

**Non-Muscle Invasive Bladder Cancer (NMIBC)**  
**Diagnostic Pearls**

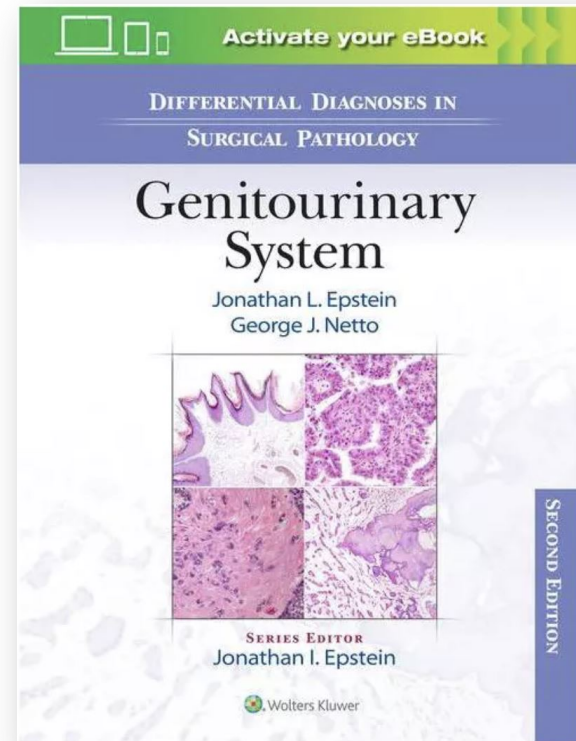
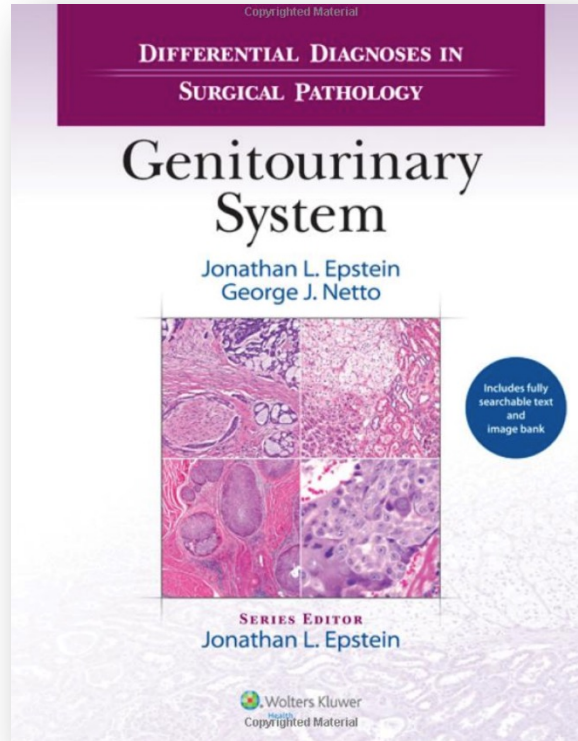
**George J. Netto, M.D.**

*Professor and Chair of Pathology*

**HEERSINK School of Medicine**

**University of Alabama at Birmingham**

# Disclosures



***J. Epstein and G.J. Netto  
Differential Diagnosis in Genitourinary System***

# Overview

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- The Dual Phenotype of Bladder Cancer
- ISUP/WHO Classification of Bladder Cancer
  - Grading
  - Staging “issues”
- NMIBC Management

# UrCa

## Disease Costs and Management Opportunities

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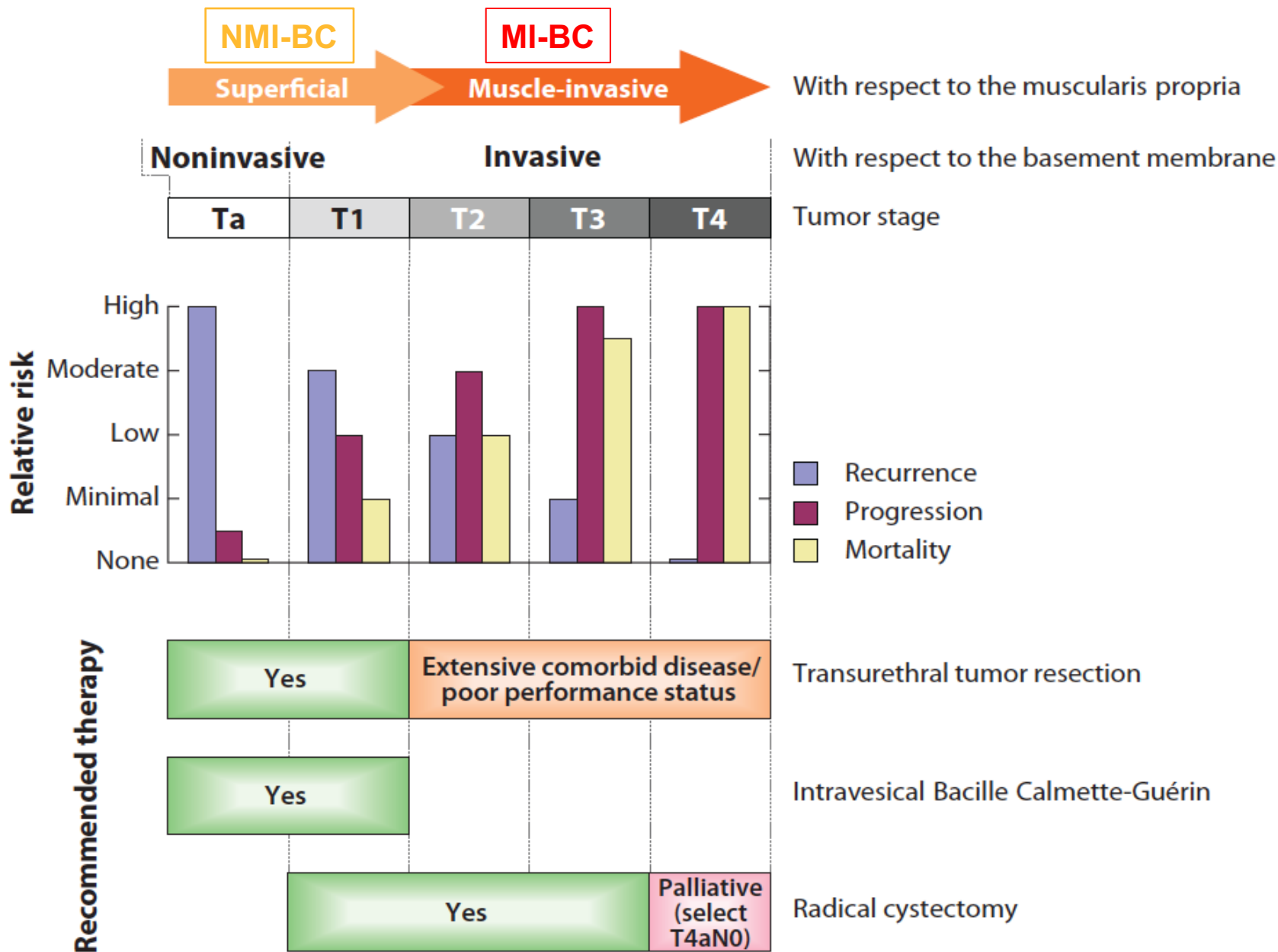
- Major health cost burden per patient:
  - Frequent cystoscopy, high rate of recurrence etc...
  - \$ 4 Billion per year in USA alone; largest cost per pt for any type of tumor
- Unique amenability to applying molecular detection methods (e.g. UroVysion FISH, FGFR3 mutation, UroSEEK) and molecular Rx delivery to target

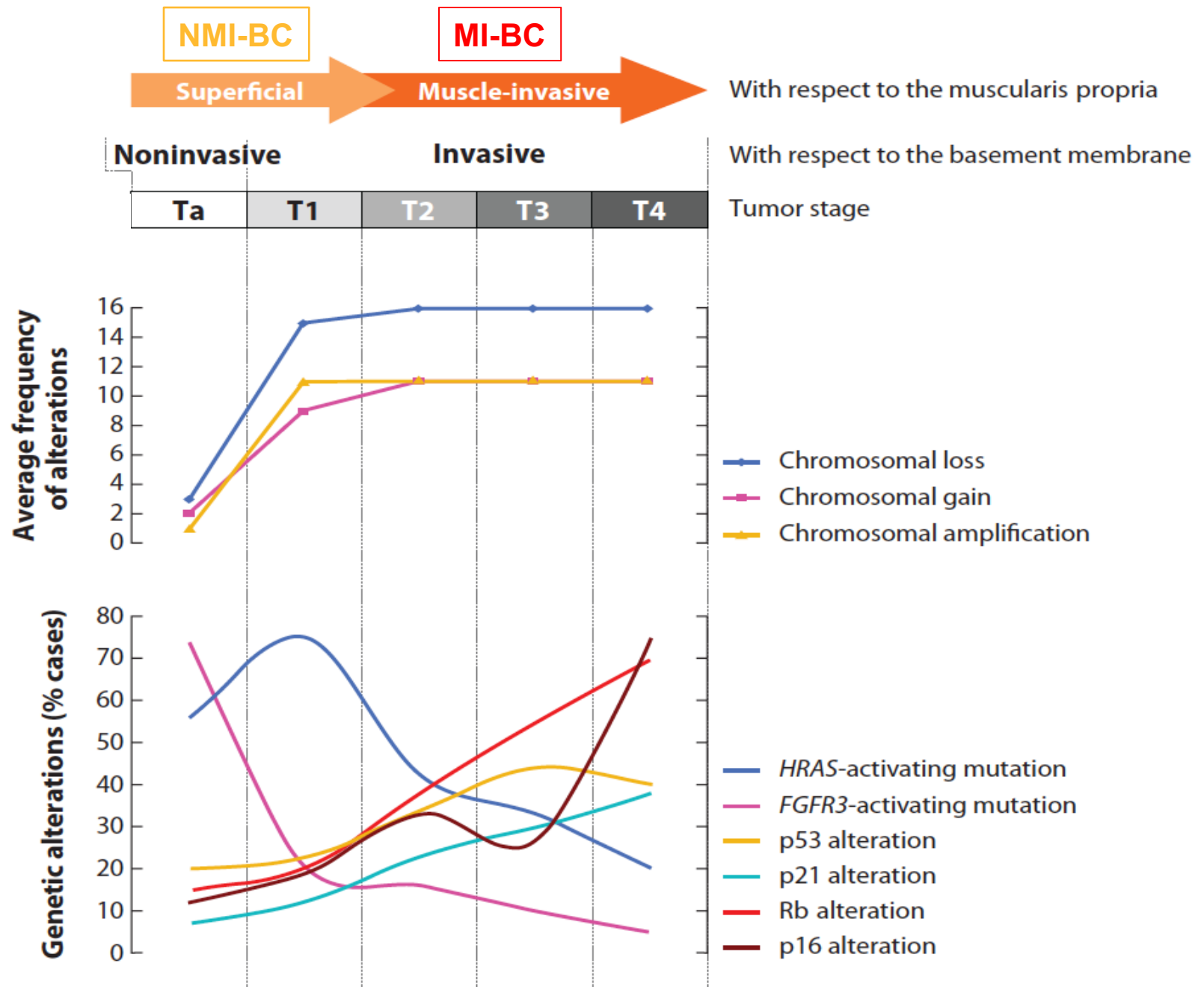
# Urothelial Carcinoma

## Two Phenotypes?

~~(Superficial)~~ Non-muscle invasive BC (**NMIBC**)  
70-80%

Muscle Invasive BC (**MIBC**)  
20-30%





# **BLADDER CANCER**

**Grading (Non-Invasive)**

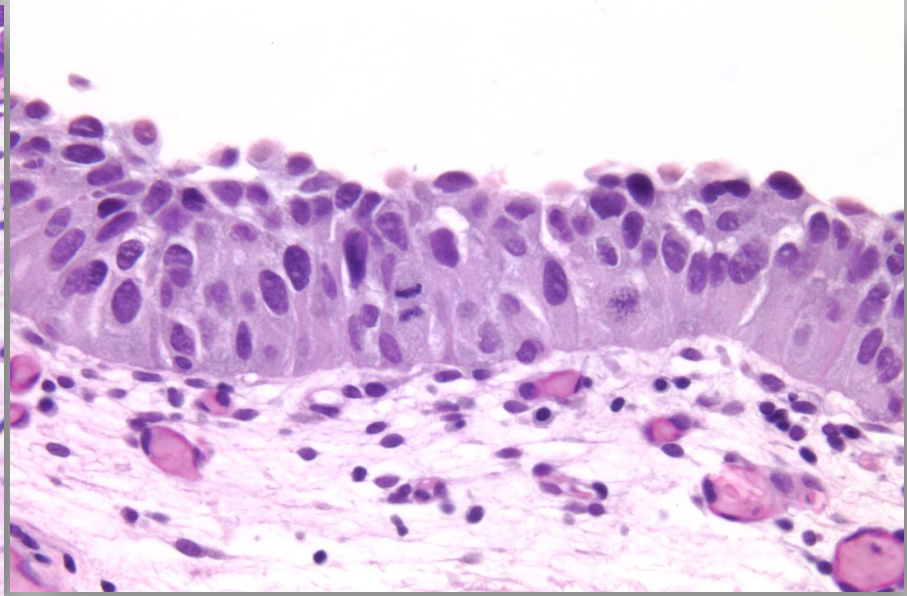
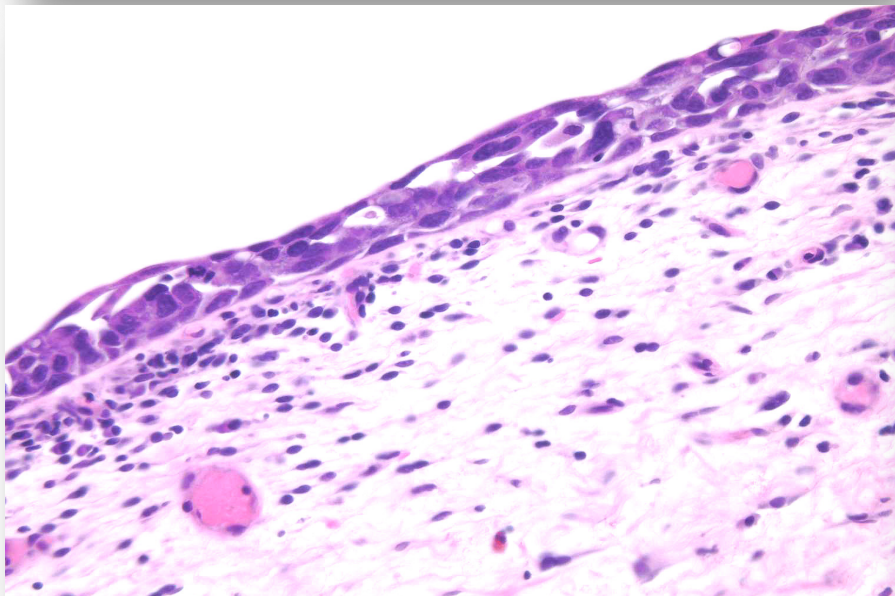
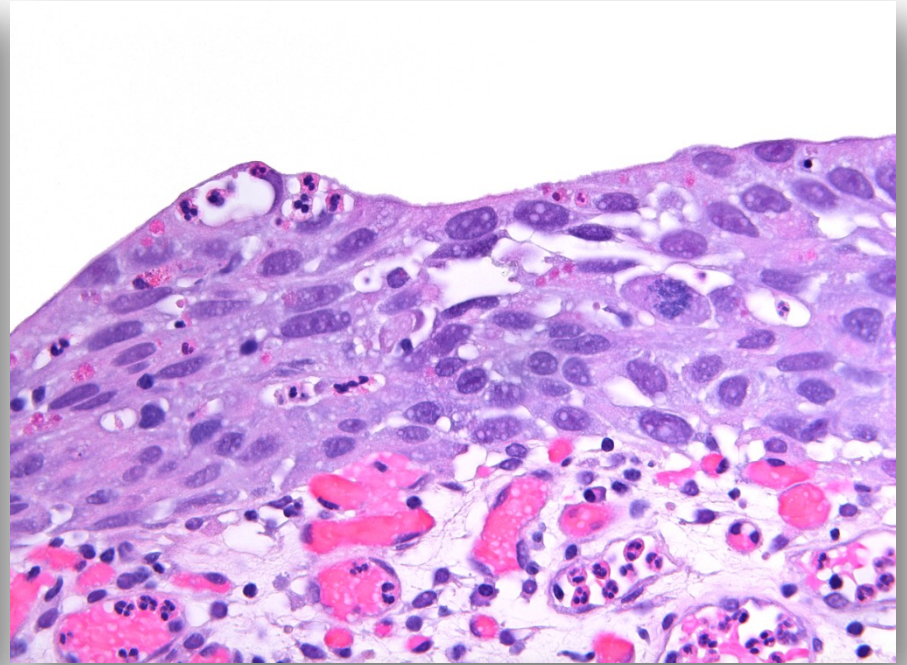
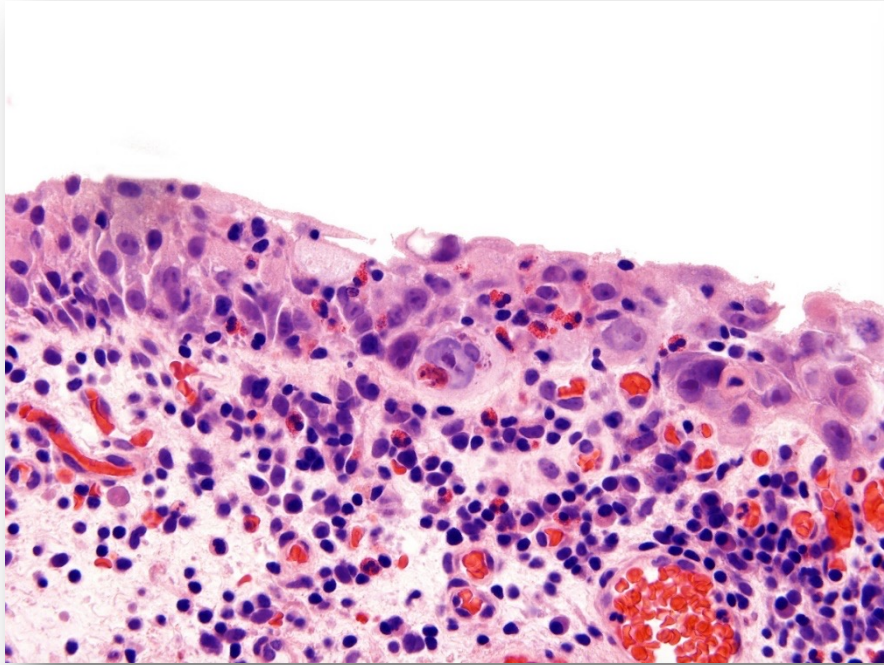


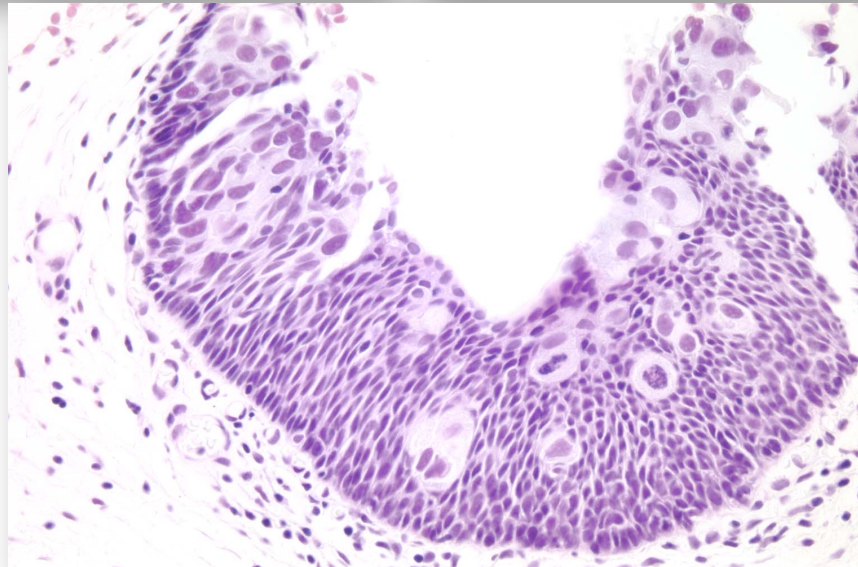
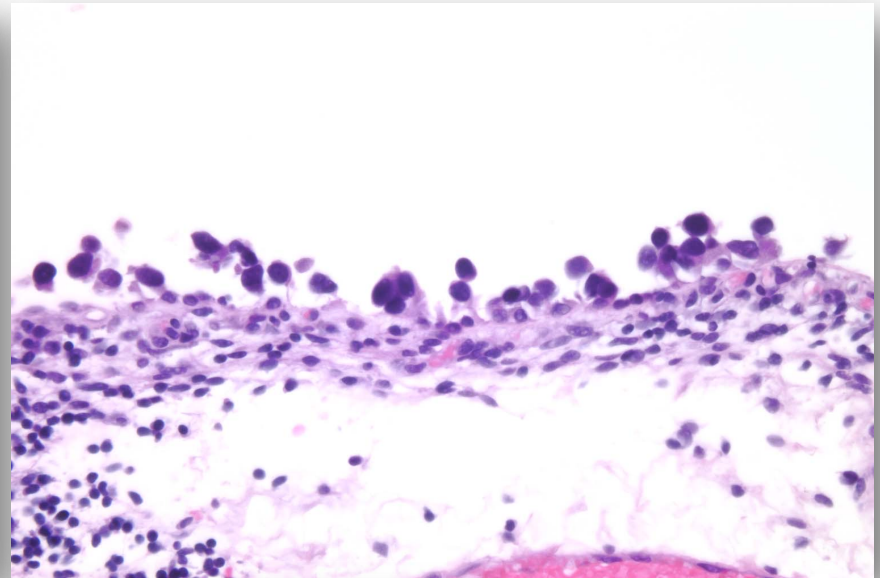
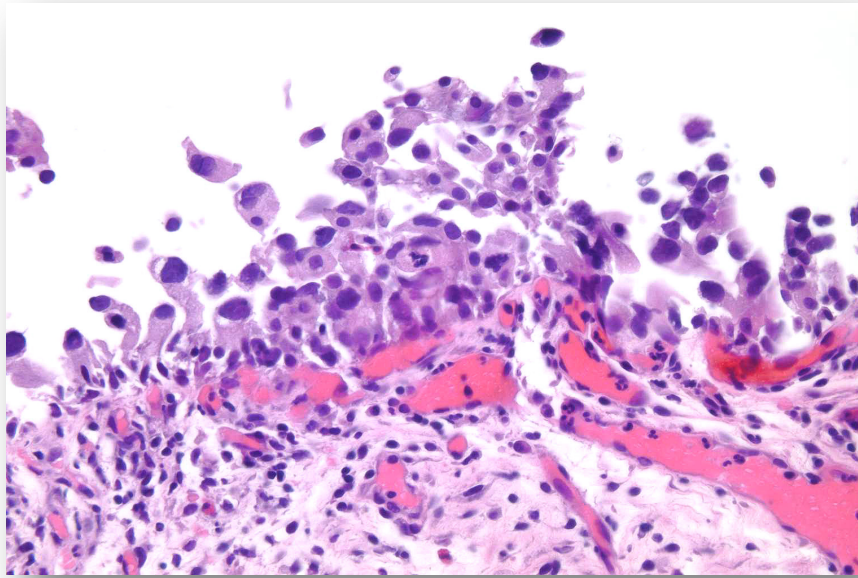
**WHO Classification of the Urinary and Male Genital Tumors**  
5th edition series 2022

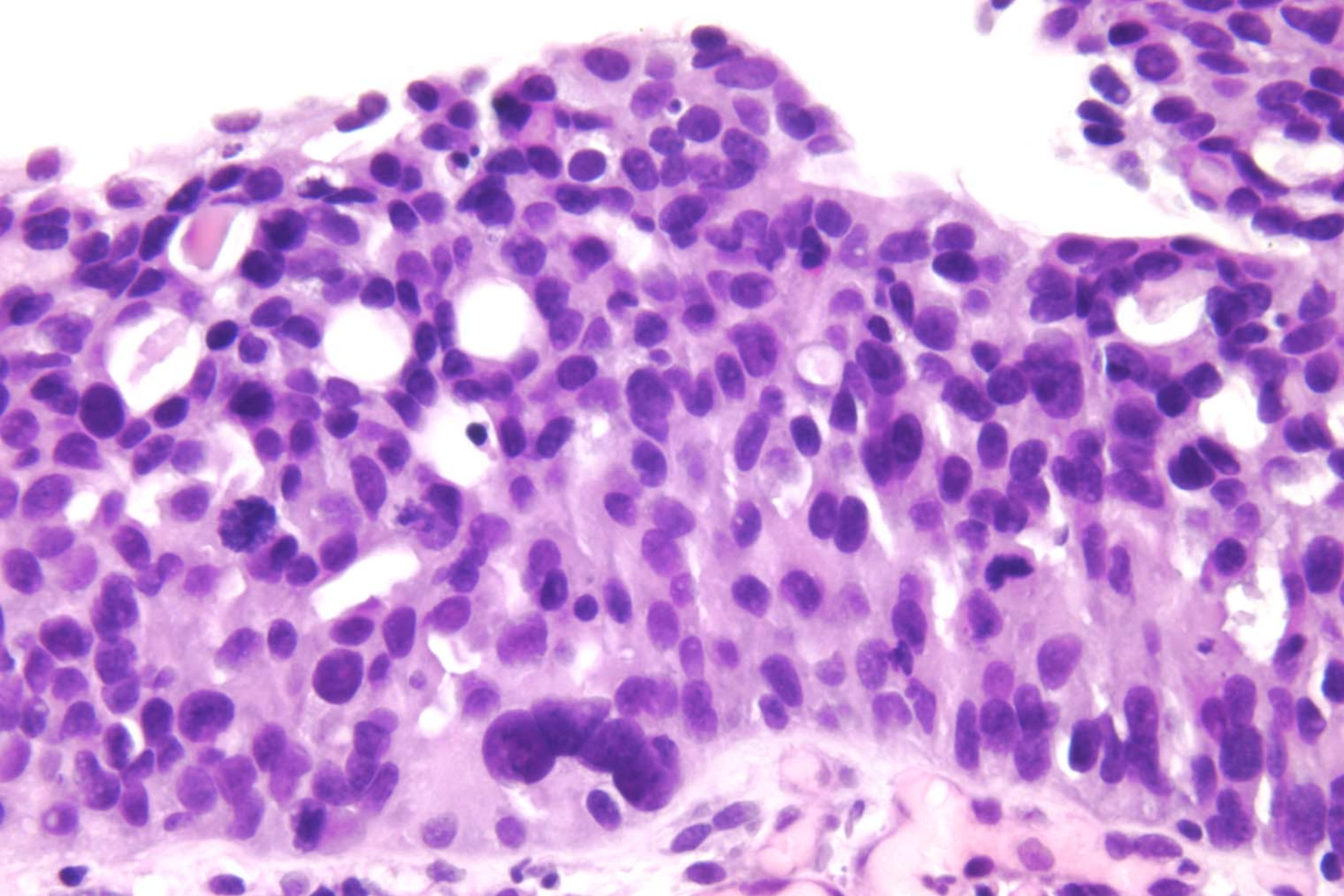
<b>Urothelial Tumours</b>
<b>Non-Invasive Urothelial Neoplasia</b>
Urothelial papilloma
Inverted urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-invasive papillary urothelial carcinoma, low-grade
Non-invasive papillary urothelial carcinoma, high-grade
Urothelial carcinoma in situ
<b>Invasive Urothelial Neoplasia</b>
Invasive urothelial carcinoma

