Objectives

- Have an awareness of the various **congenital anomalies** of the male genitourinary tract e.g. cryptorchidism
- Describe the pathology of **tumours** of the bladder, penis, testis and prostate gland
- Understand common conditions causing **obstruction** in the genitourinary tract e.g. benign prostatic hyperplasia
- Appreciate the clinical consequences of obstruction of the lower urinary tract.

Outline

I. Ureters

a. **Congenital anomalies:** *Ureteropelvic junction obstruction*
b. **Tumour and tumour-like lesions:** *Urothelial carcinoma*
c. **Obstructive lesions:** *Intrinsic vs Extrinsic causes*

II. Urinary bladder

a. **Congenital anomalies:** *Vesicoureteral reflux, Diverticula, Bladder exstrophy, Urachal anomalies*
b. **Inflammation ('cystitis'):** *Infectious vs Non-infectious*
c. **Obstruction**
d. **Metaplastic lesions:** *Cystitis cystica et glandularis, Squamous metaplasia, Nephrogenic adenoma*
e. **Neoplasms:** *Urothelium neoplasms, Other epithelial neoplasms, Mesenchymal tumours, Secondary tumours*

III. Urethra

IV. Penis

a. **Congenital anomalies:** *Hypospadias / epispadias, Phimosis*
b. **Inflammation:** *Specific vs Non-specific infections*
c. **Tumours:** *Condyloma acuminatum, Bowenoid papulosis, Peyronie disease, Penile Intraepithelial Neoplasia (PeIN), Invasive squamous cell carcinoma*

V. Testis and Epididymis

a. **Congenital anomalies:** *Cryptorchidism*
b. **Regressive changes:** *Testicular atrophy*
c. **Epididymitis and Orchitis:** *Infectious, Granulomatous (autoimmune) orchitis*
d. **Vascular disorders:** *Torsion*
e. **Spermatic cord and Paratesticular tumours:** *Spermatic cord lipoma, Adenomatoid tumour, Rhabdomyosarcoma, Liposarcoma*
f. **Testicular tumours:** *Germ cell tumours, Sex cord-stromal tumour, Gonadoblastoma, Testicular lymphoma*
g. **Miscellaneous lesions:** *Hydrocele, spermatocele, varicocele*

VI. Prostate gland

a. **Basic anatomy and Histology**
b. **Inflammation (prostatitis):** *Bacterial, Abacterial, Granulomatous prostatitis*
c. **Benign prostatic (nodular) hyperplasia**
d. **Neoplasms – Adenocarcinoma:** *Acinar, Ductal*
e. **Neoplasms - Miscellaneous tumours:** *Small cell carcinoma, Urothelial carcinoma, Mesenchymal tumours*

References

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Moch H, Humphrey PA, Ulbright TM, Reuter VE (Eds): *WHO Classification of Tumours of the Urinary Systema and Male Genital Organs* (4th edition). IARC: Lyon 2016

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. URETERS

Congenital anomalies: usually have little clinical significance apart from some that can cause urinary obstruction e.g. **ureteropelvic junction (UPJ) obstruction**, the most common cause of hydronephrosis in infants and children.

Tumours and tumour-like lesions: Primary tumours are rare. Benign tumours are usually mesenchymal, while malignant tumours are usually **urothelial carcinomas**, similar to and often occurring concurrently with those arising in the renal pelvis, calyces and bladders.

Obstructive lesions: can be intrinsic or extrinsic. Complications include hydroureter, hydronephrosis and pyelonephritis, leading to renal parenchymal damage. Unilateral ureteric obstruction usually results from proximal causes, while bilateral obstruction arises from distal causes (e.g. prostate hyperplasia)

Intrinsic causes	
Calculi	Usually <5 mm in size, from kidneys. Impact at foci of ureteric narrowing i.e. UPJ, where ureters cross iliac vessels, and where they enter bladder
Strictures	Congenital or acquired
Tumours	Usually urothelial carcinomas
Blood clots	May form from massive haematuria from renal calculi, tumours or papillary necrosis
Neurogenic	Interruption of the neural pathways to the bladder
Extrinsic causes	
Pregnancy	Pressure on ureters at the pelvic brim from enlarging uterine fundus
Periureteral inflammation	Salpingitis, peritonitis, sclerosing retroperitoneal fibrosis (a fibrotic proliferative inflammatory process which may be related to IgG4-related disease, drugs, inflammatory conditions or idiopathic)
Endometriosis	Can be associated with scarring in the pelvis
Tumours	Cancers of the rectum, bladder, female gynaecological tract etc.

