THE BRISTOL
CANCER
INSTITUTE

Bristol Testicular Cancer Service

Clinical Guidelines 2016

INDEX

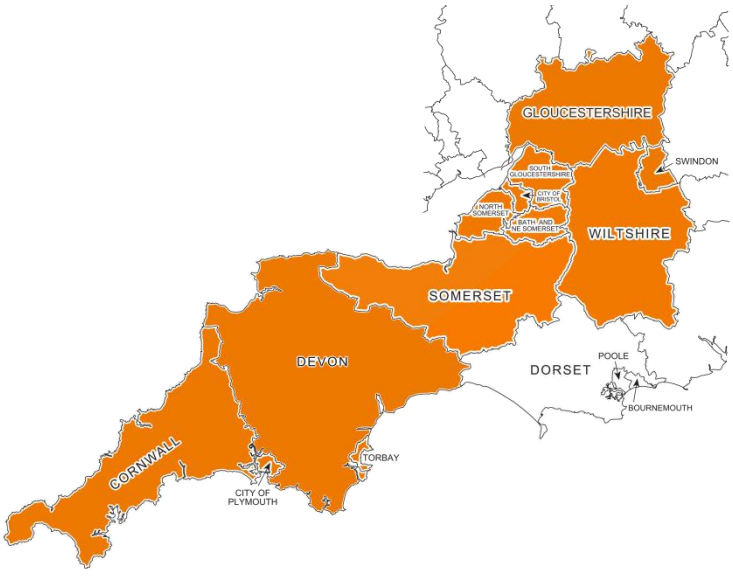
INTRODUCTION

Testicular germ cell cancers are the most common cancer of young men with approximately 2300 new cases diagnosed each year in the U.K. In Bristol, around 100 new patients are seen each year. Germ cell cancers are highly sensitive to treatment, with anticipated cure rates of 98% at 10 years (CRUK). However, the small number of patients presenting with advanced (poor prognosis) disease continue to have modest survival with only 50 – 60% alive 5 years after diagnosis.

National guidelines (COIN guidelines 2000[1], Improving outcomes in urological cancer 2002[2]) and European guidelines (European Association of Urology 2014) provide recommendations for the management of male patients with germ cell cancer and outline how care should be delivered. These guidelines form the basis for this document.

Area	Treatment Centre/s	Population
The City of Bristol **South Gloucestershire, North Somerset, Somerset** **Bath, North East Somerset & Wiltshire**	Bristol	**1.9 million**
Devon **Cornwall**	Exeter & Plymouth Truro	**1.6 million**
Gloucestershire **Herefordshire** **Worcestershire**	Cheltenham	**1.0 million**
Supra-regional combined population		**4.5 million**

Bristol Haematology and Oncology Centre (BHOC) offers a regional testicular and germ cell cancer service providing a referral centre for Taunton, Yeovil, Bath and Weston Super Mare as well as the Bristol area. The service links with Devon, Cornwall, Gloucestershire, Herefordshire and Worcestershire for specialist MDT advice and management of complex patients. Specialist urological surgery for testicular cancers in the South West is based at the North Bristol NHS Trust. The service links with gynaecology teams for management of female patients with germ cell cancer and the paediatric oncology team for patients under the age of 18 years.



All patients diagnosed with testicular cancer and primary Germ Cell Cancer should be discussed at the supra regional MDT. Patients diagnosed within the former Avon, Somerset and Wiltshire network will receive chemotherapy treatment and surveillance in the BHOC. Radiotherapy can, by arrangement, be administered in Bath or Taunton. Post treatment follow-up will revert back to BHOC. For those patients referred from the former Peninsula and Three Counties areas treatment will be agreed on an individual patient basis. Where possible, treatment and follow up will be with the patients' local oncology team.

SPECIALIST TEAM

The Bristol Testicular cancer team is based at UH Bristol NHS Foundation Trust. The team has a weekly MDT and weekly specialist testicular cancer (Germ Cell) clinic.

CORE MDT PARTICIPANTS

Role	Core Team Member	Cover
Consultant Medical Oncologist	Lead Clinician for MDT Jeremy Braybrooke Tel: 0117 342 2418 Jeremy.Braybrooke@uhbristol.nhs.uk *(lead for clinical trials recruitment)*	Anna Kuchel Tel: 0117 342 2418 Anna.kuchel@uhbristol.nhs.uk (Lead for TYA & Late Effects) Alfredo Addeo Tel: 0117 342 2418 alfredo.addeo@uhbristol.nhs.uk
Consultant Medical Oncologist	Anna Kuchel Tel: 0117 342 2418 Anna.kuchel@uhbristol.nhs.uk Alfredo Addeo Tel: 0117 342 2418 alfredo.addeo@uhbristol.nhs.uk	Jeremy Braybrooke Tel: 0117 342 2418 Jeremy.Braybrooke@uhbristol.nhs.uk
Germ Cell Clinical Nurse Specialists	Sue Brand (Patient experience lead) and Liz Allison Tel: 0117 342 3472 or Mobile 07827082328 Sue.Brand@uhbristol.nhs.uk Elizabeth.Allison@uhbristol.nhs.uk	Liz Allison (TYA lead) and Sue Brand Tel: 0117 342 3472 or Mobile 07827082328 Elizabeth.Allison@uhbristol.nhs.uk Sue.Brand@uhbristol.nhs.uk
Consultant Clinical Oncologist	Amit Bahl Tel: 0117 342 2418 Amit.Bahl@uhbristol.nhs.uk	Amar Challapalli Tel: 0117 342 2418 Amar.Challapalli@uhbristol.nhs.uk
Consultant Urologist	Tim Whittlestone Tel: via NBT 0117 950 5050 Tim.Whittlestone@nbt.nhs.uk	Salah Albuheissi Tel: via NBT 0117 950 5050 salah.albuheissi@nbt.nhs.uk
Urology Nurse Specialists	Helen Chilcott and Team	Tel: 0117 4140512 urologycns@nhs.net
Consultant Radiologist	Julian Kabala Tel: 0117 342 3854 Julian.Kabala@uhbristol.nhs.uk	Lynne Armstrong Tel: 0117 342 4181 Lynne.Armstrong@UHBristol.nhs.uk
Consultant Histopathologist	Mohammed Sohail 0117 342 4539 Mohammed.Sohail@uhbristol.nhs.uk	Zsombor Melegh Tel: 0117 323 2604 Zsombor.Melegh@nbt.nhs.uk
MDT Coordinator	**Toni-Marie Harvey** **Tel: 0117 342 0618** **Toni-Marie.Harvey@uhbristol.nhs.uk**	**Clare Maggs** **Tel: 0117 342 0622** **clare.maggs@uhbristol.nhs.uk**

EXTENDED TEAM MEMBERS

Treatment Centre	Consultant Oncologist	Key Worker
Royal Devon and Exeter Hospital	Dr Peter Stephens 01392 402118	Karen Green 01392 402747
Plymouth Hospital	Dr Martin Highley 01752 432336	Anna Wilson 01752 792444 (Ext: 52444)
Royal Cornwall Hospital	Dr Duncan Wheatley 01872 258300	Debbie Victor 01872 253143
Cheltenham General Hospital	Dr David Farrugia 0300 422 2596	Ian Ingledew 0300 422 3881

COLLABORATIVE SERVICES

Area of Care	Lead Consultant/Nurse/AHP	Contact Details
Specialist Urology	**Mr Tim Whittlestone** Consultant Urological Surgeon **Mr Salah Albuheissi** Consultant Urological Surgeon	Tim.whittlestone@nbt.nhs.uk salah.albuheissi@nbt.nhs.uk **or via NBT switchboard**
Palliative Care	**Dr Rachel McCoubrie** Consultant Palliative and Supportive Care	Rachel.McCoubrie@uhbristol.nhs.uk **0117 342 4591**
Thoracic	**Mr Tim Batchelor** Consultant Thoracic Surgeon **Mr Doug West** Consultant Thoracic Surgeon **Mr Gianluca Cassali** Consultant Thoracic Surgeon	**Tel: 0117 342 4214 Fax 0117 342 3522** **Lung MDT Coordinator Carrie Trott** **Tel: 0117 342 0617**
Hepatobiliary	**Mr Reyad Abadi,** Consultant Hepatobiliary Surgeon **Ms Meg Finch-Jones** Consultant Hepatobiliary Surgeon **Mr Ian Pope** Consultant Hepatobiliary Surgeon	**Hepatobiliary MDT Coordinator** **Tracy Smart** **Tel: 0117 342 0624**
Haematology	**Prof David Marks** Consultant in Haematology **Dr James Griffin** Consultant in Haematology	**Stem Cell Harvesting** **Stem Cell Transplant Co-ordinator** **Tel: 0117 3422128** **Tel: 0117 342 2326** **Tel: 0117 342 8817**
Neurology	**Dr Chris Herbert** Consultant Neuro-Oncology	christopher.herbert@uhbristol.nhs.uk **Referral to Neuro-Oncology MDT** http://www.nbt.nhs.uk/bnog/referral-bnog
Fertility	**Susie Heyworth** Sperm Storage Specialist Nurse	**Bristol Centre for Reproductive Medicine** **Tel: 0117 323 2007**
Endocrinology	**Prof Andy Levy** Consultant Endocrinologist **Dr Karin Bradley** Consultant Endocrinologist	**Bristol Royal Infirmary** **0117 331 3115** **Bristol Royal Infirmary** **0117 342 3082**
Sexual Function	**Wendy Hurn** Urology Specialist Practitioner	wendy.hurn@nbt.nhs.uk **0117 414 0928 or 07789616216**
TYA Services	**Jamie Cargill** **Teenage Cancer Trust Lead Nurse** **Teenager and Young Adults (TYA) South West** **TYA MDaT**	**0117 342 2468 or 07827270638** jamie.cargill@nhs.net http://www.uhbristol.nhs.uk/tya TYAMDaT@UHBristol.nhs.uk

PRIMARY DIAGNOSIS

Information to patient / GP

Testicular cancer is most commonly diagnosed in men between the age of 20 and 40 years but can occur at any age. Most men present with a lump, swelling or hardening of the testis. In around 25% this is painful. Bilateral gynaecomastia is present in up to 10% of patients. Some patients will present with symptoms from secondary disease e.g. back or abdominal pain, shortness of breath and cough.

