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# ESSENTIAL UROLOGY FOR MEDICAL STUDENTS

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***'Build it, and they will come'***

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Dr Chabert is a urological surgeon with an interest in minimally invasive surgery and diseases of the prostate gland. His practice is located at John Flynn Hospital, St Vincent's Hospital and Lismore Base Hospital. He is also an assistant professor at Bond University.

*Assistant Professor Charles Chabert*

As a final year medical student at Bond University, it was a pleasure working with Dr Chabert in Urology, and my experiences and knowledge attained have been reflected in this book, which I hope will serve as a tool for all medical students. It contains the essential Urology facts that a student must know in a clear and concise format, so enjoy reading.

*Nishanth Krishnananthan*

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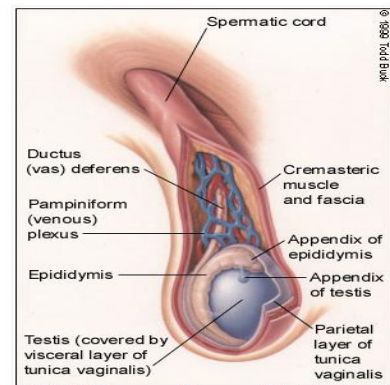
# CHAPTER 1

## Acute Scrotal Pain

Acute Scrotal Pain is the presenting symptom for a wide spectrum of surgical conditions which may present in adolescents to adults. The aim of evaluation is to identify testicular torsion due to the threat of irreversible testicular ischemia and subsequent infarction.

### Differential Diagnoses

1. **Testicular Torsion** (16.0–39.5%)<sup>1</sup>
2. **Torsion of Testicular Appendages**
3. **Epididymo-orchitis**
4. **Testicular Trauma**
5. **Testicular Neoplasm(s)**



### TESTICULAR TORSION (TT)

**IMPORTANT** → *Acute scrotal swelling in children indicates torsion of the testis until proven otherwise*<sup>2</sup>.

#### Definition:

- Twisting or rotation of the testis on the axis of the spermatic cord.
- **Surgical emergency** as it causes strangulation of the gonadal blood supply with subsequent testicular necrosis and atrophy
- Torsion can be partial or complete (vary from 180-720°)

#### Incidence:

- Neonates/young adolescents (12-18, with a peak at 14), but can occur at any age. The prevalence is 1 in 4000 males less than 25 yrs old<sup>3</sup>.

#### Types:

- Extravaginal (the whole cord and its investing layers twist, 5% of all torsions<sup>4</sup>). More commonly associated with the neonatal age group.
- Intravaginal usually occurs in older children (also referred to as the Bell Clapper Deformity).

#### Causes:

- **Bell-Clapper Deformity** (12% of all males<sup>5</sup>), a congenital abnormality in which the testicle lacks the normal attachment to the tunica vaginalis (permitting increased mobility) and rests transversely within the scrotum.
- Other: physical/sexual activity, trauma (4-8%<sup>6</sup>).

### Presentation:

#### 1. Clinical features

- Acute unilateral **severe sudden onset testicular pain**.
- Nausea and vomiting (1/3 of patients, higher in paediatric population)<sup>7</sup>
- Abdominal pain (20-30%)<sup>8</sup>
- Fever (16%)<sup>9</sup>
- Urinary frequency (4%)<sup>10</sup>

#### 2. Physical examination

- **Asymmetrically** high-riding testis on the affected side with **horizontal lie**.
- **Diffuse testicular tenderness**
- Testicular oedema + scrotal erythema
- **Ipsilateral loss of the cremasteric reflex**.
- Prehn's sign negative i.e. scrotal elevation relieves pain in epididymitis but not torsion.

#### 3. Complications: Infarction, Infertility, Infection.

### Diagnosis:

- Clinical
- Colour Doppler Ultrasound (94% sensitivity, 96% specificity.)<sup>11</sup>

### Treatment:

- **Urgent surgical de-torsion and fixation** (orchidopexy) of both testicles due to risk of contralateral torsion in the future
- A salvage rate of 90-100% is found in patients who undergo **de-torsion within 6 hours** of onset of pain - the viability rate falls to 20% and 50% after 12 hours; and 0-10% if de-torsion is delayed greater than 24 hours<sup>12</sup>.

## **TORSION OF TESTICULAR APPENDAGES (TTA)**

### Definition:

- The appendix testis (Hydatid of Morgagni), a müllerian duct remnant located at the superior pole of the testicle, is the most common appendage to undergo torsion (92%)<sup>13</sup>.

### Incidence:

- 7-14 y.o. (80%), with a mean age of 10.6<sup>14</sup>.

### Presentation:

#### 1. Clinical features:

- Acute/Subacute onset of testicular pain (less severe and more gradual in onset when compared to Testicular Torsion) → Pain at superior pole of testicle.
- Patients may endure pain for several days before seeking medical attention.
- Absence of systemic symptoms (nausea/vomiting) and urinary symptoms.

#### 2. Physical examination:

- **Localised tenderness** (upper pole of the testis)
- **Blue dot sign** → paratesticular nodule. Seen in 21% of people<sup>15</sup> (mainly light-skinned boys, or children due to their thin scrotal skin).
- Normal vertical lie

### Diagnosis:

1. Mainly clinical.
2. Testicular Ultrasound (TU)

3. Other: Colour Doppler Ultrasound (95.7% sensitivity and 48.7% specificity<sup>16</sup>)

Treatment:

- Conservative i.e. rest, analgesia and scrotal support to alleviate swelling.
  - Pain should resolve in 5-10 days with surgery reserved for patients with persistent pain<sup>17</sup>.
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## **EPIDIDYMO-ORCHITIS**

Definition:

- Acute epididymitis is the inflammation of the epididymis, and when the infection extends down to the adjacent testicle, it is referred to as acute epididymo-orchitis

Incidence:

- Bi-modal age distribution i.e. younger sexually active males or older population with BPH/LUTS (See Chapter 3)

Causes:

a.) Epididymitis:

- Prepubertal males: **E-Coli**.
- Sexually active males/males <35: **Chlamydia Trachomatis** (50-60%<sup>18</sup>), Nisseria Gonorrhoea.
- Older males/males >35: **E-Coli**

b.) Orchitis:

- Viral (most common cause) → **Mumps**. It presents mainly unilaterally (70%)<sup>19</sup> in the paediatric population. General presentation is recent mumps infection/parotitis with testicular oedema (4/5 are pre-pubertal males<sup>20</sup>).
- Bacterial infections (as above) can cause orchitis.

c.) Other causes:

- Viral (infectious mononucleosis, Coxsackie virus)
- Drugs (3-11% of people taking Amiodarone<sup>21</sup>)
- Obstruction (BPH in older males)
- Tb (immuno-compromised people)
- Vasculitic Syndromes (Sarcoidosis)
- Post surgery or catheterisation.

Presentation:

1. Clinical features (dependent on cause)

- **Acute/sub-acute onset of moderate unilateral scrotal pain** (bilateral in 5-10%<sup>22</sup>).
- Pain localizes to posterior testicle (+/- radiation to the flanks/abdomen).
- History of **frequency, urgency, dysuria, urethral discharge** (10%)<sup>23</sup>
- Nausea and/or low grade fever and chills (25% of adults, 71% of children<sup>24</sup>) – not as common as testicular torsion.
- Blood in semen.
- Painful intercourse + ejaculation
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2. Physical examination:

- Erythematous, oedematous hemi-scrotum
- Epididymis is engorged, swollen and tender
- The affected testis has a normal vertical lie

- **Cremasteric reflex is intact.**
  - **Prehn's sign is positive**
  - Scrotal oedema is present in 50% of cases<sup>25</sup>
  - Enlarged inguinal lymph nodes
3. **Complications:**
- Scrotal abscess, pyocele, testicular infarction, chronic epididymitis, infertility, cutaneous fistulisation.

