

Grading Flat and Papillary Urothelial Lesions: Genitourinary Pathology Society (GUPS) Recommendations

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Genitourinary Pathology Society (GUPS)

- **Established in 2018**
- **International organization aiming to promote the care of patients with urologic diseases by encouraging best practice, research, and education in urologic pathology**



GUPS

Genitourinary
Pathology Society

www.gupathsociety.org



Genitourinary Pathology Society (GUPS) Bladder Project

- **Critical review of the recent advances in bladder neoplasia, focusing on evidence accumulated post-2016 WHO classification**
- **2 manuscripts published in *Advances in Anatomic Pathology* (May, 2021)**
 - ✓ **Classification and grading of flat and papillary urothelial neoplasia**
 - ✓ **Variants/subtypes**
 - ✓ **Substaging and reporting T1 cancer**
 - ✓ **Molecular taxonomy**
 - ✓ **Immune checkpoint inhibitors and PD-L1 testing**



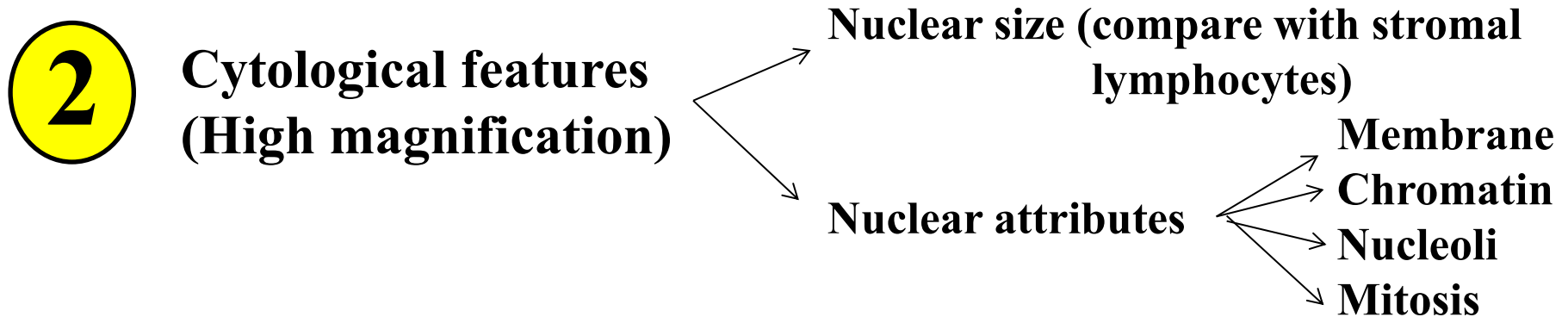
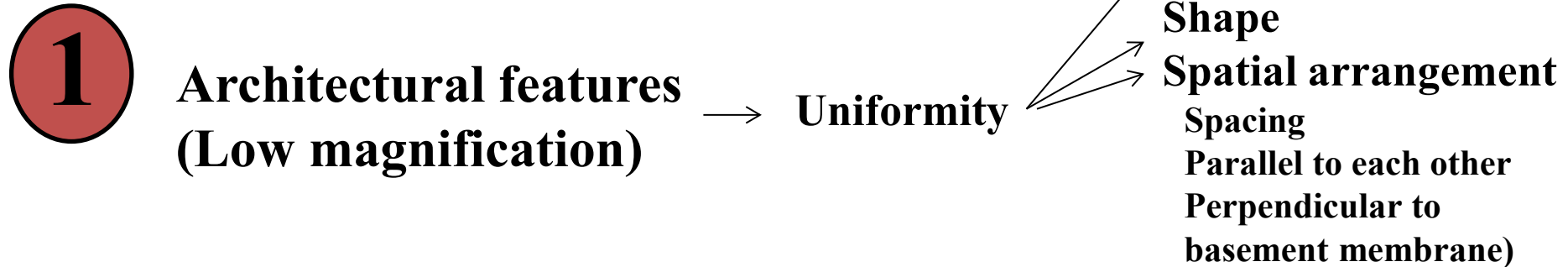
Flat Lesions of the Urinary Tract

- **Flat urothelial lesions**
 - ✓ **Flat urothelial hyperplasia**
 - ✓ **Flat lesions with atypia**
 - **Reactive atypia**
 - **Atypia of unknown significance**
 - **Urothelial dysplasia**
 - **Urothelial carcinoma in situ (CIS)**
- **Flat squamous lesions**
- **Flat glandular lesions**



Flat Urothelial Lesions with Atypia

3-Step Diagnostic Approach



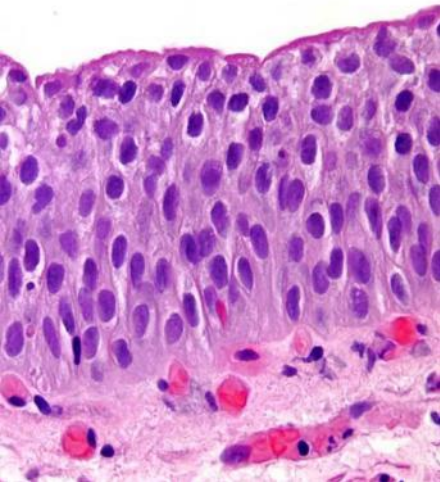
1

**Architectural features
(Low magnification)**

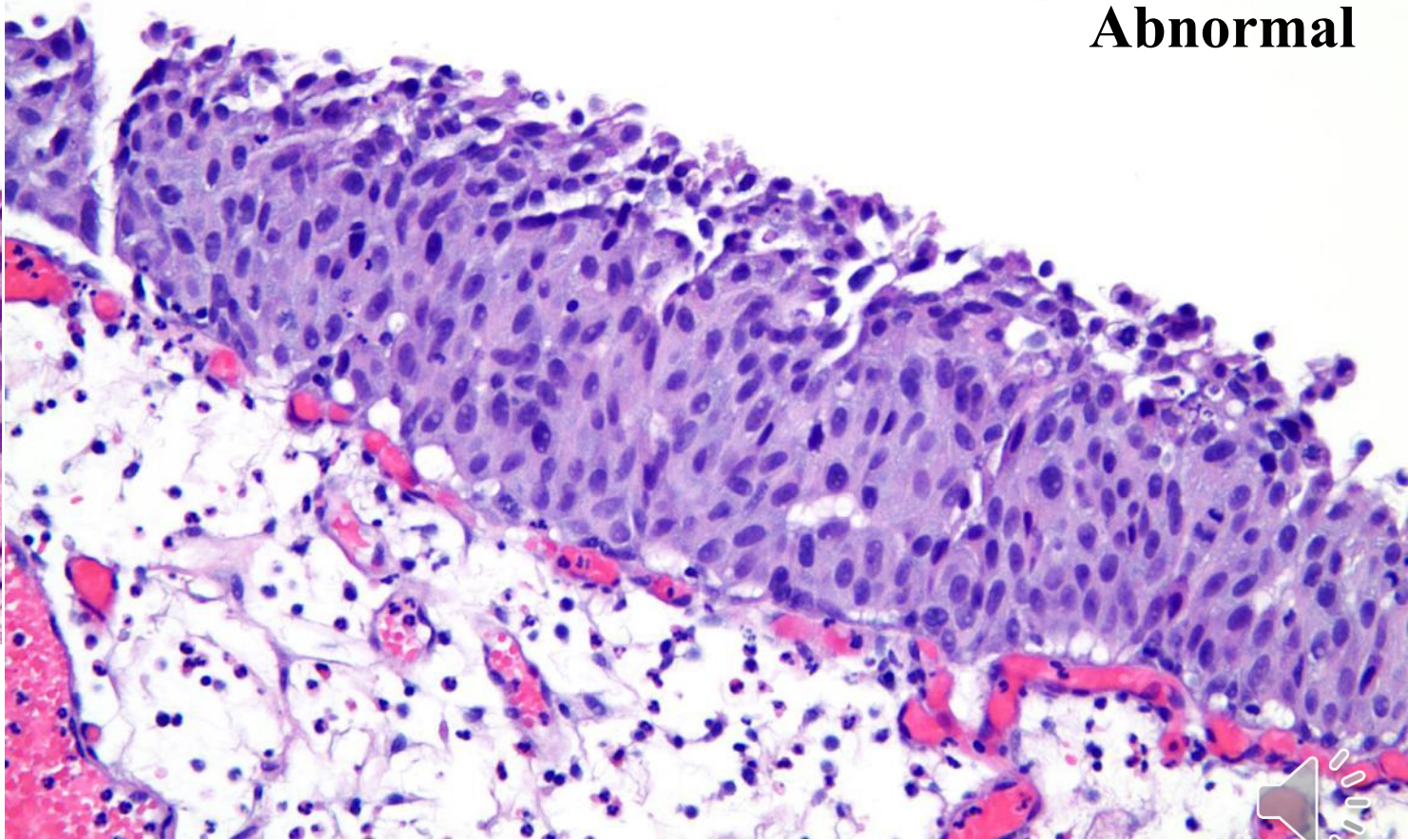
→ **Uniformity**

- Size
- Shape
- Spatial arrangement
- Spacing
- Parallel to each other
- Perpendicular to basement membrane)

Normal



Abnormal



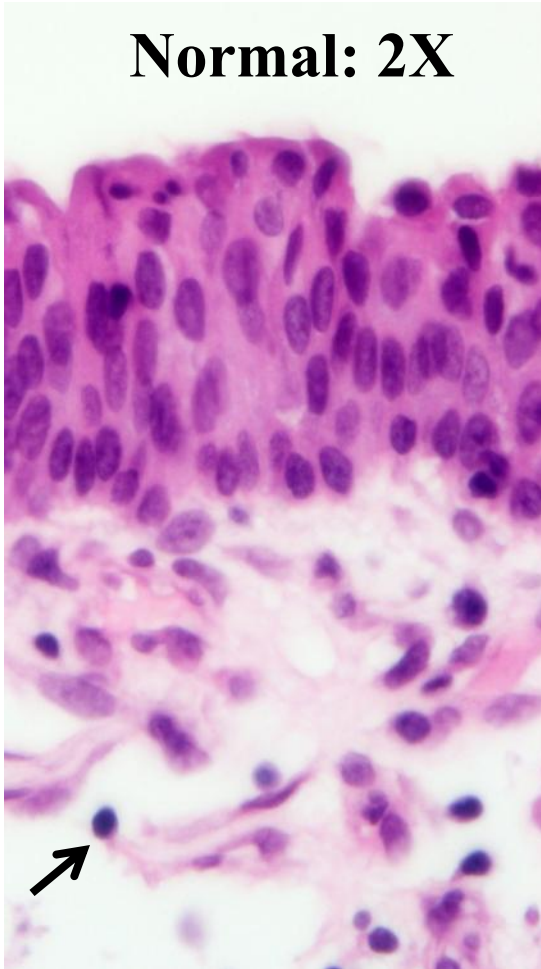
2

**Cytological features
(High magnification)**

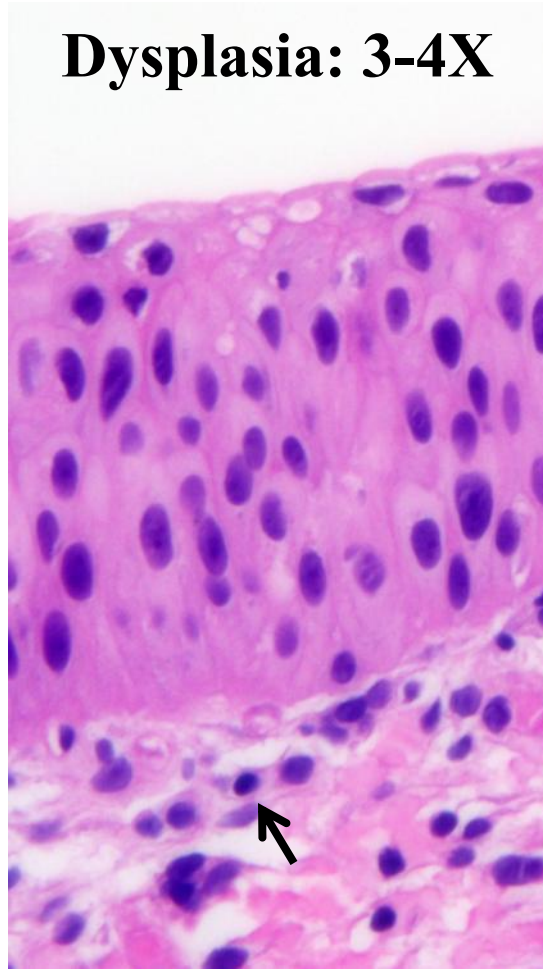
**Nuclear size (compare with stromal
lymphocytes)**

“Rule of stromal lymphocyte”

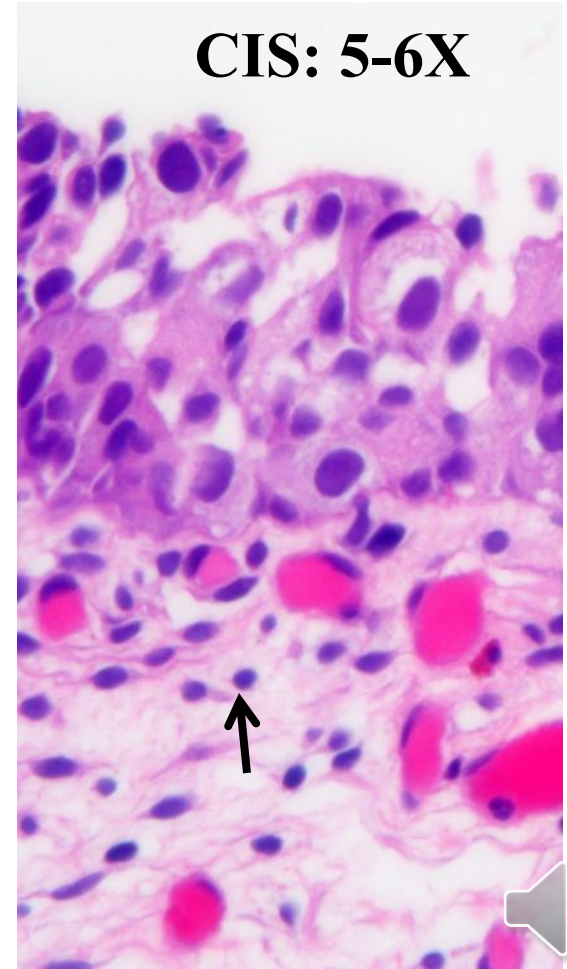
Normal: 2X



Dysplasia: 3-4X



CIS: 5-6X

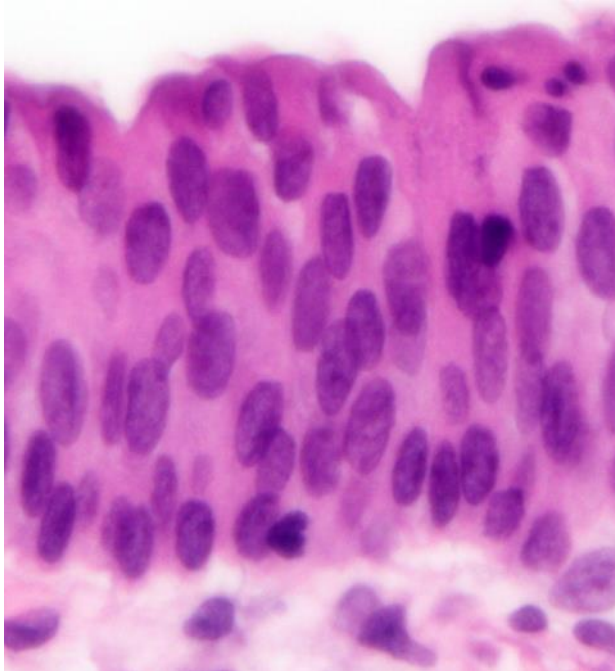


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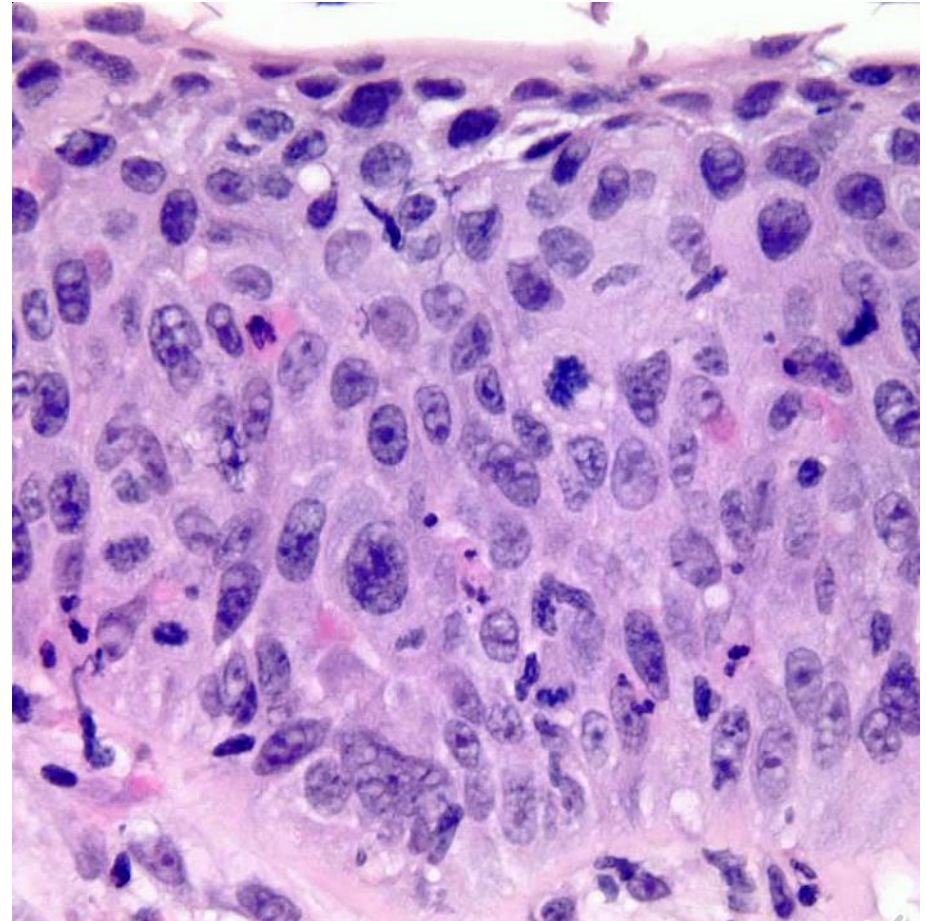
**Cytological features
(High magnification)**

Nuclear attributes

- Membrane**
- Chromatin**
- Nucleoli**
- Mitosis**



Normal

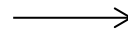


CIS

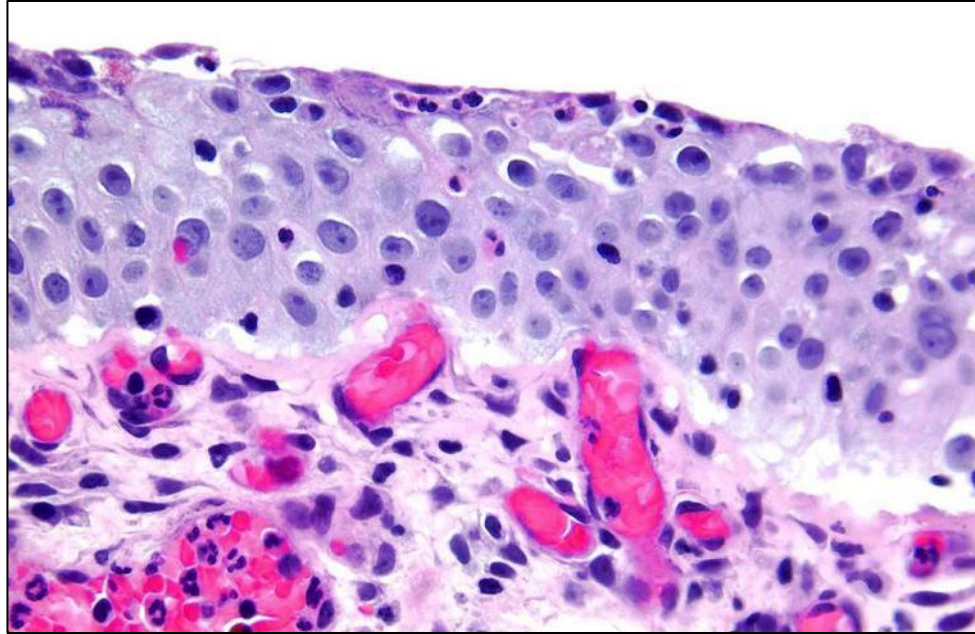


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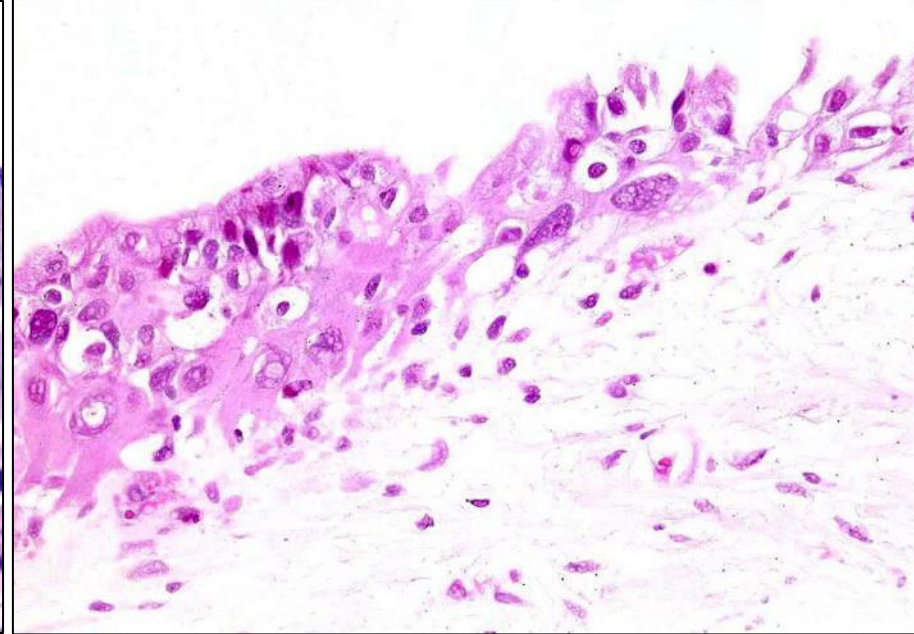
**Rule out conditions
that may cause atypia**