Recommendations:

NICE guidelines 2015

- **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for testicular cancer in men if they have a non‑painful enlargement or change in shape or texture of the testis.**
- **Consider a direct access ultrasound scan for testicular cancer in men with unexplained or persistent testicular symptoms.**

We would advise that any patient with a swelling or mass in the body of the testis should be referred urgently for bilateral testicular ultrasound and review by the local urological team. An urgent ultrasound should be considered in men with a scrotal mass that does not transilluminate and/or when the body of the testis cannot be distinguished.

Information for local urology team

Recommendations:

Patients with testicular symptoms referred urgently to the local urology team should have:

- Clinical assessment - if patients have symptoms of advanced disease at presentation discuss immediately with the Bristol Testicular Cancer Service prior to consideration for orchidectomy
- Bilateral testicular ultra-sound
- Tumour markers (AFP, HCG, LDH). These should be reported and interpreted in accordance with national guidelines.

If testicular cancer is suspected:

- Proceed with radical inguinal orchidectomy with discussion about the option of future placement of a testicular prosthesis.
  (Biopsy of suspected testicular cancers prior to orchidectomy is not recommended)
- Discuss options for Sperm Storage, organise pre-orchidectomy if appropriate.
- Tumour Markers (AFP, HCG, LDH) to be completed pre and if elevated at baseline weekly post orchidectomy.
- Complete baseline Testosterone and LH/FSH prior to orchidectomy.
- Request an urgent contrast enhanced CT scan of chest, abdomen and pelvis
  This must be performed within 2 weeks of surgery
- Referral to the Bristol Testicular Cancer Service (BTCS) to be made within 24 hours of surgery.
- Inform patients' GP of suspected diagnosis and referral to BTCS

All referrals must be made using the BTCS MDT Online Referral Form (Version 5.0 28.11.14).

Referrals must be received by 10am on Thursday in order to be discussed at that week's meeting

If pre-operative Tumour Markers are markedly raised and/or patient has symptoms of advanced disease eg severe back/abdominal pain, cough, dyspnoea or systemic symptoms- PLEASE REFER TO THE HIGH RISK GUIDELINES

HIGH RISK PATIENTS*

Sometimes patients with testicular cancer present with symptoms of metastatic disease. For this group chemotherapy before orchidectomy is recommended. If your patient has any of the following signs and symptoms please contact the Bristol Testicular Cancer Team immediately:

- AFP above 1000 ng/ml
- HCG above 5000 iU/L
- LDH > 1.5 x ULN
- Severe back/abdominal pain requiring opiates
- Shortness of breath
- Symptoms of renal obstruction

The Team are happy to give advice and arrange for emergency admission to BHOC. It is recommended that all patients with intermediate or poor prognosis disease are reviewed in Bristol.

PATIENT INFORMATION

All patients should be given a South West patient information pack that will include:

- *'BTCS Information for men with Testicular cancer'*
- Macmillan Cancer booklet *'Testicular Cancer'*
- *'BTCS Radical Orchidectomy'*
- *Contact details for:*
    - *Treatment centre team*
    - *Bristol Germ Cell Clinical Nurse Specialists (Key Worker)*
- Free prescription application form
- 'It's in the Bag Leaflet
- Feedback Form

Patients who attend the BTCS clinic will find a variety of information booklets available in the weekly clinic. The BTCS have surveyed which books are the most requested however there are more leaflets available in the Patient Information Centre on the Ground Floor.

At other centres we recommend patients are provided with extra information related to: Fertility, Sexual Function, Talking to Children about Cancer, Men and Cancer.

South West patient information packs can be requested by email to: GermCellNurses@uhbristol.nhs.uk

PRIMARY REFERRALS

Testicular Cancer (Germ Cell) Referral Pathway

Post Orchidectomy

Electronic referral within 24 hours of surgery
Do not wait for Histology and CT Scan date/result
Using the BTCS MDT referral form according to BTCS Guidelines

MDT Coordinator Toni-Marie Harvey (Toni-Marie.Harvey@uhbristol.nhs.uk)
Tel: 0117 342 0618

Please inform patient of referral

If elevated at baseline arrange weekly post-op

tumour markers (AFP, HCG and LDH) via GP

Please indicate on the referral form whether a CT scan has been requested locally or if you would like us to arrange one at UHB.

Pathology Slides will be requested by the MDT Coordinator to be sent to Dr Mohammed Sohail, NBT Pathology.

SECONDARY REFERRALS

All patients with recurrent disease will be discussed at the BTCS MDT. Patients from other treatment centres should have a referral form completed to include the following information:

- Date and stage of diagnosis
- Primary histology & relevant radiology imaging
- Treatment administered to date, including regimen and number of cycles
- Tumour markers, including trend and current values

All plans for further treatment will be documented on the Bristol Cancer Register and outcomes sent to relevant clinicians.

Please provide as much information as possible to allow the MDT to make an informed recommendation. It is helpful to have a specific question identified for the MDT to address.

Referrals must be received by 10am on Thursday in order to be discussed at that week's meeting.

BRISTOL TESTICULAR CANCER SERVICE MDT

The weekly Supra-network MDT is held on Friday's between 8.30am and 9.30am at University Hospitals Bristol NHS Foundation Trust (UHB).

Core members are expected to attend at least 75% of the MDT meetings. All meetings should have an oncologist, radiologist, pathologist, specialist nurse, specialist surgeon and MDT co-ordinator present.

Outcomes will be recorded on the Bristol Cancer Register and emailed to the referring clinician

Recommended tests for staging at diagnosis	Recommended
Serum tumour markers	AFP; hCG; LDH
CT Scan Abdomen & Pelvis	All patients
CT Scan Chest	All patients
Testis US (bilateral)	All patients
Bone Scan	In case of symptoms
MRI Brain	In case of symptoms and for patients with intermediate / poor prognosis disease

Further Investigations
Fertility investigations
Total testosterone
LH
FSH
Semen analysis
Sperm storage should be offered

AFP = Alpha fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; CT = computed tomography; LH = luteinising hormone; FSH - follicle stimulating hormone; MRI = Magnetic Resonance Imaging; US = Ultrasound

SPECIALIST CLINICS

Clinics:

Bristol Haematology and Oncology Centre.
Friday mornings starting at 9.30am
Consultants:

Dr Jeremy Braybrooke, Dr Anna Kuchel and
Dr Alfredo Addeo

Key Workers: Sue Brand and Liz Allison

1. **Germ cell clinic:**

   This is a specialist clinic for

- New Patients, primary and secondary
- Patients receiving treatment
- Patients recommended a programme of Active Surveillance
- Post treatment surveillance

All patients will be seen by a Germ Cell Clinical Nurse Specialist (key worker). Patients with additional needs may require a transfer of key worker status during significant treatment, surveillance and other hospital admissions. Examples of this include TYA Specialist Nurse, Palliative Care Nurse, Surgical Uro-oncology Specialist Nurse, Macmillan Support Worker.

The clinic provides good educational opportunities for training in the management of patients with germ cell cancers.

2. **Holistic needs clinic**

   The Germ Cell CNS team run a Holistic Needs Clinic on the first, second and third Thursday of each month. It is recommended that all patients attend at least once.

The clinics offer an opportunity for patients to support each other and get involved with developing the service. The BTCS and It's in the Bag charity work together to improve the patient experience by providing age/gender related information booklets, magazines, patient volunteers and contacts for accessing support and survivorship activities.