**Diagnosis:**

1. Mainly Clinical
2. Full Blood Count (FBC) → Leukocytosis
3. Urine M/C/S (Pyuria) + Urethral Swab Culture
4. Colour Doppler Ultrasonography (CDU) : sensitivity of 91-100% for epididymitis +/- orchitis<sup>26</sup>

**Treatment:**

- Antibiotics i.e. Ceftriaxone + Doxycycline for Chlamydia/Gonorrhoea  
Trimethoprim-Sulfamethoxazole to cover coliforms in Pre-pubertal boys<sup>27</sup>
- Analgesics + NSAIDS
- Scrotal support + elevation + bed rest.
- Pain generally self resolving (one week)
- Surgery considered for complications.

**SUMMARY**

<b><u>Acute Scrotum</u></b>						
<b><u>Condition</u></b>	<b><u>Age</u></b>	<b><u>Cause</u></b>	<b><u>Onset</u></b>	<b><u>Tenderness</u></b>	<b><u>Cremasteric Reflex</u></b>	<b><u>Treatment</u></b>
<b>Testicular Torsion</b>	12-18	Bell-Clapper deformity	Acute	Diffuse	Negative	Surgical de-torsion
<b>TTA</b>	7-14	Structural predisposition	Acute/ Subacute	Localised (upper pole)	Positive	Bed rest + Scrotal elevation
<b>Epididymo-orchitis</b>	18-50	C.Trachomatis, E-coli, Viral	Insidious	Epididymal	Positive	Antibiotics



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## CHAPTER 2

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# Prostate Specific Antigen (PSA)

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Prostate specific antigen is a serine protease produced specifically by the prostate. It can be increased by inflammation, benign prostatic hyperplasia (BPH), or by cancer of the prostate.

### Role in Body

PSA liquefies the seminal fluid.

### PSA Test

PSA is a blood test used to detect early prostate **cancer** (increased in 25-92% of people<sup>1</sup>); however elevation of PSA is not specific for cancer; it can also be increased due to **inflammation or BPH**.

Causes for an elevated PSA include:

- BPH (increased in 30-50% of people<sup>2</sup>)
- Recent rectal examination, prostate massage, prostatitis, UTI, urinary catheterization,
- Acute urinary retention, ejaculation and acute renal failure.

Evaluation of different aspects of PSA allows improvements in the utility of the test. These include:

- Age specific value
- Median value
- Free-total ratio
- Velocity, increase the utility of the test
- PSA density

#### 1. Age- Reference values + Median values.

Age	Median PSA	Normal Range
40-49	0.7ng/ml	0-2.5ng/ml
50-59	0.9ng/ml	0-3.5ng/ml
60-69	1.4ng/ml	0-4.5ng/ml
70+		0-6.5ng/ml

#### 2. Free-Total ratio

PSA is bound to alpha 1 antichymotrypsin in plasma. When produced by malignant disease, it has a higher affinity for this protein than benign produced PSA. As a result, there is an inverse correlation between F/T ratio and prostate cancer risk.

- Risk of CAP is 55% if F/T ratio <10%
- Risk of CAP 7% if F/T ratio >25%<sup>3</sup>

### 3. Velocity.

PSA velocity is calculated over a period of 12 months with at least 3 measurements.

- A velocity of **0.75ng/ml/yr<sup>4</sup>** increases the risk of CAP.
- A velocity of **0.35ng/ml/yr** is consistent with BPH.

### Prostate Biopsy

Abnormalities of PSA and DRE are evaluated further through a Trans-Rectal Ultrasound (TRUS) biopsy. See Cancer of the Prostate (CAP) for further information.

### Pros + Cons of PSA Testing

#### Positives

- Allows early detection of CAP
- Decreased risk of CAP death.
- Decreased risk of metastasis.
- Reassurance (if negative)
- Early intervention.
- The PSA test itself is inexpensive, and there are minimal side effects.

#### Negatives

- The positive predictive value of a PSA test is only 30%, and when combined with a DRE is 38-50%<sup>5</sup>.
- The PSA test has a sensitivity of 34.9% and the specificity is 63.1%<sup>6</sup>.
- Only one in three men with a high PSA level will have cancer<sup>7</sup>.
- False positives can create anxiety for the patient and his family.
- False negative rate of 25%
- Can lead to overtreatment of indolent disease.
- Further evaluation for CAP risk involves a TRUS biopsy introducing the potential for complications such as a 1% chance of infection<sup>8</sup>.



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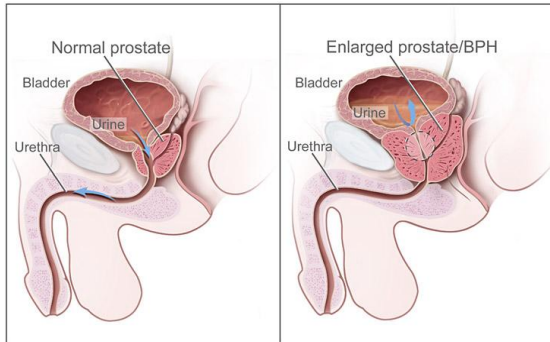
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## CHAPTER 3

### Benign prostatic hyperplasia (BPH)

BPH is the most common prostate disease in men in Australia<sup>1</sup>. It is the hyperplasia of stroma and epithelium in peri-urethral area of prostate (transition zone)<sup>2</sup>. The prevalence of



histopathologic BPH is age dependent, with initial development usually after 40 years of age<sup>3</sup>. By 60 years of age, its prevalence is greater than 50% and by age 85 is as high as 90% (incidence is proportional to age)<sup>4</sup>. The exact aetiology of BPH is unknown, although there is a possible correlation with testosterone production, impaired apoptosis, and other growth factors.<sup>5</sup>

#### Clinical Presentation

BPH causes **lower urinary tract symptoms** (LUTS). These can be broadly classified into obstructive and overactive bladder (OAB) symptoms.

Obstructive symptoms	Irritative symptoms
Hesitancy	Frequency
Weak stream	Urgency
Straining (stranguria)	Nocturia
Feeling of incomplete bladder emptying	
Dribbling (Post-micturition)	
Intermittent flow	

Objective assessment is carried out by '**The International Prostate Symptom Score**'<sup>6</sup> (IPSS) questionnaire which assesses the severity of symptoms and their effects on the patient's quality of life. (Appendix 1)

Complications secondary to BPH are:

- Urinary retention
- Renal insufficiency
- Recurrent urinary tract infections
- Macroscopic haematuria

- Bladder calculi

The presence of these complications requires to bladder outlet surgery.

### Prognosis

The prognostic features for BPH progression are:

1. PSA>1.4
2. Prostate Volume>40cc
3. Age>65
4. PVR>150mls.

Clinical assessment includes an abdominal examination and a **digital rectal examination (DRE)**. A DRE should be done to assess prostate size and consistency, to detect nodules, indurations, and asymmetry. The prostate is usually smooth, rubbery and symmetrically enlarged in patients with BPH (median sulcus remains palpable).

### Investigations

Investigating BPH includes combining History and DRE with Urinalysis, Blood tests, Imaging and occasionally a cystoscopy.

1. **DRE:** Assess prostate size, consistency and detect nodules, indurations, and asymmetry, all of which raise suspicion for malignancy.
2. **Urinalysis:** assess for the presence of blood, leukocytes, bacteria, protein, or glucose.
3. **Urine M/C/S:** assess for infection.
4. **Urine flow studies:** Evaluate max flow rate combined with post-void residual volume determination.
5. **Prostate Specific Antigen:** Refer to PSA testing in booklet.
6. **Ultrasound KUB:** useful for helping determine prostate size and screening upper tracts.
7. **Cystoscopy:** Allows bladder outlet assessment and exclusion of intra-vesicle pathology.
8. **TRUS Prostate:** may be required for the exclusion of prostate cancer in the presence of persistent elevation of PSA levels.

### Treatment

Treatment for BPH involves conservative measures, pharmacological treatments or surgical interventions depending on the severity of symptoms and degree of bother.