**Inflammation
Stone
Intravesical treatment
Radiation**



Reactive atypia due to inflammation



Degenerative atypia due to radiation

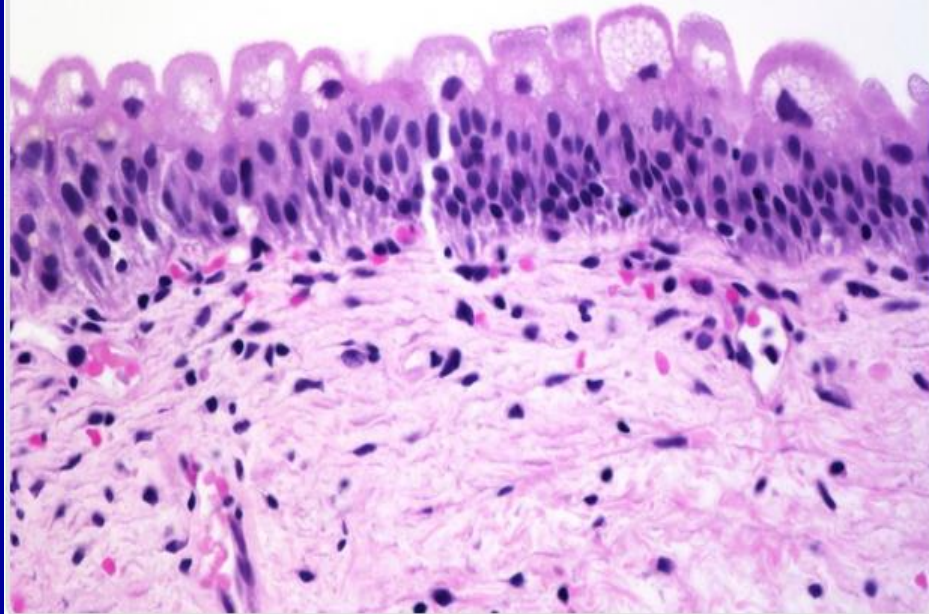


Flat Urothelial Hyperplasia

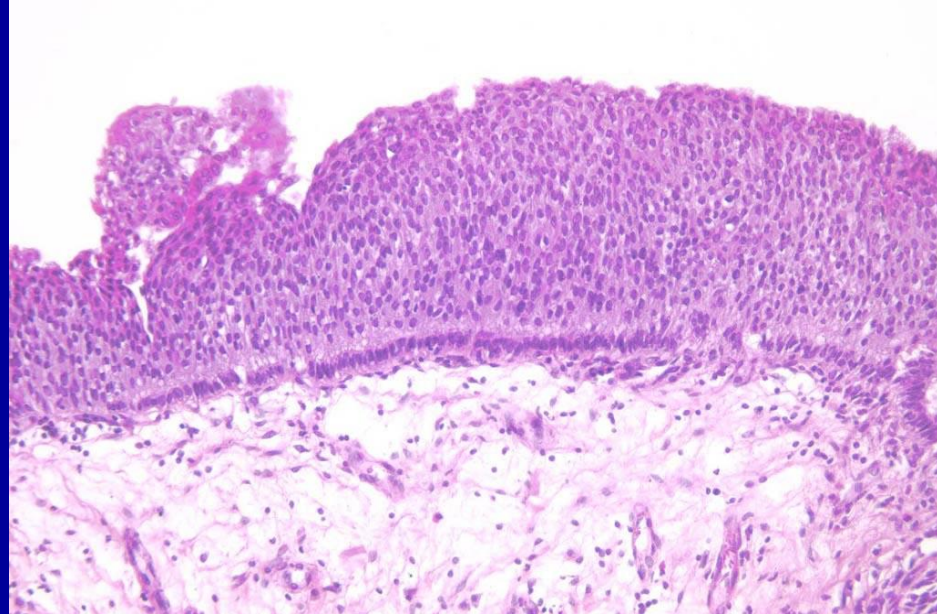
- **Significantly thickened urothelium**
 - ✓ No specific criterion (typically >9 cell layers)
 - ✓ Increased cell density
- **Minimal to no cytological atypia**
 - ✓ If significant atypia present- Dysplasia/CIS
- **Flat architecture**
 - ✓ Slight undulation of the urothelium is acceptable, but no true papillary formation
 - ✓ Tangential sectioning ruled out
- **2016 WHO renamed it with papillary hyperplasia as urothelial proliferation of uncertain malignant potential (UPUMP)**
- **GUPS: atypical urothelial proliferation- flat**



Normal



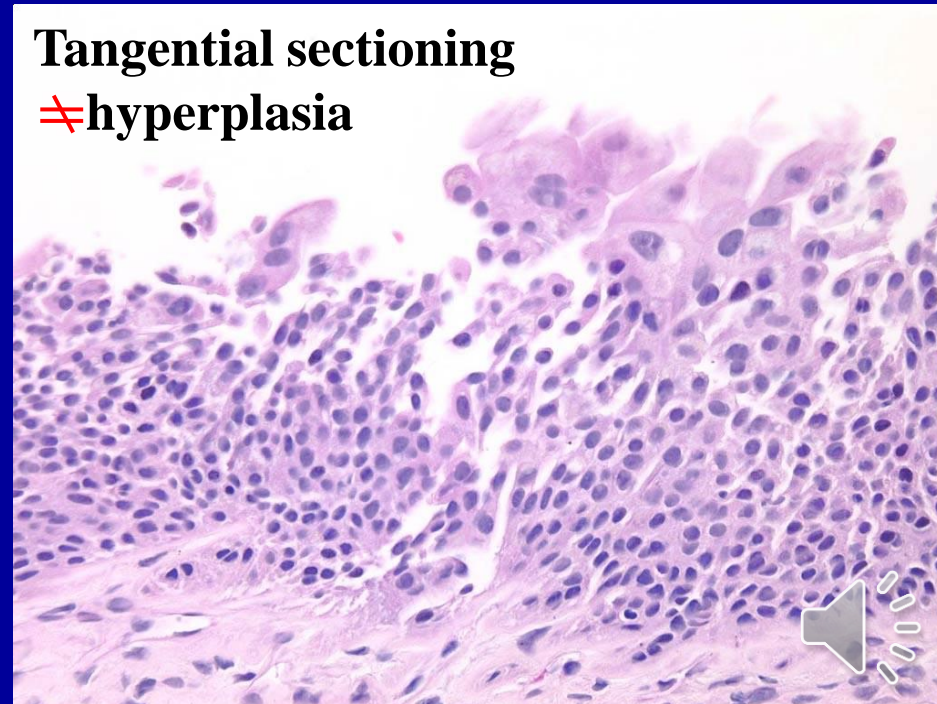
Flat hyperplasia



Flat with "tenting"

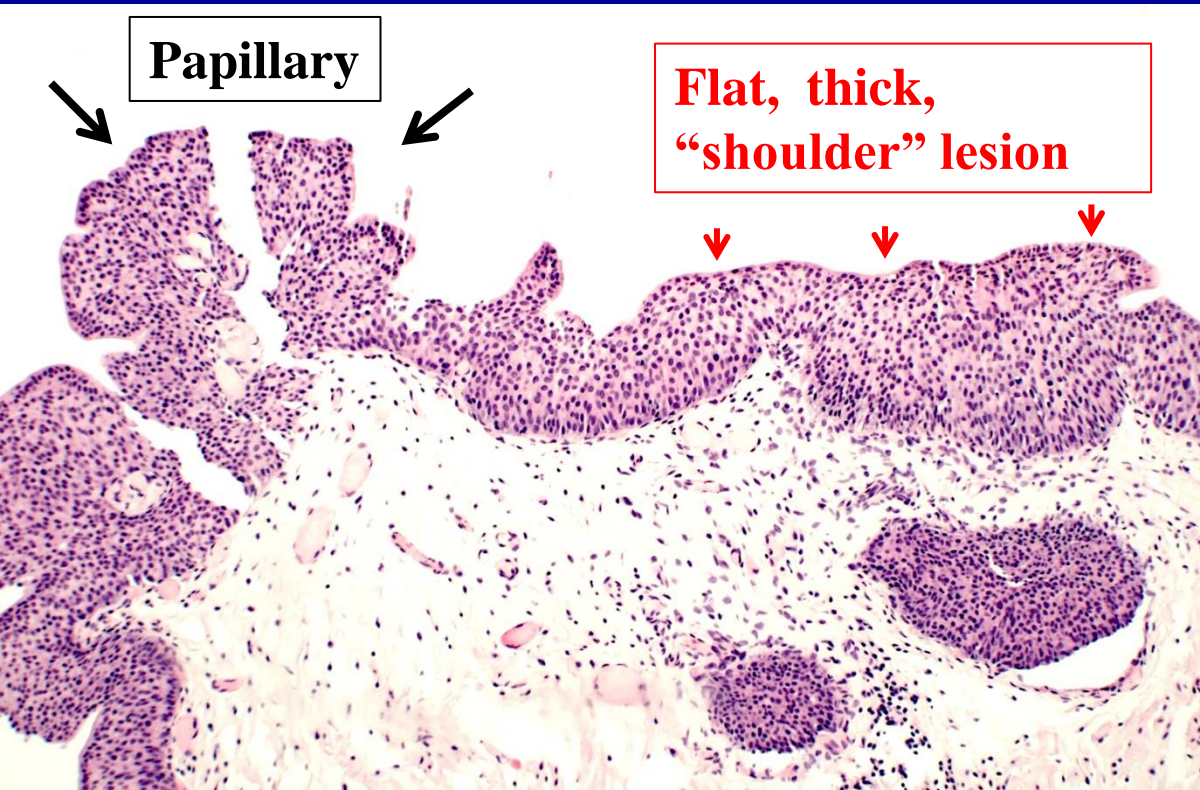


**Tangential sectioning
≠ hyperplasia**



Flat Urothelial Hyperplasia

Clinical Significance



➤ Typically a “shoulder lesion”- lateral extension of low grade urothelial neoplasia

✓ No need to report

➤ Less common as a *de novo* finding

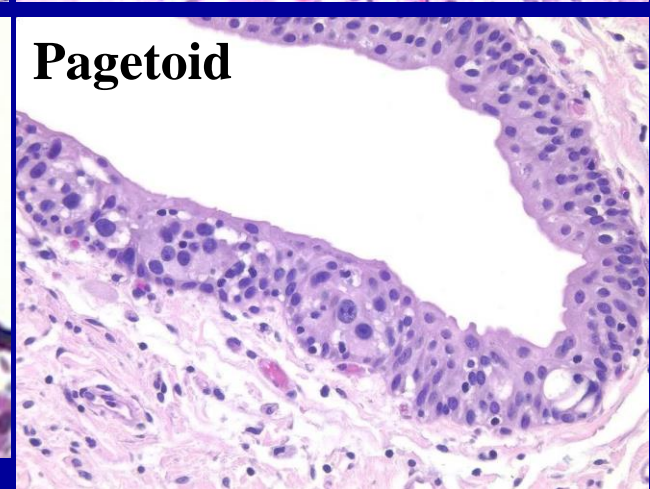
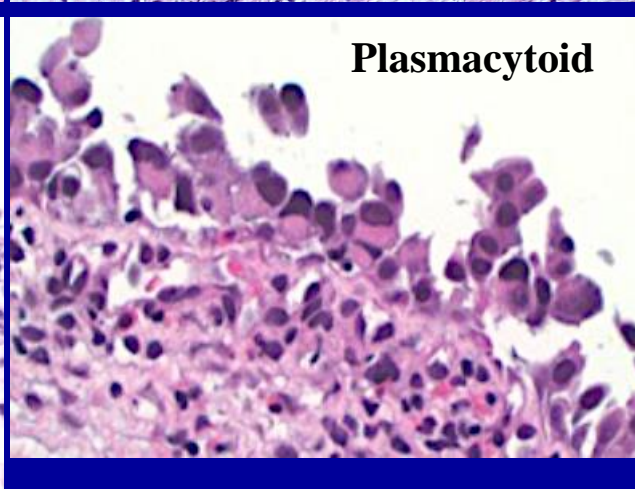
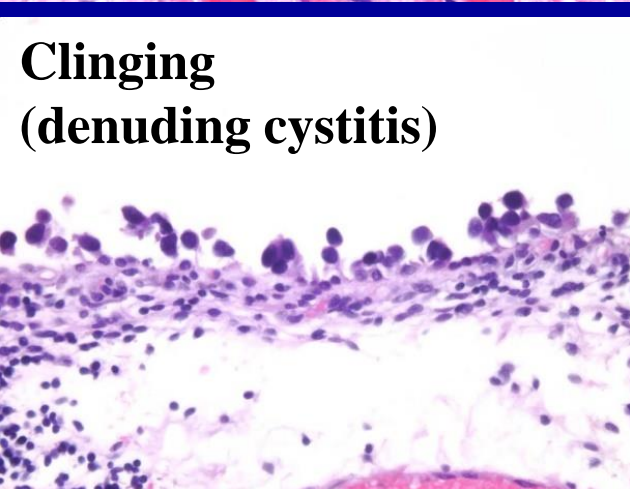
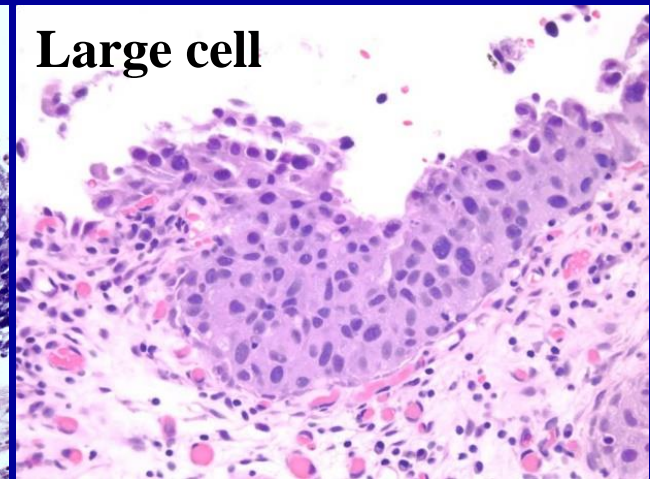
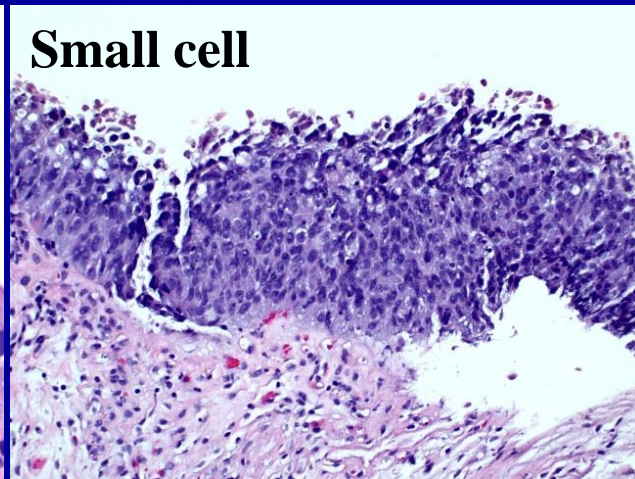
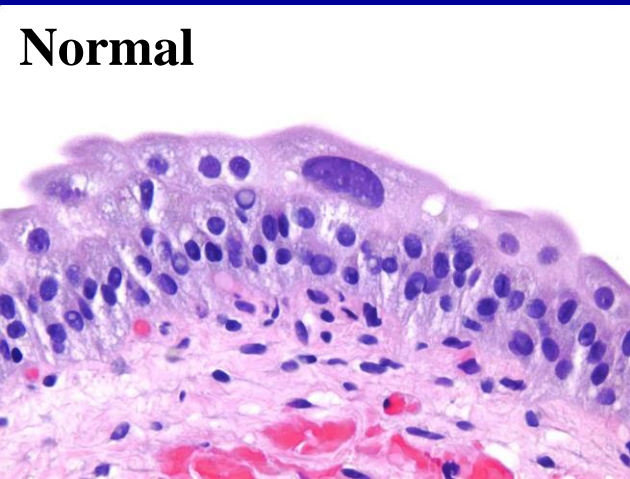
✓ Not as closely associated with subsequent neoplasia compared to papillary hyperplasia

➤ **Diagnosis: flat urothelial hyperplasia (UPUMP/atypical urothelial proliferation-flat)**

✓ May be associated with or a precursor to early non-invasive low-grade neoplasia



Urothelial Carcinoma in Situ

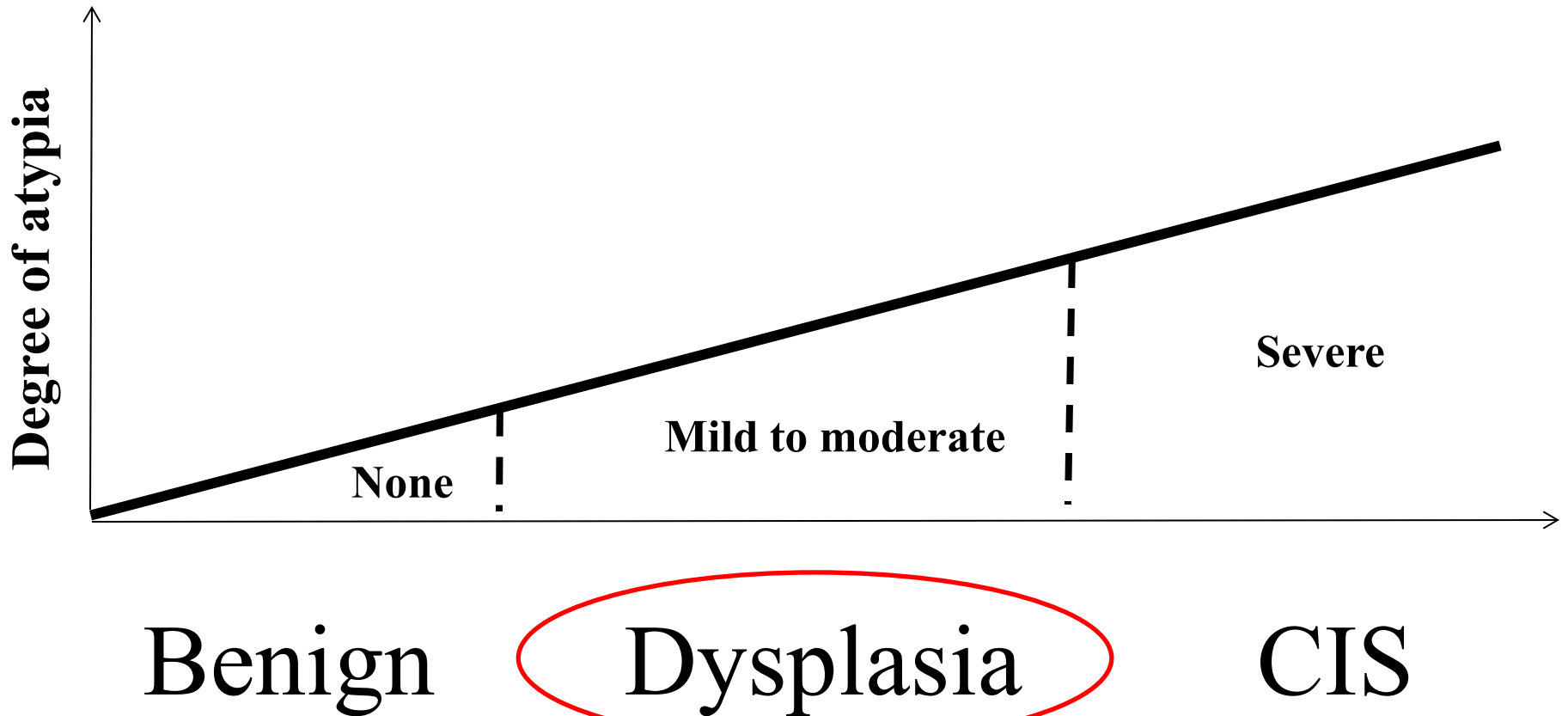


Urothelial Carcinoma in Situ

- **Primarily a cytologic diagnosis**
 - ✓ **Full thickness involvement of the urothelium not required**
 - ✓ **Umbrella cells may be present**
 - ✓ **Correlation with concurrent urine cytology: diagnostically helpful**
 - ✓ **Be aware of certain subtypes (pagetoid, plasmacytoid) at frozen sections**
- **Different patterns have no impact on clinical outcomes; do not mention in the report**