FACILITIES FOR PATIENTS

As the Supra-network centre for germ cell cancers UHBristol is equipped and staffed appropriately to provide the following,

- Dedicated Germ Cell Cancer Clinic
- Dedicated Oncology and Haematology wards
- Germ Cell and Urology Clinical Nurse Specialists
- Access to sperm storage (at North Bristol NHS Trust)
- Dedicated TYA services
- Access to specialist urology surgery (at North Bristol NHS Trust)
- Access to psychosexual counselling

- Access to specialist endocrinology
- Access to specialist thoracic, neurology (at North Bristol NHS Trust) and hepatic surgery
- Access to specialist haematology services including high dose chemotherapy
- Post treatment support
- Holistic Needs Clinic
- Late Effects monitoring
- Patient Forum

WAITING TIMES

The national milestone for testicular cancer is less than 31 days from urgent referral to treatment. In UHB there are no waiting times for access to this service with patients fast tracked immediately and treated well within the national target for surgery, chemotherapy and radiotherapy.

SOUTH WEST TREATMENT CENTRES

The BTCS recommends that all newly diagnosed men with Germ Cell Cancer have the following in their locality:

- A dedicated Clinical/Medical Oncology Consultant
- A named Key Worker (Germ Cell CNS/Uro-oncology CNS/TYA CNS/or equivalent)
- Access to specialist Urology services
- Access to TYA services
- Access to post treatment support

COMMUNICATION

Communication with referring teams and General Practitioners

Where patients are seen and assessed for treatment by the BTCS a summary clinic letter will be sent to the General Practitioner and copied to the patient. Clinicians will ensure that the GP is kept informed about patients during treatment and about any changes in treatment/care pathways. An end of treatment summary letter will be sent to the GP.

Shared Care arrangements with referring centres

Shared care arrangements are mutually agreed on a case by case basis

Referrals to extended teams:

The BTCS will refer patients requiring specialist intervention to appropriate teams, such as palliative care, TYA services, sexual counsellor and endocrinology.

TREATMENT GUIDELINES

Level of Evidence for Practice

Level	Source and characteristics of evidence
IA	Meta-analysis of randomised controlled trials (RCT) and review of RCT
IB	At least one RCT
IIA	At least one well designed controlled study without randomisation
IIB	At least one well designed quasi experimental study
III	Well-designed non experimental descriptive studies
IV	Expert committee report, opinions/clinical experience of respected authority

CLASSIFICATION AND STAGING:

Pathologic classification (modified from WHO 2004 classification):

Germ cell Tumours

- Intratubular germ cell neoplasia, unclassified type
- Seminoma (including cases with syncytiotrophoblastic cells)
- Spermatocytic seminoma (mention if there is a sarcomatous component)
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma (mature, immature, with malignant component)
- Combined tumours with more than one histologic type ie contains seminoma and non-seminoma (specify percentage of individual components). Mixed tumours refer to non-seminomas only.

Sex cord/gonadal stromal tumours

- Leydig cell tumour
- Malignant Leydig cell tumour
- Sertoli cell tumour (lipid-rich variant, sclerosing, large cell calcifying)
- Malignant Sertoli cell tumour
- Granulosa (adult and juvenile)
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours (incompletely differentiated, mixed)
- Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)

Miscellaneous nonspecific stromal tumours

_ Ovarian epithelial tumours
_ Tumours of the collecting ducts and rete testis
_ Tumours (benign and malignant) of nonspecific stroma

Patients with Non Hodgkins lymphoma or sarcoma of the testicle will be referred immediately to the appropriate MDT

Staging:

Classification: TNM Testis	
Tumour	
pTx	Primary tumour cannot be assessed
pT0	No evidence of primary tumour (eg histologic scar)
pTis	Intratubular germ cell neoplasia
pT1	Testis and epididymis, no vascular/lymphatic invasion. Tumour may invade tunica albuginea but not tunica vaginalis
pT2	Testis and epididymis with vascular/lymphatic invasion and/or invasion of tunica vaginalis
pT3	Spermatic cord invasion with/without vascular/ lymphatic invasion
pT4	Invades scrotum with/without vascular/ lymphatic invasion
Nodes	
N0	No regional lymph node metastases
N1	Regional lymph nodes ≤2 cm
N2	Regional lymph nodes 2 to ≤5 cm
N3	Regional lymph nodes >5 cm
Metastases	
M0	No distant metastases
M1a	Non-regional lymph nodes or lung
M1b	Other sites

Tumour Marker Staging

Serum levels of tumour markers are based on the lowest value recorded after surgery for the primary testicular cancer.

	LDH (U/litre)	HCG (mIU/ml)	AFP (ng/ml)
Sx	**Marker studies not available or not done**		
S0	**Normal**	**Normal**	**Normal**
S1	**<1.5 x normal**	**<5000**	**<1000**
S2	**1.5 – 10x Normal**	**5000- 50000**	**1000- 10000**
S3	**>10 x normal**	**> 50000**	**> 10000**

AJCC Staging System				
Stage 0	pTis	N0	M0	S0, SX
Stage I	pT1-pT4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2-pT4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1-3
Stage II	Any patient/TX	N1-N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0
	Any patient/TX	N1	M0	S1
Stage IIB	Any patient/TX	N2	M0	S0
	Any patient/TX	N2	M0	S1
Stage IIC	Any patient/TX	N3	M0	S0
	Any patient/TX	N3	M0	S1
Stage III	Any patient/TX	Any N	M1	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0
	Any patient/TX	Any N	M1a	S1
Stage IIIB	Any patient/TX	N1-N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1-N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S

Prognostic classification – metastatic disease:

The most widely used prognostic classification for metastatic disease is that proposed by the International Germ Cell Consensus Classification Group (IGCCCG) [3]

Non Seminoma	Seminoma
Good prognosis	
Testis/ retro-peritoneal primary; no non-pulmonary visceral metastases and AFP < 1000 ng/ml + HCG < 5000 iU/l + LDH < 1.5 x ULN	Any primary site; no non-pulmonary visceral metastases and Normal AFP + Any HCG + Any LDH
Intermediate prognosis	
Testis / retro-peritoneal primary; no non-pulmonary visceral metastases and any of AFP $\geq$ 1000 - 10 000 ng/ml HCG $\geq$ 5000 - 50 0000 iU/l LDH $\geq$ 1.5 x ULN - 10 x ULN	Any primary site; non-pulmonary visceral metastases and Normal AFP + Any HCG + Any LDH
Poor prognosis	
Mediastinal primary or non-pulmonary visceral metastases and / or any of AFP > 10 000 ng/ml HCG > 50 000 iU/l LDH > 10 x normal	

NEW PATIENTS

Information gathering and first assessment:

When new patients are seen in the BTCS and other Centres we would recommend the following baseline assessments. This will help to understand the patient's needs and provide an understanding of past medical history, risks of testicular cancer and current medical issues.

First consultation:

- History:
    - How they came about seeing the GP and what actions were taken
    - Date of USS, orchidectomy, Tumour Markers and CT scan
    - Results of pre & post-operative Tumour markers
- Past medical History, including undescended testicles, mumps with orchitis
- Current medication
- Allergies
- Social History including:
    - Family history of cancer
    - Living situation, including any children and relationships (for those who have not completed their family, discuss the possibility of sperm storage)
    - Work
    - Smoking/Alcohol/Recreational drugs
- Physical examination
- Assessment:
    - What the stage of the disease is
    - If CT scan clear, risk of recurrence
    - Treatment/surveillance options
    - Clear plan for the way forward
- Investigations:
    - FBC
    - U&Es
    - LFTs
    - Testosterone, FSH & LH
    - AFP, HCG, LDH
    - CXR

PLEASE DOCUMENT INFORMATION IN THE CLINICAL NOTES, DICTATE A LETTER TO THE GP AND SEND COPIES TO THE PATIENT AND REFERRING TEAM

TREATMENT

STAGE ONE (pT1-3, N0, M0) - No residual disease post-surgery - normal tumour markers and CT scan showing no evidence of metastatic disease:

CLASSICAL SEMINOMA

Risk of relapse is 10 – 30%, reduced to 3 –5% by adjuvant therapy.

Adverse predictive factors for recurrence are tumour >4 cm and/or invasion of rete testis. For patients with both adverse features the risk of recurrence is up to 30%. For those with no adverse features risk of relapse is < 10% and surveillance is recommended.