1. Patients with mild symptoms/minimal bother.
  - **Watchful waiting** - 40% of patients improve spontaneously.<sup>7</sup>
  - Includes lifestyle changes (e.g. evening fluid restriction, reducing consumption of mild diuretics such as caffeine and alcohol, planned voiding).
  - Herbal Therapies: Saw Palmetto<sup>8</sup>
2. Medical treatment
  - **Alpha-1-adrenergic antagonists** (e.g. tamsulosin/Flomax, Doxazosin) reduce stromal smooth muscle tone. SEs: orthostatic hypotension and dizziness.
  - **5-Alpha-reductase inhibitors** (e.g. finasteride and dutasteride) decrease the conversion of testosterone to DHT (dihydrotestosterone). It is the second line

medical treatment and has greater efficacy when combined with Alpha-1 blockers.<sup>9</sup>  
SEs: Impotence, decreased libido.

### 3 Surgical Treatments

- → **Green Light Laser Prostatectomy**: Minimally invasive option with lower incidence of complications when compared to TURP.
- **TURP** (Transurethral resection of the prostate).
- **Open Prostatectomy**



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## APPENDIX

(1) C.Chabert, Laparoscopic Urology Australia

### Assessing Prostate Symptoms

«patient\_full\_name»

By filling in this form, you will help your doctor to assess if you have an enlarged prostate, and how badly it is affecting you. An enlarged prostate is a common and benign (non-cancerous) condition that often occurs in older men. (The results *do not* help to diagnose prostate cancer.)

#### 1. The International Prostate Symptom Score (IPSS)

Please answer the following questions about your urinary symptoms.  
Write your score for each question at the end of each row.

Over the past month, how often have you...	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
1. ...had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. ...had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. ...stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. ...found it difficult to postpone urination?	0	1	2	3	4	5	
5. ...had a weak urinary stream?	0	1	2	3	4	5	
6. ...had to push or strain to begin urination?	0	1	2	3	4	5	
<b>And finally..</b>							
	None	Once	Twice	3 times	4 times	5 times or more	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
<b>Add up your total score and write it in the box.</b>							<b>Total</b>

#### Supplementary question - Quality of life due to urinary symptoms.

If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that? (Please tick which best describes how you would feel.)

- 0. Delighted
- 1. Pleased
- 2. Mostly satisfied
- 3. Mixed - about equally satisfied and dissatisfied
- 4. Mostly dissatisfied
- 5. Unhappy
- 6. Terrible

# CHAPTER 4

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## Localised Prostate Cancer

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Prostate Cancer is the most common cancer in Australian men and is the second most common cause of cancer deaths in men<sup>1</sup>. Almost all prostate cancers arise from the secretory glandular cells in the prostate. 95% are **Adenocarcinomas**<sup>2</sup>. Spread may be local (seminal vesicles, bladder, rectum) via lymphatics or haematogenously (sclerotic bone lesions).

Of prostate cancer cases, 70% arise in the peripheral zone, 15-20% arises in the central zone, and 10-15% arises in the transitional zone.<sup>3</sup>

### Risk factors

1. **Age**: One in 11 Australian men will develop Cancer of the Prostate (CAP) by age 70.<sup>4</sup>
2. **Race**: African-American men are 1.6 times more likely than white men to develop prostate cancer.<sup>5</sup> (Young African American men have testosterone levels that are 15% higher<sup>6</sup>)
3. Diet: **High fat diet** (Low vegetable intake, omega-6 fatty acids is a positive stimulant)
4. **Family History**:
  - Men with BRCA2 gene have almost four times the risk of developing prostate cancer<sup>7</sup>. BRCA1 mutation causes a lesser increase in risk.<sup>8</sup>
  - Family history of breast or ovarian cancer.
  - Men more likely to present 6-7 years earlier.<sup>9</sup>
  - A man with a first-degree relative who has been diagnosed with prostate cancer (brother or father) has at least twice the risk<sup>10</sup>. If two or more first-line relatives are affected, the risk increases 5- to 11-fold.<sup>11</sup>
  - Early age of onset in a family member also increases the risk.<sup>12</sup>
5. Industrial exposure: Exposure to **herbicides and pesticides**. Certain occupations such as farming and work in industrial chemical industry place patient at higher risk.
6. **Demographics**: Men in rural and regional Australia have a 21% higher prostate cancer mortality rate than men in capital cities.<sup>13</sup>
7. **Sexually Transmitted Infections**: 1.4 times greater chance of men developing the disease as compared to the general population.<sup>14</sup>
8. **Hormone levels**: Serum concentrations of androgens and insulin-like growth factor-I (IGF-I) have been studied as possible risk factors for prostate cancer.<sup>15</sup>

### Clinical Presentation

1. Localised → **Asymptomatic**. Detected by an increase in PSA and abnormal DRE.
2. Locally advanced → **Obstructive lower urinary tract symptoms** such as difficulty voiding and increased frequency.
3. Metastatic → **Bone pain** from metastases (most commonly vertebral bodies, pelvis, and long bones in legs), **weight loss**, loss of appetite, fatigue, malaise, oedema (due to

obstruction of venous and lymphatic tributaries by nodal metastasis) and uremic symptoms can occur from ureteric obstruction.

## Assessment

1. **DRE** (Digital Rectal Examination): An **irregular firm prostate or nodule** can be palpable. (Possible **indurations, asymmetry, enlargement**). When cancer is palpable, 60-70% has spread beyond the prostate.<sup>16</sup>
3. **PSA** (Prostate Specific Antigen): There are 4 aspects to PSA – age-specific reference value, median, free-total percentage, and velocity to evaluate risk of person having prostate cancer. (Refer to PSA topic in booklet). PSA may also be elevated due to inflammation or BPH.

The Urological Society of Australia and NZ recommend a PSA test at age 40 years.

4. **TRUS** (Transrectal ultrasonography) + **Biopsy** - main utility of ultrasonography is to guide prostate biopsy, and provide an assessment of gland size. Prostate biopsy is the gold standard for prostate cancer diagnosis – It is peripherally weighted with a minimum of 12 cores. CAP grading is by way of the Gleason grading system (See Appendix 1).

Complications of TRUS Biopsy:

- 1% chance of infection.
- If patients are on anti-platelet or anticoagulant therapy, it is discontinued 7 to 10 days prior to biopsy to minimize the risk of bleeding complications.<sup>18</sup>
- Haematospermia (51 percent), haematuria (23 percent longer than three days), fever (3.5 percent) and rectal bleeding (1.3 percent).<sup>19</sup>

## Staging + Grade

**CT Scan intermediate and high risk prostate cancer**

**Technetium (Tc 99m) bone scan** are reserved for intermediate to high risk patients.

**Staging** of CAP is done via the Tumour, nodes, metastasis (**TNM**) classification (Appendix 2).

**Grading** of CAP is done via **The Gleason Score** (Appendix 1)

The Stage, Grade and the PSA value are combined to give a pre-treatment risk stratification score i.e. low, intermediate, high risk according to the **D'Amico Risk Stratification Score** (See Appendix 3).

## Treatment

Treatment for prostate cancer depends on the staging, the grade and the histological subtype.

Conservative measures:

1. **Watchful Waiting**: Aim is to delay therapy until demonstrable signs of progression (development of LUTS or PSA concern). Ideal for elderly patients with less than 10 years life expectancy. Androgen deprivation (ADT) is commenced upon disease progression.
2. **Active surveillance**: Deferred local therapy until disease progression or patient anxiety lead to definitive local therapy. Aims to avoid potential complications of local therapy without compromising cancer control. Suitable for patients with greater than 10 years life expectancy with low volume low risk disease.<sup>20</sup> Requires compliance with regular PSA and periodic repeat TRUS biopsy.