## Urothelial CIS

- Presence of cytologically malignant cells **regardless of quantity**
  - No need to be full **thickness**
  - **Pagetoid** cells
  - **Spectrum** of atypia and cell size
  - **Umbrella** cell layer may still be present
- CIS cells **5x size** of stromal lymphocytes, compared to normal cells which are 2x size of lymphocytes
- Enlarged & hyperchromatic **ON 10X OBJECTIVE**
- Dyscohesive : “**denuding cystitis**”



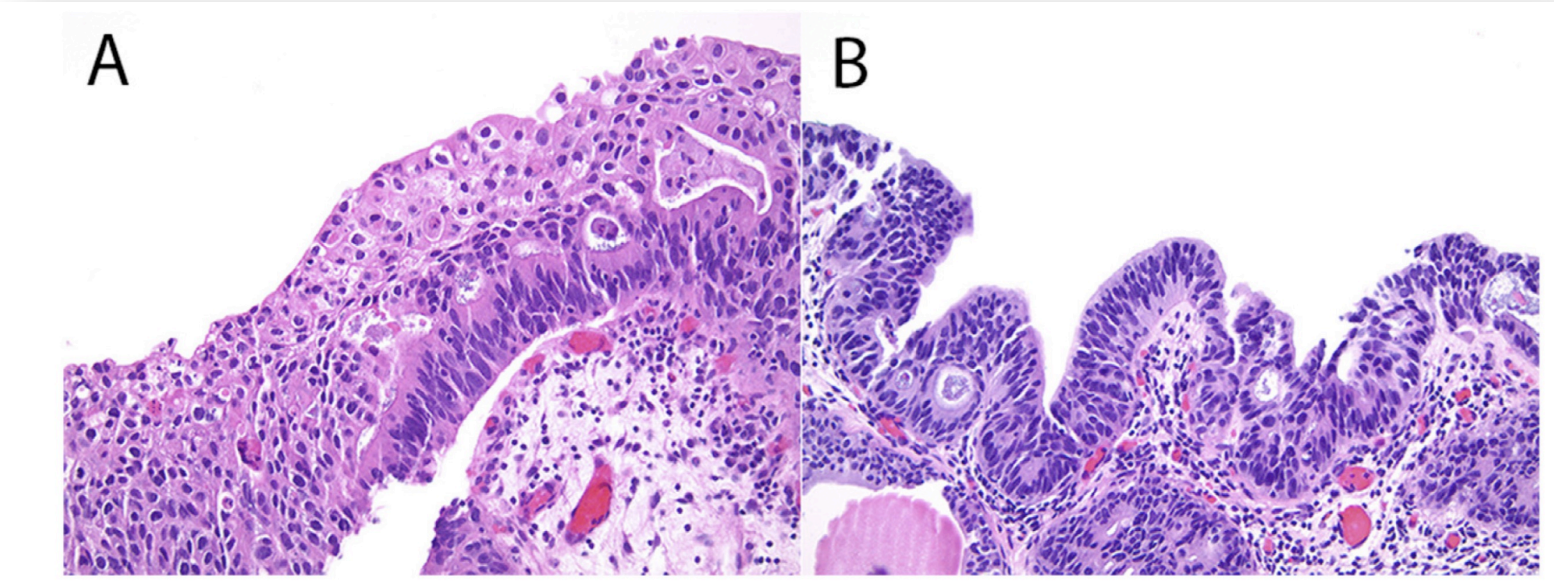




# Urothelial carcinoma *in situ*: diagnostic update

JESSE K. MCKENNEY

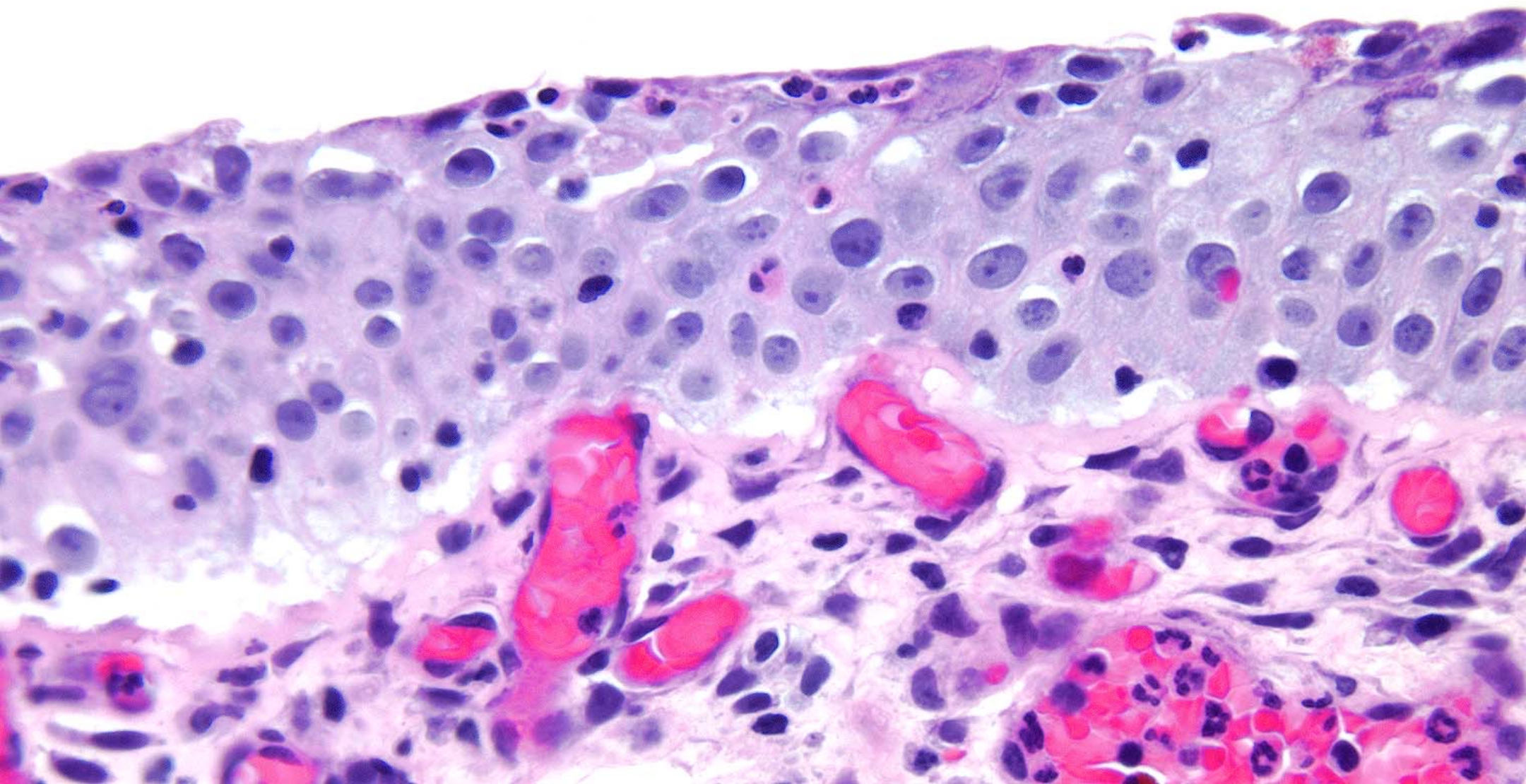
Pathology (January 2021)



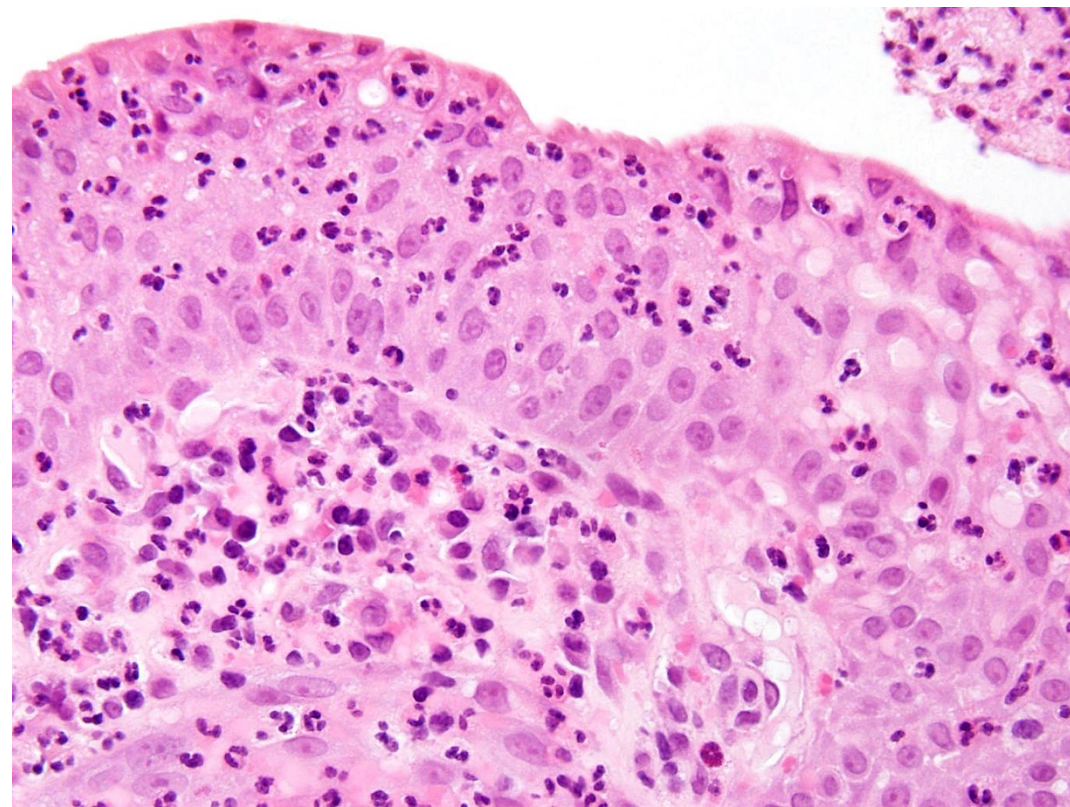
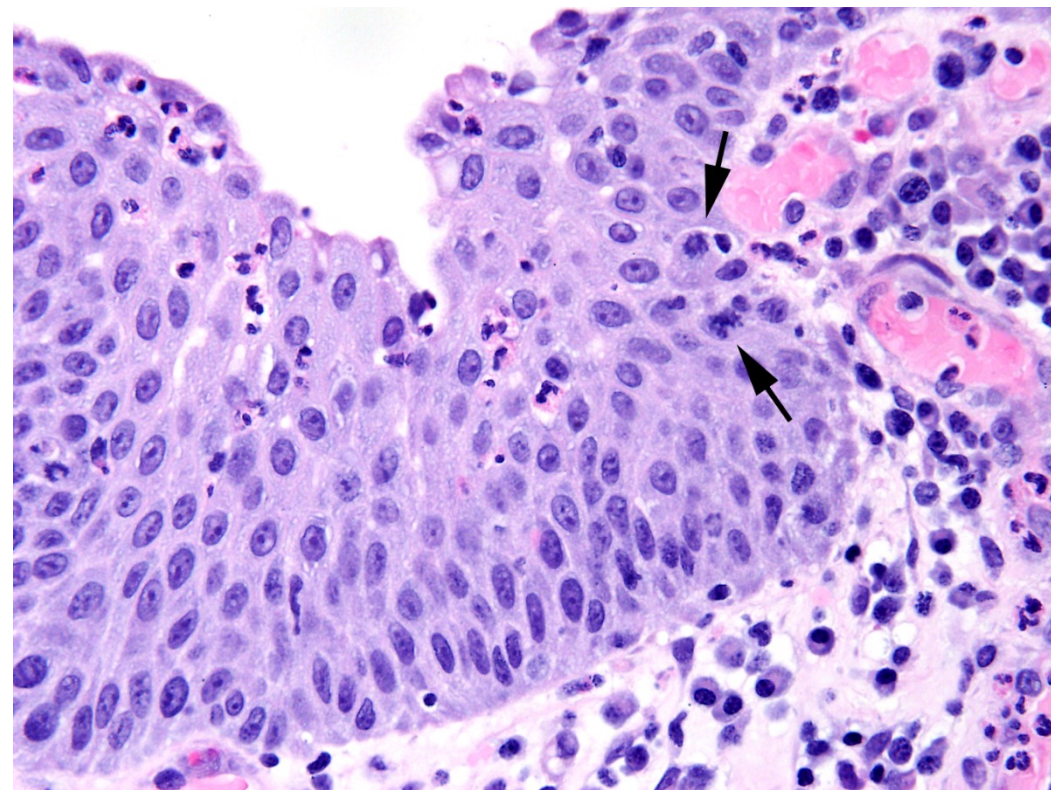
# Reactive Urothelial Atypia

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- Acute or chronically inflamed urothelium
- **Vesicular** uniformly enlarged nuclei with central **prominent nucleoli**.
- **Mitotic figures** may be common.
- History of **instrumentation**, infection, stones, therapy





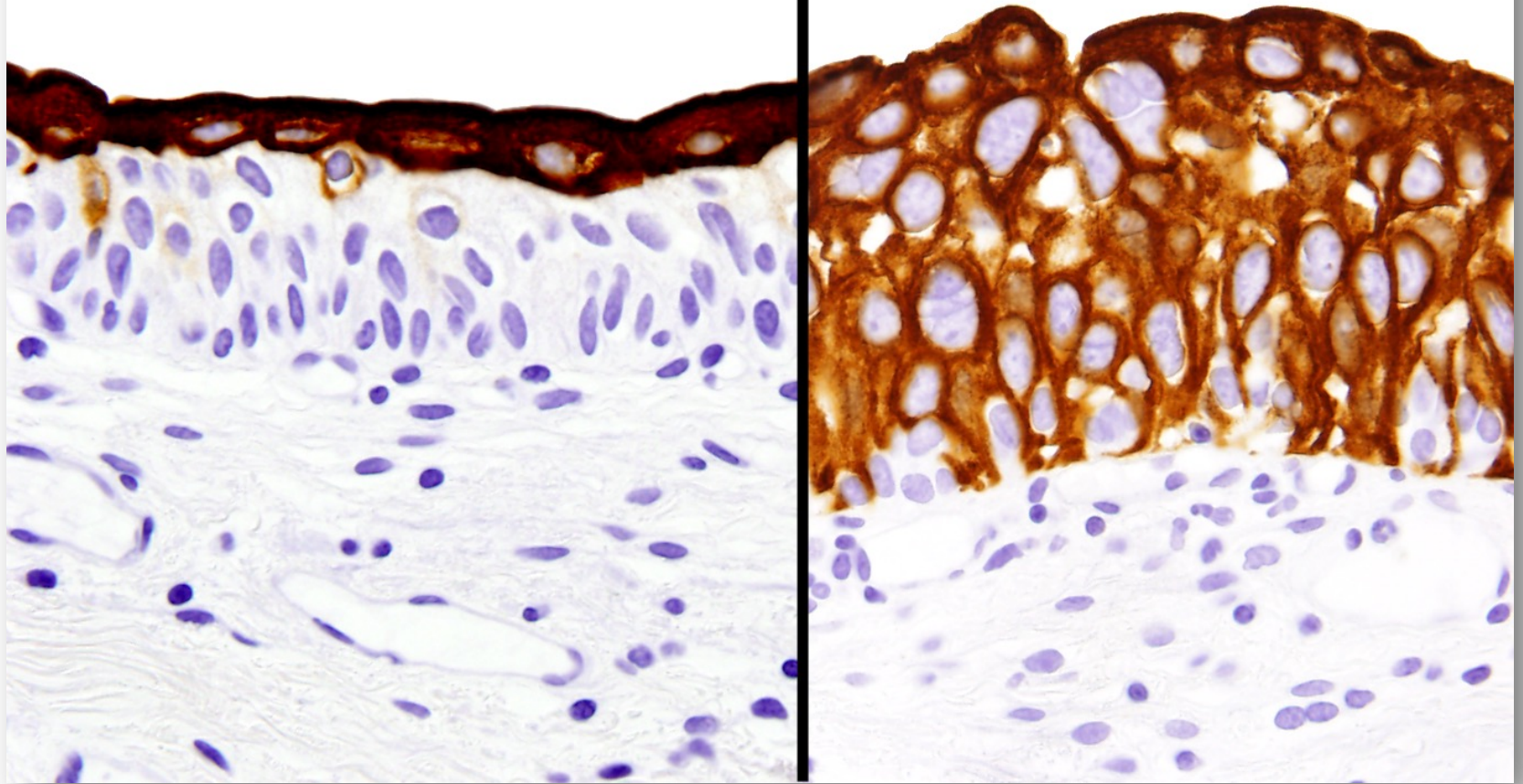


# Reactive vs. CIS

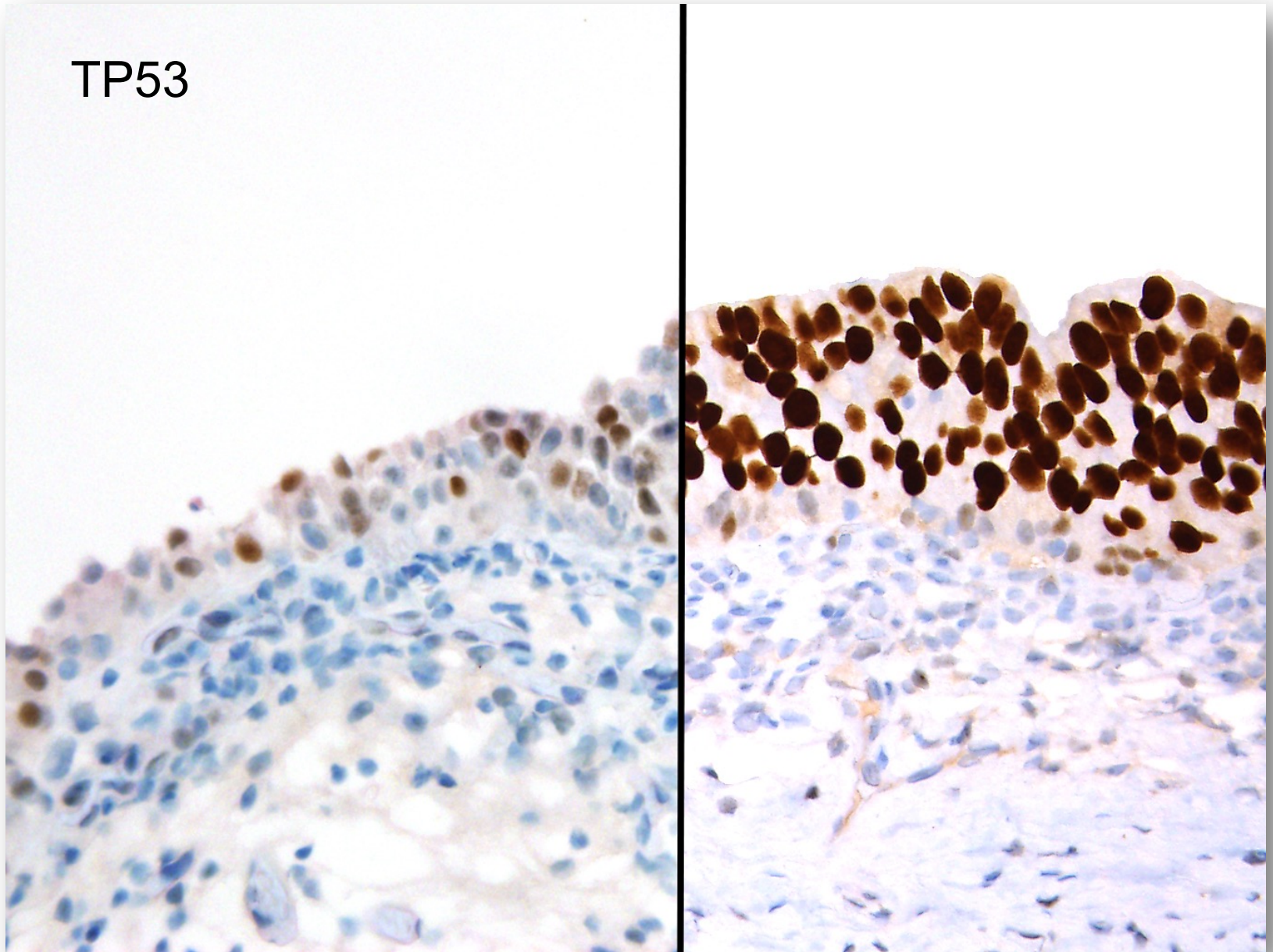
## Immunohistochemistry

	<b>CK20</b>	<b>P53</b>
<b>Normal/Reactive</b>	<i>Umbrella cell</i>	<i>None</i>
<b>CIS</b>	<i>All layers</i>	<i>Frequent</i>

CK20



TP53

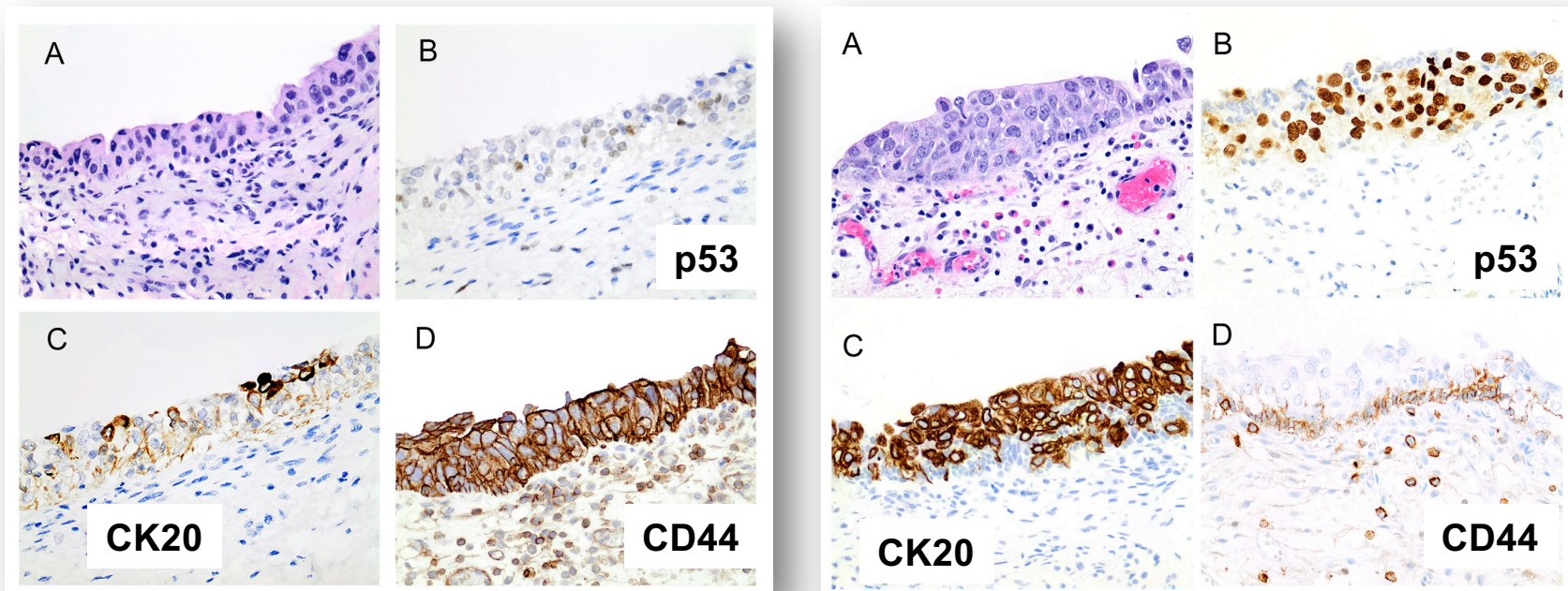


# Immunohistochemistry in the workup of bladder biopsies: Frequency, variation and utility of use at an academic center

Patrick McIntire\*, Reema Khan, Irem Kilic, Eva M. Wojcik, Stefan E. Pambuccian, Güliz A. Barkan

Loyola University Medical Center, Department of Pathology and Laboratory Medicine, Maywood, IL, United States