II. URINARY BLADDER

Congenital anomalies: variously associated with risk of infection or neoplasia

- **Vesicoureteral reflux**: most common and serious anomaly – predisposes to ascending pyelonephritis and loss of renal function
- **Congenital vesicouterine fistulae**: abnormal connection between bladder and vagina/rectum/uterus
- **Diverticula**: pouch-like invaginations of the bladder wall. **Congenital** diverticula may be due to focal failure of development of the normal musculature, or urinary tract obstruction during fetal development. **Acquired** diverticula are most often associated with urinary outflow obstruction due to prostatic hyperplasia. Usually small and asymptomatic, but can predispose to infection or calculi formation due to stasis. Rarely, carcinoma can arise in bladder diverticula
- **Exstrophy of the bladder**: developmental failure in the anterior wall of the abdomen and bladder, resulting in direct communication of the bladder with the abdominal surface. The exposed bladder mucosa can undergo colonic glandular metaplasia with increased risk of adenocarcinoma, and be subject to chronic infection that spreads to upper urinary tract

- **Urachal anomalies**: The urachal canal that connects the fetal bladder with the allantois is not obliterated at birth but instead remains fully or partially patent, forming a fistulous tract between the bladder and umbilicus, or a urachal cyst which is at increased risk for neoplastic transformation (usually adenocarcinoma)

Inflammation ('cystitis'): can be **infectious** or **non-infectious**

Infectious cystitis can occur with various organisms, most commonly bacterial (*Escherichia coli, Proteus* etc.; gas-forming *Clostridium* can cause emphysematous cystitis), but also viral (e.g. adenovirus, BK virus), mycobacterial (almost always due to renal tuberculosis) or fungal (*Candida, Cryptococcus*) especially in immunocompromised patients. Schistosomiasis (*Schistosoma haematobium*) is an important cause in certain African and Middle Eastern countries

- **Risk factors**: F>M (due to shorter urethra), bladder calculi, urinary obstruction, diabetes mellitus, instrumentation and immune deficiency
- **Clinical features**: Characterised by a triad of (1) Urinary frequency, (2) Lower abdominal /suprapubic pain and (3) Dysuria (pain/burning sensation on urination). Can be complicated by bacterial pyelonephritis (due to retrograde spread of microorganisms)
- **Morphology**: **Acute cystitis** – mucosal hyperemia and neutrophilic infiltrate. **Chronic cystitis** – mononuclear inflammation. **Follicular cystitis** – lymphoid follicles within the bladder mucosa and wall. **Malakoplakia** - a distinctive chronic inflammatory reaction apparently due to acquired defects in phagocyte function, arising in chronic bacterial infection (usually E.coli) and usually immunosuppressed individuals. Grossly, soft yellow mucosal plaques are seen, which are composed of aggregates of large foamy macrophages with laminated mineralized concretions (Michaelis-Gutmann bodies) formed from deposition of calcium in enlarged lysosomes

Non-infectious cystitis include iatrogenic causes (e.g. systemic chemotherapy causing **haemorrhagic cystitis**, pelvic irradiation causing **radiation cystitis**) or inflammatory (e.g. **eosinophilic cystitis** as a manifestation of a systemic allergic disorder, **polypoid cystitis** due to irritation of the bladder mucosa e.g. from instrumentation like indwelling catheters). **Interstitial cystitis** (chronic pelvic pain syndrome) is a disorder of unknown aetiology that occurs mostly in women characterized by intermittent, often severe, suprapubic pain, urinary frequency, urgency, haematuria and dysuria of more than 6 weeks duration, in the absence of infection or other causes. Cystoscopy shows mucosal fissures and punctate haemorrhages, while microscopic features are non-specific although mast cells are often increased in the submucosa. Treatment is empiric; some cases can be associated with chronic mucosal ulcers (Hunner ulcers)

Obstruction

Bladder outlet obstruction is important as it can eventually damage the kidneys. **Causes**: Usually due to an enlarged prostate (from benign prostatic hyperplasia) in males, or cystocele in females. Other causes include congenital or inflammatory urethral strictures, inflammatory fibrosis and contraction of the bladder, tumours within the bladder or in adjacent organs invading the bladder neck, mechanical

obstruction by foreign bodies or calculi, or neurogenic bladder due to injury of nerves controlling bladder contraction. **Gross**: smooth muscle hypertrophy causing bladder wall thickening and subsequently trabeculation with diverticula. In some cases, bladder can be extremely dilated with thinning of the bladder wall and absent trabeculation

Metaplastic lesions

- **Cystitis glandularis and cystitis cystica**: Nests of urothelium (von Brunn nests) grow downwards into the lamina propria and undergo metaplastic or cystic changes, including intestinal metaplasia. Extensive multifocal intestinal metaplasia is a precursor to adenocarcinoma
- **Squamous metaplasia**: Urothelium is replaced by nonkeratinizing or keratinizing squamous epithelium as a response to chronic injury. Extensive multifocal keratinizing squamous metaplasia is a precursor to dysplastic lesions and squamous cell carcinoma (e.g. in bladder schistosomiasis)
- **Nephrogenic adenoma**: tubular proliferation with focal replacement of overlying urothelium by cuboidal epithelium. Mimic of malignancy

Neoplasms: majority are epithelial, rarely mesenchymal

Urothelium neoplasms: 90% of all bladder tumours (can also be seen in other sites lined by urothelium). Spectrum includes benign lesions (papilloma, inverted papilloma), papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive papillary urothelial carcinomas, carcinoma in-situ and invasive urothelial carcinoma. 70-80% of urothelial neoplasms are non-muscle invasive