3. **Radical Prostatectomy:** definitive therapy – done either laproscopically, open, perineally or with robotics. Excellent treatment option with established outcomes. Ideal for men with at least 10 years life expectancy with low and intermediate risk disease. Nerve-sparing surgery in selected cases facilitates recovery of spontaneous erectile function. Urinary incontinence is now a rare long term complication. Radical Prostatectomy is the only treatment option with a demonstrable survival advantage.<sup>21</sup>
4. **Radiation therapy:** Can be delivered as external beam (EBRT) with or without a HDR (high dose rate brachytherapy) boost. Is suitable for more elderly patients or those with significant medical co-morbidities with 10 years life expectancy with intermediate or high risk disease. Is combined with neo-adjuvant ADT of 3-6 months prior to treatment.<sup>22</sup>
5. **LDR Brachytherapy:** This involves the placement of radioactive iodine seeds into the prostate. Suitable for low and intermediate risk cancers with gland sizes less than 50cc with minimal urinary symptoms. Limited data for patients less than 55 years of age.

### Prognosis + Follow up

For men who have undergone radical prostatectomy, radiation therapy, or both, follow-up care is important to detect recurrence of cancer.

1. PSA levels should be checked every three months for one year, every six months for the second year, and annually after that. Biochemical free survival is defined as a PSA less than 0.2 ng/ml after radical prostatectomy.<sup>23</sup>



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## **APPENDIX**

### 1. The Gleason Score (www.prostate.org.au)

Gleason Score	Aggressiveness of prostate cancer
2-4	Low
5-6	Moderate
7	Intermediate
8-10	High

### 2. TNM Classification (J.Moul, A.Armstrong, B.Hollenbeck, J.Lattanzi, D.Bradley, M.Hussain, *Prostate Cancer*, Chapter 17, Cancer Management Handbook 11th Edition, April 2009)

<b>TABLE I: TNM staging system of prostate cancer</b>	
<b>Localized disease</b>	
T1a	Tumor incidental histologic finding in ≤ 5% of resected tissue; not palpable
T1b	Tumor incidental histologic finding in > 5% of resected tissue
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA level)
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
<b>Local extension</b>	
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Bladder invasion, fixed to pelvic side wall, or invasion of adjacent structures
<b>Metastatic disease</b>	
N1	Positive regional lymph nodes
M1	Distant metastasis
PSA = prostate-specific antigen Adapted from Greene FI, Page DL, Fleming ID, et al (eds): <i>AJCC Cancer Staging Manual</i> , 6th ed. New York, Springer-Verlag, 2002.	

3. D'Amico Risk Stratification Score (J.Moul et al. *Prostate Cancer* 09)

**TABLE 2: D'Amico et al risk stratification for clinically localized prostate cancer**

Low risk	Diagnostic PSA < 10.0 ng/mL <i>and</i> highest biopsy Gleason score $\leq$ 6 <i>and</i> clinical stage T1c or T2a
Intermediate risk	Diagnostic PSA > 10 but < 20 ng/mL <i>or</i> highest biopsy Gleason score = 7 <i>or</i> clinical stage T2b
High risk	Diagnostic PSA > 20 ng/mL <i>or</i> highest biopsy Gleason score $\leq$ 8 <i>or</i> clinical stage T2c/T3

PSA = prostate-specific antigen

## CHAPTER 5

# Macroscopic Haematuria

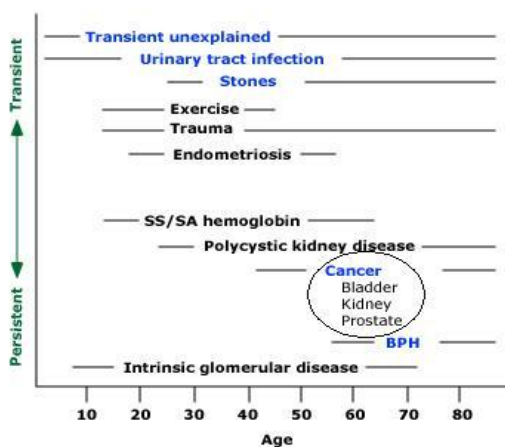
### Definition

Macroscopic Haematuria is the evidence of visible blood in the urine, and can present as pink, red, brownish-red, or tea-coloured urine. Haematuria can be of glomerular or non-glomerular origin.

- Brown-coloured urine, RBC casts, and dysmorphic (small deformed, misshapen, sometimes fragmented) RBCs and proteinuria are suggestive of glomerular haematuria.
- Reddish or pink urine, passage of blood clots, and eumorphic (normal sized, biconcavely shaped) erythrocytes are suggestive of a non-glomerular bleeding site.

### Causes

- **Cancer:** transitional cell cancer of the bladder (TCC), kidney (adenocarcinoma), Transitional Cell Cancer, Prostate cancer
- **Stones:** kidney, ureteric, bladder
- **Infection:** bacterial, mycobacterial (TB), parasitic (schistosomiasis), infective urethritis



- **Inflammation:** cystitis, interstitial cystitis
  - **Trauma:** kidney, bladder, urethra (e.g. traumatic catheterization), pelvic fracture causing urethral rupture
  - **Renal cystic disease** (e.g. medullary sponge kidney)
  - **Other urological causes:** BPH (rarely causes isolated haematuria)
  - **Nephrological causes** of haematuria tend to occur in children or young adults and include, commonly → IgA nephropathy, post-infectious glomerulonephritis.
- **Pseudohaematuria:** menses, endometriosis, dyes (beetroot, rhodamine B in drinks, candy and juices).

### History

Evaluation of Macroscopic Haematuria involves a history which is both urologic specific and general. The main set of questions are related to

1. **Pain** i.e. Nature, Location, Radiation, Onset, Duration, Aggravating/Relieving factors, Severity.  
e.g. unilateral flank pain → suggests calculus.

PAINLESS Macroscopic HEMATURIA → TRANSITIONAL CELL CARCINOMA.

2. **Lower Urinary Tract Symptoms:** Both obstructive and irritative symptoms. Ask the patient if he/she has seen **clots in the blood** (suggests an extraglomerular cause of haematuria).
3. **Systemic features:** Fever or Suprapubic pain (in acute onset) → Suggestive of UTI.

General History should include:

4. A **positive family history** of renal disease.
5. Any history of a **bleeding disorder**
6. **Travel or residences** in certain areas (Schistosoma haematobium, or tuberculosis).
7. **Presence of risk factors for TCC**

### Investigations

Evaluation of Macroscopic Haematuria includes physical examination, urinalysis, blood tests, imaging and a possible biopsy dependent on the cause.

1. **Physical Examination:** Assess for haemodynamic compromise
2. **Urine dipstick** → sensitivity in identifying haematuria is >90%<sup>1</sup>.
3. **Urine M/C/S**
4. **Urine cytology** → most sensitive for carcinoma of the bladder (90%)
5. **Blood Tests** → FBC, EUC, Coagulation studies –
6. **CT KUB Triple Phase** → Non-Contrast allows assessment of stones, nephrogram phase allows assessment of Renal Cell Carcinoma, and delayed phase allows assessment of urothelial abnormalities.
7. **Cystoscopy:** allows direct inspection of the lower tract

### Management

1. Acute → Resuscitation with fluids, blood transfusion if necessary.
2. Definitive → Depending on the underlying cause.



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## CHAPTER 6

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# Nephrolithiasis

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### Types

#### 1. **Calcium Stones** (most common – 80-85%<sup>1</sup>)

- Composed of either Calcium oxalate or phosphate
- Radio-dense (i.e. visible of abdominal radiograph)
- Occurs secondary to hypercalcaemia (more common) and hyperoxaluria.
- Causes of Hypercalcaemia →
  1. Hypercalcaemia.
  2. Excessive dietary intake of calcium.
  3. Excessive resorption of calcium e.g. from prolonged immobilization.
  4. Medical conditions: Primary hyperparathyroidism, Sarcoidosis, Malignancy, Vitamin D excess
- Causes of Hyperoxaluria →
  1. Excessive dietary intake of food high in oxalate e.g. rhubarb, spinach, and tea.
  2. Dietary restriction of calcium, leading to compensatory increase of absorption of oxalate.
  3. Medical conditions: Small bowel disease, Crohn's disease, Pyridoxine deficiency.

