with seminoma the markers are less useful: whilst 15-40% produce HCG, these are often mild elevations and AFP is not produced by pure seminoma. There are, therefore no generally applicable good serological markers for patients with seminoma. As 25-45% of NSGCTs are marker negative it is important to measure both prior to surgery. Owing to methodological differences between laboratories, great care must be taken in the interpretation of results as reference ranges may vary.

4.2 LDH

Other than as a prognostic indicator in patients with NSGCTs, lactate dehydrogenase (LDH) is not sufficiently specific for general application in disease monitoring. Mild increases in LDH during chemotherapy can be due to hepatic insult and reflect the lack of specificity of this marker.
5 Primary management

Primary orchidectomy is the treatment of choice for most testicular tumours. It is intended that this section on primary treatment should be practicable in any district general hospital in Scotland with surgical facilities, which should include the availability of testicular prostheses.

5.1 PREOPERATIVE INVESTIGATION

One or more markers are raised in 75% of cases of NSGCT and measurement is necessary for staging and follow up. Blood should be taken for assay of the tumour markers AFP, HCG and LDH before operation (see section 4).

Bilateral testicular ultrasound can confirm evidence of disease and measure testicular volume. Chest X-ray may show evidence of metastases. Other staging investigations can be deferred until after the primary orchidectomy and should be arranged in consultation with a specialist centre.

Preoperative investigations should include assay of AFP, HCG, and LDH, bilateral testicular ultrasound, and a chest X-ray.

Patients with metastases where the diagnosis is not in doubt, on account of high markers and the presence of a testicular mass, may be referred for immediate chemotherapy. In such cases, when examination or ultrasound scan demonstrates that there is a testicular tumour, delayed orchidectomy should be performed, either at the time of excision of residual masses or following chemotherapy, for those patients who are not undergoing additional surgery.

5.2 PRIMARY SURGICAL MANAGEMENT

5.2.1 INGUINAL APPROACH

The preferred surgical technique is orchidectomy through an inguinal incision with division of the cord at the internal inguinal ring. Where there is doubt about the diagnosis, an inguinal approach should be used.

Where possible an inguinal orchidectomy should be performed.

On the rare occasions when the diagnosis is in doubt, representative samples may be sent for frozen section. In this situation it is often best to bivalve the testis to be sure not to miss an abnormal area.

Biopsy of the contralateral testis should be considered in certain cases (see section 6).

5.2.2 TESTICULAR PROSTHESES

There is evidence that loss of a testicle may result in significant psychological morbidity.

A testicular prosthesis should be offered to all patients.

Patients should be offered a testicular prosthesis with careful discussion about the pros and cons of prosthesis. If possible, the discussion should happen as much in advance as possible so that the patient has enough time to reflect upon his decision and make an informed choice.

5.3 FERTILITY ISSUES

A significant proportion, possibly up to 50%, of men with testicular tumours will have low sperm counts. In addition, both chemotherapy and radiotherapy may result in infertility.

Consideration should therefore be given to undertaking semen analysis and sperm storage.

When appropriate, sperm storage should be offered to men who may require chemotherapy or radiotherapy.
Sperm storage should be undertaken in one of the Scottish centres which have a storage licence from the Human Fertilisation and Embryology Authority (HFEA). It is illegal to store sperm samples anywhere else. Centres in Scotland licensed by the HFEA are:

- Aberdeen Maternity Hospital
- Edinburgh Royal Infirmary
- Glasgow Royal Infirmary
- Monklands Hospital, Airdrie
- Ninewells Hospital, Dundee

Departments managing these patients require a counsellor familiar with HFEA consent procedures for sperm storage. The ideal timing of sperm storage will vary; not all patients undergoing orchidectomy will require further treatment. Where a biopsy of an atrophic contralateral testis is being considered to exclude carcinoma in situ (CIS), storage prior to surgery is desirable.

5.4 SPECIALIST NURSING CARE

As there is opportunity for an excellent prognosis from this tumour type the nursing care given has an essential part to play in reflecting a good treatment outcome. Problems for the patient are complex and can lead to psychological morbidity.

☑ Clinical specialist nurse involvement is recommended as early as possible in the management of patients with testicular germ cell tumours.

5.4.1 EXPERIENCE AND TRAINING

Referral to a specialist centre has been shown to be associated with improved outcome in patients with testicular cancer. It is likely that this is due to the input of the entire multidisciplinary team. Therefore nurses in specialist centres should receive training in all aspects of the management of these patients. Nurses who are well trained, have been taught good listening skills, and have access to continuing educational opportunities and support, can influence a good outcome.

☑ Postregistration education in cancer nursing skills is essential and should be available to all nursing staff to enable provision of more effective care for patients.

☑ Standards of nursing care specific to the recommended treatments and which cover all aspects of cancer nursing practice should be devised, implemented and audited.

5.4.2 PSYCHOSOCIAL SUPPORT

Despite an excellent prognosis there are high levels of morbidity in patients with testicular cancer. Psychological morbidity can occur at any stage throughout the illness perhaps as a result of treatment, unemployment or concerns over fertility issues. Nurses should have the ability to recognise anxiety and depression, as early referral to a clinical psychologist, can significantly reduce patients’ emotional distress and enhance adaptation processes. However routine adjuvant psychological therapy is not necessary.

☑ Nurses involved in the care of patients with testicular cancer should have appropriate listening/counselling skills and access to training in the assessment of emotional distress.

☑ Nurses have a key role in supplying information about fertility issues and should have specific training in this field.
5.4.3 LIAISON WITH SUPPORT SERVICES

In addition to coping with a diagnosis of a life threatening disease, patients and their families must often make significant adjustments to their lifestyle, financial status and overall life plan. Nurses are in an ideal position to access support and advice from other networks and by earlier recognition of potential problems could perhaps reduce stress.

☑ Working within a previously agreed multiprofessional care plan, nurses should focus activity on patient- and family-centred care. A named nurse should be available to provide support and information on the availability of additional services of support networks.

5.4.4 REFERRAL TO ONCOLOGY

There is evidence that treatment of testicular cancer in a specialist centre is associated with improved results.\textsuperscript{20}

☑ Management should be discussed by an appropriate multidisciplinary team.

☐ Following confirmation of a germ cell tumour, all patients should be referred to a specialist centre for the management of testicular tumours.
6 Management of the contralateral testis

6.1 Diagnosis of Carcinoma in Situ

All germ cell tumours with the exception of spermatocytic seminoma arise from carcinoma in situ (intratubular germ cell neoplasia) which is often demonstrable in the seminiferous tubules of the testis surrounding the tumour. Approximately 5% of men with testicular cancer have carcinoma in situ (CIS) of the opposite testicle. Carcinoma in situ is thought to progress to invasive germ cell tumours in 50-100% of cases and therapy should be considered.

Carcinoma in situ is more common in the subgroup of patients who have a small (<12 ml) contralateral testis and where the diagnosis of a testicular cancer is made at or less than the age of 30 years. The risk of CIS is 34% in such patients, which represents a high risk group, and biopsy should be considered. Normally this would be done at the time of orchidectomy at a specialist centre.

Patients with a testicular cancer who are 30 years old or less and have a small (<12 ml) contralateral testis should be considered for biopsy of the contralateral testis to diagnose CIS. If CIS is identified subsequent management should be in a specialist centre.

In view of the difficulties in interpretation, pathological review at a specialist centre is recommended.

Contralateral testicular biopsy should, where possible, be performed after all sperm samples have been obtained for storage and before chemotherapy or any secondary treatment.

6.2 Management of Carcinoma in Situ

No evidence was identified to indicate a single treatment pathway for managing patients with CIS. Irradiation of a testis containing CIS has been shown to eradicate early abnormal changes and prevent the progression to invasive disease. Where radiotherapy is to be given a standard dose is 20 Gy given in ten daily fractions over two weeks. A number of different doses and fractionations have been tried but an optimal dose has yet to be defined. Leydig cell function is maintained in a proportion of patients but about 40% of patients will require hormone replacement therapy.

Although the risk of progression to invasive cancer in people with untreated CIS is high, another option would be to monitor the testis and treat if an invasive cancer develops. A further option for infertile patients who already require testosterone replacement is a prophylactic orchidectomy. All of these options should be discussed with the patient.

Patients with biopsy-proven CIS of the contralateral testis should have the options of surveillance, prophylactic orchidectomy and adjuvant radiotherapy discussed with them. Where radiotherapy is given, a dose of 20 Gy in 10 fractions over two weeks is adequate to eradicate CIS and testosterone replacement may not be necessary.

Systemic chemotherapy is an inadequate treatment for CIS as late relapse has been described.
7 Clinical staging

7.1 STAGING SYSTEMS

Once the diagnosis of a testicular germ cell tumour has been made, staging investigations should be performed to assess the extent of disease and to make an assessment of the prognostic group the patient is in. In the past the most commonly used staging system was the Royal Marsden Hospital (RMH) system (see Table 1).

For metastatic germ cell tumours this classification has now largely been superseded by the International Germ Cell Consensus Classification (IGCCC) prognostic grouping (see Table 2). However, the RMH Stage II subgrouping of para-aortic nodes by size may still be of value in the staging of seminoma. The use of tumour markers is discussed in section 4 and imaging techniques for staging are discussed in section 7.2.

Marker concentrations should be used along with imaging techniques to allocate a prognostic group.

All patients should be staged and allocated a prognostic group according to the IGCCC classification.

Table 1: RMH staging

| I | No evidence of disease outside the testis |
| IM | As above but with persistently raised tumour markers |
| II | Infradiaphragmatic nodal involvement |
| IIA | Maximum diameter < 2 cm |
| IIB | Maximum diameter 2-5 cm |
| IIC | Maximum diameter > 5-10 cm |
| IID* | Maximum diameter > 10 cm |
| III | Supra- and infradiaphragmatic node involvement |
| | Abdominal nodes A, B, C, as above |
| | Mediastinal nodes M+ |
| | Neck nodes N+ |
| IV | Extralymphatic metastases |
| | Abdominal nodes A, B, C, as above |
| | Mediastinal or neck nodes as for stage III |
| | Lungs: |
| | ¼ L1 < 3 metastases |
| | ¼ L2 Multiple metastases < 2 cm maximum diameter |
| | ¼ L3 Multiple metastases > 2 cm in diameter |
| | Liver involvement H+ |
| | Other sites specified |

* The Stage IID category was formulated at the 1989 Seminoma Consensus Conference.
Table 2: IGCCC prognostic grouping

<table>
<thead>
<tr>
<th>NSGCT</th>
<th>SEMINOMA</th>
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<tr>
<td><strong>GOOD PROGNOSIS WITH ALL OF:</strong></td>
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<tr>
<td>Testis/retroperitoneal primary</td>
<td>Any primary site</td>
</tr>
<tr>
<td>No non-pulmonary visceral metastases</td>
<td>No non-pulmonary visceral metastases</td>
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<tr>
<td>AFP &lt; 1,000 ng/ml</td>
<td>Normal AFP</td>
</tr>
<tr>
<td>HCG &lt; 5,000 IU/L</td>
<td>Any HCG</td>
</tr>
<tr>
<td>LDH &lt; 1.5 upper limit of normal</td>
<td>Any LDH</td>
</tr>
<tr>
<td>[56% of NSGCTs]</td>
<td>[90% of seminomas]</td>
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<tr>
<td>[5-year survival 92%]</td>
<td>[5-year survival 86%]</td>
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<td>No non-pulmonary visceral metastases</td>
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<td>AFP ≥ 1,000 and ≤ 10,000 ng/ml or</td>
<td>Normal AFP</td>
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<td>HCG ≥ 5000 and ≤ 50,000 IU/L or</td>
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<td>LDH ≥ 1.5 normal and ≤ 10 normal</td>
<td>Any LDH</td>
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<tr>
<td>[28% of NSGCTs]</td>
<td>[10% of seminomas]</td>
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<td>[5-year survival 80%]</td>
<td>[5-year survival 73%]</td>
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<td>AFP &gt; 10,000 ng/ml or</td>
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<tr>
<td>HCG &gt; 50,000 IU/L or</td>
<td></td>
</tr>
<tr>
<td>LDH &gt; 10 normal</td>
<td></td>
</tr>
<tr>
<td>[16% of NSGCTs]</td>
<td></td>
</tr>
<tr>
<td>[5-year survival 48%]</td>
<td></td>
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</tbody>
</table>

### 7.2 RADIOLOGICAL STAGING

All patients require formal staging with contrast-enhanced computed tomography (CECT) of the chest, abdomen and pelvis to help with formulating a management plan. Ideally, the CECT scan should not be performed before a histological diagnosis has been made as histology will aid in the interpretation of the scan and a small proportion of patients will have benign disease. After orchidectomy, scanning should be avoided in the immediate postoperative period as patients may not be able to cooperate fully due to discomfort. Intercurrent infection and reactive changes related to surgery may also cause difficulties with interpretation. However, the staging scan should be regarded as urgent and should be carried out within three weeks of surgery.

- CECT scanning of the thorax, abdomen and pelvis is an essential part of the staging of all germ cell tumours.
- Meticulous and reproducible technique is important for accuracy and comparability between examinations.
It should be borne in mind that CECT is a high radiation-dose examination and every effort should be made to avoid unnecessary scanning, and to use the lowest-dose technique where practicable.

It may not be practicable for all scans to be performed at the cancer centre. In these circumstances scans should be reviewed by a radiologist with appropriate expertise.

- All CECT scans should be reviewed at a meeting of the uro-oncology multidisciplinary team by a radiologist experienced in their interpretation in patients with germ cell tumours.

- It is helpful to the radiologist to have the following clinical and pathological details:
  - **Side of primary**
    Spread to nodal groups follows a predictable course according to the side of the lesion.
  - **Histology** (if available)
    Tumour type and any adverse histological features.
  - **Marker status and current marker levels**
    Helpful in interpreting equivocal lesions.
  - **Risk factors for pelvic nodal disease**
    Although a pelvic scan should be done for initial staging it may be omitted in subsequent scans in the absence of known risk factors (previous inguino-scrotal surgery, previous retroperitoneal surgery or irradiation, tumour invasion through the tunica vaginalis, and the presence of para-aortic nodal disease).38

- Any previous imaging should be available to the radiologist.