Annals of Diagnostic Pathology 41 (2019) 124–128

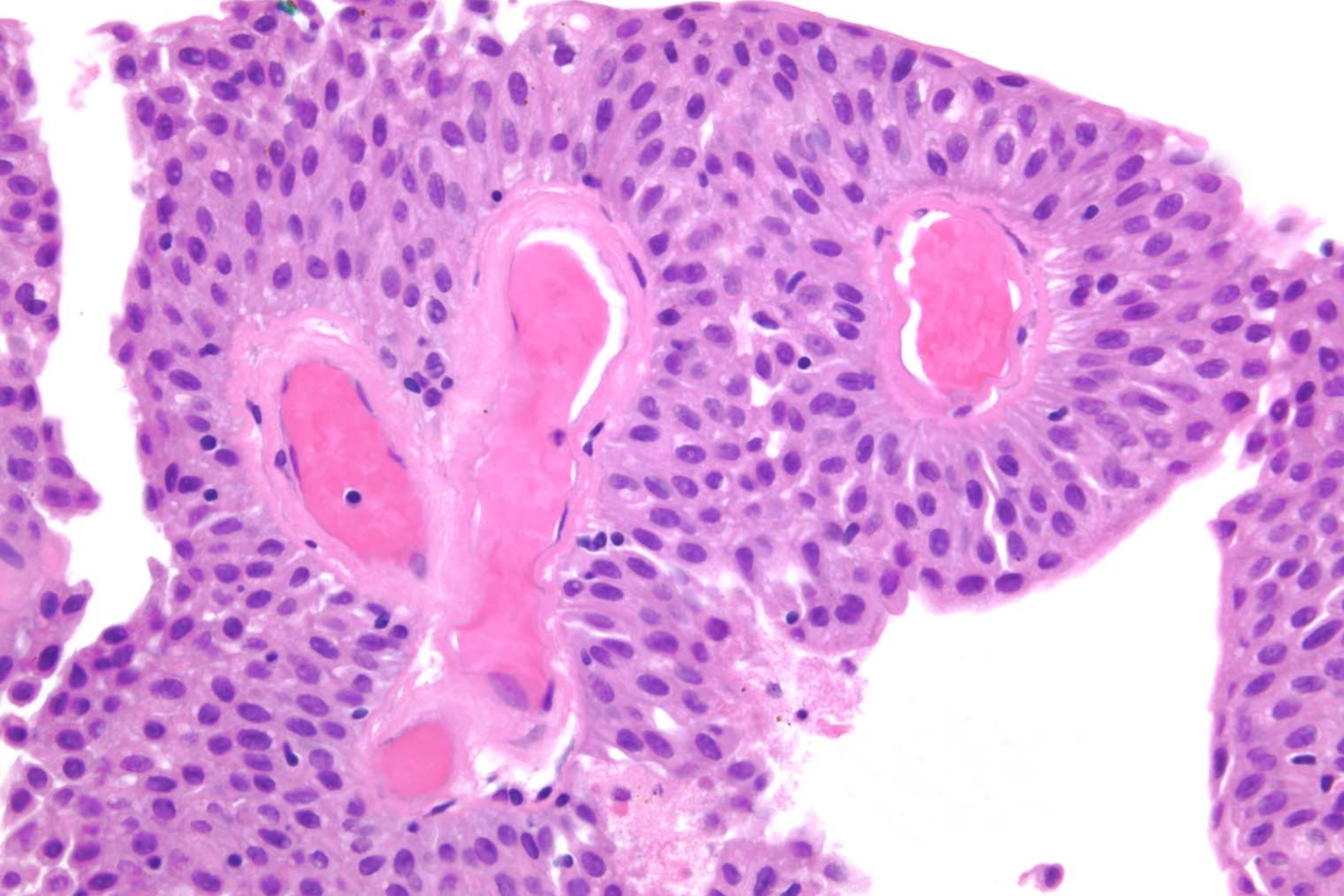


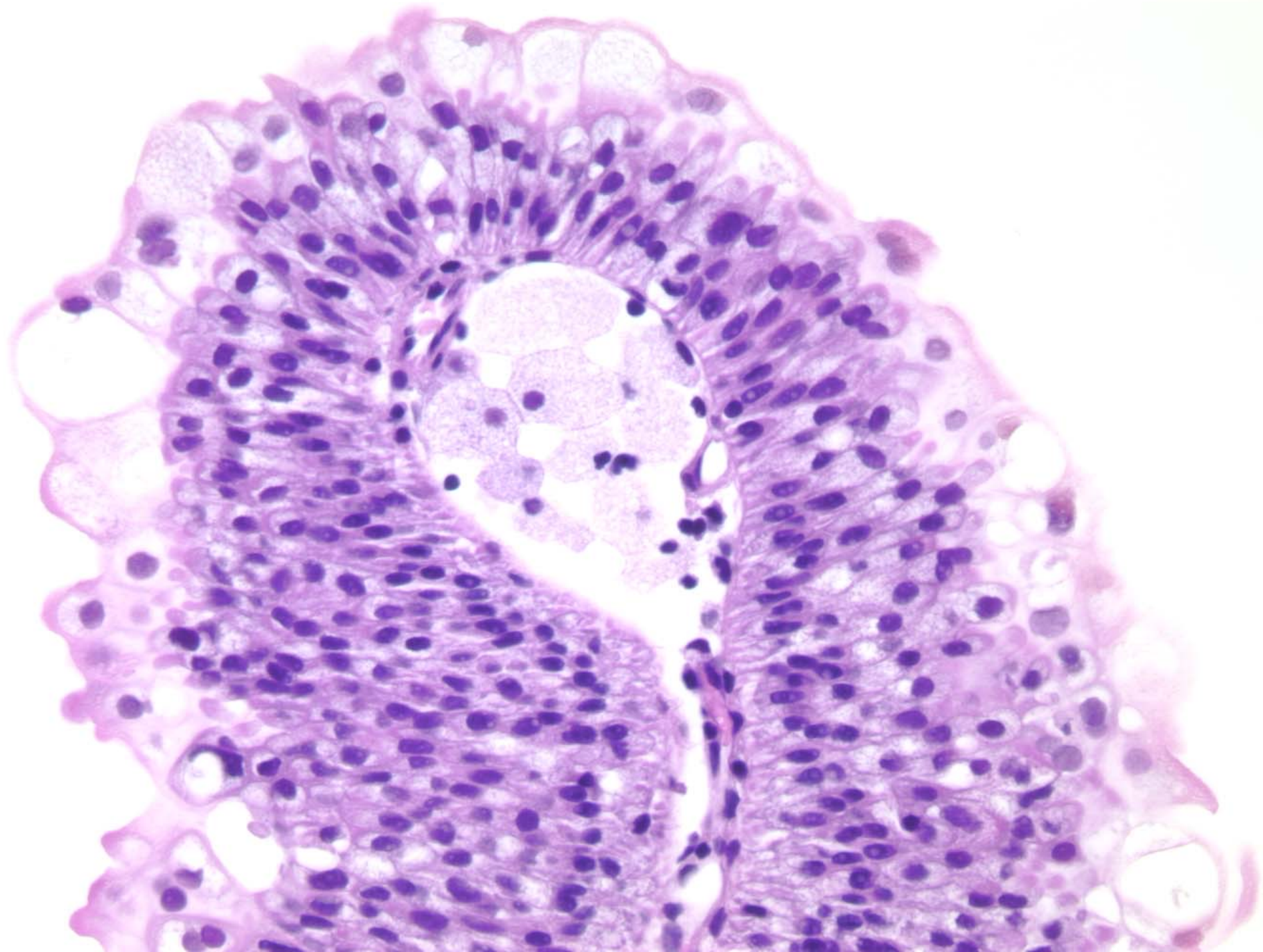
*“our institution was an early adopter of IHC but it quickly fell out of favor to a total of only 5 cases in 2017”*

# Urothelial Papilloma

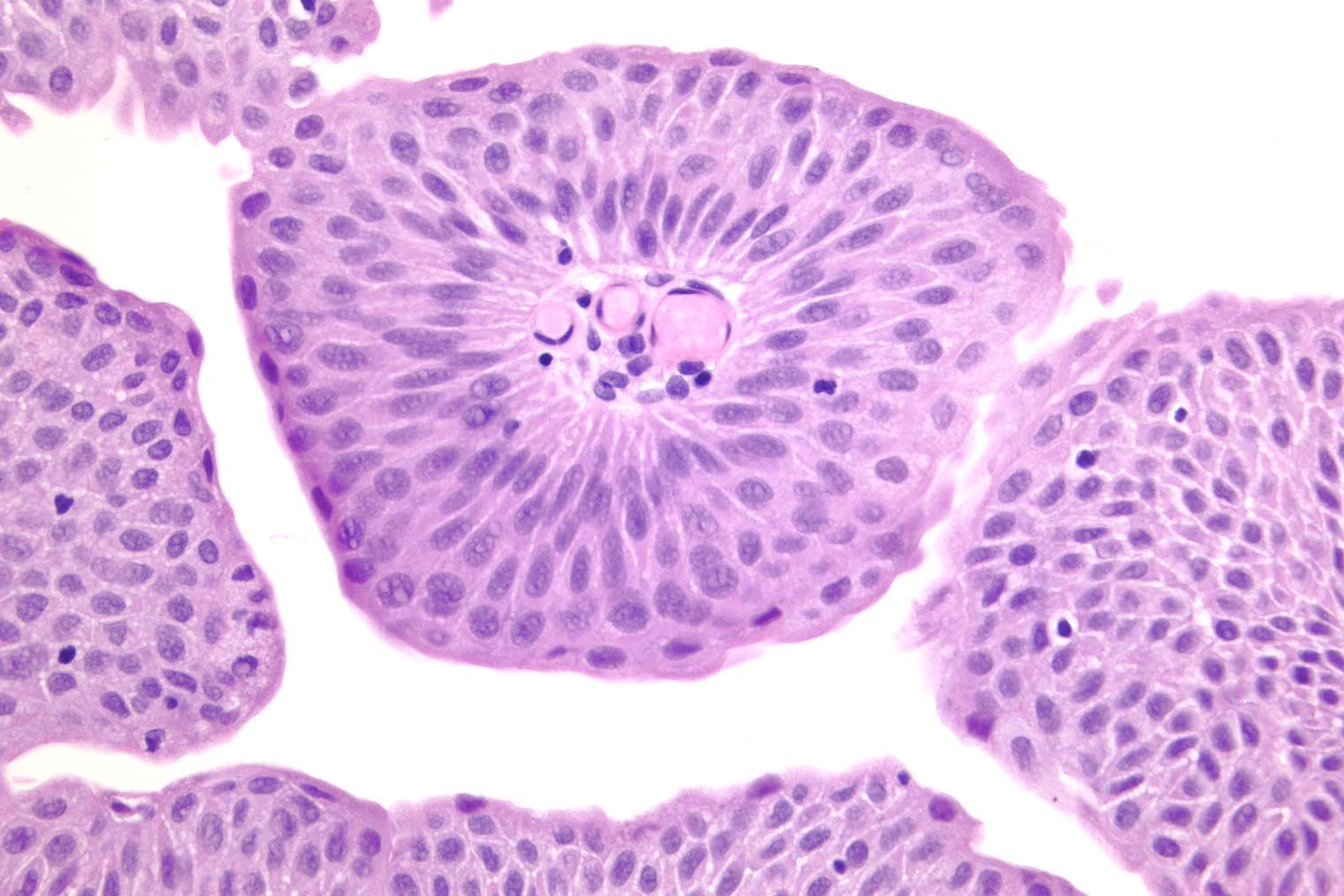
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- Discrete papillary growth with a central fibrovascular core lined by urothelium of **normal thickness and cytologic features**
- **No need to count** cell layers (7)
- Very rare lesion









# Urothelial Papilloma

*Magi-Galluzzi et al. Am J Surg Pathol 2004*

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- 34 de novo papillomas
- Mean age 58 years
- 24 males; 10 female
- F/U in 26 pts (mean 29 months)
- 3/34 **(8.8%) recurrence rate**
- 3/34 **(8.8%) progression to LG UrCa or PUNLMP**
- **No progression to invasive UrCa (pT1 or pT2)**

# Long term outcome of primary urothelial papilloma: a single institution cohort

SAMIR AL BASHIR<sup>1</sup>, ASLI YILMAZ<sup>1</sup>, GEOFFREY GOTTO<sup>2</sup> AND KIRIL TRPKOV<sup>1</sup>

<sup>1</sup>Department of Pathology and Laboratory Medicine, University of Calgary and Calgary Laboratory Services, Calgary, and <sup>2</sup>Division of Urology, University of Calgary, Calgary, Alberta, Canada

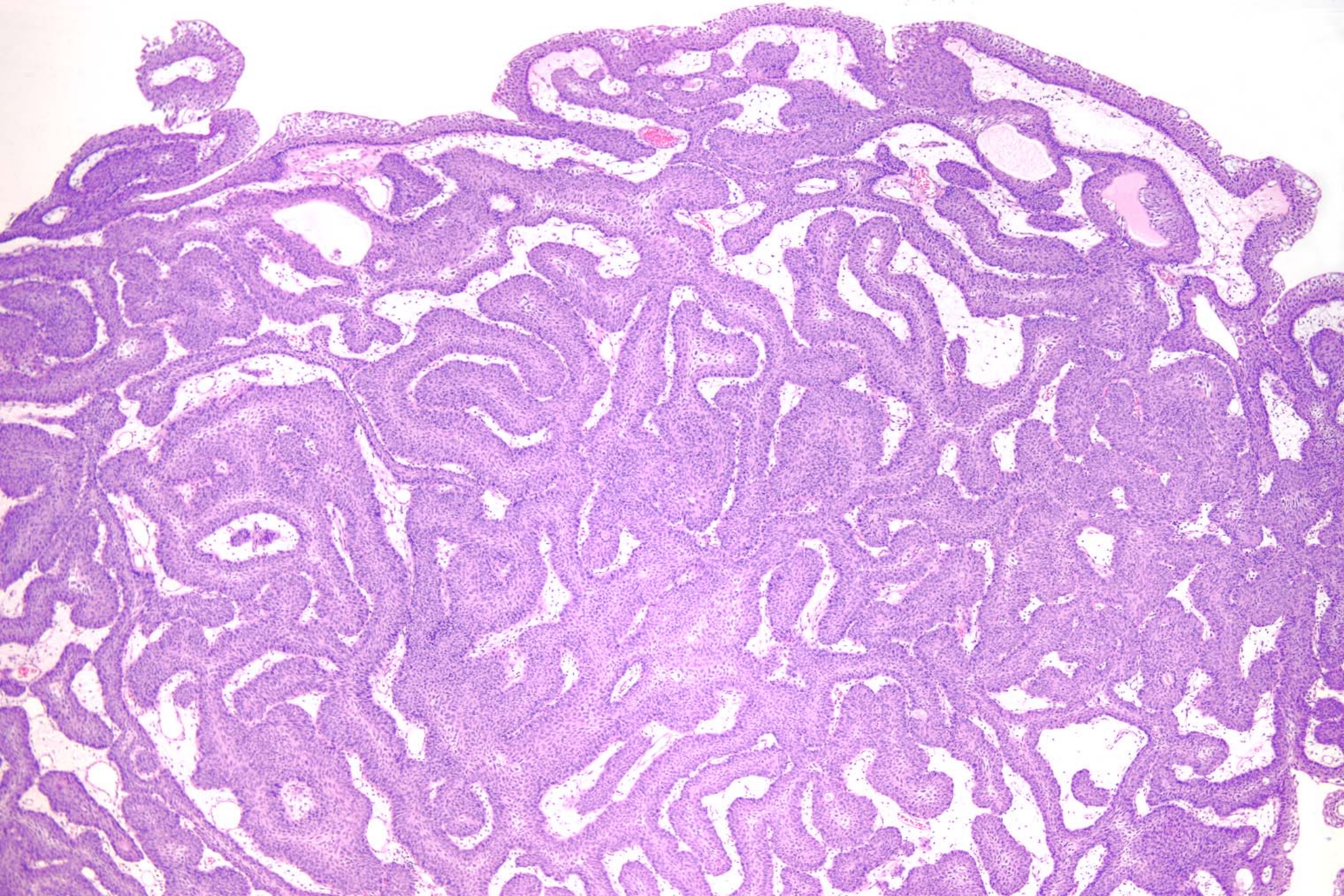
Pathology (January 2014) **46(1)**, pp. 37–40

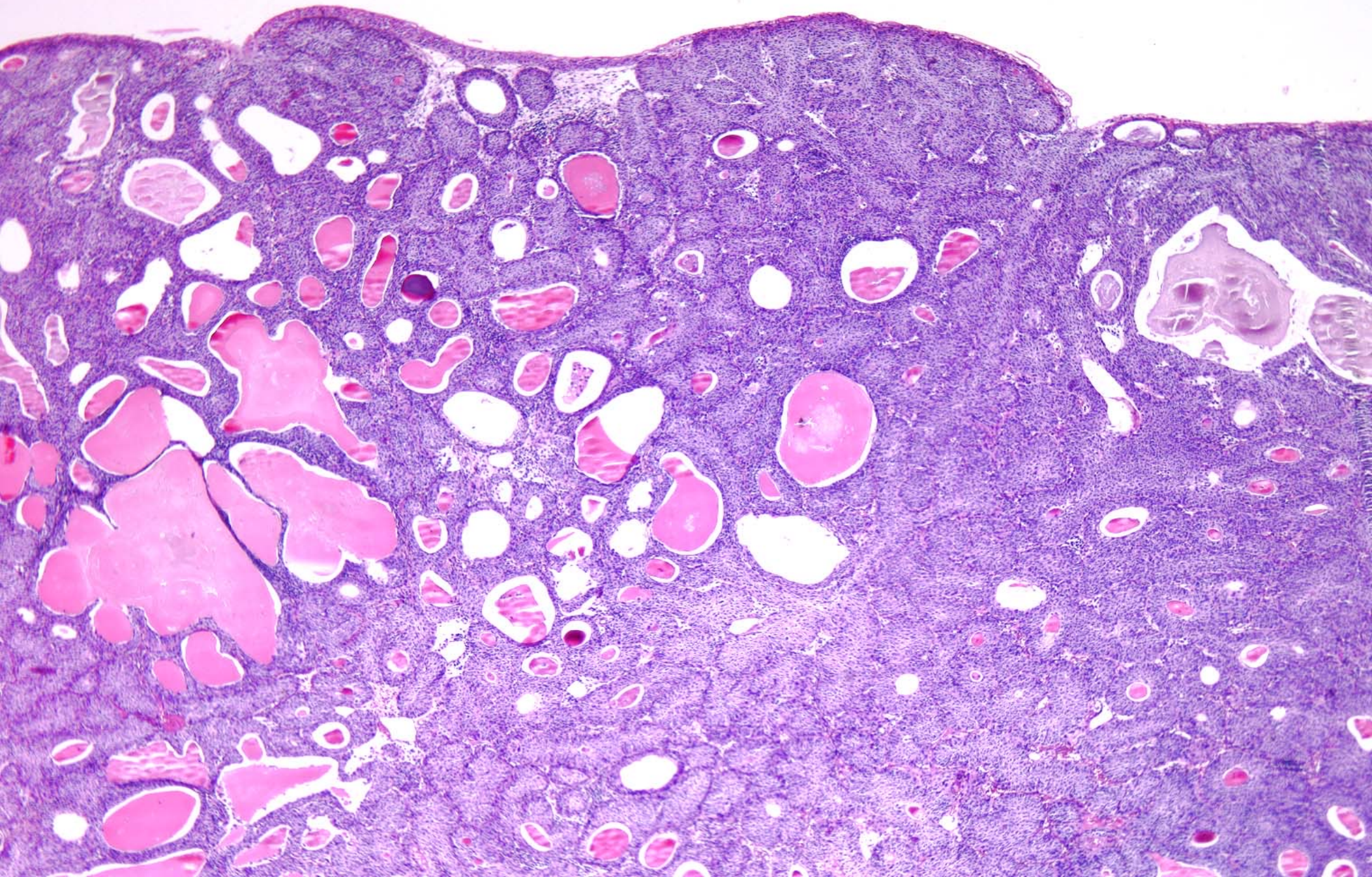
Study	No. patients	Mean average age (years)	Mean follow-up (months)	Risk of recurrence (%)	Risk of progression (%)
Cheng <i>et al.</i> <sup>4</sup>	52	57	118	8	2
McKenney <i>et al.</i> <sup>3</sup>	26	46	39	7	7
Magi-Galluzzi and Epstein <sup>5</sup>	34	57.8	28.9	8.8	8.8
Current study	41	57	81	4.9	4.9

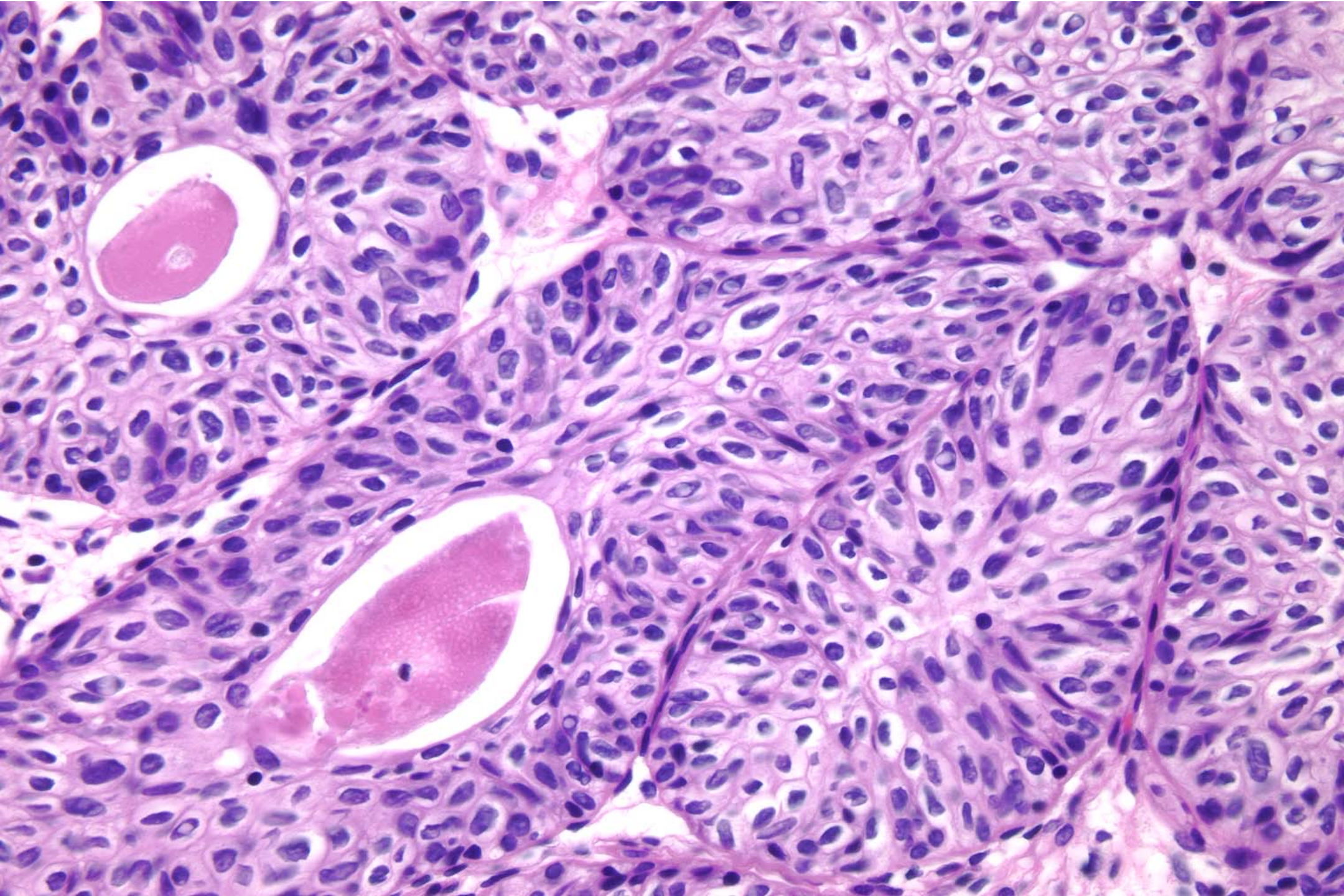
# Inverted Urothelial Papilloma

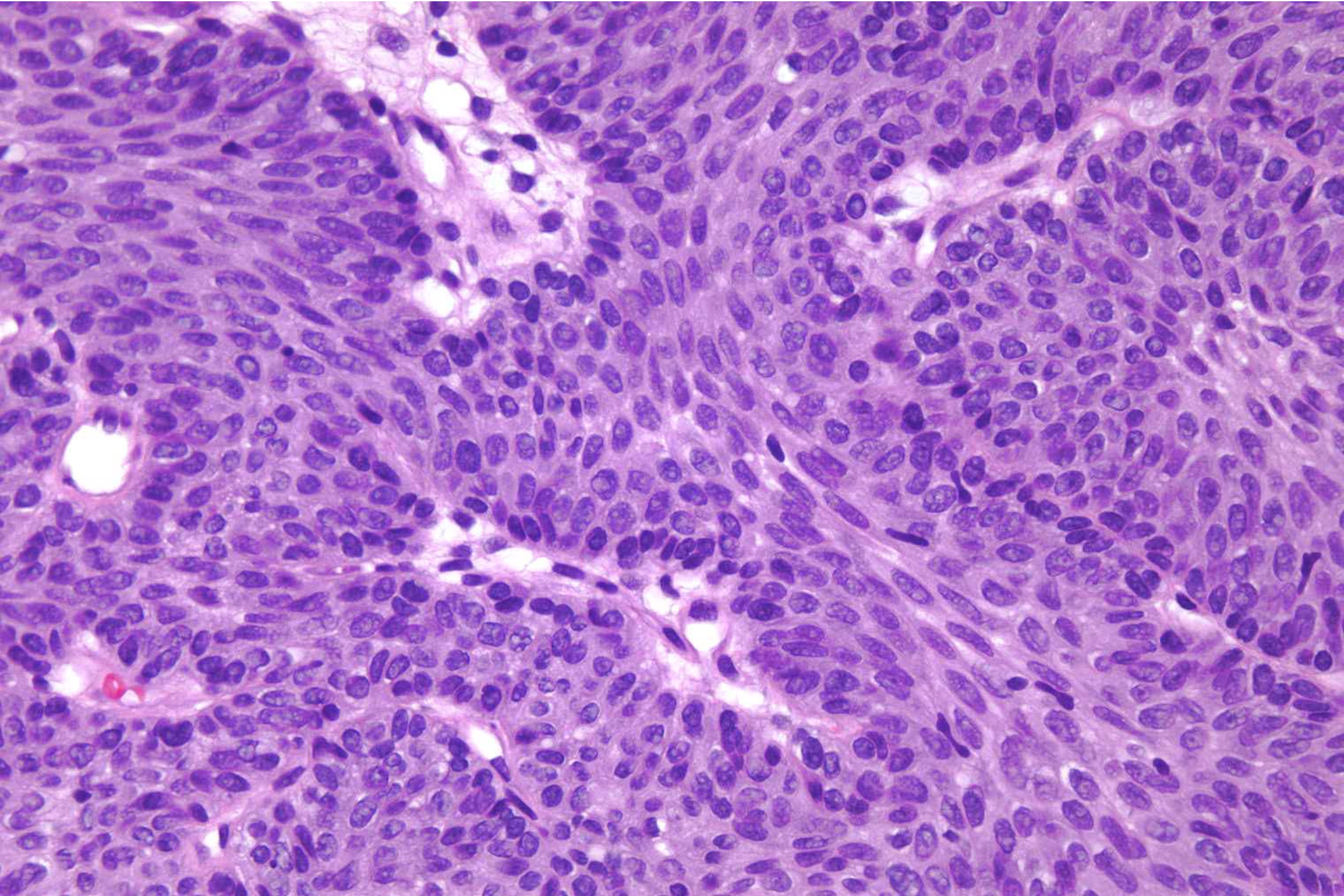
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- Most commonly seen in the **trigone** region
- Usually **solitary** (3% multiple).
- **Polypoid/sessile on cystoscopy**, smooth surface
- Size: wide range
  
