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1. Introduction

This document is a guideline for the management of patients with testicular tumours. It is a template for best practice and an aid to health practitioners involved in management from primary care through referral, treatment and follow-up.

Testicular tumours are rare but important because they occur in the young. The peak incidence for NSGCT is between 20 and 30 years and for seminoma between 30 and 40 years. Lymphoma of the testis usually occurs in the over 60s.

Testicular tumours have an excellent overall prognosis with a 95% cure rate.

Seminoma presents as disease apparently limited to the testis in over 80% of patients. For these men surveillance, adjuvant chemotherapy or radiotherapy results in similar 5 year survivals of 98%.

Non seminomatous germ cell tumour (NSGCT) of the testis without metastases have an excellent prognosis. Some cases are managed by surveillance alone and others are offered adjuvant chemotherapy.

Patients with metastases are grouped into prognostic categories using the International Germ Cell Consensus Classification (IGCCCG) (Appendix A). In summary:

- 56% of patients have a good prognosis (92% 5 year survival).
- 28% of patients have an intermediate prognosis (80% 5 year survival).
- 16% of patients have a poor prognosis (48% 5 year survival).

Standard treatment is BEP chemotherapy (Bleomycin, Etoposide and Cisplatin).

Patients are usually referred to Oncologists after orchidectomy as this is the primary treatment in most cases and needs to be done quickly. The main indication for speed is that some patients have rapidly progressive tumour and can develop further metastases with a poor prognosis. They may also suffer from renal obstruction. Deaths within 6 weeks of first symptom were not unknown in the days when curative treatment was not available. Delay is therefore to be avoided in all cases to reduce patient anxiety and establish a clear plan of management.

Usually these patients will be referred first to a Urologist. However patients with symptoms from metastases, even if they have an obviously enlarged testis, should have an urgent oncological opinion before surgery. Such patients may be detected by GPs or be seen first by A & E, Chest, GI, Orthopaedic or Neurology Consultants.

A supra-network SMDT covering East Anglia and East London has been established incorporating specialists from Addenbrookes, Barts and the London, Chelmsford, Colchester, Guys, Ipswich, Norfolk & Norwich, Southend and UCLH. A video-conference meeting is held fortnightly.
2. Outcome Measure Summary

1.1. Referral

All patients with a swelling in the testis should be referred urgently to the urologist unless they have symptoms from metastases.

All patients should be seen by the urologist within 2 weeks of referral unless they have symptoms from metastases when they should be seen within 24 hrs, if necessary via an emergency referral via A & E.

1.2. Investigations

All appropriate investigations are booked at the first appointment with the urologist.

1.3. Treatment

1.3.1. Pre-surgery

Fertility should be considered prior to orchidectomy. Sperm cryopreservation may be appropriate particularly in patients with an abnormal contralateral testis.

AFP, HCG, LDH + CXR should be done.

1.3.2. Surgery

Orchidectomy should occur within 14 days of GP referral.

Orchidectomy is carried out via an inguinal incision with division of the spermatic cord at the internal inguinal ring.

Biopsy of the contralateral testis is considered in all individuals at a high risk of CIS.

The option of a testicular prosthesis should be discussed with all patients prior to orchidectomy.

1.3.3. Post-surgery

All staging investigations (i.e. histological review of tissue samples, CT scan chest, abdomen and pelvis and post-operative tumour markers) are organised by the urologist following orchidectomy.

1.3.4. Oncology Referral

All patients should be referred to the designated oncologist at a regional Cancer Centre within 24 hours of surgery - unless referred prior to surgery - and presented at the next local MDT – this should not delay referral.

All patients fulfilling the criteria for urgent referral (as detailed in section 5, page 10) should be referred directly to the Oncologist by telephone and should be seen within 24 hours of referral.

All pathology should be reported and unstained spares or blocks forwarded for review at the cancer centre by the multidisciplinary team within 2 weeks of orchidectomy.

A centralised point for referral should be identified within each Network.
A Consultant Histopathologist should be identified at each Cancer Centre who will review the pathology of all orchidectomy specimens within 3 weeks of orchidectomy.
Any histology reviews coming directly to Dr Dan Berney, Consultant Histopathologist at BLT should be sent to:

Division of Cellular Pathology 2nd Floor
80 Newark St
Whitechapel
London
E1 2ES.

All radiology CT scans should be reported and images forwarded for review at the cancer centre by the multidisciplinary team within 2 weeks of orchidectomy.

Any radiology reviews coming directly to Dr Andrea Rockall, Consultant Radiologist at BLT should be sent via the:

Testis SMDT Co-ordinator St Bartholomew’s Hospital Cancer Strategy Unit 39-41 Little Britain London EC1A 7BE

The histology and CT scans should always be accompanied by a completed proforma which details the patients’ management history to date.

1.3.5. Multidisciplinary Team Working

All staging CT images of patients with metastatic disease must be discussed at the SMDT following review by the designated radiologist at the cancer centre within 3 weeks of orchidectomy. For uncomplicated stage I disease a proforma is completed for “information only” for the SMDT database.

The majority of uncomplicated germ cell tumour cases can be dealt with entirely by the pathologists at the regional centres. Those which require a further opinion include: rare non-germ cell tumours and occasionally germ cell tumours with an unusual or unexpected immunoprofile or unexpected clinical behaviour. These should be forwarded to Dan Berney at BLT (details above).

All post-chemotherapy CT scans to assess response, suspected relapses and any complex cases where management is uncertain will be reviewed at the SMDT.

**All patients who undergo surgery to resect residual masses should have their post chemotherapy pathology reviewed at the SMDT**

1.3.6. Oncological Management

All patients should be seen with the results of the MDT review by the designated oncologist at a regional Cancer Centre within 3 weeks of orchidectomy.

Urgent chemotherapy should start within 24-48 hours of referral to the oncologist.

Radical chemotherapy should start within 2 weeks of a decision to treat unless there are circumstances which necessitate a delay (e.g. wound infection). All adjuvant chemotherapy should be commenced within 2 months of orchidectomy (100%).
All patients receiving Cisplatin chemotherapy should have an EDTA GFR and audiogram prior to treatment.

All patients receiving Bleomycin chemotherapy should have lung function tests prior to chemotherapy.

Radiotherapy treatment should start within 4 weeks of a decision to treat.

Sperm cryopreservation should be discussed with all patients before chemotherapy or dog leg field radiotherapy.

All patients should be offered written information regarding the intended treatment and its potential side effects.

1.3.7. Management of Residual Masses after Chemotherapy - NSGCT

All NSGCT patients with a residual mass greater than 10mm post-chemotherapy should be considered for RPLND at SMDT and if appropriate they should be referred to a specialist surgeon undertaking at least 8 resections per year (100%).

1.3.8. Follow-up Management

All patients are followed-up on protocol by the designated oncology team.

All patients at high risk of CIS in the remaining testicle, who did not have a biopsy at time of orchidectomy, should be offered the opportunity to consider a contra-lateral biopsy 2 years following completion of any chemotherapy treatment.

1.3.9. Patient Care

All patients should be offered written information on their disease and its implications, treatment options and potential side effects.

All patients should have a contact number for the Specialist Nurse or Research Nurse given at their first appointment with the oncology team (100%).

1.3.10. Primary Care Team

GPs should be notified of treatment plans within 5 working days of first consultation with the oncologist.

GPs should be notified within 24 hours of a patient's discharge.

