Testis Cancer

Demographics
1% male tumours in the UK
5:100,000 male population per year
Lifetime male risk 1:500 (normally descended testes)
Incidence rising? why
20-30 (NSGCT) 30-40 (Seminoma)
Northern Europe/ USA
Whites > Blacks
US Black > African Black

Aetiology
Undescended Testis
10% GCT arise in undescended testes
RR of GCT with UDT is 4-10 (much higher in earlier studies with higher numbers
of non-operated intra-abdominal testes)
Seminoma more common cf. NSGCT (60% vs. 40%)
Risk of testis ca:
    Normal 1:500
    Unilateral UDT 1:125
    Bilateral UDT 1:45
One previous testis cancer:
    Normally descended contralateral testis 1:250
    Contralateral UDT 1:4
Histological evidence suggests ↓ spermatagonia and seminiferous tubules with
interstitial fibrosis between 2 and 3 years (Cooper 1929; Mengel and Hedinger
1970s)

Does orchidopexy reduce risk of subsequent cancer?
Controversial
Some case-control studies suggest that orchidopexy before age of ten reduced
risk of cancer (Swerdlow 1997). Some studies however suggest that risk of
cancer is actually greater in testes that have undergone orchidopexy (Forman D,
BMJ, 1994). No evidence yet of improved risk profile if orchidopexy before age of
2, although widely recommended (between 18 months and 2 years ideally).
Most complete evidence to date suggests that testes requiring orchidopexy have
an increased risk compared with normally descended testes, but that the risk can
be reduced provided orchidopexy performed before the age of 13 (Petterson
NEJM 1997)
Risk factors for testis cancer

Caucasian

UDT
- Unilateral: 4x
- Bilateral: 10x

Contralateral GCT: 8x

1st degree male relative: 6x

Subfertility: 2x

Kleinfelter’s

Kallman’s

Prenatal oestrogen exposure

Congenital abnormalities

Kleinfelter’s Syndrome (47XXY)
- De novo genetic event
- Tall and Thin
- Gynaecomastia
- Small firm testicles
- Elevated gonadotrophins

Kallman’s Syndrome
- Sporadic/familial
- Defective GnRH release
- Delayed puberty
- Anosmia
- Long limbs

Familial Risk

<2.2% of cases with positive family history

Brother of Index = RR 6-10

Father/Son of Index = RR 4-6

Dizygotic twin = RR 36

Monozygotic twin = RR 77

Xq27 locus may be responsible in up to ~25% cases

Pre-natal oestrogen exposure

Mouse studies = increased incidence with prenatal exposure to E

Human studies = Trial of DES to prevent abortion resulted in higher no. with testicular abnormalities

Testicular cancer rates higher in hyperemesis, first pregnancies and twins (all associated with higher in utero oestrogen exposure)

Male fish feminisation with oestrogenic pollutants from food packaging (bisphenols)

Previous testicular GCT

Risk of contralateral CIS = 5%
15-year risk of contralateral GCT (from SEER database Fossa 2005 n = 29,000)
synchronous (defined as within 2 months of diagnosis) – 0.6%
metachronous (> 2 months) 1.0%
Overall risk = 1.6%

No evidence:
- Vasectomy
- Genital abnormality (hypospadias, varicoceles, PPV)
- Trauma - associated with increased risk in retrospective studies but
  almost certainly due to recall bias
- Smoking
- Alcohol consumption
- Tight trousers/underwear

**Pathology**
Germ cell tumours account for 95%. Leydig-cell (3%) and sertoli-cell
(~1%) and rare others account for rest. Metastasis rare (lymphoma, prostate,
kidney in order)
Totipotent germ cells can differentiate to spermatocytic tissue (seminoma) or
somatic elements (endoderm, ectoderm or mesoderm = teratoma) or trophoblast
or yolk sac elements:
- Seminoma - divided into classic, spermatocytic and anaplastic.
- NSGCT - WHO classification superceded UK classification. Rigid
definition of teratoma as differentiated somatic elements. Undifferentiated
tissue therefore embryonal.