#### 2. **Uric Acid Stones** (2<sup>nd</sup> most common – 10%<sup>2</sup>)

- Radiolucent (cannot be seen on abdominal radiograph)
- Causes → Associated with Hyperuricemia.
- Also seen in patients who have had Gastric or intestinal bypass surgery, as patients with ileostomies are at higher risk of dehydration and from the loss of bicarbonate from gastrointestinal secretions leading to the production of acidic urine.

#### 3. **Struvite Stones** (Staghorn stones – 5-10%<sup>3</sup>)

- Radio-dense
- Causes → Often seen in patients with recurrent UTI's due to urease producing organisms (such as Proteus and Klebsiella).
- The presence of urease-producing bacteria leads to the hydrolysis of urea into ammonium and hydroxyl ions, The resulting increase in ammonium and phosphate concentrations combined with the alkalotic urine (pH >7.2) is necessary for struvite and carbonate apatite crystallization.

#### 4. **Cystine stones** (rare – 1%<sup>4</sup>)

- Cystinuria (autosomal recessive)

### Risk Factors

1. **Diet:** Low fluid intake (most common and preventable risk factor), Diet with high levels of animal protein or sugars.
2. **Family History** - the risk of stones is increased 3 fold.
3. **Male Gender** (3:1)<sup>5</sup>
4. **Medical Conditions** that predispose to stone formation

E.g. Gout, Primary hyperparathyroidism, Crohn's disease, Diabetes mellitus, Renal tubular acidosis, Primary renal disease such as Polycystic kidneys and Medullary sponge kidney.

5. **Medications** e.g. Loop diuretics, Antacids, glucocorticoids → all promote calcium formation. Chemotherapeutic drugs, thiazides, salicylates → promote uric acid stone formation.

6. **UTIs.**

### Clinical Presentation

1. Patients can be **Asymptomatic**.
2. **Colicky pain** – typically begins in the flank and radiates inferiorly and anteriorly towards the groin. It can vary from mild discomfort to severe excruciating pain. (The pain generated by renal colic is primarily caused by the dilation, stretching, and spasm caused by the acute ureteral obstruction).
3. **Haematuria** (90% of cases): Can be microscopic or macroscopic.
4. Other: **Nausea and Vomiting**.

### Diagnosis

1. **History + physical examination.**

2. **Urinalysis (Urine M/C/S)**

- Evidence of Haematuria.
- Evidence of Pyuria or bacteruria if UTI present.
- Examine urinary sediment for crystals.
- Determine urinary pH – alkaline urine may suggest struvite stones, acidic urine may suggest uric acid stones.

3. **Serum chemistry (FBC and EUC)** – Base line renal function and also calcium, uric acid, magnesium and phosphate levels.

Imaging includes:

4. **Plain abdominal radiograph KUB** – to accompany all CT scans to discern radiolucent from radio-opaque calculi.

5. **Helical CT KUB without contrast** – most sensitive test for detecting stones.

### Treatment

Treatment of Stones is best divided into acute, definitive and preventative measures.

Acute → 1<sup>st</sup> line management of a patient with stones is:

1. **Pain management** i.e. adequate analgesia i.e. IV morphine or NSAIDS.
2. **Fluid hydration**
3. **Antibiotics** if infection is present.
4. **Decompression of Renal unit** via stent or nephrostomy if: failure of conservative measures or evidence of sepsis.

### Definitive

Depends on:

- Stone factors i.e. size, location and composition.
- Patient factors
- Hospital resources

The options of surgery are:

1. ***Ureterscopy/pyeloscopy and laser lithotripsy***
2. ***Extracorporeal shock wave lithotripsy (ESWL)***
3. ***Percutaneous nephrolithotomy.***

Prevention →

1. ***Dietary measures***

- High fluid intake (keep urine volume at 2-3L/day).
- Decreased animal protein intake in patients with hyperuricosuria (uric acid stones) via red meat.
- Decreased Dairy intake (calcium)
- Decreased green vegetables.
- Decreased Coke intake (contains oxalate)

2. ***Pharmacological measures***

- Refer to ***renal physician*** if recurrent stones for 24hr urinalysis +/- pharmacological measures such as thiazide diuretics (reduce urinary calcium), Allopurinol (patients with high uric acid levels in the blood), Penicillamine (cystine stones).

The Risk of Recurrence of stones is 10% per year.



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## CHAPTER 7

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# Urothelial Cancer

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Bladder cancer is the most common malignancy involving the urinary system. It is the fourth most common cancer in men and the tenth most common cancer in women in Australia.<sup>1</sup>

### Types

1. **Transitional Cell Carcinoma** (TCC) (80-90%)<sup>2</sup> – can occur anywhere from the kidney to bladder.
2. **Squamous Cell Carcinoma** (5%)<sup>3</sup> – Is more prevalent in Middle East.
3. **Adenocarcinoma** (1-2%)<sup>4</sup>

Nearly all Adenocarcinomas and Squamous Cell Carcinomas are invasive.

### Epidemiology

1. **Race:** Bladder cancer is more common in whites than in blacks; however, blacks have a worse prognosis than whites.
2. **Age:** The median age at diagnosis is 69 years for men and 71 years for women, and the incidence increases with age<sup>5</sup>. (80% between 50-80 years old)
3. **Gender:** The male-to-female ratio is 3:1<sup>6</sup>. Women generally have a worse prognosis than men
4. **Location** – TCC highest in Western Europe and North America<sup>7</sup>.

### Risk Factors

1. **Smoking** - 2/3 of men and 30% of women<sup>8</sup>.
2. Industrial carcinogens - **Aromatic amines** in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles
3. **Cyclophosphamide** - used as long term treatment for other cancer(s) may cause hemorrhagic cystitis and increase the risk of TCC.
4. **Radiation**
5. Analgesics – **Phenacetin**.
6. Chronic irritation (cystitis, chronic catheterization, bladder stones) (associated with SCC)
7. **Family History** – chromosome 17 (high grade), chromosome 9 (low grade)
8. Spinal cord injuries - Patients with spinal cord injuries who have long-term indwelling catheters have a 16- to 20-fold increased risk of developing SCC of the bladder.
9. Schistosoma haematobium – associated with SCC, seen in underdeveloped nations.
10. Coffee, Tea, Artificial sweeteners – Weak correlation
11. Arsenic in water or long-term consumption of chlorinated water (increased risk in men)

## Clinical Presentation

1. **Painless Macroscopic Haematuria** → Presentation of 80-90% of people<sup>9</sup>. Haematuria is typically intermittent, gross and present throughout micturition.
2. **Voiding Symptoms** → 20-30% of people<sup>10</sup> present with irritative voiding symptoms (e.g., daytime and/or nocturnal frequency, urgency, dysuria, or urge incontinence). Obstructive symptoms are less common.
3. **Constitutional symptoms** → Symptoms such as fatigue, weight loss, anorexia, and failure to thrive are usually signs of advanced or metastatic disease and denote a poor prognosis. Patients with advanced disease can present with pelvic or bony pain, lower-extremity oedema from iliac vessel compression, or flank pain from ureteral obstruction. Approximately 5% of patients present with metastatic disease, which commonly involves the lymph nodes, lung, liver, bone, and central nervous system.

## Staging + Grade

Staging of Bladder Cancer is via the Tumour, nodes, metastasis (**TNM**) classification (Appendix 1).

## Investigations

Evaluation of Bladder Cancer involves:

1. History and Physical Examination
2. Full Blood Count – may reveal anaemia due to chronic blood loss.
3. **Urinalysis and urine culture** – to rule out infection.
4. **Urine cytology** – to detect malignant cells (has a 95% accuracy rate for diagnosing high-grade carcinoma and CIS)<sup>11</sup>.
5. **Triple-Phase CT Scan KUB** – for staging.
6. **Cystoscopy and biopsy** – Gold Standard + definitive diagnosis.