- **Two distinct precursor lesions** to invasive urothelial carcinoma:
    - **Noninvasive papillary urothelial carcinoma, low grade** or **high grade.** Low grade lesions may recur and only infrequently invade. High grade lesions have a higher risk of progression to muscle invasive bladder cancer
    - **Flat noninvasive urothelial carcinoma in situ (CIS)**: considered high grade. If untreated, majority (50-75%) of CIS progress to invasive cancer
- **Risk factors**:
    - Cigarette smoking (most important, increases risk 3-7x)
    - Industrial / occupational exposure to aryl amines (e.g. 2-naphthylamine)
    - *Schistosoma haematobium* infections in endemic areas: the ova deposited in the bladder wall incite a chronic inflammatory response that induces metaplasia, dysplasia and possible neoplasia (usually squamous)
    - Long term use of analgesics, exposure to cyclophosphamide and irradiation
- **Pathogenesis**: Environmental carcinogens have an important role, resulting in a high burden of somatic mutations in bladder cancers. There are 2 relatively distinct molecular pathways of tumour progression:
    - **Non-muscle invasive papillary cancers** often have gain-of-function alterations that increase signaling through growth factor receptor pathways (e.g. *FGFR3* amplifications, *RAS* activating mutation). Frequently recur; only 20% progress to **muscle-invasive cancer**

    - **Muscle-invasive cancers** mostly develop by progression from **CIS**: *TP53* and *RB* mutations occur early in the development of CIS.

  Non-muscle invasive bladder cancers have a high tendency to recur (up to 70%) and are at risk for progression to a higher grade or stage. The risk of recurrence and progression is related to several variables, including tumour size, stage, grade, multifocality, prior recurrence and presence of CIS in the surrounding mucosa. Most recurrences appear away from the original lesion; they can be clonally related, possibly arising from shedding and implantation of cells from the original tumour, or clonally distinct
- **Clinical features**: M:F = 3:1, 50-80 yo. Most commonly presents with painless haematuria +/- dysuria, frequency and urgency. **Prognosis**: stage, particularly the depth of invasion into bladder wall, is the most important prognostic factor (major decrease in survival is associated with invasion of the muscularis propria/detrusor muscle). Stage also determines **treatment** modality – **muscle-invasion** is an indication for radical cystectomy/cystoprostatectomy or radiation therapy with neoadjuvant / adjuvant chemotherapy. Metastatic tumours respond poorly to chemotherapy. Non-muscle invasive small localized low grade tumours can be treated with transurethral resection (TUR), while larger high grade multifocal or recurrent tumours are treated with intravesical instillation of an attenuated strain of *Mycobacterium bovis* (BCG) which elicits a local inflammatory reaction that destroys the tumour. Cystectomy may be indicated in cases refractory to BCG and other intravesical therapies, CIS extending into areas where instilled BCG cannot reach e.g. prostatic urethra, or extensive large multifocal lesions that cannot be cleared by TUR. Because of the risk of recurrence and progression, patients with non-muscle invasive urothelial neoplasms require lifelong surveillance and follow up (cystoscopy, urine cytology and biopsies)
- **Gross**: Papillary, nodular or flat red/granular lesions, often multifocal.
- **Microscopy**: Papillomas can be exophytic or inverted, and comprise normal-looking cytologically bland urothelium. PUNLMP looks like papilloma, but with a thicker urothelium covering. Low grade papillary urothelial carcinoma maintains an orderly architectural appearance with low grade cytologic atypia, while high-grade papillary urothelial carcinomas show both architectural and cytologic atypia. CIS is defined by the presence of cytologically malignant cells within a flat urothelium, either full-thickness or scattered malignant cells in a pagetoid manner. Invasive urothelial carcinoma can show squamous or glandular differentiation as well as other histologic variants e.g. nested, micropapillary that may have prognostic implications

Other epithelial neoplasms

- **Squamous cell carcinoma:** Uncommon unless in countries where urinary schistosomiasis is endemic. Pure squamous cell carcinoma arises from atypical keratinizing mucosa and is nearly always associated with chronic bladder irritation and infection
- **Adenocarcinoma**: rare; histologically identical to adenocarcinomas arising in gastrointestinal tract. May arise from urachal remnants or association with intestinal metaplasia
- **Small cell carcinoma**: uncommon; often seen in association with urothelial, squamous or adenocarcinoma carcinoma of the bladder

Mesenchymal tumours

- **Benign tumours**: Most commonly leiomyoma
- **Sarcomas**: Rare; more commonly seen is sarcomatoid carcinoma. Embryonal rhabdomyosarcoma is the most common bladder sarcoma in infancy or childhood; Leiomyosarcoma is the most common bladder sarcoma in adults

Secondary tumours: usually due to direct extension from adjacent organs; metastatic spread is rare