<table>
<thead>
<tr>
<th>WHO</th>
<th>British</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature teratoma</td>
<td>Teratoma differentiated</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>Malignant teratoma intermediate</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>Malignant teratoma undifferentiated</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Malignant teratoma trophoblastic</td>
</tr>
<tr>
<td>Yolk sac tumour</td>
<td>Yolk sac tumour</td>
</tr>
<tr>
<td>Mixed</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

**Seminoma**
~ 60-70% all tumours
Classic and anaplastic tumours present at 35-55 years; Spermatocytic most
common tumour over 60 years.
**Classic:** well circumscribed homogenous firm white tumour. Uniform cells with
clear cytoplasm and lymphocytic infiltrate within fibrous septa.
**Anaplastic:** similar to classic but increased numbers of mitoses and no
lymphocyte infiltrate.
**Spermatocytic:** Older men. Almost always benign - one case of malignant
spermatocytic seminoma to date. Polymorphic cells; small ones resemble
spermatocytes. No ITGCN. No IHC PLAP staining (cf. classic band ITGCN)
Markers: 10% have elevation in BHCG due to small numbers of syncytiotrophoblasts. PLAP elevated in 90% classic/anaplastic

**NSGCT**

~ 25-35% all tumours

**Mature teratoma**: heterogenous tumour composed of varying elements of fully differentiated tissue; endoderm (mucus secreting glands), ectoderm (stratified squamous and neural epithelium) and mesoderm (bone, cartilage, muscle). Least common, usually seen in children. Benign growth but may harbour areas of reduced differentiation. Markers: AFP in 20-25% due to hepatoid differentiation

**Immature teratoma**: Varying degrees of maturity present; malignant degeneration may also be seen (sarcoma, scc, adeno). Markers: AFP in 20-25% due to hepatoid differentiation

**Embryonal**: 20-30 years. Sheets of immature cells arranged in solid, tubular or papillary patterns. Macroscopically variegated with fleshy appearance. Usually seen in combination with other elements, especially chorio and yolk sac. Markers: pure embryonal = no elevation, but usually BHCG and AFP (50% AFP, 50% BHCG)

**Choriocarcinoma**: Highly malignant. Identifiable syncytiotrophoblast (synthesises BHCG/ syncytiotrophoblasts. Markers: BHCG raised in 99% of cases

**Yolk-Sac Tumours**: Pure form may be seen in children < 3 years old, but usually in mixed form. Microscopically solid, papillary and microcystic forms. Markers: AFP almost always raised

**Intratubular Germ Cell Neoplasia (ITGCN)**

Also carcinoma in-situ (CIS) and testicular intraepithelial neoplasia (TIN)

100% of cases of GCT have adjacent ITGCN

Large irregular nuclei with coarse chromatin and prominent nucleoli

50% progression to GCT at 5 years (Burke 1998)

Virtually all develop into GCT by 10 yrs (Skakkebaek 1981; Bettochi 1994)

Diagnosed by random stab biopsy – sensitivity approx 90% presumably due to field change

Biopsies must be sent in Bouins solution. Staining for PLAP makes diagnosis

Risk of contralateral CIS in established testis cancer:

- Normal contralateral testis - 1 in 20 (5%)
- < 12ml, < 30 yrs, previous UDT – 1 in 3 (33%)

Treatment: RT(20Gy in 10 fractions) - patients usually rendered infertile. Most retain hormone function. ChemoRx not effective for ITGCN.

**Molecular Biology**

Chromosomal abnormalities universal in GCT

ITGCN usually tetraploid; GCT normally triploid
Abnormalities of short arm of chromosome 12 (12p) seen in almost all cases of testis cancer: 80% have are triploid (isochromosome) for 12p; remainder have multiple 12p fragments on other chromosomes i(12p) late event – not usually seen in ITGCN
Genetic linkage studies in families with testis cancer suggest that Xp27 locus on long arm of X chromosome also important.
Investigation

Markers
Elevated tumour markers seen in ~50% testicular tumours: 5-10% seminomas (always BHCG); 90% NSGCT.

Alpha feto-protein (AFP)
Produced by yolk-sac elements
Half-life 5-7 days
Raised levels in 60% NSGCT; also seen in liver, lung, stomach and pancreas cancer

Beta subunit human chorionic gonadatrophin (BHCG)
Produced by syncytiotrophoblasts
Half-life 24 hours
HCG has alpha and beta subunits: alpha subunit identical to subunits of LH, FSH & TSH; beta subunit specific to HCG.
Very high BHCG may activate LH/FSH/TSH receptors – can present with thyrotoxicosis and gynaecomastia (T converted to E by peripheral aromatase)
Elevated BHCG in 55% NSGCT and 20% seminoma; also secreted by liver, lung, stomach and pancreas tumours, and marijuana smokers.
Unlike AFP may also be elevated in urological cancers (renal and bladder)
NB. Very high levels of BHCG found in choriocarcinoma. May bleed after chemotherapy – should always perform a CT head in these patients to exclude brain mets

Lactate dehydrogenase (LDH)
Non-specific but has prognostic significance.
Raised in 60% of NSGCT and 80% seminoma

