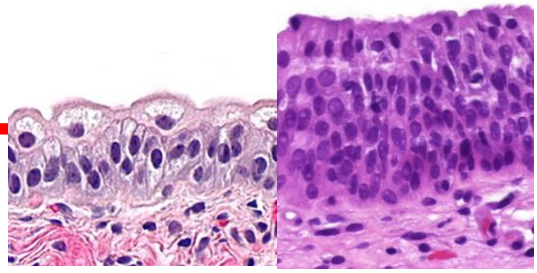
Last updated: 4/13/2020

Prepared by Kurt Schaberg

Bladder Tumors

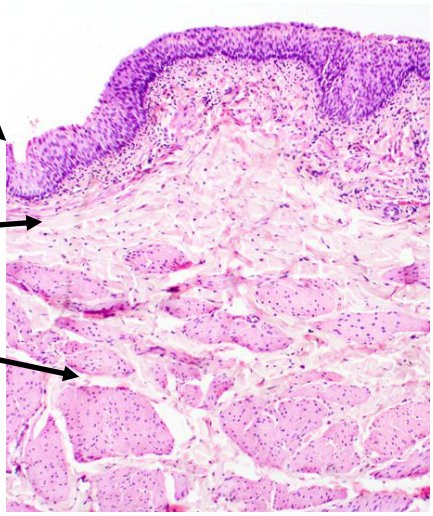
Normal Anatomy



Distended (2-3 cells)

Non-distended (5-7 cells)

Urothelium: Thickness depends on distention of bladder.
Normal thickness = 2-7 cells.
Basal and intermediate layer are often cuboidal to columnar
Normal urothelial nucleus is about the size of 2 lymphocyte nuclei
Top Umbrella/Superficial layer are large, sometimes binucleate with abundant eosinophilic, sometimes vacuolated cytoplasm

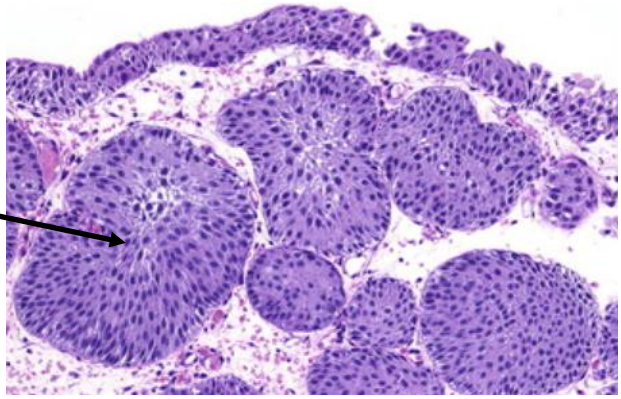


Lamina Propria: Contains vessels, connective tissue, nerves, and thin, wispy, haphazard, scattered muscularis mucosae

Muscularis propria (Detrusor muscle): More organized, thick bundles of muscle

Adventitia: Connective Tissue outside muscle. Serosa at dome.

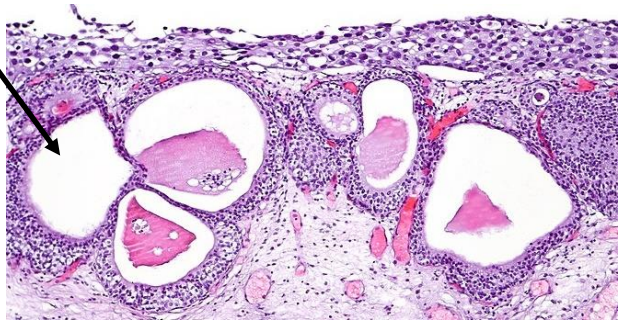
Normal Variations



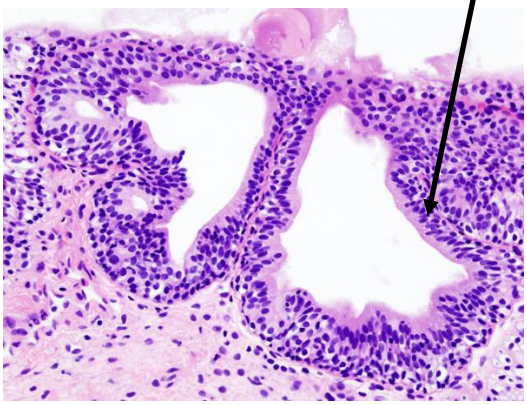
von Brunn Nests:
Invaginations of the surface urothelium into underlying lamina propria. Normal urothelium thickness & cytology. Round shape (not infiltrative), uniform size.

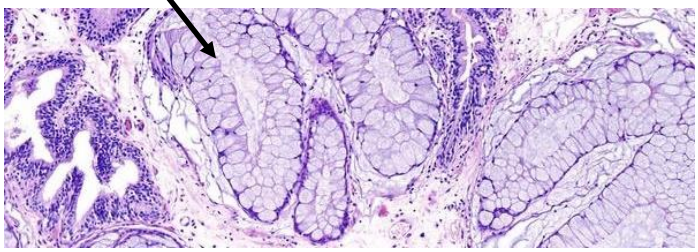
If lots of small nests, irregular size, stacked on top of each other→ consider nested variant of urothelial carcinoma

Cystitis Cystica:
Name used when these nests become cystically dilated



Cystitis Glandularis:
Name used when lining undergoes glandular metaplasia





Urothelial Tumors

Most common in **older males**. Risk factors include **smoking**, occupational exposures (e.g., paints and exhaust), radiation, and Schistosoma. Most commonly present with **hematuria**

Location: 90% in Urinary bladder; 10% upper tract;
Can often be multifocal (often attributed to a "field defect")

