Bladder tumours

Normal bladder transitional epithelium 3-7 cells thick; single basal layer and other intermediate layers. Top ‘umbrella cell’ layer with thick luminal surface composed of uroplakins. Lamina propria consists of muscle cells (muscularis mucosa).

Epithelial hyperplasia	increase in the number of cell layers without nuclear or architectural abnormalities.
Urothelial *metaplasia*	nontransitional epithelial appearance (squamous or adenomatous). Squamous metaplasia in the absence of cellular atypia or marked keratinization is a benign condition.
Von Brunn's nests	islands of benign-appearing urothelium situated in the lamina propria.
Cystitis cystica	von Brunn's nests in which urothelium in the center of the nest has undergone eosinophilic liquefaction
Cystitis glandularis	similar to cystitis cystica except that the transitional cells have undergone glandular metaplasia.
Atypical hyperplasia	similar to epithelial hyperplasia, except nuclear abnormalities and partial derangement of the umbrella layer. Proliferative, probably not pre-neoplastic (Cheng 1999)
Dysplasia	Large, round, notched, basally situated nuclei that do not exhibit the normal epithelial polarity. No mitoses or increased cell layers. Pre-neoplastic. 15% high-grade cancer at 3.5 yrs (Cheng 1999)
Inverted papilloma	benign proliferative lesion associated with chronic inflammation or bladder outlet obstruction. Papillary fronds project into the fibrovascular stroma of the bladder rather than into the bladder lumen. The lesion is usually covered by a thin layer of normal epithelium. ?? Increased association with TCC elsewhere, especially if located in upper tract
Nephrogenic adenoma	*r*are benign lesion that histologically resembles primitive renal collecting tubules. Metaplastic response of urothelium to trauma, infection, or radiation therapy often associated with dysuria and frequency.
Leukoplakia	squamous metaplasia with marked keratinization, downward growth of rete pegs (acanthosis), cellular atypia, and dysplasia. It is believed to be a response of the normal urothelium to noxious stimuli and is generally considered a premalignant lesion that may progress to SCC in up to 20% of patients.
Pseudosarcoma	aka postoperative spindle cell nodule. Reactive proliferation of spindle cells occurring several months after a lower urinary tract procedure or

infection. These lesions have been misinterpreted as being malignant, and radical surgery has been performed inappropriately. Usually, they are confused with leiomyosarcomas.

Microscopic

Bladder tumours may be primary or secondary
Primary tumours may arise from the epithelium (>95%) or from other constituents of the bladder (<5%) [NB. Epstein uses term urothelial tumour to exclusively to signify TCC]

Primary bladder tumours
- Tumours arising from the epithelium:
  - Transitional cell carcinoma >90%
  - Squamous carcinoma
  - Adenocarcinoma
  - Urachal carcinoma
  - Small cell carcinoma
  - Carcinosarcoma
- Non-epithelial tumours
  - Neurofibroma
  - Phaeochromocytoma
  - Primary lymphoma
  - Sarcoma
    - angiosarcoma
    - leiomyosarcoma
    - rhabdomyosarcoma

Secondary tumours (Top 5)
- prostate, ovary, uterus, colon and rectum

Epithelial bladder tumours

Transitional cell carcinoma

Microscopic features cf. normal epithelium
- increased number of epithelial cell layers
- papillary foldings of the mucosa
- loss of cell polarity
- abnormal cell maturation from basal to superficial layers
- increased nuclear-cytoplasmic ratio
- prominent nucleoli
- clumping of chromatin
- increased number of mitoses (Koss, 1975).
- Growth may be papillary, sessile, nodular, infiltrating, flat intraepithelial or mixed

There are now molecular and cytogenetic data to support the well-established clinical impression that low-grade (all well-differentiated and most moderately differentiated) tumors and high-grade (poorly differentiated) tumors have fundamentally different origins, with the former losing one or more suppressor genes on chromosome 9q and the latter having TP53, RB, and/or P16

abnormalities as early events. 1973 WHO grading system changed to reflect this.