Ultrasound
7-10Mz linear array transducer
Very high sensitivity
Intratesticular cysts usually < 1cm – not considered pre-malignant (Berger 1998)

Testicular microcalcification
Multiple small echogenic foci on high resolution USS (7-10 Mhz linear array transducer); At least 5 1-3mm foci on one testicular image generally regarded as diagnostic
TM is definitely associated with testicular GCT: In symptomatic patients in whom a testicular tumour is found on USS, TM is present in 23-73%.
Two unresolved questions regarding TM:

Does TM denote the presence of CIS?
The only way to definitively answer this question is to biopsy patients with and without TM. Only small studies have addressed this question in the following groups.
- Asymptomatic – Schering 2002; 0/8 patients with TM had CIS
- Infertility – von Ekardstein 2001; 2/11 patients with TM had CIS
- Contralateral GCT - Schering 2002; 7/9 patients with TM had CIS

NB. Diagnosis of CIS requires careful preparation, preservation in Bouin’s solution, and immunostaining with PLAP

**Does TM predict the development of GCT?**
No studies have addressed long-term follow-up of TM. There are 12 isolated case reports of the development of GCT in a patient with prior TM. Of these, 8 (75%) were in atrophic testes, 2 were in apparently normal testes, and 2 were not recorded. Until a large study of long term follow-up is reported, we can only speculate based on observational data – Recent data from DeCastro 2008 – 5 yr follow-up (of patients in Peterson study below) showed no difference in the incidence of cancer compared with normal patients.

Largest study of TM in asymptomatic healthy male population (US army recruits) 1504 males had scrotal US. Overall 5.6% prevalence; much higher in blacks (14.1%) compared with whites (4%). Compared with quoted incidence of 3-5 cases per 100,000 men, ~1000 fold less common, and incorrect race bias. Study criticized because should have been compared with lifetime risk of testicular GCT (1:500), but still 250x more common.

Testicular biopsy is not without its complications – bleeding, testicular atrophy, possible infertility etc. Also very high cure rates for patients with stage I make surveillance appropriate

Thus current recommendations (EAU 2010):
All asymptomatic patients with TM – testicular self-examination only
Biopsy warranted in patients < 40 yrs old with contralateral GCT and:
  - History of maldescent
  - Atrophy (volume < 12 ml)
  - Subfertility

**Testis biopsy**
Not 90-100% sensitive as previously thought
Orchidectomy specimens with mapping
  - 72% co-association of GCT with ITGCN
  - 60% focal ITGCN

**CXR**
Excludes high volume pulmonary disease – oncological emergency
Dipstick urine for pregnancy test fasted way of detecting tumour

**Computed Tomography**
Chest/Abdo/Pelvis for staging
Nodes > 10mm considered positive for nodal metastasis: excised masses < 2cm negative for mets in 30% (Donohue 1995)
If BHCG high CT brain imperative as trophoblastic elements can cause catastrophic bleeding after ChemoRx

**MRI**
No better for staging than CT, but improves imaging of great vessels when RPLND contemplated
Also reduces radiation exposure for follow-up protocols – not widespread use at present

**PET**
Limited role
Recent evidence suggest a PET scanning a valuable tool in determining the presence of cancer in patients with residual masses after chemoRx for stage IIC seminoma. ≥ 3 cm PET scanning = 80% sensitive and 100% specific viable tumour (SEMPET study De Santis 2004).
**Staging**

**Table 2** Royal Marsden Hospital staging of testis cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No evidence of metastasis</td>
</tr>
<tr>
<td>IM</td>
<td>Rising concentrations of serum markers with no other evidence of metastasis</td>
</tr>
<tr>
<td>II</td>
<td>Abdominal node metastasis</td>
</tr>
<tr>
<td>• A</td>
<td>&lt;2 cm in diameter</td>
</tr>
<tr>
<td>• B</td>
<td>2–5 cm in diameter</td>
</tr>
<tr>
<td>• C</td>
<td>&gt;5 cm in diameter</td>
</tr>
<tr>
<td>III</td>
<td>Supra-diaphragmatic nodal metastasis</td>
</tr>
<tr>
<td>• M</td>
<td>Mediastinal</td>
</tr>
<tr>
<td>• N</td>
<td>Supraclavicular, cervical or axillary</td>
</tr>
<tr>
<td>• O</td>
<td>No abdominal node metastasis</td>
</tr>
<tr>
<td>• ABC</td>
<td>Node stage as defined in stage II</td>
</tr>
<tr>
<td>IV</td>
<td>Extra lymphatic metastasis</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>• L1</td>
<td>&lt;3 metastases</td>
</tr>
<tr>
<td>• L2</td>
<td>3 metastases or more, &lt;2 cm in diameter</td>
</tr>
<tr>
<td>• L3</td>
<td>3 metastases or more, one or more of which &gt;2 cm in diameter</td>
</tr>
</tbody>
</table>