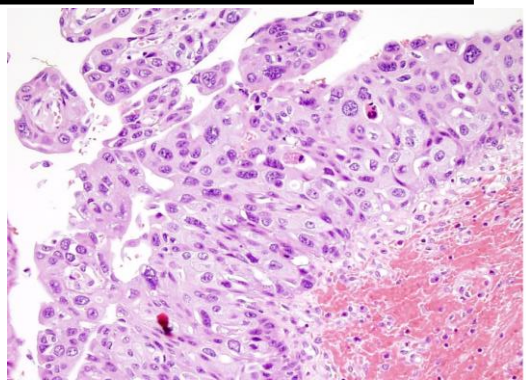
Molecular: Very high mutational rate (second only to lung!). Two main pathways

1. ***Large chromosomal alterations:*** loss/gain of large chromosomal fragments occur, corresponding to higher grade tumors
2. ***Recurrent mutations:*** Frequent mutations include deactivating **TP53** and activating **FGFR3**. Very common, **TERT** promoter mutations→ lengthens telomeres. Others include PIK3CA, RB1, and HRAS

Lynch Syndrome→ increased risk of urothelial neoplasms (esp. MSH2), particularly **upper tract**

Two main categories: 1) Flat, 2)Papillary

Carcinoma *In Situ* (CIS)

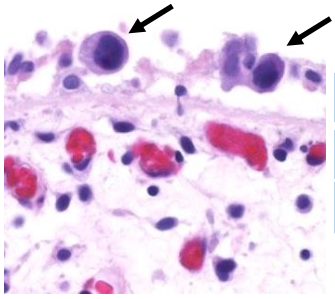


Flat lesion (No papillary structures!)
Often erythematous on cystoscopy
High-grade cytology (Pleomorphism):

- Frequent nucleomegaly (usually >5x lymphocyte nucleus)
- Hyperchromasia

Disorder: Loss of polarity; Nuclear crowding;
Increased cytoplasmic eosinophilia
Does NOT need to be full-thickness (can show Pagetoid spread)

Can be discohesive → shed into urine → remaining cells = "Clinging carcinoma"



IHC to help distinguish CIS from Reactive:

	CK20	P53	Ki67
Normal/Reactive	Umbrella cells only	Wild-type	Low (usually)
CIS	All cells (full-thickness)	Diffuse or Null	High

Prognosis: ~25% progress to invasive disease
Treatment: Cystoscopic observation, Intravesical BCG Therapy

Urothelial Dysplasia

Flat urothelium with appreciable cytologic and architectural features that are believed to be preneoplastic, but do not reach the threshold of CIS.

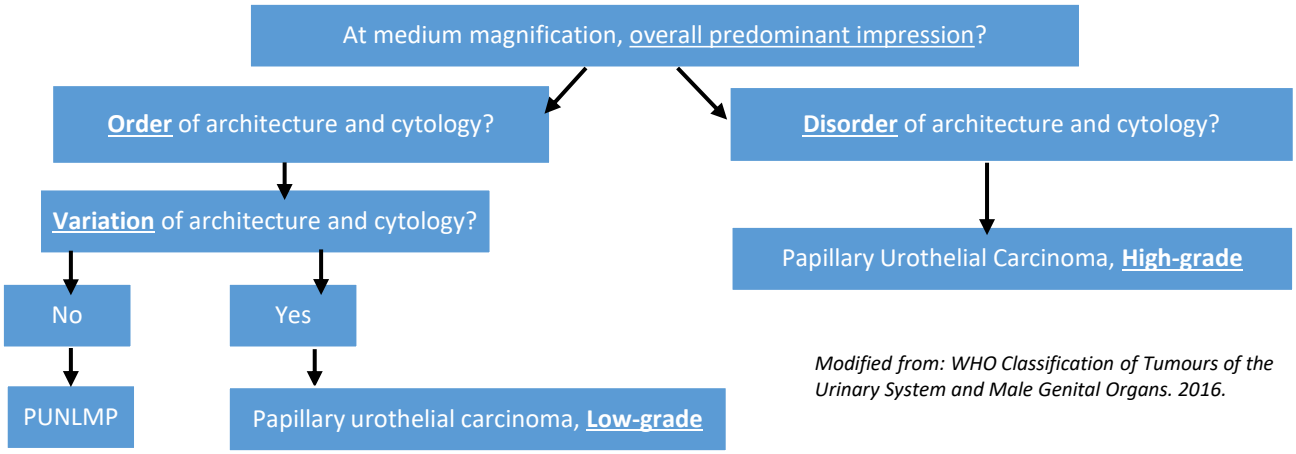
No consensus criteria. Tremendous inter-oberserver variability.
Not diagnosed routinely in clinical practice as a result

Some use terms like: "Atypia of unknown significance" or "Urothelial atypia, cannot exclude dysplasia" as are treated clinically similar

Given lack of consensus in diagnosis, prognosis not well-established

Papillary Neoplasms

Fibrovascular cores covered in urothelium.
Hierarchical branching



Modified from: WHO Classification of Tumours of the Urinary System and Male Genital Organs. 2016.

	Papilloma	PUNLMP	Low-grade, Papillary carcinoma	High-grade, Papillary carcinoma
Architecture of papillae	Delicate	Delicate	Fused to branching	Fused to branching
Architecture of cells	Normal	Polarity like normal; **Ordered**, ***no*** *variation*	**Ordered, but with variation**	**Disorder!**
Nuclear size	Normal	Normal to slightly enlarged	Enlarged with variation	Enlarged with variation
Nuclear shape	Normal	Oval-round; uniform	Round-oval; **slight variation**	**Moderate to marked pleomorphism**
Umbrella cells	Uniformly present	Present	+/-	+/-
Mitoses	Absent	Rare, basal	Occasional, any level	Frequent, at any level

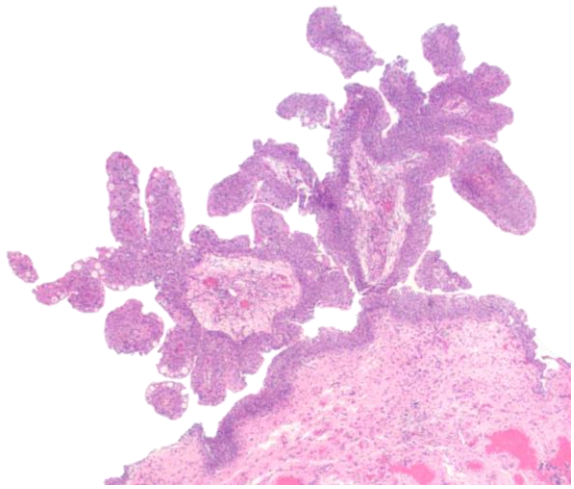
Modified from: Epstein et al. Biopsy Interpretation of the Bladder. Wolters Kluwer, 2017.

