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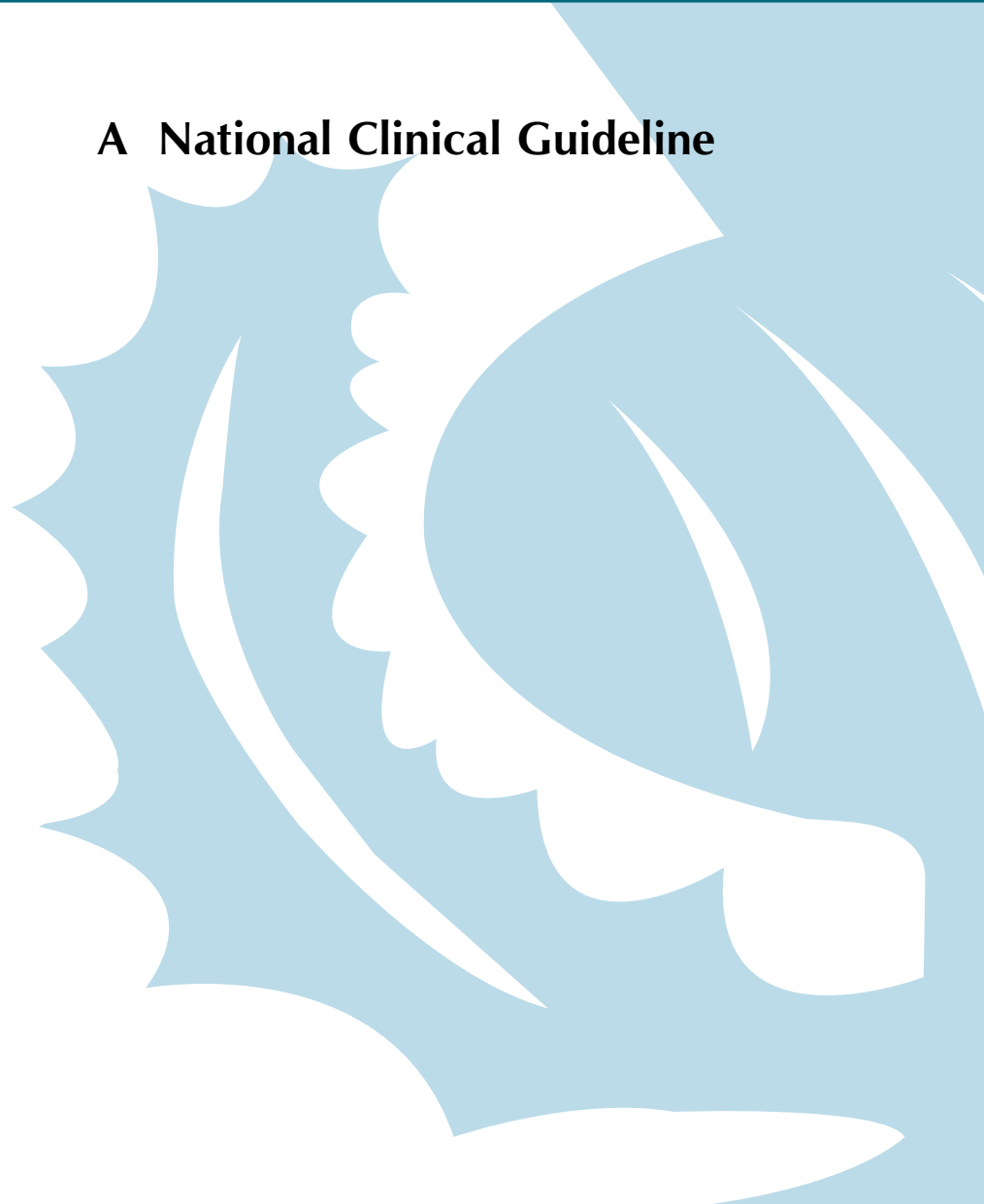
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Scottish
Intercollegiate
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Network

Management of Adult Testicular Germ Cell Tumours

A National Clinical Guideline

September 1998



KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research¹ and are set out in the following tables.

STATEMENTS OF EVIDENCE

<i>Ia</i>	Evidence obtained from meta-analysis of randomised controlled trials.
<i>Ib</i>	Evidence obtained from at least one randomised controlled trial.
<i>IIa</i>	Evidence obtained from at least one well-designed controlled study without randomisation.
<i>IIb</i>	Evidence obtained from at least one other type of well-designed quasi-experimental study.
<i>III</i>	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
<i>IV</i>	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

GRADES OF RECOMMENDATIONS

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. <i>(Evidence levels Ia, Ib)</i>
B	Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. <i>(Evidence levels IIa, IIb, III)</i>
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. <i>(Evidence level IV)</i>

GOOD PRACTICE POINTS

<input checked="" type="checkbox"/>	Recommended best practice based on the clinical experience of the guideline development group
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Notes for users of the guideline

DEVELOPMENT OF LOCAL GUIDELINES

It is intended that this guideline will be adopted after local discussion involving clinical staff and management. The Area Clinical Audit Committee should be fully involved. Local arrangements may then be made for the derivation of specific local guidelines to implement the national guideline in individual hospitals, units and practices and for securing compliance with them. This may be achieved by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

SIGN consents to the copying of this guideline for the purpose of producing local guidelines for use in Scotland. For details of other SIGN publications available, see inside back cover.

STATEMENT OF INTENT

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical 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.

These parameters of practice should be considered guidelines only. Adherence to them 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 regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

Significant departures from the national guideline as expressed in the local guideline should be fully documented and the reasons for the differences explained. Significant departures from the local guideline should be fully documented in the patient's case notes at the time the relevant decision is taken.

A background paper on the legal implications of guidelines is available from the SIGN secretariat.

REVIEW OF THE GUIDELINE

This guideline was issued in September 1998 and will be reviewed in 2000 or sooner if new evidence becomes available. Any amendments to the guideline in the interim period will be noted on the SIGN website: <http://show.cee.hw.ac.uk/sign/home.htm>. Comments are invited to assist the review process. All correspondence and requests for further information regarding this guideline should be addressed to:

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Abbreviations

AFP	Alpha-fetoprotein
BEP	Bleomycin, etoposide, cisplatin
BOP/VIP	Bleomycin, vincristine, cisplatin / etoposide, ifosfamide, cisplatin
CEB	Bleomycin, etoposide, carboplatin
CIS	Carcinoma in situ
CNS	Central Nervous System
CRAG	Clinical Resource and Audit Group
CT	Computed tomography
CXR	Chest x-ray
EC	Etoposide, carboplatin
ECOG	Eastern Co-operative Oncology Group (US)
EORTC	European Organisation for Research and Treatment of Cancer
EP	Etoposide, cisplatin
GCT	Germ cell tumour
HCG	Human chorionic gonadotrophin
HFEA	Human Fertilisation and Embryology Authority
IGCCC	International Germ Cell Consensus Classification
LDH	Lactate dehydrogenase
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Centre
MTI	Malignant teratoma intermediate
MTU	Malignant teratoma undifferentiated
NSGCT	Nonseminomatous germ cell tumours
PLAP	Placental alkaline phosphatase
POMB/ACE	Cisplatin, vincristine, methotrexate, bleomycin / actinomycin D, cyclophosphamide, etoposide
pT category	Pathological staging of the tumour
PV	Cisplatin, vinblastine
PVB	Cisplatin, vinblastine, bleomycin
RMH	Royal Marsden Hospital
RPLND	Retroperitoneal lymph node dissection
SIGN	Scottish Intercollegiate Guidelines Network
TD	Teratoma differentiated
TNM	Tumour, node, metastasis
TTP&R	Testicular Tumour Panel and Registry
UICC	International Union Against Cancer
VAB-6	Vinblastine, bleomycin, cisplatin, cyclofosfamide, dactinomycin
VIP	Etoposide, ifosfamide, cisplatin
WHO	World Health Organisation

Summary of recommendations

PRESENTATION AND INITIAL MANAGEMENT

- C** 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.
- C** Those patients suspected of harbouring a testicular malignancy, i.e. a lump in the testis, doubtful epididymo-orchitis, or orchitis not resolving within two to three weeks, **should be referred urgently for urological assessment.**
- C** Any patients suspected of having a testicular malignancy should be seen **urgently** (within two weeks) **by a specialist.**
- C** Education aimed at young men to inform them of the disease and its curability should be supported.
- C** Specialist nurse involvement is recommended at all stages of management.