Recommended:

- Active Surveillance:

STAGE ONE SEMINOMA: ACTIVE SURVEILLANCE	
YEAR 1 **3 MONTHLY**	**EACH VISIT - Tumour markers (AFP, HCG, LDH) and clinical assessment** **Please encourage all patients to perform monthly TSE***
	CXR and CT Scan Abdomen & Pelvis at 6 months & 12 months
	HNA CLINIC^ 9 Months
YEAR 2 **3 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **and clinical assessment**
	CXR and CT Scan Abdomen & Pelvis 18 months & 24 months
YEAR 3 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **and clinical assessment**
	CXR and CT Scan Abdomen & Pelvis END OF YEAR 3
YEAR 4 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **and clinical assessment**
	CXR and CT Scan Abdomen & Pelvis END OF YEAR 4
YEAR 5 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **and clinical assessment**
	CXR and CT Scan Abdomen & Pelvis END OF YEAR 5
DISCHARGE	Recommend discharge ensuring the GP has the following information: • Details diagnosis • Treatment • Potential late effects • Signs and symptoms of recurrence. Reassure patient that they will be given an opportunity to be seen if they are worried about potential recurrence.
***TSE = testicular self-examination** **^ HNA Holistic Needs Assessment Clinic. NB. Patients can be referred to the HNA clinic at any time**	
It is the responsibility of the clinician who has ordered the CT scan or any other investigation to ensure this has been added to the MDT for discussion	

Or

- Carboplatin x 1 cycle AUC 7 based on EDTA clearance
  (use absolute value for GFR uncorrected for surface area) [5]. *Evidence Level IB*
  http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/Carboplatin-Seminoma.pdf

Or

- Radiotherapy 20Gy in 10 fractions to para-aortic nodes. If there is a history of previous pelvic or scrotal surgery, including inguinal hernia repair, the ipsilateral pelvic nodes should also be irradiated with a dog leg field (usually 20Gy in 10 fractions) [4]. Vasectomy is not an indication for pelvic node irradiation. *Evidence Level IB*

NB: Practice has evolved in the UK over the past 10 years. Most patients are now offered active surveillance or adjuvant carboplatin. For pT4 disease consider adjuvant scrotal radiotherapy.

SPERMATOCYTIC SEMINOMA

For patients with pure spermatocytic seminomas the risk of recurrence is low. They should be offered surveillance according to the post adjuvant carboplatin follow up schedule (see below)

SEMINOMA: POST ADJUVANT CARBOPLATIN , ADJUVANT PARA-AORTIC RADIOTHERAPY or STAGE IIa/b TREATED WITH CARBOPLATIN/RADIOTHERAPY or STAGE ONE SPERMATOCYTIC SEMINOMA	
YEAR 1 **4 MONTHLY**	**FIRST VISIT: HNA^ 4-6 WEEKS AFTER TREATMENT**
	EACH VISIT - Tumour markers (AFP, HCG, LDH) **and clinical assessment** **Please encourage all testicular cancer patients to perform monthly TSE***
	CXR and CT Scan Abdomen & Pelvis END OF YEAR 1
YEAR 2 **4 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **and clinical assessment**
	CXR and CT Scan Abdomen & Pelvis END OF YEAR 2
	END OF YEAR 2 LATE EFFECTS
YEAR 3 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **and clinical assessment**
	CXR END OF YEAR 3
YEAR 4 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **and clinical assessment**
	CXR END OF YEAR 4
YEAR 5 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **and clinical assessment**
	END OF YEAR 5 LATE EFFECTS
	CXR and CT Scan Abdomen & Pelvis END OF YEAR 5
DISCHARGE	Recommend discharge ensuring the GP has the following information: • Details diagnosis • Treatment • Potential late effects • Signs and symptoms of recurrence. Reassure patient that they will be given an opportunity to be seen if they are worried about potential recurrence.
LATE EFFECTS MONITORING: **In Clinic:** FBC, U&Es, LFTs, MALE HORMONE PROFILE, RANDOM LIPIDS.BLOOD PRESSURE and BMI	
***TSE = testicular self-examination** **^ HNA Holistic Needs Assessment Clinic. NB.** **Patients can be referred to the HNA clinic at any time**	
It is the responsibility of the clinician who has ordered the CT scan or any other investigation to ensure this has been added to the MDT for discussion	

NON-SEMINOMATOUS GERM CELL TUMOURS (Including combined tumours)

Around 80% of recurrences occur in the first 12 months after diagnosis. For patients without vascular or lymphatic invasion the risk of recurrence is around 10 - 20% in the first 2 years [10] (*Evidence level IB).* For patients with vascular or lymphatic invasion the risk of recurrence without treatment is 45 - 50% within the first 2 years. This is reduced to <3% with chemotherapy [11]. *Evidence level IIB*

Recommendation (pT1 -) - *No evidence of vascular or lymphatic invasion*:

- Active surveillance: providing patients are able to comply with Surveillance Programme (see section 6) [7]. *Evidence level IV.*

STAGE ONE NSGCT/COMBINED: ACTIVE SURVEILLANCE	
YEAR 1 **MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH)
	ALTERNATE VISITS - Clinical assessment & CXR at baseline and 6 months **Please encourage all testicular cancer patients to perform monthly TSE***
	HNA CLINIC^ 6 Months
	CT Scan Chest, Abdomen & Pelvis 3 months & 12 months *Evidence level IB.*
YEAR 2 **2 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH)
	ALTERNATE VISITS - Clinical assessment & CXR at 6 and 12 months
YEAR 3 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH) **Clinical assessment & CXR**
YEAR 4 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR**
YEAR 5 **12 MONTHLY**	**Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CT Scan** Chest, Abdomen & Pelvis at end of year 5
DISCHARGE	Recommend discharge ensuring the GP has the following information: • Details diagnosis • Treatment • Potential late effects • Signs and symptoms of recurrence. Reassure patient that they will be given an opportunity to be seen if they are worried about potential recurrence.
***TSE = testicular self-examination** **^ HNA Holistic Needs Assessment Clinic. NB. Patients can be referred to the HNA clinic at any time**	
It is the responsibility of the clinician who has ordered the CT scan or any other investigation to ensure this has been added to the MDT for discussion	

Recommendation (pT2 - 4)

- Active surveillance providing patients are able and willing to comply with Surveillance Programme. *Evidence level IV (as above)*

Or

- 3 day BEP500 x 1 cycle (cisplatin 100mg/m^2, etoposide 500mg/m^2, bleomycin 30mg d 2, 8, 15). Total bleomycin dose = 180mg [11]. *Evidence level* IIA

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/Adjuvant-BEP500-1.pdf

European consensus guidelines [7](*Evidence level IV*) recommend consideration for 1 cycle of adjuvant BEP chemotherapy. There is concern about psychological distress for patients on surveillance. However, over 90% of patients who relapse on surveillance will be cured with 3 cycles of BEP chemotherapy. The potential long-term risks from chemotherapy (e.g. cardiovascular disease, second malignancy) must be discussed with patients before proceeding with adjuvant chemotherapy.

STAGE ONE NSGCT/COMBINED: POST ADJUVANT BEP	
YEAR 1 **3 MONTHLY**	**FIRST VISIT: 4-6 WEEKS AFTER TREATMENT:** Holistic Needs Assessment Clinic
	EACH VISIT - Tumour markers (AFP, HCG, LDH), **Clinical assessment & CXR at months 3 and 9** **Please encourage all testicular cancer patients to perform monthly TSE***
	CT Scan Chest, Abdomen & Pelvis END OF YEAR 1
YEAR 2 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR**
	END OF YEAR 2 LATE EFFECTS
YEAR 3 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR**
YEAR 4 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR**
YEAR 5 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CT Scan** Chest, Abdomen & Pelvis at end of year 5
	END OF YEAR 5 LATE EFFECTS
DISCHARGE	Recommend discharge ensuring the GP has the following information: • Details diagnosis • Treatment • Potential late effects • Signs and symptoms of recurrence. Reassure patient that they will be given an opportunity to be seen if they are worried about potential recurrence.
LATE EFFECTS MONITORING: **In Clinic:** FBC, U&Es, LFTs, MALE HORMONE PROFILE, RANDOM LIPIDS.BLOOD PRESSURE and BMI	
***TSE = testicular self-examination** **^ HNA Holistic Needs Assessment Clinic. NB. Patients can be referred to the HNA clinic at any time**	
It is the responsibility of the clinician who has ordered the CT scan or any other investigation to ensure this has been added to the MDT for discussion	

METASTATIC GERM CELL CANCERS

All patients with metastatic germ cell cancer should be discussed at the supra-regional MDT at the time of diagnosis. Patients with intermediate or poor prognosis disease should be recommended to have a clinical assessment in Bristol and offered treatment in Bristol. Patients aged between 16 and 24 years should be referred to the Teenagers and Young Adults (TYA) service and offered treatment within the Bristol TYA unit.

GOOD PROGNOSIS

GOOD PROGNOSIS METASTATIC SEMINOMA

Retroperitoneal lymphadenopathy < 3cm maximum diameter and treatable in a single radiotherapy field:

Recommended:

- Carboplatin x 1 cycle AUC 7 based on EDTA clearance (use absolute value for GFR uncorrected for surface area) *and* radiotherapy to para-aortic nodes. Usually 30 Gy in 15 fractions followed by boost 5Gy in 3 fractions. [7]. *Evidence level IV*
  (NB: follow up schedule as for patients after adjuvant chemotherapy/radiotherapy)

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/Carboplatin-Seminoma.pdf

Para-aortic lymphadenopathy > 3cm that cannot be treated in a single radiotherapy field or metastatic disease:

Recommended:

- 3 day BEP500 x 3 cycles (cisplatin 100mg/m^2, etoposide 500mg/m^2, bleomycin 30mg d 2, 8, 15). Total bleomycin dose 270 mg [8]. *Evidence level IB*

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/BEP500-1.pdf

Or

- 3 day EP500 x 4 cycles (cisplatin 100mg/m^2 and etoposide 500mg/m^2) [9]. *Evidence level IB*

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/EP500-1.pdf

There is no direct evidence that the addition of bleomycin improves outcome for patients with pure seminoma [1](*Evidence level IV*) and should normally be omitted for patients >50 years, those with impaired renal function or pre-existing lung disease because of the increased risk of pulmonary toxicity. For patients with co-morbidity BEP or EP may be given over 5 days.