Other: Chest X ray — an initial staging tool

Bone Scan - assess the presence of bone metastasis in patients with invasive or locally advanced tumours

## Treatment

Treatment of the patient depends upon staging, the grade and the histological subtype of the tumour.

1. **Non-muscle-invasive disease (Ta, T1, CIS)**  
Trans-urethral resection of bladder tumour/TURBT +/- intravesical immunotherapy: Bacillus Calmette-Guérin (BCG) + Mitomycin C.
2. **Muscle-invasive disease (T2 and greater)**  
Radical Cystectomy + Pelvic lymphadenectomy (with urinary diversion via a conduit, Indiana pouch or neo-bladder) + Neo-Adjuvant Chemotherapy (Cisplatin combination).

## Prognosis

Prognosis ranges from a 5 year survival rate of 80-90% for lesions not involving bladder muscle to 5% for those presenting with metastases.<sup>12</sup>

The high rate of disease recurrence and progression in non-muscle invasive bladder cancer underscores the need for careful follow-up studies.



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## APPENDIX

(1) M.Hurwitz et al., *Urothelial and Kidney Cancers* 09.

**TABLE I: TNM staging of urothelial tract cancers**

**Primary tumor (T)**

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary tumor
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
pT2a	Tumor invades superficial muscle (inner half)
pT2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

**Regional lymph nodes (N)**

Nx	Regional lymph nodes cannot be assessed
N0	No regional node involvement
N1	Metastasis in a single node, $\leq 2$ cm in greatest dimension
N2	Metastasis in a single node, $> 2$ cm but $\leq 5$ cm in greatest dimension; or multiple lymph nodes, none $> 5$ cm in greatest dimension
N3	Metastasis in a lymph node, $> 5$ cm in greatest dimension

**Distant metastasis (M)**

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

**Stage grouping**

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-N3	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): *AJCC Cancer Staging Manual*, 6th ed. New York, Springer-Verlag, 2002.

## CHAPTER 8

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# Renal Cell Carcinoma

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Renal cell carcinomas (RCC) make up 80-85% of all primary renal neoplasms in adults<sup>1</sup> and are commonly seen in adults over 40, with the mean age of presentation being 55 years old<sup>2</sup> (the peak incidence occurs between 60 and 70 years of age<sup>3</sup>). Australians have a 1 in 74 risk of developing RCC during their lifetime<sup>4</sup>.

### Types<sup>5</sup>

6. Clear cell carcinoma (80-90%)
7. Papillary (10-15%)
8. Chromophobe (4-5%)
9. Collecting Duct (1-2%)
10. Unclassified

### Risk Factors

1. **Cigarette Smoking**: doubles the risk of renal cell carcinoma and contributes to as many as one third of all cases.<sup>6</sup>
2. **Gender**: Males 1.6:1
3. **Obesity**
4. **Hypertension**
5. **Exposure to heavy metals**: Increased in workers exposed to asbestos, cadmium, petroleum products, dry-cleaning solvents, as well as those who work in the iron and steel industries.
6. **Analgesics (high use)**: Phenacetin, Aspirin.
7. **Acquired Cystic disease**: Acquired cystic disease develops in a large percentage of chronic dialysis patients (approximately 35 to 50 percent), approximately 6 percent of whom eventually develop RCC.
8. **Chronic dialysis**
9. Adult Polycystic Kidney Disease.
10. **Race**: More common in Northern European ancestry (Scandinavians) and North Americans.
11. **Genetic**: include von-Hippel Lindau (VHL) syndrome and Birt-Hogg-Dube syndrome etc.
12. Childhood Chemotherapy.
13. **Previous radiation therapy**: Renal cell carcinoma caused by radiation occurs in less than 1% of cases of RCC.

### Clinical Presentation

1. **Asymptomatic** - Many renal masses remain asymptomatic and non-palpable until late in the natural course of the disease. More than 50% of RCCs are detected

incidentally using non-invasive imaging to evaluate a variety of non-specific symptom complexes.<sup>7</sup>

2. The Classic Triad (Robson's) → **flank pain** (40%), **haematuria** gross or microscopic (40%), and a **palpable abdominal renal mass**. (25%)<sup>8</sup>  
Occurs in only 6-10% of patients<sup>9</sup> and when present, it strongly suggests locally advanced disease.
3. **Paraneoplastic syndrome** (30% of people)<sup>10</sup> → Weight loss, Fever, Night sweats, Malaise, Anorexia, Hypertension, Hypercalcemia, Varicocele (2% - majority left sided)<sup>11</sup>, Amyloidosis (3-5%)<sup>12</sup>, Abnormal liver function, Polycythemia (5%)<sup>13</sup>, erythrocytosis.
4. **Metastatic disease** (25-30% of people)<sup>14</sup> → Anaemia (29-88%)<sup>15</sup>, bone pain, persistent cough. Organs involved include: Lung (75%), Soft tissues (36%), Bone (20%), Liver (18%), Cutaneous sites (8%), Central nervous system (8%).<sup>16</sup>

## Investigations

Assessment of RCC involves:

1. **Medical History** looking at presenting symptoms and **Physical Examination** looking for palpable abdominal mass, palpable cervical lymphadenopathy, non-reducing varicocele, and bilateral lower extremity oedema which suggests venous involvement.
2. **Laboratory Investigations** include:
  - Full Blood Count → Haemoglobin, Calcium, ESR.
  - EUC
  - Liver function tests (ALP for metastasis)
3. **Urinalysis + Urine M/C/S**
4. Radiological investigations
  - **Triple-Phase CT with contrast** (Best evaluation test) → assesses primary tumour extension with extra renal spread and provides information on venous involvement, enlargement of locoregional lymph nodes, and condition of adrenal glands and the liver. Chest CT → accurate for chest staging if involvement.<sup>17</sup>
  - **MRI** → to delineate extent of caval thrombus, and is reserved primarily for patients with locally advanced malignancy or allergy to intravenous contrast.<sup>18</sup>

Further evaluation in the presence of metastasis involves a bone scan and brain CT.

## Treatment

Treatment of RCC depends on the tumour stage (see 'Classification' below) and involves either conservative, surgical or immunotherapy measures.

Around 40% of tumours smaller than 1cm are found to be benign<sup>19</sup>. For this reason, conservative management with regular monitoring ("watchful waiting") is the most appropriate treatment option for these patients.

For patients with a resectable stage I, II, or III tumour, surgery is the best possible option.

1. **Nephron-sparing surgery** → For patients with a solitary tumour of <4 cm maximum diameter. Partial nephrectomy which can be performed either laparoscopically or open.
2. **Laparoscopic radical nephrectomy** → for >T1b tumours and possible T3a tumours. 5% have inferior vena cava involvement, Lymph nodes involved in 10-25% patients.<sup>20</sup>
3. **Tumour nephrectomy + immunotherapy + radiotherapy** → for metastatic RCCs.

1<sup>st</sup> line immunotherapy for metastatic RCCs is Sunitinib/Bevacizumab + IFN-alpha for low-intermediate risk patients and Temsirolimus for high risk patients<sup>21</sup>.

### Classification

Classification of RCC involves the Tumour Node Metastases **(TNM) Stage Classification System** (Appendix 1) or the Robson System (Appendix 2).

### Prognosis

**Prognosis** of RCC depends on anatomical, histological, clinical and molecular factors. The 5 year survival rate is 60-70% with tumours confined to the renal parenchyma, 15-35% with lymph node involvement, and only approximately 5% in those who have distant metastases<sup>22</sup>.

The **follow up** of a patient with RCC depends on their risk stratification group i.e. risk of tumour recurrence or systemic tumour progression.