III. URETHRA

Mostly affected by **inflammation**; Infectious causes include gonococcal vs non-gonococcal urethritis, which is often accompanied by cystitis (women) or prostatis (men). Non-infectious urethritis includes reactive arthritis (clinical triad of arthritis, conjunctivitis and urethritis). Urethral caruncle is an inflammatory lesion that presents as a small red painful mass at the external urethral meatus, usually in older females. **Urethral neoplasms** are similar to those occurring in the bladder (proximal urethra) or HPV-related / squamous cell carcinoma (distal urethra)

IV. PENIS

Congenital anomalies

- **Hypospadias and Epispadias**: malformation of the urethral groove and canal creating an abnormal opening either on the ventral surface of the penis (hypospadias) or dorsal surface(epispadias). May be associated with failure of testicular descent and urinary tract malformations. Even when isolated, the abnormal opening may cause urinary tact obstruction, increased risk of ascending infection or sterility
- **Phimosis**: when the orifice of the prepuce is too small to permit its normal retraction, which may be due to anomalous development but more frequently is due to scarring of the preputial ring due to repeated infection. Causes accumulation of secretions and detritus under the prepuce, increasing risk of secondary infections and penile carcinoma

Inflammation: include a variety of specific (e.g. syphilis, gonorrhoea) and non-specific infections (balanoposthitis). Balanoposthitis refers to infection of the glands and prepuce, commonly caused by a variety of organisms including *Candida*, anaerobic bacteria etc. usually due to poor local hygiene in uncircumscised males. Common cause of phimosis

Tumours: uncommon. Mostly benign genital warts and squamous cell carcinoma

Condyloma acuminatum

- Benign sexually transmitted wart caused by human papillomavirus (HPV) (mainly low-risk serotypes HPV 6 and 11) that may occur on the mucocutaneous surface of the external genitalia in both males and females. Penile lesions usually occur in the coronal sulcus and inner surface of the prepuce

- Grossly, appear as single or multiple sessile or pedunculated red papillary excrescences. Histologically, appear as branching papillary fibrous core covered by acanthotic thickened squamous epithelium frequently displaying perinuclear cytoplasmic vacuolization (koilocytosis) characteristic of HPV infection

Bowenoid papulosis

- HPV16 related, seen in sexually active adults. Grossly appears similar to genital wart, but histologically mimics warty (Bowenoid) PeIN. However, these lesions usually regress spontaneously and almost never develop into invasive carcinoma

Peyronie disease

- Not a true tumour but likely a reactive lesion characterized by hard penile plaques comprising collagen deposition in the connective tissue between the corpus cavernosa and tunica albuginea, resulting in penile curvature towards the side of the lesion and pain during intercourse

Penile Intraepithelial Neoplasia (PeIN)

- Refers to squamous epithelial lesions with varying degrees of atypia (including carcinoma in-situ), still confined to the epithelial layer by an intact basement membrane
- Can be classified in 2 groups with general good correlation with the associated invasive carcinoma:
    1. **HPV-related PeIN**: includes **basaloid (undifferentiated) PeIN** , **warty (Bowenoid) PeIN** and **warty-basaloid PeIN**. Warty-basaloid PeIN is usually seen on the glans of younger patients. Associated with warty or basaloid invasive carcinoma (HPV-related variants of invasive carcinoma). Basaloid PeIN shows full-thickness replacement of the squamous epithelium by immature small basophilic cells, while warty PeIN shows a papillomatous surface with squamous maturation
    2. **Non-HPV-related PeIN**: refers to **differentiated (simplex) PeIN**. Usually seen on the foreskin of older patients, associated with balanitis xerotica obliterans (BXO). The most common precursor lesion of penile invasive carcinomas, particularly the keratinizing and well-differentiated variants. Shows a degree of squamous maturation albeit abnormal

Invasive squamous cell carcinoma

- **Risk factors**: Poor genital hygiene, uncircumcised, low socioeconomic status, high-risk HPV infection, cigarette smoking, chronic inflammatory conditions (e.g. BXO aka lichen sclerosis et atrophicus)
- **Pathogenesis**: 30-50% of penile cancer are **HPV-related**. High-risk HPV plays a similar role as in cervical cancer, encoding E6 and E7 proteins that inactivate the p53 and RB tumour suppressor proteins, leading to genomic instability and increased proliferation, respectively. E6 protein also stimulates telomerase expression, leading to cellular immortalization. For **non-HPV-related** penile cancers, there are two subgroups – those with *TP53* mutation, and others with high chromosomal instability

- **Clinical features**: 40-70 males, most commonly involving the glans, followed by foreskin, coronal sulcus and shaft. Usually slow growing, not painful until ulcerated / infected. **Prognosis**: depends on tumour stage at diagnosis and histologic subtype. Metastases to inguinal lymph nodes may occur early, but widespread dissemination usually only occurs if lesion is advanced
- **Gross**: Irregular fungating masses, flat indurated lesions or large papillary tumours
- **Microscopy**: **Squamous cell carcinoma, usual type**, is the most common **non-HPV-related** penile squamous cell carcinoma; it shows various degrees of squamous differentiation and keratinization. Other histologic subtypes include **verrucous carcinoma** (an extremely differentiated papillomatous keratinising carcinoma with a broad based pushing tumour-stroma interface; can recur but usually does not metastasize). **Basaloid squamous carcinoma** is a **HPV-related** penile squamous cell carcinoma histologic subtype characterized by a downward proliferation of basal-like basophilic cells, often with central necrosis; aggressive with frequent metastases.