PRIMARY TREATMENT

- B** Preoperative investigations should include assay of AFP, HCG, and LDH, an ultrasound of both testes and the abdomen, and a chest x-ray.
- C** Where possible an inguinal orchidectomy should be performed.
- C** A testicular prosthesis should be offered to all patients.
- C** When appropriate, sperm storage should be offered to men who may require chemotherapy or radiotherapy.
- C** Following confirmation of a germ cell tumour, all patients should be referred to a specialist centre for the management of testicular tumours and seen by an oncologist within 1-2 weeks.

MANAGEMENT OF THE CONTRALATERAL TESTIS

- C** In patients with a remaining small testis ($\leq 16\text{ml}$), low sperm count and ultrasound abnormality of the remaining testis, and in young patients (< 30 years) and those with a history of maldescent, biopsy should be considered and the subsequent management of CIS should be in a specialist oncology centre.
- C** In view of the difficulties in interpretation, pathological review at a specialist centre is recommended.
- C** Contralateral testicular biopsy should only be considered after all sperm samples have been obtained for storage and before chemotherapy or any secondary treatment.
- C** Paraffin sections should be stained routinely with haematoxylin and eosin, and immunocytochemically for PLAP. Comment should be made on the degree of spermatogenesis, and evidence of atrophy of seminiferous tubules.

- B** Patients with biopsy-proven carcinoma in situ of the contralateral testis should be offered irradiation of the testis (dose: 20 Gray in 10 fractions over two weeks) to prevent progression to invasive disease.

PATHOLOGY OF TESTICULAR GERM CELL TUMOURS

- C** The presence or absence of blood or lymphatic vascular invasion should be specified.
- C** The pathology should be reviewed by specialist pathologists at the referral treatment centres.

INITIAL INVESTIGATIONS AND CLINICAL STAGING

- B** Measurement of serum AFP and HCG is essential for the follow up of patients with teratoma.
- C** Marker concentrations should be used along with imaging techniques to allocate a prognostic group for patients with teratoma.
- B** CT scanning of the thorax, abdomen and pelvis is an essential part of the staging of all germ cell tumours.
- C** All CT scans should be reviewed by a radiologist experienced in their interpretation in patients with germ cell tumours.
- C** All staging should be completed and reviewed no later than three weeks after surgery, although immediate postoperative scans may be misleading.

MANAGEMENT OF STAGE I DISEASE

- B** A policy of surveillance for patients with stage I 'pure' seminoma is not recommended routinely outwith research protocols but may be considered in rare instances where there are fertility considerations or in patients who are medically or mentally unable to tolerate treatment. In such cases prolonged follow up is necessary.
- B** Adjuvant radiotherapy is recommended for stage I seminoma in most cases.
- A** Stage I seminoma of the testis without risk factors for pelvic node disease following inguinal orchidectomy may be managed by prophylactic irradiation of the para-aortic nodes alone using parallel opposed fields, extending from DV10/11 to the lower border of LV5, contralateral border at the transverse processes of the lumbar vertebrae and ipsilateral border through the renal pelvis.
- B** Stage I seminoma of the testis where there are risk factors for pelvic nodal disease following inguinal orchidectomy, should be managed by prophylactic para-aortic node irradiation with parallel opposed fields extended to include ipsilateral pelvic nodes using a dose of 30 Gray in 15 fractions over 3 weeks.
- B** Patients with stage I teratoma or mixed seminoma/teratoma of the testis with no high risk features should be managed by surveillance following inguinal orchidectomy.
- C** Patients on surveillance should be seen in a designated clinic following a strict protocol.

- B** A CT scan of the thorax and abdomen should routinely be performed as part of the follow up of patients with germ cell tumours.
- B** A pelvic CT scan is only indicated where there are known risk factors for pelvic disease.
- B** Adjuvant chemotherapy should be offered to patients with stage I teratoma or mixed seminoma/teratoma of the testis following inguinal orchidectomy if there is evidence of blood vessel or lymphatic invasion or if the patient is unable or unwilling to comply with a policy of surveillance.
- B** Outwith clinical trials, two courses of BEP chemotherapy should be given.

MANAGEMENT OF METASTATIC SEMINOMA

- B** Radiation therapy to para-aortic and ipsilateral pelvic lymph nodes ('dog leg') is recommended for the treatment of stage IIA metastatic seminoma.
- C** For stage IIB seminoma, radiotherapy or chemotherapy are recommended as initial treatment.
- B** For patients with stage IIC or IID seminoma, chemotherapy is the recommended initial treatment. Scheduling of chemotherapy is similar to that used for teratoma, 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.
- B** Patients with stage III and IV seminoma should be treated with cisplatin-based chemotherapy.
- A** Carboplatin should only be used as an alternative to cisplatin in exceptional circumstances.

MANAGEMENT OF METASTATIC TERATOMA

- B** Standard therapy for patients with metastatic teratoma should be four cycles of chemotherapy with bleomycin, etoposide and cisplatin.
- B** Chemotherapy should only be given in a specialist centre and overseen by a clinician experienced in the management of germ cell tumours.
- A** Carboplatin should only be given in circumstances in which cisplatin is contraindicated. Under normal circumstances, weekly bleomycin should be given.
- B** The total dose of bleomycin should not normally exceed 360 mg.
- C** Patients with adverse prognostic factors should be treated in specialist centres. Patients where possible should be entered into well-designed multicentre studies
- A** Outwith the trial setting, the standard initial chemotherapy for patients with intermediate and poor risk germ cell tumours is BEP.

TREATMENT OF RESIDUAL MASSES AFTER CHEMOTHERAPY

- B** Patients with teratoma who have residual masses after chemotherapy and whose markers have normalised should be treated by complete excision.
- B** If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time.
- B** Surgery for metastatic teratoma should be performed in a specialist centre with experience in the operative management of these patients.
- C** Further chemotherapy should be considered where there has been incomplete excision and pathology confirms malignant elements in the resected specimen.
- B** Patients with seminoma who have residual masses following chemotherapy can generally be managed by a policy of observation rather than radiotherapy. Surgery is not routinely indicated.

TREATMENT OF RELAPSED DISEASE

- C** Patients with relapsed disease should be referred to a specialist centre to be considered for entry into well-designed clinical trials.
- C** Surgery should be considered the mainstay of treatment for late relapse.

CENTRAL NERVOUS SYSTEM (CNS) METASTASES

- C** Initial surgical resection of accessible CNS lesions should be considered.
- C** Radiotherapy may be given as part of curative therapy or purely with palliative intent.

1 Introduction

1.1 INCIDENCE

Testicular germ cell tumours are relatively rare. In 1994, 187 new cases were diagnosed in Scotland with a crude incidence of 7.52 cases per 100,000 of the male population, making it the 14th most common cancer in Scottish men overall. It is, however, the most common cancer in men between the ages of 20 and 30 and has increased in incidence by 15.7% between 1981 and 1990.² It also takes on a greater significance than numbers alone might suggest as it is one of the few solid cancers which is curable in the majority of cases, even when it has metastasised, with a crude overall five year survival rate in Scotland of 89.3%.

1.2 TREATMENT OPTIONS

Treatments for this disease are evolving rapidly and vary from intensive 'surveillance' for stage I teratoma (nonseminomatous germ cell tumours: NSGCT) or radiotherapy for the early stages of seminoma, to intensive chemotherapy with peripheral blood stem cell support for poor prognosis metastatic teratoma.

The investigation and treatment of this disease can therefore be costly both in terms of human and economic resources. The toxicity of therapy is significant with treatment-related deaths and long term side effects being well documented. Potential effects on employment and fertility are of particular importance in this age group.

1.3 THE NEED FOR A GUIDELINE

A Scottish audit was recently funded by the Clinical Resource and Audit Group (CRAG) under the auspices of the Scottish Radiological Society and the Scottish Standing Committee of the Royal College of Radiologists. This demonstrated variation in clinical practice as well as in outcome, as measured by crude survival, and the number of treatments given that were considered to be suboptimal. There was a suggestion that results improved as the number of patients seen with this disease increased, although this finding was not universal.³ This introduces the concept of a specialist centre. There are no data on which to base a definition of a specialist centre, but this will normally be a designated cancer centre, where all the relevant expertise is available and there is a nominated interested clinician.

A recommendation was made to CRAG that guidelines should be developed to improve uniformity of practice and outcome. It was agreed that evidence-based guidelines should be developed according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria.