Flat Urothelial Proliferative Lesions: A Morphological Continuum



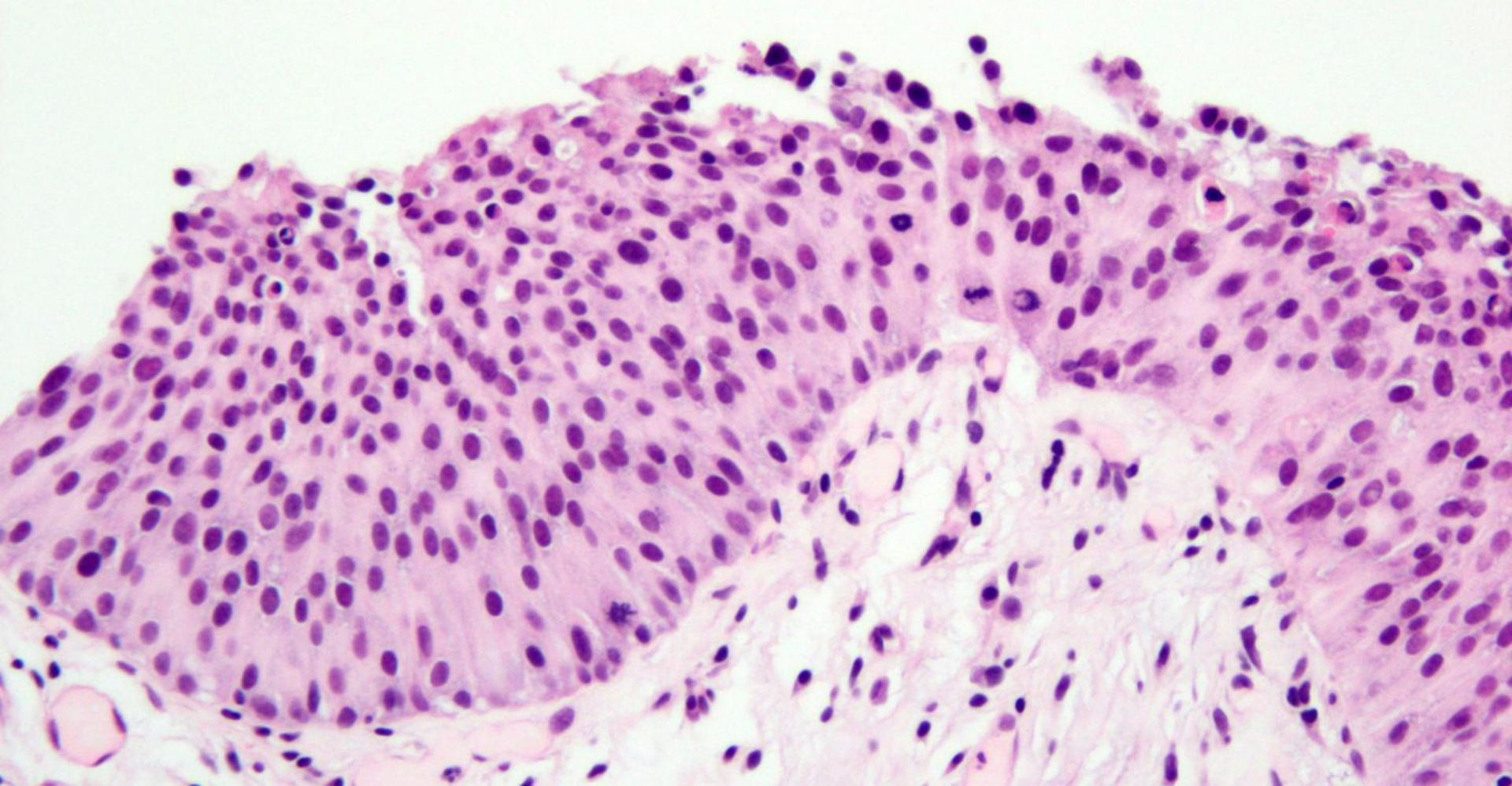
Urothelial Dysplasia

Diagnostic Criteria

- **WHO: appreciable cytological and architectural features that are believed to be preneoplastic but fall short of the diagnostic threshold for urothelial CIS**
- **Lacks objective criteria; poor reproducibility**



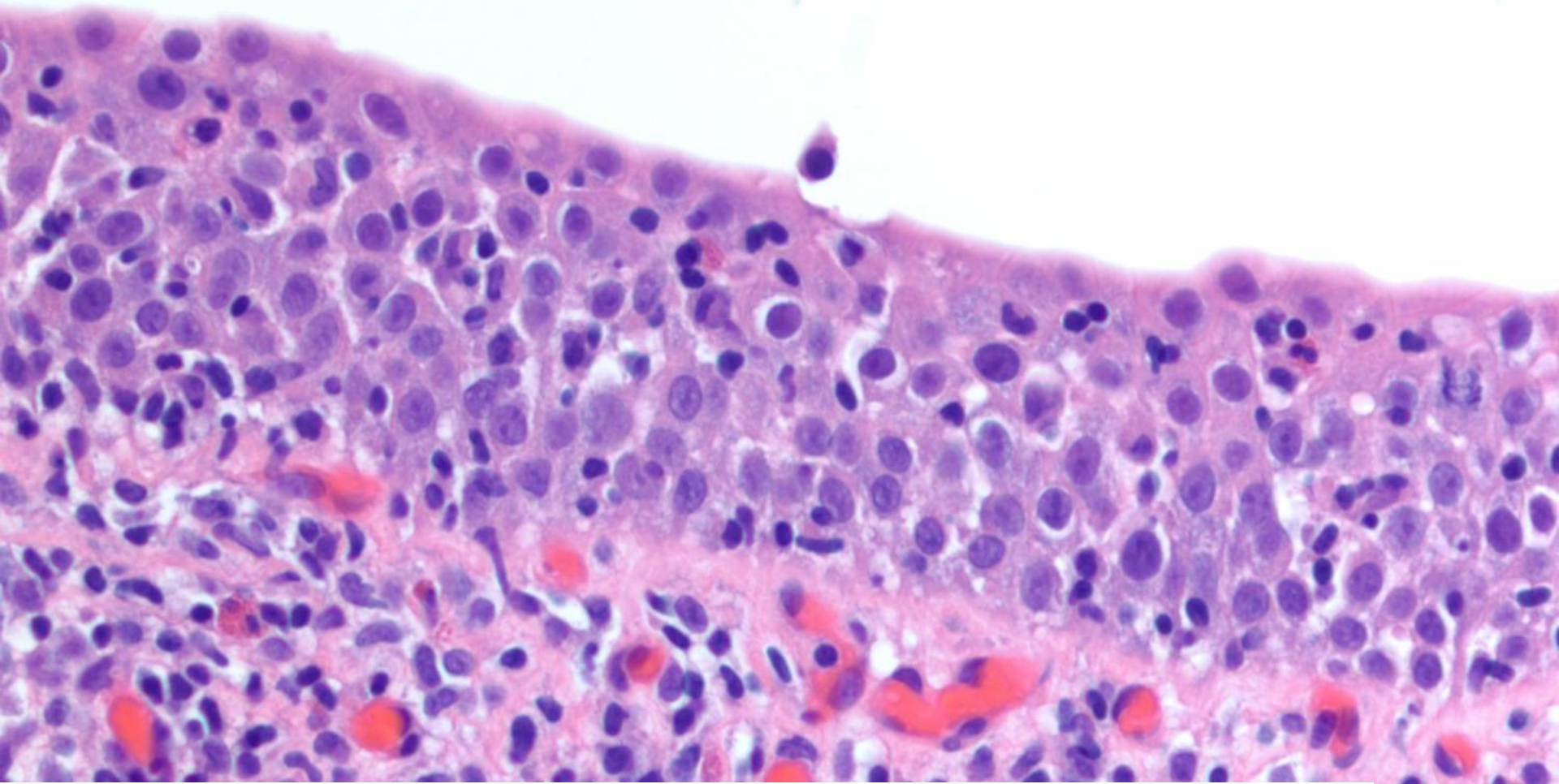
Urothelial Dysplasia



- **Architecture: slightly disordered architecture (irregular spacing)**
- **Nuclei: enlarged (3-4X), hyperchromasia, increased mitosis**
- **Inflammation: absent**



Reactive Atypia

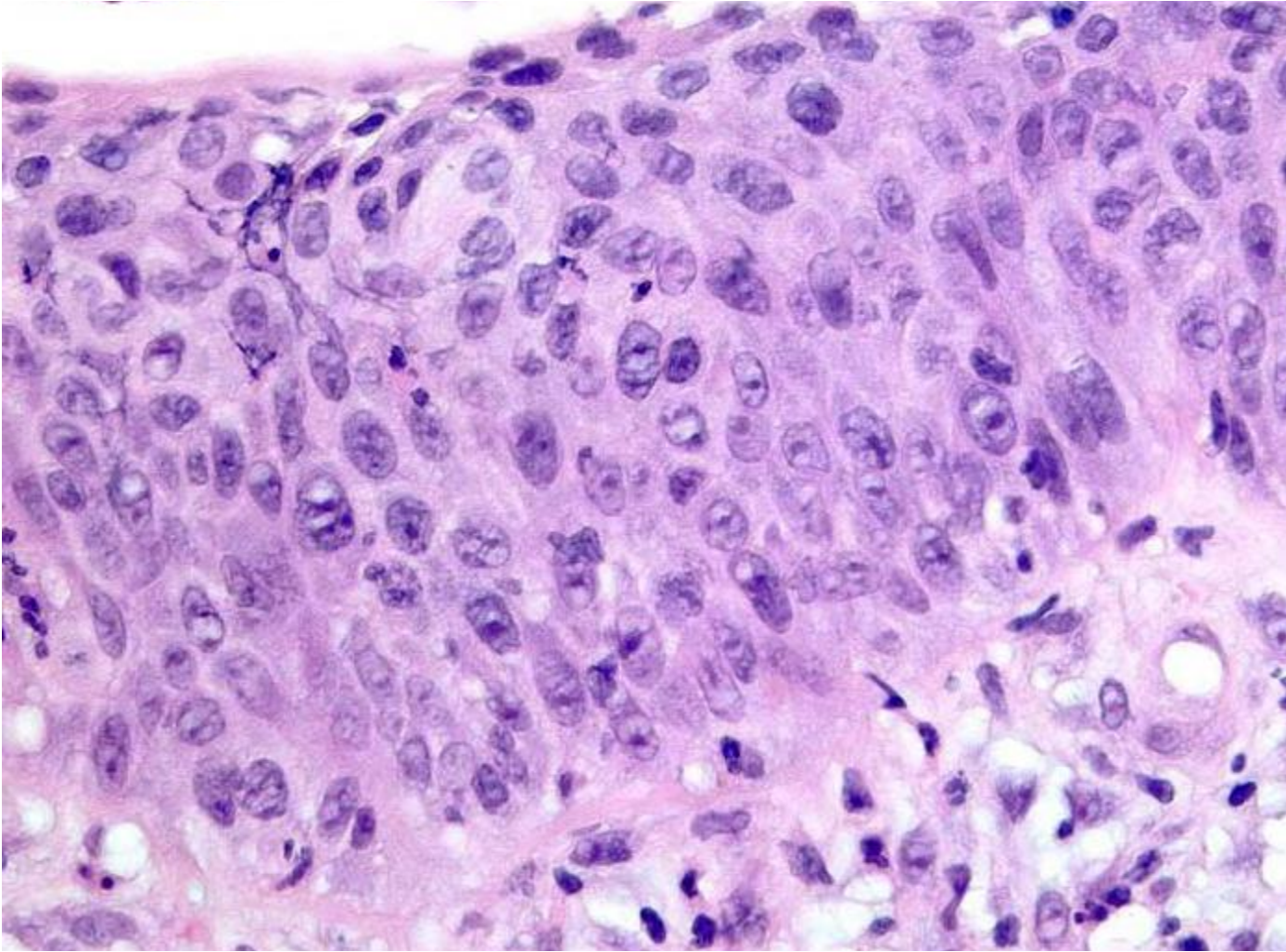


- **Uniformity maintained (size, shape, spacing); polarity may be lost**
- **Nuclei uniformly enlarged, smooth nuclear membrane and chromatin, prominent nucleoli**
- **Inflammation in the mucosa or lamina propria**
- **History of stone, trauma, cystitis, therapy**



Urothelial Atypia with Unknown Significance

(Diagnostic category, not an entity!)



- **Architecture:** Loss of polarity, irregular spacing
- **Nuclei:** enlarged (5-6X), variation in nuclear size and shape
- **Inflammation:** brisk

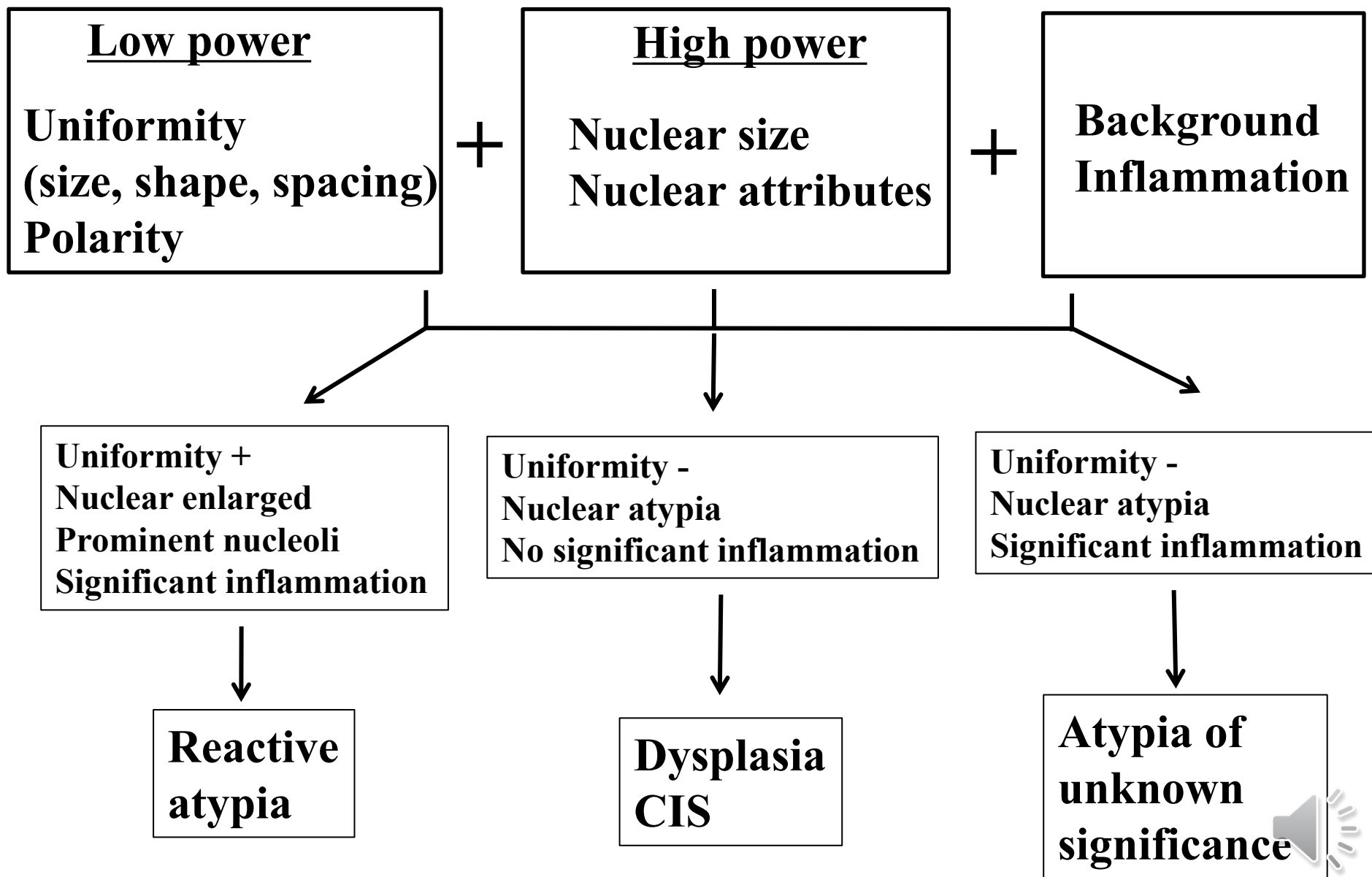


Urothelial Atypia with Unknown Significance

- Flat lesion with significant atypia AND significant inflammation
- Diagnostic category, not a biological entity
 - ✓ Reactive lesion with significant architectural and cytological atypia
 - ✓ Dysplasia or CIS associated with significant inflammation
- Implication for urologists: treat inflammation and follow up with repeat biopsy
- Do not abuse it: not for “a diagnosis that I am not sure about or have no clue for”

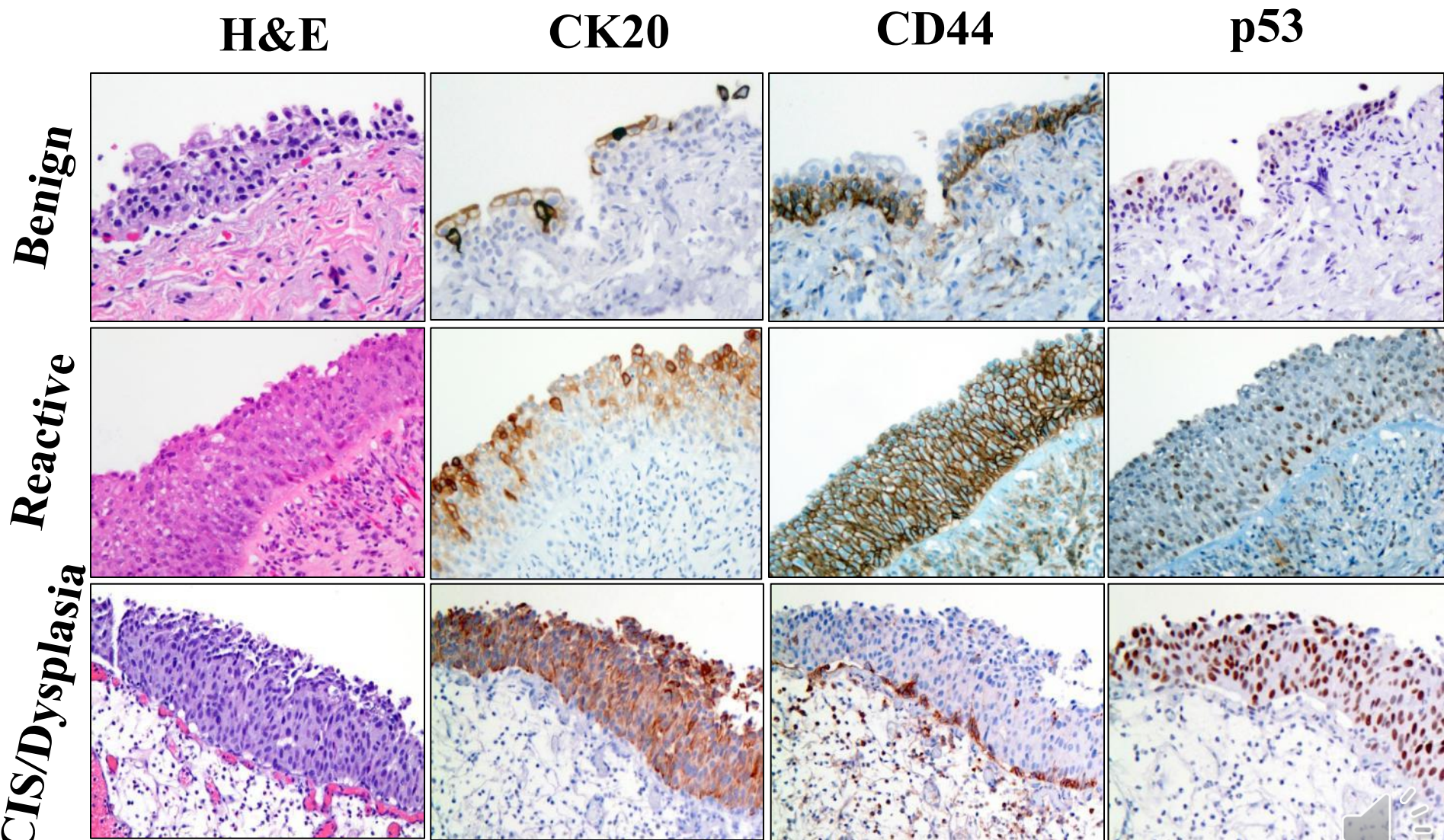


Working up Flat Urothelial Lesions



Flat Urothelial Lesions

Immunohistochemistry



Flat Urothelial Lesions

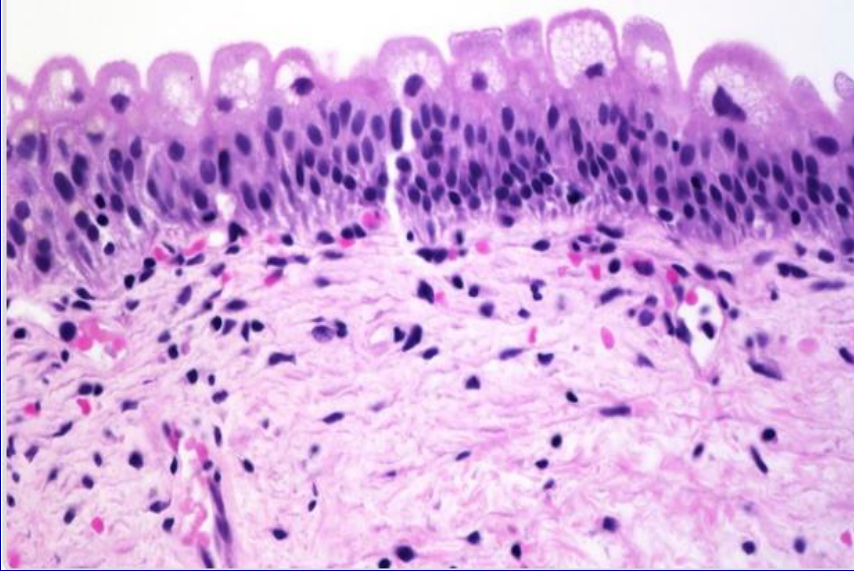
Immunohistochemistry

- **Markers often have discordant or indeterminate staining patterns**
- **For flat atypical urothelial lesions**
 - ✓ **Concurrent or history of bladder cancer, not the staining pattern, predicts recurrence** (Arias-Stella et al Arch Path Lab Med 2018)
 - ✓ **IHC does not contribute to resolving “atypical flat lesions”** (McIntire et al Ann Diag Pathol 2019)
- **Immunohistochemistry is NOT recommended to be used in this diagnostic setting**