Papilloma

Papillary urothelial neoplasm with **delicate** fibrovascular cores covered by urothelium of **normal appearance and thickness**

Relatively rare

Prognosis: Recurrence rate ~10%;
Progression to carcinoma ~1%
Treat with TURBT



Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

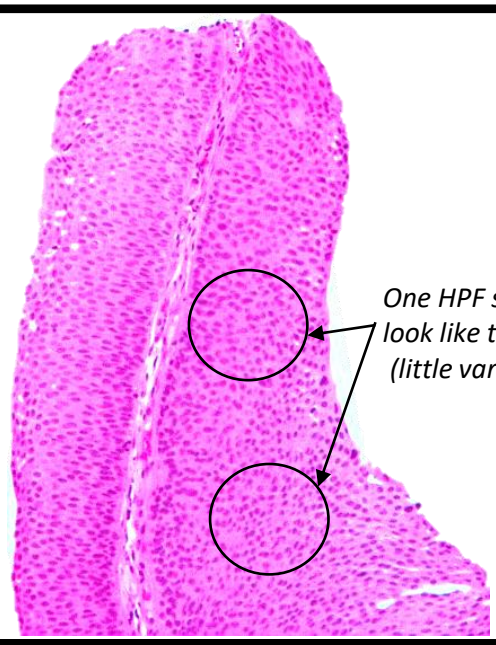
Papillary urothelial neoplasm with **minimal atypia**
Epithelial thickness usually exceeds normal (>7 cells)

Lots of order, little variation → **every high-power field should look the same**

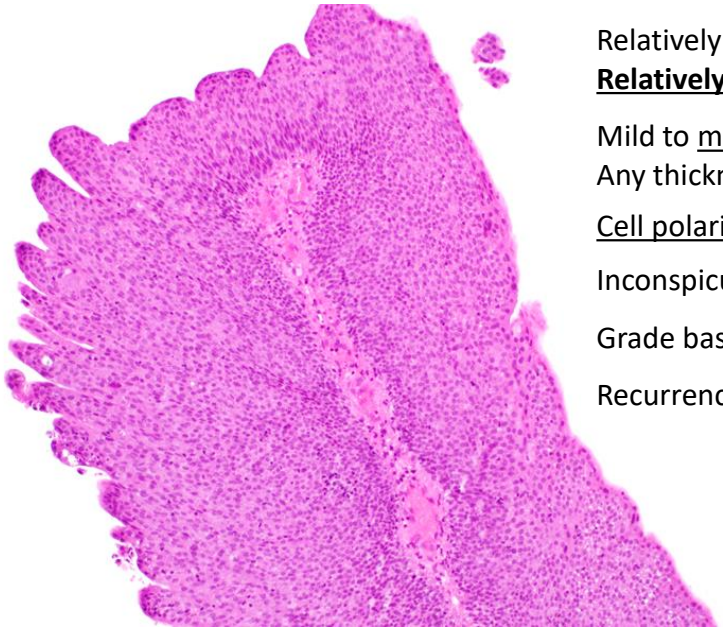
Overall, **monotonous** appearance.
Maintained cell polarity

Often hard to distinguish from Low-grade papillary urothelial carcinoma→ sometimes low interobserver agreement→ for both, treatment is TURBT and observation

Lower risk of recurrence/progression than carcinoma



Non-Invasive Papillary Urothelial Carcinoma, **Low-Grade**



Relatively delicate papillae with extensive branching
Relatively orderly, but with some variation at high-power

Mild to moderate nuclear pleomorphism
Any thickness, but often thicker than normal

Cell polarity maintained (cells know which way is "up")

Inconspicuous nucleoli.

Grade based on highest-grade component (at least if >5%)

Recurrence rate ~30%; Treat with TURBT & surveillance

Non-Invasive Papillary Urothelial Carcinoma, **High-grade**

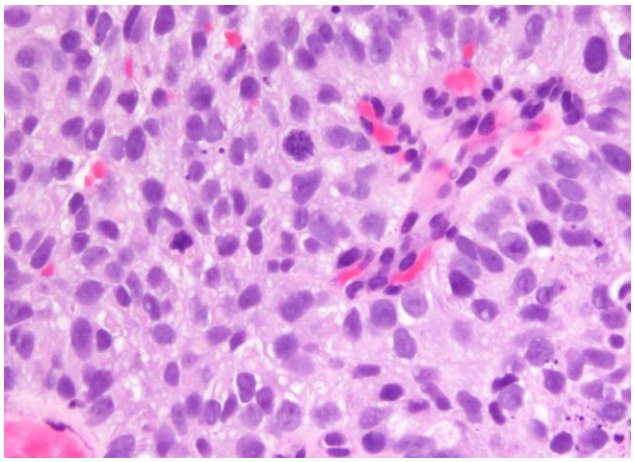
Disordered appearance: Architectural and cytologic abnormalities

Loss of cell polarity. Irregular spacing and nuclear overlap. Often discohesive.

Nuclear pleomorphism, hyperchromasia, clumped chromatin. Sometimes prominent nucleoli.