H+: liver metastases; Br+: brain metastases; Bo+: bone metastases

**TNM**

- **Tx**: Primary tumour cannot be assessed
- **T0**: No evidence of primary
- **Tis**: ITGCN (CIS)
- **T1**: Confined to testis/epididymis, no vascular/lymphatic invasion [tumour may involve t. albuginea but not t. vaginalis]
- **T2**: Confined to testis with vascular/lymphatic invasion, or t. vaginalis involvement
- **T3**: Spermatic cord invasion
- **T4**: Scrotal invasion

- **Nx**: Cannot be assessed
- **N0**: No regional LN
- **N1**: Regional LN <2cm and 5 or less
- **N2**: Regional LN 2-5cm or more than 5
N3  Regional LN >5cm diameter
Mx  Cannot be assessed
M0  No mets
M1  Distant mets
M1a  Non-regional LN or lumg
M1b  Other sites
Sx  Not recorded
S1  BHCG <5000;  AFP <1000;  LDH <1.5
S2  BHCG 5000-50000;  AFP 1000-10000;  LDH 1.5-10
S3  BHCG >50000;  AFP >10000;  LDH > 10

Prognosis (International germ-cell cancer collaborative group)

<table>
<thead>
<tr>
<th>Good prognosis</th>
<th>Intermediate prognosis</th>
<th>Poor prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of: Testis or retroperitoneal primary tumours, no non-pulmonary visceral metastases and any of: AFP &lt;1000 ng/ml, β-HCG &lt;5000 mU/ml, LDH &lt;1.5×ULN</td>
<td>Any primary site, No non-pulmonary visceral metastases, Any β-HCG, any LDH</td>
<td>Any of: Mediastinal primary site, Non-pulmonary visceral metastases, AFP &gt;10000 ng/ml, β-HCG &gt;50000 mU/l, LDH &gt;10-ULN</td>
</tr>
<tr>
<td>Good prognosis (NSGCT)</td>
<td>Intermediate prognosis (NSGCT)</td>
<td>Poor prognosis (NSGCT)</td>
</tr>
<tr>
<td>Seminoma</td>
<td>Seminoma</td>
<td>Seminoma</td>
</tr>
<tr>
<td>Good prognosis</td>
<td>Intermediate prognosis</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>All of: Testis or retroperitoneal primary tumours, no non-pulmonary visceral metastases (ie, lung metastases only)</td>
<td>Any primary site</td>
<td>Any patients in this group</td>
</tr>
<tr>
<td>Good prognosis (Seminoma)</td>
<td>Intermediate prognosis (Seminoma)</td>
<td>Poor prognosis (Seminoma)</td>
</tr>
</tbody>
</table>

Sites of extragonadal GCT:
- Mediastinum
- Retroperitoneum
- Sacrococcygeal
- Perineal

Subsequent prognosis and treatment depends on assigning patients to low and high risk stage 1 disease, and good, intermediate and poor prognosis.
<table>
<thead>
<tr>
<th>Stage</th>
<th>NSGCT (%5YS)</th>
<th>Seminoma (%5YS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Good prognosis mets</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>Intermediate prognosis mets</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>Poor prognosis mets</td>
<td>48</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Treatment**

**Radical inguinal orchidectomy**
Treatment, staging and prognostic information
Inguinal approach: theoretical reduction in lymphatic spread to scrotal wall; allows easy examination of testis; complete removal of cord lymphatic tissue (for subsequent RPLND)
Probably no value in clamping cord
CT chest, abdo and pelvis post-op
Tumour markers one week and two weeks post-op
Local recurrence after inguinal orchidectomy extremely rare; slightly higher after scrotal exploration (Leibovitch 1995; Kennedy 1986), but unlikely to affect survival given efficacy of chemotherapy

**Stage I Seminoma**
Risk of relapse 15-20% after 5 years.
32% risk with rete testis invasion & tumour > 4cm; 12% without either (Warde 2002)
Options active surveillance, post-orchidectomy RT or single-agent chemotherapy

**Surveillance:**
Avoids unnecessary Rx in 80%, but needs high compliance. Relapse amenable to radiotherapy in 70%. 20% of these patients require further chemoRx (overall half of patients required multi-agent chemotherapy). Relapse occurs within 2 years in 70%. Late relapse > 5 yrs in 7%.