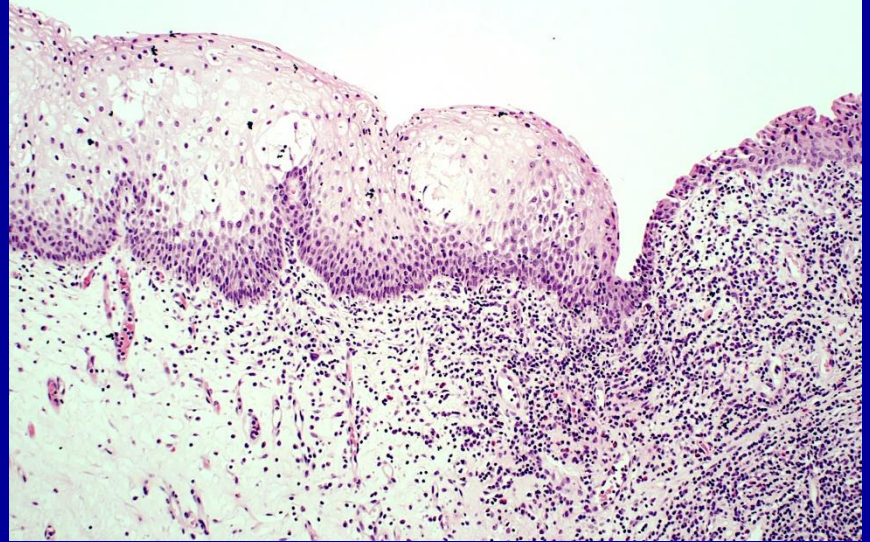


Flat Squamous Lesions of the Urinary Tract

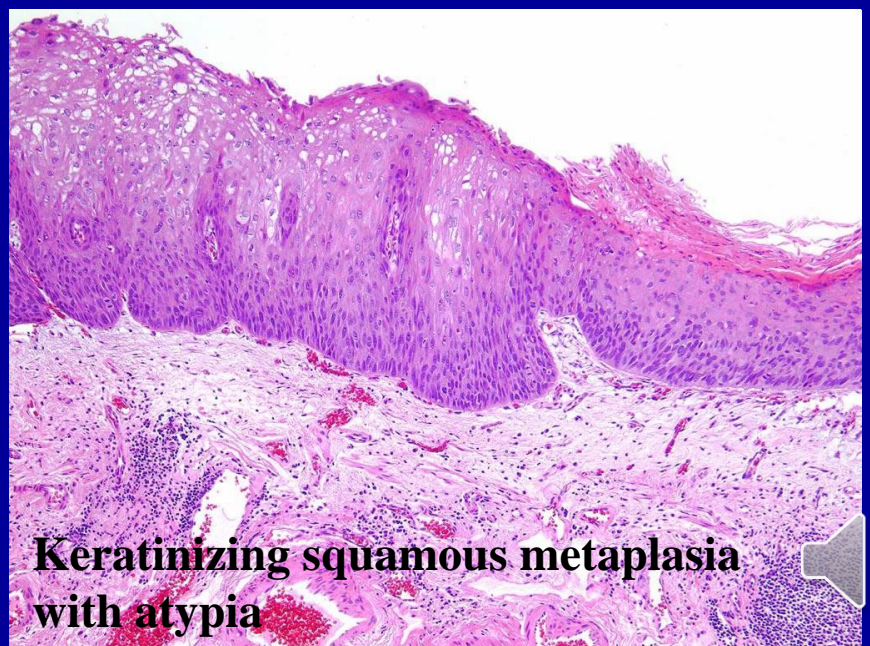
Normal



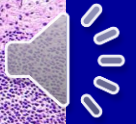
Non-keratinizing squamous metaplasia



Keratinizing squamous metaplasia without atypia



Keratinizing squamous metaplasia with atypia



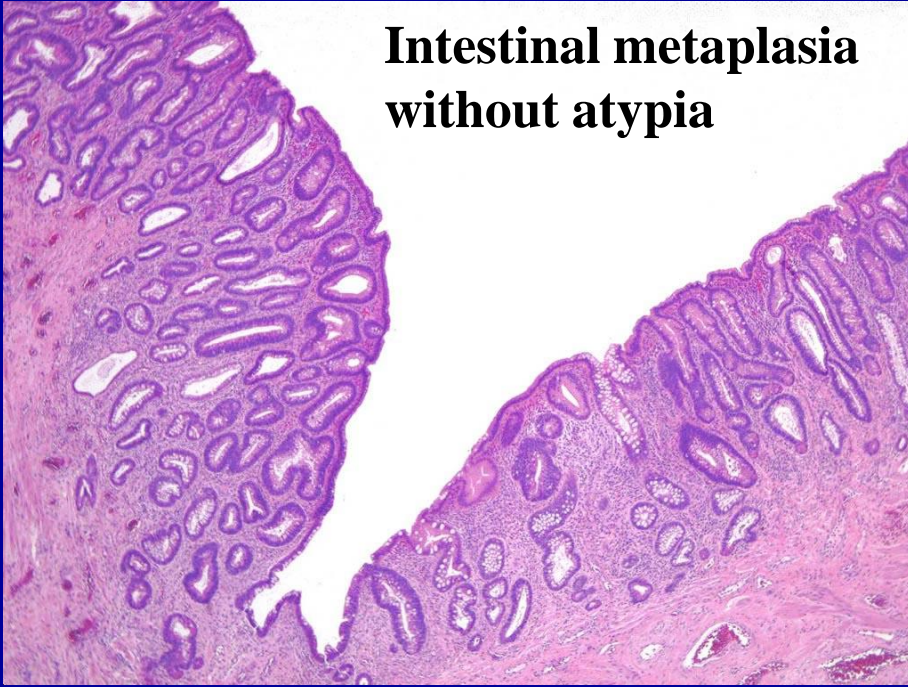
Flat Squamous Lesions

Lesion	Significance	Reporting
Non-keratinizing squamous metaplasia	Common in women Normal variant histology	Do not report
Keratinizing squamous metaplasia without atypia	<ul style="list-style-type: none">- Commonly adjacent to squamous cell Ca- Predisposing factor for squamous neoplasia (risk difficult to determine)- Extensive (>50% bladder mucosa) more likely to be associated with adverse outcomes (bladder Ca, contracture)	Report and comment on the significance of “extensive”
Squamous dysplasia	Definitive precursor to invasive squamous cell Ca	Report

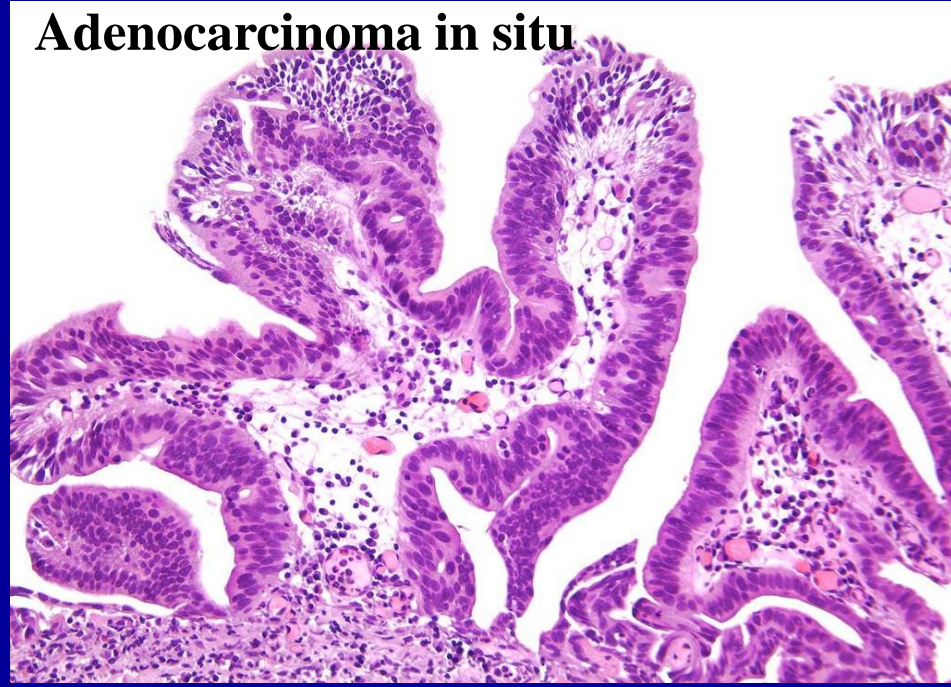


Non-invasive Glandular Lesions

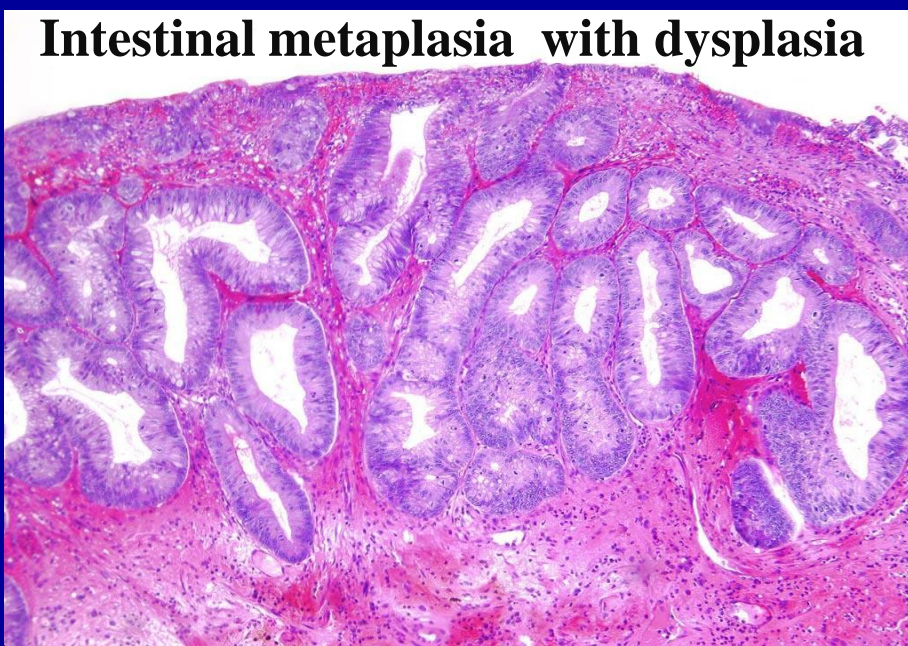
**Intestinal metaplasia
without atypia**



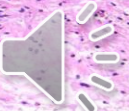
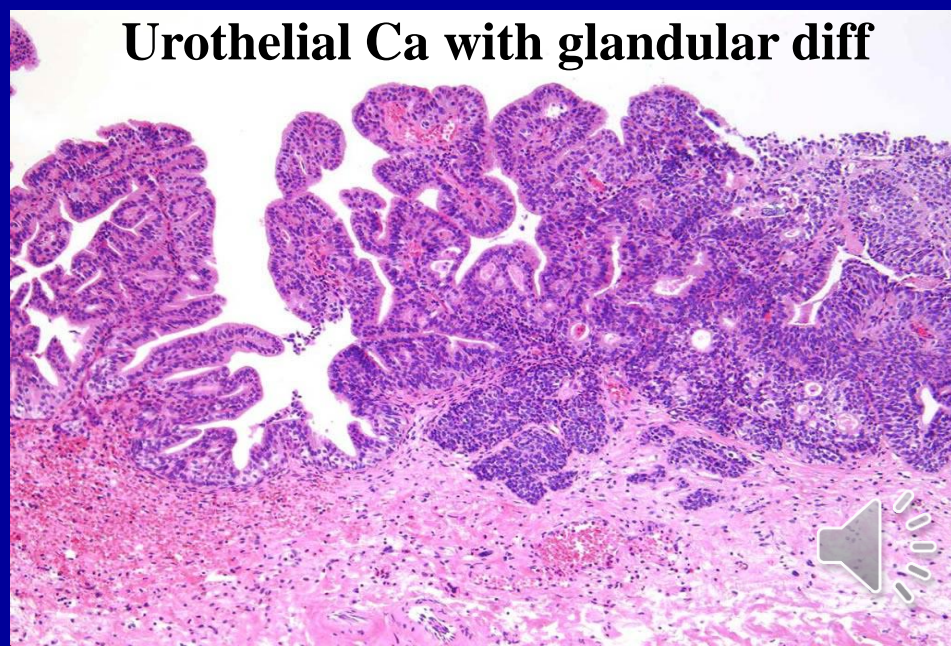
Adenocarcinoma in situ



Intestinal metaplasia with dysplasia



Urothelial Ca with glandular diff



Non-invasive Glandular Lesions

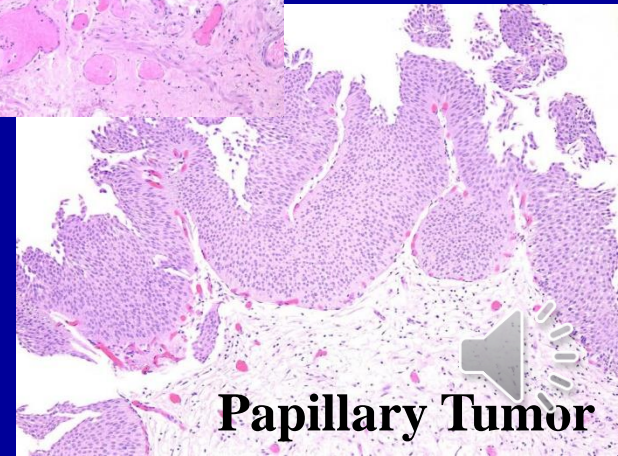
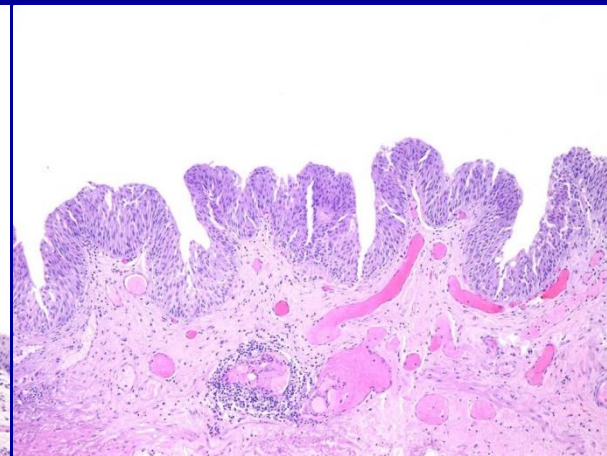
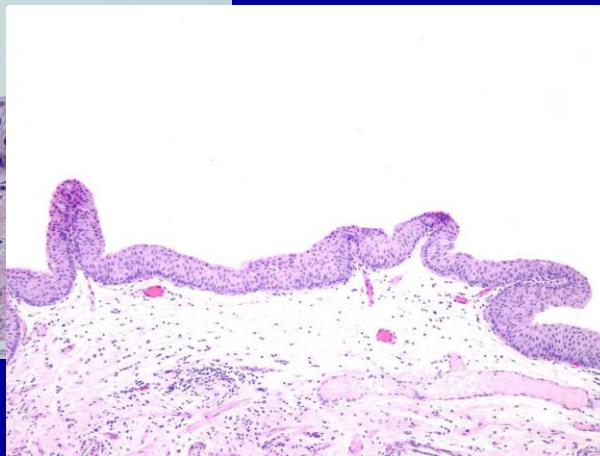
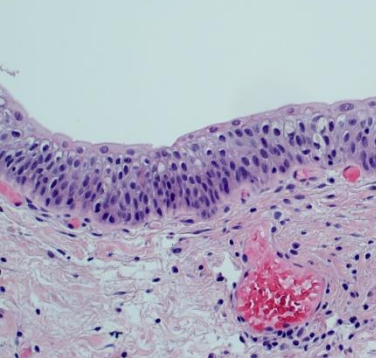
Lesion	Significance	Reporting
Urothelial CIS with glandular diff	Most common Often seen with invasive HGUC/small cell Ca	Optional to report
Intestinal metaplasia w/o dysplasia	- 0.1-0.9% - Associated with chronic irritation/inflammation - Not an obligate precursor lesion for Ca (oncogenic mutations in some cases)	No need to report
Intestinal metaplasia with dysplasia	- Concurrent with adenoca (often) and UC (rarely) - Risk for adenoca and UC	Report



Early Proliferative Papillary Lesions

- “Tweener” lesions, not fully developed papillary architectures
 - ✓ Tented/undulating appearance
 - ✓ No discrete and detached papillae

Normal

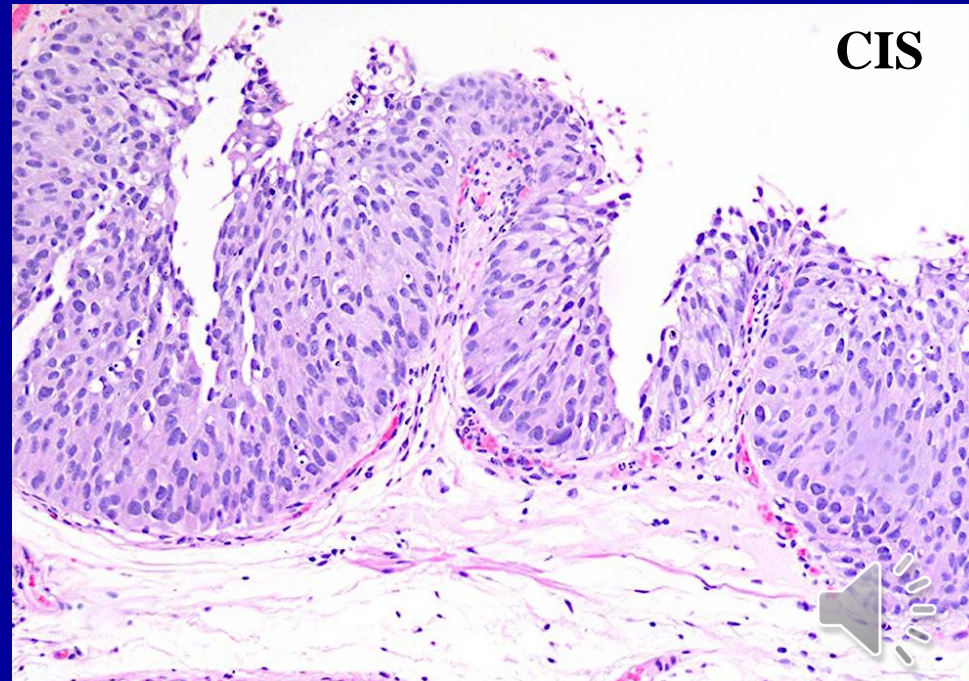
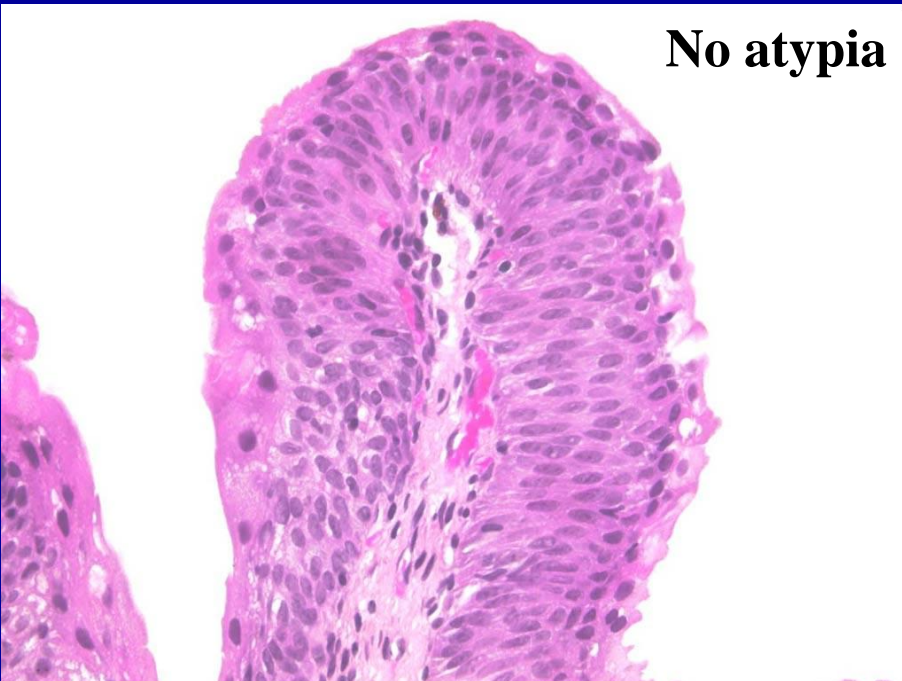


Flat vs papillary?