Often fusion of papillae

Recurrence rate ~50%; Treat with TURBT & surveillance



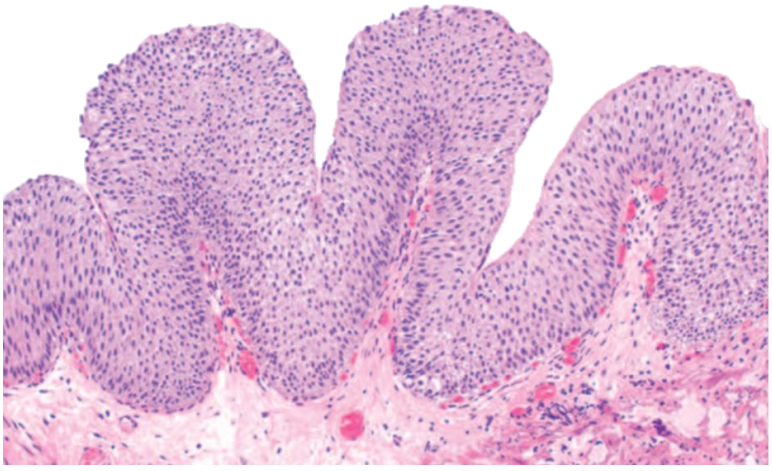
Urothelial Proliferation of Uncertain Malignant Potential (UPUMP)

Markedly **thickened urothelium** (> 10 cells)
No or minimal atypia
Increased cell density

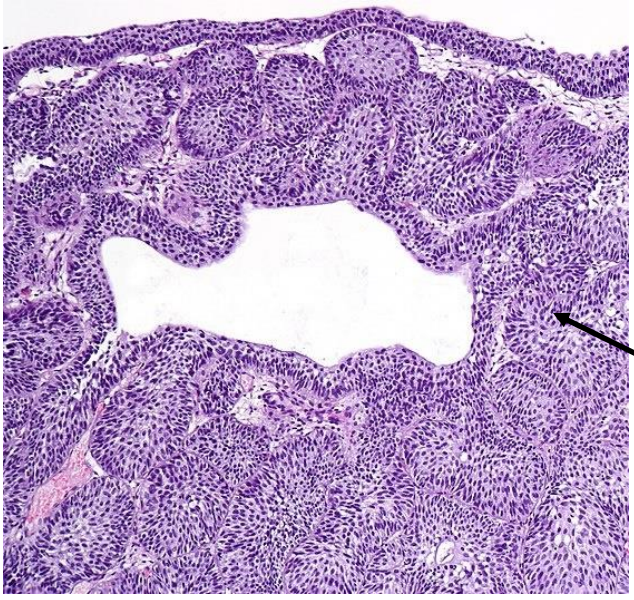
No true papillary fronds with fibrovascular cores

Undulating mucosal folds

Clonal. May be early pre-cursor to low-grade papillary urothelial carcinoma (often at "shoulder").
Followed clinically.



Inverted Urothelial Lesions



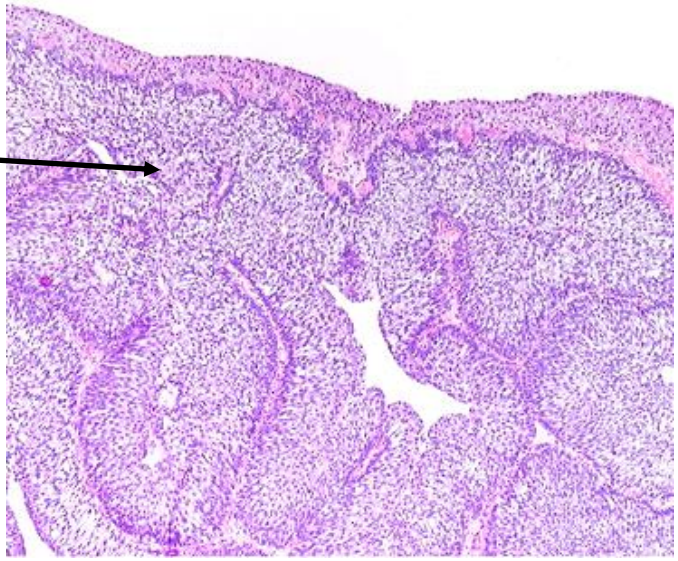
- **Complex, branching, anastomosing inverted growth cords** of urothelium
- Peripheral basal cells in nests
- **Smooth stromal-epithelial interface** (no infiltrative growth)
- **No stromal reaction**
- Do not involve muscularis propria
- May have cystic areas (like cystitis cystica)

Inverted Urothelial Papilloma

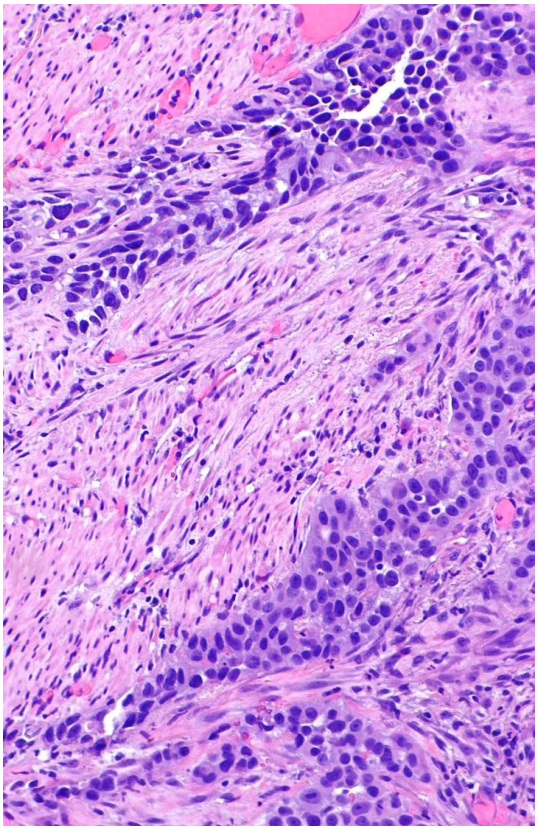
- 5-10 cells layers thick
- No significant atypia
- Benign with low recurrence risk

Inverted Papillary Urothelial Carcinoma

- More than 10 cell layers thick
- More nodular, expansile growth
- More mitoses
- More significant cytologic atypia
    - Irregular chromatin
    - Enlarged, irregular nucleoli



Invasive (Infiltrating) Urothelial Carcinoma



Invasive <u>beyond the basement membrane</u>

Usually, cytologically **High-Grade** (Nuclear pleomorphism, Hyperchromasia, Numerous mitoses)

Moderate amounts of eosinophilic cytoplasm

<u>Various architectures</u> (nests, single cells, etc…), but often elicits a **desmoplastic stromal response**

<u>Diversity</u> in morphologic manifestations, including specific variants and divergent differentiation.