### 7.3 OTHER STAGING INVESTIGATIONS

#### 7.3.1 MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is equivalent to CT for detection of pelvic or abdominal nodes, and involves no ionising radiation.37 However, MRI is less sensitive for the detection of pulmonary metastases and examination times are longer than CT.39 The utility of MRI for routine staging and follow up is also limited by lack of availability. Magnetic resonance imaging remains the modality of choice for suspected bone marrow or central nervous system involvement and generally may be useful for problem solving in difficult cases.

- Magnetic resonance imaging may be helpful when CT scanning is inconclusive, is contraindicated because of allergy to contrast media, or where there is concern about radiation dose.

#### 7.3.2 BRAIN SCANNING

Either MRI or CT scanning of the brain should be considered where there are multiple lung metastases and/or HCG > 10,000 IU/L.

#### 7.3.3 OTHER INVESTIGATIONS

Other staging investigations such as cerebrospinal fluid tumour markers and bone scanning may be indicated on an individual basis.

- All staging should be completed and reviewed at a meeting of the uro-oncology multidisciplinary team no later than three weeks after surgery, although immediate postoperative scans may be misleading.
8 Management of stage I disease

Stage I disease is defined as no known residual disease following orchidectomy, with no evidence of metastatic disease on clinical examination, a normal CT scan of chest, abdomen and pelvis and normal postoperative tumour markers. Ninety per cent of seminomas and 57% of NSGCTs, will present as stage I disease.\(^7\)

8.1 MANAGEMENT OF STAGE I SEMINOMA

There are a number of options for patients with stage I pure seminoma following orchidectomy. These include active surveillance, adjuvant radiotherapy and adjuvant carboplatin chemotherapy. No randomised studies have been identified that compare all three management strategies directly. The data regarding efficacy and toxicity (in particular the risk of second malignancies and cardiovascular toxicity) for each option are described in this section.

One systematic review assessing relapse with time for each of the stage I management strategies identified a 17% relapse rate for patients on surveillance and <5% relapse rates for patients following adjuvant treatments (radiotherapy or chemotherapy).\(^40\) The annual rate of relapse falls below 1% at four years for surveillance patients, and at two to three years for patients receiving either adjuvant radiotherapy or adjuvant carboplatin.

Patients with stage I seminoma should have the advantages and disadvantages of the various post-orchidectomy management options discussed with them, including surveillance, single-dose adjuvant carboplatin and adjuvant radiotherapy.

Patients in whom compliance for follow up is likely to be poor may be advised to pursue adjuvant therapy over surveillance.

Spermatocytic seminoma is pathologically different to classical seminoma and no further treatment is indicated following orchidectomy.

8.1.1 ACTIVE SURVEILLANCE

An analysis of studies with median follow up ranging from 30 to 145 months showed that active surveillance for patients with stage I seminoma results in a relapse rate of 17% and a cause-specific survival of 99.7%. Approximately 2% of patients with stage I seminoma on active surveillance will relapse after two years, accounting for 9% of all relapses.\(^41\)

In the largest study addressing the issue of risk factors for seminoma recurrence on surveillance, statistically significant prognostic factors for relapse on multivariate analysis include primary tumour size >4 cm and rete testis invasion.\(^42\)

The risk of second malignancy in patients treated with orchidectomy alone for testicular germ cell tumours (seminoma and NSGCT) is not increased in comparison with an age and period-matched population. It is not clear what imaging follow up these patients underwent, and therefore their exposure to ionising radiation from CT scanning is unknown.\(^43\)

In the two studies that separated patients receiving radiotherapy from those undergoing orchidectomy alone (in seminoma and NSGCT) no statistically significant increased risk of cardiovascular disease (CVD) was seen in the surgery alone group.\(^43,44\)

In patients with stage I seminoma post-orchidectomy, active surveillance may be considered as a management option.
8.1.2 ADJUVANT RADIOThERAPY

In an RCT of 478 post-orchidectomy patients with stage I seminoma who had undergone no prior inguinoscrotal surgery, adjuvant radiotherapy to a dose of 30 Gy in 15 fractions solely to the para-aortic nodes resulted in equivalent three year relapse-free survival rates (96%) and three year overall survival rates (99.3%) when compared to para-aortic strip and ipsilateral pelvic node (‘dog-leg’) radiotherapy. Pelvic relapse-free survival was 1.8% lower in the para-aortic radiotherapy alone arm of the study compared with the ‘dog-leg’ arm. Para-aortic radiotherapy is associated with less acute toxicity (leucopenia, diarrhoea and reduction in sperm counts).45

In patients with stage I seminoma who have undergone no previous inguinoscrotal surgery and who are to receive adjuvant radiotherapy following orchidectomy, the volume should be limited to the para-aortic nodal strip.

If para-aortic nodal irradiation is used, CT scanning of the pelvis may be considered during follow up.

In patients with stage I seminoma who have undergone previous inguinoscrotal surgery and who are to receive adjuvant radiotherapy following orchidectomy, the para-aortic nodal strip volume should be extended to include the ipsilateral pelvic nodes (‘dog-leg radiotherapy’).

A randomised trial of 625 patients concluded that in post-orchidectomy patients with stage I seminoma, a radiotherapy dose of 20 Gy in ten fractions is equivalent to 30 Gy in 15 fractions to the para-aortic strip or to ‘dog-leg’ fields in terms of two year relapse-free survival (97% (95% confidence interval (CI) 94.4% to 98.4%) v 97.7% (95% CI 94.4% to 98.4%)) and results in less acute toxicity (leucopenia and moderate-severe lethargy). A significantly greater proportion of patients are unable to return to work at four weeks following radiotherapy with 30 Gy compared with 20 Gy (46% v 28%).46

In patients with stage I seminoma who are to receive adjuvant ‘dog-leg’ or para-aortic strip radiotherapy, a dose of 20 Gy in ten fractions over two weeks should be prescribed to the International Commission on Radiation Units (ICRU) reference point.

One systematic review of over 6,900 patients with testicular cancer showed that the risk of second malignant neoplasms (excluding contralateral germ cell tumours) was increased by a factor of between two and three in those who had received radiotherapy, although many patients would have been treated to larger volume and greater dose than is current practice.47 The risk of malignancy in organs which lay at least partly within the radiotherapy portals increased by a factor of between three and seven. A number of more recent and large retrospective cohort studies show consistent findings of an excess of second malignancies (non-germ cell tumour) with a latency of approximately 10-15 years before the excess risk is apparent.48-50

In a cohort of more than 2,000 testicular cancer survivors, a statistically significant association between radiation dose and second malignancy risk was reported, with patients treated with 26-35 Gy and 40-50 Gy para-aortic strip or ‘dog-leg’ radiotherapy having a hazard ratio of 2.3 (95% CI 1.5 to 3.6) and 3.2 (95% CI 2.1 to 5.1) respectively, when compared with patients undergoing orchidectomy alone (p value for trend <0.001).41

The standardised incidence ratio (SIR) for the development of a second malignant neoplasm following radiotherapy for testicular cancer decreases with increasing age at diagnosis (p value for trend <0.001). Thus, the SIR for patients aged under 30 at diagnosis who receive adjuvant radiotherapy is 3.9 (95% CI 2.9 to 5.3), compared with 1.3 (95% CI 1.0 to 1.7) in those aged 50 or over at diagnosis.41,48
In patients with seminoma undergoing adjuvant radiotherapy to the mediastinum, the SIR for cardiovascular disease (myocardial infarction (MI) and/or angina) is significantly increased at 2.48 (95% CI 1.77 to 3.37), and the standardised mortality ratio for cardiac-specific mortality is increased. One study showed that the relative risk of a cardiovascular event was 2.4 (95% CI 1.04 to 5.45) in patients with testicular cancer undergoing radiotherapy (but not chemotherapy) post-orchiectomy compared with those on surveillance (absolute risk reduction 5.85%), but a proportion of these patients received treatment to the mediastinum as well as the infra-diaphragmatic nodes. When the patients who received mediastinal radiotherapy were excluded from the dataset, an increased risk of CVD persisted in the remaining irradiated patients. In another study that separated infra-diaphragmatic radiotherapy (RT) from infra- and supradiaphragmatic RT in patients with seminoma, no statistically significant increased risk of CVD was noted in patients receiving only infra-diaphragmatic RT.

In one study with a median of 13.3 years follow up after treatment with radiotherapy for stage I and II seminoma excess mortality was seen in patients with greater than 15 years follow up, with a standardised mortality ratio (SMR) of 1.85 (95% CI 1.42 to 2.38). However, such patients were likely to have been irradiated to a larger field size and to a greater radiation dose than current patients with stage I seminoma.

C The potential risk of second malignant neoplasms should be outlined to patients where adjuvant radiotherapy is being considered.

8.1.3 ADJUVANT CHEMOTHERAPY

In post-orchiectomy patients with stage I seminoma the Medical Research Council (MRC) TE19 study found that, with a median follow up of four years, single-dose carboplatin (AUC7) results in two- and three-year relapse-free survival equivalent to adjuvant radiotherapy. Patients receiving carboplatin experience significantly less dyspepsia and lethargy but more thrombocytopenia than patients receiving radiotherapy. Patients receiving radiotherapy are less likely to be able to return to work by four weeks post-treatment than patients treated with adjuvant carboplatin (62% v 81%, p<0.0001).

The dose and scheduling of carboplatin is important. At a dose of 400 mg/m², two cycles of carboplatin result in a trend to lower relapse rates than a single cycle. At a dose of AUC 7 (based on ethylene diamine tetra-acetic acid (EDTA) clearance), the dose of carboplatin is 10-15% greater than that calculated for a single dose of 400 mg/m².

In patients receiving a single dose of adjuvant carboplatin, the dose should be AUC7 (ie that dose required to achieve an area under the concentration time curve of 7 mg/ml per minute) based on EDTA clearance.

A risk adapted strategy (using the risk factors of tumour size (>4 cm) and presence or absence of rete testis invasion) is feasible and can spare >30% of patients from adjuvant therapy. In one study of such a strategy, patients with low-risk stage I seminoma (tumour <4 cm and no rete testis invasion) underwent surveillance and patients with high-risk features underwent adjuvant carboplatin. The study showed a 6% relapse rate in the low-risk surveillance group, and a 3.3% relapse rate in the high-risk carboplatin-treated group. The five year disease-free survival was 93.4% for surveillance and 96.2% for the carboplatin group. Five-year overall survival was not compromised and 100% of patients in both groups survived.

Early follow up in a trial of adjuvant carboplatin suggested a reduction in the risk of developing contralateral germ cell tumours, however, longer term outcomes from a cohort study yields conflicting results, raising the possibility that carboplatin may delay rather than prevent contralateral tumours.
One small cohort study of 199 patients with stage I seminoma treated with adjuvant carboplatin showed no excess risk of second non-germ cell malignancy when compared to an age- and period-matched population, although median follow up was nine years with only a small percentage of patients being followed up for longer than 15 years. The same study showed no increase in SMR for cardiovascular mortality. The incidence of non-fatal cardiovascular disease was not analysed in this study. No excess overall mortality was seen compared to the reference population.

In post-orchidectomy patients with stage I seminoma, adjuvant carboplatin chemotherapy may be considered as a management option.

Follow up treatment in patients with stage I seminoma is covered in section 13.1.

### 8.2 MANAGEMENT OF STAGE I NSGCT AND MIXED SEMINOMA/NSGCT

#### 8.2.1 SURVEILLANCE

In patients with stage I NSGCT or mixed seminoma/NSGCT of the testis surveillance is desirable to avoid possible treatment morbidity with adjuvant chemotherapy and is feasible because of the high chance of cure with chemotherapy on relapse.

Studies of surveillance show a consistent relapse rate of around 30%. The MRC surveillance study for stage I NSGCT has enabled identification of subgroups of patients who have a high risk of relapse on surveillance. The single most important histological feature of high-risk subgroups is blood vessel and/or lymphatic invasion, with a recurrence risk of approximately 40% in the presence of testicular vein or lymphatic tumour invasion. A similar conclusion was reached in a European Organisation for Research and Treatment of Cancer (EORTC) study of surveillance for stage I NSGCT.

Although the mean age at presentation is older for patients with combined tumours than for those with NSGCT, the pattern of relapse is identical. The majority of patients (80%) relapse within the first year; 47% in abdominal nodes, 13% abdominal nodes and lung, 17% lung and 23% marker rise only. Scrotal interference prior to removal of the primary tumour is not a contraindication to surveillance.

Patients with stage I NSGCT or mixed seminoma/NSGCT of the testis with no high-risk features should be managed by surveillance following inguinal orchidectomy.

Surveillance is generally only recommended for patients without pathological risk features for relapse and who have no social, psychological or geographic factors which would preclude them from such a strategy. Patients on surveillance are followed up monthly for the first year with clinical examination and serum markers at every visit. A recent study found that a CT scan performed at three and 12 months is adequate for most patients. Based on relapse rates and clinical experience the guideline development group has provided a suggested surveillance protocol (see section 13).

Patients on surveillance should be seen in a designated clinic following a strict protocol.

In low-risk patients under surveillance, CT scanning at three and 12 months post-orchidectomy is recommended.

An abdominal CT should be performed in all patients under surveillance. Practice regarding chest CT and X-ray varies, due to a lack of evidence on whether chest scanning at each clinic visit is necessary, or whether scanning could be limited to at-risk groups.
A pelvic CT may not be necessary in all patients. Pelvic nodal disease is strongly associated with well established risk factors, namely, previous scrotal/inguinal surgery, previous retroperitoneal surgery/irradiation, invasive tumour (through tunica albuginea of testis), bulky abdominal nodes. If presence of risk factors can be reliably excluded using clinical information and the appearance of a previous scan, pelvic CT can be omitted from surveillance or reassessment. Previous scans should be available.

D A pelvic CT scan is only indicated where there are known risk factors for pelvic disease.

8.2.2 ADJUVANT CHEMOTHERAPY

Patients with stage I NSGCT or combined tumour and high-risk features should be offered two courses of standard adjuvant bleomycin, etoposide and cisplatin (BEP) i.e., two courses of cisplatin 50 mg/m² on days 1-2 per three weekly cycle, bleomycin 30 IU on days 2, 8 and 15 per three weekly cycle and etoposide 120 mg/m² on days 1, 2 and 3 per three weekly cycle. It is important to recognise that adjuvant chemotherapy should only be given to patients with (high-risk) stage I NSGCT once the tumour markers have reached normal levels. If markers are elevated but still falling it is possible that they would begin to rise, in which case two courses of chemotherapy may be inadequate. Such patients should, therefore, have weekly tumour marker estimations until the trend has become apparent.