- Can be associated with urothelial carcinoma, yet **not thought to be directly related**









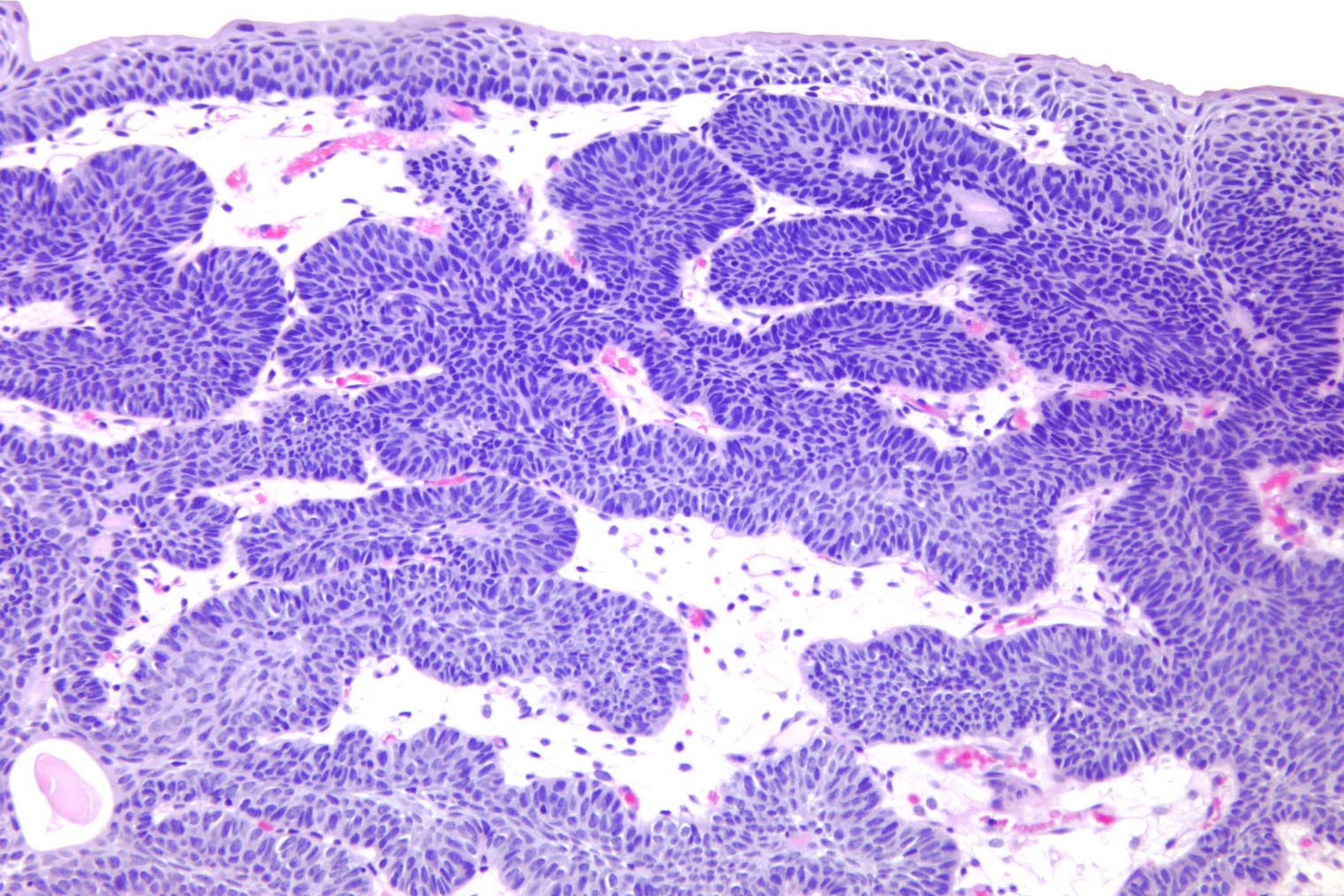


# Inverted Papilloma

## Comparison to Urothelial Carcinoma

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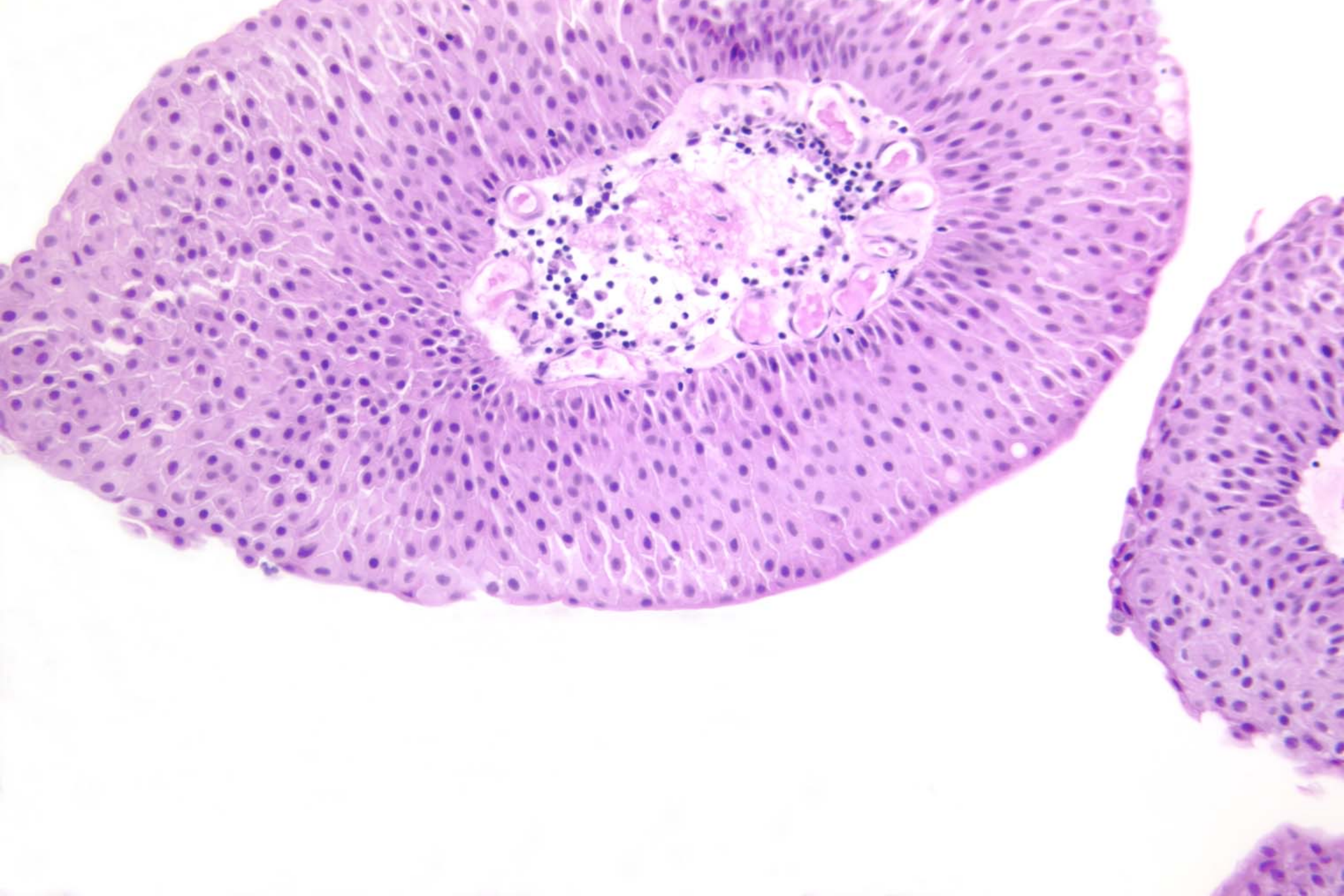
- Lacks cytological **atypia**
- **Mitotic** activity limited to basal cell layer
- Lacks inflammation and **reactive stroma**
- Squamous metaplasia **lacks keratin** formation
- Lacks muscularis propria invasion

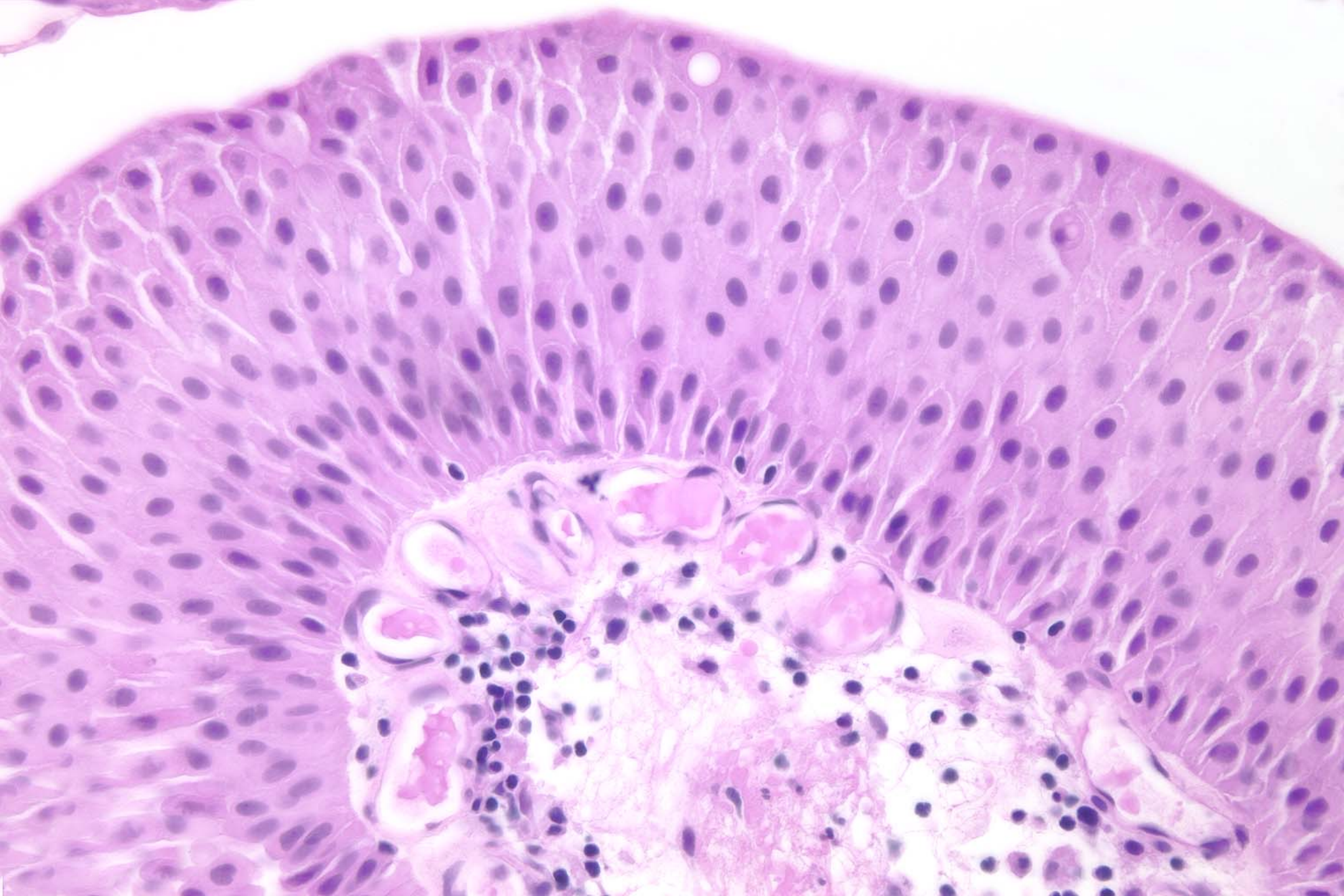


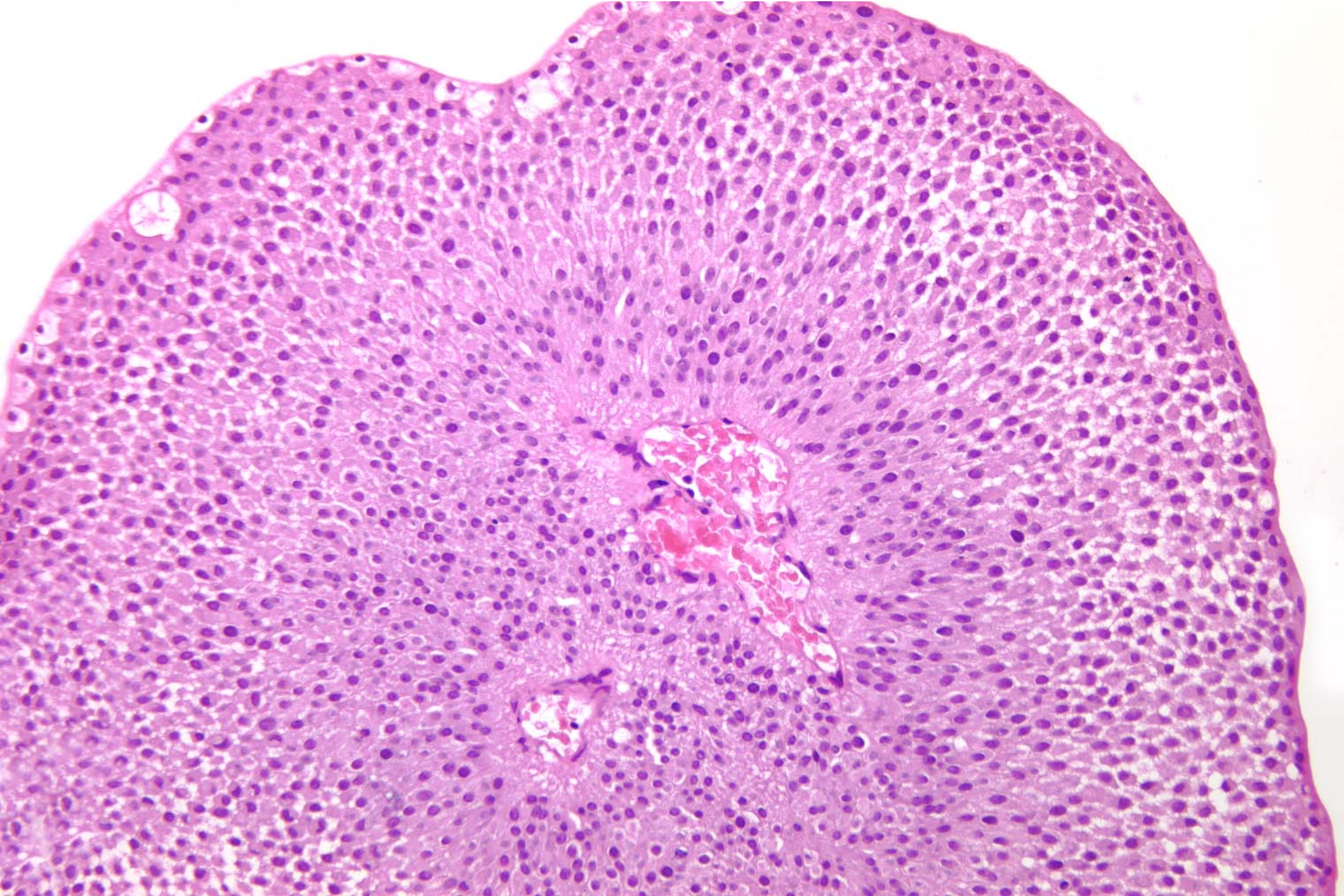
# Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

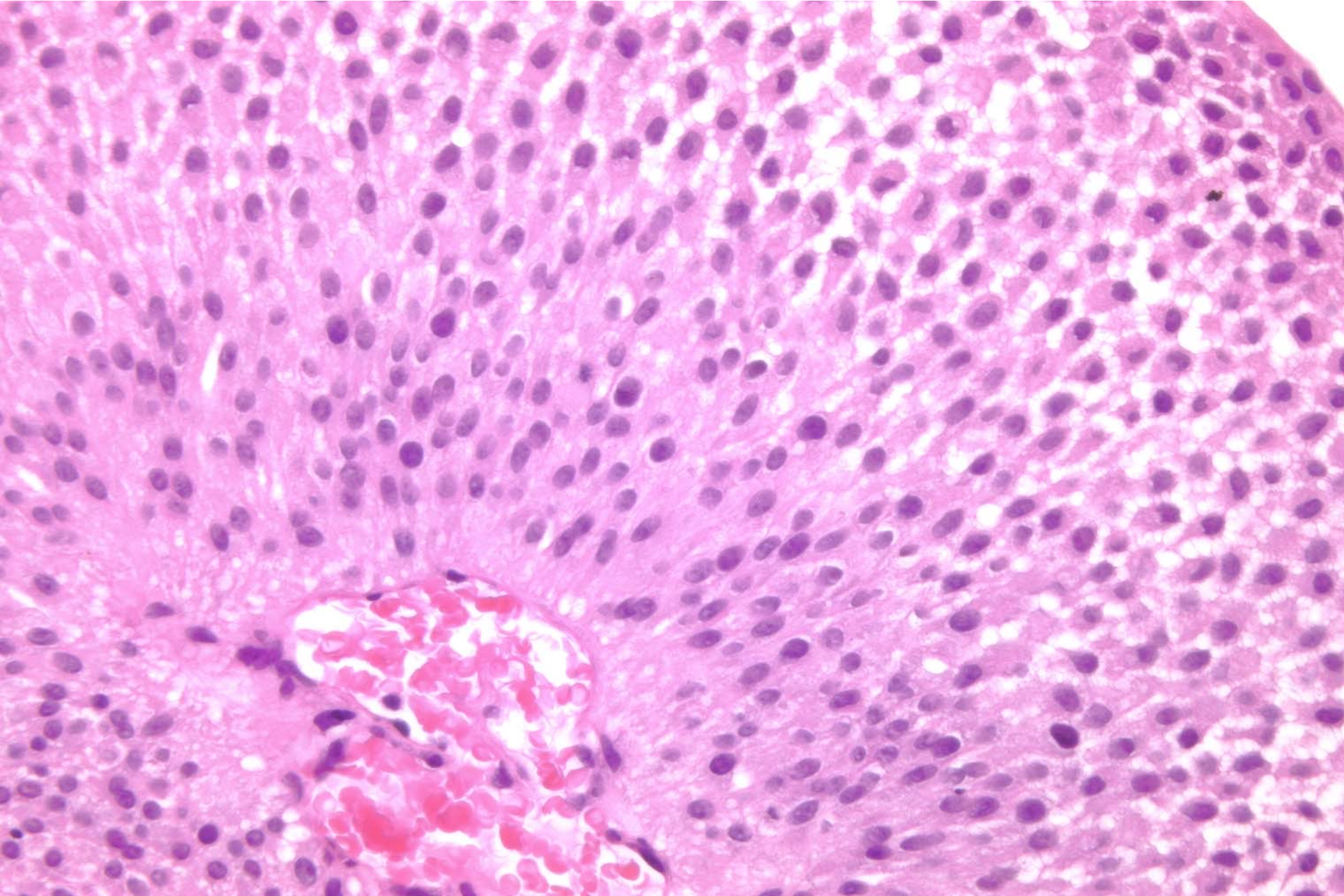
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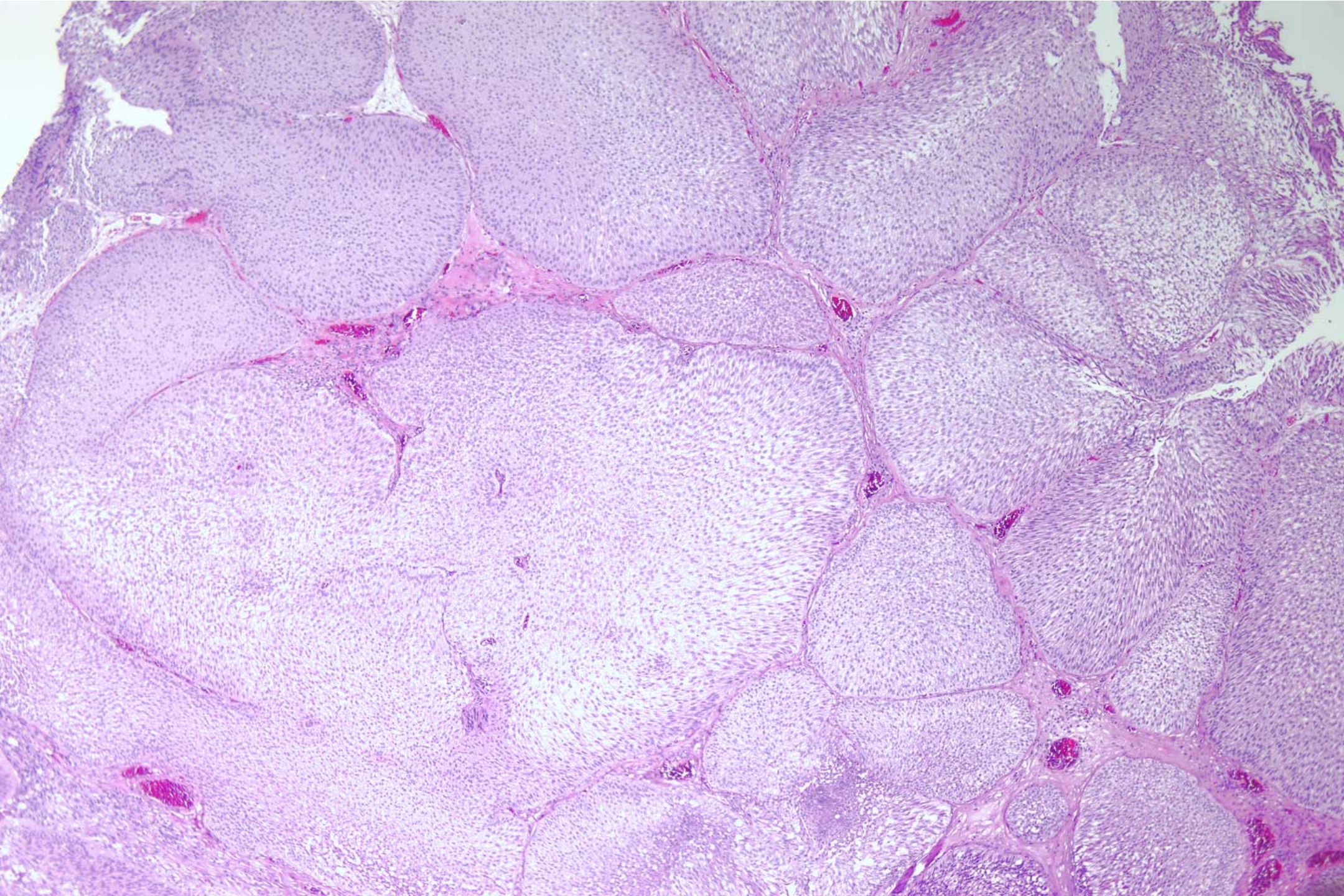
- **Orderly** arrangement
- **Thicker** than papilloma
- **No atypia**, at most nuclear enlargement
- At most rare **mitoses at base**
- Not associated with invasion