GOOD PROGNOSIS METASTATIC NON-SEMINOMA (INCLUDING COMBINED TUMOURS)

Recommended:

- 3 day BEP500 x 3 cycles (cisplatin 100mg/m^2, etoposide 500mg/m^2, bleomycin 30mg d 2, 8, 15). Total bleomycin dose 270 mg [8]. *Evidence level IB*
    - Omission of bleomycin [12] *(Evidence level III*) should be considered if:
    - > 50 years of age
    - Creatinine clearance <60ml/min
    - Pre-existing lung disease and patients with a significant smoking history

    http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/BEP500-1.pdf

Alternatives:

If bleomycin is omitted:

- 3 day EP500 x 4 cycles (Cisplatin 100mg/m^2 and etoposide 500mg/m^2) [9]. *Evidence level IB*

In patients with poor performance status or where there are specific concerns about potential toxicity BEP500 or EP500 can be administered over 5 days.

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/EP500-1.pdf

INTERMEDIATE PROGNOSIS METASTATIC (SEMINOMA AND NON SEMINOMA)

To date, no randomised trial has demonstrated a convincing survival advantage compared to 5-day BEP500 for intermediate prognosis NSGCT. 3-day BEP500 has been shown to be equivalent to 5-day BEP500 for good prognosis metastatic disease but has not been evaluated in intermediate disease and cannot be routinely recommended in this setting.

Recommended:

- 5-day BEP500 x 4 cycles (cisplatin 100mg/m^2, etoposide 500mg/m^2, bleomycin 30mg d 2, 8, 15). Total bleomycin dose 360mg [1, 14-18]. *Evidence level IB*
    - Omission of bleomycin [12] *(Evidence level III*) should be considered if:
    - > 50 years of age
    - Creatinine clearance <60ml/min
    - Pre-existing lung disease and patients with a significant smoking history

    http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/BEP500-1.pdf

Alternatives:

- 5 day EP500 x 4 cycles (Cisplatin 100mg/m^2 and etoposide 500mg/m^2) [9]. There is limited evidence for EP500 alone in patients with intermediate prognosis disease.
  or
- 5 day VIP (Cisplatin 100mg/m^2 and etoposide 375mg/m^2 and ifosfamide/mesna 6 g/m^2)[37]

POOR PROGNOSIS METASTATIC (NON SEMINOMA ONLY)

MRC TE23 Randomised phase II trial of intensive induction chemotherapy (CBOP/BEP) compared to standard BEP chemotherapy in poor prognosis male germ cell tumours demonstrated higher response rates and improved progression free but not overall survival advantage for patients with poor prognosis metastatic disease. Where appropriate CBOP-BEP is the preferred schedule.

Recommended:

- CBOP-BEP [19]. *Evidence level IIA*. Schedule is:
    - CBOP for 6 weeks:
    - Cisplatin 100mg/m^2 wk 1 and 3; 40mg/m^2 wk 2 and 4
    - Carboplatin AUC 3 wk 2 and 4
    - Vincristine 1.4mg/m^2 (max. 2mg) weekly for 6 wks
    - Bleomycin 75mg as 5-day infusion wks 2 and 4; 15mg weekly on all other weeks including during BEP. Total bleomycin dose 345mg.
    - **Then** 3 x BEP with 5 day schedule of etoposide 100mg/m^2/day, cisplatin 20mg/m^2/day and Bleomycin **15mg** weekly

      NB: Aim to harvest peripheral blood stem cells during cycle 2 or 3 of BEP

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/CBOP-BEP.pdf

Or

- 5-day BEP500 x 4 cycles (cisplatin 100mg/m^2, etoposide 500mg/m^2, bleomycin 30mg d 2, 8, 15). Total bleomycin dose 360mg [1, 14-18]. *Evidence level IB*

  NB: Aim to harvest peripheral blood stem cells during cycle 2 or 3 of BEP

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/BEP500-1.pdf

Or

- *If absolute contra-indication to bleomycin consider 5 day* VIP (Cisplatin 100mg/m^2 and etoposide 375mg/m^2 and ifosfamide/mesna 6 g/m^2)

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/VIP.pdf

INDUCTION CHEMOTHERAPY

In exceptional circumstances a patient may require induction chemotherapy to stabilise their clinical symptoms prior to full dose CBOP-BEP or BEP. Where this is administered full dose treatment should proceed as soon as the clinical situation allows. Patients are at higher risk of myelosuppression with the first cycle of full dose treatment. Induction chemotherapy is usually:

Cisplatin 40mg/m^2 (ie 20mg/m^2/day) and etoposide 200mg/m^2 (ie 100mg/m^2/day) over 2 days

Or

Carboplatin AUC 3 day one only and etoposide 200mg/m^2 (ie 100mg/m^2/day) over 2 days

MANAGEMENT OF BRAIN METASTASES:

For patients with brain metastases initial treatment is usually with chemotherapy as above. All patients should be discussed at the neuro-surgical MDT and where appropriate considered for surgical resection, gamma knife or whole brain radiotherapy as well as chemotherapy.

MANAGEMENT OF PATIENTS DURING CHEMOTHERAPY

Prior to chemotherapy all patients having chemotherapy for metastatic germ cell cancers should have:

CLINICAL REVIEW PRIOR TO EACH CYCLE OF CHEMOTHERAPY	
BLOOD TEST	**Tumour markers** (AFP, HCG, LDH). Repeat weekly in patients with metastatic disease whilst on chemotherapy Patients with very high markers/poor prognosis disease twice weekly markers may be recommended.
	Full blood count
	Biochemical profile including Ca^{2+}, Mg^{2+}.
	Calculated creatinine clearance (before each cycle). EDTA clearance should be arranged for intermediate/poor prognosis patients, if calculated creatinine clearance <60ml/min and for patients having second or subsequent lines of treatment.
RADIOLOGY	**CXR.** This should be repeated every cycle for patients receiving bleomycin containing chemotherapy.
	CT scan of chest, abdomen and pelvis. Consider repeat after 2 cycles for patients with marker negative disease or intermediate/poor prognosis or relapsed disease. **Intermediate and poor prognosis metastatic patients should have a baseline MRI brain.**
PRE-CHEMOTHERAPY ASSESSMENTS & PROCEDURES	**Audiogram** (before 1st cycle and then if clinically indicated).
	Pulmonary function tests (bleomycin containing schedules only) to include FEV1/FVC and transfer factor (before 1st cycle and then if clinically indicated. An absolute drop of >20% in transfer factor, new respiratory symptoms or changes on CXR must be discussed with the consultant before proceeding with further bleomycin.
	Sperm Storage must be discussed with all patients prior to chemotherapy. Referrals should be made to Bristol Centre for Reproductive Medicine according to the UHBristol Standard Operating Procedure. Patient to be given and information leaflets: *Virology Screening for Sperm Storage* Patient information leaflet from BCRM Macmillan booklet *Men and Fertility* Map of Southmead Hospital Patients will be asked to consent to HIV, Hepatitis B, Hepatitis C and Syphilis testing. Procedure will be carried out according to the current Standard Operating Procedure

POST TREATMENT ASSESSMENT FOR METASTATIC DISEASE:

CT scan 8 weeks after the start of the last cycle of chemotherapy to assess overall response
Intermediate and poor prognosis metastatic patients should also have a post chemotherapy MRI brain.

All tests to be reviewed at MDT.

METASTATIC: POST TREATMENT SURVEILLANCE	
YEAR 1 **First visit post chemotherapy**	**4 WEEKS POST TREATMENT: CNS telephone follow up call**
	CLINIC REVIEW AFTER CT SCAN **Discuss CT scan results** **Tumour markers** (AFP, HCG, LDH), FBC, U&ES & LFTS and **Clinical assessment** **Please encourage all testicular cancer patients to perform monthly TSE*** **Where appropriate refer patients for RPLND. These patients will have a further 'first visit post treatment' to discuss histology and commence follow up.**
YEAR 1 **2 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR alternate appointments** **HNA^** 3 MONTHS POST TREATMENT
	ALL PATIENTS - **CT Scan** Chest, Abdomen & Pelvis end of year one (or according to MDT)
YEAR 2 **3 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR alternate appointments**
	END OF YEAR 2 LATE EFFECTS
YEAR 3 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR**
YEAR 4 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment & CXR**
YEAR 5 **12 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical assessment**
	CT Scan Chest, Abdomen & Pelvis end of year 5 **END OF YEAR 5 LATE EFFECTS**
CONSIDER DISCHARGE	**Do not discharge if patient has residual disease (discuss at MDT).** For all other patients recommend discharge ensuring the GP has the following information: • Details diagnosis • Treatment • Potential late effects • Signs and symptoms of recurrence. Reassure patient that they will be given an opportunity to be seen if they are worried about potential recurrence.
LATE EFFECTS MONITORING: **In Clinic:** FBC, U&Es, LFTs, MALE HORMONE PROFILE, RANDOM LIPIDS, BLOOD PRESSURE and BMI	
***TSE = testicular self-examination** **^ HNA Holistic Needs Assessment Clinic. NB. Patients can be referred to the HNA clinic at any time**	
It is the responsibility of the clinician who has ordered the CT scan or any other investigation to ensure this has been added to the MDT for discussion	

SURGERY/RADIOTHERAPY FOR RESIDUAL DISEASE POST CHEMOTHERAPY:

SEMINOMA

Surgical resection of retroperitoneal masses is not routinely recommended.