Patients with low-risk stage I NSGCT or combined tumours, who are unable or unwilling to follow a policy of surveillance, may be treated with two courses of BEP chemotherapy.

☑ Risks and benefits of adjuvant chemotherapy and surveillance, in particular risk of relapse, should be discussed with patients to agree an appropriate management strategy.

D Two courses of adjuvant BEP chemotherapy should be offered to patients with stage I NSGCT or mixed seminoma/NSGCT of the testis following inguinal orchidectomy if high-risk features are present (blood vessel and/or lymphatic invasion) or if the patient is unable or unwilling to comply with a policy of surveillance.

Patients with rising markers postoperatively (stage IM) should be considered to have metastatic disease and should be treated accordingly (see section 9.2).
9 Management of metastatic disease

9.1 MANAGEMENT OF METASTATIC SEMINOMA

9.1.1 STAGE II SEMINOMA

The RMH stage II category encompasses a wide range of disease extent (see Table 1). Approximately 15% of patients fall into this category, and these are further subdivided into A, B, C and D reflecting the prognostic significance of bulk retroperitoneal disease.

No systematic reviews or RCTs are available comparing treatments for stage II seminoma. Only observational primary studies were identified, of which only one was a comparative study (with an historical control group). Two non-systematic reviews were also identified.

9.1.2 STAGE IIA AND IIB SEMINOMA

Results after treatment with both chemotherapy and radiotherapy are good, particularly in stage IIA disease. There are no data to support the use of one treatment over another.

The adverse effect profile is different for chemotherapy and radiotherapy and the optimal treatment for an individual patient will depend on clinical judgement and patient preference.

One study, comparing 33 patients with IIA/B seminoma treated with carboplatin and radiotherapy to 80 historical controls treated with radiotherapy alone, found a trend towards better relapse-free survival in favour of combination therapy (97% vs 81%). The treatment effect was more pronounced for patients with stage IIB tumours (overall survival 100% vs 94%, relapse-free survival 100% vs 73%). Sequential chemotherapy and radiotherapy can be considered as an alternative to radiotherapy alone in stage IIB.

In stage IIA seminoma both chemotherapy and radiotherapy treatment options should be considered and discussed with the patient. The optimal treatment for an individual patient will depend on clinical judgement and patient preference.

9.1.3 STAGE IIC AND IID SEMINOMA

Three series in the literature separate out patients with larger masses and show that this is an unfavourable group when treated with initial irradiation therapy alone. In the three series, a total of 49 patients received primary irradiation with either infra-diaphragmatic or infra- and supra-diaphragmatic radiotherapy. Seventeen patients (35%) relapsed following this treatment. In addition, the irradiation volume would, of necessity, be large and include renal or hepatic parenchyma, adding to toxicity.

Scheduling of chemotherapy in patients with stage IIC or IID seminoma is similar to that for patients with good prognosis NSGCT which is described in section 9.2.1.

For patients with stage IIC or IID seminoma, chemotherapy is the recommended initial treatment.

Scheduling of chemotherapy is similar to that used for NSGCTs, although the risks of bleomycin pulmonary toxicity may be higher in this generally older age group and bleomycin omission should be considered.

Where chemotherapy is contraindicated, radiotherapy may be an acceptable alternative.
9.1.4 STAGE III AND IV SEMINOMA

Collected data on radiation therapy for stages III and IV disease show a survival of 36% (136/375). As treatment with radiation therapy involves at least infra- and supra-diaphragmatic fields to cover sites of known disease, and due to the risk of relapse and need for salvage chemotherapy, initial systemic therapy is preferable. The use of initial radiation therapy in stage III and IV disease has been supplanted by the use of cisplatin-based chemotherapy.\(^{71-73}\)

C Patients with stage III and IV seminoma should be treated with cisplatin-based chemotherapy.

Carboplatin has been assessed as a possible alternate to cisplatin, but an MRC randomised study of 130 patients who received either carboplatin or etoposide and cisplatin was closed prematurely due to poor accrual. Data showed an inferior disease-free survival for carboplatin in a parallel trial in NSGCT. It was concluded that etoposide and cisplatin should remain standard therapy and that carboplatin should only be used in exceptional circumstances.\(^{74}\)

B In patients with stage III and IV seminoma carboplatin should only be used as an alternative to cisplatin in exceptional circumstances.

9.2 MANAGEMENT OF METASTATIC NON-SEMINOMATOUS GERM CELL TUMOURS

These cancers spread by both lymphatic and blood vessel channels. Prognosis relates not only to anatomical extent of spread but also to the extent of production of the tumour markers AFP, HCG and LDH which may reflect the underlying biological aggressiveness of these cancers. These features have been incorporated by the International Germ Cell Consensus Classification into the prognostic factor based staging of good, intermediate, and poor prognosis (see Table 2).\(^{35}\)

Patients with no radiological abnormalities but rising markers are labelled stage IM and should be treated as having metastatic disease. Current issues in the treatment of these patients include the need for:
- the reduction of treatment-related toxicity (for the good prognosis group, with a predicted cure rate of over 90%),
- an increase in efficacy of chemotherapy in the other groups.

9.2.1 MANAGEMENT OF GOOD PROGNOSIS DISEASE

The important consideration in this group, with a predicted cure rate of over 90%, is the reduction of treatment-related toxicity,\(^{35}\) for example by reducing the number of cycles of chemotherapy from four to three.

\textbf{BEP} refers to the 3-weekly regimen using bleomycin 30 mg on days 1 or 2, 8 and 15, and etoposide 500 mg/m\(^2\) and cisplatin 100mg/m\(^2\) during week 1.

\textbf{3-day BEP} involves delivery of cisplatin over days 1 and 2 and etoposide over days 1-3.

\textbf{5-day BEP} involves delivery of cisplatin and etoposide over days 1-5.

Systematic reviews have shown three cycles of BEP to have equal efficacy to four cycles in terms of relapse-free survival, disease-free survival and progression-free survival. Three cycles of BEP are also associated with less toxicity and better quality of life than four cycles. There was no difference in efficacy between 3-day BEP and 5-day BEP.\(^{75,76}\)

A Patients with a good prognosis metastatic non-seminomatous germ cell tumour should receive three cycles of BEP chemotherapy in either a 3-day or 5-day schedule.

Other attempts to reduce the incidence of treatment-related toxicity have particularly concentrated on the problems associated with cisplatin, etoposide and bleomycin.
Cisplatin and carboplatin

The side effects of cisplatin comprise a significant component of both the early and late toxicity of the BEP regimen. These toxicities include renal impairment, neuropathy, high tone hearing loss and additionally, in the short term, severe gastrointestinal toxicity. The amelioration of renal damage by the use of intensive hydration techniques is important although this adds to the inpatient stay for continuous intravenous infusion therapy. However, the renal damage of cisplatin even with intensive hydration techniques tends to cause loss of approximately 18% of the patient’s glomerular filtration capacity and, although this causes little immediate problem, for successfully treated patients who reach their fifth and sixth decades of life there may be a considerable burden, especially an increased risk of hypertension.77

Carboplatin causes little renal toxicity at conventional dosage and does not cause significant neurotoxicity or ototoxicity.78 As a result it is an attractive candidate as an alternative to cisplatin in the management of patients with good prognosis disease. Trials comparing carboplatin with cisplatin in this group of patients have been undertaken to assess if efficacy can be maintained with a reduction in toxicity. These trials found that substitution of cisplatin with carboplatin results in either no difference or inferior response rates, relapse-free survival and overall survival.75,76

A In patients with good prognosis metastatic non-seminomatous germ cell tumours carboplatin should only be given in circumstances in which cisplatin is contraindicated.

Etoposide

Reducing the etoposide dose below 500 mg/m² per cycle results in inferior progression-free survival and overall survival.75,76

Bleomycin

Bleomycin treatment can cause a number of side effects, including skin rashes and allergic reactions, but pneumonitis is the most serious because of the potential for fatal pulmonary toxicity in 1% of patients.79 Patients with impaired renal function are at increased risk of developing pneumonitis, especially in those aged >40 years, with stage IV disease or with cumulative bleomycin dose greater than 300 mg.79

Four cycles of etoposide and cisplatin (EP) was equivalent to three cycles of BEP in terms of favourable response rates (although the relevant study was underpowered to show a difference in event-free or overall survival).75,80 Four cycles of EP result in greater neutropenia but less skin toxicity and less neuropathy than three cycles of BEP.75,80

Reducing the bleomycin dose results in inferior progression-free survival and overall survival than conventional dosing, except where four cycles of EP are used.75,76

A Patients with good prognosis metastatic non-seminomatous germ cell tumour and in whom bleomycin is contraindicated should receive four cycles of EP chemotherapy (with 500 mg/m² etoposide and 100 mg/m² cisplatin per cycle).

Randomised trials have demonstrated no significant improvement in relapse rate following maintenance therapy, but report that the associated toxicity was greater.76

There is evidence that treatment of testicular cancer in a specialist centre is associated with improved results.20

D Chemotherapy should only be given in a specialist centre and overseen by a clinician experienced in the management of germ cell tumours.
9.2.2 MANAGEMENT OF PATIENTS WITH INTERMEDIATE AND POOR PROGNOSIS NON-SEMINOMATOUS GERM CELL TUMOURS

In this group, with a predicted cure rate of 50-80%, the main challenge is to increase the efficacy of chemotherapy. A number of approaches are under evaluation including dose escalation of cisplatin, alternating regimens and reduction of inter-cycle interval-accelerated chemotherapy.\textsuperscript{81} Improvement of therapeutic results in those patients with aggressive disease can conceivably be achieved by adding new drugs to the current regimens or by increasing the efficacy of the drugs already in use. In vitro experiments and early clinical trials have shown that a dose effect relationship exists for the action of cisplatin on germ cell tumours.\textsuperscript{82,83}

The dose of cisplatin in most standard regimens has been 20 mg/m\textsuperscript{2} for five days combined with bleomycin and vinblastine or etoposide. Increase in the intensity of cisplatin treatment can be achieved by increasing the dose, (eg by a factor of two) or by giving cisplatin at shorter intervals. Randomised trials, however, have proved negative in both respects. In the USA, a randomised trial in patients with poor-risk germ cell tumours showed no benefits for double-dose cisplatin as part of the BEP regimen.\textsuperscript{84}

The MRC/EORTC randomised trial (n = 380) compared standard chemotherapy with six cycles of BEP/EP against BOP/VIP (three cycles of bleomycin, vincristine and cisplatin given every 10 days followed by three cycles of etoposide, ifosfamide and cisplatin given every three weeks). The BOP/VIP schedule incorporated rapid induction followed by potentially non-cross resistant chemotherapy but found no advantage to the more intensive schedule.\textsuperscript{81,85}

The use of alternating regimens has also been addressed in other studies. The rationale for alternating administration of different chemotherapy combinations is based on the theoretical consideration that a given tumour mass contains cell populations which are sensitive to one combination but resistant to the other and vice versa. Drug combinations in sequence have been explored in non-randomised studies of cisplatin, vincristine, methotrexate, bleomycin/actinomycin D, cyclophosphamide, etoposide (POMB/ACE) chemotherapy.\textsuperscript{86} One hundred and six out of 193 fully evaluable patients had large volume metastatic disease and their overall survival was almost 80%.

High-dose chemotherapy with peripheral blood stem cell or autologous bone marrow transplantation has been used predominantly as salvage chemotherapy, and this technique has been assessed in non-randomised studies in certain centres earlier in the disease where a particularly adverse prognosis can be recognised. One study involving 141 patients with advanced disease confirmed the feasibility and efficacy of repeated cycles of high-dose chemotherapy.\textsuperscript{87}

Randomised trials of this approach as both salvage and first line treatment are now ongoing but currently the role of high-dose chemotherapy remains unclear.\textsuperscript{88}

In summary, at present there are no randomised studies to indicate superiority for treatment other than BEP but other approaches are being examined.

\begin{itemize}
\item[D] Patients with adverse prognostic factors should be treated in specialist centres. Where possible, patients should be entered into well designed multicentre studies to define the optimal treatment for this group.
\item[B] Outwith the trial setting standard initial chemotherapy for patients with intermediate and poor-risk germ cell tumours is four courses of 5-day BEP.
\end{itemize}
10 Management of residual masses after chemotherapy

10.1 RADIOLOGICAL IMAGING FOR RESIDUAL MASS

Residual masses are commonly seen following chemotherapy at a site of previous disease and are often considerably smaller than at initial diagnosis. Testicular tumours tend to spread initially via lymphatic spread to abdominal nodes (para-aortic and inter-aortocaval) and hence, this is the most common site for a residual mass.

CT scanning is the most commonly used radiological investigation for assessment of residual masses due to availability, ease of examination and reproducibility. CT is currently only able to identify a residual mass by virtue of its size and is unable to discriminate active tumour from treated fibrotic tissue. Using ionising radiation, there is a significant radiation dose.

MRI scanning is rarely used to assess residual masses due to significantly longer scanning times and the inability to scan the lungs as part of a testicular tumour follow-up protocol. However, it is as accurate as CT in identification of a residual mass but is currently unable to discriminate active tumour from treated fibrotic tissue. A significant advantage of MRI scanning is the absence of a radiation dose and it therefore should be considered if serial scans are required over a short period of time.

PET (positron emission tomography) imaging using 2-\([^{18}\text{F}]\) fluoro-2-deoxy-D-glucose (FDG) is a diagnostic technique that allows the visualisation of tumour cells with a higher than normal metabolic rate when compared with tissue cells. PET/CT scanning with FDG combines the functional imaging of PET scanning with the anatomical imaging of CT and can distinguish residual viable tumour from fibrotic tissue. Care must be exercised with NSGCT masses as differentiated teratoma may not show uptake on FDG-PET scanning. It is, however, more accurate in seminoma masses where a negative result correlates closely with the absence of active disease.

A study of FDG-PET for detection and therapy control of metastatic germ cell tumour, concluded that PET scanning should not be performed earlier than two weeks after completion of therapy.

- In patients with a residual mass post-chemotherapy, FDG-PET/CT is not routinely recommended, however may be used as a problem solving tool.
- FDG-PET/CT scans should not take place less than two weeks after chemotherapy due to false positives secondary to inflammatory responses.