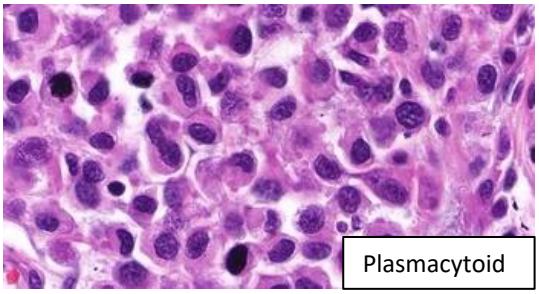
IHC: GATA3, Uroplakin III, Thrombomodulin, High-Molecular Weight Cytokeratin (e.g., CK5/6), p63, p40, CK7, CK20, S100-P

<u>Divergent differentiation:</u>

Squamous—intercellular bridges and/or keratinization. Very common (up to almost 50% of urothelial cancers)

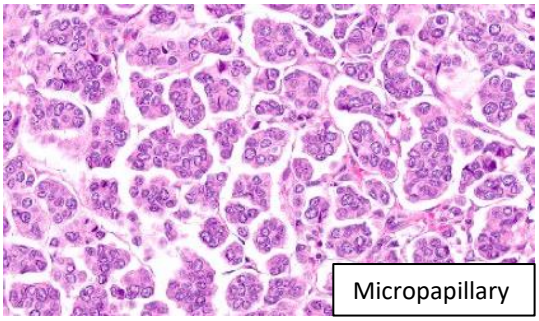
Glandular—presence of gland formation (up to 20%). Often has enteric appearance and immunophenotype

Trophoblastic—giant cells resembling syncytiotrophoblasts. Can secrete βhCG.



<u>Specific Variants:</u>

Plasmacytoid—Bland cells resembling plasma cells. E-cadherin loss (like lobular breast). Express CD138. Aggressive. Poor prognosis.



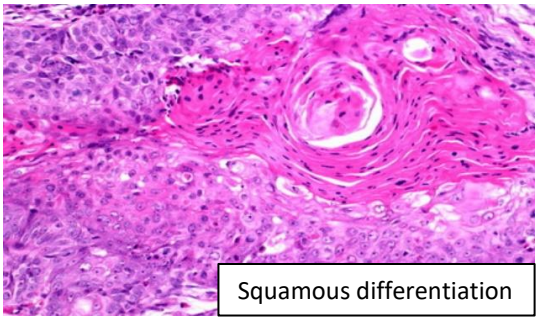
Micropapillary—Nests surrounded by lacunae. Peripherally located nuclei. Aggressive. Often high stage.

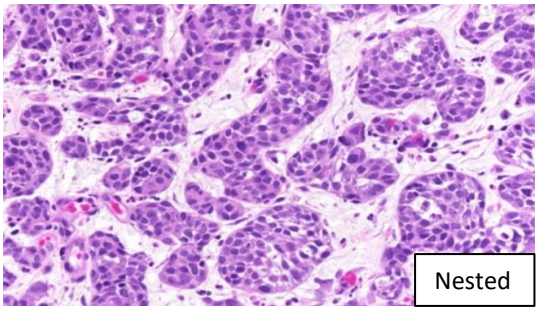
Nested—Cytologically bland discrete to crowded infiltrating nests. Can be hard to dx on biopsy unless into muscle.

Lymphoepithelial-like—High-grade syncytial cells with prominent inflammatory infiltrate. EBV negative.

Sarcomatoid—Resembles a sarcoma, possibly including heterologous differentiation (e.g., osteosarcoma).

(And others!)





Diagnosis of Lamina propria invasion:

Can be challenging→ Look especially hard in high-grade tumors

Pattern of invasion: single cell infiltration, irregularly shaped, jagged, haphazard nests, finger-like projections, architecturally complex proliferations not conforming to normal papillary neoplasms

Paradoxical maturation: invading cells have more abundant cytoplasm and more pleomorphism

Stromal response: desmoplastic stroma, retraction artifact, inflamed stroma, myxoid stroma (although sometimes there is *no* response!)

Potential pitfalls:

Tangential sectioning/von Brunn's nests→ Smooth, round, regular contours of cells that look like the surface favors non-invasive/benign

Thermal injury→ don't over interpret burned tissue

Muscularis propria invasion:

A big decision clinically, if stage T ≥2 (into musclularis propria), then often proceed with "definitive therapy" (chemo then cystectomy). If T <2, then often conservative treatment with TURBT

For muscularis propria invasion, look for thick, organized smoot muscle bundles

Thin, wispy muscle with associated vessels→ favors muscularis mucosae

Some use smoothelin (stronger in muscularis propria) and vimentin (stronger is musclaris mucosae) IHC to distinguish the two, but this can be problematic and is not recommended routinely

Other Epithelial Tumors

Squamous Cell Carcinoma

Pure SCC has no urothelial component (otherwise just squamous differentiation in urothelial carcinoma—which is much more common!)
Uncommon in US, but predominates in some parts of Africa and Middle-east, largely related to prevalence of ***Schistosoma haematobium***

Other risk factors: Smoking, occupational, chronic UTI's
Chronic inflammation → Increased proliferation and oxidative stress → Squamous metaplasia → keratinizing dysplasia → SCC

Keratin pearls and intercellular bridges. No urothelial CIS or traditional urothelial component.