V. TESTIS AND EPIDIDYMIS

Epididymis is usually affected by inflammatory diseases, while testis is affected by tumours

Congenital anomalies: extremely rare apart from cryptorchidism

Cryptorchidism

- Complete or partial failure of the intra-abdominal testes to descend into the scrotal sac
- **Pathogenesis**:
    - Normal testicular descent occurs in 2 phases – (1) **Transabdominal phase**, controlled by Mullerian-inhibiting substance. Testis comes to lie within the lower abdomen / pelvic brim; (2) **Inguinoscrotal phase**, androgen dependent. Testis descends through the inguinal canal into the scrotal sac
    - In cryptorchidism, arrest may occur anywhere along the pathway of descent, most commonly in the inguinal canal. Although testicular descent is controlled by hormonal factors, a well-defined hormonal disorder is rarely found
- **Clinical features**: ~1% of 1 year old boys; usually unilateral and isolated anomaly, but may be accompanied by other malformations e.g. hypospadias. Asymptomatic, usually discovered when scrotal sac is found to be empty by patient, parent or doctor. **Complications**: Associated with testicular dysfunction (sterility), inguinal hernia and increased risk of testicular cancer (including in the contralateral normally descended testis). **Treatment**: Majority usually descend spontaneously into the scrotum in the 1st year; if not, surgical correction by orchidopexy
- **Gross**: small and firm testis
- **Microscopy**: basement membrane thickening of the spermatic tubules with loss of spermatogonia

Regressive changes: Testicular atrophy may result from various conditions, including atherosclerotic narrowing of the blood supply in old age, end-stage inflammatory orchitis, cryptorchidism, cirrhosis, prolonged administration of antiandrogens, genetic conditions e.g. Klinefelter syndrome

Epididymitis and Orchitis: some may arise in epididymis first before involving testis (e.g. tuberculosis, gonorrhea), while others involve testis first (e.g. syphilis)

- Commonly due to infections in the urinary tract that reach the epididymis and testis through the vas deferens or lymphatics of the spermatic cord
- Uncommon in children; usually associated with a congenital genitourinary abnormality and infection with gram-negative rods. In young sexually active men (<35yo), mostly *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. In older men, mostly urinary tract pathogens e.g. *E.coli* and *Pseudomonas*
- Infection usually starts in the interstitium and subsequently the spermatic tubules, which may result in abscess formation and followed by fibrous scarring that may cause sterility. Leydig cells are usually not destroyed, hence androgen production is relatively unaffected
- **Granulomatous (autoimmune) orchitis** usually presents in middle age as a tender testicular mass of sudden onset, sometimes with fever, but can also mimic a painless testicular tumour. Cause is unknown (idiopathic). Microscopically, granulomas are restricted to spermatic tubules unlike mycobacterial infection, whereby the granulomatous inflammation is associated with caseous necrosis and often involves the epididymis

Vascular disorders - Torsion

- Twisting of the spermatic cord cuts off the testicular venous drainage while the thick-walled arteries remain patent, leading to vascular congestion and potentially testicular haemorrhagic infarction – urologic emergency! Manual untwisting within 6 hours of onset can avoid orchiectomy
- Presents as sudden onset of testicular pain. Can be seen in **neonates** (either in utero or shortly after birth; no associated anatomic defect) or **adolescents/adults** (often due to a bilateral anatomic defect (bell-clapper abnormality) that leads to increased mobility of the testes; contralateral orchiopexy should be done to prevent recurrence in the unaffected testis)

Spermatic cord and paratesticular tumours

- Benign tumours include spermatic cord lipoma and adenomatoid tumour (mesothelial origin, usually near the upper pole of the epididymis)
- Malignant tumours include rhabdomyosarcoma (in children) and liposarcomas (in adults)

Testicular tumours: most are germ cell tumours (GCT) (95%) or sex-cord stromal tumours

Germ cell tumours: (i) derived from Germ Cell Neoplasia In Situ (GCNIS) (90%) (ii) unrelated to GCNIS

- **Pathogenesis:** Contribution from both environmental and genetic factors: GCT are associated with testicular dysgenesis syndrome including cryptorchidism (proposed to be increased by in utero exposure to pesticides and nonsteroidal estrogens) as well as several genetic foci linked to familial GCT risk e.g. genes encoding the ligand for KIT and BAK
    - The cell of origin of GCTs derived from GCNIS is thought to be a primordial germ cell with an acquired defect in differentiation, which encounters growth stimulating events e.g. *KIT*

activating mutations , resulting in proliferation and development of germ cell neoplasia in situ (a precursor lesion). GCNIS is thought to arise in utero and stay dormant until puberty, when hormonal influences may stimulate germ cell growth. These cells retain expression of transcription factors important in maintenance of pluripotent stem cells (OCT3/4 and NANOG), and are at high risk of progression to GCT (70% of individuals with GCNIS develop invasion within 7 years of diagnosis). Subsequent reduplication of the short arm of chromosome 12 (isochromosome 12p) and other late events result in progression to invasive GCT