GPs should receive an evaluation of the patient's condition after each follow-up appointment.
3. Contact Details for Members of the Testicular Tumours Multi-Professional Team

Addenbrookes
Dr Michael Williams – Consultant Clinical Oncologist
Dr Danesh Mazhur – Consultant Medical Oncologist
Addenbrooke’s NHS Trust,
Oncology Centre, Box 193, Hills Road,
Cambridge CB2 2QQ
Secretary: 01223 217020

Barts
Dr Jonathan Shamash - Consultant Medical Oncologist
Dr Thomas Powles - Consultant Medical Oncologist
Barts and the London Hospitals
Medical Oncology
7th Floor, Gloucester House
West Smithfield
EC1A 7BE
Secretary(s): 020 7601 7313 or 020 7601 8522

Chelmsford (Broomfield)
Dr Patricia Leone - Consultant Clinical Oncologist
Broomfield Hospital
Court Road, Broomfield
Chelmsford
Essex CM1 7ET
Secretary: 01245 514397

Colchester (Essex County)
Dr Alan Lamont – Consultant Clinical Oncologist
Colchester Hospital University NHS Foundation Trust,
Turner Road, Colchester, Essex
CO4 5JL
Secretary: 01206 744582

Guys
Dr Simon Chowdhury – Consultant Medical Oncologist
Guys Hospital
10th Floor, Tower Wing
Great Maze Pond
London SE1 9RT
Secretary:
4. Referral Guidelines

Tumours of the testis can be rapid growing. Delay in referral for urological opinion adversely affects the long-term outcome for the patient and the intensity of treatment.

All patients suspected of having a testicular malignancy should be urgently referred for urological assessment and seen within 2 weeks (100%). (See Referral Guidelines for Suspected Cancer Consultation Document, DOH Steering Group, November 1999).

Any swelling in the body of the testis in a man aged 15-55 years is an indication for urgent referral and should be seen within 2 weeks (DOH Steering Group 1999). However any such patients with symptoms from metastases should be referred for an emergency oncology opinion within 24 hours, if necessary via A & E.

1.4. Common Presenting Symptoms Indicating Need for Referral to a Urologist

80-90% of patients will present with an enlarged testicle or lump in the testicle. This may be painless but 15% have pain. In 97% of patients a lump is present on examination. If this is clearly within the testis there is a high probability of cancer.

Newly developing varicocele or hydrocele.

A tender lump or enlargement persisting 10 days after starting antibiotics – (infection is an uncommon cause of testicular symptoms in men under 40 years old).
Other suspicious features include a dragging sensation or a recent history of trauma.

A history of testicular maldescent is present in 10% of patients. There is no association with vasectomy unless it was complicated by a major haematoma.

1.5. Urgent Referral to Oncologist

Rarely, a patient will present with advanced metastatic disease, requiring emergency admission.

Findings may include:
- Backache, due to enlarged para-aortic nodes.
- Cough, breathlessness or haemoptysis, due to pulmonary metastases.
- Renal impairment due to ureteric obstruction from abdominal metastases.
- Gynaecomastia, usually due to production of excessive HCG by the tumour.
- Poor general condition associated with abnormality in testis.
- HCG >5000 or AFP >1000
- Brain Metastases

Such patients may already be under the care of a consultant surgeon or physician. They should be referred immediately by telephone to the regional specialist and seen within 24 hours (100%). A pathological diagnosis is not a prerequisite for referral in these circumstances.

5. Investigations

Pre-operative assessment of patients suspected of having testicular malignancy should include:
- AFP (alpha fetoprotein)
- B-HCG (beta human chorionic gonadotrophin)
- LDH (lactate dehydrogenase)
- Chest x-ray
- Palpation of abdomen and neck for metastases
- Urgent ultrasound scan of the testis if required to confirm the diagnosis
- U&Es, LFTs, alkaline phosphatase & FBC

Investigations should be carried out at the patient’s first appointment with the urological team. Decision to operate should not be made until the chest radiograph has been reviewed. Patients with widespread metastases should have emergency tumour markers (or urinary pregnancy test) and reviewed jointly with an Oncologist before deciding about orchidectomy.

If a diagnosis is certain pre-operatively on clinical grounds and node enlargement is suspected, a CT scan of the chest abdomen and pelvis should be requested pre-operatively and a referral to the oncologist should be initiated after discussion with the patient.

If patients present with signs of advanced metastatic disease, as above, CT scan of the chest, abdomen and pelvis will be required but may be best undertaken after patient transfer. MRI of the brain will also be required (CT of the brain may be substituted if delay in obtaining MRI is unacceptable).
6. Surgical Management

1.6. Pre-surgery

Preparation for surgery will include:
- Informed consent
- Investigations (as above)
- Further investigations where appropriate (as above).

Histological diagnosis is not always necessary before referral to an oncologist as clinical near certainty can be achieved by ultrasound of the testis, tumour markers and physical examination. Orchidectomy can be undertaken after chemotherapy.

Fertility should be considered prior to orchidectomy. Sperm cryopreservation may be appropriate particularly in patients with an abnormal contralateral testis. Virology screen of hepatitis B & C & HIV needs to be done first. If the patient has one testicle and this contains a suspected tumour, they should be seen for consideration as to whether or not they are candidates for pre operative chemotherapy and a partial orchidectomy.

1.7. Surgery

Surgery has two aims – diagnostic and therapeutic:
1. Histological diagnosis
2. Excision of the primary tumour

Surgery should occur within 14 days of GP referral (or less).

The preferred orchidectomy approach involves an inguinal incision with division of the spermatic cord at the internal inguinal ring.

Orchidectomy via a scrotal incision is usually contra-indicated.

Biopsy of the contralateral testis should be considered for individuals at high risk of intratubular germ cell neoplasia (ITGCN) (i.e. <31 years and testicular volume <12ml or with a history of mal descent) (Harland et al 1998). About 5% of men with testicular cancer have ITGCN of the contralateral testicle, ITGCN is thought to progress to invasive germ cell tumour (GCT) in 50% of these cases within 5 years and it is believed that in time the majority will develop invasive malignancy. This progression can be reduced by chemotherapy with recovery of fertility (but risk of late relapse) or testicular radiotherapy (at the price of fertility). Even though the long-term prognosis of second testicular tumours is excellent, second orchidectomy results in infertility and necessitates hormone replacement. (See Section 13).

The option of a testicular prosthesis should be discussed with all patients prior to orchidectomy.

1.8. Post-surgery

Post-operative investigations should be organised by the urologist. These investigations should include:
- Histological review of tumour.
- CT scan of chest, abdomen and pelvis.
- Post-operative AFP, HCG and LDH (if these are raised pre-op, should be repeated weekly until normal).
These investigations should be reported within two weeks of orchidectomy.

1.9. Oncology Referral

Although further treatment may not be required, all patients should be referred to the designated oncologist at the Cancer Centre by fax within 24 hours of surgery.

Results of all pre-op and post-op investigations should be faxed to the oncologist as soon as they are reported.

Radiology CT images and pathology slides should be forwarded to the regional cancer centre for review within 2 weeks of orchidectomy.

7. Oncology Management

1.10. Multidisciplinary Team Working

All cases of metastatic testicular cancer should be managed by the multidisciplinary team (SMDT).

A video-conferenced SMDT covering East London and East Anglia is held fortnightly on Mondays from 1.00pm to 2.00pm. All cases of GCT are registered and complex cases are discussed.