Papillary Tumor

Early Proliferative Papillary Lesions

- Thickened urothelium with varying degree of atypia
 - ✓ No cytological atypia
 - ✓ Atypia analogous to dysplasia
 - ✓ Atypia analogous to CIS

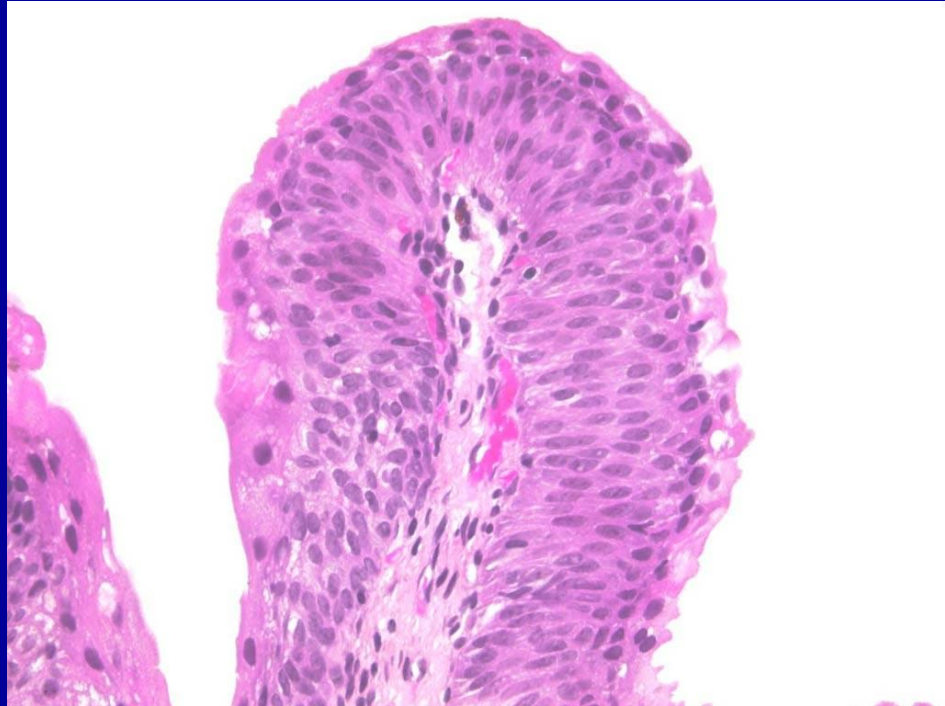
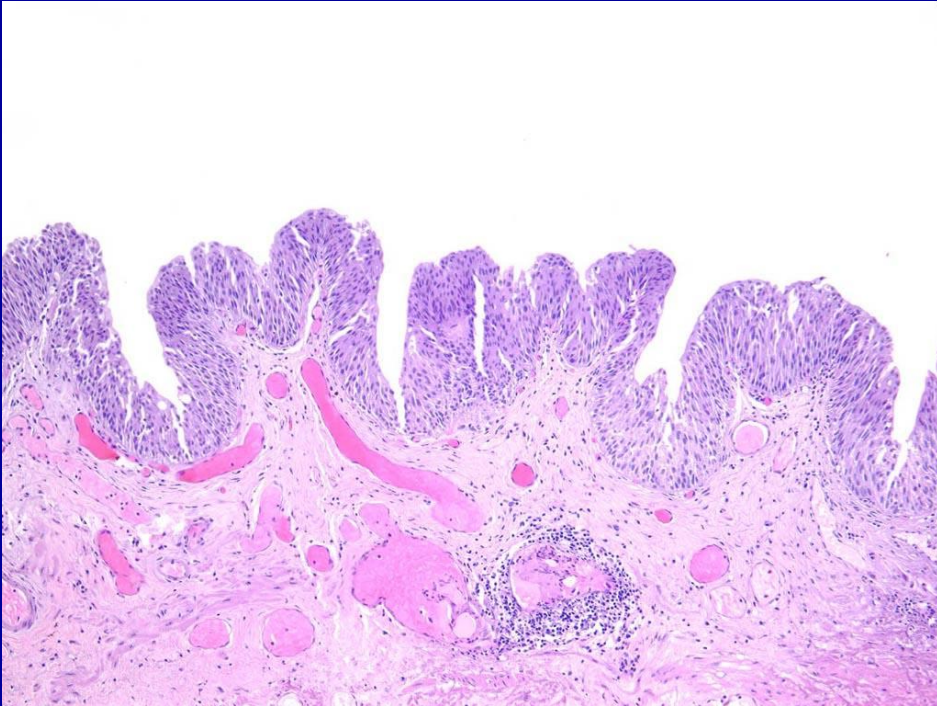


Early Proliferative Papillary Lesions

- Classification based on cytological features
 - ✓ No/minimum cytologic atypia: Papillary urothelial hyperplasia
 - ✓ With cytological atypia: Papillary urothelial carcinoma
- Two scenarios where morphology is “early proliferative papillary (neither completely flat nor papillary)”
 - ✓ “Early” papillary lesions may be biopsied due to frequent cystoscopic surveillance
 - ✓ “Truncated papillae” following intravesical treatment of papillary tumors



Papillary Urothelial Hyperplasia



- Undulating mucosa with tented morphology, no discrete and detached papillae
- Increased vascularity at the base of folds
- Thickened urothelium w/o atypia



Papillary Urothelial Hyperplasia

- 2016 WHO renamed papillary hyperplasia and flat urothelial hyperplasia as urothelial proliferation of uncertain malignant potential (UPUMP)
- Not well accepted
- GUPS recommendation: Atypical Urothelial Proliferation (AUP)-tentative

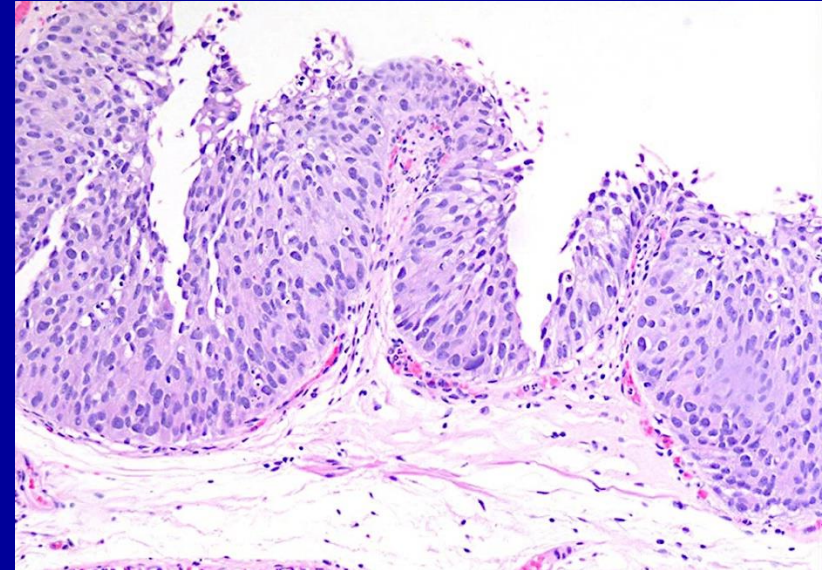
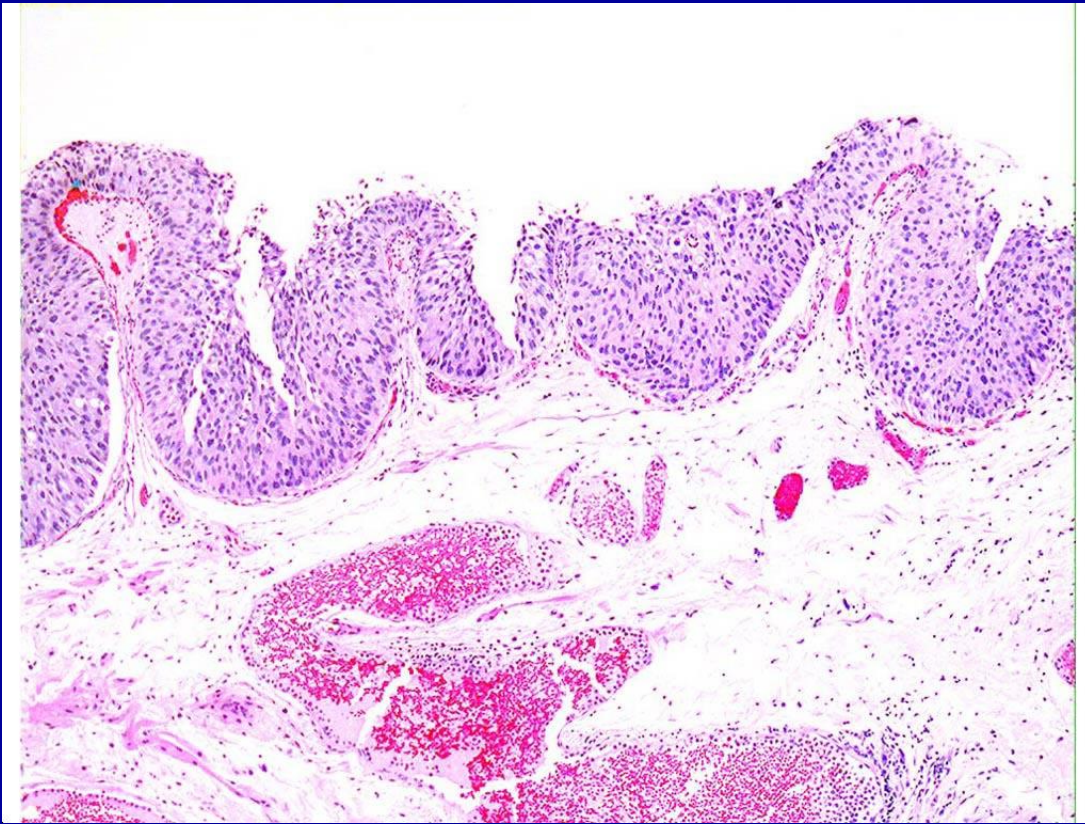


Papillary Urothelial Hyperplasia/AUP-tented

- Typically discovered on routine follow-up cystoscopy for papillary urothelial tumors
- Likely a precursor lesion to low grade papillary tumors
- Less commonly *de novo* diagnosis (in patients w/o concurrent or prior h/o urothelial neoplasia)
- Reasonable to suggest that patients require clinical follow up



Papillary Hyperplasia with Atypia



- Undulating mucosa, not completely flat or papillary, no discrete and detached papillae
- Early papillary lesions without fully developed papillae
- Cytological atypia analogous to dysplasia/CIS



Papillary Hyperplasia with Atypia

- **Atypia analogous to low grade/dysplasia**
 - ✓ “Early low grade papillary urothelial carcinoma”
 - ✓ Do not report as dysplasia with early papillary formations, as the clinical, biological and prognostic significance of urothelial dysplasia is not clearly established
- **Atypia analogous to high grade/CIS**
 - ✓ “CIS with early papillary formations”
 - ✓ CIS and high grade papillary UC may have distinct clinical significance
- **Diagnosis of papillary UC is appropriate if there is a history of papillary UC and cystoscopically evident papillary tumor**



WHO Classification of Papillary Urothelial Neoplasms (2016/2021)

- **Papilloma**
 - **Papillary neoplasm of low malignant potential (PUNLMP)**
 - **Papillary carcinoma, low grade**
 - **Papillary carcinoma, high grade**
-
- **First introduced in 1998 to replace 1973 WHO classification**
 - **PUNLMP- to define a group of papillary tumors with minimal cytologic and architectural atypia, never associated with invasion at the time of first diagnosis, and rarely, if ever, progress to invasive disease**
 - **Poor inter-observer reproducibility (similar to 1973 classification)**
 - **Continuous effort to revisit/revise the classification**



Simplified Approach for Grading Papillary Urothelial Tumors

**Normal urothelium
on a simple stalk**



Papilloma

**Thick, normal
appearing urothelium
on a stalk**



PUNLMP

**Abnormal urothelium
w/ uniformity
on a stalk**



Low grade

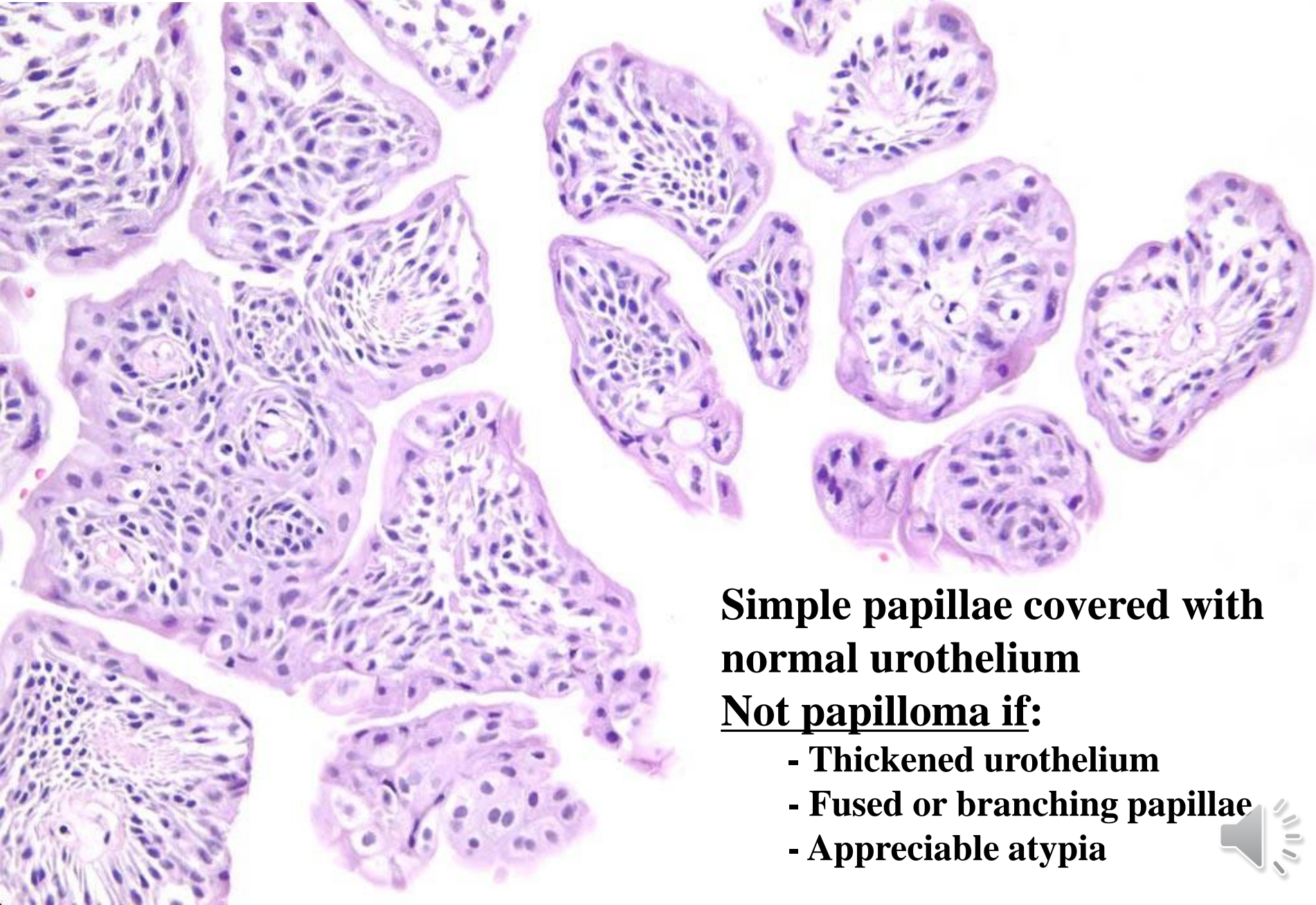
**Abnormal urothelium
w/o uniformity
on a stalk**



High grade



Papilloma



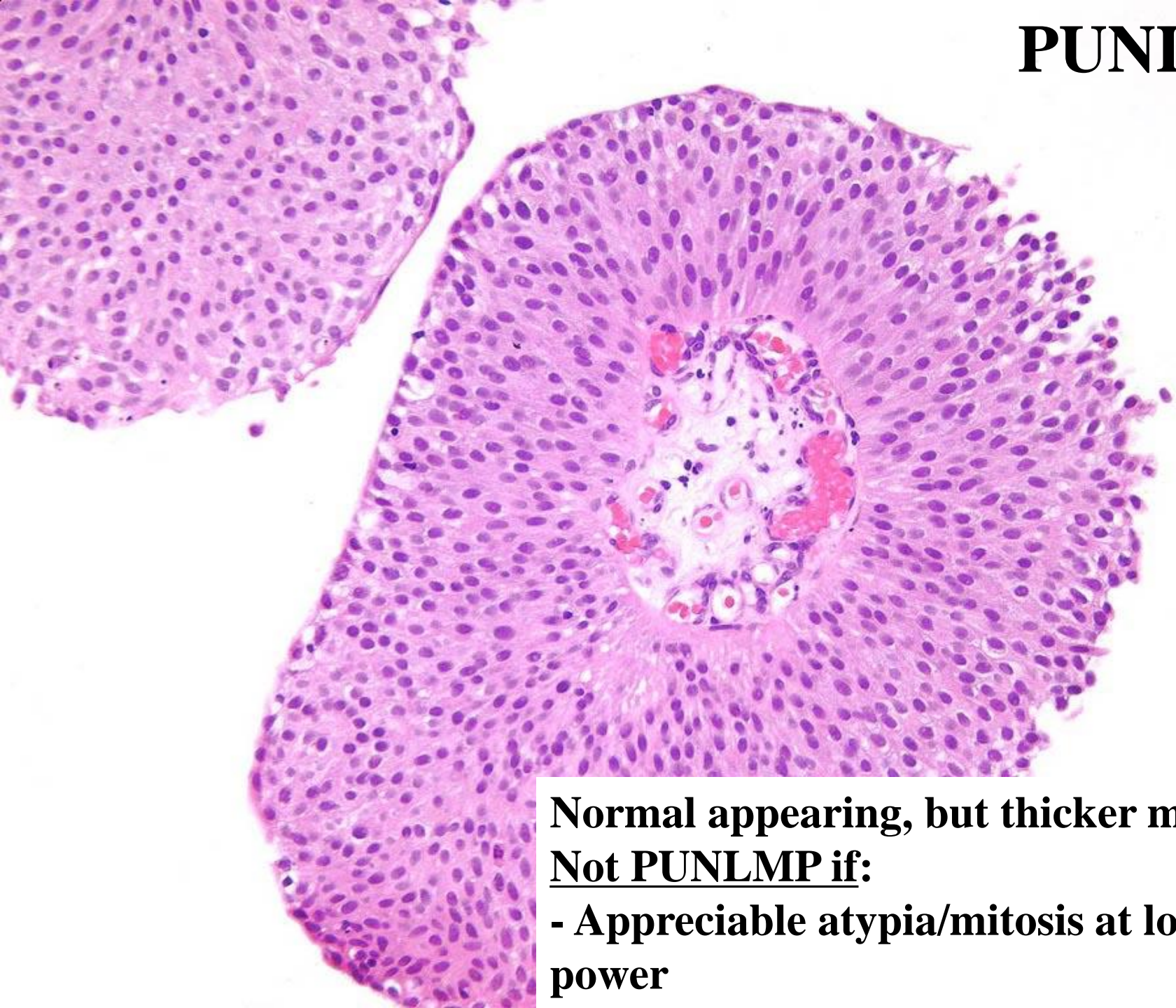
Simple papillae covered with normal urothelium