- **Clinical features**: Mostly 15-45 year old males, Caucasian>>Asian. Classically presents with painless testicular enlargement. Serum biomarkers include hCG and AFP (secreted by syncytiotrophoblasts and yolk sac tumours, respectively) and LDH (reflects tumour burden). **Prognosis**: Depends on the clinical and pathologic stage, and histologic type (seminomas are radio- and chemo-sensitive with best prognosis; most non-seminomatous GCT are relatively radio-resistant but can be cured with aggressive chemotherapy. Embryonal carcinoma and choriocarcinoma have poor prognosis). Lymphatic spread common; haematogenous spread usually later (more common in non-seminomatous GCT). Histology of metastasis may differ from primary lesion (reflecting their derivation from pluripotent germ cells or dominance of a chemoresistant component in the primary tumour). **Treatment**: Radical orchidectomy on presumption of malignancy (as biopsy risks tumour spillage and contamination of surgical field)
- **Histologic classification**:

GCT derived from GCNIS	
Seminoma	Most common type of GCT (50%). 30-40yo. Similar to dysgerminoma in the ovary, or germinoma in the central nervous system (e.g. pineal gland) • **Gross**: Bulky homogenous soft gray-white cut surface • **Microscopy**: Solid lobules/nests of uniform round to polygonal cells separated by thin fibrous septa with a lymphocytic infiltrate. Neoplastic cells display a large central nucleus, prominent nucleoli and clear cytoplasm (glycogen) with a distinct cell membrane. May have syncytiotrophoblasts. C-KIT+, OCT3/4+, CK-
Non-seminomatous GCT	
Embryonal carcinoma	20-30 yo. More aggressive than seminoma. • **Gross**: Variegated with foci of haemorrhage and necrosis • **Microscopy**: Alveolar, tubular, papillary or solid patterns. Neoplastic cells appear epithelioid, large, anaplastic and pleomorphic, with indistinct cell borders. Frequent mitoses. C-KIT-, OCT3/4+, CK+
Yolk sac tumour, post-pubertal type	Frequently occurs in combination with embryonal carcinoma or other components. • **Gross**: Solid, variegated with haemorrhage, necrosis and cystic change • **Microscopy**: Heterogeneous growth patterns including reticular (lace-like) network, papillary structures, solid cords. Tumour cells are cuboidal, flattened or spindled, with less cytologic atypia than embryonal carcinoma. Schiller-Duval bodies (structures resembling endodermal sinuses) seen in 50%. Eosinophilic hyaline-like globules seen. AFP+, CK+
Teratoma, post-pubertal type	Rare (2-3%); more often found mixed with other components. Regarded malignant. • **Gross**: Large mass with cystic areas, solid areas +/- cartilaginous areas • **Microscopy**: Mixture of tissue elements derived from mesoderm, ectoderm and endoderm. Can be mature elements (i.e. adult-type tissues) or immature

	(i.e. fetal/embryonic tissue). Rarely can have somatic-type malignant transformation (i.e. malignant non-germ cell tumours arising within the teratoma e.g. squamous cell carcinoma – these are chemoresistant and require resection)
Choriocarcinoma	Pure form very rare (<1%), highly malignant with widespread haemorrhagic metastases. Can also arise in the female genital tract. hCG+++ • **Gross**: Primary tumour often small with extensive haemorrhage and necrosis • **Microscopy**: 2 intermixed cell types – syncytiotrophoblasts and cytotrophoblasts.
Mixed germ cell tumour	Non-seminomatous germ cell tumour of more than 1 histological type (clinically regarded as non-seminoma regardless of the presence of a seminoma component) Common (~60%).
GCT unrelated to GCNIS	
Spermatocytic tumour	Uncommon (1-2%). >65yo. Slow-growing, does not metastasize. Lacks i12p and never admixed with other GCTs • **Gross**: Circumscribed, fleshy, sometimes myxoid/cystic • **Microscopy**: 3 intermixed cell types – intermediate-sized cells with spireme-type chromatin, smaller cells with dense chromatin and scant rim of cytoplasm, and scattered giant cells which may by multinucleated.
Yolk sac tumour, prepubertal type **Teratoma, pre-pubertal type**	YST is the most common testicular tumour in infants and children <3yo – good prognosis. Microscopy similar to post-pubertal YST, other than not being associated with GCNIS or mixture with other components. Teratoma is 2nd most common testicular tumour in infants and children <3yo. Benign. Tissues are arranged in a more organoid fashion. Can be admixed with YST.