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## APPENDIX

### 1. TNM Classification (M.Hurwitz et al., *Urothelial and Kidney Cancers 09*)

<b>TABLE 3: TNM staging of renal cell carcinoma</b>			
<b>Primary tumor (T)</b>			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidneys		
	T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidneys	
	T1b	Tumor > 4 cm but not > 7 cm in greatest dimension, limited to the kidneys	
T2	Tumor > 7 cm in greatest dimension, limited to the kidneys		
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia		
	T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia	
	T3b	Tumor grossly extends into renal vein or its segmental (muscle-containing) branches or vena cava below the diaphragm	
	T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava	
T4	Tumor invades beyond Gerota's fascia		
<b>Regional lymph nodes (N)</b>			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single regional lymph node		
N2	Metastasis in more than one regional lymph node		
<b>Distant metastasis (M)</b>			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
<b>Stage grouping</b>			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3a	N0-N1	M0
	T3b	N0-N1	M0
Stage IV	T3c	N0-N1	M0
	T4	N0-N1	M0
	Any T	N2	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

### 2. Robson Staging (J.Richie et al., *Renal Cell Carcinoma, 03*)

Stage	
I	Tumor is confined within the kidney capsule
II	Tumor invades through the renal capsule but is confined within Gerota fascia
III	Tumor has invaded the regional lymph nodes, ipsilateral renal vein, or inferior vena cava
IV	Documentation of distant metastases or involvement of adjacent organs other than the ipsilateral adrenal gland

Adapted from Flocks RH and Kadesky MC<sup>47</sup> and Robson CJ et al.<sup>51</sup>

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## CHAPTER 9

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# Testicular Cancer

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Testicular cancer is the second most common form of cancer in men aged 18-39, and is diagnosed in around 680 Australians each year. It has a very good cure rate (95%) if found and treated early<sup>1</sup>. There has been a steady increase (2% each year) in the number of men diagnosed with testicular cancer in Australia since 1982<sup>2</sup>.

### Risk factors

1. History of **cryptorchidism/undescended testis**: risk of developing germ cell tumour is increased 4-8 fold<sup>3</sup>. About 1 in 10 men with testicular cancer have had undescended testes in childhood<sup>4</sup>.
2. **Infertility**.
3. **Familial history** of testicular tumours among first-grade relatives (brothers, father): 1-3% of affected men have a family member with the disease<sup>6</sup>. Genetic markers specifically i(12p) have been found in germ cell tumours<sup>7</sup>.
4. **Contralateral testicular tumour**.
5. **Down Syndrome** or Klinefelter's syndrome.
6. **HIV infection** (particularly seminomas)<sup>8</sup>.
7. Hypotrophic (< 12 ml) or atrophic testicle.

### Types

Approximately 95% of testicular tumours are **Germ Cell Tumors**<sup>9</sup>.

These are divided into two types: **pure seminoma** (peak incidence in 4<sup>th</sup> decade of life<sup>10</sup>) and **non-seminomatous germ cell tumours** (NSGCT) (peak incidence is in the 3<sup>rd</sup> decade of life<sup>11</sup>). Mixed germ cell tumours (i.e. those containing two or more germ cell types) constitute approximately one third of testicular cancer<sup>12</sup>, while yolk cell tumours are the most common testicular tumour in infants and young children<sup>13</sup>.

Determining the cell type is important for estimating the risk of metastasis and the response to chemotherapy. (See Appendix 1 for the World Health Organisation (WHO) classification of Testicular Cancer).

### Clinical Presentation

#### Localised testicular cancer:

**Painless, unilateral intrascrotal mass** (painful or tender in 10%<sup>14</sup>, bilateral in 1-2%<sup>15</sup>) is the most common finding.

Other symptoms include:

- A dull ache or 'heaviness' in the lower abdomen, perianal area or scrotum. (33%)<sup>16</sup>
- Gynaecomastia (7%)<sup>17</sup> (more common in non-seminomatous tumours)
- Back and flank pain (11%)<sup>18</sup>

#### Metastasis (10% of patients)<sup>10</sup>

- A neck mass (supraclavicular adenopathy)

- Chest pain, cough or dyspnoea (pulmonary metastasis)
- Anorexia, nausea, vomiting, or gastrointestinal haemorrhage (retroduodenal metastasis)
- Lumbar back pain (bulky retroperitoneal disease involving the psoas muscle or nerve roots)
- Bone pain or CNS involvement are rare.

Physical examination:

Any solid, firm mass within the testis should be considered testicular cancer until proven otherwise<sup>19</sup>. This involves a **bimanual examination of the scrotal contents, starting with the normal contralateral testis**. Any firm, hard, or fixed area within the substance of the tunica albuginea should be considered suspicious. There can also be a spread to the epididymis or spermatic cord (10-15%)<sup>20</sup>.

The examination should also include signs such as supraclavicular nodes, bone tenderness, and gynaecomastia that would suggest metastasis, and an evaluation of the abdomen for lymphadenopathy and hepatomegaly<sup>21</sup>.

Evaluation

The diagnostic evaluation of men with suspected testicular cancer includes scrotal ultrasound followed by radiographic testing, blood chemistry workup (with serum tumour markers) and radical inguinal orchidectomy.

1. **Scrotal ultrasound** (100% sensitivity<sup>22</sup>): When evaluating a palpable mass by ultrasound, the primary goal is localization of the mass (intratesticular versus extratesticular) and further characterization of the lesion (cystic or solid). With rare exception, solid intratesticular masses should be considered malignant<sup>23</sup>. Ultrasounds are unreliable for staging purposes.
2. **Radiographic testing:** CT scan of the abdomen and pelvis and a Chest X/R are ordered as part of the initial staging workup. Regional metastases of testicular cancer first appear in the retroperitoneal lymph nodes, and can be visualised by CT (44% false negative rate)<sup>24</sup>
3. **Serum tumour markers:** In addition to a complete blood chemistry workup (e.g. full blood count), three serum tumour markers should be ordered i.e. **AFP** (alpha fetoprotein, produced by yolk sac cells), **Beta-hCG** (expression of trophoblasts) and **LDH** (lactate dehydrogenase, a marker for tissue destruction).
  - Globally, there is an increase in these markers in 51% of cases of testicular cancer<sup>25</sup>.
  - Serum levels of AFP and/or beta-hCG are elevated in approximately 80% to 85% of patients with NSGCTs, even when nonmetastatic<sup>26</sup>.
  - Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease<sup>27</sup>.
  - LDH is a less sensitive marker, and may be elevated in 80% of patients with advanced testicular cancer<sup>28</sup>.
  - It is important to remember that elevation of serum beta-hCG and AFP levels, alone or in combination, are not sufficiently sensitive or specific to establish the diagnosis of testicular cancer in the absence of histological confirmation. They are used for determining diagnosis, staging, and prognosis and for following response to therapy<sup>29</sup>.

#### 4. Inguinal exploration and orchidectomy

Radical inguinal orchidectomy is the definitive procedure to permit histological evaluation of the primary tumour and provide local tumour control<sup>30</sup>. Thus, every patient with suspected testicular mass or abnormal ultrasound findings must undergo inguinal exploration, with orchidectomy performed if a tumour is found. For patients with a mass post-chemotherapy, retroperitoneal lymph node dissection (RPLND) is performed. This procedure is the gold standard for identifying nodal micro-metastases and provides accurate pathologic staging of the retroperitoneal disease<sup>31</sup>. Both the number and size of involved retroperitoneal lymph nodes have prognostic importance.

#### Staging

Staging for testicular cancer is done via the tumour, nodes, metastasis (TNM) classification as defined by the American Joint Committee on Cancer (AJCC) (See Appendix 2) and aids in risk classification.

#### Treatment

95% of testicular cancers are curable<sup>32</sup>. Initial therapy is selected according to IGCCCG (International Germ Cell Cancer Collaborative Group) risk stratification (good, intermediate, or poor risk) (See Appendix 3) and histological subtype (seminoma versus non-seminoma).

Stage 1 seminoma patients are treated either by adjuvant radiotherapy to the para-aortic nodes or alternatively one dose of carboplatin therapy. NSGCT is treated with adjuvant chemotherapy (PEB - Cisplatin, Etoposide, and Bleomycin) or nerve-sparing RPLND<sup>33</sup>. Surveillance as an option for treatment is reserved for the low risk/low compliance patient.

The primary treatment of choice for advanced disease is three or four cycles of PEB combination chemotherapy (cycles dependent on prognosis).