1.4 REMIT OF THE GUIDELINE

Although the audit concentrated on the management of teratoma it was decided that the guideline should include testicular seminoma, which is largely managed by the same group of professionals according to similar principles.

2 Presentation and initial management

2.1 PRESENTATION

Most GPs will see a patient with a testicular malignancy only very infrequently, if ever. 86% or more of these patients present with an *enlarged testicle* or a *lump in the testicle* and in 97% of patients a lump is present on examination.⁴ It should be noted that a decrease in testicular size may also occur. *Pain* and symptoms suggesting *inflammation* can cause confusion but these features should not delay referral as they are present in 31% (pain)⁴ and 15% (inflammation) of patients with tumours at presentation. Other features which should heighten suspicion include a *dragging sensation*, which is present in 29% of patients, and a *recent history of trauma*, in 10%.⁴ Rare presentations include *hydrocele* and *gynaecomastia*.⁴ Backache is present in 5% of patients⁴ but is a very common and non specific symptom. Recent reports have not confirmed an association with vasectomy.⁵

Evidence level III

- ☑ Due to the rarity of testicular malignancy and its variable, complex and 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.

2.2 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 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. It is thus logical to refer for treatment urgently (within 2 weeks).

- C** 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, may be helpful in making this distinction.

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

- C** Any patients suspected of having a testicular malignancy should be seen urgently (within two weeks) by a specialist.

2.3 PATIENT AWARENESS

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.^{6,7}

Evidence level III

There is no evidence to recommend routine testicular self examination, however, men should be aware of how their testicles feel. Knowledge of early signs and symptoms of testicular cancer, i.e. a change in size or shape of the testicle or a feeling of heaviness in the scrotum, especially in men with a history of uncorrected testicular maldescent or surgical correction carried out after the age of 10 years, should be included in general health education.

C Education aimed at young men to inform them of the disease and its curability should be supported.

3 Primary treatment

It is intended that this guideline for primary treatment should be practicable in any district general hospital in Scotland with surgical facilities, which should include the availability of testicular prostheses.

3.1 PREOPERATIVE INVESTIGATION

One or more markers are raised in 75% of cases of teratoma and measurement is necessary for staging and follow up.⁸ Blood should be taken for assay of the tumour markers alpha fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) before operation. Ultrasound, of both testes and the abdomen, and chest x-ray may show evidence of disease. Other staging investigations can be deferred until after the primary orchidectomy and should be arranged in consultation with a specialist centre.

Evidence level III

B Preoperative investigations should include assay of AFP, HCG, and LDH, an ultrasound of both testes and the abdomen, and a chest x-ray.

- Patients who are ill with high markers or widespread metastases should be referred for immediate chemotherapy without having an orchidectomy. 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 (see section 9.1) or following chemotherapy, for those patients who are not undergoing additional surgery.

3.2 PRIMARY SURGICAL MANAGEMENT

3.2.1 INGUINAL APPROACH

The preferred surgical technique is orchidectomy through an inguinal incision with division of the cord at the internal inguinal ring.⁹ Where there is doubt about the diagnosis, an inguinal approach should be used.

Evidence level III

C Where possible an inguinal orchidectomy should be performed.

SUGGESTED PROCEDURE: The testis should be delivered out through the wound and the cord should be occluded using non crushing clamps. The testis is then separated from the wound with towels and incised. 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. In the event of malignancy not being confirmed, the testis is reconstituted and replaced in the scrotum. It must be explained to patients preoperatively that this procedure is being done to exclude any cancer in a situation where there is high index of suspicion and that following such a bivalving procedure in those situations where malignancy is not confirmed and where the testis is replaced there may be moderate to severe testicular damage.

Biopsy of the contralateral testis should be considered in certain cases (see section 4).

3.2.2 SCROTAL EXPLORATION

From time to time a scrotal exploration is performed for what is thought to be an inflammatory non malignant condition but tumour is found and it is necessary to proceed to orchidectomy. In this situation there is no need to perform secondary wound excision and the postoperative management should continue in exactly the same way as if the operation had been performed through the conventional inguinal approach.¹⁰

3.2.3 TESTICULAR PROSTHESES

There is evidence that loss of a testicle may result in significant psychological morbidity.¹¹ | *Evidence level III*

C A testicular prosthesis should be offered to all patients.

For those who wish a prosthesis, written consent for placement of a prosthesis should be obtained in addition to consent for the orchidectomy. The prosthesis is best and most easily placed at the time of the primary orchidectomy. In view of the concerns about silicon gel filled breast prostheses the newer 'solid' silicon prostheses should be used.

3.3 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.¹² Consideration should therefore be given to undertaking semen analysis and sperm storage.

C 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 Royal Infirmary
- Edinburgh Western General
- Edinburgh Royal Infirmary
- Glasgow Royal Infirmary
- Ninewells Hospital, Dundee.

Departments managing these patients require a counsellor familiar with HFEA consent requirement for sperm storage. The ideal timing of sperm storage will vary: not all patients undergoing orchidectomy will require further treatment. Where a biopsy of the contralateral testis is being considered to exclude CIS, storage prior to surgery is desirable.

3.4 REFERRAL

There is evidence that treatment of testicular cancer in a specialist centre is associated with improved results.³ | *Evidence level III*

C Following confirmation of a germ cell tumour, all patients should be referred to a specialist centre for the management of testicular tumours and seen by an oncologist within 1-2 weeks.

4 Management of the contralateral testis

4.1 CARCINOMA IN SITU

All germ cell tumours with the exceptions of spermatocytic seminoma arise from carcinoma in situ (intratubular germ cell neoplasia)^{13,14} 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.¹⁵ Carcinoma in situ is thought to progress to invasive GCT in 50-100% of cases and therapy should be considered.¹⁶

A higher percentage of carcinoma in situ is found in association with a remaining small (≤ 16 ml) testis, low sperm count and ultrasound abnormality of the remaining testis and in young patients (< 30 years) and those with a history of maldescent.^{17,18} These patients constitute a high risk group.

Evidence level III

- C** In patients in this high risk group, biopsy should be considered and the subsequent management of CIS should be in a specialist oncology centre.
- C** In view of the difficulties in interpretation, pathological review at a specialist centre is recommended.¹⁹
- C** Contralateral testicular biopsy should only be considered after all sperm samples have been obtained for storage and before chemotherapy or any secondary treatment.

4.2 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.¹⁵ The biopsy should be placed in Bouin's fixative for a minimum of 2 hours (smaller biopsies) and a maximum of 24 hours. Further fixation in Bouin's fluid results in poor histological sections. Occasionally, the immunocytochemical assessment of placental alkaline phosphatase (present in CIS cells) is helpful in a biopsy showing equivocal morphology. As demonstration of placental alkaline phosphatase (PLAP) is more reliable on formalin than Bouin's fixed tissue, ideally two biopsies should be taken for fixation in Bouin's and formalin respectively. In situations where only one biopsy is taken, Bouin's fixation takes precedence.

- C** Paraffin sections should be stained routinely with haematoxylin and eosin.
- C** Comment should be made on the presence or absence of CIS, the degree of spermatogenesis, and evidence of atrophy of seminiferous tubules.
- C** Immunocytochemical assessment of PLAP may be helpful in a minority of cases.

4.3 MANAGEMENT OF CIS OF THE CONTRALATERAL TESTIS

Irradiation of the testis prevents progression to invasive disease whilst preserving potency in the majority of patients but will result in infertility in those not already infertile.²⁰

Evidence level III

B Patients with biopsy-proven carcinoma in situ of the contralateral testis should be offered irradiation of the testis (dose: 20 Gray in 10 fractions over two weeks) to prevent progression to invasive disease.

Systemic chemotherapy is an inadequate treatment for CIS as late relapse has been described.^{21, 22}

5 Pathology of testicular germ cell tumours

In view of the lack of studies specifically addressing the pathological assessment, this section describes good practice in the pathological and histological examination and staging of testicular germ cell tumours.

5.1 CLASSIFICATION

Testicular germ cell tumours (GCTs) can be subdivided into *seminoma* and *teratoma* (non seminomatous germ cell tumour: NSGCT), 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 teratomas 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. The main classifications in common use are those of the British Testicular Tumour Panel and Registry (TTP&R)²³ and the World Health Organisation (WHO).²⁴ A new unified system of classification has been proposed but not yet fully accepted.²⁵ Pathology reports should include both the TTP&R and the WHO terminologies (see *table 1*).