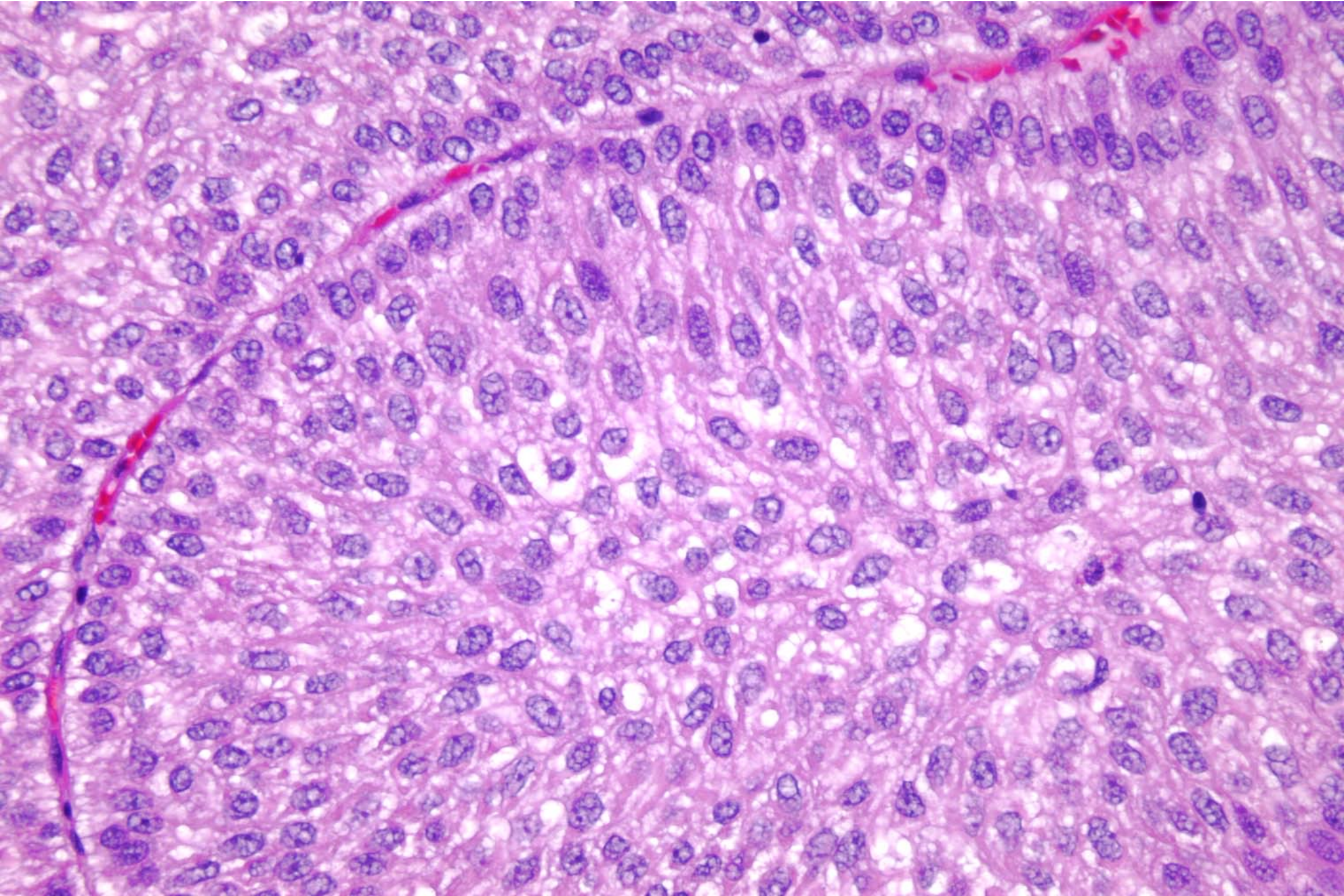












# Urothelial Papillary Carcinoma

## Terminology Issues

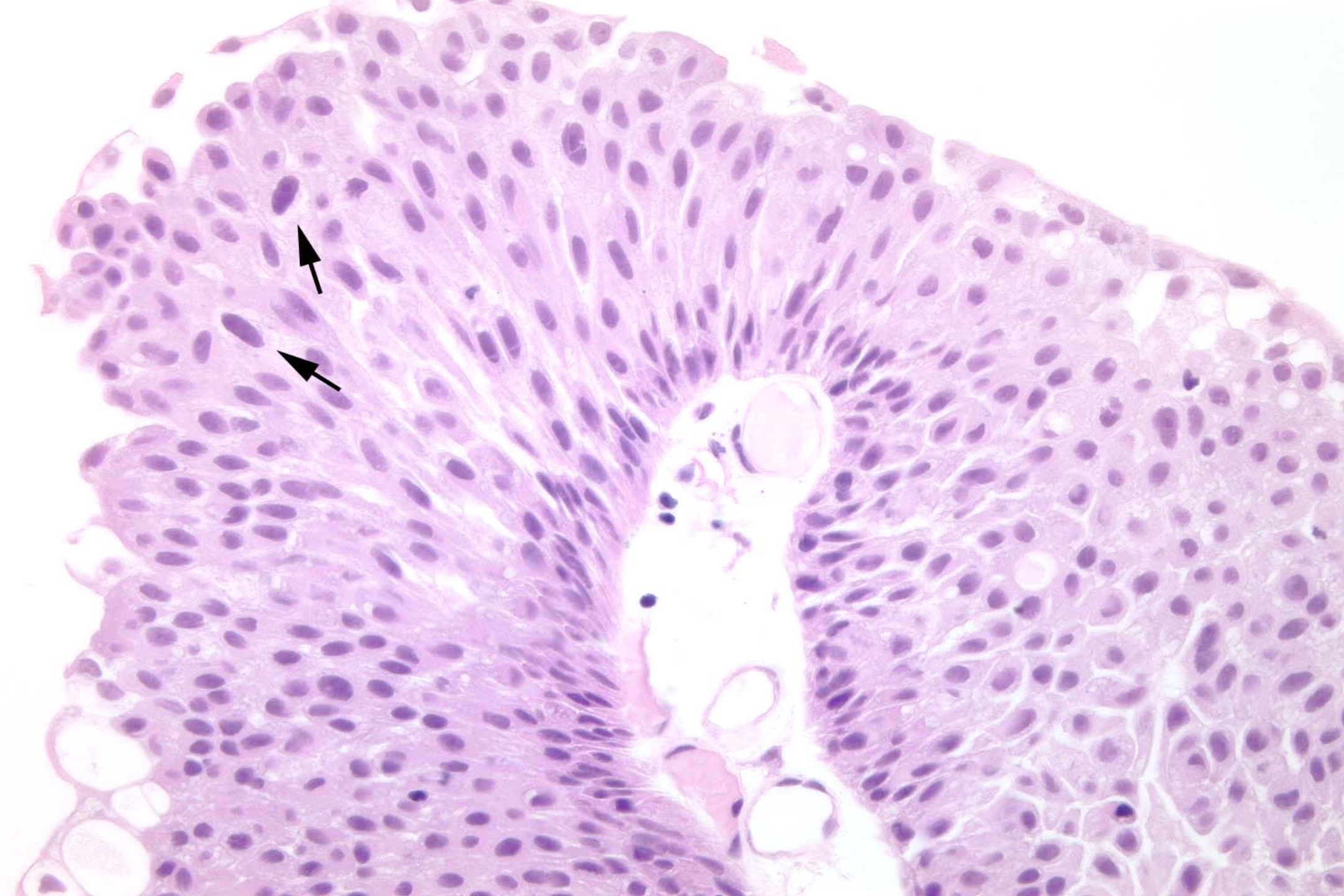
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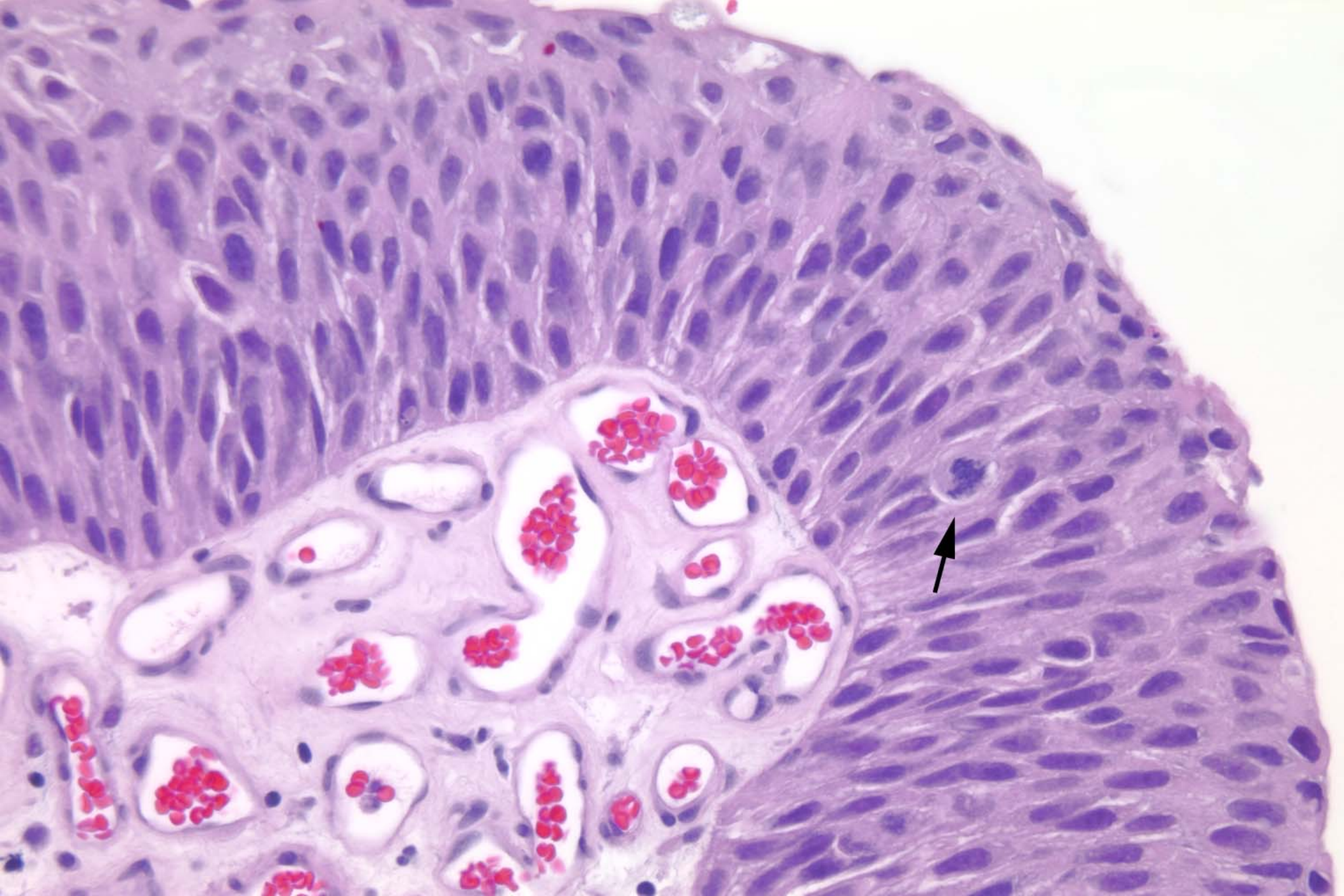
- *Non-invasive papillary carcinoma, Low grade*
- *Non-invasive papillary carcinoma, High grade*
- **Do Not use: “In situ papillary urothelial carcinoma”**
- **Non-invasive** papillary urothelial carcinoma
- **Invasive** papillary urothelial carcinoma
- Grade by the **worst component**
- **? HG component <5%**

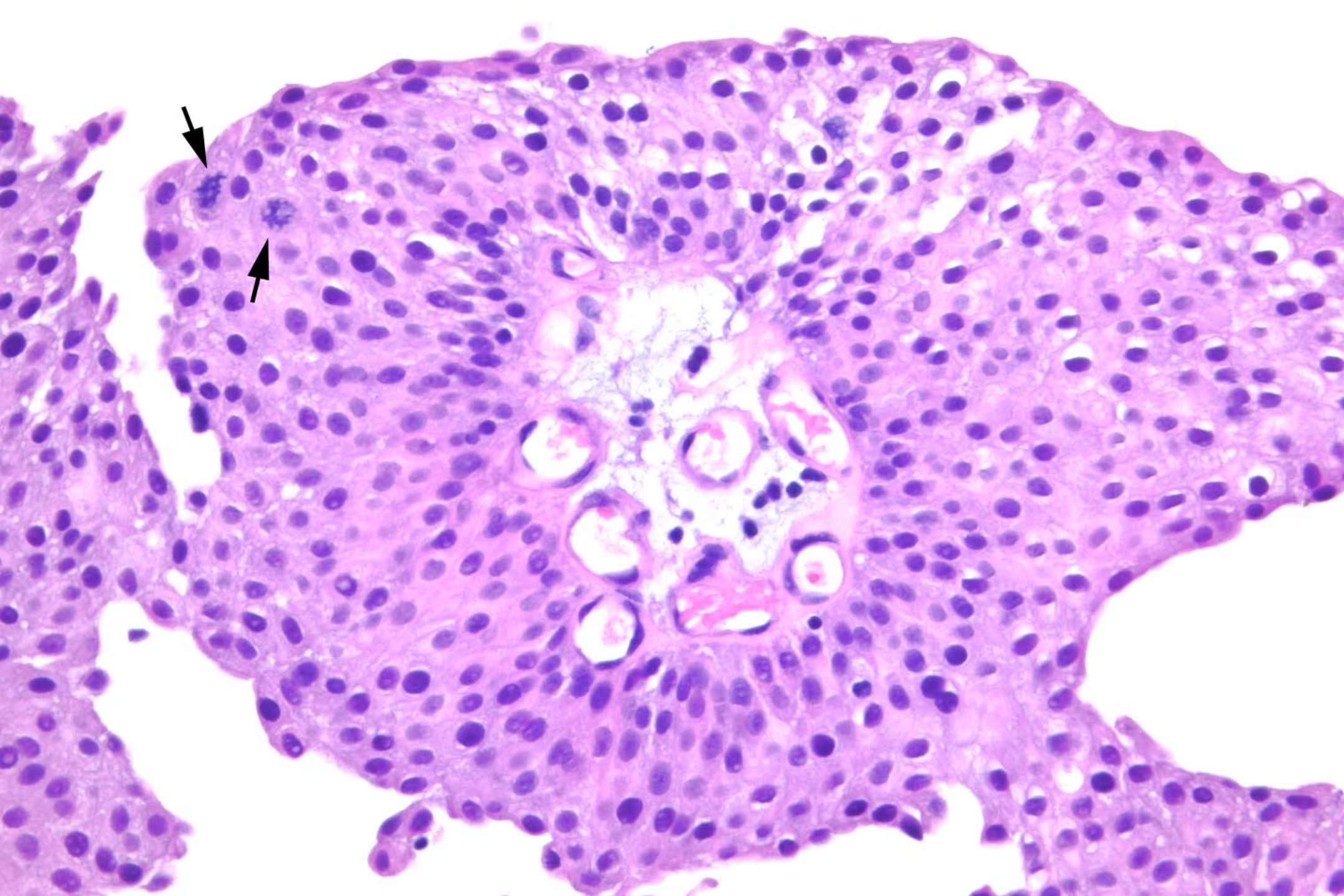
# Non-Invasive Papillary Carcinoma, Low Grade

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- **Overall orderly arrangement** with minimal variation in polarity (clonal appearance)
- On low power **looks “pink”** due to low N/C ratio
- Mild atypia consisting of **scattered enlarged hyperchromatic nuclei**
- Scattered **mitotic** figures some at levels **higher than base layer**
- **Inconspicuous nucleoli**



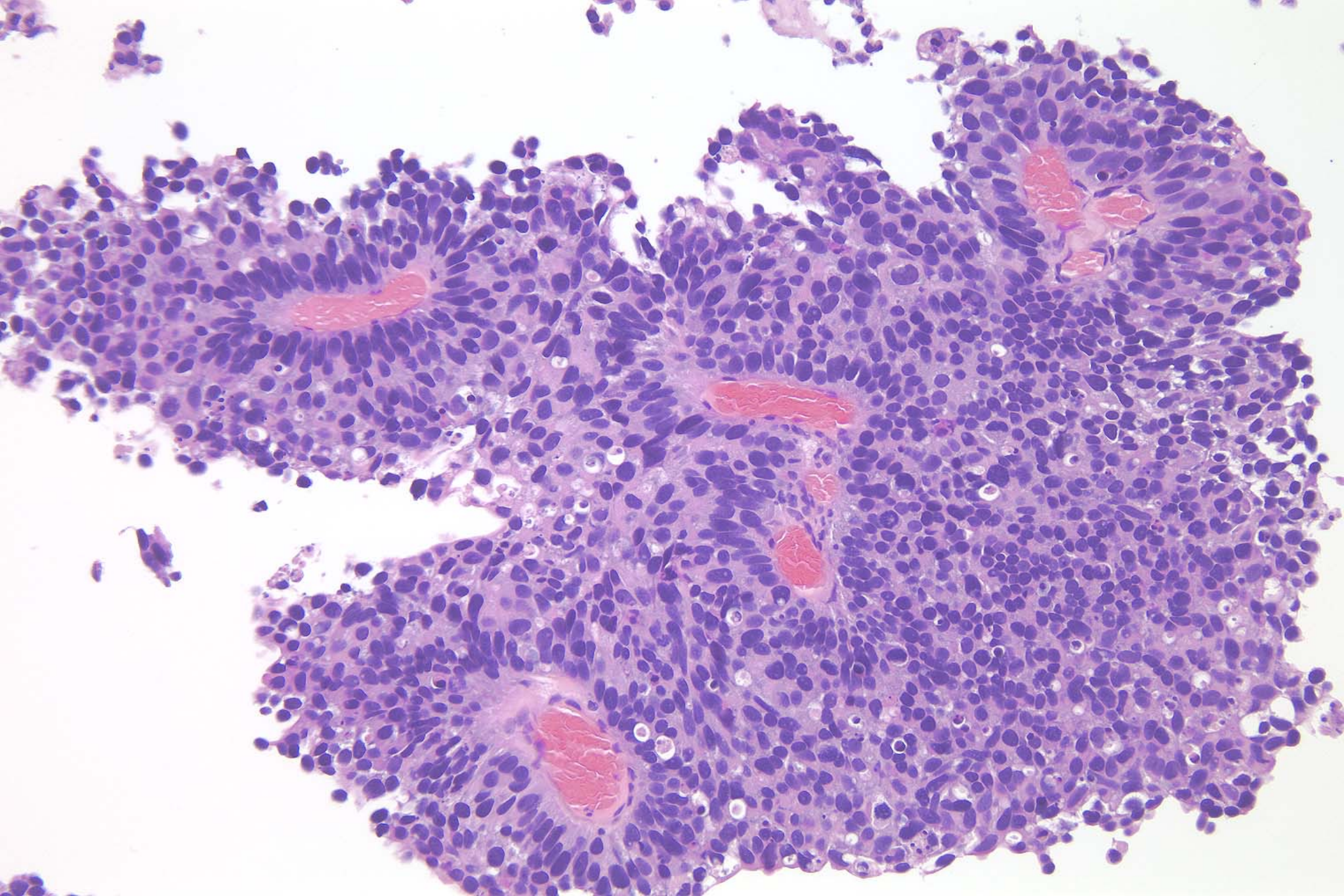




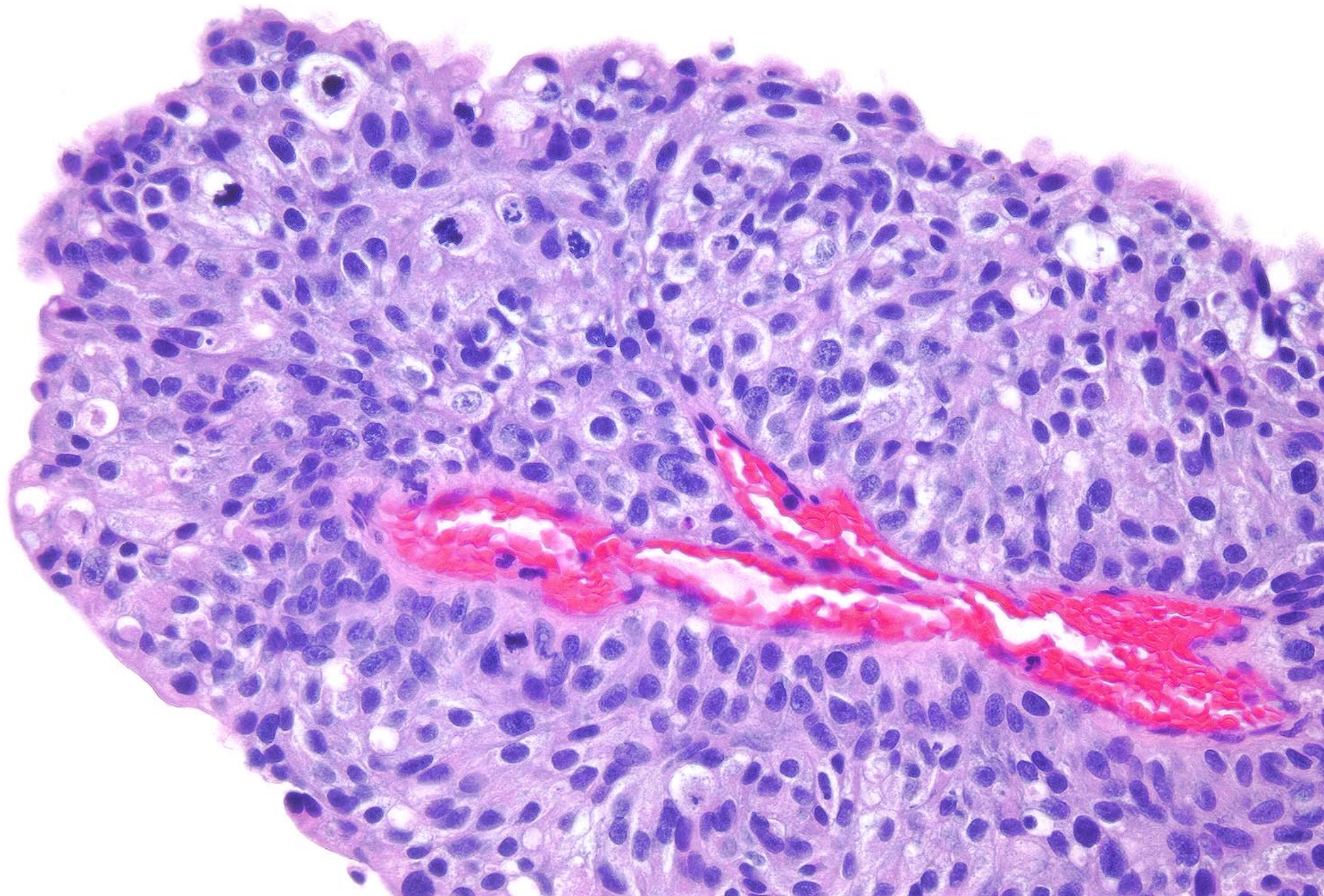
# Non-Invasive Papillary Carcinoma, High Grade

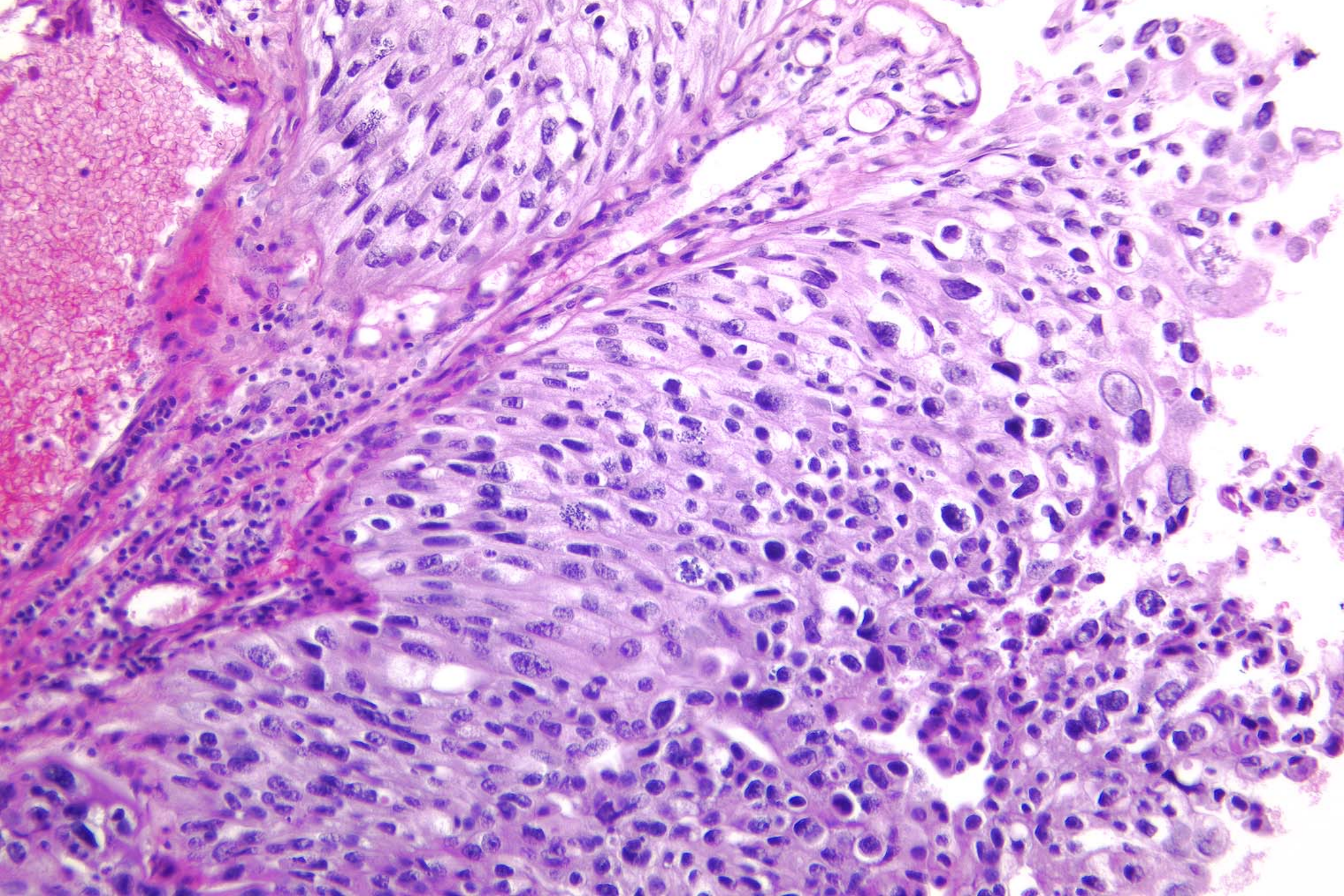
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- **Overall disorderly** arrangement with irregularly clustered cells, **fused** papillae
- **Marked atypia** analogous to CIS
- **Numerous mitotic figures** including atypical forms at all levels
- **Discohesive** single cells
- Prominent nucleoli