10.2 SURGERY

10.2.1 SEMINOMA

Resection of seminoma is difficult and potentially dangerous due to lack of clear tissue planes and tumour infiltration beyond resection margins, and is limited to exceptional cases where the mass is well circumscribed and looks as though it can be resected completely.

- Surgery is not routinely indicated for patients with seminoma who have residual masses.

10.2.2 NSGCT

Residual masses may remain after chemotherapy and marker normalisation. They may contain viable embryonal carcinoma/yolk sac tumour/choriocarcinoma, differentiated teratoma, fibrosis/necrosis or show transformation into non-germ cell malignancy. It should be made clear to patients at the start of treatment that residual masses may have to be removed surgically. There is a subgroup of patients with residual masses where immediate surgery may not be necessary and careful monitoring is adequate. These are patients where the mass is \( \leq 2 \text{ cm} \) and is not
The aim of surgery is complete excision of the residual mass and associated abnormal tissue. Further clearance of the retroperitoneal nodes or complete para-aortic lymphadenectomy can be performed but with an increased risk of retrograde ejaculation. Patients should receive preoperative counselling with particular regard to the possibility of retrograde ejaculation and the possible extent of surgery (e.g., the possibility of a nephrectomy being performed).

**D** Patients with NSGCT who have residual masses after chemotherapy and whose markers have normalised should be treated by complete excision.

If the primary tumour has not been removed, this should be done at the time of the resection of residual masses as chemotherapy will not reliably cure the primary tumour.

**D** If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time as retroperitoneal lymph node dissection.

Incomplete excision is associated with poor prognosis. Series in which several surgeons have operated sporadically have had higher rates of incomplete resection than those managed by a single surgeon.

Surgery for metastatic NSGCTs in Scotland should be performed in a specialist centre with experience in this operation. Surgeons should work closely with the oncology department undertaking surgery for abdominal disease and cooperating with similarly specialised thoracic surgeons. Thoracic surgery involves excision of mediastinal and pulmonary masses. Coexisting abdominal and thoracic disease may be best excised either at a single operation or by sequential operations depending on the extent of disease and condition of the patient. Anaesthesia and postoperative care, especially where bleomycin lung toxicity has occurred, present particular problems with which anaesthetists and intensive therapy unit staff caring for these patients must be familiar.

**☑** Surgery for metastatic NSGCTs should be performed in a specialist centre with experience in the operative management of these patients.

The role of chemotherapy or radiotherapy after surgery is unclear and is not necessary in all patients even when there is viable tumour in the resected specimen. Some predictors for relapse have been identified and include incomplete resection, greater than 10% of tissue being viable tumour, the amount of embryonal carcinoma and the proliferation index. There is no clear survival benefit in offering immediate chemotherapy post resection but in patients at high risk of recurrence this should be considered.

For selected patients whose response to chemotherapy is inadequate, and markers plateau or rise, consideration may be given to interventional surgery. In this group, patients with completely resectable tumour and elevated AFP alone have the highest chance of benefit from post chemotherapy retroperitoneal lymph node dissection (RPLND) and surgery must be planned in close cooperation between surgeon and oncologist. Chemotherapy may need to be restarted immediately after initial recovery from surgery. Laparoscopic post chemotherapy RPLND is feasible in expert hands but remains experimental.

### 10.3 RADIOTHERAPY

In patients with bulky stage II seminoma, radiotherapy has been given frequently to patients with residual masses following chemotherapy. There are no data to confirm its value and a retrospective review of MRC data indicates that there is no evidence to support its use.

**D** Patients with seminoma who have residual masses following chemotherapy can generally be managed by a policy of observation rather than radiotherapy.
11 Treatment of relapsed disease

Following achievement of complete remission with chemotherapy for metastatic testicular cancer, relapse is very unlikely. It occurs in less than 10% of patients with good prognosis disease, but is more likely in patients with more advanced disease.75

There are two broad approaches which may be adopted to manage patients with relapsed disease; standard-dose salvage or high-dose chemotherapy (HDCT). There is little evidence from RCTs comparing these strategies. Within each strategy there are different approaches and patient characteristics. They are usually reported in single institution or small multicentre studies making comparison and conclusion hard to achieve. This highlights the need to apply prognostic factors to this heterogeneous patient population to offer the most appropriate salvage therapy.

Although patients failing to be cured with first line chemotherapy will be candidates for salvage therapy, occasionally the radiological appearance of progressive disease may mislead physicians to initiate inappropriate salvage chemotherapy, for example, if the serum markers are falling appropriately but progressive pulmonary disease is noted during cisplatin chemotherapy one might suspect pseudo-progression from either bleomycin lung disease or enlarging differentiated teratoma. Complete surgical excision of differentiated teratoma remains the treatment of choice.

Compared to early relapse, those relapsing more than two years from initial treatment have better survival outcomes especially if the disease is unifocal and can be completely surgically resected.103

☑ Surgery should be considered the mainstay of treatment for late relapse where feasible.

The small number of patients presenting with relapsed disease necessitates a specialist centre approach. There is evidence that the outcomes for salvage therapies are worse in units who see less than 20 first line metastatic patients per year.104,105

Patients with testicular germ cell cancer who relapse after first line cisplatin based chemotherapy should be managed in specialised centres.

Patients with rising markers found to have more than one site of disease will require further salvage chemotherapy. This includes patients who after first line chemotherapy have non-resectable and radiologically progressive disease.

This is a small, heterogeneous group of patients and some studies have used criteria to predict survival outcomes. These scoring criteria are based on cohort studies which lack external validation. An analysis of 1,984 patients relapsing after standard first line chemotherapy identified a number of prognostic factors that can be combined in a model (see Table 3) to estimate two year progression-free and overall survival (see Table 4).106
Table 3: International Prognostic Factors Study Group Prognostic Score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary site</td>
<td>Gonadal</td>
<td>Extragonadal</td>
<td>Mediastinal</td>
<td>nonseminoma</td>
</tr>
<tr>
<td>Prior response</td>
<td>complete remission/partial remission, negative markers</td>
<td>partial remission, positive markers/stable disease</td>
<td>progressive disease</td>
<td>-</td>
</tr>
<tr>
<td>Progression-free interval, months</td>
<td>&gt;3</td>
<td>≤3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AFP salvage</td>
<td>Normal</td>
<td>≤1,000</td>
<td>&gt;1,000</td>
<td>-</td>
</tr>
<tr>
<td>HCG salvage</td>
<td>≤1,000</td>
<td>&gt;1,000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>liver, bone, brain metastases</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3
- Add histology score points: pure seminoma = -1; non-seminoma or mixed tumours = 0
- Final prognostic score (-1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)

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Table 4: Survival rates according to prognostic categories

<table>
<thead>
<tr>
<th>Prognostic category (n=564)</th>
<th>Score</th>
<th>No. of patients</th>
<th>%</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>2-year progression-free survival (%)</th>
<th>3-year overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>-1</td>
<td>76</td>
<td>13.0</td>
<td>1</td>
<td>75.1</td>
<td>77.0</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>132</td>
<td>22.6</td>
<td>2.17</td>
<td>1.32 to 3.58</td>
<td>51.0</td>
<td>65.6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
<td>219</td>
<td>37.4</td>
<td>3.20</td>
<td>2.00 to 5.11</td>
<td>40.1</td>
<td>58.3</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
<td>122</td>
<td>20.9</td>
<td>4.85</td>
<td>2.98 to 7.89</td>
<td>25.9</td>
<td>27.1</td>
</tr>
<tr>
<td>Very high</td>
<td>3</td>
<td>36</td>
<td>6.1</td>
<td>11.70</td>
<td>6.70 to 20.45</td>
<td>5.6</td>
<td>6.1</td>
</tr>
<tr>
<td>No classification</td>
<td></td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The International Prognostic Factors Study Group’s model should be applied to guide prognostic information for patients who relapse after first line platinum based chemotherapy.
The use of platinum in first line treatment is essential. The sensitivity to platinum, which is indicated by response to subsequent salvage therapies with either high-dose or standard-dose regimens, helps predict outcome. Thus, platinum chemotherapy is a crucial component of any salvage regimen offered with a potential of cure.

The Beyer criteria have been used to predict the likely benefit from high-dose chemotherapy and should only be used to score patients prior to consideration of high-dose treatment (see Tables 5 and 6).107

Table 5: Beyer prognostic groupings

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease before HDCT</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal primary tumour</td>
<td>1</td>
</tr>
<tr>
<td>Refractory disease (stable disease, but with evidence of tumour progression within four weeks of the last chemotherapy) before HDCT</td>
<td>1</td>
</tr>
<tr>
<td>Absolute refractory disease (failing to achieve stable disease) before HDCT</td>
<td>2</td>
</tr>
<tr>
<td>HCG &gt; 1,000 IU/L before HDCT</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 6: Beyer Risk Score

<table>
<thead>
<tr>
<th>Prognostic groups</th>
<th>Failure-free survival (%)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
<td>2 year</td>
</tr>
<tr>
<td>Good (score 0)</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>Intermediate (score 1 or 2)</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Poor (&gt;2)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Due to the low survival predicted for the Beyer poor prognosis group (score > 2) such patients should not be subjected to high-dose chemotherapy. Those with intermediate and good Beyer prognostic score (0 to 2) may be considered for high-dose chemotherapy.

There are few randomised controlled trials of patients with relapsed disease as the numbers of patients remain small. The only RCT comparing a cycle of high-dose chemotherapy to conventional chemotherapy did not show a significant benefit in terms of event-free and overall survival for high-dose chemotherapy.108

This is in contrast to smaller phase II trials and a large matched pair analysis.109-111,112 The former suggested an increase of 29-90% in disease-free rates with high-dose strategies compared to standard approaches, at a minimum of two years follow up. The latter suggested an improvement in overall survival of 9-11% and event-free survival of 6-12%.112

High-dose chemotherapy cannot be recommended as routine treatment for relapsed germ cell tumours although it may still remain a treatment option, in selected cases, using the prognostic models described above.

One RCT which compared a single cycle of high-dose chemotherapy to two consecutive cycles showed the survival benefit was similar for both groups but that sequential high-dose chemotherapy was better tolerated with a lower death rate due to toxicity in the sequential treatment arm.113
Due to the many different regimens used for high-dose chemotherapy in each study, and the lack of direct comparisons, it is difficult to recommend an optimal regimen, however, two cycles of high-dose carboplatin and etoposide may be better tolerated than one cycle with more than two chemotherapy agents.

**B High-dose chemotherapy is not routinely recommended as salvage therapy for germ cell cancer patients who relapse after standard platinum based chemotherapy.**

At time of relapse most patients retain platinum sensitivity and standard-dose salvage regimens should be cisplatin- and ifosfamide-based. Response rates are generally around 50% with long term disease-free survival rates of 20-30%. The largest body of evidence for standard-dose salvage therapy is for the paclitaxel-based, TIP (paclitaxel, ifosfamide and cisplatin)\textsuperscript{114} or vinblatin-based, VIP (etoposide, ifosfamide and cisplatin).\textsuperscript{115} Increasingly, TIP is being used but there is no randomised comparison in terms of efficacy or toxicity of these two regimens. The doses used in TIP have been reported to lead to better outcomes in terms of response rates and survival,\textsuperscript{114} although patients in this study had good prognostic features compared to other series. Furthermore, some patients may have had suboptimal first line therapy accounting for some of the apparent improved results compared to other TIP regimens.\textsuperscript{116}

In patients who relapse after standard-dose salvage therapy only high-dose chemotherapy offers a chance of cure.\textsuperscript{110} For others, further lines of treatment are generally considered to be palliative. The choice of third line therapy will be heavily dependent on the patient’s bone marrow reserve, performance status and resolution of toxicity from prior regimens. There are a number of single agent and combination regimens, containing gemcitabine, oxaliplatin, paclitaxel and epirubicin, none of which have been subject to comparative studies.\textsuperscript{117-120} These regimens lead to a low overall response rate of 18-24% with short duration of response (median 4.5 to 17 months) and significant haematological toxicity.

The only independent predictor of response to third-line therapy was a long progression-free interval following high-dose therapy.\textsuperscript{121} The most active regimen in this area is single agent oral etoposide which has the advantage of outpatient administration.\textsuperscript{121}

There is a need for further evidence of effective treatment strategies in this patient group.

- The aim of treatment following progression after high-dose chemotherapy or where high-dose chemotherapy is not considered beneficial should be for palliation. Careful consideration should be given to benefit/risk ratios of standard cytotoxics in this setting due to heavy prior treatment.

- Recruitment to clinical trials is strongly recommended in patients with relapsed disease, where appropriate.
12 Late toxicity

12.1 EPIDEMIOLOGY

Germ cell tumours occur in relatively young patients representing the commonest cancer in teenage and young adults in Scotland. As survival and incidence rates continue to increase more young men will live longer with potential toxicities of their therapy.\textsuperscript{122,123} There are well documented short, medium and long term effects of treatment such as neurotoxicity, nephrotoxicity, pulmonary toxicity and androgen deficiency.\textsuperscript{75} There is also an emerging body of evidence of very late toxicity occurring well beyond the time most people are discharged. The most serious of these late effects, with the largest volume of evidence, pertains to the risk of second cancers and cardiovascular (CV) events. These have been studied in the LATENT (Late Adverse Treatment Effects in Netherlands Testis Cancer patients) study which showed a cumulative incidence of either major late effect of 17.6\% by 20 years after diagnosis, accounting for an absolute excess risk for second malignancy and CV disease of 32 and 15 cases per 10,000 person-years, respectively.\textsuperscript{43} There have been major changes in the management of testicular cancer which will affect emerging late toxicity patterns.\textsuperscript{124} However, there remains an unmet information need for patients and their GPs regarding long term effects. Many of the studies of commonly applied therapies have short follow up with little late toxicity reporting and no reporting of very late toxicity.\textsuperscript{125,53,62}

12.1.1 OVERALL MORTALITY

One large population based study of almost 39,000 patients looking at non-cancer deaths showed a raised SMR of 1.06 (95\% CI 1.02 to 1.17) from several pooled cancer registries.\textsuperscript{126} This equates to an absolute excess number of deaths of 3.7 per 10,000 person years. The SMRs were generally higher from NSGCTs compared to seminomas. It is notable that when SMRs were analysed according to era of treatment no decline was seen despite the introduction of more modern therapies. Mortality for those diagnosed before age of 35 was significantly elevated regardless of treatment.