**Radiotherapy:**
Traditionally dogleg from ipsilateral renal hilum to ipsilateral pelvic and local testicular nodes; 30Gy in 15 fractions over 3 weeks (T10 to L5).
Limited para-aortic field has equivalent 3-yr survival, lower morbidity and slightly higher pelvic relapse (4% vs. 3.4%) cf. dogleg (MRC testicular tumour working group; Fossa TE10 trial 1999)
Para-aortic RT: 20 Gy in 10 fractions equivalent to 30 Gy in 15 fractions at 5 years follow-up with better side-effect profile (MRC TE18; Jones 2005) Main side-effects nausea and vomiting, long term peptic ulceration and tiny increase in 2nd Ca (currently unquantified).

**Single-agent chemotherapy:**
Single agent carboplatin (single IV injection 7x GFR+25mg) not statistically different from adjuvant RT in preventing relapse. Both groups reduced relapse rate to 4-5% at 3 years. Slight trend to PA node relapse in chemotherapy arm.
Increased second cancers (2% vs. 0.5%) in radiotherapy arm (MRC TE19/EORTC 30982; Oliver 2005). Long term data required.

**RPLND:**
Relapse double that of RT when RPLND performed (Warsawski 1997). Not performed

**Stage IIA/B Seminoma**
Metastatic disease confined below diaphragm
Options depend on volume of nodal disease:

- **Low volume disease (IIA/IIB)**
  Very radiosensitive. Dogleg (p/a and ipsilateral iliac nodes) radical radiotherapy 30Gy in 15 fractions over 3 weeks; relapse rates 95% (IIA) and 89% (IIB). Overall survival 99% at 5 yrs
  Alternatively 3 cycles of BEP associated with 5 yr overall survival of 98% with no late chemo toxicity (Garcia Del Muro 2004 – abstract only)
  Trials of chemo vs. RT awaited
  
- **High volume disease (IIC – any node >5 cm)**
  Larger LN mets respond less well and damage due to RT higher.
  Relapse-free survival after RT 35%. Overall 5YS (including salvage) 77%.
  Therefore chemotherapy favoured, but commonly residual masses.
  Post-chemo masses:
  Usually necrotic material, but viable tumour may be present in up to 25% of masses > 3cm.
  < 3cm surveillance CT
  ≥ 3 cm PET scanning = 80% sensitive and 100% specific viable tumour (SEMPET study De Santis 2004). Surgery very difficult for chemotherapy-treated seminoma. Consider surgical resection if CT/PET looks favourable. Alternatively salvage RT.

**Stage I NSGCT**
Overall relapse rate 30%
Dependent on RF:

- **Lymphovascular invasion**
  T2 +
  Embryonal component
  Absence of yolk sac component
  No risk factors = 10-15% relapse rate
  Vascular invasion alone 38%
  More than one risk factor = 50%
  Low risk disease - surveillance generally recommended
  High risk disease – surveillance with chemo for relapse, primary chemotherapy, or RPLND

**No prospective trial comparing the options in high-risk disease. Overall cure rate 99% irrespective of modality.** Arguments:
Surveillance
98% patients relapse within 3 years
Avoids unnecessary treatment in 50% with high-risk disease
Requires high motivation and compliance
Recommended follow-up regime intense
Risks of radiological imaging need to be considered (figures)

Chemotherapy
Adjuvant chemotherapy BEP x2
Relapse rates from 50% to <5%
No contemporary trials of chemo vs. surveillance. Historical data suggest almost halving of mortality (2.6% to 1.4%) with chemo (Anglian GCCG; Oliver RT 2004) but inherent problems with retrospective data. However primary chemotherapy exposes 50% of patients to unnecessary chemotherapy with its attendant risks. However, no reported impact on fertility (Bohlen 1999).

RPLND
30% of stage I disease have micrometastases not identified on CT. RPLND offers a cure rate for these patients of 70%, obviating the need for chemotherapy. Follow-up also much easier (infradiaphragmatic recurrences should not occur) and radiation exposure reduced.
In experienced hands morbidity low: Retrograde ejaculation < 5%, adhesions 1%, hernia 3-5%.
However, 70% of patients have unnecessary surgery; of the remaining 30%, 9% require adjuvant treatment in the form of chemotherapy. Thus NNT approximately 5 (very high cost given that salvage chemo so effective).

Ultimately because outcomes the same, decisions should be carefully discussed with patient. For a highly motivated, fit patient keen to avoid intervention, surveillance realistic option. Alternatively chemo relatively well tolerated in a majority of patients in UK/Europe.