Not papilloma if:

- Thickened urothelium
- Fused or branching papillae
- Appreciable atypia



PUNLMP



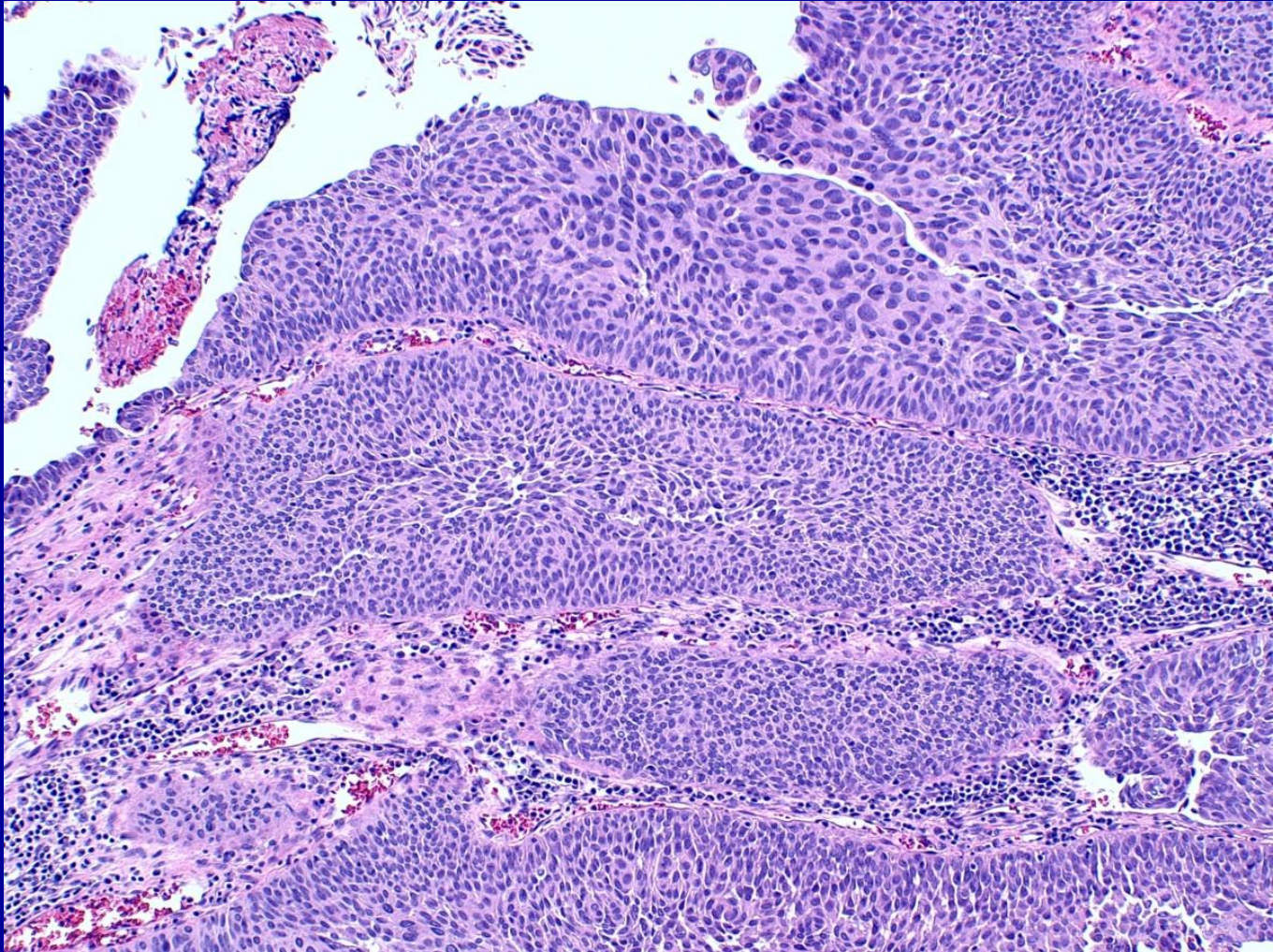
Normal appearing, but thicker mucosa

Not PUNLMP if:

- Appreciable atypia/mitosis at low power



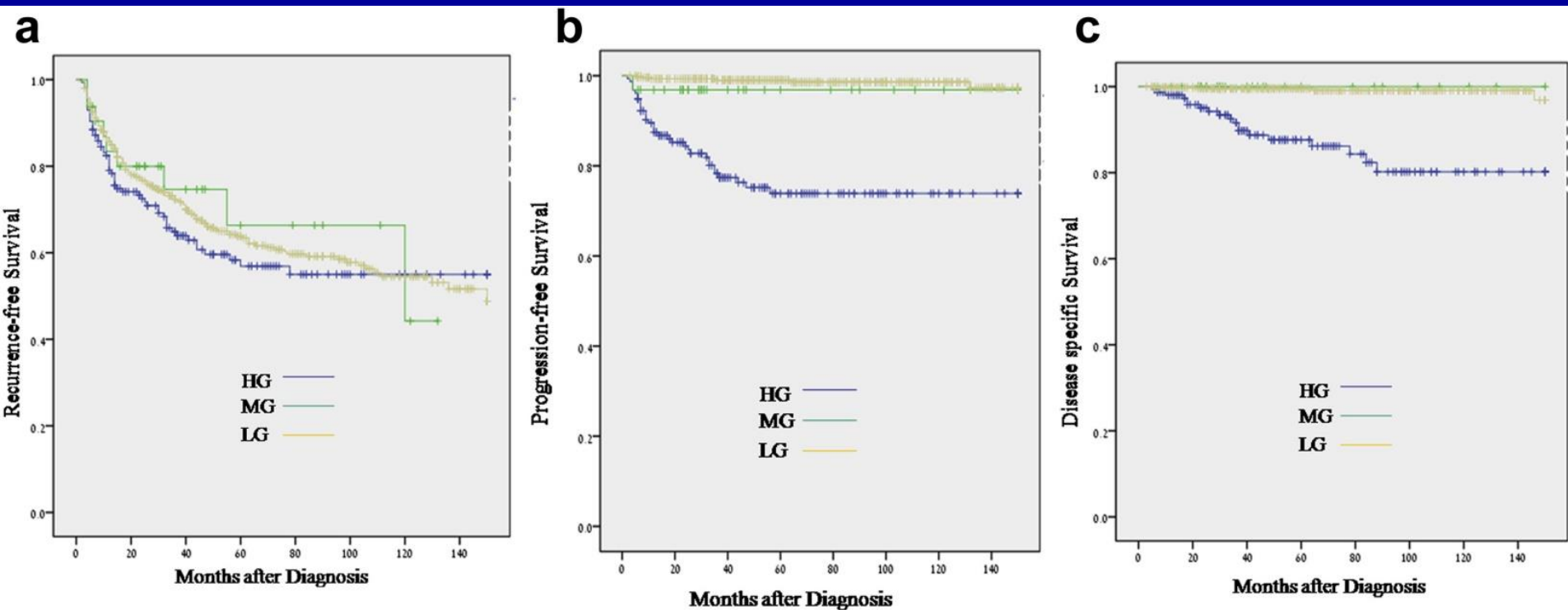
Low Grade Papillary Carcinoma with Focal High-grade Component



- Grade heterogeneity in up to 1/3 papillary tumors



Low Grade Papillary Carcinoma with Focal High-grade Component



Gofrit ON et al J Urol 2014

LG: low grade; MG: mixed grade (<10% HG); HG: high grade

- Limited % of high grade cells (<10%), does not significantly change the outcomes of low grade cancer



Papillary Carcinoma with Mixed Grades: Diagnosis

➤ Mixed tumors with $>10\%$ high grade component:

High grade papillary urothelial carcinoma

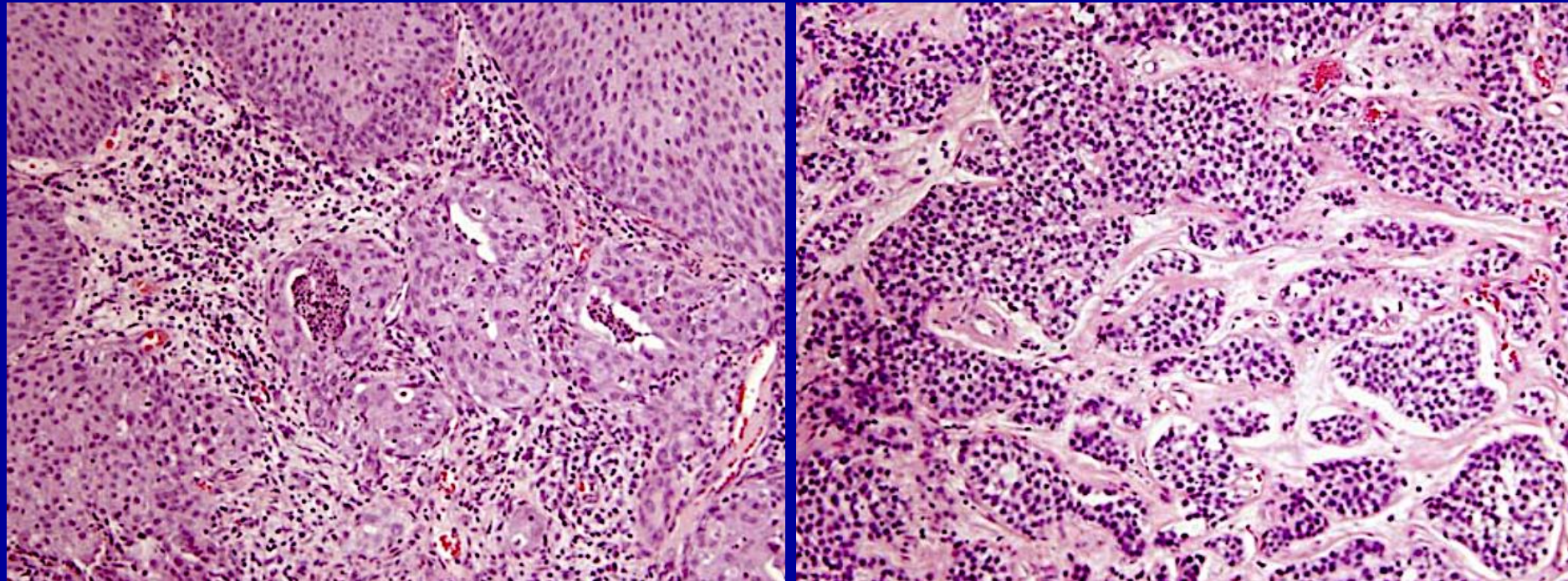
➤ Mixed tumors with $\leq 10\%$ high grade component:

Noninvasive low-grade papillary urothelial carcinoma with a focal ($<10\%$) high-grade component

Comment: There is limited data on the prognostic significance of a minor component of high-grade tumor in an otherwise lower grade carcinoma, and the studies suggest that they generally behave more like low-grade tumors.



Invasive Low Grade Papillary Urothelial Carcinoma with Low Grade Invasive Component



Invasive Low Grade Papillary Urothelial Carcinoma with Low Grade Invasive Component

- **Rare, may be under-reported (pathologists may report any invasive UC as high grade)**
- **Prognostic significance uncertain**
 - ✓ **T1 low grade similar to T1 high grade**
 - ✓ **Risk stratification tools put more weight on staging rather than grade**

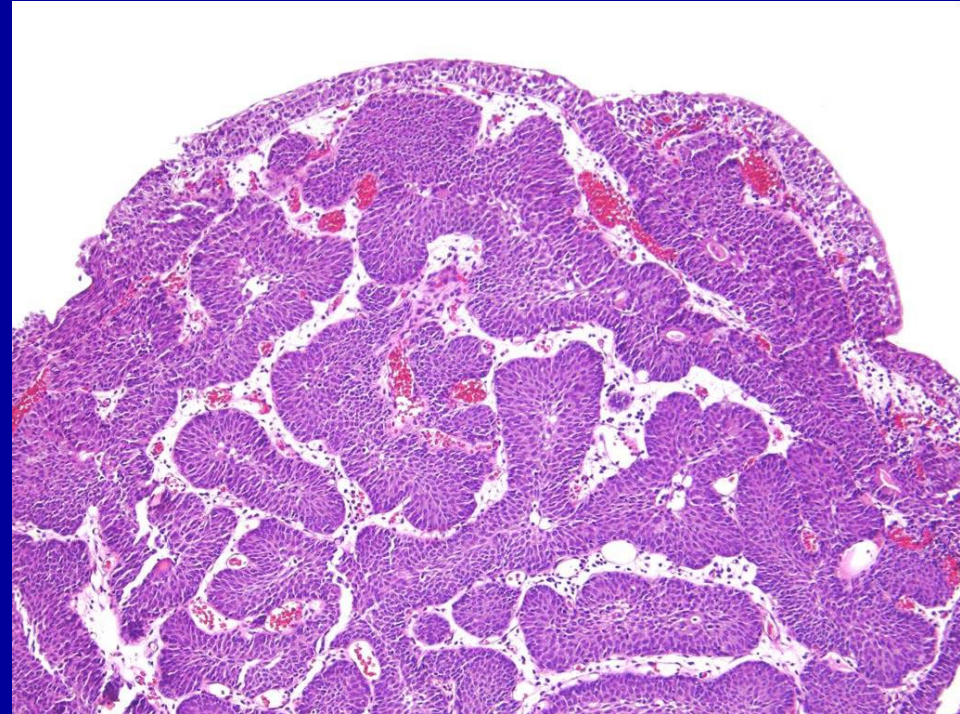
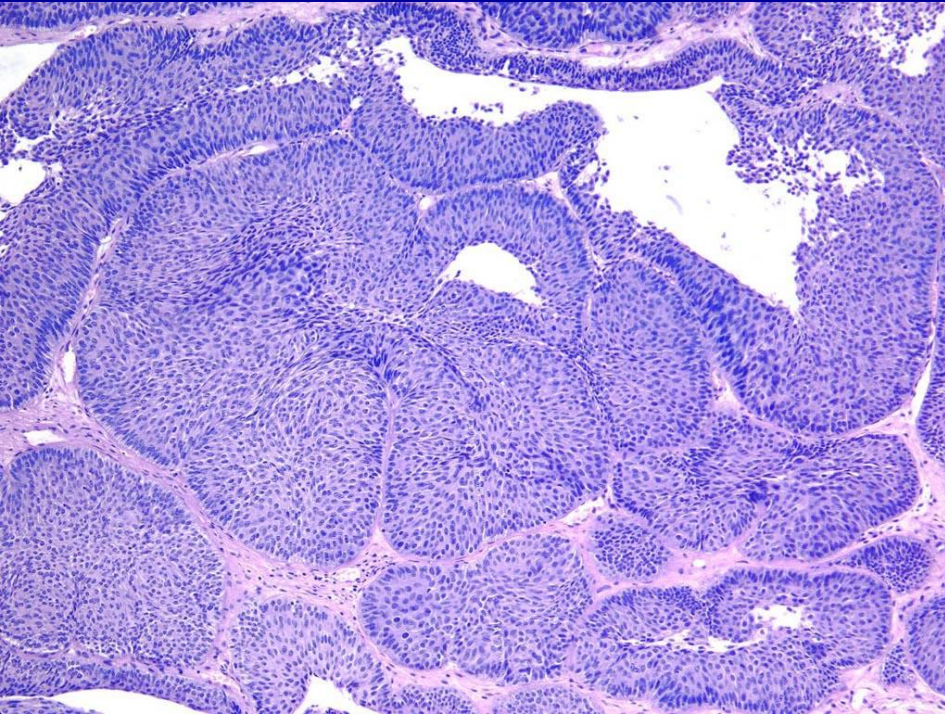
Diagnosis:

Invasive low grade papillary urothelial carcinoma

Comment: Invasive low grade UCs are uncommon and have a similar prognosis, stage for stage, comparable to invasive high grade UCs; there are no data to suggest there should be difference in therapy based on the histological grade of the invasive component



Urothelial Lesions with Inverted Growth



Urothelial nests in lamina propria, not necessarily invasive



Urothelial Lesions with Inverted Growth

➤ Reactive conditions

- ✓ Florid von Brunn nests, cystitis cystica *et* glandularis
- ✓ Pseudocarcinomatous hyperplasia (radiation, chemotherapy)

➤ Benign urothelial neoplasm

- ✓ Inverted papilloma

➤ Urothelial neoplasms

- ✓ Non-invasive PUNLUMP, low and high grade urothelial carcinoma with inverted growth
- ✓ Urothelial carcinoma with inverted growth pattern and invasion
- ✓ Nested variant urothelial carcinoma, including large nested variant



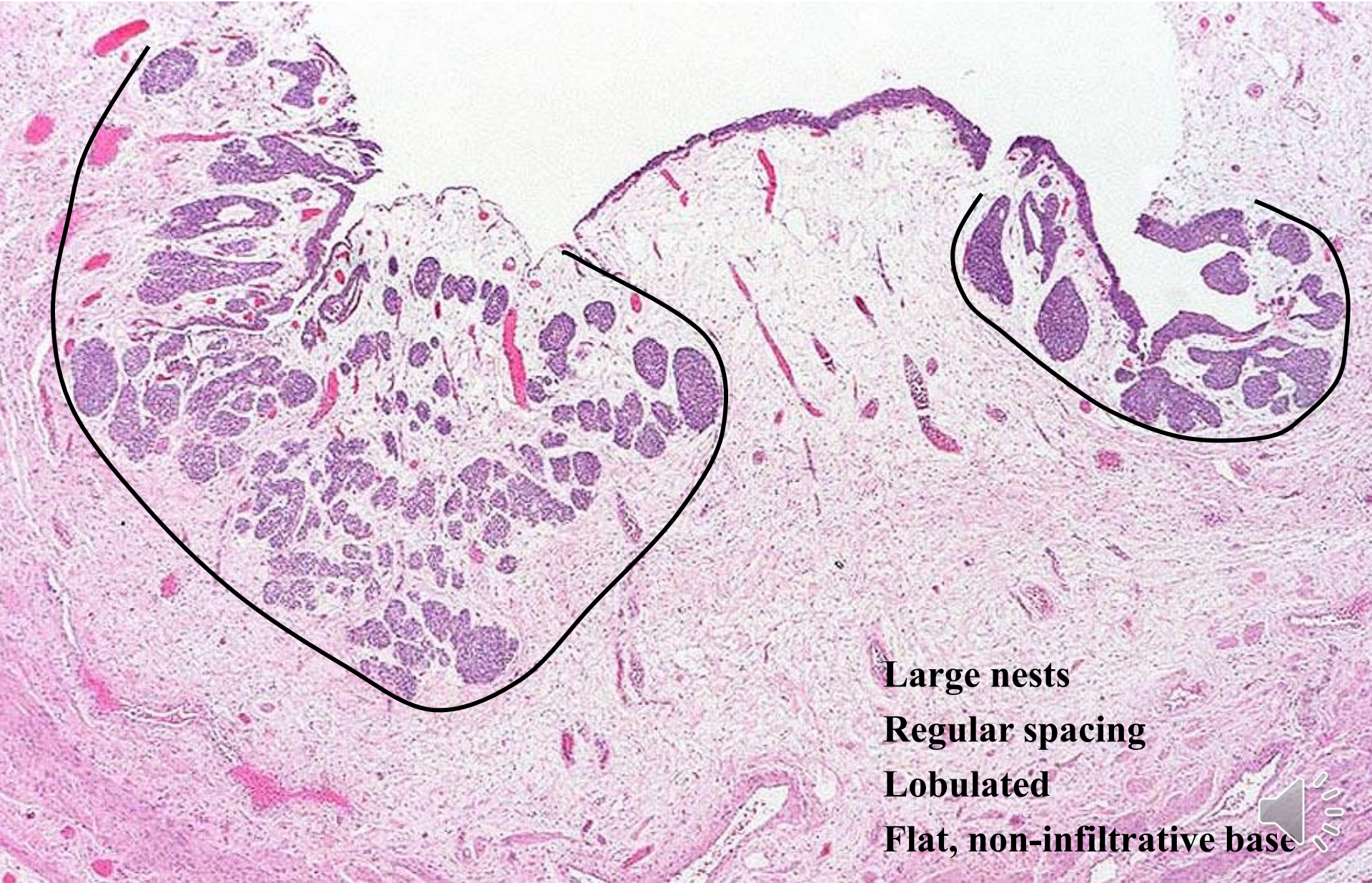
Urothelial Lesions with Inverted Growth

Critical Differential Diagnosis

- **Florid von Brunn nests vs nested variant urothelial carcinoma**
- **Inverted papilloma vs non-invasive urothelial carcinoma with inverted growth**