Sex cord-stromal tumours: Mostly Leydig cell tumours and Sertoli cell tumours

- **Leydig cell tumours:** Secretes androgens (+/-estrogens and steroids) and may present with hormonal effects (e.g. gynaecomastia, sexual precocity in children); otherwise most commonly presents as testicular mass. Associated with Klinefelter syndrome, cryptorchidism and hereditary leiomyomatosis and renal cell carcinoma syndrome. 10% in adults are malignant
- **Sertoli cell tumours:** Most are hormonally silent, presenting as testicular mass. Associated with Carney complex, Peutz-Jegher syndrome and familial adenomatosis polyposis (FAP) syndrome. 10% are malignant

Gonadoblastoma: Very rare; mix of germ cell and sex cord-stromal elements, usually associated with testicular dysgenesis

Testicular lymphoma: Primary lymphomas are rare (~5%) but are the most common testicular neoplasm in men older than 60yo. Usually aggressive, frequently bilateral and involve the spermatic cord. Predilection for metastases to central nervous system

Miscellaneous lesions: tunica vaginalis is the mesothelial-lined surface exterior to the testis

- **Hydrocele**: accumulation of serous fluid in the tunica vaginalis, causing scrotal enlargement
- **Hematocele**: collection of blood in the tunica vaginalis, usually post-trauma or torsion
- **Chylocele**: collection of lymph in the tunica vaginalis, usually in patients with elephantiasis with widespread lymphatic obstruction

- **Spermatocele**: small cystic accumulation of semen in dilated efferent ducts / rete testis
- **Varicocele**: dilated vein in the spermatic cord

VI. PROSTATE GLAND

Basic anatomy and histology

- ~20g in normal adults
- Has 4 biologically and antomically distinct regions: Peripheral, central, transition and peri-urethral zones, which are at risk for different pathologies (inflammation, hyperplasia and tumours)
- Histologically comprises bilayered glands (peripheral basal cell layer and columnar secretory epithelial layer) within fibromuscular stroma. Growth and survival is controlled by testicular androgens; castration leads to atrophy

Inflammation (prostatitis)

- **Acute bacterial prostatitis**: usually caused by bacteria similar to those causing urinary tract infections (e.g. *E.coli*), which reach the prostate mostly through urinary reflux from the posterior urethra or bladder. May also be caused by surgical manipulation of the urethra/prostate
- **Chronic bacterial prostatitis**: usually have a history of recurrent urinary tract infections caused by the same organism. Antibiotics have poor penetration into the prostate, thus the prostate continues to see the urinary tract
- **Chronic abacterial prostatitis**: most common form of prostatitis. Clinically presents as chronic pelvic pain syndrome. No history of recurrent urinary tract infection
- **Granulomatous prostatitis**: can be infectious (caused by a specific infectious agent e.g. fungi in immunocompromised patients; instillation of BCG for bladder cancer) or non-infectious (non-specific granulomatous prostatitis referring to a pattern of tissue reaction to secretions from ruptured prostatic ducts and acini)

Benign prostatic (nodular) hyperplasia

- Most common benign (not premalignant) prostatic disease in men >50yo
- **Pathogenesis**: Ultimate cause is unknown but is believed to be facilitated by **androgenic stimulation** (dihydrotestosterone (DHT), the main androgen in the prostate).
    - Type 2 5α-reductase (expressed in prostatic stromal cells) converts testosterone to DHT; type 1 5α-reductase does so similarly in extraprostatic locations e.g. skin/liver
    - DHT binds and activates androgen receptors (ARs) in both stromal and epithelial prostatic cells with a higher affinity than testosterone. This stimulates translocation of ARs from the cytoplasm to the nucleus, and activates the transcription of androgen-dependent genes encoding several growth factors and receptors (e.g. FGF, TGFβ). This increases the proliferation of stromal cells and decreases death of epithelial cells
    - Estrogens may also have a role by favouring proliferation

- **Clinical features**: Presents with urinary obstruction due to prostatic enlargement (predominantly affecting the transition/periurethral zone) and stromal smooth muscle-mediated contraction (via α1-adrenergic receptors) – urinary frequency, nocturia, difficulty in starting and stopping urine stream, dribbling and dysuria. **Complications**: Urinary retention (which may be acute requiring emergency catherisation) with increased risk of infection, calculi, bladder hypertrophy, distension (with hypotonia), diverticulum and upstream dilatation (hydronephrosis, hydroureter, chronic kidney disease). **Treatment**: Medication (α-adrenergic blockers which decrease smooth muscle tone and 5α-reductase inhibitors which decrease DHT synthesis) or surgery for severe cases recalcitrant to medication (e.g. transurethral resection, laser therapy etc.)
- **Gross**: Enlarged prostate often 60-100g in weight. BPH affects the transition/peri-urethral zone, and may compress the urethra to a slit-like orifice. Cut surface may be soft yellow-pink to firm pale grey
- **Microscopy**: Nodular proliferation of bilayered glands with papillary epithelial infoldings within fibromuscular stroma