The multidisciplinary team brings together expertise in pathology, radiology, surgery and oncology. Core members of the SMDT are the consultant oncologists, specialist nurses, consultant pathologist, consultant radiologist and uro- oncology surgeons as detailed in section 3 of this document. Extended members of the team include cardiothoracic, hepatobiliary and neurological surgeons to whom referrals are made post-chemotherapy for surgery to residual masses.

The aim of the SMDT is to ensure the highest standard of care for testicular cancer patients. All new referrals with metastatic disease are discussed and relevant pathology and radiology will be reviewed at the SMDT, prior to reaching a treatment decision based on the expertise of those involved. All stage I patients are noted but not routinely discussed unless pathology is unusual or their management is proposed to differ from the agreed pathway.

In addition to new referrals, all post chemotherapy CT scans to assess response, suspected relapses and any complex cases where management is uncertain will be reviewed.

Attendance records and minutes of the meetings are kept for audit purposes. All patients (new and follow up) to be discussed at the SMDT must have a proforma completed prior to the meeting detailing their management history to date and this must be submitted to the Testis SMDT coordinator. Decisions reached at the SMDT are noted on the proforma and entered into the patient’s notes. Decisions are communicated to the GP following consultation with the patient (Appendix F).

1.11. Pathology and Radiology

All pathology and radiology must be received by the Cancer Centre by the designated deadline prior to the appropriate meeting to ensure patient's case history can be discussed at the SMDT within 3 weeks of orchidectomy.

Unstained spares or blocks from cases sent for review to the designated Cancer Centre Pathologist within 2 weeks of the orchidectomy.

CT images from all cases should be reviewed by the designated Cancer Centre Radiologist within 3 weeks of orchidectomy.
All cases should be reviewed at the Testicular MDT (SMDT) within 3 weeks of orchidectomy.

These are maximum times and earlier referral of imaging and pathology will expedite patient management.

See page 8 for contact details.

1.12. Treatment Regimens

Patients should be seen with the results of their staging investigations and MDT review within 3 weeks of orchidectomy by the designated consultant oncologist at a Regional Cancer Centre. This facilitates a consultation at which a definitive decision on further management can be made.

Management depends on the histological type and stage of the disease. A combination of the Royal Marsden Hospital staging system and the WHO Classification (2004) is used to define stage and prognosis (see appendices A and B).

The standard treatments are as follows; but the possibility of the patient entering into a clinical study will be discussed at the MDT (please see appendix C).

1.12.1. Seminoma

Spermatocytic Seminoma

Spermatocytic seminoma is rare and occurs in an older population (> 60 years). They never metastasize unless they show sarcomatoid change and are managed with a policy of surveillance.

Stage I Seminoma

Standard Treatment: Chemotherapy: Carboplatin (AUC x 7) x 1 cycle. An EDTA clearance is required to determine GFR.

Surveillance is an acceptable option in patients expressing a preference and who can be relied on to attend for necessary blood tests and scans.

Radiotherapy, which was given historically, for the treatment of stage I seminoma, is now no longer the preferred option due to the long-term potential of inducing a second cancer within the radiotherapy field. It should only be considered where chemotherapy and surveillance are contraindicated.

IGCCCG – Good prognosis (metastatic seminoma)

There is not a consensus on treatment of metastatic seminoma.

- 3 or 5 day BEP (generally acceptable for patients with >50mm abdominal masses)*
- 4 cycles of EP (equivalent to 3 cycles of BEP in one trial) can also be considered
- Carboplatin AUC 10 (3 or 4 cycles depending on whether or not CR was achieved after the first cycle)
- For older patients particularly those who smoke, it is probably wise to consider avoiding Bleomycin.
Radiotherapy to a dog-leg field should only be considered where chemotherapy is contraindicated.

IGCCCG – Intermediate prognosis (metastatic seminoma)
More advanced cases of seminoma who fall into the intermediate prognosis category should receive 4 cycles of standard 3 or 5 day BEP or VIP if they have pre-existing impaired pulmonary function.

*There is no significant difference in long term toxicity between 3 or 5 day BEP when 3 cycles are being given. If 4 are required, then there is an increased risk of ototoxicity when the 3 day BEP is given and this should be explained to patient when they are making their decision.

1.12.2. Non seminomatous germ cell tumours
Stage I NSGCT
Patients are categorised into high (40%) or low (20%) risk of recurrence according to the presence or absence of lymphatic or vascular invasion as defined by histological review by the designated pathologist.

Low Risk Cases
These patients will enter the surveillance protocol unless they specify that they wish to have adjuvant chemotherapy or surgery (see below).

High Risk Cases
There are three options for these patients:
1. Surveillance – associated with a relapse rate of 40% (within 3 years).
2. Adjuvant therapy – two cycles of BOPq10 associated with relapse rate of 1-2% or 2 cycles of BEP (etoposide 360mg/m2)
3. Primary RPLND is a third option that carries a higher risk of recurrence than adjuvant chemotherapy. It is essentially a more accurate staging procedure. Many patients who are found to have pathological stage II disease are offered adjuvant chemotherapy.

IGCCCG - Good Prognosis Metastatic NSGCT
BEP 3 or 5 day* x 3 cycles over 9 weeks (Bleomycin, Etoposide, Cisplatin) (see Appendix C). (Total Etoposide dose 500mg per cycle).

IGCCCG - Intermediate and Poor Prognosis Metastatic NSGCT
BEP 3 or 5 day* x 4 cycles over 12 weeks (see Appendix C) (Total Etoposide dose 500mg per cycle).

GAMEC x 4 cycles – particularly if the patient has brain metastases.

*There is no significant difference in long term toxicity between 3 or 5 day BEP when 3 cycles are being given. If 4 are required, then there is an increased risk of ototoxicity when
the 3 day BEP is given and this should be explained to patient when they are making their decision.

### 7.4. Non Germ Cell Tumours of the Testis

#### 7.4.1. Epidermoid Cysts

A rare diagnosis in adolescents. Difficult to entirely exclude monomorphic teratoma differentiates. Recommend CT staging and then limited follow up to 5 years.

#### 7.4.2. Sertoli Cell Tumours and Leydig Cell Tumours

Indolent malignant tumours which rarely metastasise. Recommend CT staging and then limited follow up for 5 years. The optimum management for metastatic disease is uncertain. In those with stage 1 disease and adverse histological features (high mitotic rate and/or vascular invasion) consideration of a primary retroperitoneal lymph node dissection is recommended.

#### 7.4.3. Testicular Lymphoma

Urgent referral to the regional specialist and managed in accordance with relevant lymphoma protocol. Currently this is retuximab – CHOP with intra-thecal methotrexate and possible irradiation of the contralateral testis.

### 7.5. Pre-treatment Management of intermediate/poor prognosis

For patients with poor prognosis disease, MRI brain is required to complete staging investigations (CT as an alternative if delay for MRI is unacceptable) required to complete staging investigations.

#### 7.5.1. Chemotherapy

Baseline investigations should be undertaken, as per chemotherapy treatment protocol. All patients should have an audiogram before Cisplatin treatment begins.

All patients should have dosage adjusted on the basis of calculated creatinine clearance unless it is less than 60ml/min when GFR should be measured by EDTA clearance.

All patients should be offered sperm cryopreservation before chemotherapy.

Lung function tests should be requested for all patients who are to receive Bleomycin chemotherapy.

All patients should be offered entry into appropriate clinical trials where they exist (see Appendix D).
Patients should be given written information to reinforce verbal explanations, regarding their treatment and potential side effects, prior to giving consent.