Florid von Brunn Nests



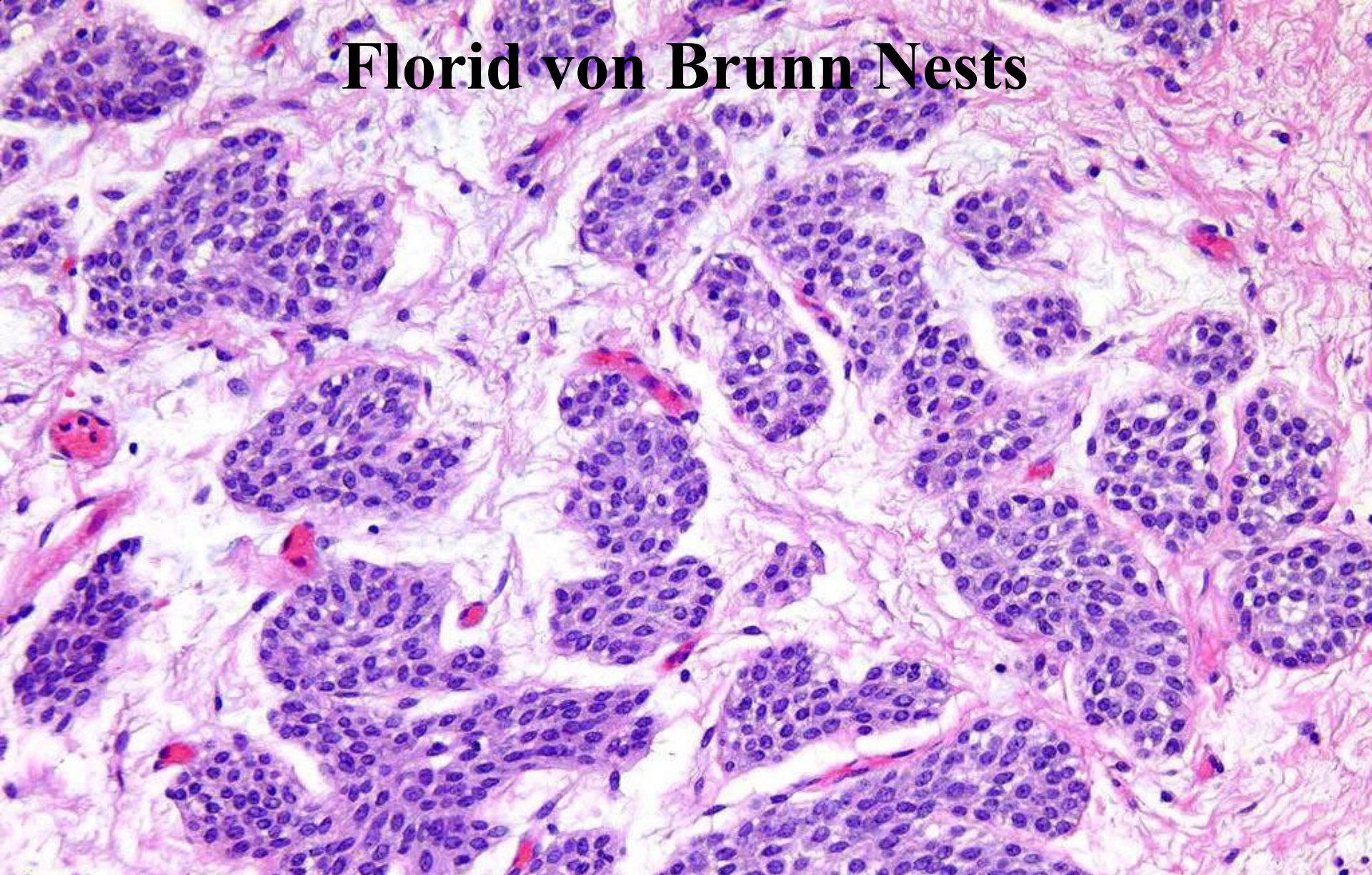
Large nests

Regular spacing

Lobulated

Flat, non-infiltrative base

Florid von Brunn Nests



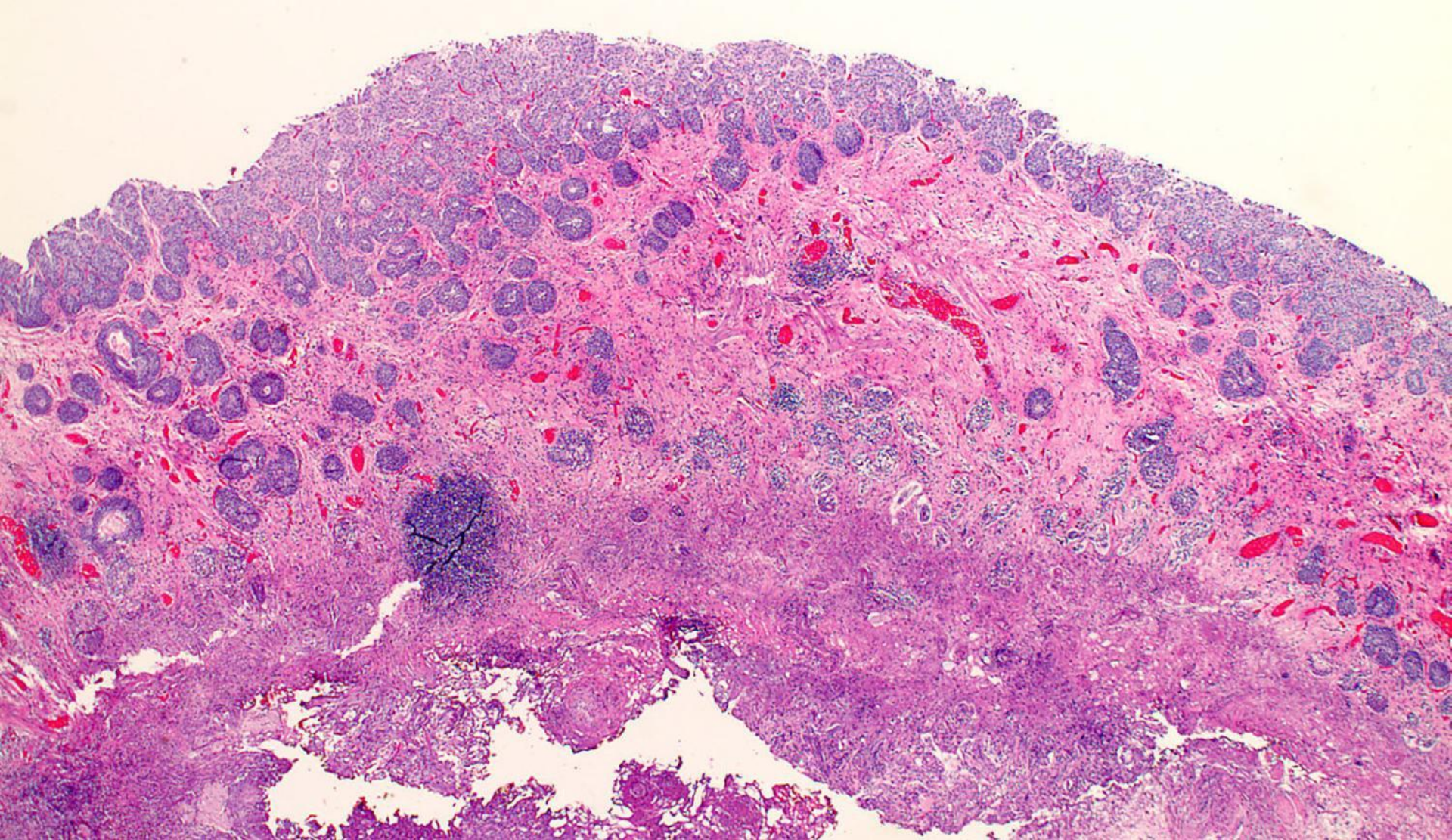
Cytological atypia: absent

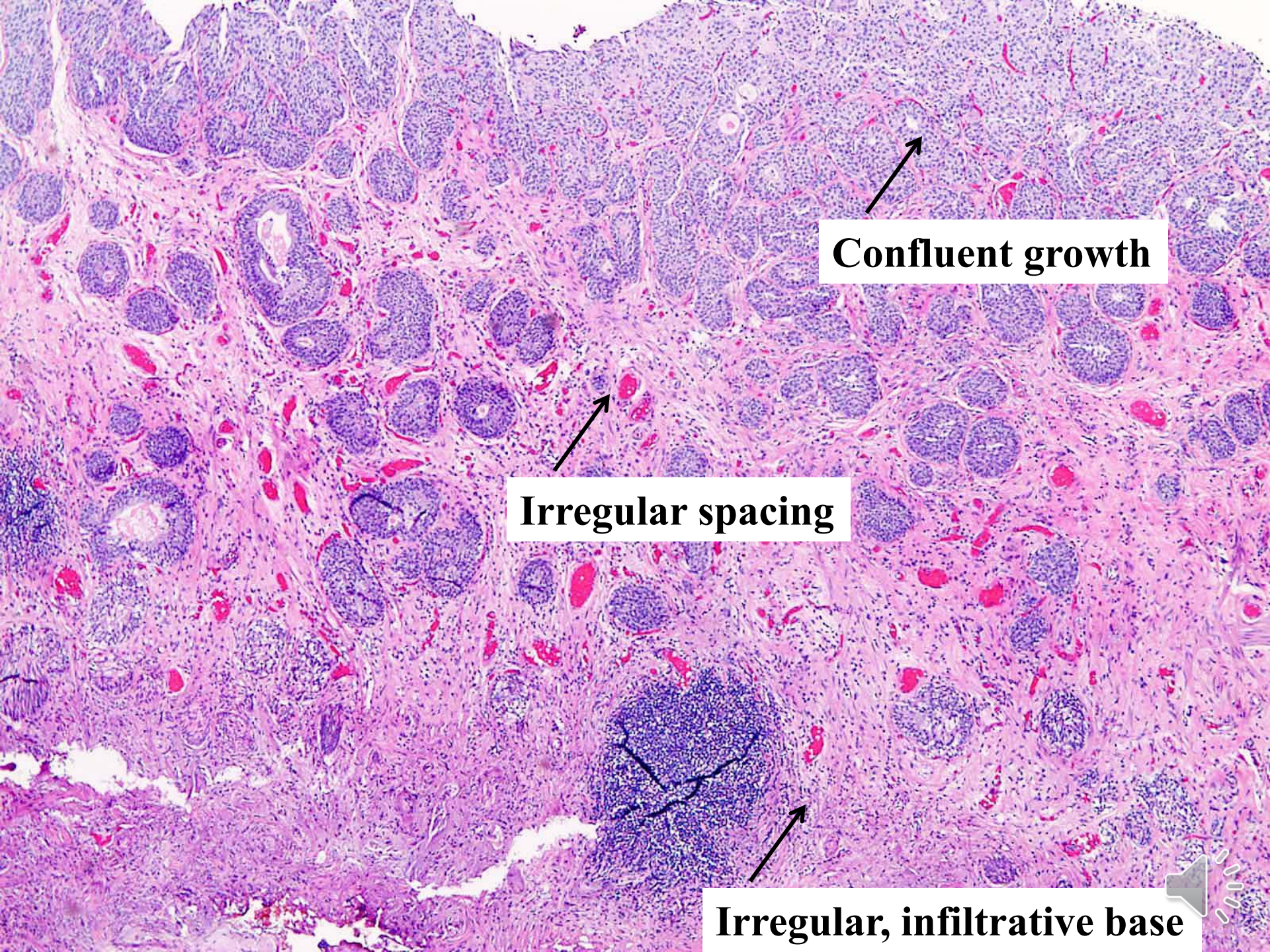
Stroma: loose and edematous, inflammation

Muscularis propria invasion: absent



Invasive Urothelial Carcinoma, Nested Variant



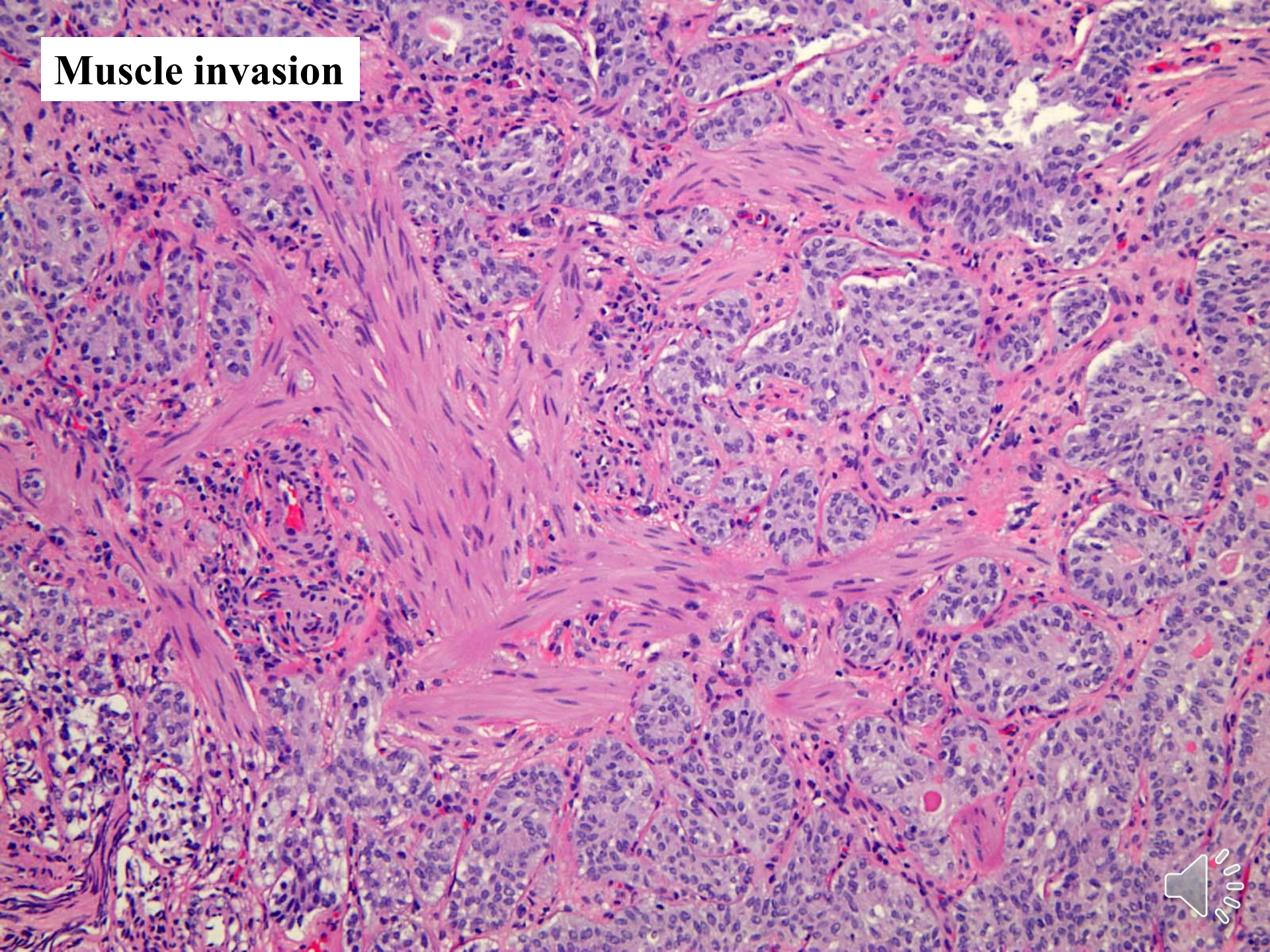


Confluent growth

Irregular spacing

Irregular, infiltrative base

Muscle invasion



Nested Variant Urothelial Carcinoma vs Florid von Brunn Nests

	Urothelial carcinoma, nested variant	Florid von Brunn nests
Urothelial nests	Crowded nests of variable sizes and shapes	Large, regularly spaced, rounded nests
Lumen formation	Uncommon	Commonly associated with cystitis cystica et glandularis
Architecture	Not circumscribed	Circumscribed
Base of the lesion	Uneven, infiltrative	Smooth, flat, not infiltrative
Muscle invasion	Yes, frequent	No
Cytological atypia	Present, especially at the invasive front	No



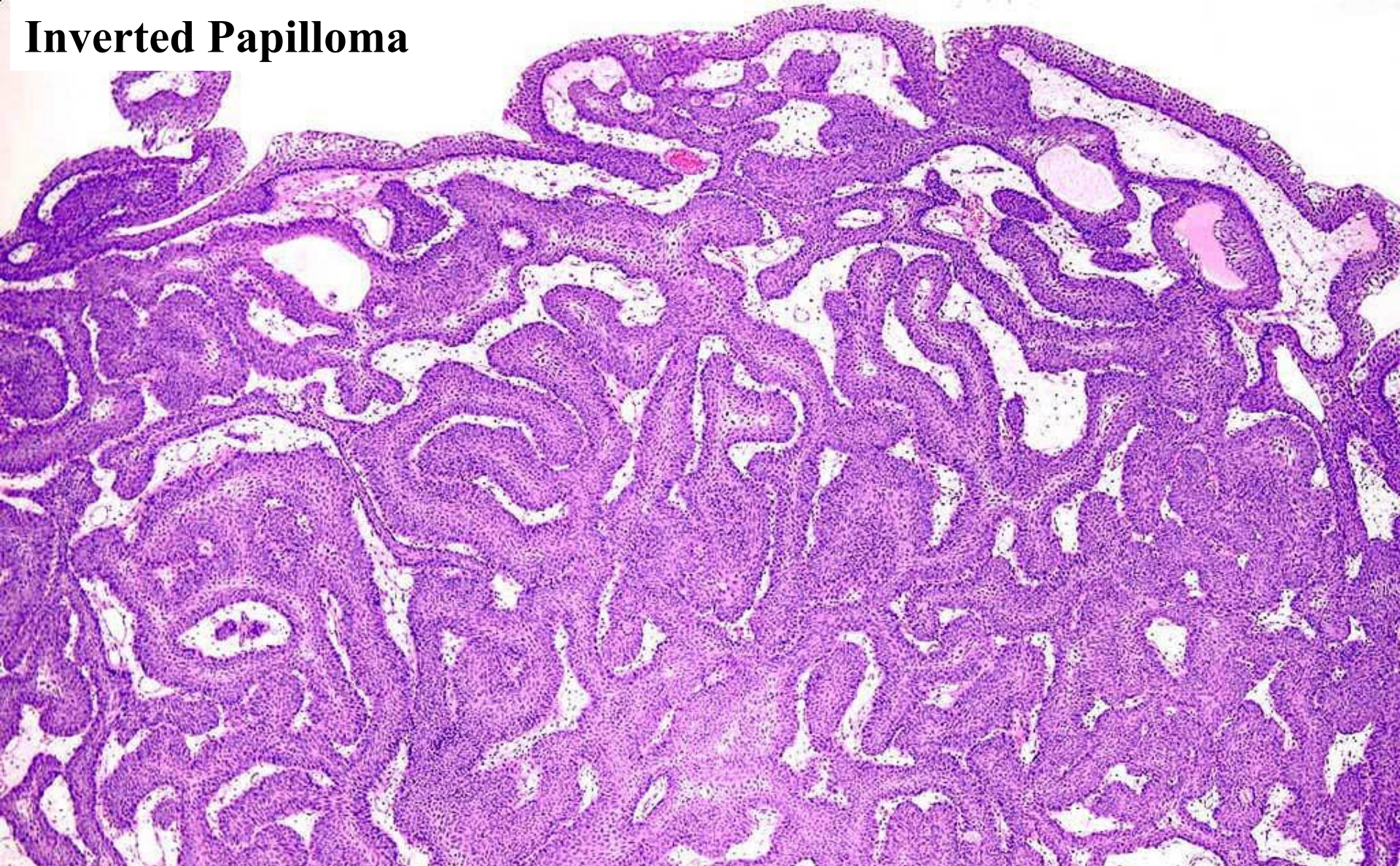
Urothelial Lesions with Inverted Growth

Critical Differential Diagnosis

- **Florid von Brunn nests vs nested variant urothelial carcinoma**
- **Inverted papilloma vs non-invasive urothelial carcinoma with inverted growth**