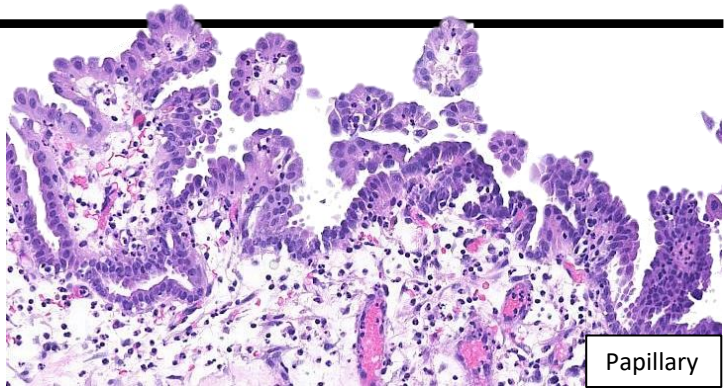
Neuroendocrine Tumors

Small cell neuroendocrine carcinoma—same has pulmonary (and other organ) small cell carcinoma. Frequently associated with traditional urothelial carcinoma (that then de/transdifferentiates). Can express TTF1. Aggressive.

Large cell neuroendocrine carcinoma—Very rare. Aggressive.

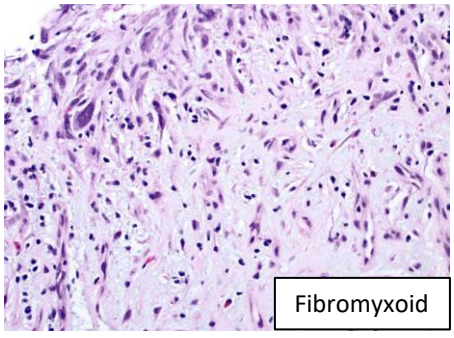
Well-differentiated neuroendocrine tumors—resemble those of the GI tract. Often have prominent pseudoglandular pattern (resembling cystitis cystica/glandularis). Often mucosal and excellent prognosis.

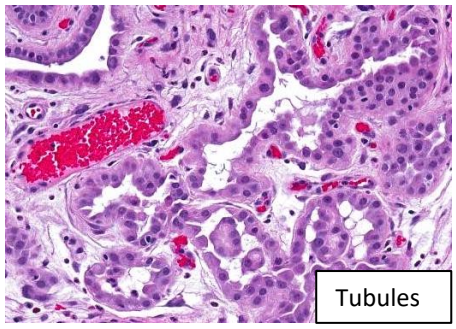
Nephrogenic Adenoma


Papillary

Benign
Often arise in the setting of **prior urothelial injury**

Histologic spectrum:
Tubules lined by cuboidal to columnar cells
Papillary structures
Fibromyxoid variant has spindled cells surrounded by fibromyxoid stroma

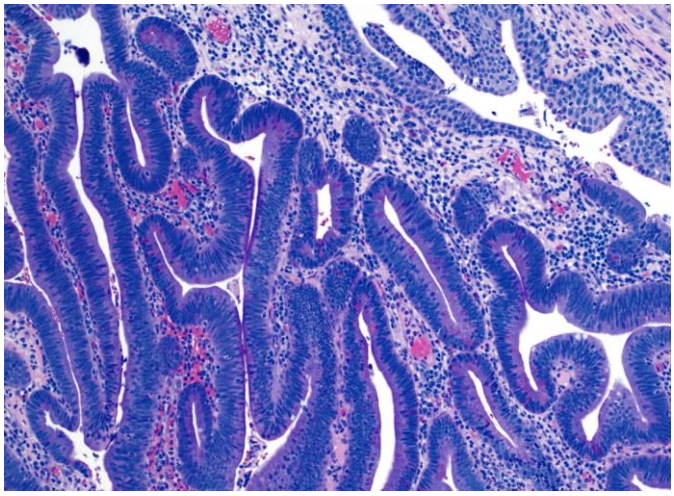

Fibromyxoid


Tubules

Cells can be **hobnailed**
Often thick basement membrane
No significant nuclear atypia

Histogenesis is a little controversial. Possibly derived from shed renal tubule cells→ Stain with **Pax8** by IHC

Villous Adenoma



Histologically identical to colonic adenomas
(Hyperchromatic, pencillate nuclei)
Papillary architecture. Rare.

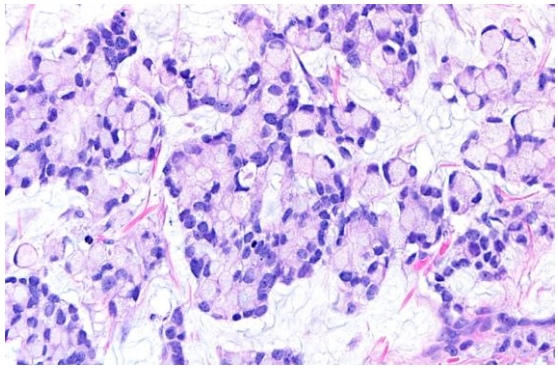
↓ Can progress

Adenocarcinoma

Purely glandular malignant tumor (as opposed to divergent glandular differentiation in a urothelial carcinoma)

Can be hard to distinguish from a GI metastasis.
IHC: β-Catenin strong nuclear reactivity in most colon cancers, but not in bladder adenocarcinomas. Other markers (e.g., CDX2) can be positive in both