Table 2: WHO grading in 1973 and in 2004 (7,8)

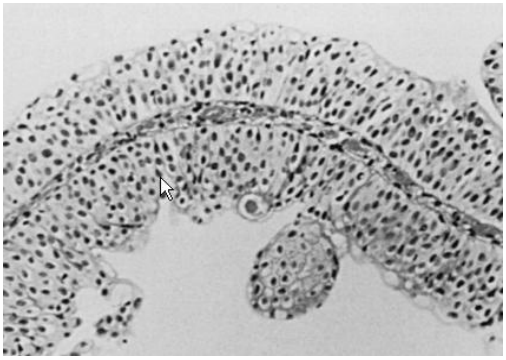
1973 WHO grading	
Urothelial papilloma	
Grade 1:	well differentiated
Grade 2:	moderately differentiated
Grade 3:	poorly differentiated
2004 WHO grading	
Urothelial papilloma	
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	
Low-grade papillary urothelial carcinoma	
High-grade papillary urothelial carcinoma	

Papilloma — papillary lesion with a fine fibrovascular core covered by normal bladder mucosa. Normal layers and no cytological abnormalities. Extremely rare. If solitary and no co-existent TCC can be considered benign.

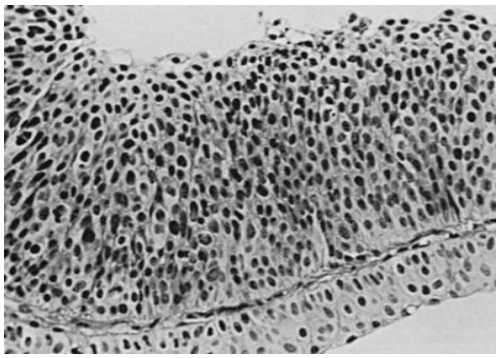
PUNLMP — Old grade 1
thin fibrovascular stalk with a thickened urothelium containing more than seven cell layers
slight anaplasia and pleomorphism with rare mitotic figures.
often recur, and recurrences may be of higher histologic grade and stage

LGPUC — Old grade 2
Wider fibrovascular core, greater disturbance of the base-to-surface cellular maturation, and a loss of cell polarity. The nuclear- cytoplasmic ratio is higher, with more nuclear pleomorphism and prominent nucleoli. Mitotic figures are more frequent. May be difficult to differentiate between PUNLMP and LGPUC in new classification

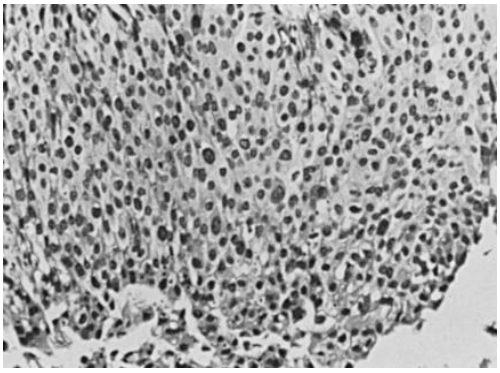
HGPUC — Old grade 3
No differentiation from basement membrane to the surface. Marked nuclear pleomorphism with high nuclear-cytoplasmic ratio and mitoses.



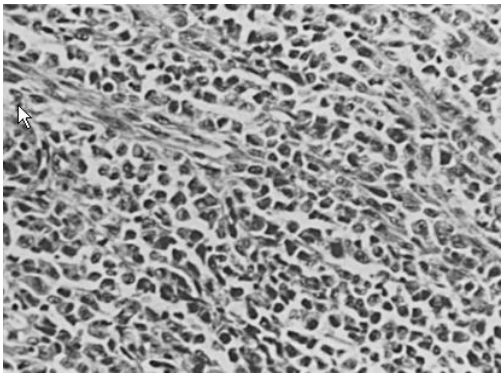
Papilloma



PUNLMP



LGPUC



HGPUC

Squamous cell carcinoma

1% of bladder cancers in UK (Costello)
3% in US, 75% in Egypt
Aetiology
- Bilharzia (S. haematobium) infection
  - Younger patients
  - male:female ratio equal
  - Low-grade lesions cf. TCC
  - Lower stage disease at presentation ? lymphatic obstruction 2' to chronic infection
- Chronic irritation
  - Male:female raio 1.3:1
  - Indwelling catheter
  - Bladder calculus
  - Bladder diverticulum
  - Recurrent UTI

Pathology
- Exophytic, nodular & fungating
- Keratinized islands that contain eccentric aggregates of cells called squamous pearls. Varying degrees of histologic differentiation.
- Cytology unhelpful. Psoriasin 100% sensitive but not specific (picks up squamous metaplasia)
- p53 and RB mutations often seen as for aggressive TCC.
- Stage for stage, similar prognosis cf. TCC