# **BLADDER CANCER**

## **STAGING ISSUES**

# Terminology - Muscle

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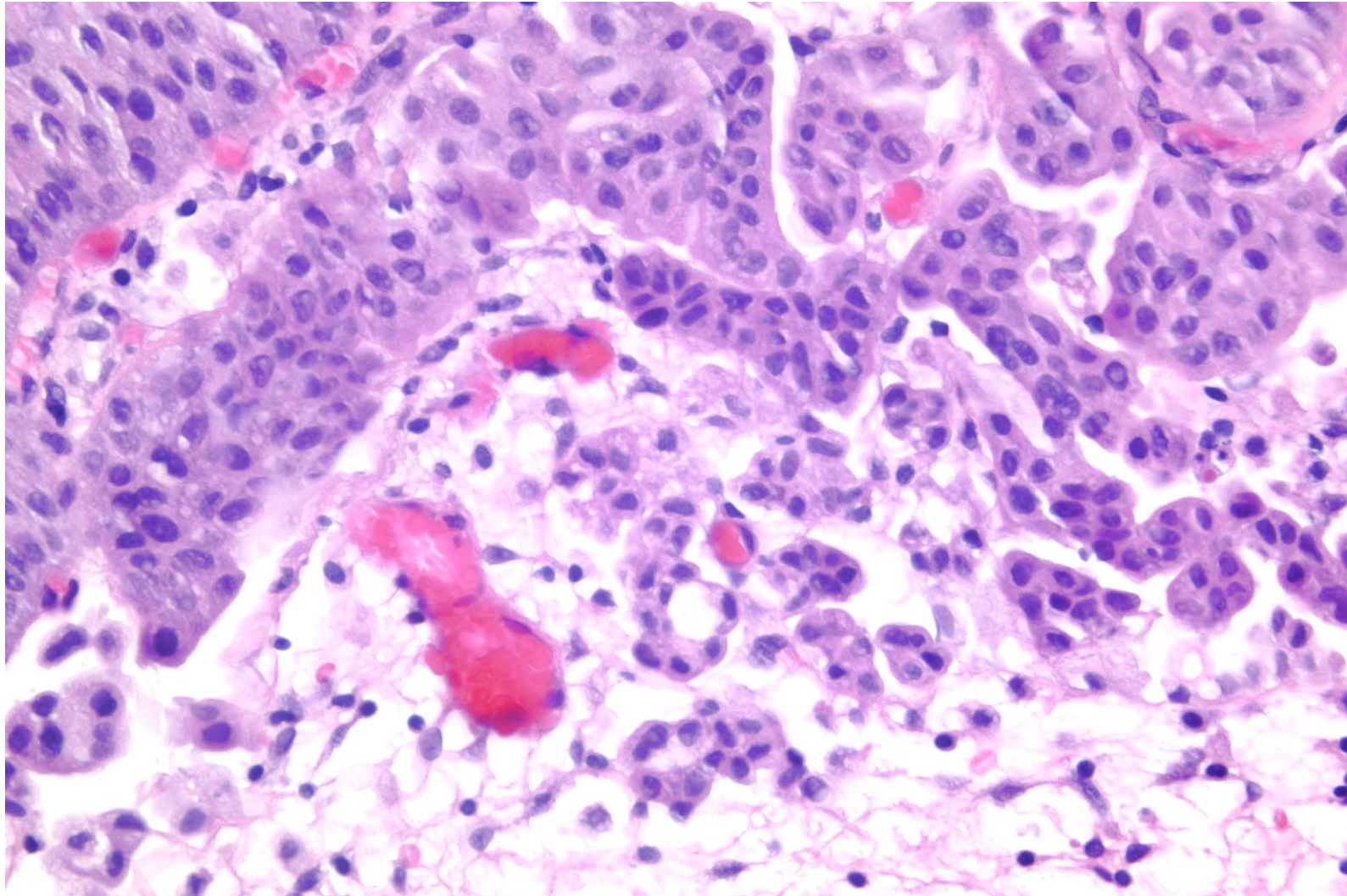
- **Muscularis propria** (detrusor muscle) invasion
- **Muscularis mucosae** invasion (do not report?)
- **Do not use** “superficial muscle” or “deep muscle”
- **Do not use** “superficial bladder cancer”

# Lamina Propria Invasion

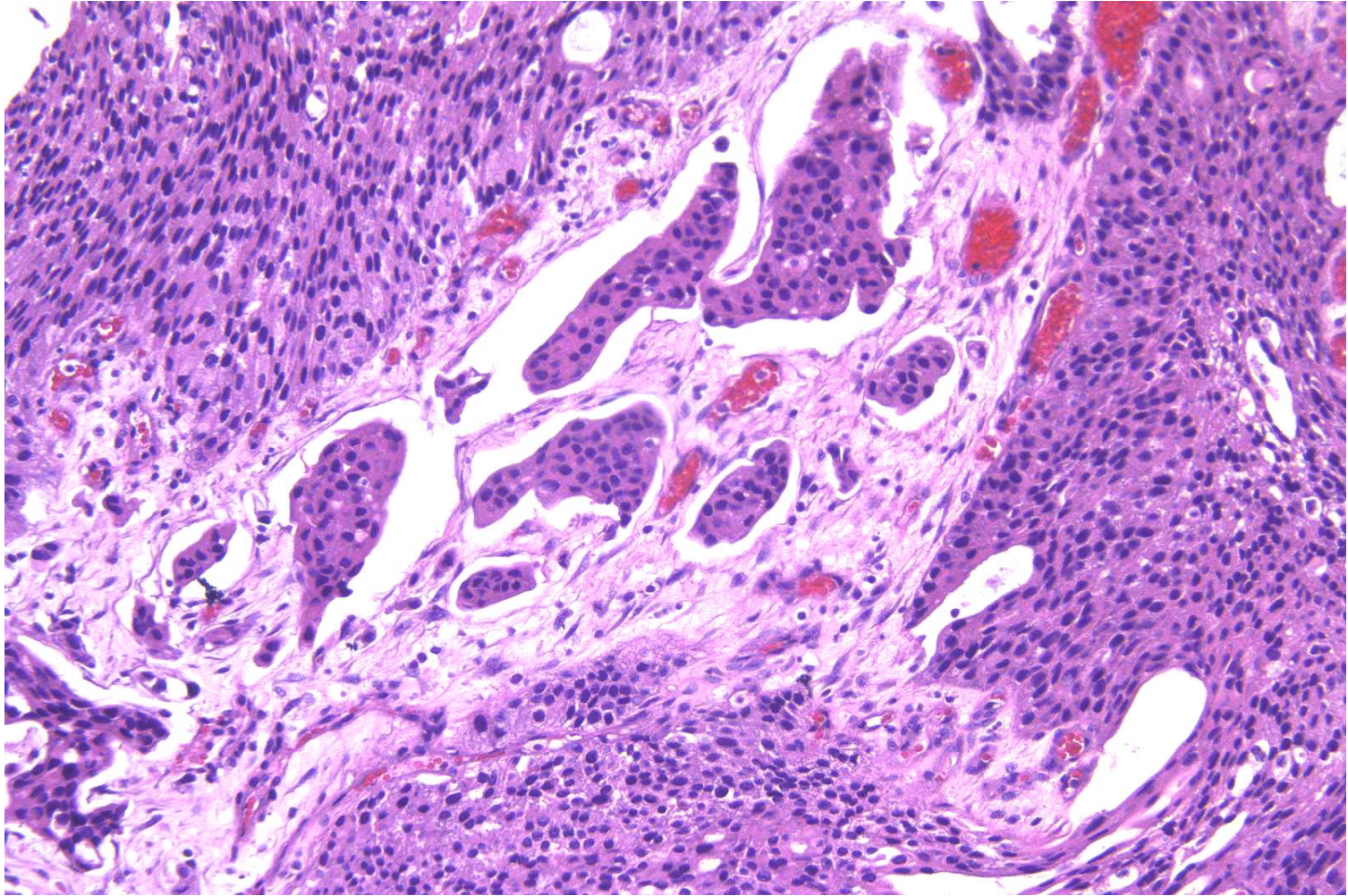
## pT1 substaging

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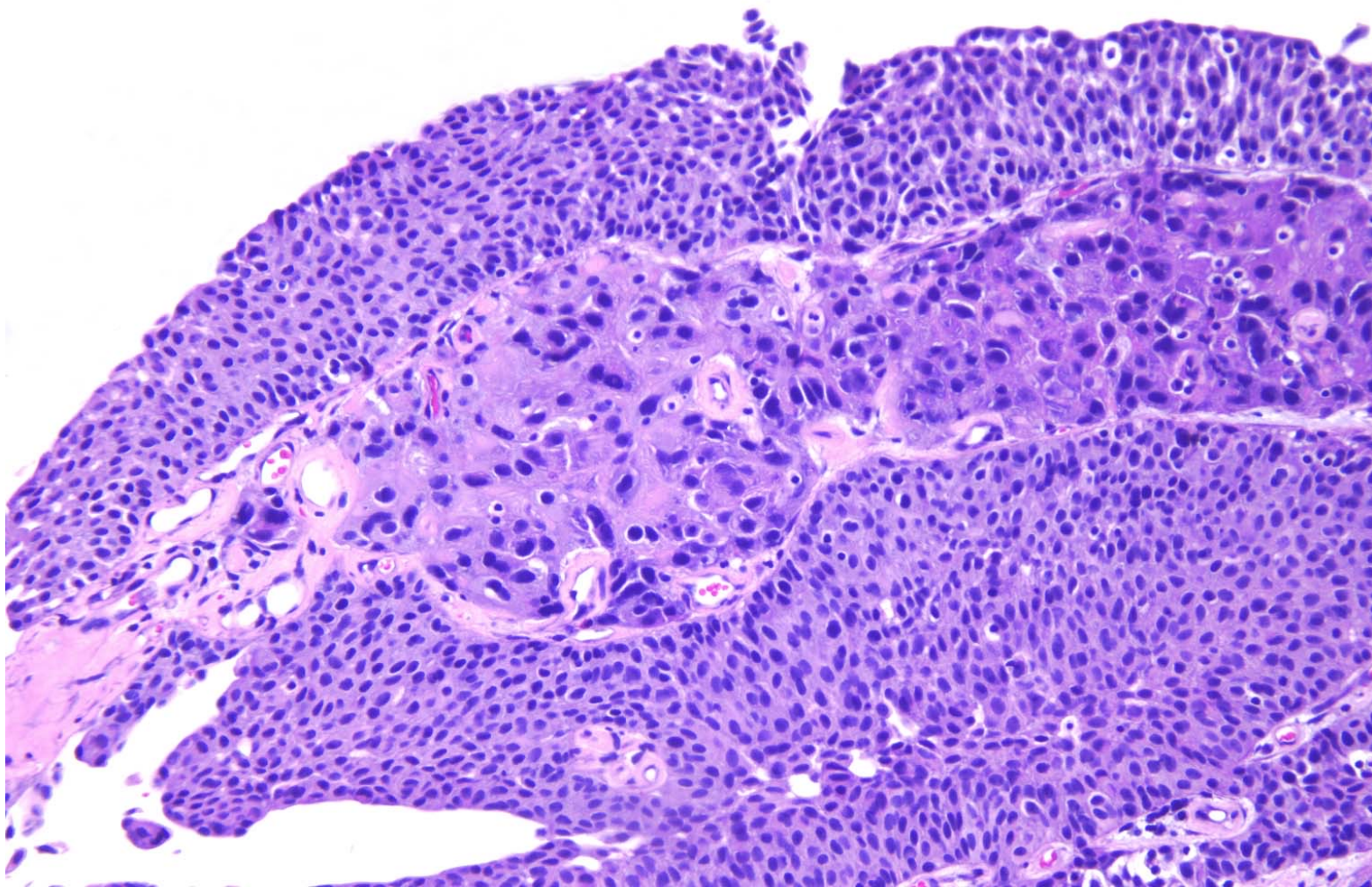
- **Inverted growth vs true invasion:**
  - Small nests
  - Retraction artifact
  - **Paradoxical differentiation/maturation**
- **Substaging:**
  - Microscopic vs. extensive (m/e)
  - **Depth**
    - *relative to muscularis mucosae (LAM1 vs. LAM 2)*
    - *micrometer (0.5/1.5 MM)*
  - **Maximum diameter/length** of invasive foci (3MM vs 6MM)



LAM1/pT1a

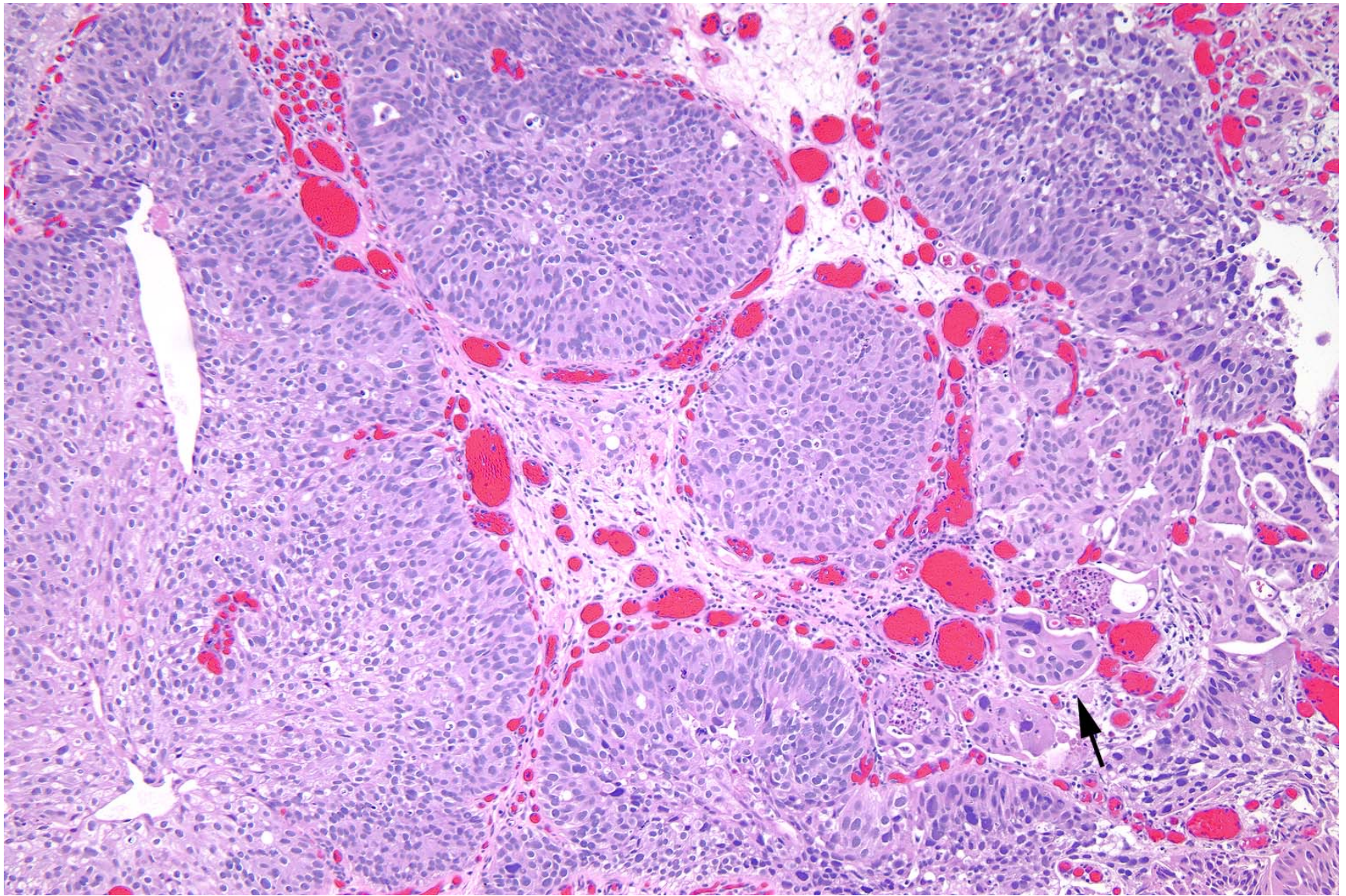


LAM1/pT1a

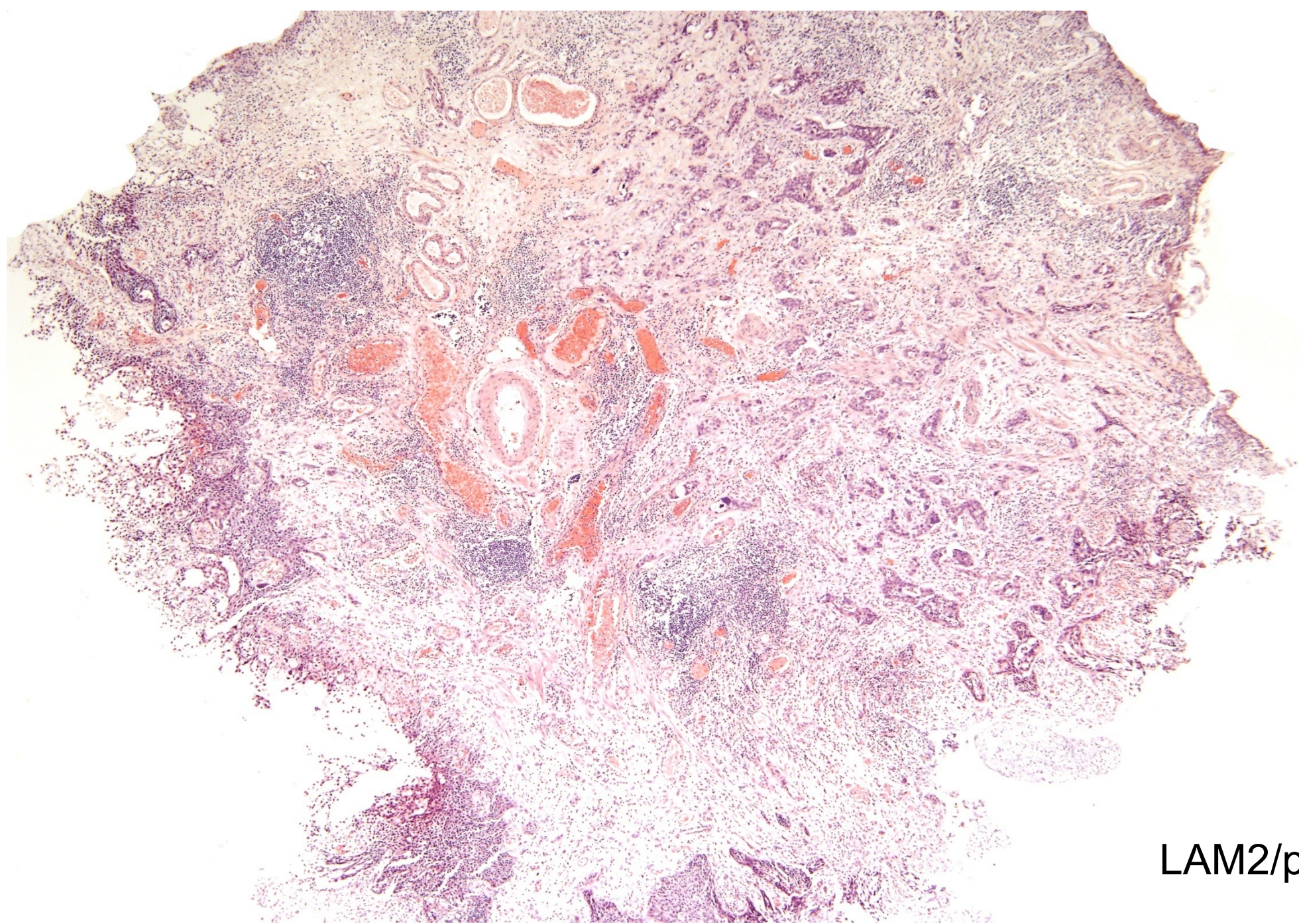


LAM1/pT1a

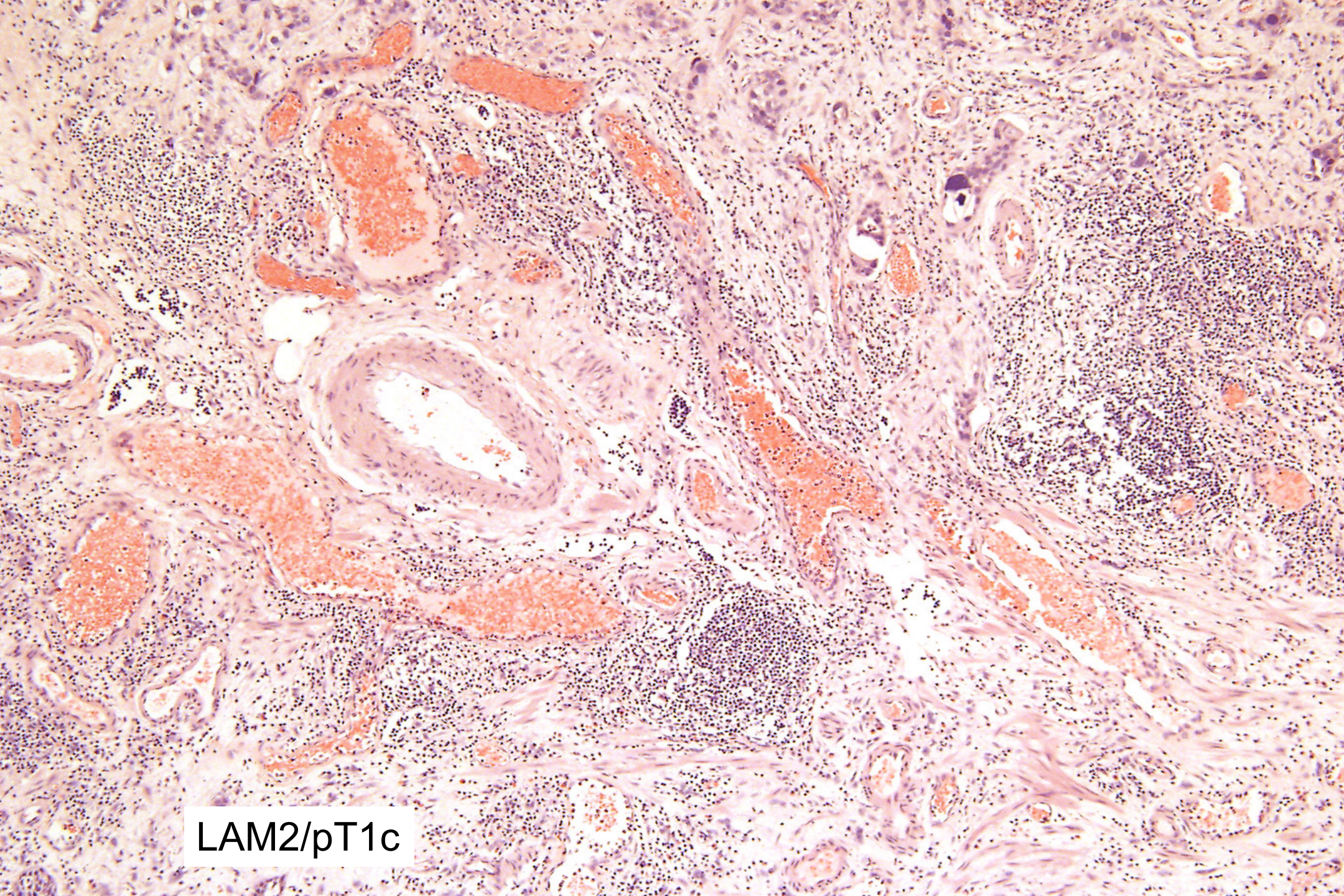




LAM1/pT1a



LAM2/pT1c



LAM2/pT1c

# Non-Muscle Invasive UrCa (NMIBC) pTa/pT1

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## Pathologic Prognosticators

- Tumor Grade
- pT: pTa vs pT1
- Depth of Lamina propria Invasion: pT1a,b,c **Or OTHER**
- CIS, Prostatic duct involvement
- LVI ?
- Size: >3 cm
- Multifocality/Extent: ureter, upper tract and urethral involvement
- Failed Intravesical Rx /Recurrence within 6 month
- Duration of Disease