#### Prognosis

The median time for recurrence is 7 months, and 90% of patients who experience recurrence do so within 2 years<sup>34</sup>. Hence, an intensive schedule of follow-up and imaging is required for the first 2 years, with timing of surveillance and associated tests varied depending on the type and outcome of testicular cancer found.



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### 1. WHO histological classification of testis tumours

<b>Germ cell tumours</b>		Sex cord/gonadal stromal tumour:	
Intratubular germ cell neoplasia, unclassified	9054/2 <sup>1</sup>	Incompletely differentiated	8591/1
Other types		Sex cord/gonadal stromal tumours, mixed forms	8592/1
		Malignant sex cord/gonadal stromal tumours	8590/3
<b>Tumours of one histological type (pure forms)</b>		Tumours containing both germ cell and sex cord/gonadal stromal elements	
<b>Seminoma</b>	9061/3	Gonadoblastoma	9073/1
Seminoma with syncytiotrophoblastic cells		Germ cell-sex cord/gonadal stromal tumour, unclassified	
Spermatocytic seminoma	9063/3		
Spermatocytic seminoma with sarcoma		<b>Miscellaneous tumours of the testis</b>	
Embryonal carcinoma	9070/3	Carcinoid tumour	8240/3
Yolk sac tumour	9071/3	Tumours of ovarian epithelial types	
Trophoblastic tumours		Serous tumour of borderline malignancy	8442/1
Choriocarcinoma	9100/3	Serous carcinoma	8441/3
Trophoblastic neoplasms other than choriocarcinoma		Well differentiated endometrioid carcinoma	8380/3
Monophasic choriocarcinoma		Mucinous cystadenoma	8470/0
Placental site trophoblastic tumour	9104/1	Mucinous cystadenocarcinoma	8470/3
Teratoma	9080/3	Brenner tumour	9000/0
Dermoid cyst	9084/0	Nephroblastoma	8960/3
Monodermal teratoma		Paraganglioma	8580/1
Teratoma with somatic type malignancies	9084/3		
		<b>Haematopoietic tumours</b>	
<b>Tumours of more than one histological type (mixed forms)</b>		<b>Tumours of collecting ducts and rete</b>	
Mixed embryonal carcinoma and teratoma	9081/3	Adenoma	8140/0
Mixed teratoma and seminoma	9085/3	Carcinoma	8140/3
Choriocarcinoma and teratoma/embryonal carcinoma	9101/3		
Others		<b>Tumours of paratesticular structures</b>	
<b>Sex cord/gonadal stromal tumours</b>		Adenomatoid tumour	9054/0
<b>Pure forms</b>		Malignant mesothelioma	9050/3
Leydig cell tumour	8650/1	Benign mesothelioma	
Malignant Leydig cell tumour	8650/3	Well differentiated papillary mesothelioma	9052/0
Sertoli cell tumour	8640/1	Cystic mesothelioma	9055/0
Sertoli cell tumour lipid rich variant	8641/0	Adenocarcinoma of the epididymis	8140/3
Sclerosing Sertoli cell tumour		Papillary cystadenoma of the epididymis	8450/0
Large cell calcifying Sertoli cell tumour	8642/1	Melanotic neuroectodermal tumour	9363/0
Malignant Sertoli cell tumour	8640/3	Desmoplastic small round cell tumour	8806/3
Granulosa cell tumour	8620/1		
Adult type granulosa cell tumour	8620/1	<b>Mesenchymal tumours of the spermatic cord and testicular adnexae</b>	
Juvenile type granulosa cell tumour	8622/1	<b>Secondary tumours of the testis</b>	
Tumours of the thecoma/fibroma group			
Thecoma	8600/0		
Fibroma	8810/0		

<sup>1</sup> Morphology code of the International Classification of Diseases for Oncology (ICD-O) (808) and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade III intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

## 2. TNM classification of germ cell tumours of the testis

TNM classification <sup>1,2</sup>						
<b>T – Primary tumour</b> Except for pT1s and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchiectomy; see pT. In other circumstances, TX is used if no radical orchiectomy has been performed						
<b>N – Regional lymph nodes</b> NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension N2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension N3 Metastasis with a lymph node mass more than 5 cm in greatest dimension		pNX Regional lymph nodes cannot be assessed pN0 No regional lymph node metastasis pN1 Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension pN2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour pN3 Metastasis with a lymph node mass more than 5 cm in greatest dimension				
<b>M – Distant metastasis</b> MX Distant metastasis cannot be assessed M0 No distant metastasis M1 Distant metastasis M1a Non regional lymph node(s) or lung M1b Other sites		<b>S – Serum tumour markers</b> SX Serum marker studies not available or not performed S0 Serum marker study levels within normal limits				
<b>pTNM pathological classification</b> pT – Primary tumour pTX Primary tumour cannot be assessed (See T–primary tumour, above) pT0 No evidence of primary tumour (e.g. histologic scar in testis) pT1s Intratubular germ cell neoplasia (carcinoma in situ) pT1 Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis pT2 Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis pT3 Tumour invades spermatic cord with or without vascular/lymphatic invasion pT4 Tumour invades scrotum with or without vascular/lymphatic invasion		<b>LDH</b> S1 <1.5 x N S2 1.5–10 x N S3 >10 x N N indicates the upper limit of normal for the LDH assay				
		<b>hCG (mIU/ml)</b> and <5,000 or 5,000–50,000 or >50,000				
		<b>AFP (ng/ml)</b> and <1,000 or 1,000–10,000 or >10,000				
		<b>Stage grouping</b>				
		Stage 0	pT1s	N0	M0	S0, SX
		Stage I	pT1–4	N0	M0	SX
		Stage IA	pT1	N0	M0	S0
		Stage IB	pT2	N0	M0	S0
			pT3	N0	M0	S0
			pT4	N0	M0	S0
		Stage IS	Any pT/TX	N0	M0	S1–3
		Stage II	Any pT/TX	N1–3	M0	SX
		Stage IIA	Any pT/TX	N1	M0	S0
			Any pT/TX	N1	M0	S1
		Stage IIB	Any pT/TX	N2	M0	S0
			Any pT/TX	N2	M0	S1
		Stage IIC	Any pT/TX	N3	M0	S0
			Any pT/TX	N3	M0	S1
		Stage III	Any pT/TX	Any N	M1, M1a	SX
		Stage IIIA	Any pT/TX	Any N	M1, M1a	S0
			Any pT/TX	Any N	M1, M1a	S1
		Stage IIIB	Any pT/TX	N1–3	M0	S2
			Any pT/TX	Any N	M1, M1a	S2
		Stage IIIC	Any pT/TX	N1–3	M0	S3
			Any pT/TX	Any N	M1, M1a	S3
			Any pT/TX	Any N	M1b	Any S

<sup>1</sup> (944,2662).  
<sup>2</sup> A help desk for specific questions about the TNM classification is available at <http://tnm.uicc.org>.

## 3. IGCCCG Risk Stratification

Classification	Nonseminoma	Seminoma
Good risk	Gonadal or retroperitoneal primary tumor No nonpulmonary visceral metastases Good tumor markers (AFP <1,000 µg/l and hCG <5,000 IU/l and LDH <1.5 × N*)	Any primary site No nonpulmonary visceral metastases Normal AFP, any hCG, and any LDH
Intermediate risk	Gonadal or retroperitoneal primary tumor No nonpulmonary visceral metastases Intermediate tumor markers (AFP 1,000–10,000 µg/l or hCG 5,000–50,000 IU/l or LDH 1.5–10 × N*)	Any primary site Nonpulmonary visceral metastases Normal AFP, any hCG, and any LDH
Poor risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Poor tumor markers (AFP >10,000 µg/l or hCG >50,000 IU/l or LDH >10 × N*)	NA

\*N indicates the upper limit of normal for the LDH assay. Abbreviations: AFP, α fetoprotein; GCT, germ cell tumor; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; NA, not applicable.