For patients with a residual mass ≥ 3cm PET-CT scan should be performed [20,21]. If PET negative then repeat CT scan in 3 - 6 months and review at MDT. If PET positive discuss at MDT and consider surgical resection or, if inoperable radiotherapy. *Evidence level IIB.*

NON-SEMINOMAS (INCLUDING COMBINED TUMOURS)

Any patients with a residual mass > 1cm post chemotherapy (including mediastinal disease, pulmonary metastases) should be discussed at the MDT and considered for surgery [7,22]. *Evidence level IIA.*

Normally surgery is only appropriate if tumour markers have stabilised and complete excision is considered to be technically possible.

Residual mass may contain viable tumour, differentiated teratoma or fibrosis/necrosis. The role of further salvage chemotherapy, for patients with incomplete excision and undifferentiated tumour in the resection specimen is uncertain but should be considered [7]. *Evidence level IV.* Studies suggest that "adjuvant" treatment may improve progression free survival but not necessarily overall survival [23]. *Evidence level III*.

Repeat CT scan 3 months after completion of surgery.

RELAPSED DISEASE

SEMINOMA / NON SEMINOMA – surveillance; no previous treatment for metastatic disease

Treat as first line metastatic disease (see above)

SECOND LINE TREATMENT

Options for patients with relapsed disease include chemotherapy, surgery or radiotherapy. In general, patients with late relapse of NSGCT (> 2 years) are more likely to be chemotherapy resistant and, where possible, should be considered for immediate surgical resection [7] (*Evidence level IV*).

There is no accepted standard chemotherapy schedule for relapsed disease. Typical salvage treatments have included VIP (vinblastine or etoposide, ifosfamide and cisplatin), TIP (paclitaxel, ifosfamide and cisplatin) and high dose therapy [24-30]. Currently the recommendation in Bristol is for initial treatment with:

- TIP x 4 (5-day schedule of paclitaxel 175mg/m^2 (day 1 only), cisplatin 100mg/m^2, ifosfamide 5g/m^2) [30](MRC TIP). *Evidence level IIB*.

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/TIP.pdf

Or

- High dose chemotherapy (see below)

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/High-Dose-Carboplatin-and-Etoposide.pdf

HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL SUPPORT:

This may be considered for patients at first or second relapse following conventional dose treatment for patients who have had a successful peripheral blood stem cell harvest. For high risk patients a peripheral stem cell harvest is advised during first line BEP or in the BEP phase of CBOP/BEP. Alternatively stem cell harvests may be obtained during TIP or for some patients treatment with EP is more appropriate. If it is not possible to harvest cells from standard dose chemotherapy, subject to funding, a Plerixafor stimulated harvest may be attempted.

The benefits of and risks from high dose chemotherapy should be discussed carefully with patients and their family/carers. The use of prognostic scores can help inform estimates of benefit [39,40].

PROGNOSTIC MODEL:

Factors		Points
Primary site	Gonadal	0
	Retroperitoneal	1
	Mediastinal (NSGCT)	3
Response to first-line therapy	CR/PRm-	0
	PRm+/SD	1
	PD	2
Progression-free interval after first-line therapy	> 3 months	0
	≤ 3 months	1
Serum HCG level	≤ 1000 IU/l	0
	> 1000 IU/l	1
Serum AFP level	Normal	0
	≤ 1000 ng/ml	1
	> 1000 ng/ml	2
Liver, bone or brain metastases	Absent	0
	Present	1

Add points for preliminary score (0-10); regroup into category score (0): 0: (1-2); 1: (3-4); 2: (5 or more); 3 add histology points as below to category score to determine final risk category			
Histology	Seminoma	-1	
	NSGCT/combined	0	
Stratification	**Points**	**2 year PFS (%)**	**3 year OS (%)**
Very low risk	-1	75	77
Low risk	0	51	66
Intermediate risk	1	40	58
High risk	2	26	27
Very high risk	3	6	6

AFP: a-feto protein; CR: complete response; DFS: Disease-free survival; FFS: Failure-free survival; hCG: Human chorionic gonadotropin; NSGCT: Non-seminomatous germ cell tumour; OS: Overall survival; PD: Progression of disease; PFS: Progression-free survival; PRm-: Partial response with negative markers; PRm+: Partial response with positive markers; SD: Stable disease.

Prognostic Groups : Estimated survival for high dose versus conventional dose

Estimated Survival	All n=(1594)	Very Low n=(76)	Low n=(257)	Intermediate n=(646)	High n=(351)	Very High n=(106)
2 year PFS (%)	CDCT - 27.8 HCCT - 49.6	CDCT – 58.4 HDCT – 91.6	CDCT – 40.0 HDCT – 64.3	CDCT – 31.9 HDCT – 53.5	CDCT – 17.2 HDCT – 33.3	CDCT – 1.9 HDCT – 22.0
5 Year OS	CDCT – 40.8 HDCT – 53.2	CDCT – 64.5 HDCT – 88.7	CDCT – 66.2 HDCT – 64.5	CDCT – 45.5 HDCT – 58.3	CDCT – 23.0 HDCT – 35.2	CDCT – 3.4 HDCT – 27.0

For patients who are fit enough for high dose chemotherapy the preferred schedule is two cycles of carboplatin and etoposide administered with a 28 day interval [41]. Doses may be modified if patients are heavily pre-treated and the second cycle may be omitted if there is prolonged toxicity. The suggested schedule is 2 cycles of:

- Carboplatin AUC 24 (divided into AUC 8 days 1 – 3) and etoposide 2250 mg/m^2 (divided into 750 mg/m^2 days 1 – 3). Peripheral blood stem cells (minimum 1.0 x 10^6/kg) are re-infused on day 5. The second cycle should be administered on day 28 or when blood counts have recovered and subject to careful assessment of non-haematological toxicity recovery and no evidence of disease progression.[38]

THIRD AND SUBSEQUENT LINES OF TREATMENT:

Treatment in this situation is normally palliative although some patients may get prolonged survival benefit. Possible schedules that can be used include gemcitabine – oxaliplatin [31], gemcitabine [32], re-challenge with cisplatin (or carboplatin) and etoposide or single agent oral etoposide [33]. *Level of evidence IIA*. Where available, patients should be considered for appropriate clinical trials.

http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/Oxaliplatin-and-Gemcitabine.pdf

TESTICULAR STROMAL TUMOURS

Leydig and Sertoli cell tumour account for 2 – 4 % of adult testicular tumours. Most are benign but some show malignant features and will require surveillance. There is limited clinical evidence for optimal surveillance strategies.

Leydig cell tumours

About 10% are malignant. Adverse features include size >5cm, cytological atypia, mitotic activity >3 per 10 high power field, vascular invasion, necrosis, increased MIB-1 expression, infiltrative margins and extension beyond testicular parenchyma

Sertoli cell tumours

Rate of malignancy reported to be 10 – 20% although very few published case reports/series. Features of malignancy include size >5cm, pleomorphic nuclei with nucleoli, mitotic activity > 5 per 10 high power fields, necrosis and vascular invasion. Up to 10% of patients with malignant disease will develop metastases.

Treatment:

Most patients will have an orchidectomy or, where possible partial orchidectomy as initial treatment. Baseline investigations should include:

- **LH, FSH, Testosterone (+ oestradiol, progesterone, cortisol)**
- **Inhibin a / b for sertoli cell tumours**
- **Ultrasound of both testes**
- **CT of chest/abdo/pelvis**

Patients with malignant tumours should be considered for retro-peritoneal lymph node dissection to reduce the risk of metastases.

There is no clear evidence to support the use of chemotherapy or radiotherapy.

There is no optimal surveillance strategy but patients with malignant tumours should be seen 3 monthly in the first year, 6 monthly in years 2 and 3 and then annually to 5 years.

Staging CT scans of the chest/abdo/pelvis should be performed at the end of years 1, 2 and 5 and then if clinically indicated.

Patients with benign tumours should be offered an initial appointment in the BTCS clinic and then discharged.