*Soloway et al J Urol 2002*

*O'Donnell et al Sem Oncol 2007*

JAMA | Review

# Bladder Cancer A Review

Andrew T. Lenis, MD, MS; Patrick M. Lec, MD; Karim Chamie, MD, MSHS

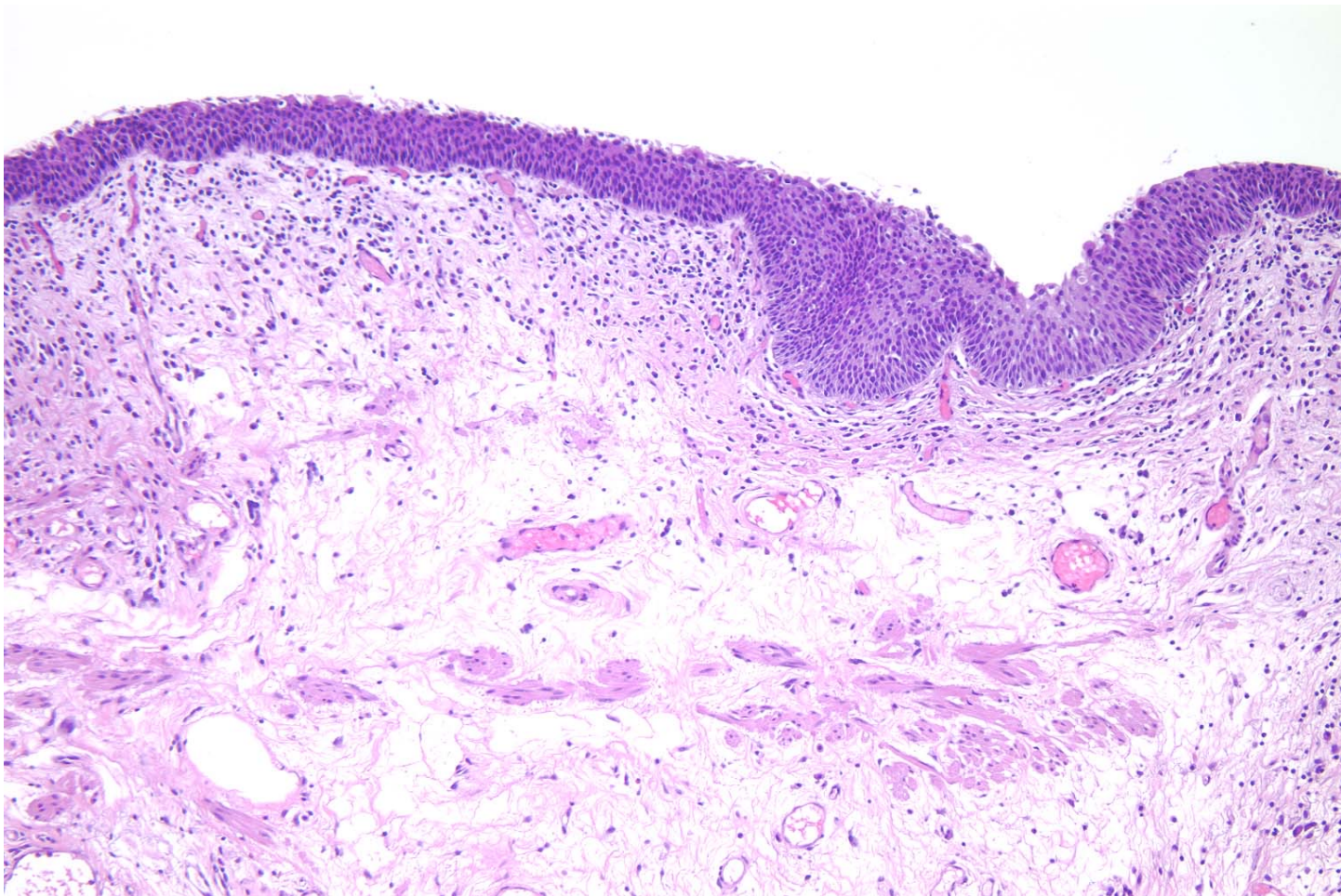
American Urological Association risk group		
Low	Intermediate	High
<b>Definitions</b>		
Low-grade solitary Ta $\leq$ 3 cm PUNLMP	Recurrence within 1 y, low-grade Ta Solitary low-grade Ta $>$ 3 cm Low-grade Ta, multifocal High-grade Ta $\leq$ 3 cm Low-grade T1	High-grade T1 Any recurrent high-grade Ta High-grade Ta $>$ 3 cm or multifocal Any CIS Any BCG failure in patient with high-grade disease Any variant histology Any LVI Any high-grade prostatic urethral involvement
<b>Outcomes<sup>43</sup></b>		
5-y relapse-free survival: 43%	5-y relapse-free survival: 33%	5-y relapse-free survival: 23%
5-y progression-free survival: 93%	5-y progression-free survival: 74%	5-y progression-free survival: 54%

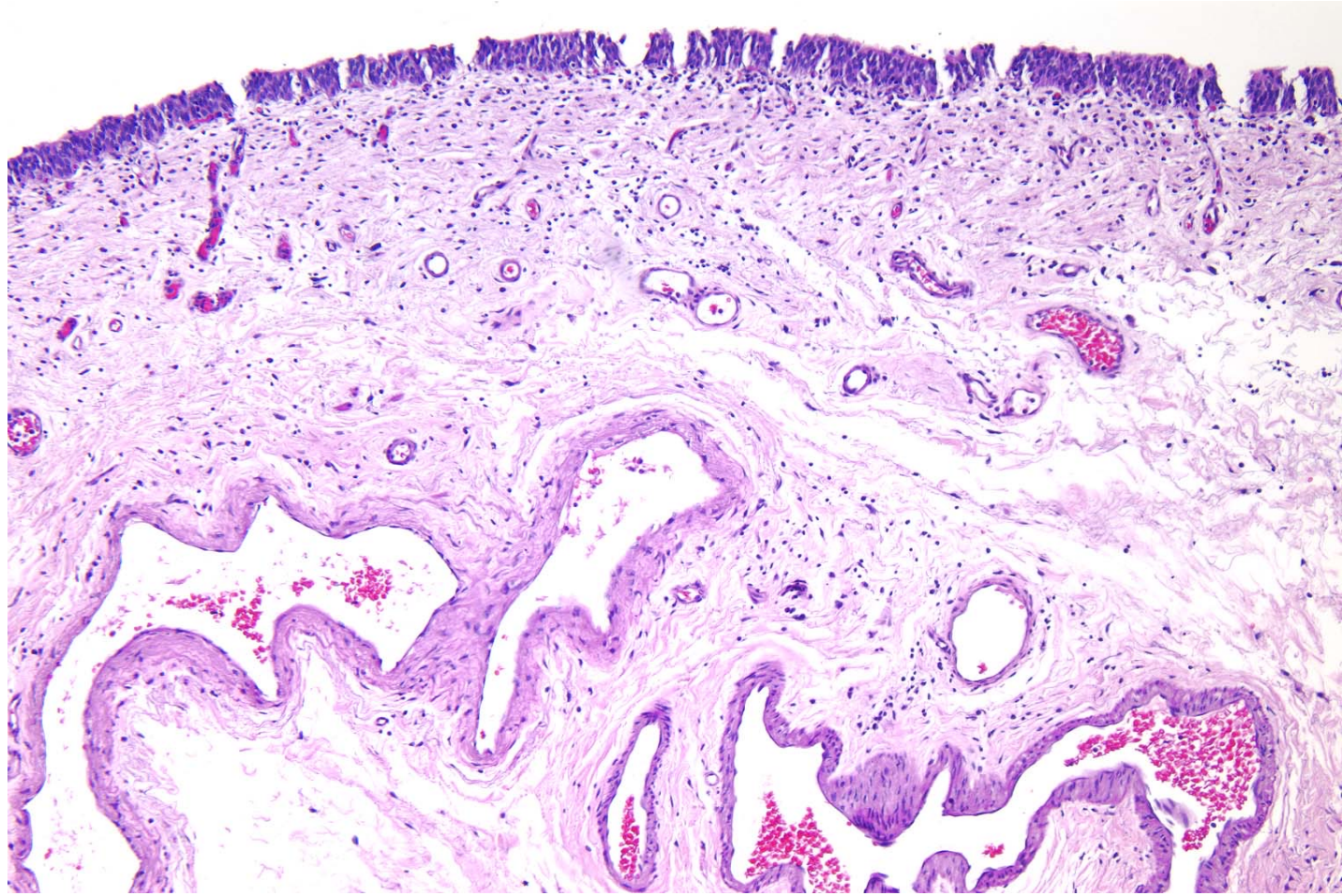
JAMA. 2020;324(19):1980-1991.

# Muscularis Propria (MP) Invasion

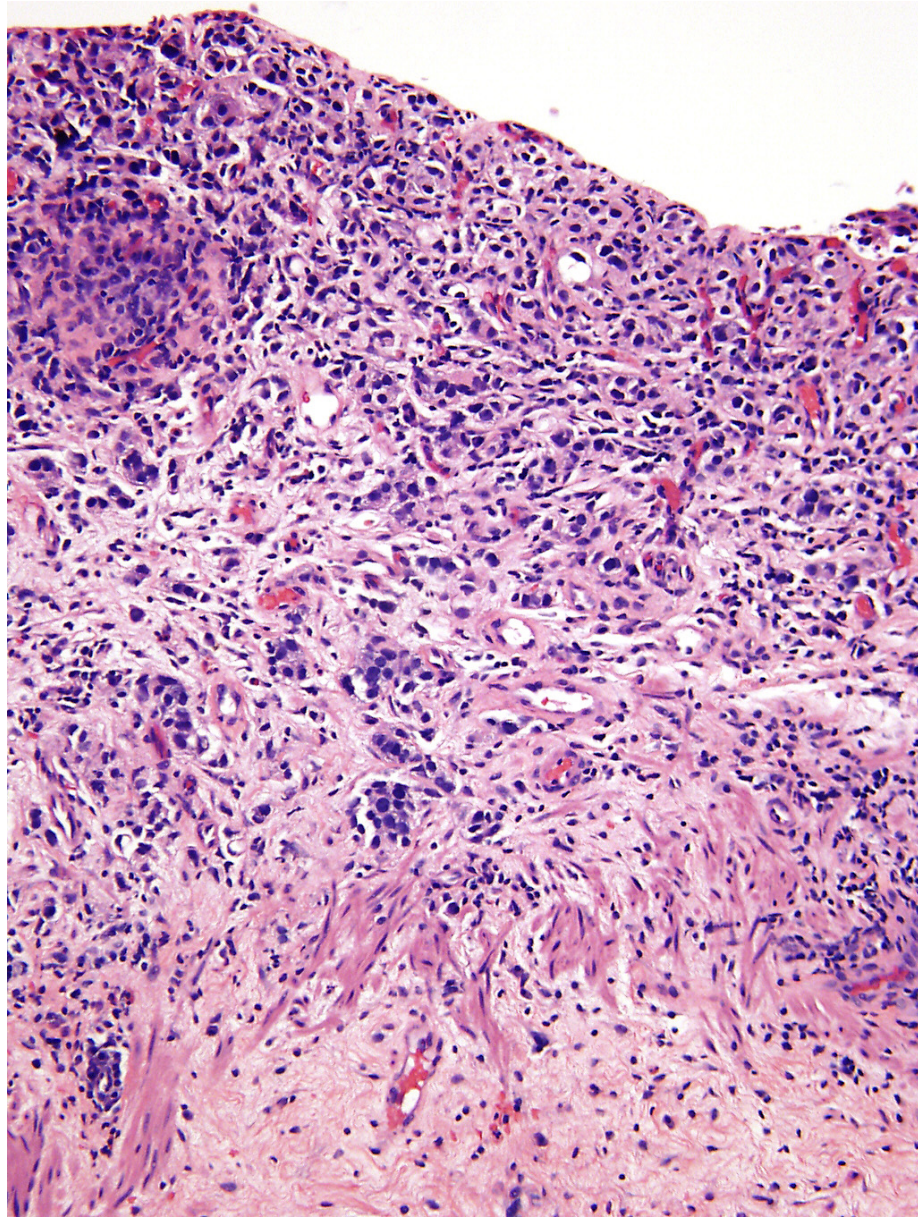
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- Infiltration of **thick muscle bundles**
- If **uncertain** MP vs. MM indicate uncertainty to urologist
- **Do not attempt** to substage MP invasion
- **Fat** seen at all levels, such that does not indicate extension out of the bladder