Adenocarcinoma

- <2% bladder tumours
- Three groups
  - Primary vesical
    - Often at dome but may arise anywhere
    - Commonest cancer in exstrophy
    - Often mucin producing
    - Typically poorly differentiated and aggressive
    - Stage for stage equal to TCC bladder
  - Urachal
    - <1% of all bladder tumours
    - ~ one third of bladder adenocarcinoma
    - Men > women

Arise outside bladder initially, often invading into dome, making differentiation from primary vesical adeno. difficult
Normally sharp demarcation from bladder epithelium however
Usually haematuria, but may present with bloody discharge from umbilicus or subumbilical mass.
Stippled calcification occasionally seen on plain x-ray
Worse prognosis cf. primary vesical adenocarcinoma

The Urachal Cancer Staging System as Defined by Sheldon et al.*

Stage	Definition
Stage I	Urachal cancer confined to urachal mucosa
Stage II	Urachal cancer with invasion confined to urachus itself
Stage IIIA	Local urachal cancer extension to bladder
Stage IIIB	Local urachal cancer extension to abdominal wall
Stage IIIC	Local urachal cancer extension to peritoneum
Stage IIID	Local urachal cancer extension to viscera other than bladder
Stage IVA	Metastatic urachal cancer to lymph nodes
Stage IVB	Metastatic urachal cancer to distant sites

* See Sheldon et al., 1984.[2]

Management
- Partial cystectomy with excision of median umbilical ligament and umbilicus (wide excision necessary as subepithelial lateral infiltration commonly more extensive than appreciated macroscopically – therefore always perform with bladder empty)
- Role of pelvic lymphadenectomy undefined

Prognosis
- Overall five year survival 49% at 5 yrs (Ashley 2006). Worse prognosis in those with grade 3 disease and those without umbilectomy
- No benefit for adjuvant therapy in Mayo clinic series above (but only given for positive margins or LN metastases)
- Further surgery for recurrent disease results in long-term cure in 50%
- Chemotherapy associated with small chance of cure in patients with metastatic disease (MVAC/GemCis)

Metastatic
- prostate, bowel, breast etc.

<u>Small cell carcinoma</u>
Rare
Derived from neuroendocrine cells or dendritic cells
Positive for neurone-specific enolase
Should exclude metastasis from lung or prostate (staging CT chest and DRE)
Typically advanced and aggressive

Responsive to platinum based chemotherapy (typically cisplatin and etoposide)
Better results for chemo +/- salvage (RT/surgery) vs. radical treatment alone (Syed 2004)

Carcinosarcoma
Rare
Mixed mesenchymal/epithelial malignancy
Mesenchymal elements – osteosarcoma or chondrosrcoma
Epithelial elements – TCC, adeno, squame
Typically middle aged men
Extremely aggressive and advanced at presentation
Universally poor prognosis irrespective of treatment modality
Recent reports of partial response to gem/cis

Non-epithelial bladder tumours

Neurofibroma (commonest)
- Arise from bladder wall ganglia
- Almost always in patients with neurofibromatosis
- Stain for S100 protein and positive for type 4 collagen
- Often present in children with bladder outflow obstruction, LUTS, haematuria or bladder mass

Primary lymphoma (second commonest)
- From submucosal lymphoid follicles
- 40 – 60 yrs
- Women > men
- Rx as for lymphoma elsewhere

Phaeochromocytoma
- <1% of all bladder tumours and <1% phaeos
- derived from para-ganglionic cells in bladder wall
- 20-40 yrs
- male:female ratio equal
- Submucosal nodule with overlying normal epithelium
- If suspected – don't TUR as may precipitate hypertensive crisis
- Partial cystectomy treatment of choice (10% malignant)

Haemangioma
- Benign
- Quite rare
- Haematuria
- Rx = TUR

Angiosarcoma
- Very rare
- Malignant
- Life-threatening massive haematuria
- Early metastasis

Leiomyosarcoma
- Uncommon
- Male:female 2:1
- Submucosal nodule or ulcerating mass

- Rx = aggressive surgical extirpation (5yr survival 62% - Rosser 2003)

Rhabdomyosarcoma

- Rare
- Bimodal distribution
  - Children (sarcoma botryoides)
    - embryonal polypoid lesion in base of bladder (11p loss)
  - Adults
    - Three types (spindle cell, alveolar cell, giant cell)
    - Specific staining for myogentin and myo-D1
    - Chemo and radioresistant. Do badly with surgery