12.2 CARDIOVASCULAR LATE EFFECTS

12.2.1 CARDIOVASCULAR MORTALITY

A Norwegian registry of 3,378 patients showed a marginally increased SMR of 1.2 (95\% CI 1.0 to 1.5), for all CV disease in germ cell patients although the SMR for myocardial infarction was not statistically raised.\textsuperscript{127}

Mortality from hypertension related disorders is significantly raised in germ cell cancer patients, SMR = 1.39 (95\% CI 1.01 to 1.89); for those treated aged less than 35 years the SMR for CV disease was 1.23 (95\% CI 1.09 to 1.39).\textsuperscript{126}

12.2.2 CARDIOVASCULAR INCIDENCE

The LATENT study\textsuperscript{43} of 2,707 patients had a median follow up of 17.6 years and showed, 20 years post-diagnosis, a cumulative excess incidence for either serious late effect of 4\% for those treated with chemotherapy and 1.5\% for those receiving sub-diaphragmatic radiotherapy. This increased to >10\% for those treated with extended field radiotherapy or combined modality treatments.

In a large study a twofold or greater age-adjusted relative risk of developing CV disease that was not explained by increases in cardiac risk factors was observed for all treatment modalities. The estimated event rate at 10 years was 1.4\% for patients managed with surveillance compared to 7.2\% for patients treated with radiotherapy, 3.4\% for those treated with chemotherapy and 4.1\% for those treated with both modalities.\textsuperscript{52} In a smaller cohort study of patients with metastatic testicular cancer, which had a longer median follow up of 14 years, the CV disease event rate was sevenfold that of stage I patients.\textsuperscript{128}
A study comparing CV disease incidence in 2,512 five-year survivors of testicular cancer, found that SIR for MI specifically was elevated for survivors of NSGCT aged less than 45 years (2.06, 95% CI 1.15 to 3.41) and for those aged 45-54 (1.86, 95% CI 1.2 to 2.74). However, beyond the age of 55, SIR rate for MI was not elevated above that of age-matched controls. A similar trend for the SIR for MI in seminoma to decrease with increasing follow-up time was documented in this study.

The latency of cardiac events is around 5-8 years but up to 16 years post-treatment.

12.2.3 CARDIOVASCULAR RISK

One study showed that 97% of patients treated with chemotherapy had at least one CV risk factor (hypertension, hypercholesterolaemia, a smoking history, or a positive family history for CV events), with all risk factors being statistically significantly more frequent in those treated with chemotherapy compared to stage I controls. There are, however, inconsistencies in the evidence with regard to individual CV risk factors. For example, in an underpowered study investigators were unable to demonstrate any adverse effect of cisplatin-based chemotherapy on lipid profiles, whilst others have documented significant increases in lipids compared to national estimates. In a further study, a significant difference was noted in low density lipoprotein (LDL)-cholesterol or the use of lipid lowering drugs in a cohort of testis cancer patients treated with chemotherapy (mostly BEP) compared to controls.

A large case control study (n = 1,289) of blood pressure found, at median follow up of 11 years, an age-adjusted increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with stage I patients, with an odds ratio for hypertension of 1.24 (95% CI 0.88 to 1.75) for radiotherapy patients, 1.62 (95% CI 1.14 to 2.32) for patients treated with < 850 mg of cisplatin and 2.37 (95% CI 1.4 to 4.01) for patients treated with > 850 mg of cisplatin. However, in a smaller study, with shorter median follow up of seven years, no significant differences were noted in hypertension rates.

Obesity is seen more frequently in those treated with the highest doses of cisplatin compared to controls and those treated with other therapies (age-adjusted odds ratio 2.4, 95% CI 1.3 to 4.4).

The LATENT study showed that the increased risk due to smoking, which in itself is an independent predictor of CV disease in this patient group, was significantly greater (hazard ratio 1.8, 95% CI 1.3 to 2.4). In multivariate analysis for CV disease, including peripheral vascular disease, chemotherapy was associated with a hazard ratio of 1.7 (95% CI 1.2 to 2.4). The largest study of CV risk factors suggests clustering of these factors in testis cancer patients, especially in those treated with a cumulative dose of cisplatin > 850 mg (age-adjusted odds ratio for metabolic syndrome 2.8, 95% CI 1.6 to 4.7). In this study a smoking history of ≥ 20 pack-years was an independent predictor of the presence of the metabolic syndrome.

12.2.4 INDIVIDUAL MANAGEMENT STRATEGIES

Three single-centre studies, in which patients with stage II A/B seminoma represented up to 37% of the total series, reported late radiotherapy toxicity. The use of extended field radiotherapy and outdated techniques, in terms of dose and fractionation schedules, are associated with an increased CV risk, although this is difficult to quantify from these studies due to small numbers, extent of radiotherapy field and different reporting of the CV risk. The largest study of 477 patients (although only 17% had stage II seminoma) showed a SMR of 1.6 (95% CI 1.21 to 2.24). The SMR was higher for those treated below the age of 40 years and with mediastinal radiotherapy. When analysis is restricted to stage II patients SMR is non-statistically elevated (SMR 1.54, 95% CI 0.62 to 3.19).

Two cohort studies examined the late effects following adjuvant chemotherapy for stage I high risk NSGCT, with BEP over two cycles, but neither study commented on adverse CV effects.
For metastatic disease, the documented increase in CV risk is more marked with regimens that may be considered outdated systemic therapy for germ cell cancer, such as cisplatin, vinblastine and bleomycin (PVB) and less prominent for MI specifically with BEP, though follow up of this group is relatively short (12.2 years). There is limited evidence demonstrating a lack of heterogeneity of effect with carboplatin- versus cisplatin-based therapies and regimens with or without bleomycin. Studies that have analysed the increased risk by era of treatment have generally not shown a decline in excess morbidity with more recent therapies.

Assessing risk

Combined modality chemotherapy and radiotherapy for germ cell cancer is associated with an increased SIR for MI (2.06, 95% CI 1.17 to 3.35) and CV disease overall 2.78 (95% CI 1.09 to 7.07). There is little evidence to support the use of standard CV risk factor screening tools in patients with testicular cancer, such as the Framingham index. However, in a Scandinavian study over 50% of testicular cancer survivors fell into an intermediate or high risk group on the Systematic Coronary Risk Evaluation (SCORE) model for estimating risk of fatal CV event within 10 years. Those patients treated with a cumulative cisplatin dose of >850 mg have an odds ratio (relative to surgically treated patients) of 3.4 (95% CI 1.3 to 8.7).

- Oncologists should advise survivors of testicular cancer and their GPs of the increased risk of cardiovascular disease.
- GPs should reinforce advice to survivors of testicular cancer on prevention of cardiovascular disease as outlined in SIGN 97.

Survivors of testicular cancer should be advised not to smoke.

12.3 SECOND MALIGNANCIES

One systematic review suggested an approximately twofold higher risk of second malignancy for chemotherapy and radiation alone and a threefold risk for combined modality treatment in survivors of testicular cancer compared with the general population. Various solid cancers and leukaemias are seen with significantly increased frequency following therapy for testicular cancer. The survival rates for these second cancers are similar to those seen in patients with no prior cancer history.

No studies investigating the information which should be given to patients regarding potential second cancers (excluding new germ cell primaries) resulting from cancer treatment were identified. The most useful evidence was derived from large registry based observational studies. Evidence was considered only from studies analysing outcomes from standard treatment approaches.

12.3.1 SECOND NON-GERM CELL CANCER MORTALITY

Deaths due to cancers of stomach, lung and pancreas had significantly elevated SMRs. As yet there does not appear to be a reduction in second malignancy related mortality despite the introduction of newer management strategies.
12.3.2 SECOND NON-GERM CELL CANCER INCIDENCE

The increased risk of second malignant neoplasm (SMN) after treatment for a germ cell tumour appears to be around twofold (SMR 2.0, 95% CI 1.7 to 2.4), representing an absolute excess risk of 14.1 cases per 10,000 person-years of follow up for a Norwegian population.\(^{127}\)

In pooled cancer registry data of 29,511 survivors of testicular cancer, including Scottish, second non-germ cell cancers were reported with increased SIRs from sex-, age- and population-adjusted controls, (SIR 1.65, 95% CI 1.57 to 1.73).\(^{139}\) There are similar SIRs from individual national studies including 1.7-fold, (95% CI 1.5 to 1.9), representing an absolute excess of 32.3 cases per 10,000 person years of follow up for a Dutch population.\(^ {43}\) Amongst an English population living more than 20 years after a diagnosis of testicular cancer, the SIR of second cancers for seminoma patients was 2.18 (95% CI 1.79 to 2.64) and 1.97 for NSGCT patients (95% CI 1.4 to 2.69).\(^ {140}\)

SIRs of >2 are reported for solid cancers including gastrointestinal cancers (stomach, pancreas, bile duct, small bowel, colorectal), lung cancer, urinary tract (bladder, kidney, prostate), melanoma and non-melanaomatous skin cancer, thyroid cancer and soft tissue sarcoma.\(^ {43, 139, 140}\)

The SIR for haematological malignancies (excluding chronic lymphocytic leukaemia) ranges from 1.6, (95% CI 0.6 to 3.5)\(^ {43}\) to 2.6 (95% CI 2.1 to 3.2)\(^ {141}\) leading to an excess cumulative risk of 0.23% by 30 years after treatment for testicular cancer. However, SIRs can be considerably higher (approximately sixfold) for NSGCT\(^ {139}\) in the early years of follow up.\(^ {140}\) The risk appears to be higher after treatment with chemotherapy alone compared to radiotherapy alone.\(^ {141}\) Risk appears to be increased with the more recent introduction of etoposide to regimes containing cisplatin\(^ {39}\) and appears to be dose-related for both chemotherapy and radiotherapy.\(^ {142}\)

12.3.3 LATENCY OF SECOND NON-GERM CELL CANCER

There is evidence of a latency effect for both leukaemias and for solid tumours which appears to be longer for the latter. There is a trend to increasing SIR with various common solid cancers with increasing follow-up time, particularly for seminomas, with evidence that the risk continues after 20 years.\(^ {139, 140}\)

For leukaemia, median latency is around five years.\(^ {139, 142}\) The risk was found to decline sharply after the first five years following initial treatment, but remained significantly elevated beyond 15 years of follow up, the risk being higher for chemotherapy compared to radiotherapy.\(^ {141}\) Further evidence suggests an early increase in risk of leukaemia with an increased excess in the first 10 years following treatment for both seminoma and NSGCT amongst UK patients.\(^ {140}\)

The median latency for solid second malignancies after radiotherapy for stage IIA/B appears to be in the range of eight\(^ {134}\) to 15 years,\(^ {46}\) usually within or at the edge of the radiotherapy field.

12.3.4 RISK FACTORS FOR SECOND NON-GERM CELL CANCER

Radiotherapy

In a multivariate analysis of potential risk factors for second malignancies hazard ratios of 2.6 (95% CI 1.7 to 4.0) for subdiaphragmatic radiotherapy and 3.6 (95% CI 2.1 to 6.0) for subdiaphragmatic and mediastinal radiotherapy were found.\(^ {43}\)

In six single-centre studies\(^ {49, 51, 134, 135, 143}\) of up to 453 patients, the use of extended field radiotherapy (using generally outdated techniques in terms of dose and fractionation schedules) was associated with an increased non-germ cell second malignancy rate, with a relative risk up to fourfold. The risk appears higher if patients are treated at a younger age,\(^ {31}\) but may not be apparent until after many years. No increase was noted until after 15 years of follow up in some series.\(^ {31}\)
Chemotherapy

There is an increased risk for second malignancy after combination chemotherapy (either BEP or PVB), (SIR 2.1, 95% CI 1.4 to 3.1). The risk of second malignancy after cisplatin-containing regimens was associated with a hazard ratio of 2.1-fold compared to patients treated with surgery alone. The SIRs for individual tumour types were significantly raised for carcinoma of the bladder and melanoma. Two studies looking at stage I NSGCT and adjuvant BEP did not comment on second malignancy but both had only short median follow-up times of four years and 9.4 years respectively.

Surgery

There appears to be no significant increase in risk for those treated by orchidectomy alone, compared with age- and period-matched population controls.

Smoking

There is evidence that smoking can increase the risk of SMN, hazard ratio 1.6 (95% CI 1.3 to 2.4), however, increased risks persisted for all treatments after adjustment for smoking.

Age

There is evidence to suggest decreasing relative risk of second malignancies with increasing age at diagnosis. The excess relative risk of leukaemia after seminoma decreased strongly with increasing age.

- Oncologists should advise patients and their GPs of the increased risk of non-germ cell second malignancies. It should be noted that the risks are greatest for those treated before age 30 years. Increased risks continue beyond 15 years following treatment.

- General health advice should be reinforced, particularly avoidance of smoking, and patients should be encouraged to maintain a healthy diet and level of physical activity in order to reduce cancer risk (see also section 2 of SIGN 67: Management of Colorectal Cancer).

- Patients should remain vigilant of any unusual or alert symptoms, particularly relating to the gastrointestinal, respiratory or urinary tract, and report these promptly to their GPs.

- There should be increased awareness of the risk of haematological malignancies especially after chemotherapy and solid malignancies in or near the fields of radiotherapy. There should be a low threshold for further investigation and appropriate referral to secondary care if any alert symptoms are reported. Annual urinalysis for haematuria may be considered.

There is no evidence to suggest that organ-specific surveillance for second malignancy is recommended, in view of the level of increased risk compared to that of the general population and the wide range of potential malignancies. The risks of surveillance procedures that may be invasive or involve cumulative exposure to radiation and the effectiveness of current procedures to detect early stage malignancy must be taken into account. For example, in the case of a family history of colorectal cancer, the risk must be assessed as being greater than fivefold that of the age-matched population before surveillance is recommended. This situation may change significantly in the future, with the development of more effective surveillance strategies.
13 Post-treatment follow up

The rationale for follow up is to:

- detect relapse at a stage where therapy has the best chance of being effective
- monitor and treat treatment-related toxicity
- detect metachronous cancers in particular contralateral testicular cancers
- offer support and counselling with particular reference to issues such as employment and fertility.

Suggested follow up regimens are illustrated in tables 7 to 10 below.

The optimum timing of imaging in the follow up of patients is not clear but is being investigated.