Stage 1S NSGCT
Persistent tumour markers despite inguinal orchidectomy
87% have retroperitoneal nodes if RPLND performed (Pizzocarro 1996)
Therefore BEP x3

Stage IIA/B NSGCT
Chemotherapy is standard in UK standard but USA favour RPLND for stage IIA/B (so-called small volume disease)
Second treatment rate irrespective of treatment is 30%
Equivalent survival rates of 90% at 5 years
Primary ChemoRx: Complete remission in 70%; surgery required for 30% with residual masses. therefore 30% get both treatments
Primary RPLND: 20% inadequate resection/ unfavourable histo and 30% relapse; therefore 50% get both treatments
**Advanced GCT**
Good prognosis: BEP x3 (every 3 weeks)
Intermediate prognosis: BEP x 4 (q 3 wks); alternatively enrol in trial of BEP vs. BEP & paclitaxel
Poor prognosis: BEP x 4; No evidence to date that high-dose chemoRx any more effective vs. standard dose. Trials ongoing (eg. EORTC 30974)

**Post-chemotherapy masses**
Seminoma – PET if >3cm; resection or salvage chemo if viable tumour
NSGCT - 25% of patients have post-chemotherapy masses:
- 40% necrosis/fibrosis
- 40% mature teratoma (TD)
- 20% residual NSGCT

~60% masses either malignant tumour or TD. TD insensitive to chemotherapy and benign growth (usually due to mucin production) can limit organ function (especially problematic in brain metastases rendered TD by chemotherapy); TD also has potential for malignant transformation. 5% risk of malignant transformation in one of the elements of TD (carcinoma, sarcoma, lymphoma/leukaemia) (Comiter 1998). Therefore complete resection necessary. Malignant transformation of TD is a very poor prognostic factor. Prognosis related to degree of stromal invasion within the resected mass rather than degree of differentiation. Contrary to common opinion, cannot definitely predict that all sites will have same histology after chemotherapy.

**Salvage chemotherapy**
**Seminoma**
Cisplatin based salvage chemoRx = 50% long-term remission
Regimens:
- PEI x4 cisplatin, etoposide, ifosfamide
- VeIP x4 Vinblastien, ifisfamide, cisplatin
- TIP Taxol, ifosfamide, cisplatin
**NSGCT**
PEI x4 = long-term remission in 15-40%
Better with: testis/retroperitoneal primary; good response to primary chemo; long remission, low markers
?Improvement response with gemcitabine/taxols and cisplatin ovarian has activity in truly platinum-refractory tumours

**Brain metastases**
At presentation - 30-40% 5YS
Recurrent disease – 2-5% 5S
CT head should be requested in patients with very high levels of BHCG at presentation or significant embryonal component
Consideration should be given to concomitant radiotherapy as results of chemo across BBB variable.
Other considerations

Radiotherapy
Major toxicities gastrointestinal (usually N&V), lethargy
PA node RT associated with long-term risk of PUD – need gastroprotection
Increased risk of second malignancy = 0.2% (2.6 fold increase). Usually solid in-field tumours (stomach, pancreas, kidney, bladder) – median onset 20 years. In addition risk of cardiovascular disease and hypertension (renal damage).
No definite evidence that radiation treatment for seminoma associated with increased risk of solid tumours occurring in or adjacent to radiation field.

Chemotherapy
Bleomycin: lung fibrosis
Etoposide: acute myloid leukaemia (increased risk 0.3%: median onset 10 yrs)
Cisplatin: ototoxicity, nephropathy, sensory neuropathy, Raynaud’s
NB. Carboplatin is much less nephrotoxic – used as an alternative to cisplatin in patients with renal impairment, but small risk of bone marrow suppression.

Each cycle of BEP
  Inpatient for 1 week (B + E+ P)
  Outpatient bleomycin for next 2 weeks
  In total 9 injections of bleomycin and 3 each of etoposide and cisplatin

Carboplatin
  Dose (mg) = (GFR+25) x 7
  Given over one hour
  Outpatient administration

Surgery for post-chemo masses
Remove all masses at every site where feasible
Very predictable response to chemo ie. if all masses fibrosis in abdomen, chest likely to be fibrosis as well. No need for resection.
Surgery 4-8 weeks after chemoRx completion. Watch out for bleomycin induced ARDS (limit by reducing inspired oxygen)
Abdomen - Removal of full lymphatic field; if necessary resect IVC/ involved kidney where possible. Chylous ascites may be problematic (Mx = paracentesis, high protein/low fat/high medium-chain TG diet + somatostatin. If fails TPN & somatostatin. If still problematic lymphangiogram and attempt surgical repair or shunt peritoneovenous shunt).