7.5.2. Radiotherapy
Baseline investigations should be undertaken as per staging protocol.

7.6. Management during treatment

7.6.1. Chemotherapy
Urgent chemotherapy for advanced metastatic disease should start within 24 hours of referral to the oncologist.

Chemotherapy with adjuvant or curative intent should start within 2 weeks of the decision to treat.

Blood tests should be undertaken, as per the chemotherapy treatment protocol.

Bleomycin toxicity
Patient should have clinical assessment performed, as per the relevant Centre protocol, a minimum of once per cycle for Bleomycin toxicity and if suspected, CXR and CT (preferably HRCT) should be performed. The diagnosis is a clinical one and pulmonary function tests are of little assistance (See Appendix E for details).

7.6.2. Radiotherapy
Radiotherapy should start within 4 weeks of the decision to treat (Joint Council for Clinical Oncology, 1993).

Patients will be reviewed weekly during treatment and a FBC will be taken.

The radiation dose to the contralateral testis will be measured during treatment and will not exceed 5Gy.

7.7. Management post-treatment

7.7.1. Chemotherapy
Patients should complete their planned 3 or 4 cycles of therapy.

Investigations will be undertaken as per the chemotherapy management protocol.
Metastatic disease should be re-assessed by CT within a month of completing the final cycle of chemotherapy. Patients should have a CT scan of all previously abnormal areas to assess response.

If markers are still elevated but stable or falling, they should be observed weekly. Persisting elevation of AFP may be congenital (up to 25 ng/ml) or due to liver toxicity from chemotherapy.

**7.7.2. Radiotherapy**

Patients will be reviewed in the Radiotherapy Review Clinic at the end of their treatment and a follow up appointment will be made in the follow up clinic within 2 months, as per relevant follow-up protocol.

**7.8. Management of symptomatic advanced metastatic disease**

Patients presenting with symptomatic metastatic disease require urgent referral to the oncologist and transfer to the cancer centre so that chemotherapy can commence as soon as possible.

**7.8.1. Aims**

To obtain the diagnosis and initiate treatment with minimum delay and distinguish the subgroup requiring disease stabilising mini chemotherapy before starting full therapy.

**7.8.2. Initial Assessment**

The patient should be managed at the regional Cancer Centre.

**7.8.3. Essential Investigations**

The following are mandatory before chemotherapy starts:

- A positive pregnancy test (urinary B-HCG) is adequate for diagnosis. Blood tumour markers, (AFP and B-HCG) should be sent for urgent analysis.
- Confirmation of metastatic disease, e.g. with chest X-ray or abdominal ultrasound scan.
- Assessment of renal function by serum creatinine can be calculated using the Cockcroft and Gault formula \((1.25 \times (140\text{-age}) \times \text{weight (kg)} \div \text{serum creatinine})\). If creatinine is elevated (> 125), the cause of renal dysfunction should be determined.
- An EDTA GFR should be arranged urgently.

**7.8.4. Initial Treatment**
• Patients may be severely dehydrated and require additional intravenous fluids as well as usual chemotherapy pre-hydration.
• Post renal obstruction may be an indication for ureteric stent or external drainage prior to any chemotherapy – refer urologist on-call if the patient not suitable for disease stabilising mini-chemotherapy.
• Those with bulky metastatic disease are at risk of tumour lysis syndrome (Pentheroudakis et al 2001) and Allopurinol should be commenced immediately on admission as per local protocol. Those with an elevated urate should receive treatment with rasburicase instead of Allopurinol particularly if they have renal impairment.
• Enoxaparin 40mg or Tinzaparin 4500units OD should be administered for prophylaxis of thromboembolic events if there is bulky metastatic disease adjacent to major vessels. This should be continued at home until re-scan shows resolution. If IVC invasion is seen, therapeutic LMWH should be given.

7.8.5. **Chemotherapy**

Those requiring disease stabilising chemotherapy will receive either baby-BOP or 2-day EP.

7.8.6. **Further Investigations**

If not done before treatment, the following can be completed during working hours:

• Blood samples taken before chemotherapy for AFP, B-HCG and LDH can be stored in the lab for later analysis. These provide important prognostic information and assist in treatment monitoring.
• Ultrasound scan of the testes.
• Full staging with CT scan of thorax, abdomen and pelvis. For poor prognosis patients, MRI of the brain will also be required (CT of the brain may be substituted if delay in obtaining MRI is unacceptable).
• Accurate assessment of renal function by EDTA clearance following correction of pre renal and post renal causes of dysfunction. Assessment of renal function using a calculated clearance should always be made where an EDTA is not immediately available.
• Bone scan only if symptoms are suggestive of bone metastases.
• Baseline audiometry.
• Baseline lung function tests (gas transfer and lung volumes) if patient is to receive Bleomycin.
• Sperm banking should be offered if patient is fit enough.

The Specialist Nurse or Research Nurse should meet the patient as soon as possible following admission to provide further information and support.
2. Management of Residual Masses after Chemotherapy

All cases should be reviewed by the MDT following completion of completing radical treatment.

2.1. Seminoma

Resection of post-chemotherapy residual masses of less than 30mm is not routinely indicated for seminoma as surgery is difficult and potentially dangerous. A policy of surveillance is adopted as residual masses usually shrink over 12-24 months. CT scans are performed 6 monthly until complete remission or disease stabilisation.

However, in masses greater than 30mm there is an increased risk of the mass containing viable tumour and these patients should be discussed at the SMDT regarding the possibility of surgery. A PET CT scan in this situation may be helpful. If the mass is not glucose avid, it is reasonable to observe as the risk of finding viable cancer is low.

There is no evidence that radiotherapy after chemotherapy for residual masses in seminoma influences long term outcome.

2.2. NSGCT

Residual masses may remain after chemotherapy and marker normalisation. They may contain viable tumour, differentiated teratoma or fibrosis/necrosis. The aim of surgery is complete excision of the residual mass and associated abnormal tissue and may involve template clearance of para-aortic nodes. Incomplete excision is associated with poor prognosis.

This type of surgery is rare and should only be undertaken by a specialist surgeon as identified in section 3 for the relevant Centre.

- Residual abdominal masses Consultant Urological Surgeon
- Residual pulmonary masses Consultant Thoracic Surgeon
- Hepatobiliary surgery Consultant Hepatobiliary Surgeon
- Neurological surgery Consultant Neurological Surgeon

2.3. Retroperitoneal lymph node dissection

2.3.1. Indications for RPNLD in NSGCT

1. New patients at risk should be identified at presentation and discussed in outline at the SMDT.
2. Men with residual masses of 10mm unless there is > 70% shrinkage should be referred for RPLND. Any men with residual masses not for surgery, particularly those
of low attenuation, should have radiology discussed at SMDT before embarking on surveillance.
3. Markers should have normalized before surgery, however in patients with very high pre treatment markers, often this is not the case and as long as markers are not rising at the end of treatment, surgery should not be delayed.
4. Surgery should be performed as a planned procedure after completion of 1st line chemotherapy.
5. In patients with multiple masses the retroperitoneal mass should usually be resected first because if only necrosis is present, surgery for the other masses may be avoided. The exception is if the other masses are significantly larger than the retroperitoneal masses.
6. Surgery should not be carried out in patients whose masses have completely resolved in the final post chemotherapy CT unless this follows salvage therapy.
7. “Desperation” surgery should be considered in patients with rising markers who have completed at least two regimens of chemotherapy.