Teratomas and seminomas have different clinical outcomes²⁶ and require different clinical management, although in some instances it may be difficult to distinguish between poorly differentiated seminomas and teratomas.²⁷ All teratomas including teratoma differentiated (mature teratoma), with the exception of epidermoid cyst, are capable of metastasising²⁸ and must be considered malignant.

Table 1

COMPARISON OF BRITISH (TTP&R) AND WHO CLASSIFICATIONS

British	WHO
Seminoma	Seminoma
Spermatocytic seminoma	Spermatocytic seminoma
Teratoma	Non seminomatous germ cell tumour
— teratoma differentiated (TD)	— mature teratoma
— malignant teratoma intermediate (MTI)	— embryonal carcinoma with teratoma (teratocarcinoma)
— malignant teratoma undifferentiated (MTU)	— embryonal carcinoma
— yolk sac tumour	— yolk sac tumour
— malignant teratoma trophoblastic	— choriocarcinoma

5.2 PATHOLOGICAL EXAMINATION AND SAMPLING OF ORCHIDECTOMY SPECIMENS

After fixation, samples 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. Teratoma 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 (at least one block per cm of maximum dimension of the tumour) including samples of the main tumour and any satellite lesions. Haemorrhagic foci are sampled because such areas often 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 formaldehyde fixative.
- The specimen should be bivalved through the rete testis and epididymis either in theatre by the surgeon or as soon as it arrives in the pathology department in order to allow proper fixation.
- At least 1 block of tumour should be taken for each cm of maximum tumour dimension and blocks should be taken from the surrounding testis, the rete testis and adjacent epididymis, the mid portion of cord and the resection margin of cord.

5.3 HISTOLOGICAL EXAMINATION OF TESTICULAR TUMOURS

The histology report should describe all the different elements present, and should indicate if there is involvement of tunica albuginea, rete testis, epididymis, or spermatic cord. The final report should give both the TTP&R and WHO classifications (see *table 1*).

The incidence of relapse of clinical stage I teratomas after orchidectomy is related to the presence of blood or lymphatic vascular invasion, and a detailed examination should be made to detect this.²⁹ There is often confusion about the exact meaning of the term 'vascular invasion'. Vascular invasion implies invasion of blood vessels or lymphatic vessels.

Evidence level IIb

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

5.3.1 SEMINOMA

Seminomas are subdivided into classical, anaplastic and spermatocytic seminoma.

- *Classical seminomas* contain large polygonal cells with clear cytoplasm and distinct cell boundaries. There is little cellular pleomorphism and mitotic figures are not frequent. There is usually a prominent lymphocytic infiltrate in the stroma and large areas of necrosis may occur. The tumour is usually well demarcated from the surrounding testis.
- *Anaplastic seminomas* show greater cellular pleomorphism and more mitotic figures. The lymphocytic infiltrate is less prominent and there is often a more infiltrative border. Anaplastic seminomas tend to be more aggressive than classical seminomas

but respond as well to therapy. The stage of the seminoma is more important than the subdivision into anaplastic or classical types. Seminomas may contain syncytiotrophoblastic giant cells which secrete HCG, but seminoma cells do not produce AFP. Seminomas usually stain for PLAP but not for AFP or for cytokeratin.

- *Spermatocytic seminoma* is a separate entity from classical or anaplastic seminoma.³⁰ It consists of solid sheets of cells resembling spermatocytes and shows prominent cellular pleomorphism and mitotic activity. It does not have a lymphocytic infiltrate in the stroma and is not associated with CIS. It does not stain for PLAP, HCG, AFP, cytokeratin or lymphocyte markers. Spermatocytic seminoma does not metastasise, and no further therapy is indicated after orchidectomy.

5.3.2 TERATOMA (NONSEMINOMATOUS GERM CELL TUMOUR: NSGCT)

Teratomas may consist entirely of well-differentiated tissues and structures and are classified as TD (teratoma differentiated). These must not be considered benign neoplasms when they arise in the post pubertal testis. Malignant teratoma intermediate (MTI) contains a mixture of differentiated structures and undifferentiated malignant tissue in any proportion, whereas MTU (malignant teratoma undifferentiated) contains only undifferentiated malignant tissue. Teratomas may also contain extra embryonic structures such as yolk sac elements (yolk sac tumour) and trophoblastic elements (malignant teratoma trophoblastic, or choriocarcinoma).

The WHO classification uses ‘teratoma’ only if differentiated structures are present, and a mature teratoma is equivalent to TD in the British classification. Embryonal carcinoma is equivalent to MTU, and embryonal carcinoma with teratoma is equivalent to MTI. All the components which are recognised within a teratoma should be mentioned in the pathology report.

Teratomas often stain for cytokeratin, AFP, HCG and PLAP in a patchy distribution depending on the components present within the tumour. Stains for AFP and HCG should not be considered diagnostic of yolk sac and trophoblastic differentiation, respectively.

An epidermoid cyst of the testis is sometimes considered to be a monodermal teratoma,³¹ but should be treated as a benign condition not requiring further therapy.

5.4 PATHOLOGICAL TUMOUR STAGING

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 1997 UICC TNM classification (see table 2).³²

Table 2

PATHOLOGICAL TUMOUR STAGING CATEGORIES

pT0	no evidence of primary tumour
pT1	tumour limited to testis and epididymis without blood or lymphatic vascular invasion
pT2	tumour limited to testis and epididymis with vascular invasion or tumour extending through tunica albuginea to involve tunica vaginalis
pT3	tumour invasion of spermatic cord
pT4	tumour invasion of scrotum

5.5 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 competent 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 by pathologists and clinicians together before a decision is taken on definitive treatment.

C 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 primarily the British (TTP&R) nomenclature with the equivalent WHO nomenclature added in parenthesis.
- The extent of tumour invasion should be specified with particular reference to involvement of rete testis, tunica albuginea, epididymis, cord and resection margins.
- The UICC pathological stage (pT category) should be given.

5.6 PATHOLOGY OF RESIDUAL TUMOUR MASSES

In the UK, retroperitoneal lymph node dissection (RPLND) is not performed routinely in patients with a testicular germ cell tumour, however, residual masses after chemotherapy should be surgically excised and examined pathologically. 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. Complete regression is more likely to be achieved with seminoma and undifferentiated teratoma than with differentiated teratomatous elements which are more resistant to therapy. Therefore, residual masses following treatment for metastatic MTI often show areas of fibrosis and necrosis, and also foci of differentiated teratoma without evidence of residual undifferentiated teratoma.

Persistent differentiated mature teratoma (TD) has potential for continued growth and complete resection of residual masses should be performed. The histological features of resected residual masses are important in determining further management. If only fibrosis, necrosis, and completely resected TD are found, the patient is likely to be cured without further treatment being required. However, if residual masses after chemotherapy contain undifferentiated teratoma, or spindle cell sarcomatous malignant tumour, this indicates tumour resistance to drug treatment and surgical excision is less likely to be curative.

- Resected residual masses should be adequately sampled in order to look for residual viable tumour.
- Particular mention should be made of the presence or absence of differentiated teratoma, undifferentiated or viable teratoma, or so-called non germ cell tumour (sarcomatous) elements.
- The adequacy of excision should be stated.

5.7 THE PATHOLOGY REPORT

The pathology report should include a comprehensive macroscopic and microscopic description of the orchidectomy specimen.

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, vaginal sac or spermatic cord. The number and site of blocks taken for histology should be stated.

The microscopic report should describe all tumour components present giving both the TTP&R (British) and WHO nomenclature. It is often difficult to quantitate the relative properties of each tumour component present, and such quantitation may not be of relevance to clinical management. It is important to comment on the presence or absence of invasion of blood vessels or lymphatic vessels. The condition of the residual testicular tissue should be described paying particular attention to tubular atrophy, Leydig cell hyperplasia (which often accompanies HCG secretion by the tumour) and the presence or absence of carcinoma in situ.

The final diagnosis should be summarised at the end of the report giving TTP&R and WHO terminology.

The pathology report should be issued without delay in order to facilitate rapid decisions on future clinical management, especially if the clinical and pathological diagnoses are at variance. If the clinical and pathological diagnoses are at variance, the pathologist should inform the clinician immediately by telephone. This will avoid unnecessary radiological investigations if the clinical suspicion of malignancy is not confirmed pathologically, and will expedite further investigations if an unsuspected malignancy is discovered.