Follow-up radiation exposure

Increased risk of new malignancy with one CT = 0.2%
### Follow-up - Seminoma

#### Table 8: Follow-up in surveillance policy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4-5</th>
<th>Year 6-10</th>
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</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Abdominal CT scan</td>
<td>4 times</td>
<td>4 times</td>
<td>Twice</td>
<td>Once/year</td>
<td>If indicated</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>*</td>
<td>*</td>
<td>Twice²</td>
<td>Once/year*</td>
<td>If indicated</td>
</tr>
</tbody>
</table>

#### Table 7: Follow-up for post-orchiectomy radiotherapy or chemotherapy - stage I seminoma

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice/year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice/year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice/year</td>
</tr>
<tr>
<td>Abdominal CT scan</td>
<td>Once</td>
<td>Once</td>
<td>If indicated</td>
<td>If indicated</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Once²</td>
<td>Once²</td>
<td>Once</td>
<td>If indicated</td>
</tr>
</tbody>
</table>

#### Table 10: Follow-up of seminoma stage IIIa-IIIb after radiotherapy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
<td>Twice</td>
<td>Once/year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
<td>Twice</td>
<td>Once/year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
<td>Twice</td>
<td>Once/year</td>
</tr>
<tr>
<td>CT abdomen and pelvis*</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
</tr>
<tr>
<td>CT chest²</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
</tr>
</tbody>
</table>

#### Table 11: Follow-up of advanced NSGCT and seminoma

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>12 times</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
<td>Once/year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>12 times</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
<td>Once/year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>12 times</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
<td>Once/year</td>
</tr>
<tr>
<td>Abdominal CT²</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td>Chest CT²</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td>Brain CT²</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
</tr>
</tbody>
</table>
### Follow-up - NSCGT

**Table 5: Recommended follow-up schedule in a surveillance policy - stage I non-seminoma**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>2</th>
<th>3-5</th>
<th>6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>Monthly</td>
<td>4-6 times</td>
<td>Twice/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>9-12 times (Monthly for the first 6 months)</td>
<td>4-6 times</td>
<td>Twice/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>9-12 times (Monthly for the first 6 months)</td>
<td>4-6 times</td>
<td>Twice/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Abdominal CT scan</td>
<td>3-4 times</td>
<td>Twice</td>
<td>Once/year</td>
<td>If indicated</td>
</tr>
</tbody>
</table>

**Table 6: Recommended follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy - stage I non-seminoma**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>2</th>
<th>3-5</th>
<th>6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>6 times</td>
<td>3 times</td>
<td>Twice/year</td>
<td>Once/year*</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>6 times</td>
<td>3 times</td>
<td>Twice/year</td>
<td>Once/year*</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>6 times</td>
<td>3 times</td>
<td>Twice/year</td>
<td>Once/year*</td>
</tr>
<tr>
<td>Abdominal CT scan</td>
<td>Twice</td>
<td>Once</td>
<td>If indicated</td>
<td>If indicated</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Twice*</td>
<td>Twice*</td>
<td>Twice/year</td>
<td>Once/year</td>
</tr>
</tbody>
</table>

**Table 11: Follow-up of advanced NSGCT and seminoma**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>2</th>
<th>3-4</th>
<th>5</th>
<th>Thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>12 times</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>12 times</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>12 times</td>
<td>6 times</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
</tr>
<tr>
<td>Abdominal CT*</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td>Chest CT*</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td>Brain CT*</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
<td>As indicated</td>
</tr>
</tbody>
</table>
Appendix

Retroperitoneal Lymph Node Dissection

Landing sites

<table>
<thead>
<tr>
<th>Side</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right side</td>
<td>Aortocaval first, then pre-aortic and pre-caval</td>
</tr>
<tr>
<td>Left side</td>
<td>Para-aortic and pre-aortic</td>
</tr>
</tbody>
</table>

Very rare for left-sided tumours to have positive right sided nodes (<1%). Much more common for right-sided tumours to have left-sided nodes

Templates

Options include bilateral, modified right and modified left. Nerve sparing templates designed to preserve antegrade ejaculation. Emission is controlled by T12-L3 sympathetic outflow. Most important areas for preservation is the paravertebral sympathetic chain, post-ganglionic sympathetic fibres and particularly their confluence in the midline around the origin of the IMA to form the hypogastric plexus.

Bilateral RPLND
Thoracoabdominal and transabdominal approaches
Transabdominal

- Full midline
- Reflection of TC and omentum onto chest
- Incision along left edge of root of small bowel mesentery from DJ flexure to caecal pole
- Incision continued up ascending colon to foramen of Winslow; kocherisation of duodenum. Entire small bowel and ascending colon can
now be placed along with TC on chest wall in a bowel bag – identify and preserve SMA.