2.3.2. Counselling for node dissection
1. Indications as above.
2. Rationale is diagnosis of residual masses and removal with the intention of cure if teratoma (mature tissue) present. Identification of persistent cancer may require further chemotherapy.
3. Information about outcomes in literature and personal surgical experience.
4. Open RPLND involves a long (usually midline, occasionally transverse) incision and a hospital stay of about 5 to 10 days.
5. Risk of death is 1% in post-chemotherapy patients.
6. Risk of small bowel obstruction or ileus is 5-10%.
7. Risk of lymphocele requiring percutaneous drainage is 5 to 10%.
8. Weak or absent ejaculation may occur, the precise incidence depends on the size and nature of the mass, and on the operative procedure required.
9. Chylous ascites may result.

2.3.3. Indications and additional counselling for laparoscopic node dissection
1. A single node before chemotherapy or low volume disease (maximum node size <40mm) after chemotherapy which is apparently technically straightforward.
2. Patients should be informed that at present laparoscopic post chemotherapy node dissection remains investigational and it is not standard treatment as long-term outcome is not yet clear.

2.3.4. Indications for RPLND in Seminoma
Infrequent and confined to patients with solitary, surgically resectable (i.e. globular) masses > 30 mm after second-line salvage chemotherapy, surgery being carried out to exclude non-seminomatous elements.
Further chemotherapy should be considered where there has been incomplete excision and/or pathology confirms viable GCT in the resected specimen.

8.4. Orchidectomy

All patients treated with emergency chemotherapy prior to orchidectomy should be referred for consideration of orchidectomy following chemotherapy treatment though in exceptional circumstances such as patient achieving complete remission on ultrasound, the decision may be deferred provided ultrasound surveillance is initiated.
9. Management of Recurrent Disease (excluding mediastinal germ cell tumour)

Management will depend upon the stage of disease at diagnosis and previous treatment.

9.1. Seminoma

Patients who relapse following radiotherapy for stage I disease will usually receive BEP chemotherapy (see section 8.2). Patients who relapse after adjuvant Carboplatin chemotherapy for stage I disease and who have good prognosis disease at relapse should receive 3 cycles of BEP followed by 1 cycle of EP. Patients who relapse with intermediate prognosis disease should receive 4 cycles of BEP.

9.2. NSGCT

Patients who relapse on surveillance should be treated with first-line BEP chemotherapy (see section 8.2).

For patients who relapse more than 2 years after initial chemotherapy at an isolated site, surgical excision of the site of relapse should be considered before systemic chemotherapy. Marker negative relapse may be due to teratoma (mature tissue). An FD glucose PET scan should be performed prior to surgery. If this is positive chemotherapy may be given prior to surgery. If it is negative, then straight to surgery.

In pre-chemotherapy treated patients, on first relapse, second-line therapy will depend upon the nature of the relapse. If a complete marker remission was achieved following first-line BEP chemotherapy and the patient relapses between 6 months and 2 years after first-line chemotherapy TIP x 4 or GAMEC can be offered and administered at the regional Cancer Centre. Patients who relapse within 6 months of first-line chemotherapy should be offered GAMEC chemotherapy. Prior to GAMEC, if patients have a raised LDH or are >35 yrs, stem cells should be collected prior to starting chemotherapy. IPO is usually a third line but may be used second line if GAMEC is thought to be inappropriate. Third line therapy is consolidated with HDCT.
10. Management of Central Nervous System Metastases and Primary Extragonadal Germ Cell Cancer

CNS metastases are rare but may be seen in three circumstances:
- at initial presentation (usually in the context of gross wide spread disease with very high serum markers)
- as an apparently isolated relapse site
- in the context of chemotherapy resistant systemic relapse. The first two presentations are potentially curable.

Unless there is evidence of raised intra-cranial pressure, newly diagnosed patients should receive combination chemotherapy (as per section 8.2) as primary treatment but all patients with potentially resectable lesions who are fit for surgery should be evaluated by a neurosurgeon.

Radiotherapy can be considered for isolated CNS relapse if there is any doubt about resectability or completion of resection or as palliation in end stage disease.

10.1 Primary extragonadal tumours – Mediastinal:
Pure seminomas do not carry a poor prognosis and should receive 3 cycles of BEP.

NSGCT should be treated as poor risk and at the completion of chemotherapy have attempted surgical excision.

Those patients with isolated mediastinal masses only and no metastases should be offered surgery on completion of chemotherapy regardless of whether or not the markers have normalised as 40% have been cured.

Relapsed mediastinal NSGCT carry a poor prognosis and currently receive two cycles of IPO followed by tandem high dose chemotherapy (ToPCaT).

11. Follow-Up Management

All patients should be followed-up on protocol by the designated oncology team.

Patients at high risk of intratubular germ cell neoplasia (ITGCN) in the remaining testis (i.e.: under 30 years of age at primary diagnosis and with a testicular volume less than 12ml, or with a history of testicular mal descent), who did not have a biopsy at the time of orchidectomy, should be offered the opportunity to consider a contra-lateral biopsy 2 years after completion of treatment if they have not recovered fertility (see Management of the Contralateral Testis, Section 13).
12. Management of the Contralateral Testis

There is not consensus over management of the contralateral testis because of the potential complications of treatment. Patients with a testicular GCT have an overall risk of a second testicular tumour of approximately 2-5%. However, it is possible to identify a sub-group who are at greater risk.

There are three factors which are associated with an increased risk:

- an early age at diagnosis of first primary (less than 31 years), and a low testicular volume (less than 12 mls).
- or a history of mal descent.

Within this subgroup, the risk of a second testicular tumour rises to approximately 35% if they are treated without chemotherapy on a surveillance program.

For those identified at a higher risk, the option of a biopsy of the contralateral testicle will be discussed. This issue may be raised by the surgeon at the time of orchidectomy or by the oncologist at a later date. It can be carried out at the time of the first orchidectomy or following treatment.

The reason for a biopsy is to detect any signs of pre-cancerous cells in the healthy testicle which may develop into a malignant cancer at a later date. This is known as intratubular Germ cell neoplasia (ITGCN). The risks of ITGCN progressing into histologically proven but in the majority still microscopic cancers over five years is 50%, but some suggestion that this will occur in all patients with ITGCN if follow up is long enough.

The biopsy is carried out under general anaesthetic. A small incision is made in the scrotum and a small amount of testicular tissue is removed for analysis. If the patient has been treated with chemotherapy, it is important to wait for at least two years following completion of the treatment. This is so that a reliable result is obtained as chemotherapy can affect healthy cells in the short term and obscure the result.

If ITGCN is diagnosed, there are two options for management. One is close surveillance of the remaining testicle with an annual ultrasound scan to assess for signs of a developing tumour. At the first sign that the ITGCN is progressing into cancer, the Ultrasound should be reviewed at the SMDT and consideration given to a testis preserving approach before doing a second orchidectomy.

The long term side effects of a second orchidectomy are:

- Permanent infertility
- Hypogonadism requiring lifelong hormone replacement with testosterone.

In addition, there is the risk that the tumour is not detected before it has metastasised, reducing the overall prognosis and potentially exposing the patient to the harmful side effects of cytotoxic chemotherapy or radiotherapy.
The other option following an ITGCN positive biopsy is treatment up-front to prevent progression. Treatment involves either 2 cycles of BEP chemotherapy or radiotherapy of 20Gy in 10 fractions to the testicle. Radiotherapy will reduce the risk of cancer but unfortunately has the unpleasant side effects noted above, (i.e.: infertility and potential endocrine failure).