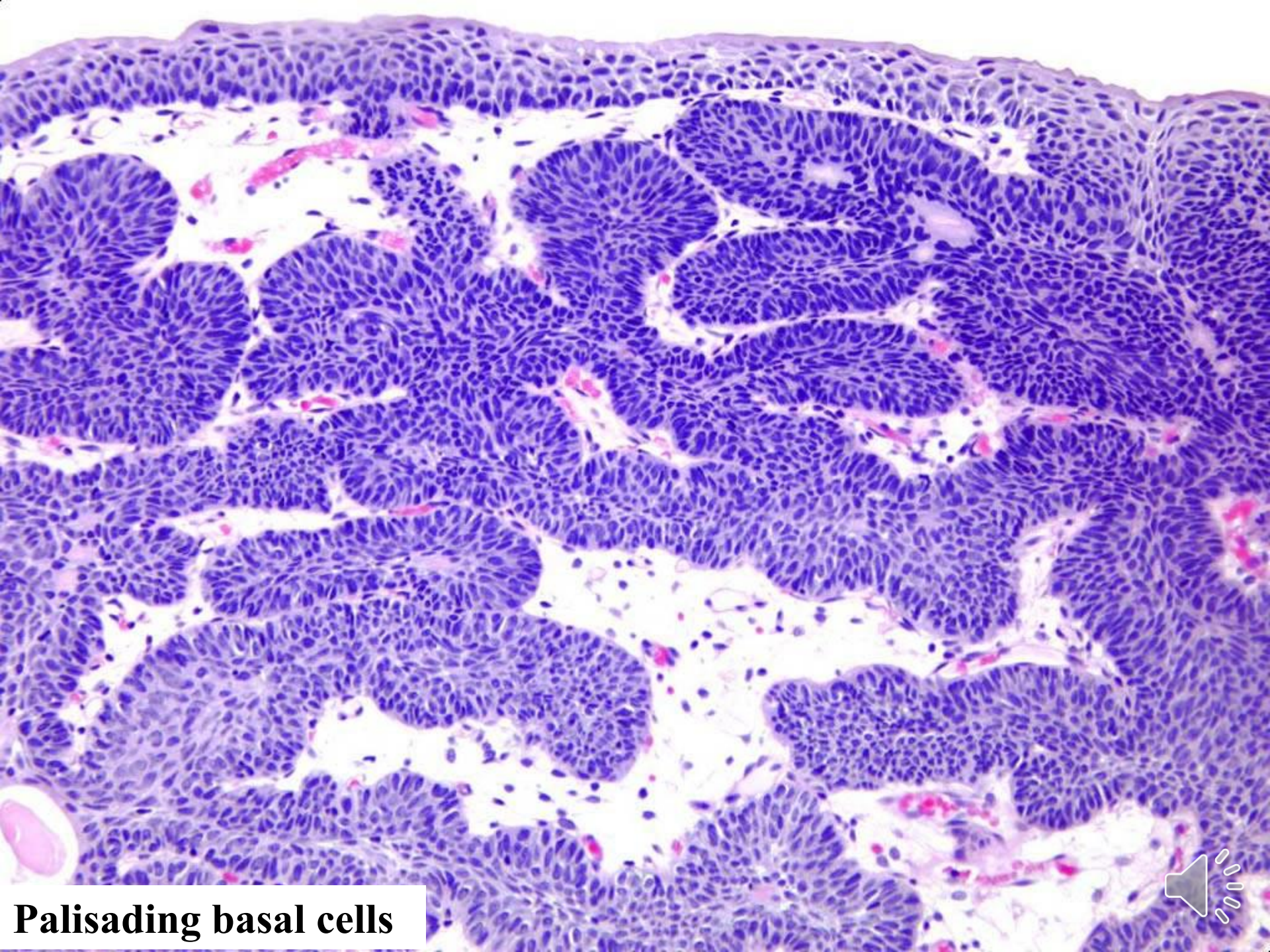


Inverted Papilloma



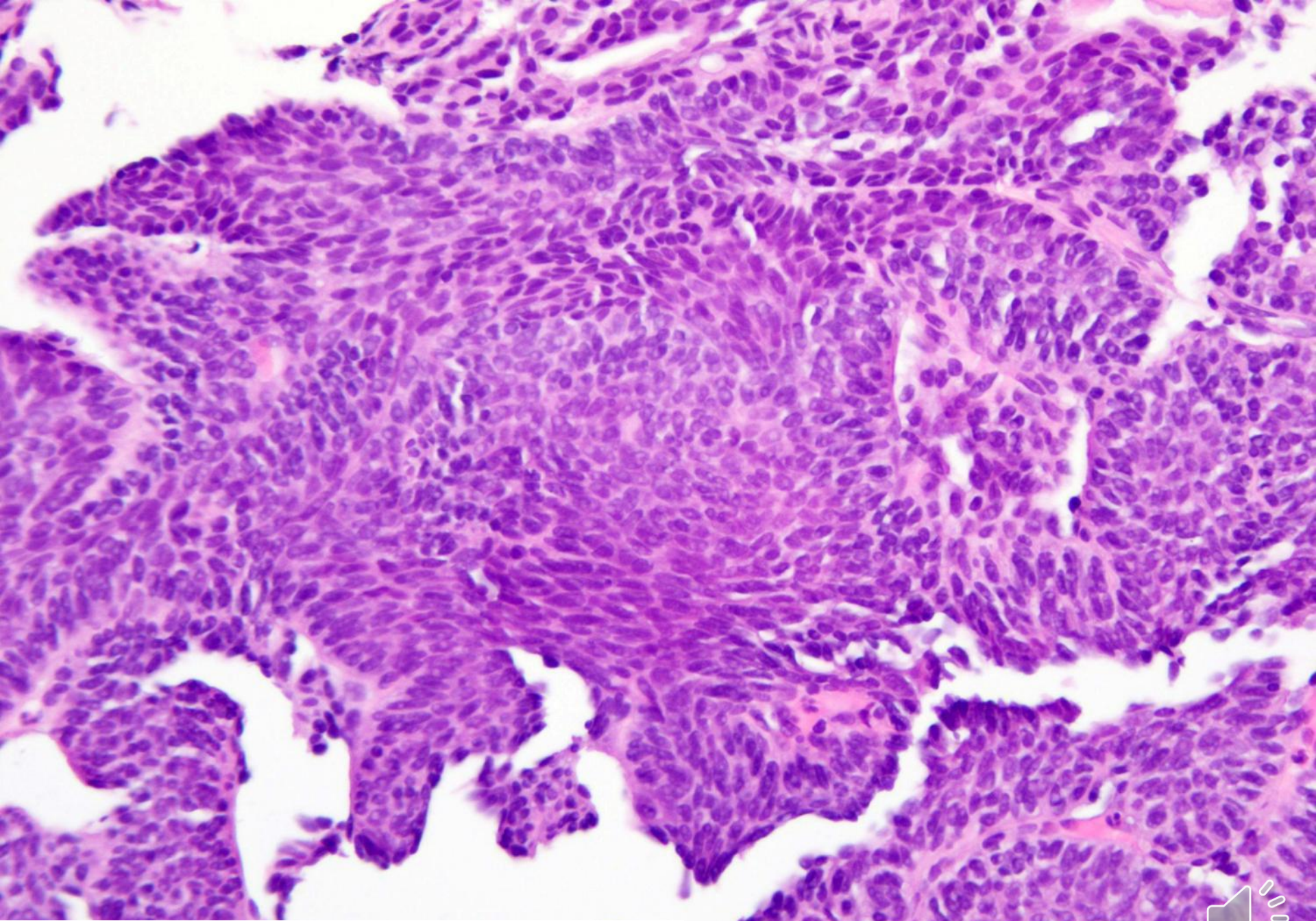
Ramifying cords and trabeculae extending down from the smooth surface
Trabeculae of uniform thickness
Extensively involves lamina propria but spare muscularis propria





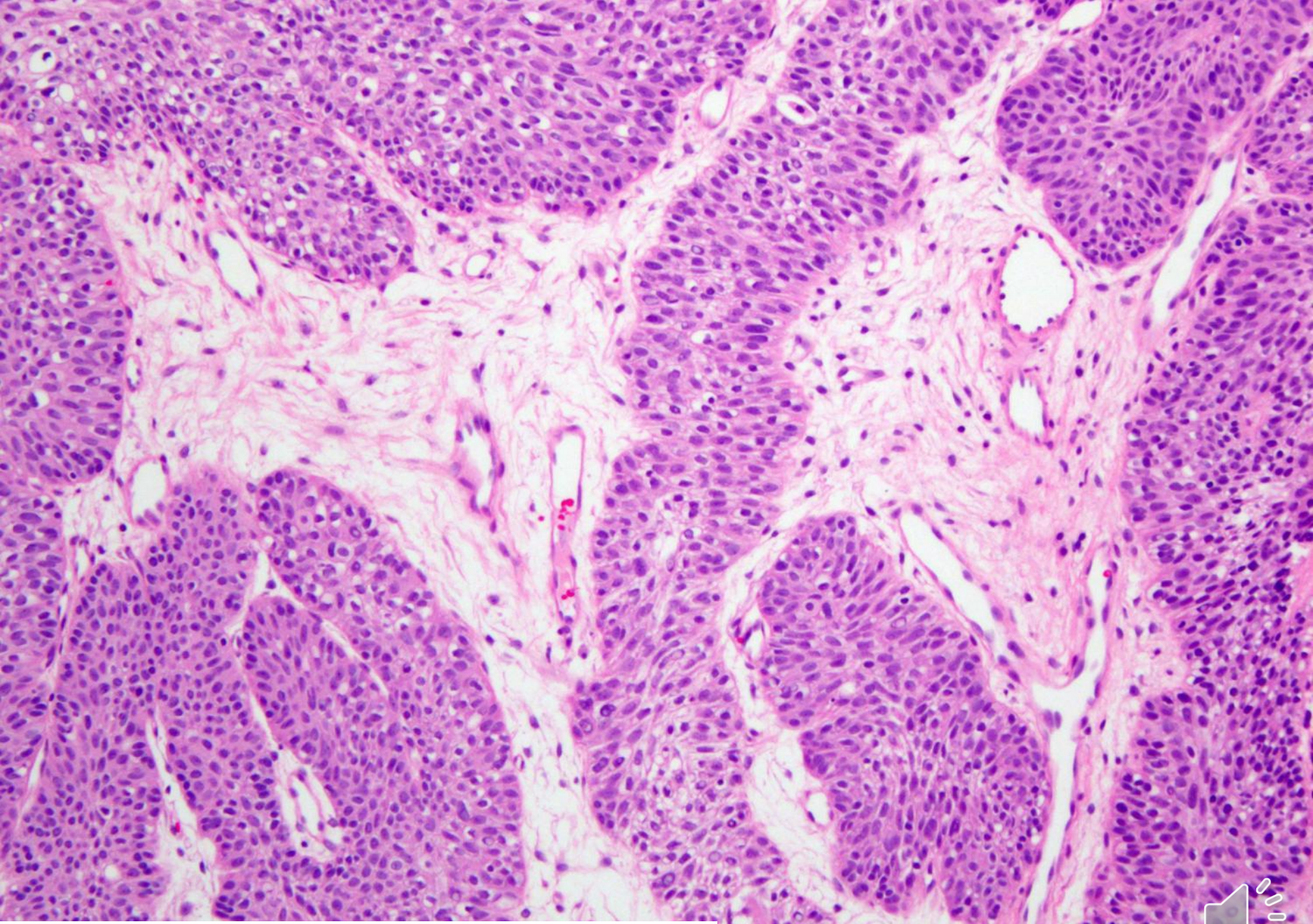
Palisading basal cells





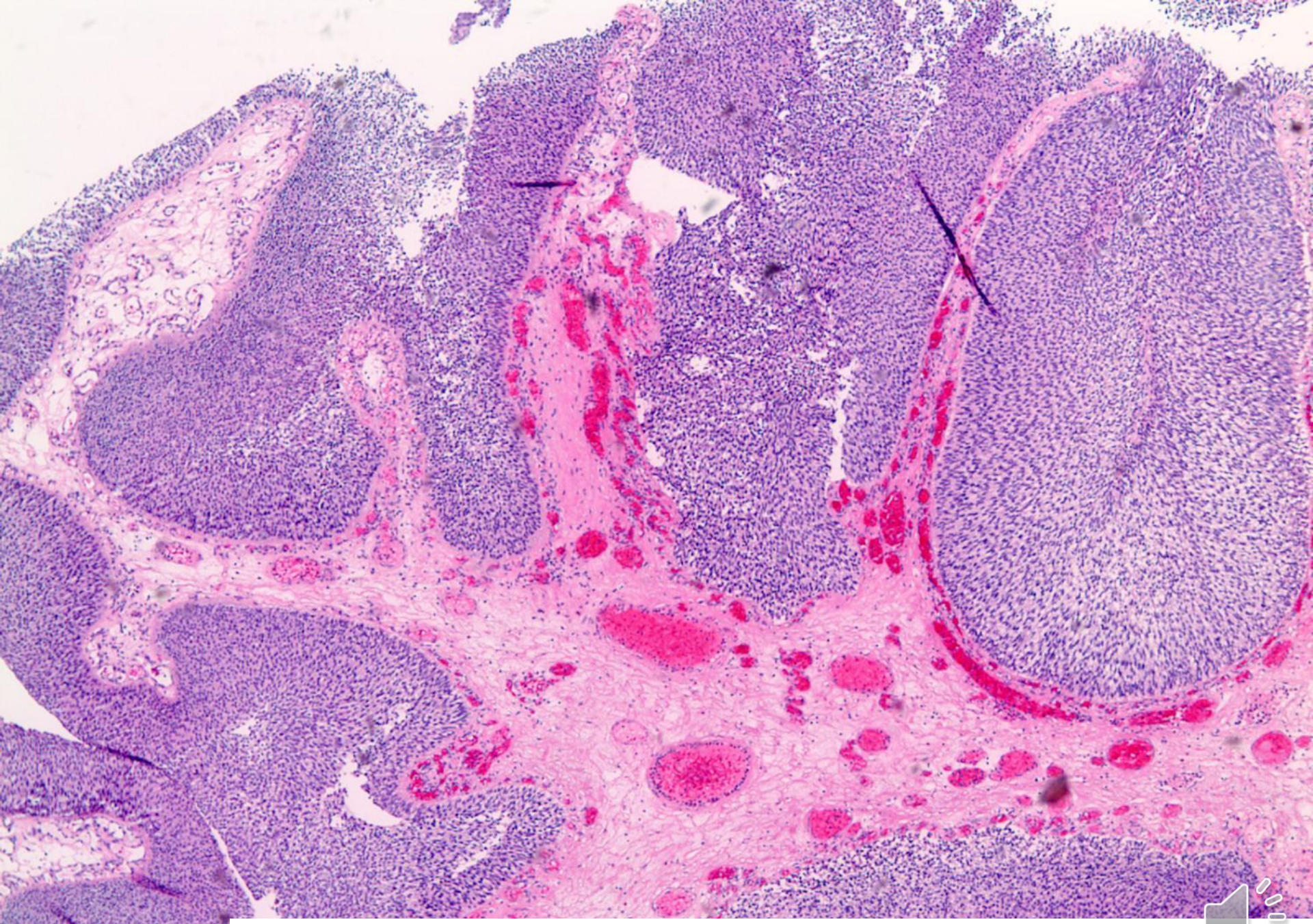
Central spindling and streaming





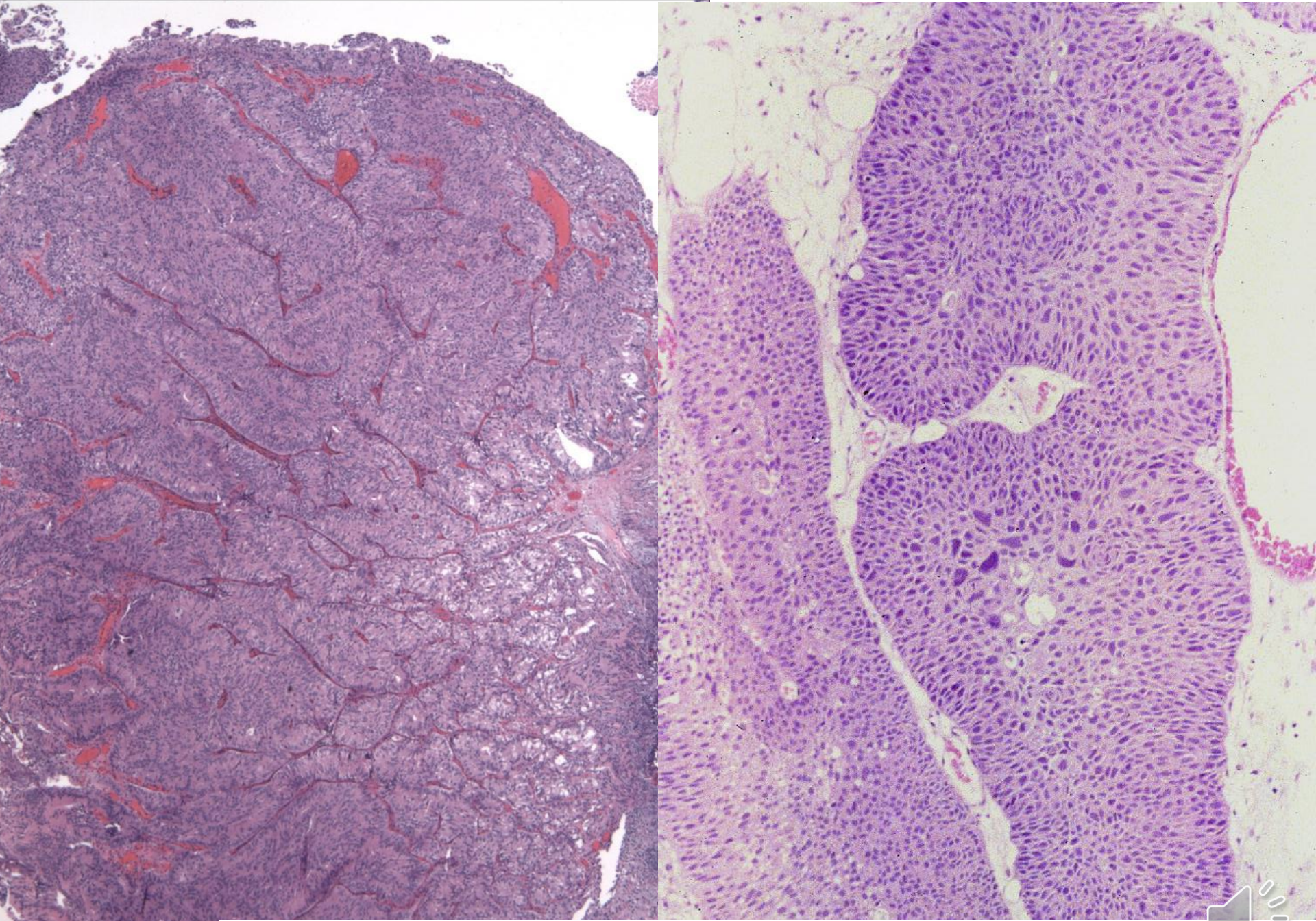
Stroma: non-reactive, no inflammation





Low Grade Urothelial Carcinoma with Inverted Growth





High Grade Urothelial Carcinoma with Inverted Growth

Differential Diagnosis of Inverted Papilloma and Urothelial Carcinoma with Inverted Growth

	Inverted Papilloma	Urothelial Carcinoma with Inverted Growth
Surface	Smooth, minimal/no exophytic component	Often have exophytic component
Shape of trabeculae	Thin, uniform thickness	Uneven, solid
Base	Smooth without infiltration	May have obvious invasion
Cytological atypia	Minimum/no	May be significant



Urothelial Tumors with Inverted Growth

- **Vast majority are non-invasive with a variable exophytic papillary component**
- **Wide spectrum of morphologic and cytologic features**
 - ✓ PUNLMP
 - ✓ Low grade
 - ✓ High grade
- **Grading criteria same as those for exophytic papillary tumors**
- **Inverted urothelial tumor with pure to predominant inverted growth: >80% of inverted growth morphology**



Urothelial Tumors with Pure to Predominant Inverted Growth: Clinical outcomes

➤ Data extremely limited

- ✓ A trend towards better prognosis in inverted tumors

Lesion	PUNLMP with pure inverted growth	PUNLMP w/o inverted growth
Recurrence/progression	0%	21%

Maxell et al Diagn Pathol 2015

➤ Low grade non-invasive: inverted vs exophytic

- ✓ Lower recurrence rate, longer time to first recurrence and fewer recurrence episodes
- ✓ All inverted tumors with recurrence recurred only once, no tumor with >80% inverted growth recurred (Arslankoz et al Balkan Med J 2017)

➤ Report pure or predominant inverted growth in PUNLMP and low grade tumors, and comment on its significance



Grading Flat and Papillary Urothelial Lesions: Summary

- **IHC is not recommended for work-up of difficult flat urothelial lesions**
- **Extensive keratinizing squamous metaplasia is more likely to be associated with adverse outcomes (neoplasia and contracture)**
- **Low grade UC with <10% high grade: low grade with focal high grade**
- **T1 low grade UC: prognostically similar stage for stage to T1 high grade**
- **Report papillary UC with >80% inverted component as “papillary UC with inverted histology”; may have better prognosis**



Questions?

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