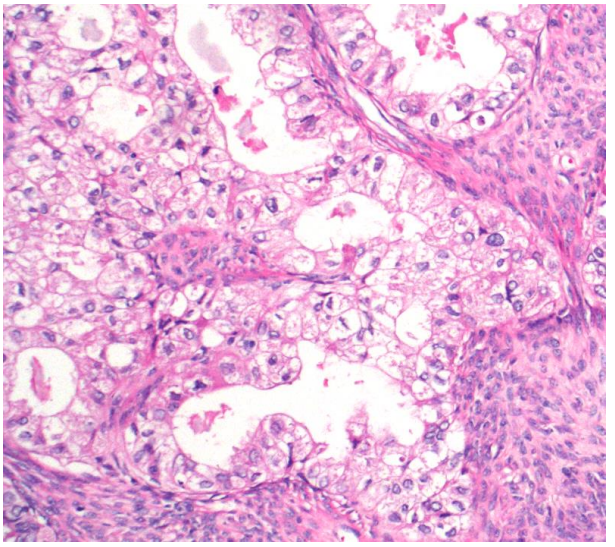
Urachal Carcinoma



Arise from urachal remnants. Often adenocarcinomas. Frequently intestinal-type and/or mucinous appearing

Criteria:
1) **Location in bladder dome or anterior wall** (midline)
2) **Epicenter in bladder wall** (not mucosal)
3) Absence of widespread cystitis cystica near tumor
4) Absence of other known primaries

Clear Cell Carcinoma



Derived from pre-existing Müllerian precursors
(Accordingly more common in women, can also get endometrioid carcinomas)

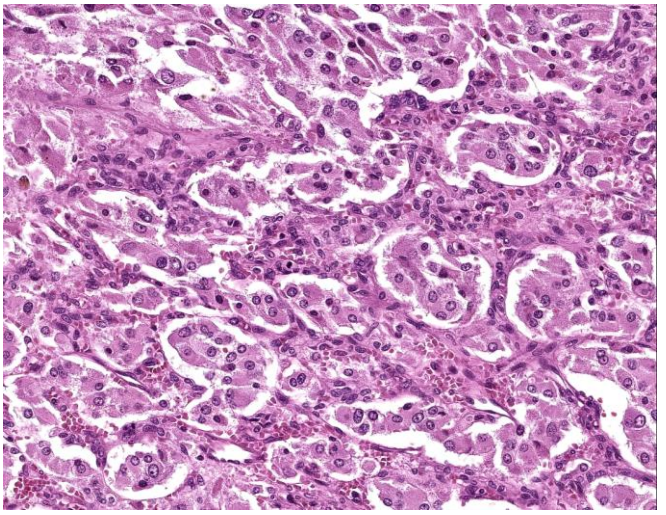
Most common in **urethra**, bladder neck, and trigone.

Characteristic morphology:
Abundant clear to eosinophilic cytoplasm.
Severe cytologic atypia. Hyperchromatic nuclei.
Varied architecture: Tubules, papillary, diffuse, etc..

IHC: Positive CAM5.2, **CK7**, **PAX8**, HNF1β, AMCAR
Negative PSA, PSAP, p63, HMWCK, ER, PR, GATA3

Often advanced with poor prognosis.

Paraganglioma



Present with symptoms of **catecholamine secretion**
Urinate→ Hypertension or loss of consciousness

Derived from paraganglion cells of the bladder, so **submucosal**

Typical architecture: "**Zellballen**" with nests separated with a rich vascular network of sustentacular cells.

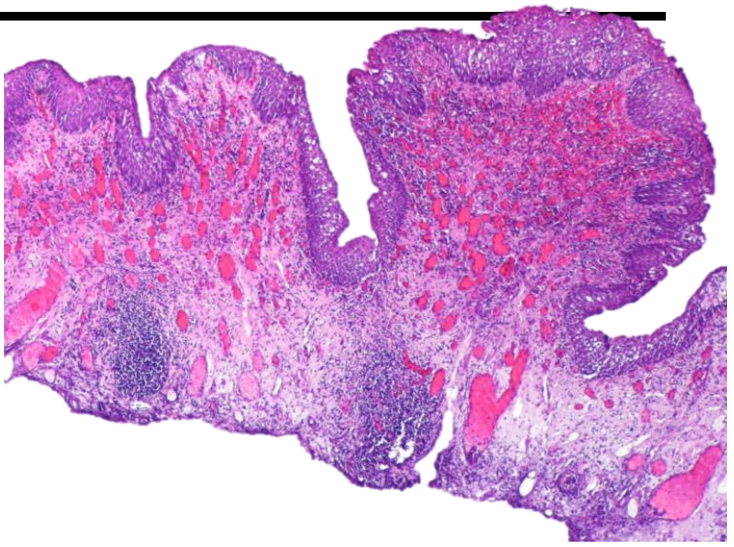
Cell have amphophilic to acidophilic cytoplasm

IHC: **Synaptophysin**/Chromogranin positive in tumor cells; **S100**/Sox10 positive in sustentacular cells. CK negative. **GATA3 positive**.

Germline SDH mutations present in some cases (Carney-Stathakis syndrome) with familial GIST

Often benign behavior if low stage, but can metastasize.

Polypoid cystitis



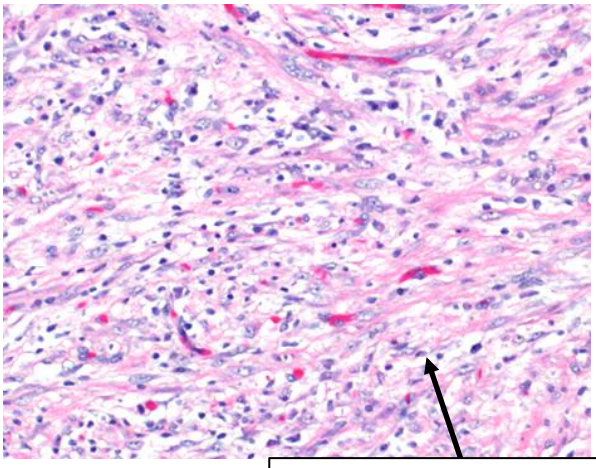
Benign. **Reaction to any inflammatory insult**
(most commonly an indwelling catheter)