If the biopsy is negative, then the risks of developing a second tumour remain low.

The side effects will be discussed in detail with the patient before a decision is reached. It is important to remember that the risk of a second tumour for those in the high risk group is less than 40% and that, because patients usually detect second tumours themselves early through testicular self examination, they have a very good prognosis and are often cured with orchidectomy alone.
13. **Hormone Replacement Therapy**

For patients who have a unilateral orchidectomy for a primary testicular tumour, serum testosterone should be maintained within normal limits by the remaining contra-lateral testis. Standard chemotherapy and radiotherapy treatment does not usually effect hormone production. However, some patients may develop primary hypogonadism due to damage to, or loss of, healthy testicular tissue. Primary hypogonadism will be induced in those who undergo bilateral orchidectomy. There is also a risk that those who receive radiotherapy to the contralateral testis for CIS following an orchidectomy, may develop primary hypogonadism secondary to treatment.

13.1. **Testosterone Production**

The pituitary gland releases pulses of luteinising hormone (LH) and follicle stimulating hormone (FSH) in response to gonadotrophin-releasing hormone (GnRH) secreted by the hypothalamus. LH stimulates testicular leydig cells to produce androgens, including testosterone. FSH (with testosterone) stimulates testicular sertoli cells to release the hormone inhibin which, together with testosterone, induces spermatogenesis. Both testosterone and inhibin reduce GnRH, and thereby gonadotrophin secretion by negative feedback.

13.2. **Diagnosis**

The effect of low testosterone levels can be dramatic and disabling. Clinical features of postpubertal hypogonadism are low libido, erectile dysfunction, loss of ejaculation, muscle atrophy, loss of bone density, low stamina, decreased secondary sexual hair and beard growth and depressed mood. A single measurement of morning serum LH, FSH and testosterone is usually sufficient to confirm a diagnosis of hypogonadism.

Patients who have undergone a single orchidectomy can have elevated levels of LH and FSH but usually have a normal testosterone level and suffer no disabling symptoms. Patients with primary hypogonadism have increased levels of LH and FSH, with a low level of serum testosterone. There can be a transitory upset in testosterone levels following treatment and some patients report gynaecomastia (enlargement of breast tissue) between 2 and 9 months after chemotherapy or radiotherapy (Saeter, Fossa & Norman 1987) but this should settle after a mean duration of 4 - 5 months.

13.3. **Androgen Therapy**

The aim of androgen therapy is to provide near physiological blood testosterone levels while avoiding over-treatment. Testosterone should restore primary and secondary sexual characteristics, maintain bone and muscle mass and improve wellbeing.

Testosterone can be given orally, by intramuscular injection, dermal gel or patches or sub-dermal implants and treatment should be tailored to meet the individual needs of the patient. Following a second orchidectomy, therapy should commence within 10 days before serum concentrations of testosterone levels have fallen to below normal levels.
Recent developments in testosterone replacement therapy have led to more effective and well tolerated treatments.

Nebido, (a three monthly IM injection) has surplanted Sustanon 250 (a three weekly IM injection) as the treatment favoured by the majority of patients and clinicians. The longer acting injectable testosterone more closely mimics the body’s natural rhythm of testosterone production and reduces the incidence of ‘peak and trough’ effects sometimes experienced with Sustanon 250. Patients also find the reduced amount of injections per annum preferable. Nebido is injected once every 10 to 14 weeks, though after the first injection, a second should be administered after only 6 weeks so that a therapeutic level of testosterone is reached quickly. The interval between injections should be titrated to the patient depending on evidence of any signs or symptoms of testosterone insufficiency. A trough measurement of testosterone should be taken immediately prior to administration of the injection to ensure that therapeutic levels are maintained.

Another recent development in testosterone therapy is Testogel, a dermal gel applied daily (5g sachet containing 50mg of testosterone). Many patients like the un-intrusive method of delivering the therapy. Occasionally a single daily sachet is insufficient and the dose will need to be titrated to the patient’s response.

Testosterone subdermal implants are available. They are inserted under local anaesthetic and the dose titrated to the individual. The advantage of the subdermal implants is that plasma testosterone levels peak at 1 month and then are maintained at physiological levels for up to 6 months after a single implantation procedure. The disadvantages are those associated with a minor surgical procedure (infection, extrusion, bleeding, scarring and fibrosis) and these should be weighed against the advantages of a therapy given every 4 to 6 months.

Testosterone patches are available but are not commonly used due to difficulties in adhering to male skin due to the presence of body hair and unacceptable localized skin reactions. Oral preparations are also available but due to unpredictable variations in serum levels between individuals, they are inconvenient and unreliable and so are not recommended.

Depending on Centre protocol, all patients requiring testosterone replacement therapy may need to be referred to an endocrinologist so that they are able to discuss the benefits and risks of testosterone replacement therapy and to explore the options available to them.

13.4. Monitoring

Close monitoring of the patient for efficacy of the treatment and for potential complications is essential. The Endocrinologist or oncologist managing testosterone replacement will ensure that appropriate tests are undertaken at appropriate intervals.
Testosterone is monitored more frequently in the first instance until the patient is stable on their replacement regimen of choice and then monitoring of this depends upon which preparation is prescribed.

PSA, liver function tests, a full blood count and haematocrit is monitored on an annual basis, with annual digital rectal examination to assess the prostate. A dexa scan is also indicated two to three yearly as appropriate.

It is not the routine practice to discharge patients to their primary care physician and patients on hormone replacement therapy continue to be reviewed by the team on an annual basis.

14. Specialist Palliative Care

Palliative care focuses on maintaining and improving quality of life by effectively managing the side-effects of the disease or treatment. As palliative care is a speciality in its own right, only brief general advice can be given here about particularly high risk cases. Advice can be given without full referral, particularly when the patient is sensitive or concerned about the idea of referral to a palliative care service which they may associate with the end of life only.

The following patients should be considered at particularly high risk:

- Those with difficult pains, e.g. neuropathic pain.
- Patients with difficult to control, distressing symptoms

There are specialist palliative care teams throughout the network and referral guidelines are available locally.

15. Pathology

All pathology must be received by the Cancer Centre by the Thursday afternoon prior to the appropriate meeting to ensure patient’s case history can be discussed at the SMDT within 3 weeks of orchidectomy.

Unstained spares or blocks from all cases should be sent for review to the designated Cancer Centre Pathologist within 3 weeks of the orchidectomy.

Any histology reviews coming directly to Dr Dan Berney, Consultant Histopathologist at BLT should be sent to:
Division of Cellular Pathology 2nd Floor
80 Newark St
Whitechapel
London
E1 2ES
16. Radiology

All radiology must be received by the Cancer Centre by the Thursday afternoon prior to the appropriate meeting to ensure patient’s case history can be discussed at the SMDT within 3 weeks of orchidectomy.

Any radiology reviews coming directly to Dr Andrea Rockall, Consultant radiologist at BLT should be sent via the:

Testis MDT Co-ordinator
St Bartholomew’s Hospital
Cancer Strategy Unit
39-41 Little Britain London
EC1A 7BE

MRI (or CT if no MRI slots available) of brain for all IGCCCG poor risk patients

17. Primary Care Team

General Practitioners will have access to referral guidelines.

General Practitioners will be notified of the patients’ treatment plan within 5 working days of a decision being made and of the patients discharge within 24 hours.