13.1 FOLLOW-UP STRATEGIES FOR STAGE I SEMINOMA

One well conducted systematic review assessed the rates of relapse with time for each of the stage I management strategies. The crude relapse rates (17% for surveillance, <5% for adjuvant strategies) are consistent with other studies (median follow up ranged from 28 to 208 months). The data regarding relapse for each of the management strategies are itemised in the following sections.

13.1.1 SURVEILLANCE

In approximately 92% of patients with stage I seminoma who relapse on surveillance, the site of first detected relapse is in the infradiaphragmatic nodes (primarily the para-aortic nodes). The annual hazard rate for relapse on surveillance exceeds 5% for two years after diagnosis, lies between 1% and 5% during years 3 and 4, and falls below 1% thereafter.40

13.1.2 ADJUVANT RADIOTHERAPY

In approximately 78% of patients with stage I seminoma who relapse following 'dog-leg' radiotherapy, the site of first detected relapse is in the chest or palpable lymph node areas (neck, supraclavicular fossa or inguinal regions). The annual hazard rate for relapse following 'dog-leg' radiotherapy lies between 1% and 5% from years 1 to 3, and falls below 1% thereafter.40

In approximately 59% of patients with stage I seminoma who relapse following para-aortic nodal radiotherapy, the site of first detected relapse is in the infradiaphragmatic (mostly pelvic) nodes. The annual hazard rate for relapse following para-aortic radiotherapy lies between 1% and 5% from years 1 to 3, and falls below 1% thereafter.40

13.1.3 ADJUVANT CARBOPLATIN

In approximately 85% of patients with stage I seminoma who relapse following a single dose of carboplatin, the site of first detected relapse is in the infradiaphragmatic nodes (primarily the para-aortic nodes), with half of the rest being detected in the chest. The annual hazard rate for relapse following carboplatin lies between 1% and 5% during years 1 to 3, and falls below 1% thereafter.40

Patients who undergo surveillance or adjuvant therapy for stage I seminoma should be followed up according to protocols which take into account the likely site and timing of first relapse to define the frequency of clinic visits, blood tests and radiology investigations. This should include cross-sectional imaging of the abdomen in patients under surveillance and after adjuvant carboplatin, and chest imaging in all patients. Cross-sectional imaging of the pelvis may also be indicated in selected patients (eg after para-aortic radiotherapy alone, or where the risk of pelvic nodal disease is considered to be elevated).
An example follow-up schedule is described in Table 7. This schedule takes into account the likely timing and site of relapse for each postorchidectomy strategy. Cross-sectional imaging with CT is recommended in patients undergoing surveillance as well as following para-aortic radiotherapy and adjuvant carboplatin, however, studies are ongoing (such as the MRC Trial of imaging and schedule in seminoma testis (TRISST) study) on this topic.

Table 7: Suggested follow-up protocol for stage I seminoma post-treatment

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Years 6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>3-monthly clinic visit*</td>
<td>3-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>annual clinic visit</td>
</tr>
<tr>
<td></td>
<td>6-monthly CT of abdomen§</td>
<td>6-monthly CT of abdomen§</td>
<td>annual CT of abdomen§</td>
<td>annual CT of abdomen§</td>
<td>annual CT of abdomen§</td>
<td></td>
</tr>
<tr>
<td>Adjuvant para-aortic nodal RT</td>
<td>3-monthly clinic visit*</td>
<td>3-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>discharge from clinic</td>
</tr>
<tr>
<td></td>
<td>annual CT of pelvis</td>
<td>annual CT of pelvis</td>
<td>annual CT of pelvis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant 'dog-leg' RT</td>
<td>3-monthly clinic visit*</td>
<td>3-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>discharge from clinic</td>
</tr>
<tr>
<td></td>
<td>annual CT of abdomen§</td>
<td>annual CT of abdomen§</td>
<td>annual CT of abdomen§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant carboplatin</td>
<td>3-monthly clinic visit*</td>
<td>3-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>annual clinic visit</td>
</tr>
<tr>
<td></td>
<td>annual CT of abdomen§</td>
<td>annual CT of abdomen§</td>
<td>annual CT of abdomen§</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* each clinic visit involves an assessment of symptoms, clinical examination, chest X-ray and tumour markers (AFP and HCG); LDH has not been shown to be helpful in the follow up in patients with germ cell tumours (see section 4.2)

§ may include CT of pelvis as well (if prior inguinoscrotal surgery)
13.2 FOLLOW-UP STRATEGIES FOR STAGE I NSGCT

Table 8: Suggested follow-up protocol for stage I post orchidectomy low-risk NSGCT

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Years 6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>monthly clinic visit*</td>
<td>2-monthly clinic visit*</td>
<td>3-monthly clinic visit*</td>
<td>4-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>annual clinic visit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider stopping in uncomplicated cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT scan of abdomen at 3 and 12 months§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>monthly clinic visit* for 6 months, then 2-monthly for 6 months</td>
<td>3-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>annual clinic visit*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT of chest, abdomen after adjuvant treatment and if CT appears normal, no further routine CT scans.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* each clinic visit involves an assessment of symptoms, clinical examination, chest x-ray and tumour markers (AFP and HCG); LDH has not been shown to be helpful in the follow up in patients with germ cell tumours (see section 4.2)/

§ May include CT of pelvis as well (if prior inguinoscrotal surgery)

For high risk stage I NSGCT surveillance, it is suggested that CT scans of thorax and abdomen should be done at 3, 6, 9, 12, and 24 months.

13.3 FOLLOW-UP STRATEGY FOR METASTATIC SEMINOMA

Table 9: Suggested follow-up protocol for metastatic seminoma (postradiotherapy for stage IIA/B, postchemotherapy for stages II-IV)

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Years 6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>After radical radiotherapy or chemotherapy</td>
<td>3-monthly clinic visit*</td>
<td>3-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>annual clinic visit*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If post-treatment CT abdomen and pelvis scan is normal, no further routine CT scans. If post-treatment CT scan is abnormal, repeat the CT scan every six months for 18 months but stop as soon as CT scan is normal or appearance is stable.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* each clinic visit involves an assessment of symptoms, clinical examination, chest X-ray and tumour markers (AFP and HCG); LDH has not been shown to be helpful in the follow up in patients with germ cell tumours (see section 4.2);
### 13.4 FOLLOW-UP STRATEGY FOR METASTATIC NSGCT

Table 10: Suggested follow-up protocol for metastatic NSGCT

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Years 6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>After chemotherapy (+/- resection of residual masses)</td>
<td>monthly clinic visit* for 6 months, then 2-monthly for 6 months</td>
<td>3-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>6-monthly clinic visit*</td>
<td>annual clinic visit*</td>
</tr>
</tbody>
</table>

CT of chest, abdomen after treatment and if CT appears normal, no further routine CT scans. If post-treatment CT is abnormal, then ongoing imaging of the area of abnormality is required.

* each clinic visit involves an assessment of symptoms, clinical examination, chest X-ray and tumour markers (AFP and HCG): LDH has not been shown to be helpful in the follow up in patients with germ cell tumours (see section 4.2);
14 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing testicular germ cell tumours with patients and carers and in guiding the production of locally produced information materials.

14.1 INFORMATION AND COMMUNICATION

One of the major concerns to this group of patients and their carers is their fear of the unpredictable nature of the disease. Initial explanation by the doctor is not always understood or retained. Nurses can play a key role in ensuring that the necessary information is repeated tactfully, with sensitivity and in terms which patients and carers can understand.

- The provision of appropriate information should be made available to patients and their carers to promote maximum understanding and to assist coping mechanisms. Access to written materials, computerised information and a named nurse should be readily available at all stages of disease management.

- It is imperative that the patient’s general practitioner and other community services are well informed and involved in treatment and follow up.

14.2 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Testicular cancer can be very traumatic for patients and their families, both in terms of the acute illness and the potential for long term complications. There are many issues with which families may have to cope and they need support and reassurance from healthcare professionals throughout the patient journey.

<table>
<thead>
<tr>
<th>PATIENT AWARENESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>As early presentation is crucial, health awareness is to be supported and encouraged. Education, particularly through schools and youth groups, should be planned to encompass signs and symptoms of testicular cancer and to encourage young men to be aware of the shape, size and feel of their scrotum so that changes or abnormalities may be noted and reported. Awareness should be raised of predisposing factors (uncorrected testicular maldescence, or surgical correction carried out after the age of 10 years) and that having a first-degree relative with a history of testicular cancer may increase their risk up to tenfold although it remains low in absolute terms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INITIAL PRESENTATION AND REFERRAL FROM GP TO UROLOGIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Ensure patients presenting with a suspected testicular malignancy have an understanding of the necessity of referral to a specialist, usually an urgent referral within two weeks.</td>
</tr>
<tr>
<td>▪ Explain to patients that testicular cancer is usually diagnosed by scrotal ultrasound, then surgery.</td>
</tr>
<tr>
<td>▪ Explain the aetiology of testicular cancer and inform them of the excellent prognosis.</td>
</tr>
<tr>
<td>▪ Offer specialist nurse support from the Cancer Centre as early as possible.</td>
</tr>
</tbody>
</table>
### Diagnosis: Urology

- Explain the cause of testicular cancer to patients.
- Reassure patients by offering advice on curability and prognosis.
- Advise patients of the need for blood tests (for tumour markers) and staging CT scans, usually three weeks postsurgery.
- Offer patients verbal and written information outlining a clear pathway of how they will be treated and cared for.
- Allow sufficient time to discuss the following issues and ensure patients are involved in discussions:
  - sexual function/relationships
  - introduce discussion of fertility and sperm storage
  - body image/insertion of prosthesis at time of orchidectomy
  - depression and anxiety.
- Discuss the immediate effects of the orchidectomy and advise on the following:
  - recovery period, e.g., how long to stay off work and when to resume physical activity
  - managing the prosthesis
  - pain relief.
- Ensure patients are aware of where they can go for further information and support (see section 14.4).

### Treatment: Oncology

- Inform patients of treatment plans/options and advise them on the timeframe for treatment.
- Offer support and written information to help patients make an informed choice. The following should be discussed:
  - advantages and disadvantages of treatment
  - stage of cancer and how this effects treatment choice and prognosis
  - side effects from treatment (including cardiovascular and secondary cancer risks) and how they can be managed
  - confirm decisions on fertility and sperm storage
  - participation in clinical trials, if appropriate.
- Ensure patients are given information on how to access a named nurse who can offer support and advice at all stages of treatment.
- Discuss the importance of lifestyle changes including:
  - diet
  - exercise
  - smoking/alcohol/drugs.
- Advise patients of where they can receive information on financial issues (see section 14.4).
- Discuss the possibility of hormone deficiency and advise patients when hormone replacement therapy is likely to be offered.
- Ensure patients understand the importance of attending follow-up appointments (usually for at least 5 years) and inform them of how they are likely to be followed up, i.e., by whom, where, and when.
POST-TREATMENT: ONCOLOGY/GP

- Discuss the fear of recurrence and offer reassurance on curability and prognosis.
- Advise patients on the importance of checking the remaining testicle.
- Inform patients of the need to carry out further tests, eg blood tests, chest X-rays and CT scans at regular intervals.
- The following issues should be discussed with patients:
  - returning to work and insurance issues. Insurance companies should note the excellent prognosis for most men with testicular tumours
  - depression, anxiety and psychosexual issues and the availability of specialist services
  - infertility and information about fertility clinics
  - stored sperm
  - symptoms for monitoring late effects.
- The following issues should be discussed with patients who have had a relapse:
  - treatment choices
  - physical effects of treatment
  - treatment outcomes
  - referral to other specialists as required to manage toxicities of treatment.

14.3 PSYCHOSEXUAL ISSUES

Despite good treatment outcomes and excellent prognosis, there remains a significant risk of psychological morbidity associated with the complex physical and emotional affects of the disease and treatments. Psychosexual research studies provide limited evidence as they address variable questions from patients, usually in small numbers, who have had different levels of treatment. They serve to highlight, however, areas of concern, ie body image, sexual function, relationship issues, fertility, gender disruption, stress and depression. Therefore, health professionals are advised to be alert to these issues, assess their patients and make referrals to specialists when appropriate.
14.4 SOURCES OF FURTHER INFORMATION

14.4.1 NATIONAL ORGANISATIONS

Macmillan Cancer Support (Scotland)
Osborne House, 1-5 Osborne Terrace
Edinburgh EH12 5HG
Tel: 0131 346 5346 • Fax: 0131 346 5347
www.macmillan.org.uk
Email: agow@macmillan.org.uk

The Scottish office of the UK charity, which supports people with cancer (and their families) with specialist information, treatment and care.

Maggie’s Centres Scotland
www.maggiescentres.org
Email: maggies.centre@ed.ac.uk

Maggie’s provides practical, emotional and social support to people with cancer, their family and friends. Built alongside NHS cancer hospitals and staffed with professional experts, Maggie’s Centres are warm and welcoming, full of light and open space, with a big kitchen table at their heart.

Maggie’s Dundee
Tom McDonald Avenue, Ninewells Hospital
Dundee DD2 1NH
Tel: 01382 632999 • Fax: 01382 632998
Email: dundee@maggiescentres.org

Maggie’s Edinburgh
The Stables, Western General Hospital
Crewe Road South
Edinburgh EH4 2XU
Tel: 0131 537 3131 • Fax: 0131 537 3130
Email: edinburgh@maggiescentres.org

Maggie’s Fife
Victoria Hospital, Hayfield Road
Kirkcaldy KY2 5AH
Tel: 01592 647997 • Fax: 01592 649646
Email: fife@maggiescentres.org

Maggie’s Glasgow
The Gatehouse, Western Infirmary
10 Dumbarton Road
Glasgow G11 6PA
Tel: 0141 330 3311 • Fax: 0141 330 3363
Email: glasgow@maggiescentres.org

Maggie’s Highlands
Raigmore Hospital, Old Perth Road
Inverness IV2 3UJ
Tel: 01463 706306 • Fax: 01463 706305
Email: highlands@maggiescentres.org

Maggie’s Lanarkshire
Flat 78, Residential accommodation
Wishaw General Hospital
50 Netherton Road
Wishaw ML2 ODP
Tel: 01698 358392 • Fax: 01698 366943
Email: lanarkshire@maggiescentres.org
Marie Curie Cancer Care (Scotland)
29 Albany Street
Edinburgh EH1 3QN
Tel: 0131 456 3710 • Fax: 0131 456 3711
www.mariecurie.org.uk
Marie Curie Cancer Care, a care charity, provides practical nursing care at home and specialist care across its ten Marie Curie centres.