FEMALE GERM CELL CANCER

All female germ cell tumours (GCT) of the ovary/retroperitoneum will be discussed both in the gynaecology MDT and BTCS supra-regional MDT for treatment decisions. Most will undergo initial surgery and discussion with the gynaecology team. As soon as a germ cell tumour is suspected or diagnosed they should be referred to the BTCS MDT. All chemotherapy is administered at BHOC.

Surgery

Primary fertility sparing surgery with consideration for egg/embryo freezing if for adjuvant BEP. Should achieve complete resection outside remaining ovary and uterus. Patients with Liver/lung metastases are managed as for the men where chemotherapy is normally given prior to resection.

Chemotherapy

Stage 1 dysgerminoma and stage 1aG1 immature teratoma are offered surveillance. For other stage 1 patients, there is a choice of surveillance or adjuvant chemotherapy with chemotherapy preferred for patients with stage 1c (see below for ESMO guidance). There is limited clinical trial evidence for female GCT and usually 3 cycles of BEP500 are recommended as adjuvant treatment

All stage 2 and above are offered 3-4 cycles of BEP500 chemo (bleomycin omitted for cycle 4 for most). Higher risk patients are offered BEP500 x 4 cycles

MANAGEMENT OF GERM CELL TUMOURS OF THE OVARY

Stage	Surgery (Fertility Sparing Surgery when indicated)	Chemotherapy	Surveillance Policy
Dysgerminoma			
Stage IA	X	-	X
Stage IB - IC	X	X	(X)
Stage IIA - IV	X	X	
Immature Teratoma			
Stage IA G1	X	-	X
Stage IA G2-G3	X	X	(X)*
Stage IB - IC	X	X	(X)
Stage IIA - IV	X	X	
Yolk Sac Tumour			
Stage IA - IB	X	X	X
Other Stages	X	X	

X = Suggested
(X) = Suggested by some authors
*** = Properly Surgical Staged**
- = No therapy

POST TREATMENT SURVEILLANCE	
YEAR 1 **3 MONTHLY**	**4 WEEKS POST TREATMENT: CNS telephone follow up call**
	FIRST VISIT: (POST SCAN) Tumour markers (AFP, HCG, LDH) FBC, U&ES & LFTS **Clinical Examination**
	HNA 2 MONTHS POST TREATMENT
	CT Scan Chest, Abdomen & Pelvis POST TREATMENT
YEAR 2 **3 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical Examination**
	END OF YEAR 2 LATE EFFECTS & CT SCAN
YEAR 3 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical Examination**
YEAR 4 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical Examination**
YEAR 5 **6 MONTHLY**	**EACH VISIT - Tumour markers** (AFP, HCG, LDH), **Clinical Examination**
	END OF YEAR 5 LATE EFFECTS & CT SCAN
CONSIDER DISCHARGE	Consider discharge, ensure GP has the following information: • Details diagnosis • Treatment • Potential late effects • Signs and symptoms of recurrence. Reassure patient that they will be given an opportunity to be seen if they are worried about potential recurrence.
LATE EFFECTS MONITORING: **In Clinic:** FBC, U&Es, LFTs, RANDOM LIPIDS, BLOOD PRESSURE & BMI **TVUS every 6 months for those having had fertility sparing surgery**	

Relapse

All patients with relapsed disease should be discussed at the BTCS MDT. Treatment options considered are usually the same as for men with relapsed disease.

OTHER MONITORING & SUPPORT

Microlithiasis:

In the absence of other risk factors (size <12ml, atrophy, maldescent of testis) testicular microlithiasis is not an indication for biopsy or further routine ultrasound screening and will be monitored as per MDT decision.

LATE EFFECTS MONITORING

There is increasing evidence that men who have received intensive chemotherapy for testicular cancer are at increased risk of cardiovascular disease and metabolic syndrome later in life [34, 35]. There is a risk of developing testosterone deficiency syndrome post orchidectomy, which also increases the risk of long term health related issues.

All patients should undergo late effects screening to identify testosterone deficiency and factors potentially contributing to cardiovascular disease.

This will be carried out at 2 years and 5 years post treatment:

At Clinic visit: Male Hormone Profile
Full blood count, biochemical profile & random lipids
Weight and BMI
BP

On discharge, ensure GP has the following information (Appendix 1):

- Details of diagnosis
- Treatment received
- Potential late effects
- Signs and symptoms of recurrence

Reassure patient that they have open access to the clinic if they are worried about potential recurrence.
NB: Please remember to inform the GP to monitor FBC (Haematocrit) regularly if patient is discharged on testosterone replacement therapy.

TESTOSTERONE DEFICIENCY SYNDROME

After treatment, some men experience Testosterone Deficiency Syndrome (TDS) which can cause long term issues and side effects.

- Low testosterone is linked to increased blood pressure, dyslipidaemia, atherosclerosis, arrhythmia, thrombosis, endothelial dysfunction and impaired LV function.
- High levels of Testosterone are linked to inhibited spermatogenesis; prostate hypertrophy - mild, self-limiting; decrease in visceral fat mass. (42, 43)

The following plan is a guide to practice.
All men to have a random blood test for Testosterone; FSH & LH at their first visit.
If levels are within normal limits they do not need to be repeated unless further treatment is administered.

<table>
<tr><th colspan="2">MALE REPRODUCTIVE HORMONES</th></tr>
<tr><th colspan="2">TOTAL TESTOSTERONE</th></tr>
<tr><td>EVENT</td><td>Total testosterone > 12 nmol/L</td></tr>
<tr><td>ACTION</td><td>Testosterone result normal.
Patients' symptoms unlikely to be due to male hypogonadism.</td></tr>
<tr><td>EVENT</td><td>First Total testosterone < 12 nmol/L</td></tr>
<tr><td>ACTION</td><td>If sample taken at after 11am, repeat sample between 0800 – 1100

If first sample and taken between 0800 - 1100, repeat between 8-11 am in two weeks, along with measurement of LH, Prolactin, Albumin and SHBG</td></tr>
<tr><td>EVENT</td><td>Repeat Total testosterone < 8 nmol/L</td></tr>
<tr><td>ACTION</td><td>Recommend endocrinology referral for investigation and consideration of treatment</td></tr>
<tr><td>EVENT</td><td>Repeat Total testosterone 8 – 12 nmol/L</td></tr>
<tr><td>ACTION</td><td>Calculate free testosterone using the Vermeulen equation[1] (an online version is available at http://www.issam.ch/freetesto.htm).
Free testosterone reference ranges:
<table>
<tr><th></th><th>n=</th><th>Haslam et al 2013,[2] parametric 95% interval (nmol/L)</th><th>n=</th><th>Roche kit insert, 90% non-parametric interval (nmol/L)</th></tr>
<tr><td>< 50 years</td><td>129</td><td>0.190-0.593</td><td>136</td><td>0.198-0.619</td></tr>
<tr><td>50+ years</td><td>130</td><td>0.149-0.432</td><td>78</td><td>0.163-0.473</td></tr>
</table>
If free testosterone normal, this suggests low total testosterone is secondary to low SHBG and does not support a diagnosis of hypogonadism.
If free testosterone low, this suggests appointment in the HNA clinic or endocrinology referral.</td></tr>
</table>

If the levels do not normalise and/or the patient has the following symptoms, consider a trial of testosterone gel 50mgs daily for 3 months and then review in the HNA clinic in 2 months.

- Fatigue and lethargy
- Reduced sex drive and erectile dysfunction
- Poor concentration and or memory
- Depression, anxiety, irritability
- Reduced exercise tolerance and strength
- Excessive sweating and night sweats

When levels and/or symptoms recover, inform GP of plan to treat TDS with testosterone replacement therapy. Consider referral to endocrinology team for long term maintenance. For those who have not completed their family consider pre-replacement sperm analysis and post replacement analysis at 3-4 months. On the rare occasion where a bilateral orchidectomy is required please commence Testosterone replacement therapy immediately and refer to the endocrinology service.

Monitor haematocrit (on FBC) at baseline and 3 months after starting testosterone replacement therapy. If normal, this should be checked yearly with LFT and fasting lipids. Monitor PSA at least yearly in men on testosterone replacement therapy, but consider this more frequently (twice a year), along with digital rectal examination in men who have lower urinary symptoms, a first degree relative with prostate cancer, or those above 50 years.

RESEARCH AND TEACHING

The BTCS is committed to research and teaching. Where possible all suitable National Cancer Research Network trials in testicular cancer will be open to recruitment at BHOC. The team actively encourages in-house research projects.

The weekly testicular cancer clinic provides good opportunities for teaching of medical and nursing staff. The team will also provide regular teaching sessions for nurses and junior doctors

PATIENT INVOLVEMENT

The BTCS has an active patient forum that is involved in helping the team to develop services. They are led by the Germ Cell CNS team and are frequently asked for their views when developing new initiatives. Patient experience surveys are completed annually and the recommendations are published on the BTCS Website.