General Practitioners will receive an evaluation of the patients’ condition after each follow-up appointment.

18. Familial Disease

An increased risk of developing testicular germ cell cancer has been noted in first degree relatives, though the risk to fathers or sons of cases has been reported to be half that of the risk to brothers (Heimdal et al 1996, Forman et al 1992). Though the relative risk to brothers of testicular cancer patients has been found to lie between 6 and 10 (Tollerud et al 1985, Forman et al 1992, Heimdal et al 1996) – the absolute risk is still low (the spontaneous annual risk is 7 per 100,000 while for familial to sibs is 70 per 100,000)

Patients who have a history of testicular cancer in their first degree relatives or multiple cases in their extended family are of interest to researchers. Referral to Dr Huddart at the Royal Marsden Hospital for participation in his research programme will be discussed during their initial consultation with the oncologist.

No genetic screening test yet exists which indicates pre-dispositions to germ cell cancer of the testes. The risks to sons and brothers of testicular cancer cases will be explained to the patient at their initial consultation and they are encouraged to promote testicular self-examination in their male siblings and children.
19. References

APPENDICES

Appendix A  International Germ Cell Consensus Classification 1997
Appendix B  Royal Marsden Hospital Staging Classification  Appendix C  Summary of treatment options
Appendix D  Tables of treatment for testicular tumour
Appendix E  Bleomycin Toxicity
### Appendix A

<table>
<thead>
<tr>
<th>PROGNOSTIC GROUPS IN METASTATIC NSGCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>International Germ Cell Consensus Classification 1997</em></td>
</tr>
</tbody>
</table>

#### GOOD PROGNOSIS
56% teratoma. 5 year survival – 92%
- Testis / retroperitoneal primary
- No non-pulmonary visceral (NPV) metastases
- Good markers – all of
  - AFP < 1,000 mg / ml
  - B-HCG < 5,000 iu / l
  - LDH < 1.5 x ULN

#### INTERMEDIATE PROGNOSIS
28% teratoma. 5 year survival – 80%
- Testis / retroperitoneal primary
- No NVP metastases
- Intermediate markers – any of
  - AFP > 1,000 < 10,000
  - B-HCG > 5,000 < 50,000
  - LDH > 1.5 x < 10 x ULN

#### POOR PROGNOSIS
16% teratoma. 5 year survival – 48%
- Mediastinal Primary
  - or
  - NVP metastases
  - or
  - Poor markers – any of
    - AFP > 10,000
    - B-HCG > 50,000
    - LDH > 10 x ULN

### PROGNOSTIC GROUPS FOR METASTATIC SEMINOMA

#### GOOD PROGNOSIS
90% seminoma. 5 year survival – 82%
- Any primary site
- No NPV metastases
- Normal AFP, any B-HCG, any LDH

#### INTERMEDIATE PROGNOSIS
10% seminoma. 5 year survival – 72%
- Any primary site
- NPV metastases
- Normal AFP, B-HCG, any LDH

*No seminoma patients classified as poor prognosis*

### Royal Marsden Hospital Staging Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to testis</td>
</tr>
<tr>
<td>I&lt;sub&gt;m&lt;/sub&gt;</td>
<td>Rising post-orchidectomy markers only</td>
</tr>
<tr>
<td>II</td>
<td>Abdominal Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>A &lt; 20mm</td>
</tr>
<tr>
<td></td>
<td>B 20-50mm</td>
</tr>
<tr>
<td></td>
<td>C &gt; 50mm</td>
</tr>
<tr>
<td>III</td>
<td>Supradiaphragmatic Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>No abdominal disease</td>
</tr>
<tr>
<td></td>
<td>O Abdominal node size as in Stage II</td>
</tr>
<tr>
<td></td>
<td>ABC</td>
</tr>
<tr>
<td>IV</td>
<td>Extralymphatic Metastases</td>
</tr>
<tr>
<td></td>
<td>L1 &lt; 3 lung mets</td>
</tr>
<tr>
<td></td>
<td>L2 &gt; 3 lung mets all &lt; 20mm diameter</td>
</tr>
<tr>
<td></td>
<td>L3 &gt; 3 lung mets 1 or more &gt; 20mm</td>
</tr>
<tr>
<td></td>
<td>H+ Liver involvement</td>
</tr>
<tr>
<td></td>
<td>C Cerebral metastases</td>
</tr>
<tr>
<td></td>
<td>O Bony metastases</td>
</tr>
</tbody>
</table>

Appendix C

Summary Treatment Options for GCT

CONFIRMED GCT TESTIS
- US testis and
- Histology or
- Marker (AFP HCG LDH) elevation

URGENT CT CHEST ABDOMEN PELVIS
POST ORCHIDECTOMY AFP HCG LDH
HISTOLOGICAL REVIEW
REFERRAL TO REGIONAL SPECIALIST
EMERGENCY PRESENTATION WITH METASTATIC DISEASE

- **Seminoma**
  - **Stage I**
  - **Stage II, III, IV**
  - **Spermatocytic Seminoma**

- **NSGCT**
  - **Stage I**
  - **NSGCT**
  - **Metastatic NSGCT**

**Single cycle carboplatin AUC7**

**Surveillance**

**Good Prognosis**

**Intermediate Prognosis**

**High risk**

**Low risk**

**Good Prognosis**

**Intermediate Prognosis**

**Poor Prognosis**

**If chemo and surveillance are contraindicated, then Radiotherapy can be considered**

**BEP 3 or 5 day x4 or Trial TE3**

**Carbo EP AUC10 x 4**

**BEP**

**Adj. BOPq 10 x 2 or BEP x2**

**Primary RPLND**

**If chemo is contraindicated, then Radiotherapy can be considered**

**Gamecx4 (particularly if pt has brain mets)**

**Adj. BEP or TE23**

**VIPx4 or BEPx4 +/- surgical resection**

**Non-trial standard treatment options are also shown**

**Bold Print indicates current trial**
### Appendix D

#### Seminoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Standard treatment</th>
<th>Clinical trials</th>
<th>Trials in preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td>Carboplatin AUC 7 x 1</td>
<td>NCRN TE24 (TRISST)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surveillance</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage II– IV (good prognosis)</strong></td>
<td>3 cycles BEP</td>
<td>Bleomycin infusion study – TE3</td>
<td>CAR-PET</td>
</tr>
<tr>
<td></td>
<td>4 cycles EP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboplatin AUC10 x3 or x4 cycles</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage II-IV (intermediate prognosis)</strong></td>
<td>4 cycles BEP</td>
<td>Accelerated BEP</td>
<td></td>
</tr>
</tbody>
</table>
### Non-seminoma germ cell tumour (NSGCT)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Standard treatment</th>
<th>Clinical trials</th>
<th>Trials in preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (low risk)</td>
<td>Surveillance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I (high risk)</td>
<td>Surveillance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 cycles of BEP</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2 cycles of BOP</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>RPLND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II-IV (good prognosis)</td>
<td>3 cycles BEP and consider post chemo-RPLND</td>
<td>Bleomycin infusion study – TE3</td>
<td></td>
</tr>
<tr>
<td>Stage II-IV (intermediate prognosis)</td>
<td>4 cycles BEP and consider post chemo-RPLND</td>
<td>Accelerated BEP</td>
<td></td>
</tr>
<tr>
<td>Stage II-IV (Poor prognosis)</td>
<td>4 cycles BEP and consider post chemo-RPLND</td>
<td>Accelerated BEP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 cycles GAMEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 cycles VIP</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Accelerated BEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TE23</td>
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</table>
## Relapsed germ cell tumour