Submucosal edema, fibrosis, and inflammation
→ broad bulbous projections covered with reactive urothelium

(*No* epithelial branching, epithelial thickening, atypia or delicate cores, like in papillary neoplasms)

Mesenchymal Lesions

Inflammatory Myofibroblastic Tumor



Fibroblastic/myofibroblastic origin
Most common in children and young adults

Loose stellate to spindled cells in a myxoid background
Admixed inflammatory cells
Mild amounts of collagen
Infiltrative, often into muscle
Mitoses, but no atypical ones
Delicate vascular network
NO significant hyperchromasia

IHC: Positive SMA; Sometimes aberrant CK; **ALK positive in ~60%** (FISH or IHC)

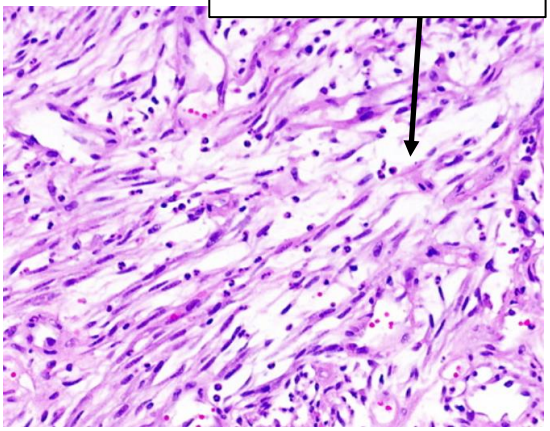
May recur, but very rarely metastasize.
Usually treated with TURBT or partial cystectomy

Neoplastic (clonal)

Myofibroblastic Proliferations

Reactive (after instrumentation)

Pseudosarcomatous Myofibroblastic Proliferation



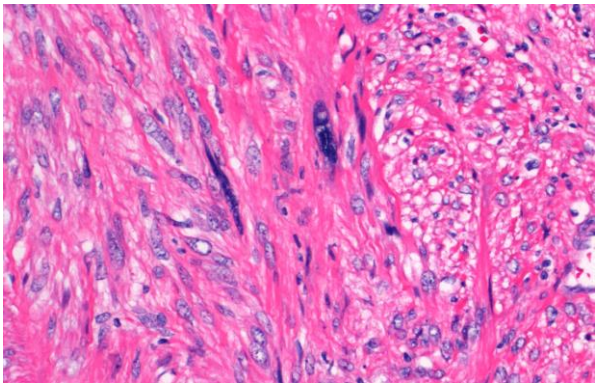
Aka: "inflammatory pseudotumor," or "Post-operative spindle cell nodule"

Can get what are thought to be reactive spindle cell lesions after instrumentation.

A little **controversial** if this is the ***same entity as inflammatory myofibroblastic tumor (IMT)***

- Identical appearance (nodular fasciitis-like with inflammatory cells and myxoid background)
- Identical IHC in many cases
- Some people use a single combined Dx (IMT/PMP)

Leiomyosarcoma



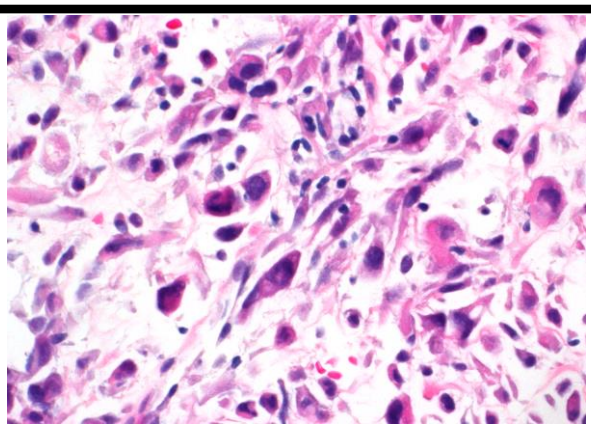
Malignant tumor arising from or differentiating along the lines of **smooth muscle**.
Most common urinary bladder sarcoma

Infiltrative. **Intersecting fascicles**.
Eosinophilic **spindled cells with cigar-shaped nuclei**
Cytologic atypia, high cellularity, mitotic activity, tumor necrosis.

IHC: Positive SMA, desmin, h-caldesmon, calponin

Poor prognosis

Rhabdomyosarcoma



Malignant tumor with **skeletal muscle differentiation**

Often Children and Embryonal subtype

Composed of primitive spindled to rhabdoid cells in a myxoid background. Numerous rhabdomyoblasts and/or strap cells. Can see cross-striations.

Botryoid type forms multiple grape-like polypoid projections with characteristic cellular cambium layer below mucosa

IHC: Positive Desmin, **MyoD1, Myogenin**. Sometimes patchy CK or neuroendocrine markers.

(Very rare in adults, more commonly sarcomatoid urothelial carcinoma with heterologous differentiation)

Other Mesenchymal Tumors

PEComa
Angiosarcoma
Solitary Fibrous Tumor
Leiomyoma
Hemangioma
Granular cell tumor
Neurofibroma

Immunohistochemistry for Spindle Cell Lesions of the Bladder

Recommended First Panel: ALK1, SMA, desmin, cytokeratin (AE1/AE3), GATA3, and p63 with a HMWCK (e.g., CK5/6) *(with possible second panel with myogenin, S100, etc..)*

IHC Stain	IMT/PMP	Sarcomatoid Carcinoma	Leiomyosarcoma	Rhabdomyosarcoma
ALK1	+/-	-	-	-
SMA	+/-	+/-	+	-/+
Desmin & h-caldesmon	-/+	-	+	+
Myogenin & MyoD1	-	-	-	++
CK AE1/AE3	-/+	+/-	-	-
p63 & p40	-	+	-	-
HMWCK (e.g., CK5/6)	-	+	-	-
GATA3	-	+/-	-	-