Bristol Testicular Cancer Service website:

The website is available to all patients to ensure they are well informed about testicular cancer, treatment, side effects and survival. Originally designed by patients for patients, it has sections for after treatment, and support. There are useful links to patient information and explanation about how the MDT works. It is supported by It's in the Bag charity and patient forum, which helps to promote all aspects of testicular cancer awareness and support.

www.uhbristol.nhs.uk/BTCS

There is a section for clinicians to access guidelines, minutes of meetings, audit results and referral forms.

PATIENT SUPPORT:

All support activities and courses are advertised in the BTCS clinic and regularly updated on both the NHS and It's in the Bag website.

Patient Volunteers:

We have a programme where men can become hospital volunteers and support other men in the BTCS Friday morning clinic. This is open to men who are 1 year post diagnosis and able to volunteer every 6 weeks for 2 hours.

Buddies:

There are a number of men who are happy to talk to others who have just been diagnosed or undergoing treatment. This is organised by the BTCS. This support might be via email, text or face to face

It's in the Banter:

Support Activities are organised by the It's in the Bag Cancer Support Charity. They are activities that men have voted for as enjoyable but also give an opportunity to talk together outside of a formal environment. They are available to all patients and some are open to partners & families too.

Get into your NEW PANTS:

This is a section of the website to help men get on with their lives post treatment. There is information about getting better and living a healthier lifestyle. There are also links to other helpful sites to encourage self-management.

Survivorship Toolkit:

The BTCS and It's in the Bag have worked to produce a programme to help men get back on their feet after a diagnosis of germ cell cancer. Following treatment patients will be booked onto a day course. This is a stand-alone course and takes place 5 times a year. After attending the day course some patients may feel they require more intervention and support, so we have also designed a residential personal development weekend course.

Dates will be posted on the NHS and It's in the Bag websites.

All courses are funded by It's in the Bag. Refreshments are available throughout the day and the weekend.

Travel Grants

The BTCS together with It's in the Bag can provide limited travel grants for those who are struggling to meet the cost of consultations in the South West.

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APPENDIX 1:

Templates for Treatment Summary Letters

Orchidectomy

Low risk of Testosterone deficiency syndrome – symptoms are:
Fatigue; Low mood; Irritability; Lack of libido; Low Self-esteem; the symptoms are similar to clinical depression. Patients treated with Testosterone Replacement therapy please monitor haematocrit (on FBC) at baseline and 3 months after starting testosterone replacement therapy. If normal, this should be checked yearly with LFT and fasting lipids. Monitor PSA at least yearly in men on testosterone replacement therapy, but consider this more frequently (twice a year), along with digital rectal examination in men who have lower urinary symptoms, a first degree relative with prostate cancer, or those above 50 years.

Low risk of fertility issues
There is a potential for a reduction in sexual function and issues related to body image and masculinity
Fear of recurrence – this is more common in the first 6 months post orchidectomy.
There is a slight increased risk of a **second primary testicular cancer** so we would encourage testicular self-examination and further investigations such as Ultrasound Scan if uncertain. We are happy to see men back in the clinic if you are concerned.

Possible signs and symptoms of recurrence are:
Rise in Tumour Markers (AFP, HCG & LDH); persisting back and/or abdominal pain; shortness of breath

Lifestyle and Support Needs:
The following support structure is available to all those diagnosed with Germ Cell Cancer and we actively encourage attendance.

- We provide a Holistic needs clinic
- It's in the Bag Cancer Support Charity provides support activities
- Survivorship Toolkit courses (Health and Wellbeing Days)
- Access to a Macmillan Support Worker & contact details of Key Worker

We encourage:

- At least 150 minutes of exercise per week
- Stopping smoking with NHS support
- Reducing alcohol consumption
- Reducing recreational drug consumption
- Use the After Treatment advice on the website: www.uhbristol.nhs.uk/itsinthebag

Adjuvant Carboplatin

This is a well-tolerated adjuvant chemotherapy given as a single cycle.

Short Tem side effects:
Fatigue, nausea, vomiting is very rare, constipation for 1-2 days and risk of infection due to suppression of bone marrow

Late effects:
These are not seen commonly with this treatment; however there may be some effects on the kidneys and a very small risk of altering fertility.

Adjuvant BEP

Short Term side effects
Common: Increased risk of infection, fatigue, nausea, vomiting, hair loss, constipation or diarrhoea, indigestion, renal toxicity, peripheral neuropathy, tinnitus, reduced fertility.
Less Common: Bleomycin lung toxicity (dry unproductive cough) & rash

Late effects
There is a 10% Risk of cardiac disease in the next 10 years and a 20% risk of infertility. We recommend monitoring late effects at 2 years, 5 years and 10 years post treatment. This is U&Es, LFTs, FBC, Testosterone, FSH, LH, Random Lipids, BMI and BP.
Rarely: Second cancers, increased risk of metabolic syndrome, hearing loss, peripheral neuropathy.

Please advise all surgeons and anaesthetists in the future that this patient has received Bleomycin.

Radiotherapy

Short Term side effects:
Common: Moderate fatigue, nausea, vomiting, diarrhoea, indigestion, bladder irritation, anaemia, dry sore skin,

Late effects:
Rarely: Second cancers, irritable bowel syndrome

Late effects: We recommend monitoring late effects at 2 years, 5 years and 10 years post treatment. This is U&Es, LFTs, FBC, Testosterone, FSH, LH, Radom Lipids, BMI and BP.

BEP for metastatic disease

Short Term side effects:
Common: Increased risk of infection, fatigue, nausea, vomiting, hair loss, constipation or diarrhoea, indigestion, renal toxicity, peripheral neuropathy, tinnitus, reduced fertility.
Less Common: Bleomycin lung toxicity (dry unproductive cough) & rash

Late effects:
There is a 10% Risk of cardiac disease in the next 10 years and a 20% risk of infertility. We recommend monitoring late effects at 2 years, 5 years and 10 years post treatment. This is U&Es, LFTs, FBC, Testosterone, FSH, LH, Random Lipids, BMI and BP.
Rarely: Second cancers, infertility, increased risk of metabolic syndrome, hearing loss, peripheral neuropathy.

Please advise all surgeons and anaesthetists in the future that this patient has received Bleomycin.

EP for metastatic disease

Short Term side effects:
Common: Increased risk of infection, fatigue, nausea, vomiting, hair loss, constipation or diarrhoea, indigestion, renal toxicity, peripheral neuropathy, tinnitus, reduced fertility.

Late effects:
There is a 10% Risk of cardiac disease in the next 10 years and a 20% risk of infertility. We recommend monitoring late effects at 2 years, 5 years and 10 years post treatment. This is U&Es, LFTs, FBC, Testosterone, FSH, LH, Random Lipids, BMI and BP.

Rarely: Second cancers, infertility, increased risk of metabolic syndrome, hearing loss, peripheral neuropathy.

TIP

Short Term side effects:
Common: Increased risk of infection, severe fatigue, nausea, vomiting, hair loss, constipation or diarrhoea, indigestion, renal toxicity, peripheral neuropathy, tinnitus, reduced fertility, skin and nail problems, cardiac toxicity, haemorrhagic cystitis, low calcium & magnesium.
Late effects:
There is a 10% Risk of cardiac disease in the next 10 years and a 20% risk of infertility. We recommend monitoring late effects at 2 years, 5 years and 10 years post treatment. This is U&Es, LFTs, FBC, Testosterone, FSH, LH, Random Lipids, BMI and BP.
Rarely: Second cancers, infertility, increased risk of metabolic syndrome, hearing loss, peripheral neuropathy.

CEBOP/BEP

Short Term side effects:
Common: Increased risk of infection, severe fatigue, nausea, vomiting, hair loss, constipation or diarrhoea, indigestion, renal toxicity, peripheral neuropathy, tinnitus, reduced fertility, low calcium & magnesium.
Less Common: Bleomycin lung toxicity (dry unproductive cough) & rash
Late effects:
There is a 10% Risk of cardiac disease in the next 10 years and a 20% risk of infertility. We recommend monitoring late effects at 2 years, 5 years and 10 years post treatment. This is U&Es, LFTs, FBC, Testosterone, FSH, LH, Random Lipids, BMI and BP.
Rarely: Second cancers, infertility, increased risk of metabolic syndrome, hearing loss, peripheral neuropathy.
Please advise all surgeons and anaesthetists in the future that this patient has received Bleomycin.
Late effects: We recommend monitoring late effects at 2 years, 5 years and 10 years post treatment. This is U&Es, LFTs, FBC, Testosterone, FSH, LH, **Radom Lipids, BMI and BP.**

RPLND (Retroperitoneal Lymph Node Dissection)

This is a procedure to remove lymph nodes from the abdomen; this could be either laparoscopic or open.
Short Term side effects:
Common: Increased risk of infection, pain, bowel changes, retrograde ejaculation (10-25% of cases), body image, major surgery considerations, no driving for 4-6 weeks, no heavy lifting or abdominal gym work for 10 – 12 weeks.
Long Term effects:
Retrograde ejaculation and risk to natural fertility, hernias, relapse at site.