Tak Tent Support (Scotland)
Flat 5, 30 Shelley Court
Gartnavel Complex
Glasgow G12 0YN
Tel: 0141 211 0122
Email: tak.tent@care4free.net
www.taktent.org
Tak Tent offers information, support, education and care for people with cancer, their families and friends and professionals. They have support groups throughout Scotland.

Teenage Cancer Trust
www.teenagecancertrust.org
Teenage Cancer Trust funds specialist cancer units in NHS hospitals that are designed specifically for young people. It also funds clinical and research staff, an education programme for schools, family support networks and an annual conference for young cancer patients.

Orchid
St Bartholomew’s Hospital, Dominion House
London EC1A 7BE
Tel: 020 7601 7167 • Fax: 020 7600 1155
www.orchid-cancer.org.uk
Orchid aims to raise awareness of prevention, diagnosis and treatment of testicular cancer. It provides a range of awareness and information leaflets.

Urological Cancer Charity (UCAN)
Polwarth Building, Foresterhill
Aberdeen, AB25 2ZD
www.ucanhelp.org.uk
UCAN is a charity dedicated to raising awareness of urological cancers, and improving support and quality of life for people and families who are affected.

14.4.2 OTHER ORGANISATIONS

Cancer Research UK/CancerHelp UK
Tel: 0800 800 4040
www.cancerhelp.org.uk
CancerHelp UK is a free information service about cancer and cancer care for people with cancer and their families. It is provided by Cancer Research UK. The site includes a comprehensive range of information including cancer prevention, diagnosis, treatment and follow up.

Testicular Cancer Awareness Scotland (TCAS)
Tel: 01875 341158
Email: info@tcas.fsnet.co.uk
www.freewebs.com/tcas/index.htm

Human Fertilisation and Embryology Authority
www.hfea.gov.uk
For advice about sperm storage and fertility clinics.
14.4.3 USEFUL PUBLICATIONS FOR PATIENTS AND CARERS

**Testicular cancer.** Cancerbackup

Available from Cancerbackup/Macmillan Cancer Support, Osborne House, 1-5 Osborne Terrace, Edinburgh, EH12 5HG, Tel: 0131 346 5346, Fax: 0131 346 5347, www.macmillan.org.uk

**NHS Health Scotland**

Woodburn House
Canaan Lane
Edinburgh EH10 4SG

Leaflets on testicular self examination, healthy living, diet, exercise
15 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

15.1 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- Survey of survivors of testicular cancer and their GPs regarding information needs for long term follow up.
- Audit of long term side effects of treatment for germ cell tumours.
- Audits of compliance with local imaging and staging protocols.

Core data for subsequent audit should include an assessment of:

- any delay in patients presenting to a doctor
- timing from presentation to referral and further investigation
- preoperative investigations
- number of patients offered and receiving a testicular prosthesis
- number of patients offered and having sperm stored
- time from surgery to seeing oncologist
- number of patients having biopsy of contralateral testis
- adequacy of and time for completion of staging
- details of radiotherapeutic management
- details of chemotherapeutic management
- details of further surgical management
- details of timing of clinic follow up and subsequent investigations
- details of toxicity of treatment
- survival and relapse details.

15.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No resource implications for key recommendations were identified.
16 The evidence base

16.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, CINAHL and the Cochrane Library. The year range covered was 1998-2010. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

16.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to management of testicular germ cell tumours. Databases searched include Medline, Embase, CINAHL and PsycINFO, and the results were summarised and presented to the guideline development group. A copy of the Medline version of the patient search strategy is available on the SIGN website.

16.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

- Clinical studies to investigate the exact prevalence of late effects, mechanisms and potential intervention studies
- The optimum management of poor prognosis germ cell tumours
- The optimum management of relapsed germ cell tumours
- The optimum management of seminoma IIA/B
- The role of PET/CT in prediction of response to chemotherapy
- The role of PET/CT in the management of late relapses
- The diagnostic accuracy of PET/CT for residual tumours
- Identification of the benefits and optimum structure of rehabilitation programmes
- Investigation into psychosexual and gonadal function in men following treatment for germ cell tumours.

16.3 REVIEW AND UPDATING

This guideline was published in 2011 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk
17 Development of the guideline

17.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

17.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Grahame Howard  Consultant Clinical Oncologist, Western General Hospital, Edinburgh  
(Chair)
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Dr Margaret Brooks  Consultant Radiologist, Lorn and Islands Hospital, Oban
Dr John Brush  Consultant Radiologist, Western General Hospital, Edinburgh
Mrs Juliet Brown  SIGN Information Officer
Dr David Dodds  Consultant Clinical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow
Dr Helen Gregory  General Practitioner and Associate Specialist in Medical Genetics Cancer, Aberdeen
Dr Ken Grigor  Consultant Pathologist, Western General Hospital, Edinburgh
Mr David Hendry  Consultant Urologist, Gartnavel Hospital and Beatson West of Scotland Cancer Centre, Glasgow
Dr Farida Hamza-Mohamed  SIGN Programme Manager
Ms Sheila Liggatt  Clinical Nurse Specialist, Western General Hospital, Edinburgh
Dr Graham Macdonald  Consultant Clinical Oncologist, Aberdeen Royal Infirmary
Mr Param Mariappan  Consultant Urologist, Western General Hospital, Edinburgh
Mr Brian McGlynn  Urology Cancer Specialist Nurse, Ayr Hospital
Dr Moray Nairn  SIGN Programme Manager
Mr Kenneth Pallister  Patient Representative, Glasgow
Dr Morag Seywright  Consultant Pathologist, Western Infirmary, Glasgow
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Dr Ashita Waterston  Consultant Medical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow
Dr Jeff White  Consultant Medical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow
Mr Phil Wilson  Patient Representative, Glasgow
The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request. In particular, the following staff are thanked for their involvement.

Ms Mary Deas  
**Distribution and Office Coordinator**

Mrs Lesley Forsyth  
**Events Coordinator and Executive Secretary to SIGN Council**

Mrs Karen Graham  
**Patient Involvement Officer**

Miss Katie Kerr  
**Administrative Assistant**

Mr Stuart Neville  
**Publications Designer**

Miss Gaynor Rattray  
**Guideline Coordinator**

17.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 28 Management of Adult Testicular Germ Cell Tumours, on which this guideline is based and Dr Alan James, Consultant Clinical Oncologist and Dr Peter Correra Specialist Registrar in Clinical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, for their contribution to Annex 2 of this guideline.

17.3 CONSULTATION AND PEER REVIEW

17.3.1 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

17.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers’ comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

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Dr Sara Davies  
**Public Health Consultant, Scottish Government, Edinburgh**

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**MacMillan Clinical Nurse Specialist – Testicular Cancer, University College London Hospitals NHS Foundation Trust, London**

Mr Chris Goodman  
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17.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers’ comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Keith Brown  Chair of SIGN; Co-Editor
Ms Beatrice Cant  SIGN Programme Manager
Dr Roberta James  Acting Programme Director of SIGN
Dr Elizabeth Junor  Royal College of Radiologists
Dr Sara Twaddle  Director of SIGN; Co-Editor
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
</tr>
<tr>
<td>AUC7</td>
<td>area under the curve rate of 7 mg/ml per minute</td>
</tr>
<tr>
<td>BEP</td>
<td>bleomycin, etoposide, cisplatin</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>BOP/VIP</td>
<td>bleomycin, vincristine, cisplatin/etoposide, ifosfamide, cisplatin</td>
</tr>
<tr>
<td>BTTP&amp;R</td>
<td>British Testicular Tumour Panel and Registry</td>
</tr>
<tr>
<td>CECT</td>
<td>contrast-enhanced computed tomography</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIS</td>
<td>carcinoma in situ</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylene diamine tetra-acetic acid</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EP</td>
<td>etoposide and cisplatin</td>
</tr>
<tr>
<td>FDG</td>
<td>fluorodeoxyglucose</td>
</tr>
<tr>
<td>GP</td>
<td>general practitioner</td>
</tr>
<tr>
<td>Gy</td>
<td>gray</td>
</tr>
<tr>
<td>HCG</td>
<td>human chorionic gonadotrophin</td>
</tr>
<tr>
<td>HDCT</td>
<td>high-dose chemotherapy</td>
</tr>
<tr>
<td>HFEA</td>
<td>Human Fertilisation and Embryology Authority</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases, 10th revision</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units</td>
</tr>
<tr>
<td>IGCCC</td>
<td>International Germ Cell Consensus Classification</td>
</tr>
<tr>
<td>IU</td>
<td>international unit</td>
</tr>
<tr>
<td>LATENT</td>
<td>Late Adverse Treatment Effects in Netherlands Testis Cancer patients</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LDL</td>
<td>low density lipoprotein</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MTA</td>
<td>multiple technology appraisal</td>
</tr>
<tr>
<td>MTI</td>
<td>malignant teratoma intermediate</td>
</tr>
<tr>
<td>MTU</td>
<td>malignant teratoma undifferentiated</td>
</tr>
<tr>
<td>NHS QIS</td>
<td>NHS Quality Improvement Scotland</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NSGCT</td>
<td>non-seminomatous germ cell tumour</td>
</tr>
<tr>
<td>OCT4</td>
<td>octamer-binding transcription factor 4</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PET/CT</td>
<td>positron emission tomography/computed tomography</td>
</tr>
<tr>
<td>PLAP</td>
<td>placental alkaline phosphatase</td>
</tr>
<tr>
<td>POMB/ACE</td>
<td>cisplatin, vincristine, methotrexate, bleomycin/actinomycin D, cyclophosphamide, etoposide</td>
</tr>
<tr>
<td>PVB</td>
<td>cisplatin, vinblastine, bleomycin</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>RMH</td>
<td>Royal Marsden Hospital</td>
</tr>
<tr>
<td>RPLND</td>
<td>retroperitoneal lymph node dissection</td>
</tr>
<tr>
<td>RT</td>
<td>radiotherapy</td>
</tr>
<tr>
<td>SCORE</td>
<td>Systematic Coronary Risk Evaluation</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>SIR</td>
<td>standardised incidence ratio</td>
</tr>
<tr>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
</tr>
<tr>
<td>SMN</td>
<td>second malignant neoplasm</td>
</tr>
<tr>
<td>SMR</td>
<td>standardised mortality ratio</td>
</tr>
<tr>
<td>TD</td>
<td>teratoma differentiated</td>
</tr>
<tr>
<td>TIP</td>
<td>paclitaxel, ifosphamide and cisplatin</td>
</tr>
<tr>
<td>TRISSST</td>
<td>Trial of imaging and schedule in seminoma testis</td>
</tr>
<tr>
<td>UICC</td>
<td>Union for International Cancer Control</td>
</tr>
<tr>
<td>VIP</td>
<td>etoposide, ifosphamide, cisplatin</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Annex 1
Key questions addressed in this update

The update of this guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

THE KEY QUESTIONS USED TO DEVELOP THE GUIDELINE

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Key question</th>
<th>See section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In patients with a diagnosed testicular germ cell tumour, when is biopsy of the contralateral testis indicated? Consider pick up rate of intratubular germ cell neoplasia and toxicity</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>2. In adult males with stage I testicular seminoma, which of the following interventions:</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>• surveillance,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• chemotherapy (adjuvant),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• radiotherapy (adjuvant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>has the best outcome on survival, long term toxicity and quality of life (including comments on pathological risk factors)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. In adult males with stage I testicular NSGCT what is the optimal surveillance ie has the best outcome on picking up relapse at an early stage?</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>• schedules (CT v MRI and what is scanned)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• tumour markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. In adult males with stage IIA and IIB seminoma, which of the following interventions have the best outcome on survival, long term toxicity and quality of life?</td>
<td>9.1.2</td>
<td></td>
</tr>
<tr>
<td>• radiotherapy and chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• radiotherapy alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. In adult males with good prognosis metastatic NSGCT which chemotherapy regimen has the best outcome in terms of response and toxicity?</td>
<td>9.2.1</td>
<td></td>
</tr>
<tr>
<td>6. In adult males with residual mass post chemotherapy which is the best cross-sectional imaging to predict residual active disease?</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>• CT scanning,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. In post chemotherapy patients (both seminomas and non-seminomas) which patients should have residual masses resected and which has the best outcome on survival (compared with surveillance)? Consider all sites, relevance and types of pathologies, surgical toxicity</td>
<td>10.2</td>
<td></td>
</tr>
</tbody>
</table>
8. In adult males with relapsed testicular germ cell tumours (seminoma and non-seminoma), is there evidence of any chemotherapy schedule (e.g., VIP, TIP, BEP POMB-ACE, high dose) having better outcomes on survival, response rate, toxicity?

9. In view of the potential late physical effects emerging due to the standard treatments for testicular germ cell cancer, what information should be given to patients and their GPs regarding?
   - cardiovascular toxicity
   - second cancers (exclude new germ cell primary tumours)

10. What new evidence is there for good practice in preparation of testicular germ cell tumour histopathology?

<table>
<thead>
<tr>
<th>Question</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. In adult males with relapsed testicular germ cell tumours (seminoma and non-seminoma), is there evidence of any chemotherapy schedule (e.g., VIP, TIP, BEP POMB-ACE, high dose) having better outcomes on survival, response rate, toxicity?</td>
<td>11</td>
</tr>
<tr>
<td>9. In view of the potential late physical effects emerging due to the standard treatments for testicular germ cell cancer, what information should be given to patients and their GPs regarding?</td>
<td>12</td>
</tr>
</tbody>
</table>
| • cardiovascular toxicity
| • second cancers (exclude new germ cell primary tumours)                                           | 14.2 |
| 10. What new evidence is there for good practice in preparation of testicular germ cell tumour histopathology? | Annex 2 |
Annex 2

Pathology of testicular germ cell tumours

CLASSIFICATION

The main classifications in common use are those of the British Testicular Tumour Panel and Registry (BTTP&R) and the World Health Organization (WHO). Pathology reports should include both the BTTP&R and the WHO classifications (see Table 11).