Relapse is diagnosed by a progressive rise in tumour markers and new or persistent radiological abnormalities. Persisting but not rising markers and rising markers without radiological abnormality are not an indication for retreatment with chemotherapy (exclude brain metastases and new testicular primary).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Standard treatment</th>
<th>Clinical trials</th>
<th>Trials in preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RELAPSE FROM SURVEILLANCE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminoma/NSGCT</td>
<td>Manage as appropriate for seminoma or NSCGT if previously untreated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>RELAPSE POST-RADIOThERAPY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>Manage with appropriate chemotherapy option as under seminoma, usually not eligible for clinical trials</td>
<td></td>
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<tr>
<td><strong>RELAPSE POST-CHEMOTHERAPY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First relapse</td>
<td>4 cycles GAMEC&lt;br&gt;4 cycles VIP/VeIP or 4 cycles TIP&lt;br&gt;Following failure of combination chemotherapy for metastatic seminoma, tandem high dose carboplatin and etoposide followed by oral etoposide.</td>
<td>GAMEC S&lt;br&gt;GAMIO</td>
<td></td>
</tr>
<tr>
<td>Second relapse</td>
<td>IPO and High dose chemotherapy</td>
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</tbody>
</table>
Appendix E

Bleomycin Toxicity

Clinical Monitoring for Bleomycin Toxicity during BEP and ABVD Chemotherapy

Bleomycin is an effective cytotoxic agent but considerable care and close patient supervision with formal review according to the following plan is required to ensure its safe administration.

1. As outlined above the detection of toxicity is a clinical diagnosis centering on symptoms and signs. The patient should therefore be formally reviewed with a history and a chest examination immediately prior to each dose of Bleomycin. This should be documented in the notes and compliance will be audited.

2. Chest X-rays can contribute to the diagnosis of Bleomycin toxicity and in particular are useful for retrospective comparison of a series of images looking for subtle changes in the lung bases and reduction in inspiratory lung volume.

All patients should have a chest X-ray performed on day 1 of the cycle and the images and the report should be reviewed before that day’s chemotherapy proceeds.

Chest X-rays will therefore be taken every 3 weeks for BEP patients and every 4 weeks for Hodgkin’s disease patients on ABVD.

Introduction

This short paper reviews Bleomycin pulmonary toxicity, its detection and management, drawing largely on the germ cell literature.

Bleomycin is an essential component of the BEP protocol for the management and cure of germ cell tumours. It is usually administered as a short intravenous infusion (minimum 2 hours) but it can also be administered subcutaneously, intramuscularly or by intravenous bolus. There is equivocal evidence that prolonged infusions are less toxic to the lungs. In BEP, Bleomycin is given in a dose of 30,000 units weekly to a total of 270,000 or 360,000 units, irrespective of surface area.

Bleomycin is also a component of the ABVD regimen for Hodgkin’s disease. In that regimen Bleomycin is given in a dose of 10,000 units/m² at fortnightly intervals. The average dose is therefore 17,000 units per fortnight (for 1.7/m²). After 6 cycles a cumulative dose will be 204,000 units and after 8 cycles it will be 272,000 units. The dose administered in ABVD is therefore in general terms lower and the dose intensity is reduced as it is given at fortnightly rather than weekly intervals.
Prediction of Bleomycin Toxicity

There have been attempts to predict the development of Bleomycin pulmonary toxicity and to modify treatment to prevent the progression of this complication. It has been shown that pulmonary function tests are not predictive in routine clinical practice and indeed that reliance on them can lead to Bleomycin being stopped inappropriately after low DLCO measurements (McKeage et al, 1990). This conclusion has been disputed (Comis, 1990), but supporters of the use of pulmonary function tests have to rely on “a linear fall in DLCO to 40% of the initial value (i.e. 0.4 x the initial value)” (Comis, 1992). Subsequent research comparing patients treated with BEP or EP has shown that major changes in pulmonary function occur in patients who do not receive Bleomycin so that changes in KCO or TLCO are not predictive of Bleomycin injury (Sleijfer et al, 1995). It is now accepted that Bleomycin pulmonary toxicity is a clinical diagnosis based on (Saxman et al, 1997):

- Radiographic findings consistent with an active interstitial process
- Clinical examination findings suggestive of an interstitial process including the development of basilar crackles or an inspiratory lag
- Symptoms suggestive of an interstitial process including the development of a persistent dry cough or dyspnoea

A retrospective study at Indiana University showed that overall 29/86 (34%) were believed to have clinically significant Bleomycin toxicity and had the drug discontinued. Three of these patients died of respiratory complications (Saxman et al, 1997). Most patients make a full recovery from Bleomycin injury and there are no long-term effects on pulmonary function tests (Osanto et al, 1992). Overall, the discontinuation rate ranges from 34% (Saxman et al, 1997) to 5% (Nichols et al, 1998). In large studies the death rate from Bleomycin toxicity is 1-2% (Williams et al, 1987; Nichols et al, 1998; Kaye et al, 1998; O’Sullivan et al, 2003).

A recent retrospective review of 835 patients at the Royal Marsden has shown a death rate of 1% directly attributable to this complication. Identified risk factors are:

- Poor renal function
- Age over 40
- Stage IV disease at presentation
- Dose of Bleomycin greater than 300,000 units

In such cases the authors recommend the consideration of dose restriction (O’Sullivan et al, 2003). Similar prognostic factors were identified by Simpson et al (1998). The decision to exceed 300,000 units rests on balancing the risks and benefits for each individual patient.

Patient management and review

Patients should be closely monitored for symptoms and signs as described above. Formal clinical review should occur prior to starting each 3 weekly treatment cycle. It should
include clinical review for symptoms and signs and a review of serial chest X-rays looking for early changes of an interstitial process or evidence of loss of volume.

Discontinuation of Bleomycin is a clinical decision.

Close clinical monitoring is required to limit Bleomycin toxicity and as treatment proceeds the risks and benefits of each dose will need to be weighed for individual patients (Nichols et al, 1998 and O'Sullivan et al, 2003). Patients may therefore need review more than once a cycle as their treatment progresses.

Management of Bleomycin pulmonary toxicity

It is useful to obtain baseline lung function tests at the outset of therapy. Management of suspected Bleomycin toxicity should be in conjunction with a chest physician who may advise further investigations including open lung biopsy to establish diagnosis. It is a diagnosis of exclusion. Once confirmed, high doses of steroids (Prednisolone 60mg daily) are required for a number of months. Fatalities may still occur.

Long term pulmonary risks

Patients who have received Bleomycin are at risk of acute respiratory distress syndrome following surgery. It is likely that this relates to abnormalities in fluid balance and close attention to this is required post-operatively (Donat & Levy, 1998). It was also suspected that exposure to elevated concentrations of oxygen might be a factor and if possible this should be limited only 25%. Theoretically, such exposure could also be a risk to those undertaking either scuba-diving or flying at altitude using pure oxygen (Hamilton et al, 1988). It now believed that these risks are not supported by the available clinical evidence and that scuba diving 6-12 months after BEP is acceptable (De Wit et al, 2007).

Summary

Bleomycin is an effective cytotoxic agent but considerable care and close patient supervision is required with formal review as indicated in the review policy outlined at the start of this document.

Michael Williams
Consultant Clinical Oncologist 13

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References