- The pathology report should be issued without delay in order to facilitate a rapid decision on future clinical management, especially if the clinical and pathological diagnoses are at variance.

6 Initial investigations and clinical staging

6.1 TUMOUR MARKERS

6.1.1 AFP AND HCG

Management of patients with teratoma 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 teratoma. However, neither marker should be regarded as specific for teratoma 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 teratoma 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.³³

Evidence level IIb

B Measurement of serum AFP and HCG is essential for the follow up of patients with teratoma.

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 teratoma 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.

6.1.2 LDH

Other than as a prognostic indicator in patients with teratoma, LDH is not sufficiently specific for general application in disease monitoring. Markedly elevated levels may be of value in certain patients with advanced disease who have normal AFP and HCG concentrations. Mild increases in LDH during chemotherapy can be due to hepatic insult and reflect the lack of specificity of this marker.

6.1.3 PLAP

Placental alkaline phosphatase (PLAP) has been studied, particularly in patients with seminoma, but the current evidence is that the relatively low sensitivity (15-30%) and specificity seriously undermine its clinical value and its use is not recommended.

6.1.4 GOOD PRACTICE IN THE USE OF TUMOUR MARKERS

- Serum markers (assay of AFP, HCG and LDH) should be performed prior to surgery and 24-48 hours after surgery.
- If raised, these should be monitored weekly until within the reference range.

6.2 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 3).

For teratoma this classification has now largely been superseded by the International Germ Cell Consensus Classification (IGCCC) prognostic grouping (see table 4).³⁴ However, the RMH Stage II subgrouping of para-aortic nodes by size may still be of value in the staging of seminoma.

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

Table 3

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 3 Lungs: — L1 <3 metastases — L2 Multiple metastases < 2 cm maximum diameter — 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.³⁵

Table 4

IGCCC PROGNOSTIC GROUPING

TERATOMA (NSGCT)	SEMINOMA
<i>GOOD PROGNOSIS with all of:</i>	
Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP < 1000 ng/ml HCG < 5000 iu/l LDH < 1.5 upper limit of normal <i>56% of teratomas</i> <i>5-year survival 92%</i>	Any primary site No non-pulmonary visceral metastases Normal AFP Any HCG Any LDH <i>90% of seminomas</i> <i>5-year survival 86%</i>
<i>INTERMEDIATE PROGNOSIS with all of:</i>	
Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP ≥ 1000 and ≤ 10000 ng/ml or HCG ≥ 5000 and ≤ 50000 iu/l or LDH ≥ 1.5 normal ≤ 10 normal <i>28% of teratomas</i> <i>5-year survival 80%</i>	Any primary site Non-pulmonary visceral metastases Normal AFP Any HCG Any LDH <i>10% of seminomas</i> <i>5-year survival 73%</i>
<i>POOR PROGNOSIS with any of:</i>	
Mediastinal primary or non-pulmonary visceral metastases AFP > 10,000 ng/ml or HCG > 50,000 iu/l or LDH > 10 normal <i>16% of teratomas</i> <i>5-year survival 48%</i>	<i>No patients classified as poor prognosis</i>

6.3 RADIOLOGICAL IMAGING

All patients require formal staging with computed tomography (CT) of the chest, abdomen and pelvis to help with formulating a management plan.⁸ The CT scan should not be performed before a histological diagnosis has been made as a few 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.

Evidence level IIb

B CT 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 (see Annex).

It should be borne in mind that CT 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.

C All CT scans should be reviewed 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*).³⁶

Any previous films should be available to the radiologist.

6.4 OTHER STAGING INVESTIGATIONS

6.4.1 MAGNETIC RESONANCE IMAGING (MRI)

MRI is equivalent to CT for detection of pelvic or abdominal nodes, and involves no ionising radiation. The utility of MRI for routine staging and follow up is limited by lack of availability and less versatility than CT. 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.

6.4.2 BRAIN SCANNING

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

6.4.3 OTHER INVESTIGATIONS

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

C All staging should be completed and reviewed no later than three weeks after surgery, although immediate postoperative scans may be misleading.

7 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, normal CT scan of chest and abdomen/pelvis, and normal postoperative tumour markers.

7.1 MANAGEMENT OF STAGE I SEMINOMA

7.1.1 SURVEILLANCE

Seminoma of the testis has a different natural history from teratoma or combined germ cell tumours (mixed teratoma/seminoma). Surveillance has been used as a research protocol in the management of stage I seminoma. However, there is no reliable marker and there is a risk of delayed relapse, relapses being spread over the first five years, usually occurring in the para-aortic nodes.²⁶ The Royal Marsden Surveillance study showed a 15% probability of recurrence by three years.³⁷ Prolonged surveillance is therefore required with the possibility of falling compliance. This is compared with a 2-3% risk of relapse after adjuvant retroperitoneal irradiation, relapse occurring usually outwith the radiation field in other node groups.³⁸

Evidence level III

B A policy of surveillance for patients with stage I 'pure' seminoma is not recommended routinely outwith research protocols but may be considered in rare instances where there are fertility considerations or in patients who are medically or mentally unable to tolerate treatment. In such cases prolonged follow up is necessary.

7.1.2 ADJUVANT CHEMOTHERAPY

Initial results with adjuvant chemotherapy are encouraging. Single agent carboplatin is currently being assessed in an MRC randomised trial but this should be considered experimental therapy at present.

7.1.3 RADIOTHERAPY

Radiotherapy to the para-aortic nodes and in specific cases pelvic lymph nodes reduces the rate of relapse to about 3%.³⁸

Evidence level III

B Adjuvant radiotherapy is recommended for stage I seminoma in most cases.

Stage I seminoma without risk factors for pelvic nodal disease

Para-aortic node irradiation for management of stage I seminoma of the testis without known risk factors for pelvic spread³⁶ (see section 6.3) was studied in an MRC randomised trial in comparison with standard 'dog-leg' irradiation (including the ipsilateral pelvic nodes). On follow up, pelvic node relapses were only seen in the group treated with a para-aortic strip. There was no significant difference in sperm counts between the treatment groups at 18 months.^{39,40}

Evidence level Ib

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

A Stage I seminoma of the testis without risk factors for pelvic node disease following inguinal orchidectomy may be managed by prophylactic irradiation of the para-aortic nodes alone using parallel opposed fields, extending from DV10/11 to the lower border of LV5, contralateral border at the transverse processes of the lumbar vertebrae and ipsilateral border through the renal pelvis.

A dose of 30 Gray in 15 fractions is current standard practice.

Stage I seminoma with risk of pelvic node disease

Where there has been previous inguino-scrotal surgery, the field should be extended to include the ipsilateral pelvic nodes ('dog-leg'). This is also suggested as standard radiotherapy in the management of stage IIA pure seminoma of the testis, i.e. with involved infra-diaphragmatic nodes of less than 2 cm maximum size.³⁶

Evidence level III

After dog-leg radiotherapy to a dose of 25-30 Gray in 15-20 fractions for stage I and II disease there is a 6% incidence of failure all at distant sites.⁴¹ Minimally raised serum HCG, returning to normal after orchidectomy, is not thought to increase the risk of recurrence.

B Stage I seminoma of the testis where there are risk factors for pelvic nodal disease following inguinal orchidectomy, should be managed by prophylactic para-aortic node irradiation with parallel opposed fields extended to include ipsilateral pelvic nodes using a dose of 30 Gray in 15 fractions over 3 weeks.

In the case of an orchidectomy via a scrotal incision, the scrotum is only included in the radiotherapy fields if there is felt to be a high risk of contamination.

7.2 MANAGEMENT OF STAGE I TERATOMA AND MIXED SEMINOMA/TERATOMA

7.2.1 SURVEILLANCE

In patients with stage I teratoma or mixed seminoma/teratoma tumours of the testis surveillance is desirable in order 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%.⁴² The MRC surveillance study for stage I teratoma^{14,43} has enabled subgroups of patients to be identified 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 tumour invasion of testicular veins or lymphatics.^{14,26} A similar conclusion was reached in an EORTC study of surveillance for stage I teratoma.⁴⁴

Evidence level IIa

Although the mean age at presentation is older for patients with combined tumours than for those with teratoma the pattern of relapse is identical.²⁶ 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.³⁸ Scrotal interference prior to removal of the primary tumour is not a contraindication to surveillance.

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

How often should patients be followed up?