Table 11: Comparison of British (BTTP&R) and WHO classifications

<table>
<thead>
<tr>
<th>British</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>Seminoma</td>
</tr>
<tr>
<td>Spermatocytic seminoma</td>
<td>Spermatocytic seminoma</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Non-seminomatous germ cell tumour</td>
</tr>
<tr>
<td>- teratoma differentiated (TD)</td>
<td>- teratoma</td>
</tr>
<tr>
<td>- malignant teratoma intermediate (MTI)</td>
<td>- embryonal carcinoma/yolk sac tumour with teratoma</td>
</tr>
<tr>
<td>- malignant teratoma undifferentiated (MTU)</td>
<td>- embryonal carcinoma</td>
</tr>
<tr>
<td>- yolk sac tumour</td>
<td>- yolk sac tumour</td>
</tr>
<tr>
<td>- malignant teratoma trophoblastic</td>
<td>- choriocarcinoma</td>
</tr>
</tbody>
</table>

PATHOLOGICAL EXAMINATION AND SAMPLING OF ORCHIDECTOMY SPECIMENS

The macroscopic description should state if the specimen was received intact or bivalved. The length of cord and the dimensions of the testis and epididymis should be recorded. The size, number and shape of any tumour masses should be given together with a description of the appearance of the cut surface, the extent of replacement of the testis, and macroscopic evidence of extension into rete testis, epididymis, tunica vaginalis or spermatic cord. The number and site of blocks taken for histology should be stated.

Blocks should be taken from the resection margin of cord, middle cord, lower cord and from the interface between testis and rete testis. These blocks should be taken before cutting into the tumour in order to reduce the chance of tumour cells being deposited at these sites. Seminoma macroscopically is usually pale, uniform, solid and well demarcated, although large areas of yellow necrosis may be present. NSGCT is usually irregular, friable, variegated and dark in colour with multiple irregular foci of haemorrhage and necrosis. Cystic areas are frequently present. Multiple blocks of tumour should be taken including samples of the main tumour and any satellite lesions. Haemorrhagic foci are sampled because such areas may contain trophoblastic tissue which has a higher incidence of vascular spread. The periphery of the tumour is more likely to contain viable tissue than the centre which may be necrotic. The surrounding testis should be sampled to detect the presence of carcinoma in situ (CIS).

- The orchidectomy specimen should be placed in an adequate volume (at least 5:1) of formalin fixative.
- After taking blocks from the cord the specimen should be bivalved through the rete testis and epididymis as soon as it arrives in the pathology department in order to allow proper fixation. It should not normally be bivalved by the surgeon in theatre unless there is going to be undue delay in the specimen being transported to pathology.
- At least one block of tumour should be taken for each centimetre of maximum tumour dimension and blocks should be taken from the surrounding testis, the rete testis and adjacent epididymis, the lower and mid portions of cord and the resection margin of cord.
HISTOLOGICAL EXAMINATION OF TESTICULAR TUMOURS

The histology report should describe all the different tumour elements present, and should indicate if there is extension through the tunica albuginea to involve tunica vaginalis and involvement of rete testis, epididymis, or spermatic cord. The report should give both the BTT&P&R and WHO classifications (see Table 11).

The condition of the residual testicular tissue should be described paying particular attention to tubular atrophy and the presence or absence of carcinoma in situ.

The pathology report should describe the extent of local spread of the tumour so that the T category can be assessed. The pathological staging of the tumour (pT category) follows the 2002 UICC tumour, node, metastasis classification 6th edition (see Table 12).148

Table 12: Pathological tumour staging

<table>
<thead>
<tr>
<th>pT0</th>
<th>no evidence of primary tumour (eg histological scar tissue in testis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTis</td>
<td>intratubular germ cell neoplasia (carcinoma in situ)</td>
</tr>
<tr>
<td>pT1</td>
<td>tumour limited to testis and epididymis without blood or lymphatic vascular invasion. Tumour may invade tunica albuginea but not tunica vaginalis</td>
</tr>
<tr>
<td>pT2</td>
<td>tumour limited to testis and epididymis with blood or lymphatic vascular invasion or tumour extending through tunica albuginea to involve tunica vaginalis</td>
</tr>
<tr>
<td>pT3</td>
<td>tumour invasion of spermatic cord with or without lymphatic/vascular invasion</td>
</tr>
<tr>
<td>pT4</td>
<td>tumour invasion of scrotum with or without lymphatic/vascular invasion</td>
</tr>
</tbody>
</table>

The incidence of relapse of clinical stage I NSGCTs after orchidectomy is related to the presence of blood or lymphatic vascular invasion, and a detailed examination should be made to detect this.62 Vascular invasion implies invasion of blood vessels or lymphatic vessels.

C The presence or absence of blood or lymphatic vascular invasion should be specified.

SEMINOMA

Classical seminomas contain large polygonal cells with clear cytoplasm and distinct cell boundaries. There is little cellular pleomorphism. There is usually a prominent lymphocytic infiltrate in the stroma and aggregates of epithelioid histiocytes forming non-caseating granulomas are also common in association with the tumour. Areas of necrosis, which can be extensive, may occur. The tumour is usually well demarcated from the surrounding testis.

Some seminomas show greater cellular pleomorphism and more mitotic figures. The lymphocytic and histiocytic infiltrate is less prominent and there is often a more infiltrative border. These have been termed ‘anaplastic’ seminomas. Seminomas with these features can histologically mimic embryonal carcinoma but show immunocytochemical features of classical seminoma and appear to respond as well as classical seminomas to therapy. The stage of pure seminoma is more important than its histological appearance.

Seminomas may contain syncytiotrophoblastic giant cells which secrete HCG, but seminoma cells do not produce AFP. Seminomas usually stain for placental alkaline phosphatase (PLAP), CD117 and octamer-binding transcription factor 4 (OCT4) but not for AFP or for cytokeratin.

Spermatocytic seminoma is a separate entity from classical seminoma and occurs in older men.149 This tumour consists of solid sheets of cells resembling spermatocytes and shows prominent cellular pleomorphism and mitotic activity. It does not have a lymphocytic or histiocytic infiltrate in the stroma and is not associated with CIS. It does not stain for OCT4, PLAP, HCG, AFP, cytokeratin or lymphocyte markers. Pure spermatocytic seminoma does not metastasise, and no further therapy is indicated after orchidectomy. Rare cases of spindle cell sarcoma development have been described in spermatocytic seminoma.

Where the initial pathology sections show pure seminoma but the patient has an elevated serum AFP the entire tumour should be processed for histology to investigate for small foci of NSGCT within the tumour.
NON-SEMINOMATOUS GERM CELL TUMOUR

Tumours consisting of well differentiated tissues only are classed as teratoma by WHO and teratoma differentiated (TD) by BTTP&R. Although these tumours do not contain any histologically malignant elements they must not be considered benign neoplasms when they arise in the post-pubertal testis.

Tumours consisting only of undifferentiated malignant tumour are classed as embryonal carcinoma (WHO) or malignant teratoma undifferentiated (MTU) by BTTP&R.

NSGCTs may also contain extra embryonic structures such as yolk sac elements (yolk sac tumour) and trophoblastic elements (malignant teratoma trophoblastic or choriocarcinoma).

In the WHO classification NSGCTs containing a mixture of different germ cell tumour types are classed as mixed germ cell tumours and all the tumour elements present are listed in the pathology report. Tumours containing a mixture of embryonal carcinoma or yolk sac tumour and teratoma (TD) are classified as malignant teratoma intermediate (MTI) in the BTTP&R classification.

Combined tumours containing both seminoma and NSGCT also occur.

All the components which are recognised within an NSGCT should be mentioned in the pathology report.

Embryonal carcinoma usually stains positively for cytokeratin, CD30 and OCT4. There may also be some positivity for PLAP although this is usually weaker and more patchy than PLAP positivity in seminoma. Yolk sac tumour elements are positive for cytokeratin and focally for AFP.

Epidermoid cyst of the testis, consisting only of a squamous epithelial lined cyst with no skin appendages or any other tissue elements, has sometimes been considered to be a monodermal NSGCT, but there is no associated CIS and the lesion should be treated as a benign condition not requiring further therapy.

REVIEW PATHOLOGY

Germ cell tumours of the testis are not common, and many pathologists do not see a sufficient number of cases to be fully experienced in giving a comprehensive report, which is essential for further clinical management. The patient should be referred to a specialised treatment centre where the pathology of the tumour should be reviewed by a pathologist with a special interest and experience in germ cell tumours. The case should be discussed at a specialist multidisciplinary team meeting which should include the specialist pathologist before a decision is taken on definitive treatment.

- The pathology should be reviewed by specialist pathologists at the referral treatment centres.
- All types of tumour component identified should be recorded in the pathology report using both the WHO and BTTP&R classifications.
- The extent of tumour invasion should be specified with particular reference to involvement of rete testis, tunica vaginalis, epididymis, cord and resection margins and noting the presence or absence of vascular invasion.
- The 2002 UICC 6th edition pathological stage (pT category) should be given.
PATHOLOGY OF RESIDUAL TUMOUR MASSES

In the UK, primary retroperitoneal lymph node dissection (RPLND) is not performed routinely in patients with a testicular germ cell tumour, however, residual masses after chemotherapy for NSGCT should be surgically excised and examined pathologically. The specimen should be measured and the resection margins inked. It should be extensively sampled so that all residual viable tumour elements can be identified and adequacy of excision assessed. Untreated germ cell tumour metastases to lymph nodes or extranodal sites are usually similar in appearance to the primary tumour in the testis, but after successful treatment, metastatic deposits are replaced by necrotic tissue or fibrosis with no evidence of residual malignancy. Differentiated teratoma elements are more resistant to therapy than embryonal carcinoma, therefore residual masses following treatment for metastatic malignant teratoma intermediate (mixed embryonal carcinoma and teratoma) often show areas of fibrosis and necrosis, and also foci of differentiated teratoma without evidence of residual embryonal carcinoma.

The pathology report should indicate whether the resection specimen consists only of fibrosis and necrosis. If viable tumour is present the report should state whether it consists of differentiated teratoma only or whether there is viable histologically malignant germ cell tumour present eg embryonal carcinoma or yolk sac tumour. Transformation to non-germ cell malignancy may also occur. The resection margins should be examined carefully and their status recorded in the pathology report.

☐ Resected residual masses should be extensively sampled in order to look for residual viable tumour.

☐ Particular mention should be made of the presence or absence of viable differentiated teratoma, histologically malignant germ cell tumour, or transformation to non-germ cell malignancy.

☐ The adequacy of excision of viable tumour elements should be stated.

PATHOLOGICAL EXAMINATION OF BIOPSIES FROM THE CONTRALATERAL TESTIS

SUGGESTED PROCEDURE: A contralateral biopsy should be 0.3-1.0 cm in maximum dimension and should be removed atraumatically without squeezing the tissue or handling it with forceps. Open biopsy is considered the normal procedure but needle biopsy may be adequate.

There are differing practices concerning the fixation of contralateral testicular biopsies. The morphological detail is better with Bouin’s fixative than with formalin and cytological artefacts mimicking CIS can be produced by formalin fixation. Immunocytochemical demonstration of PLAP and OCT4 (present in CIS cells) is, however, more reliable on formalin rather than Bouin’s fixed tissue. Ideally, if both fixatives are available, two biopsies should be taken for fixation in Bouin’s and formalin respectively and any immunocytochemistry should be performed on the formalin fixed biopsy. Bouin’s fixation should be for a minimum of two hours and a maximum of 24 hours. Further fixation in Bouin’s fluid results in poor histological sections.

☐ Paraffin sections should be stained routinely with haematoxylin and eosin.

☐ Comment should be made on the presence or absence of CIS, the degree of spermatogenesis, and evidence of atrophy of seminiferous tubules.

☐ Immunocytochemical assessment for PLAP and OCT4 is helpful in the diagnosis of CIS.
Annex 3
CNS metastases in germ cell tumours - sample management protocol

Central nervous system (CNS) metastases are rare in germ cell tumours, tending to occur in poor-risk patients. About one per cent of patients in the report of the International Germ Cell Cancer Collaborative Group\textsuperscript{35} had brain metastases at initial diagnosis. Evidence is sparse and retrospective, and treatment should be individualised. It is clear however that neurosurgery, chemotherapy and radiotherapy all play a potential role in each patient.

**CATEGORISATION OF CNS INVOLVEMENT WITH CNS DISEASE**

Patients with CNS spread can be readily subdivided into three distinct categories:

**Group 1 - CNS disease at presentation** (including within weeks of starting definitive chemotherapy). All IGCCC poor-risk patients (mediastinal primary, MTT histology (choriocarcinoma element), HCG at presentation > 10,000 IU/L) are at risk; many patients are asymptomatic. All poor risk or symptomatic patients should have CNS staging (MRI scanning) as standard. Radical treatment is feasible and cure can be achieved.

**Group 2 - Isolated CNS relapse.** Chemotherapy-resistant clones, or sanctuary site growth are theorised as causes of this rare phenomenon. CNS symptoms or asymptomatic rising markers in face of responding/no systemic disease should raise suspicion and prompt investigation. Radical treatment is feasible and cure can be achieved.

**Group 3 - Multi-site relapsed metastatic disease** including CNS disease. This situation requires palliation and cure is highly unlikely.

**THERAPEUTIC OPTIONS**

**Group 1** - Early neurosurgical resection should be considered due to the risk of haemorrhage and is appropriate for large deposits causing significant pressure symptoms. The mainstay of management is systemic chemotherapy. Radiotherapy carries a high risk of significant sequelae, including neurocognitive decline. If complete radiological response is achieved, withhold adjuvant radiotherapy. If residual disease is present on postchemotherapy imaging, neurosurgical resection is advised; if unresectable, stereotactic radiosurgery is an option. Only in the event of a viable resected tumour, or unresectable disease, wide-field radiotherapy (whole brain, 40-45 Gy) as adjuvant is recommended, depending on performance status.

**Group 2** - Local therapy is recommended. There is no clearly defined role for second line chemotherapy. Neurosurgical resection should be attempted; if unresectable, stereotactic radiosurgery is unproven but an option. Focal therapy should be followed by adjuvant whole brain radiotherapy.

**Group 3** - Management depends on individual cases. Symptomatic sites should be appropriately targeted, with chemotherapy/radiotherapy. If CNS disease is the priority, palliative neurosurgical resection or palliative radiotherapy may be justified. Long term survival is unusual, and performance status must be considered.

*Adapted from the Beatson West of Scotland Cancer Centre\textsuperscript{151,152}*
MANAGEMENT OF ADULT TESTICULAR GERM CELL TUMOURS