Template dissection as above:
From superior aspect of renal vein on either side, along medial margins of the ureter to iliac artery on each side. Along iliac artery to aortic bifurcation
Starts at left renal vein; division of adrenal, gonadal and lumbar arteries. Anterior 'split and roll' technique for en-bloc dissection (see below)
NB. For nerve-sparing, initial anterior split OK for IVC but not for aorta

Figure 36-11 A to G. Sequentially, this diagram shows the "split and roll" technique that allows for en bloc removal of the nodal packages. The lumbar vessels must be divided twice, first at the wall of the great vessels and again as they enter the retroperitoneal space along the vertebral bodies.
Modified templates
Typically used for primary RPLND, especially left sided, and occasionally for well-demarcated unilateral disease (must proceed to complete bilateral RPLND if frozen-section positive)

Complications (25%)
- Infection, bleeding, DVT/PE, scar, hernia
- Lymphocele
- Retrograde ejaculation/anejaculation
- Chylous ascites
- Renovascular injury/nephrectomy
- Small bowel injury/obstruction
- Death (1-3%)
**Leydig-cell tumours**
3% primary testicular tumours (most common interstitial tumour of testis)
3% bilateral
Bimodal age distribution; 20% kids 5-10 yrs, 80% adults 30-60yrs
A/w Kleinfelter’s syndrome
Yellow/brown tumour
Most small < 5cm
80% produce hormones,
  Adults - typically oestrogen or FSH in adults: 30% with gynaecomastia
  Children – typically virilisation due to production of testosterone (diff. diagnosis CAH)
Diagnosis: cytological atypia + lipofuscin + crystal of Reinke. Absent IHC for PLAP, AFP or BHCG, but stain positive for inhibin
Prognosis: 10% malignant [high mitoses, increased MIB-1, >5cm, vascular invasion, necrosis, extratesticular extension]
Treatment: Organ preserving surgery may be appropriate in patients who are confidently predicted to have non-GCT (ie. new gynaecomastia and hormonal abnormalities). All others = radical inguinal orchidectomy and follow-up staging investigations. In those with high chances of malignancy, RPLND recommended. Established mets poorly sensitive to chemoRx or RRT and survival poor.

**Sertoli-cell tumours**
1% primary testicular tumours
Most common testicular tumour in dogs!
Mean age 45 yrs
Associated with AIS & Peutz-Jeghers syndrome
Yellow/brown
Typically < 5 cm
Hormonal imbalance less common but still 30% with gynaecomastia
Negative for PLAP, AFP, BHCG, positive for inhibin and calretinin
Three subtypes:
  Classic Sertoli
  Large cell calcifying (syndromes eg. PJ, MEN 1 and 2, 44% bilateral)
  Large cell sclerosing
Overall 10% malignant. Risk factors same as for Leydig.
20% malignancy in large-cell sclerosing subtype
Treatment: Organ preserving surgery may be appropriate in patients who are confidently predicted to have non-GCT (ie. new gynaecomastia and hormonal abnormalities). All others = radical inguinal orchidectomy. In those with high chances of malignancy, RPLND recommended. Established mets poorly sensitive to chemoRx or RRT and survival poor.

**Adenomatoid tumours of epididymis**
Commonest paratesticular tumour - accounts for ~30%
Typically males in 20-30s
Usually epididymis, occasionally tunical layers
Lower pole > upper pole
Epithelial cells and fibrous stroma – often vaculoles within epithelial cells
Universally benign – never been a reported case
Rx by surgical excision (exclude even rarer cases of paratesticular mass – mesothelioma and rhabdomyosarcoma)

**Testicular epidermoid tumours**

Testicular epidermoid cyst accounts for 1-2% testicular tumours.

Radiological features: Well circumscribed hypoechoic lesion

- Hyperechoic margins
- Normal surrounding parenchyma
- “onion ring appearance”

MRI: does not enhance

**PRICE histological criteria (1969):**

1. Cyst within testicular parenchyma
2. Lumen of cyst contains keratin
3. No teratomatous elements or adnexal structures
4. Absence of CIS
5. Absence of scar in remaining testis
6. The cyst wall should contain fibrous tissue and squamous epithelium

**Treatment:**

1. Radical orchidectomy if diagnostic uncertainty

2. Organ preserving surgery if two intraoperative biopsies from the cyst show no GCT and biopsy of the rest of the parenchyma shows no GCT or CIS