Surveillance is only recommended for patients without pathological risk features and who have no social, psychological or geographic factors which would preclude them from such a policy. The optimal timing of a CT scan for patients on surveillance is not known but is the subject of a forthcoming MRC study. Patients on surveillance are followed up monthly for the first year with clinical examination and serum markers at every visit. At present chest x-ray is performed at each visit and chest and abdomen CT at three, six, nine and 12 months. In the second year follow up should be two-monthly with CT scans at 18 and 24 months. Subsequent follow up should be three-monthly for the third year, six-monthly to the fifth year and annually thereafter to ten years, with clinical examination, serum markers and chest x-ray at every visit.

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

Which body parts should be imaged by CT on surveillance?

An abdominal CT is performed in all cases. A chest CT is generally performed at each visit, although there is no firm evidence on whether this frequency of chest scanning is necessary, or whether scanning could be limited to at-risk groups.

A pelvic CT may not be necessary in all cases. Pelvic nodal disease is strongly associated with well established risk factors, viz. 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 from clinical information and appearance of previous scan, pelvic CT can be omitted from surveillance or reassessment.³⁶ Previous scans should be available.

Evidence level III

B A CT scan of the thorax and abdomen should routinely be performed as part of the follow up of patients with germ cell tumours.

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

7.2.2 ADJUVANT CHEMOTHERAPY

Patients with stage I teratoma or combined tumour and high risk features should be considered for entry into current MRC studies of adjuvant chemotherapy. Those patients not entered into studies should be offered two courses of standard adjuvant platinum-based chemotherapy, i.e. bleomycin, etoposide and cisplatin (BEP).²⁹ It is important to recognise that adjuvant chemotherapy should only be given to patients with 'high risk' stage I teratoma 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.

Evidence level IIIb

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

B Adjuvant chemotherapy should be offered to patients with stage I teratoma or mixed seminoma/teratoma 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.

B Outwith clinical trials, two courses of BEP chemotherapy should be given.

Note: those patients with rising markers postoperatively (stage IM) should be considered to have metastatic disease and should receive a minimum of three courses of BEP.

8 Management of metastatic disease

8.1 MANAGEMENT OF METASTATIC SEMINOMA

8.1.1 STAGE II

The stage II category encompasses a wide range of disease extent. 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.

8.1.2 STAGE IIA

The data on the specific results of radiation therapy in the management of IIA i.e. nodal disease less than 2 cm in maximum diameter are scanty as these patients have been included in reports of patients with tumour masses less than 5 cm. There are two specific reports relating to this subgroup.

The first is from the Royal Marsden Hospital, which reported that 32 patients with IIA disease were treated with 35 Gray to the para-aortic and ipsilateral pelvic nodes.⁴⁵ 11% relapsed following initial radiation and 7% died of recurrent seminoma. The second report, from the MD Anderson, describes 36 patients, four of whom had masses less than 2 cm in diameter. None of these four patients relapsed following radiotherapy.⁴⁶ A dose of 30 Gray is probably adequate.

Evidence level IIa

B Radiation therapy to para-aortic and ipsilateral pelvic lymph nodes ('dog leg') is recommended for the treatment of stage IIA metastatic seminoma.

8.1.3 STAGE IIB

Patients with stage IIB seminoma have a lower expectation of cure with radiotherapy alone.⁴⁵

Evidence level III

Since it is now clear that metastatic seminoma is equally as chemosensitive as teratoma, this group of patients have increasingly been treated with chemotherapy, although there have been no randomised trials comparing chemotherapy and radiotherapy. Progression-free survival rates range from 85% to 100%. Chemotherapy may be preferred as initial therapy as it may prove more problematic to deliver in patients who relapse after radiotherapy, but radiotherapy should still be considered an effective treatment for stage IIB disease.

C For patients with stage IIB seminoma, chemotherapy or radiotherapy are recommended as initial treatment.

8.1.4 STAGE IIC AND IID

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.⁴⁶⁻⁴⁸ 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.

Evidence level IIa

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

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

B Where chemotherapy is contraindicated, radiotherapy may be an acceptable alternative.

8.1.5 STAGE III AND IV

Collected data from the literature on radiation therapy for stages III and IV disease show a survival of 36% (136/375).⁴⁹ Because treatment with radiation therapy involved at least infra- and supra-diaphragmatic fields to cover sites of known disease, and because of the risk of relapse and thus the 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.^{37, 50, 51}

Evidence level IIa

B 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 because of data showing an inferior outcome for carboplatin in a parallel trial in teratoma. It was concluded that etoposide and cisplatin should remain standard therapy and that carboplatin should only be used in exceptional circumstances.⁵²

Evidence level Ib

A Carboplatin should only be used as an alternative to cisplatin in exceptional circumstances.

8.2 MANAGEMENT OF METASTATIC TERATOMA

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 alpha-fetoprotein (AFP), human chorionic gonadotrophin (HCG) and lactate dehydrogenase (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 4).³⁴

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:

- (a) less aggressive chemotherapy in patients with a good prognosis; and
- (b) an increase in efficacy of chemotherapy in the other groups.

Current evidence suggests that four courses of bleomycin, etoposide and cisplatin (BEP) produces an outcome equivalent to more prolonged treatment for metastatic teratoma.⁵³

Evidence level III

B Standard therapy for patients with metastatic teratoma should be four cycles of chemotherapy with bleomycin, etoposide and cisplatin.

For four courses of BEP chemotherapy the minimum total dose of etoposide is 360 mg/m² (with some centres using 500 mg/m²). Conventionally, this is given over five days (along with cisplatin 20 mg/m² for five days). If fewer than four courses are given the higher dose of etoposide per course should be prescribed. An alternative regimen (with cisplatin over two days and etoposide over three days in the same total doses) is being assessed in the current MRC/EORTC study, and may offer the advantage of a shorter hospital stay.

There is evidence that treatment of testicular cancer in a specialist centre is associated with improved results.³

Evidence level III

B Chemotherapy should only be given in a specialist centre and overseen by a clinician experienced in the management of germ cell tumours.

8.2.1 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.

One significant advance would be the demonstration that three rather than four courses of chemotherapy is sufficient in this group. One US study comparing three and four courses of BEP revealed equivalent results of either treatment.⁵⁴ As elimination of the final course of therapy results in diminished toxicity three courses of BEP may be the preferred regimen for patients with good prognosis disease.

Evidence level Ib

However, this study, though clearly important, was of relatively small size and would not have been capable of detecting a small but clinically significant difference in the two arms (up to 10%). Further data is awaited from the current MRC/EORTC study (protocol TE20) for good prognosis patients, which is addressing the issue of three vs. four cycles of BEP and is of sufficiently large size to ensure that any difference of this magnitude would be detected.

In attempting to reduce the incidence of treatment-related toxicity, investigations have particularly concentrated on the problems associated with cisplatin and bleomycin.

Cisplatin

The side effects of cisplatin comprise a significant component of both the early and late toxicity of treatment. 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 25% of the patients 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 price to pay, especially an increased risk of hypertension.⁵⁵

Carboplatin

Carboplatin causes little renal toxicity at conventional dosage and does not cause neurotoxicity or ototoxicity. It would therefore appear to be an attractive candidate as an alternative to cisplatin in the management of these patients. The Royal Marsden Hospital Testicular Unit performed a phase II trial of the combination of carboplatin, etoposide and bleomycin in patients with metastatic nonseminoma of testes who fall into the good prognosis group⁵⁶ and, following this, a large MRC/EORTC study comparing BEP with bleomycin, etoposide and carboplatin (CEB) was initiated. This was closed with clear evidence that the carboplatin arm was inferior.⁵⁷ A total of 589 patients were entered and a significantly worse one year failure-free survival rate was noted for patients treated on the CEB arm (90% vs. 80%).

Evidence level Ib

A similar conclusion was reached in the USA in a study of 265 patients treated at MSKCC with three courses of either etoposide/cisplatin (EP) or etoposide/carboplatin (EC). Relapse free survival was significantly inferior in the EC arm ($p=0.001$),⁵⁸ and no further trials involving carboplatin for metastatic disease have been recommended.

A Carboplatin should only be given in circumstances in which cisplatin is contraindicated.