Neoplasms – Adenocarcinoma

- Most common cancer in men in US and 2nd cause of cancer-related death in men; correlates with aging. Putative precursor lesion is **prostatic intraepithelial neoplasia** (PIN)
- **Pathogenesis:** Interplay of environmental factors and inherited genetic factors, the latter which may also act by modifying the risk associated with environmental exposures
    - **Environmental factors**: Exposure to carcinogens, estrogens and oxidants are hypothesized to damage prostatic epithelium, predisposing to acquisition of genetic and epigenetic changes that lead to cancer. Suspects include the "Western diet" with carcinogenic heterocyclic aromatic amines and polycyclic aromatic hydrocarbons
    - **Inherited genetic factors**: May be related to variants in regulatory regions that influence *MYC* oncogene expression or mutations that disrupt the function of DNA repair genes or genes encoding transcription factor HOXB13.
    - **Androgens:** Androgens bind to androgen receptors and induce the expression of pro-growth and pro-survival genes, and are thus important in maintaining the growth and survival of prostate cancer cells. Androgen blockage through castration or anti-androgens usually induce disease regression; however, most tumours eventually escape through various mechanisms e.g. acquisition of hypersensitivity to low levels of androgen, ligand-independent AR activation or alternative signaling pathways that bypass the need for AR
    - **Acquired genetic and epigenetic alterations:** These alter the expression of tumour suppressor genes and oncogenes, leading to the acquisition of cancer hallmarks. The most common is a chromosomal rearrangement juxtaposing the coding sequence of an ETS family transcription factor gene (most commonly *ERG* or *ETV1*) next to the androgen-regulated *TMPRSS2* promoter, leading to its overexpression in an androgen-dependent fashion. Other common events include silencing of p27 gene, *MYC* amplification, *TP53* loss, epigenetic silencing by DNA methylation of *GSTP1* which may enhance the genotoxic effects of environmental carcinogens etc

- **Clinical features:** >50yo. Localised prostate cancer is mostly asymptomatic and incidentally discovered on digital rectal examination as a palpable nodule, or through elevated serum prostate-specific antigen (PSA) level. Clinically advanced prostate cancer can present with urinary obstruction or bone pain. **Diagnosis**: Histologic diagnosis (through needle biopsy) required to confirm diagnosis, although subject to sampling error. Serum PSA levels can assist with diagnosis and management of prostate cancer in some cases. PSA is a product of prostatic epithelium and normally secreted in semen, with only minimal amounts in serum. Elevated serum PSA can be seen localized or advanced prostate cancer, but also benign conditions e.g. BPH, prostatitis. It thus has low sensitivity and specificity as a screening test, but has value when used as serial measurements after treatment of disease to monitor recurrence and disease progression. **Prognosis**: **Grade** and **stage** are the most important prognostic factors. **Grading** is performed using the Gleason system (see 'Microscopy' below). The higher the Gleason score or grade group, the worse the prognosis. Together with grade, **pathologic stage** is used to stratify management of prostate cancer. pTNM stage is based on tumour extent, and presence of nodal or distant metastases. Local invasion involves periprostatic tissue, seminal vesicles, the urinary bladder base or adjacent structures e.g. pelvic wall, rectum. Lymphatic spread involves obturator and para-aortic nodes. Hematogenous spread primarily involves bones (axial skeleton mostly), which are classically osteoblastic unlike bone metastases from other primary cancers. **Margin status** is also important for prognosis post-surgery. **Management**: Depends on how biologically significant the cancer is (i.e. likely to progress or metastasize), to avoid overtreatment. Many prostate cancers picked up on PSA levels are so indolent as to be clinically significant. Tumour grade as well as genomic tests using gene panels are used to predict which cancers can be followed by active surveillance alone, and which need surgery (radical prostatectomy) or radiation (external beam or brachytherapy) +/- androgen deprivation therapy (through orchiectomy or chronic administration of LH-releasing hormone agonists that desensitize pituitary cells and suppress release of LH required for testosterone production by Leydig cells)
- **Gross:** ~70% of cases arise in the peripheral zone, classically posterior location where it may be palpable on rectal examination. Grossly often difficult to identify, but may be firm/gritty
- **Microscopy:** Most common variant is prostatic acinar adenocarcinoma, whereby glands are arranged in architectural patterns that are graded using the Gleason grading system, ranging from well-formed glands (grade 1-3) to poorly-formed glands (4), solid islands, cords or single cells (5). Tumours are given a primary and secondary grade, which are added together to give the Gleason score which then corresponds to grade groups 1-5. E.g. Gleason score 3+5 = 8, corresponding to grade group 4. Malignant glands lack the outer basal cell layer of normal glands, and display enlarged nuclei with prominent nucleoli. **PIN** retains at least partially an intact layer of basal cells but lined by atypical epithelial cells that may be cytologically identical to carcinoma
  Ductal adenocarcinoma arise from prostatic ducts rather than acini, and are associated with a relatively poor prognosis

Neoplasms – Miscellaneous tumours

- **Small cell carcinoma:** Most aggressive variant of prostate cancer; most often seen as recurrent disease in patients with typical prostate cancer undergoing treatment with antiandrogen therapies due to the emergence of an androgen-independent subclone with a neuroendocrine phenotype
- **Urothelial carcinoma:** Most common tumour to secondarily involve the prostate – from direct invasion by large bladder urothelial carcinomas or extension of bladder CIS into the prostatic urethra into the prostatic ducts and acini
- **Mesenchymal tumours:** May be derived from prostatic stroma