Bleomycin

Bleomycin treatment can cause a number of side effects, including skin rashes and allergic reactions, but pneumonitis is the most feared because of the potential for fatal pulmonary toxicity in 2-3% of patients. Four studies have addressed this problem, by means of randomised trials in which bleomycin has been deleted in one arm, all in good prognosis patients.⁵⁹⁻⁶²

Evidence level Ib

An Australasian study which compared PVB with PV (four cycles) showed a significant increase in tumour-related deaths in patients treated with PV.⁶¹ An ECOG study which compared BEP with EP (three cycles) was terminated early because an interim analysis suggested less favourable responses with EP.⁶⁰ Long-term follow up of an EORTC study comparing BEP with EP (four cycles) showed a significant difference in complete response rate in favour of BEP.⁶² Only one trial showing no difference has been reported.⁵⁹ This study compared treatment with VAB-6 with EP and was thus complicated by the use of other drugs.

Evidence level Ib and IIb

Overall, the data indicate that bleomycin should continue to be part of standard chemotherapy. The total dose of bleomycin should not exceed 360 mg. Where risks of toxicity are increased (e.g. in patients with poor renal function, previous mediastinal irradiation and older patients) its omission may be appropriate.

A Under normal circumstances, weekly bleomycin should be given.

B The total dose of bleomycin should not normally exceed 360 mg.

8.2.2 MANAGEMENT OF PATIENTS WITH INTERMEDIATE AND POOR RISK GERM CELL TUMOURS

In this group, with a predicted cure rate of 40-70%, 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.⁶³

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. From in vitro experiments⁶⁴ and early clinical trials⁶⁵ we know that a dose effect relationship exists for the action of cisplatin on germ cell tumours.

The dose of cisplatin in most standard regimens has been 20 mg/m² for five days combined with bleomycin and vinblastine or etoposide. Increase in the intensity of cisplatin treatment can be achieved by increasing the dose, (e.g. 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.⁶⁶

In 1990 the MRC/EORTC initiated a randomised trial comparing 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 three weekly). The BOP/VIP schedule incorporates rapid induction followed by potentially non-cross resistant chemotherapy.⁶³ A total of 380 patients were randomised and preliminary analysis suggests no advantage to the more intensive schedule.⁶⁷

Evidence level Ib

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 at Charing Cross Hospital with POMB/ACE chemotherapy.⁶⁸ 106 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 in Germany involving 141 patients with advanced disease has confirmed the feasibility and efficacy of repeated cycles of high dose chemotherapy.⁶⁹ Randomised trials of this approach both as salvage and as first line treatment are now ongoing.

Evidence level IIa

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

C Patients with adverse prognostic factors should be treated in specialist centres. Patients where possible should be entered into well designed multicentre studies to define the best treatment for this group of patients.

A Outwith the trial setting standard initial chemotherapy for patients with intermediate and poor risk germ cell tumours is BEP.

9 Treatment of residual masses after chemotherapy

9.1 SURGERY

9.1.1 SEMINOMA

Surgery is usually only indicated for teratoma. 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.

9.1.2 TERATOMA

Residual masses may remain after chemotherapy and marker normalisation.⁷⁰ They may contain viable tumour, differentiated teratoma or merely fibrosis/necrosis. It should be made clear to patients at the start of treatment that residual masses will have to be removed surgically. 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.⁷¹ 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).

Evidence level III

B Patients with teratoma 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.⁷²

Evidence level III

B If the primary testicular tumour has not already been removed, an orchidectomy should be performed at the same time.

Incomplete excision is associated with poor prognosis.⁷² Series in which several surgeons have operated sporadically have had higher rates of incomplete resection⁷³ than those managed by a single surgeon.^{70, 72}

Evidence level IIIb

Surgery for metastatic teratoma in Scotland should usually be performed in the two specialist centres with experience in this operation. In each, one surgeon, working closely with the oncology department, undertakes surgery for abdominal disease and co-operates with a similarly specialised thoracic surgeon. 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.

B Surgery for metastatic teratoma should be performed in a specialist centre with experience in the operative management of these patients.

At present, most patients in Scotland are managed in Glasgow or Edinburgh.

C Further chemotherapy should be considered where there has been incomplete excision and pathology confirms malignant elements in the resected specimen.

For selected patients, where response to chemotherapy is inadequate, and markers plateau or rise, consideration may be given to interventional surgery.⁷⁴ Interventional surgery is only needed in exceptional cases, when failure of response to chemotherapy has been demonstrated unequivocally, and must be planned by close co-operation between surgeon and oncologist. Such an approach is most likely to be useful if residual lesions are localised and can be completely excised. Chemotherapy may need to be restarted immediately after initial recovery from surgery.

9.2 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 recent retrospective review of MRC data indicates that there is no evidence to support its use.⁷⁵ A policy of observation is therefore reasonable, with radiotherapy reserved for those patients in whom residual large masses persist.

Evidence level III

B Patients with seminoma who have residual masses following chemotherapy can generally be managed by a policy of observation rather than radiotherapy. Surgery is not routinely indicated.

10 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.⁷⁶

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 e.g. 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 mature teratoma. Complete surgical excision of mature teratoma remains the treatment of choice.

Patients with rising markers will require further chemotherapy. The available options include further treatment with platinum combinations together with alternative drugs such as ifosfamide in the VIP schedule (etoposide, ifosfamide and cisplatin). Other agents such as paclitaxel are active in this setting.⁷⁷ A further approach is to increase the dose intensity; specifically by enhancing the doses of active drugs one may achieve improved therapeutic results. High dose chemotherapy with autologous bone marrow transplantation or peripheral blood stem cells has produced complete responses but in patients with progressive disease these have tended to be brief.⁷⁸ At present the procedure is probably best reserved as consolidation for relapsed patients who have achieved a second remission through conventional chemotherapy and/or surgery. Overall the cure rate for patients with relapsed disease is 30%.

C Patients with relapsed disease should be referred to a specialist centre to be considered for entry into well-designed clinical trials.

The outlook is better for patients whose relapse occurs more than two years after initial therapy. In these cases, surgery plays a major role and should be considered as the initial strategy for treatment of later relapse.⁷⁹

Evidence level III

C Surgery should be considered the mainstay of treatment for late relapse.

11 Central nervous system metastases

Metastatic disease in the central nervous system is an uncommon initial presentation. Most of these patients have concomitant advanced pulmonary metastases with testicular histology comprising mainly choriocarcinoma or yolk sac elements. The presence of CNS metastases does not preclude cure and such patients should be treated with curative intent. Of concern is that haemorrhage into metastases following chemotherapy may occur and surgical excision of accessible lesions should be considered.⁸⁰

- C** Initial surgical resection of accessible CNS lesions should be considered.
- C** Radiotherapy may be given as part of curative therapy or purely with palliative intent.

12 Nursing care

As there is opportunity for an excellent prognosis from this rare tumour type the nursing care given has an essential part to play in reflecting a good treatment outcome (see section 2.1). Problems for the patient are complex and psychological morbidity has been shown to be an outcome.

C Specialist nurse involvement is recommended at all stages of management.

12.1 EXPERIENCE AND TRAINING

Referral to a specialist centre has been shown to be associated with improved outcome in patients with testicular cancer.³ It is likely that this is due to the input of the whole multidisciplinary team. Therefore nurses in specialist centres should receive training in all aspects of the management of these patients. Nurses who are well educated, have been taught good listening skills, and have access to continuing educational opportunities and support, can influence a good outcome.

- Post registration education in cancer nursing skills is essential. This will enable nurses to provide more effective care for patients. This should be available to all nursing staff.
- Standards of nursing care should be devised, implemented and audited, specific to the recommended treatments and covering all aspects of cancer nursing practice.

12.2 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 they can understand.

- The provision of appropriate information should be made available to patients and their carers in order 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.

12.3 PSYCHOSOCIAL SUPPORT

Despite an excellent prognosis there are high levels of morbidity in patients with testicular cancer.⁸¹ Psychological morbidity can occur at any stage throughout the illness perhaps as a result of treatment, unemployment or concerns over fertility issues. Nurses must have the ability to recognise anxiety and depression because early referral to a clinical psychologist, can significantly reduce patient's emotional distress and enhance adaption processes.⁸² However, there is evidence that routine adjuvant psychological therapy is not necessary.⁸³

- 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.

12.4 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. The multiprofessional team has in the past given little recognition or support to this area. 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.

13 Post treatment follow up

The rationale for follow up is to:

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

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

A suggested follow up regimen is illustrated in table 5:

Table 5

SUGGESTED FOLLOW UP REGIMEN

SEMINOMA	
STAGE I POST RADIOTHERAPY	
No routine follow up CT scans.	
Chest x-ray and clinical examination	— at one month — then three-monthly for one year — then six-monthly stopping at five years.
STAGE IIA AND IIB POST RADIOTHERAPY	
If post treatment CT abdomen and pelvis scan is normal: no further routine CT scans.	
If post treatment CT scan abnormal: repeat the CT scan every six months for 18 months but stop as soon as CT scan is normal.	
Subsequent follow up as stage I.	
OTHER STAGES POST CHEMOTHERAPY	
As stage IIA and IIB above.	

Table 5 (continued)

SUGGESTED FOLLOW UP REGIMEN

TERATOMA
<p>SURVEILLANCE See section 7.2.1.</p>
<p>AFTER ADJUVANT CHEMOTHERAPY Clinical examination at each attendance. HCG and AFP monthly for 12 months — every two months for 12 months — then every three months for 12 months — then every six months for two years — then yearly to 10 years.</p> <p>CT thorax, abdomen and pelvis after treatment. No further routine scans. Chest x-ray every two months in first two years then at each attendance.</p>
<p>AFTER CHEMOTHERAPY FOR METASTATIC DISEASE Clinical examination at each attendance. HCG and AFP monthly for 12 months — then every two months for 12 months — then every three months for 12 months — then every six months for two years — then yearly.</p> <p>If CT appearances return to normal after chemotherapy no more routine scans. If residual masses are visible, resection should be performed.</p> <p>Further scan frequency will depend on pathological findings and completeness of excision. After complete resection no routine scans are necessary after a baseline postoperative scan.</p>

14 Recommendations for audit

Core data for subsequent audit should include an assessment of:

1. Any delay in patients presenting to a doctor
2. Timing from presentation to referral and further investigation.
3. Preoperative investigations.
4. Number of patients offered and receiving a testicular prosthesis.
5. Number of patients offered and having sperm stored.
6. Time from surgery to seeing oncologist.
7. Number of patients having biopsy of contralateral testis.
8. Adequacy of and time for completion of staging.
9. Details of radiotherapeutic management.
10. Details of chemotherapeutic management.
11. Details of further surgical management.
12. Details of timing of clinic follow up and subsequent investigations.
13. Details of toxicity of treatment.
14. Survival and relapse details.

Annex

COMPUTED TOMOGRAPHY: TECHNICAL AND RADIATION DOSE CONSIDERATIONS

CT TECHNIQUE

Meticulous and reproducible technique is important for accuracy and also for comparability between examinations.

- Oral contrast for all abdominopelvic examinations.
- IV contrast – not routine, but consider in cases of difficulty.
- Use same scanner for all scans on the same patient if possible.
- Use same scanning technique on all patients if possible, including field of view.
- Ideally perform scans at specialist centre with oncological radiology expertise.

Chest

Spiral CT should be used if available as it is more sensitive than single-section CT.^{84, 85} Spiral pitch of up to 1.5 can be employed to reduce radiation dose and time to perform scan.⁸⁶ If spiral CT is not available, contiguous single-section slices should be used.

Abdomen/pelvis

There is controversy over exact scan parameters, e.g. 10 mm contiguous slices, 8 mm slices with 4 mm gap or 10 mm slices with 5 mm gap. The latter protocol is acceptable as in the abdomen/pelvis significantly enlarged nodes are between 7 mm and 12 mm in diameter (depending on the anatomical site), and therefore a 5 mm gap is unlikely to reduce sensitivity. The reduction in radiation from this protocol is significant. The role of spiral CT with increased pitch in the abdomen is as yet uncertain.

LONG TERM FOLLOW-UP

After any period of intensive surveillance/reassessment, longer term follow-up is carried out using chest x-ray alone (with clinical examination, markers, etc.), not CT.

RADIATION DOSE

CT confers a high radiation dose per examination compared with plain radiography. CT in 1989 was responsible for 19% of medical ionising radiation from only 2% of imaging examinations.⁸⁷ The radiation dose from the scanner in use at Western General Hospital Edinburgh has been calculated for the following body areas:

chest	contiguous spiral scanning	6.0 mSv effective dose equivalent
abdomen	10 mm contiguous slices	5.3 mSv EDE
	10 mm slices with 5 mm gap	3.5 mSv EDE
pelvis	10 mm contiguous slices	3.9 mSv EDE
	10 mm slices with 5 mm gap	2.6 mSv EDE

In view of the high radiation dose used in CT staging and routine reassessment of this group of young patients with good prognosis, every effort should be made to reduce radiation from diagnostic sources as this may constitute a significant risk to the patient.

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Quick Reference Guide

PATIENT EDUCATION AND AWARENESS

- Testicular germ cell tumours are relatively rare (7.5 cases per 100,000 of the male population) but are the most common cancer in men aged 20-30
- The majority of cases are curable, even when metastasised (5 year survival ≈90%)
- Delay in presentation is a greater problem than delay in referral

C Education aimed at young men to inform them of the disease and its curability should be supported

REFERRAL

- 86% of patients present with an *enlarged testicle* or a *lump* in the testicle
- In 97% of patients a lump is present on examination
- A *decrease in testicular size* may also occur
- Other symptoms include *pain, inflammation, a dragging sensation, and a recent history of trauma*
- Abnormal masses in the epididymis are unlikely to be testicular tumours
- Ultrasound, if available, may help in distinguishing between lumps arising from the body of the testis and other intrascrotal swellings

C Patients suspected of harbouring a testicular malignancy should be referred urgently for urological assessment

B Patients should be seen urgently (within two weeks) by a specialist

PRIMARY TREATMENT

- Measurement of tumour markers is necessary for staging and follow up
- One or more markers are raised in 75% of cases of patients with teratoma
- Ultrasound, of both testes and the abdomen, and chest x-ray may show evidence of disease

C Preoperative investigations should include assay of AFP, HCG, LDH, an ultrasound of both testes and the abdomen, and a chest x-ray

Patients who are ill with high markers and widespread metastases should be referred for immediate chemotherapy

C Where possible an inguinal orchidectomy should be performed

C A testicular prosthesis should be offered to all patients

C Contralateral testicular biopsy should be considered in patients at high risk of carcinoma in situ (small remaining testis (≤16 ml), low sperm count, ultrasound abnormality, age < 30 years, or history of maldescent)

KEY: **A** **B** **C** indicates grade of recommendation

Good practice point

INVESTIGATION AND STAGING

- Treatment of testicular cancer in a specialist centre leads to improved results

C Following confirmation of a germ cell tumour, all patients should be referred to a specialist centre for the management of testicular tumours and seen by an oncologist within 1-2 weeks

C Marker levels (AFP and HCG) should be used along with imaging techniques (CT of thorax, abdomen and pelvis) for staging and to allocate a prognostic group for patients with teratoma

C All staging should be completed and reviewed within three weeks of surgery

C Specialist nurse involvement is recommended at all stages of management

C Pathology and radiology should be reviewed by specialists at the referral treatment centre

C When appropriate, sperm storage should be offered to men who may require chemotherapy or radiotherapy

MANAGEMENT

CARCINOMA IN SITU (CIS)

B Consider testicular radiotherapy

SEMINOMA

Stage I

B Radiotherapy to para-aortic nodes (unless risk factors for pelvic node disease)

Stage I with risk factors
Stage IIA

B Radiotherapy to para-aortic nodes and pelvic lymph nodes ('dog-leg')

Stage IIB

C Radiotherapy or chemotherapy

Stage IIC, IID, III, IV

B Chemotherapy with BEP (consider omitting bleomycin if age > 40)

TERATOMA (including mixed seminoma/teratoma)

Stage I

B Surveillance unless high risk (blood vessel / lymphatic invasion)

if high risk

B Chemotherapy (two courses BEP)

Stage II, III, IV

B Chemotherapy (standard treatment: four cycles BEP)

FOLLOW UP

C Surgery not routinely considered, but monitor regressing masses

B Radiotherapy not routinely given to residual masses

FOLLOW UP

C In specialist clinic, adhering to strict surveillance protocol

B One post treatment CT scan as routine only

B Post treatment CT scan
Resect residual masses if markers normal

RELAPSED DISEASE

- Salvage chemotherapy is curative in 25% cases

C Refer to specialist centre for entry into clinical trial

C Consider surgery for late relapse

CENTRAL NERVOUS SYSTEM (CNS) METASTASES

C Surgical resection of accessible lesions
Radiotherapy may be given with curative or palliative intent