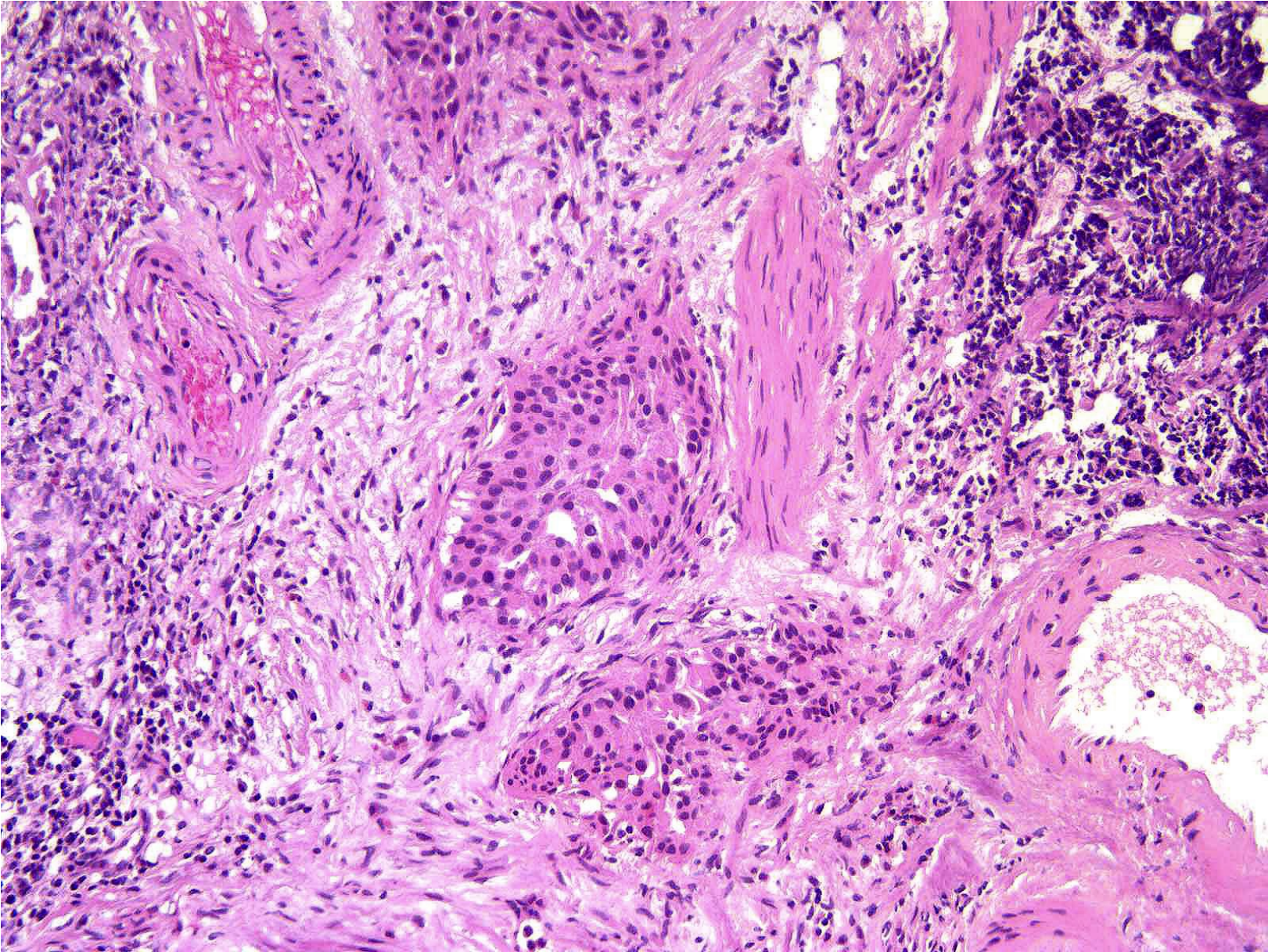




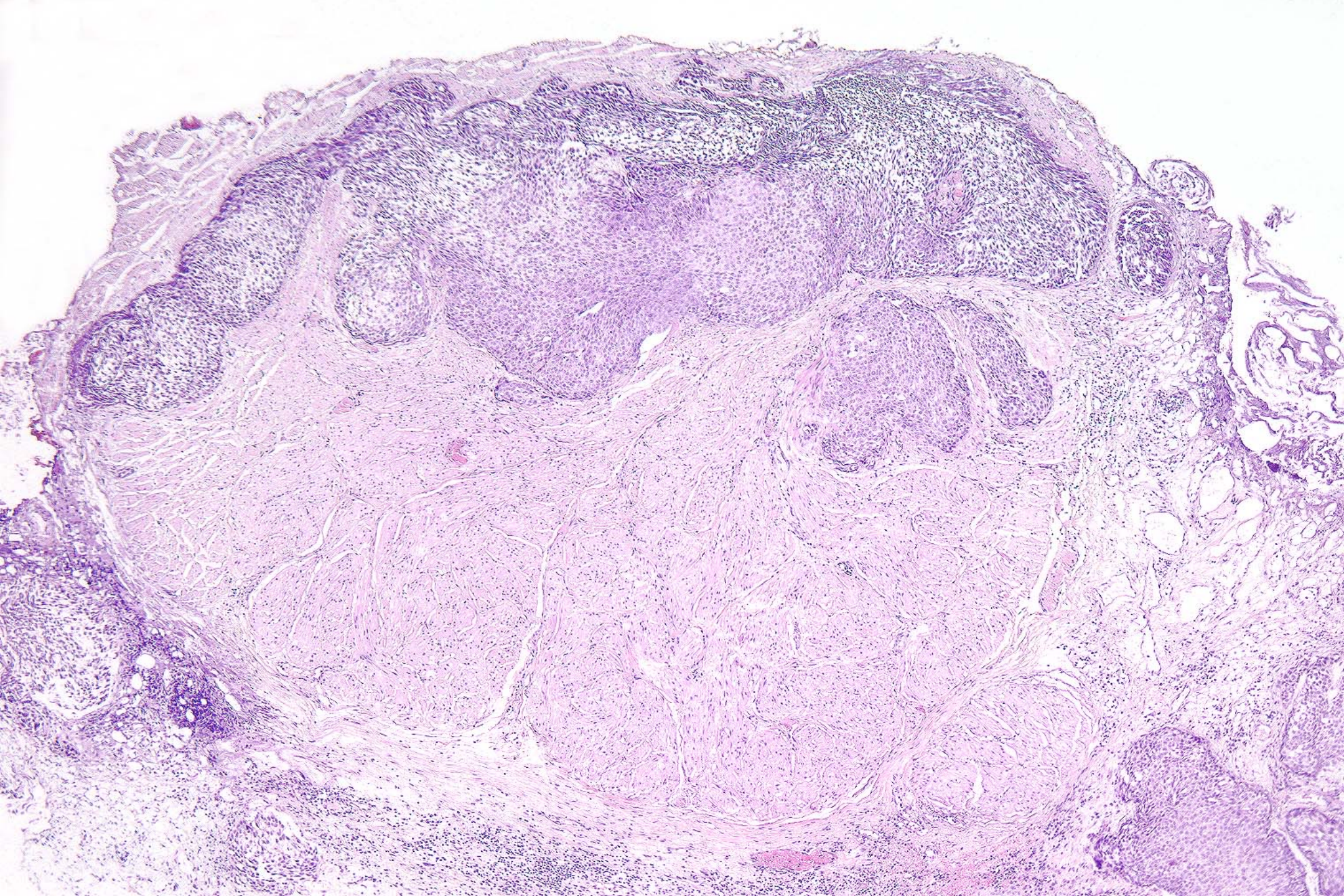


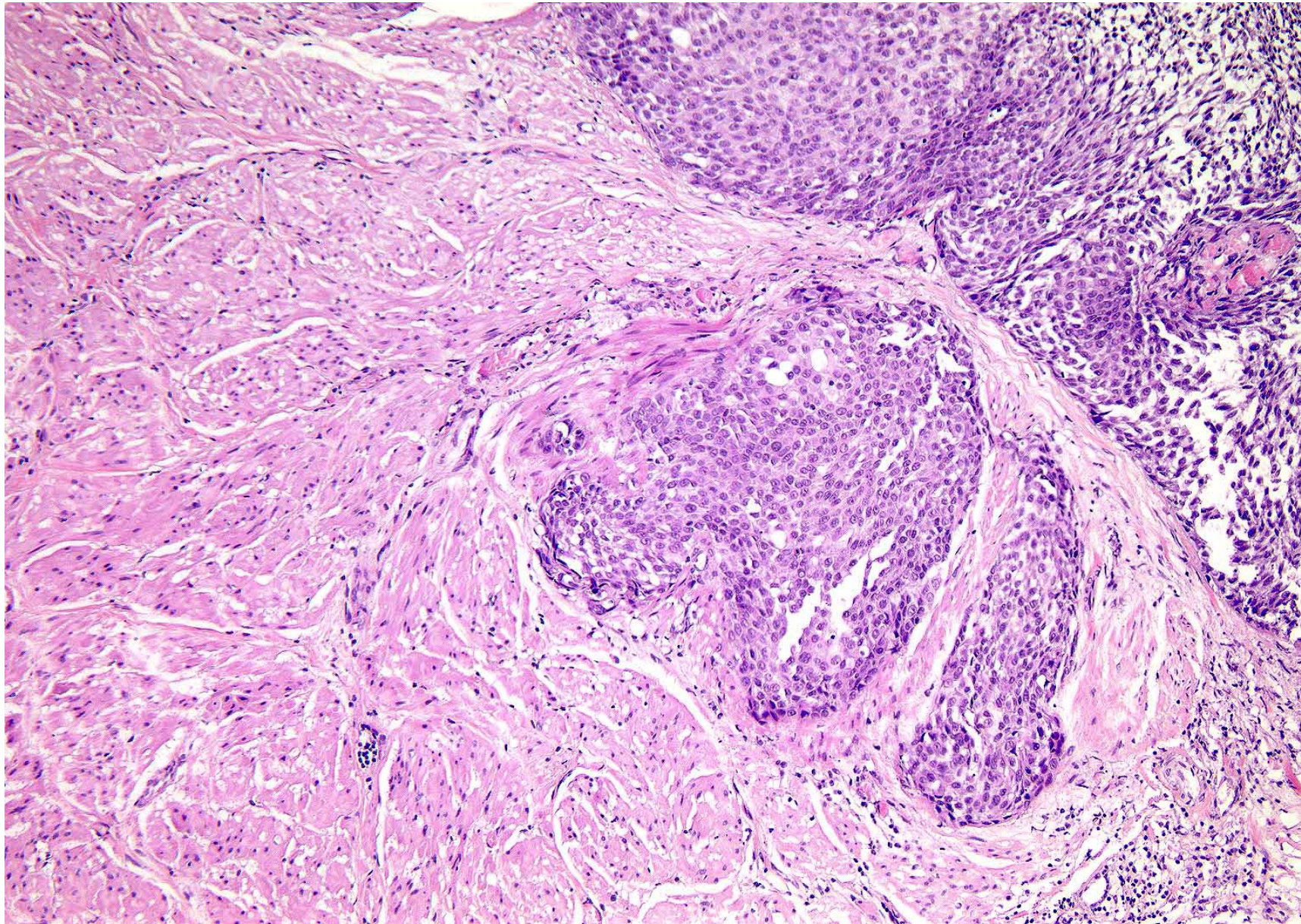


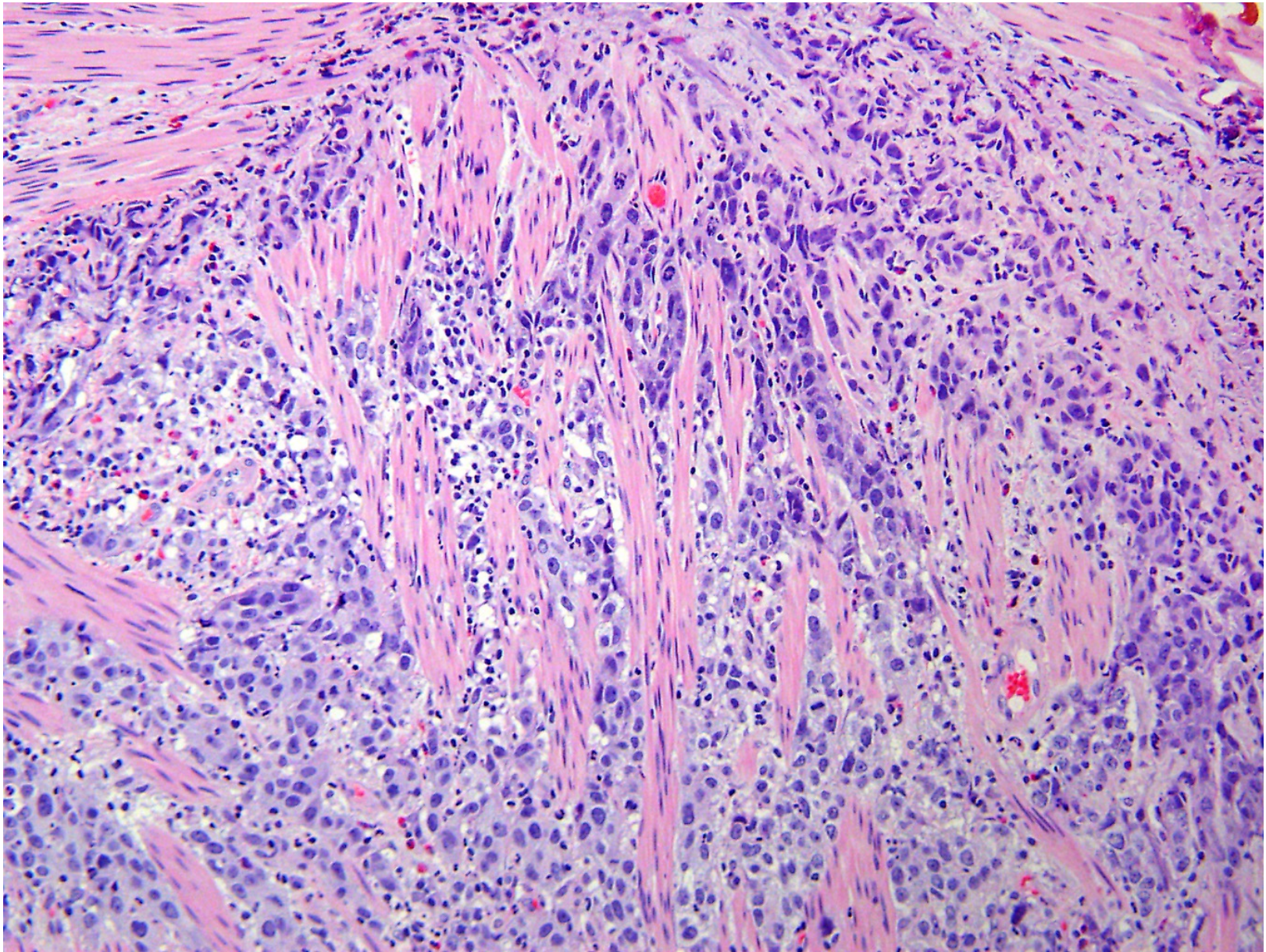
M Mucosae

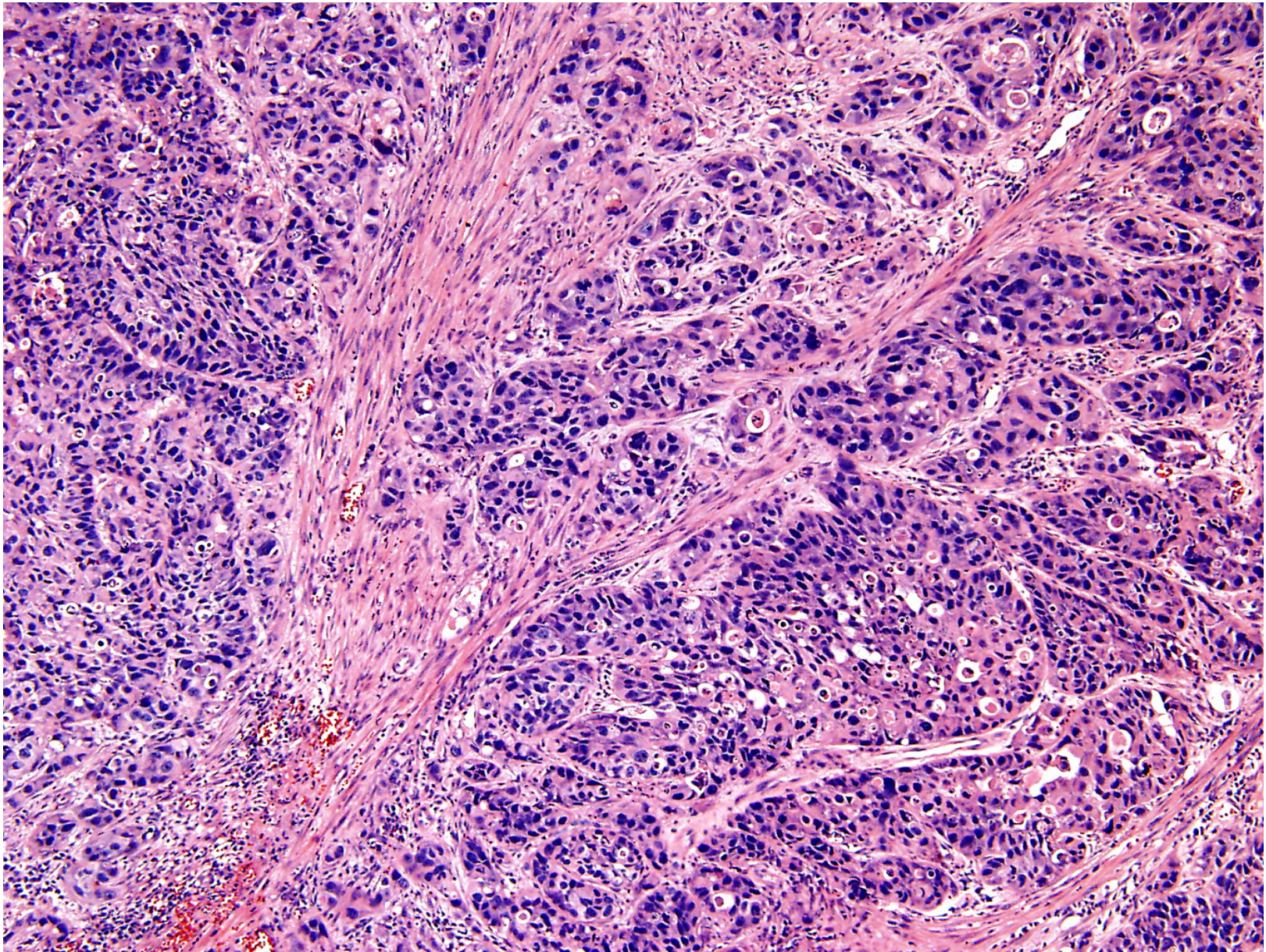


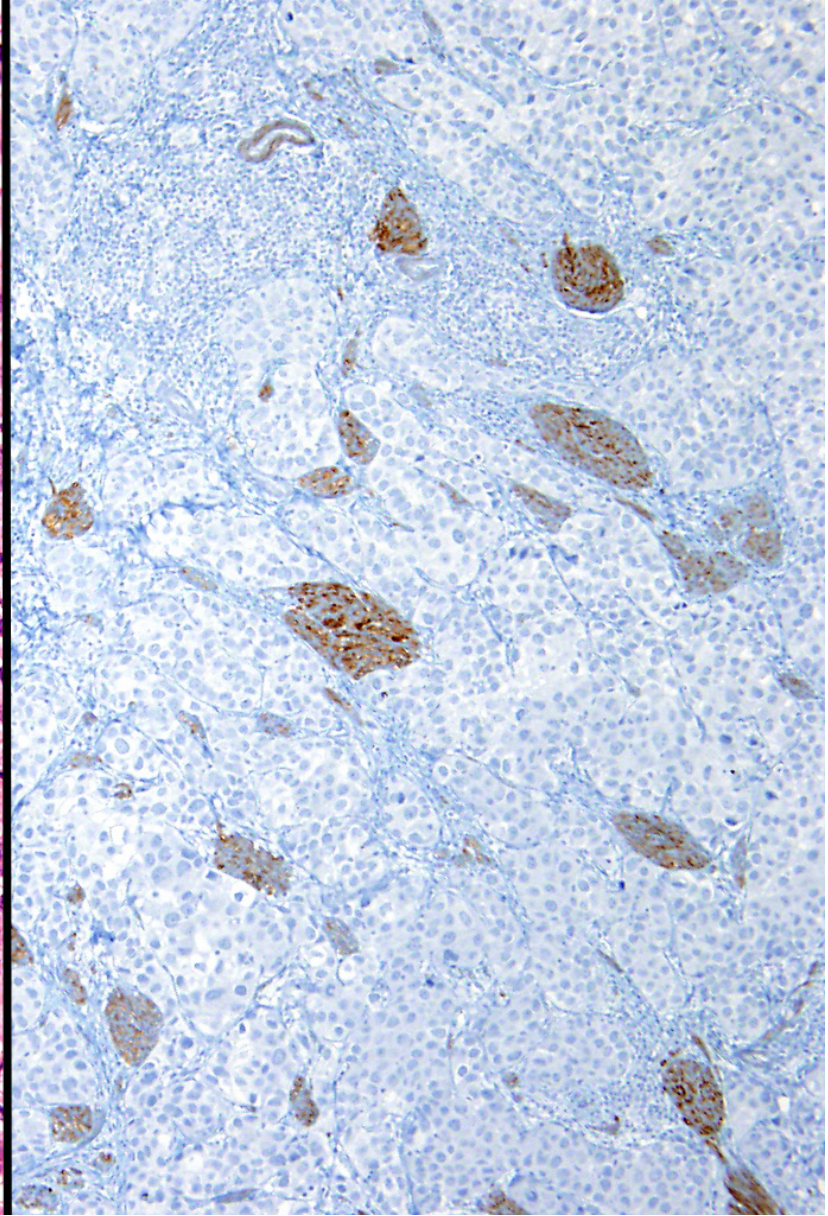
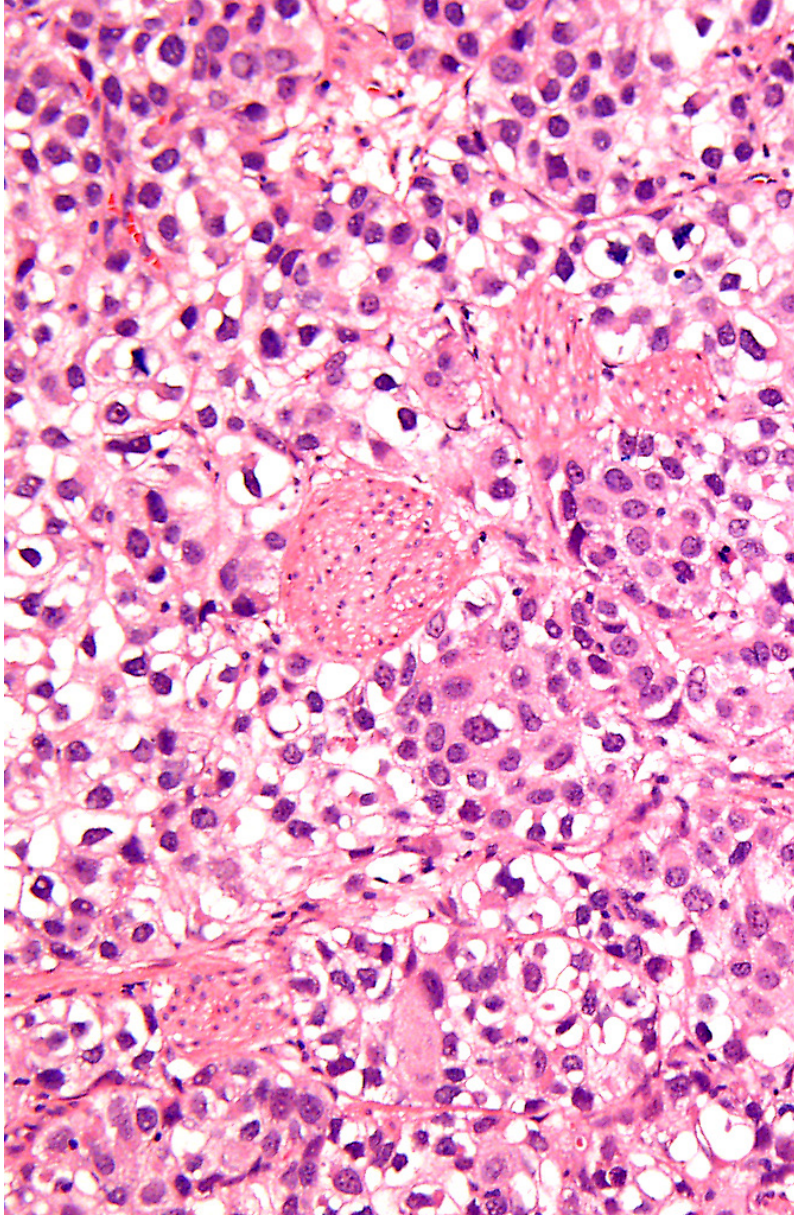
M Mucosae



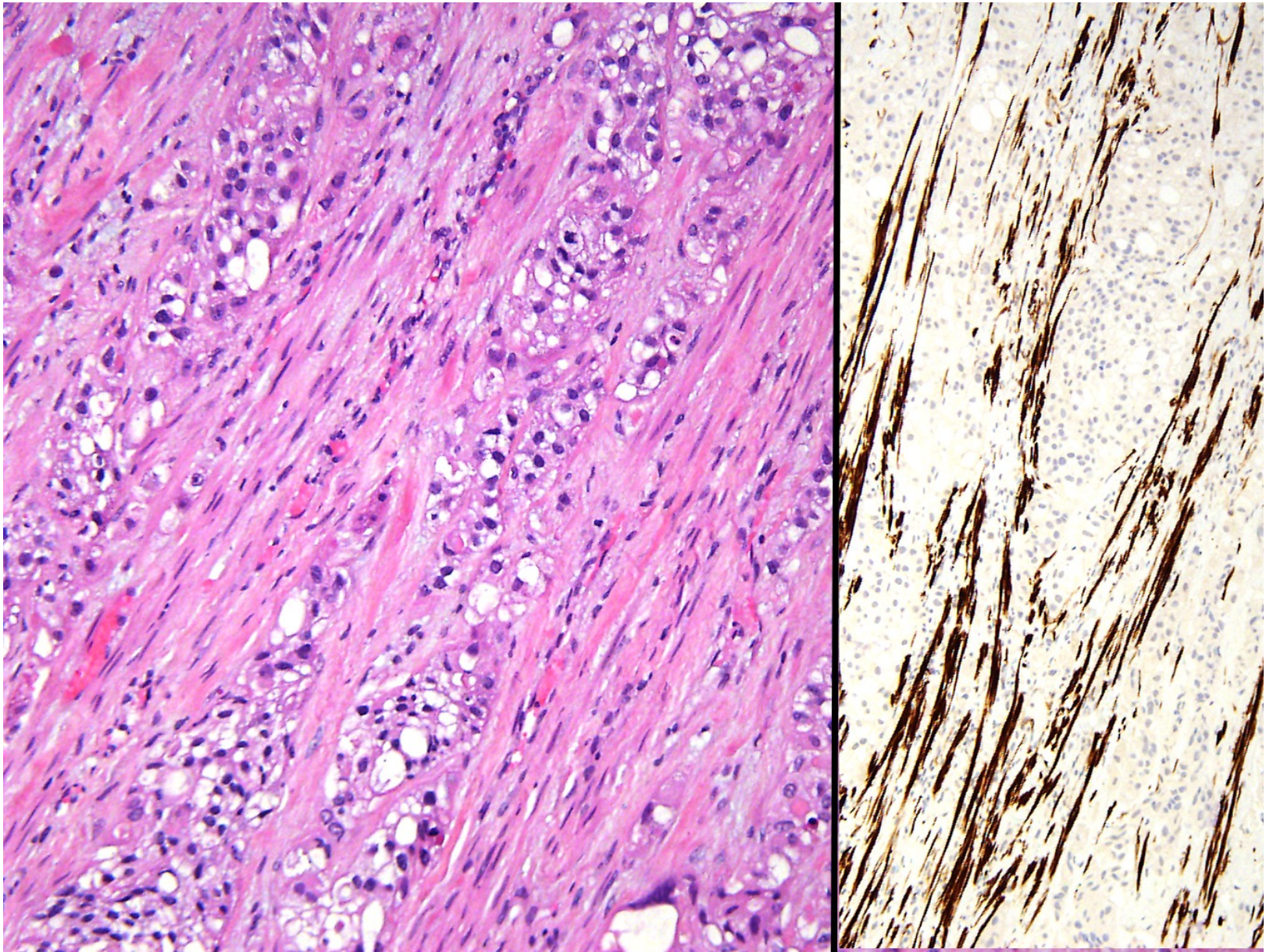






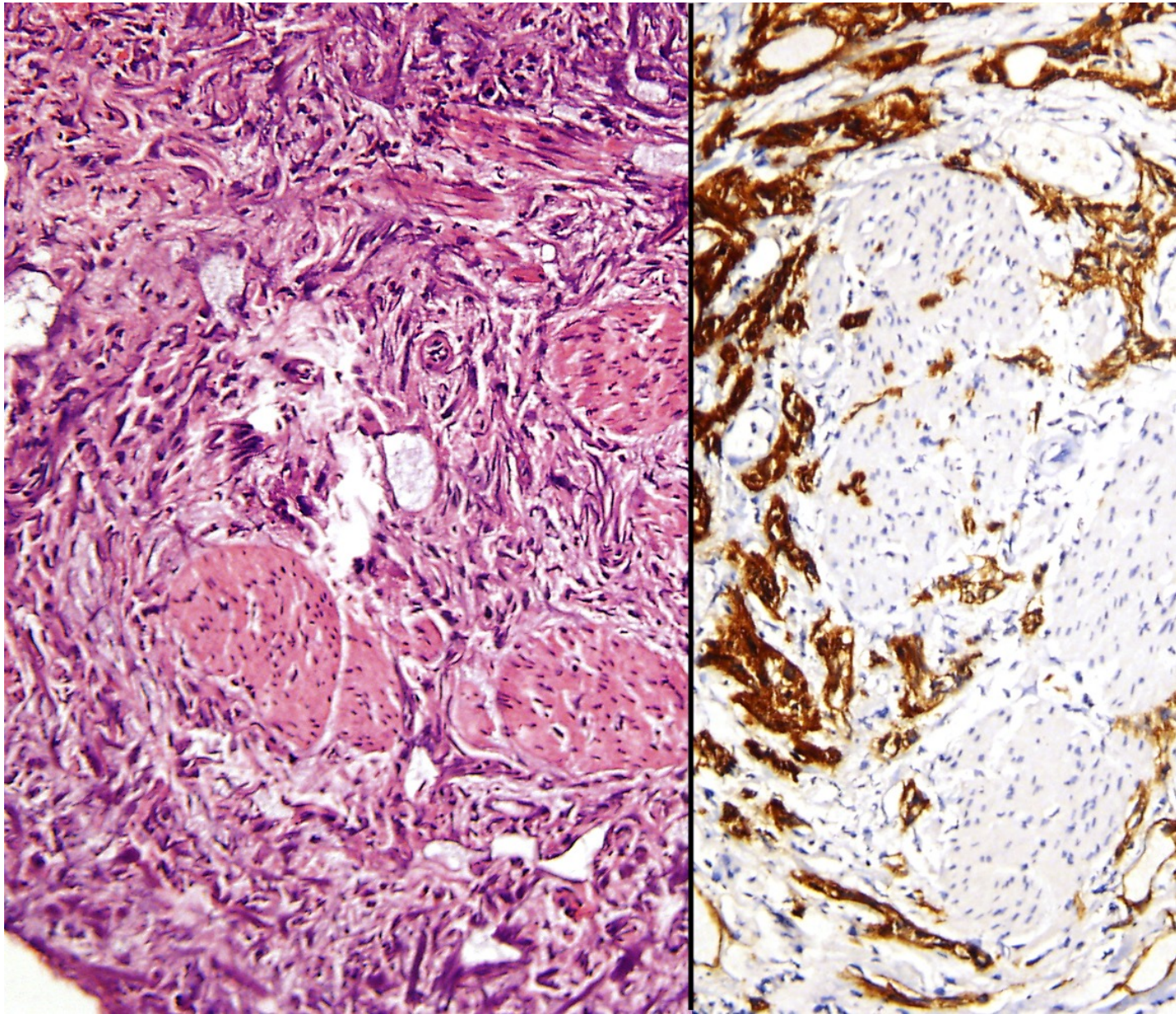


Desmin

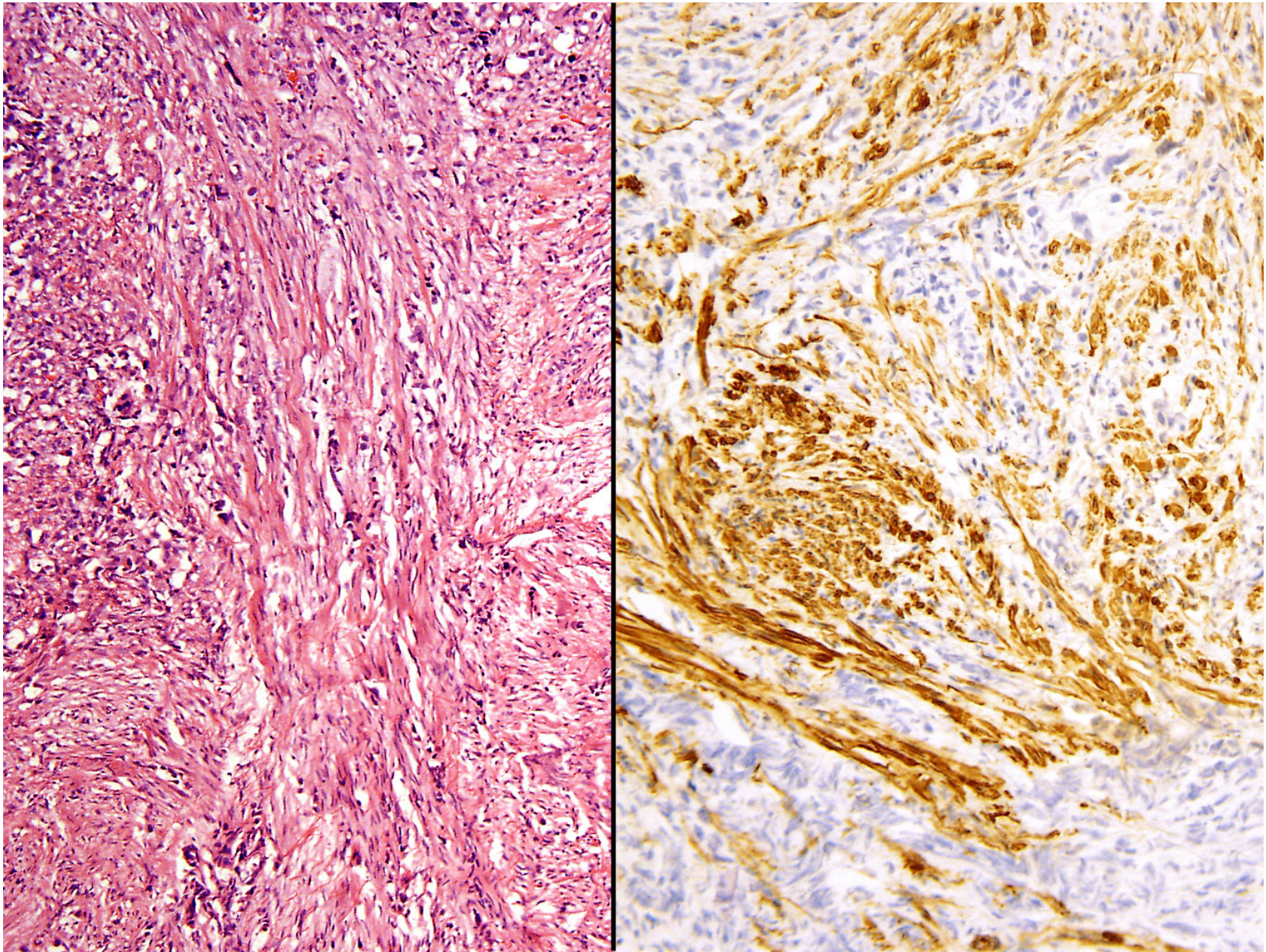


Desmin

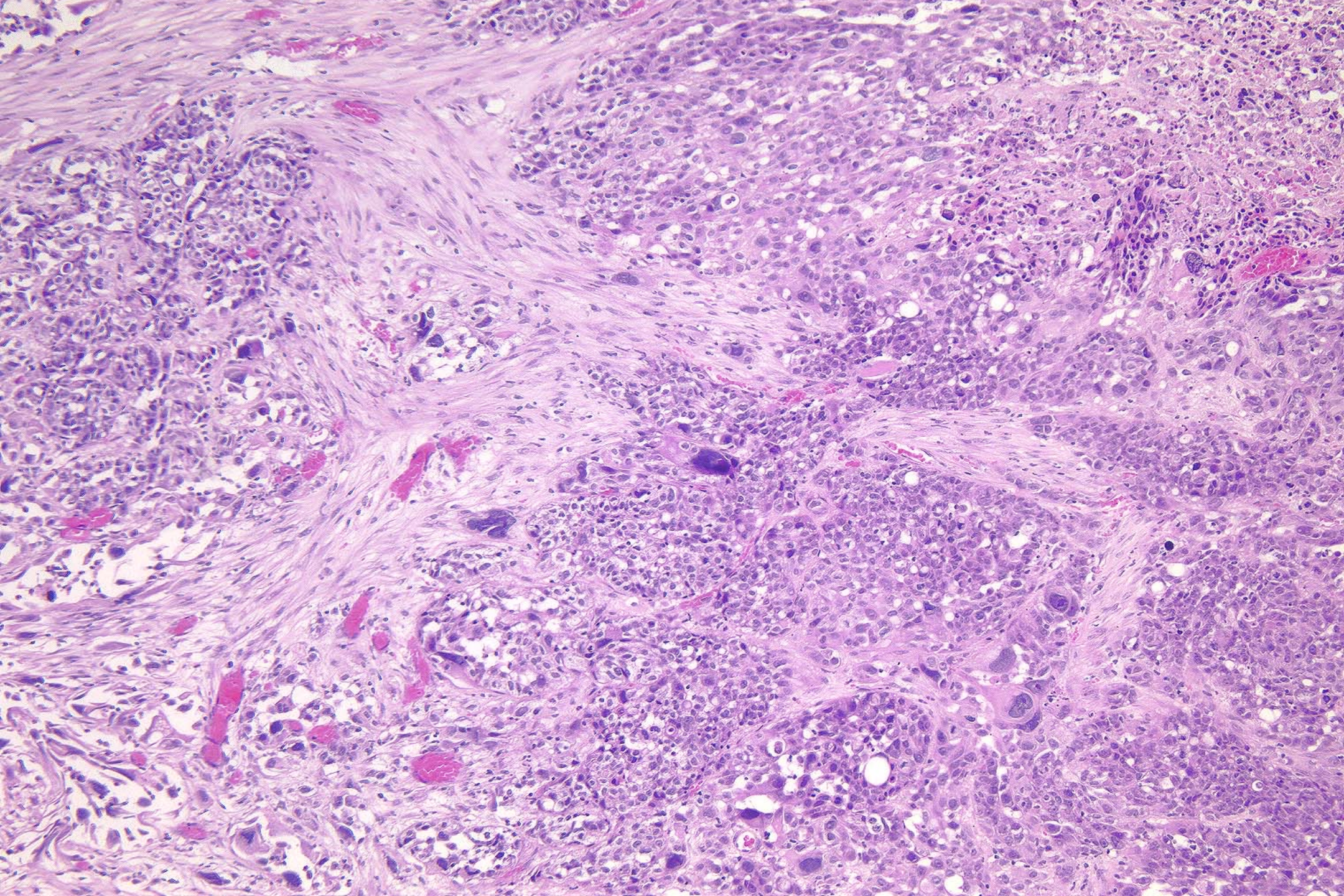


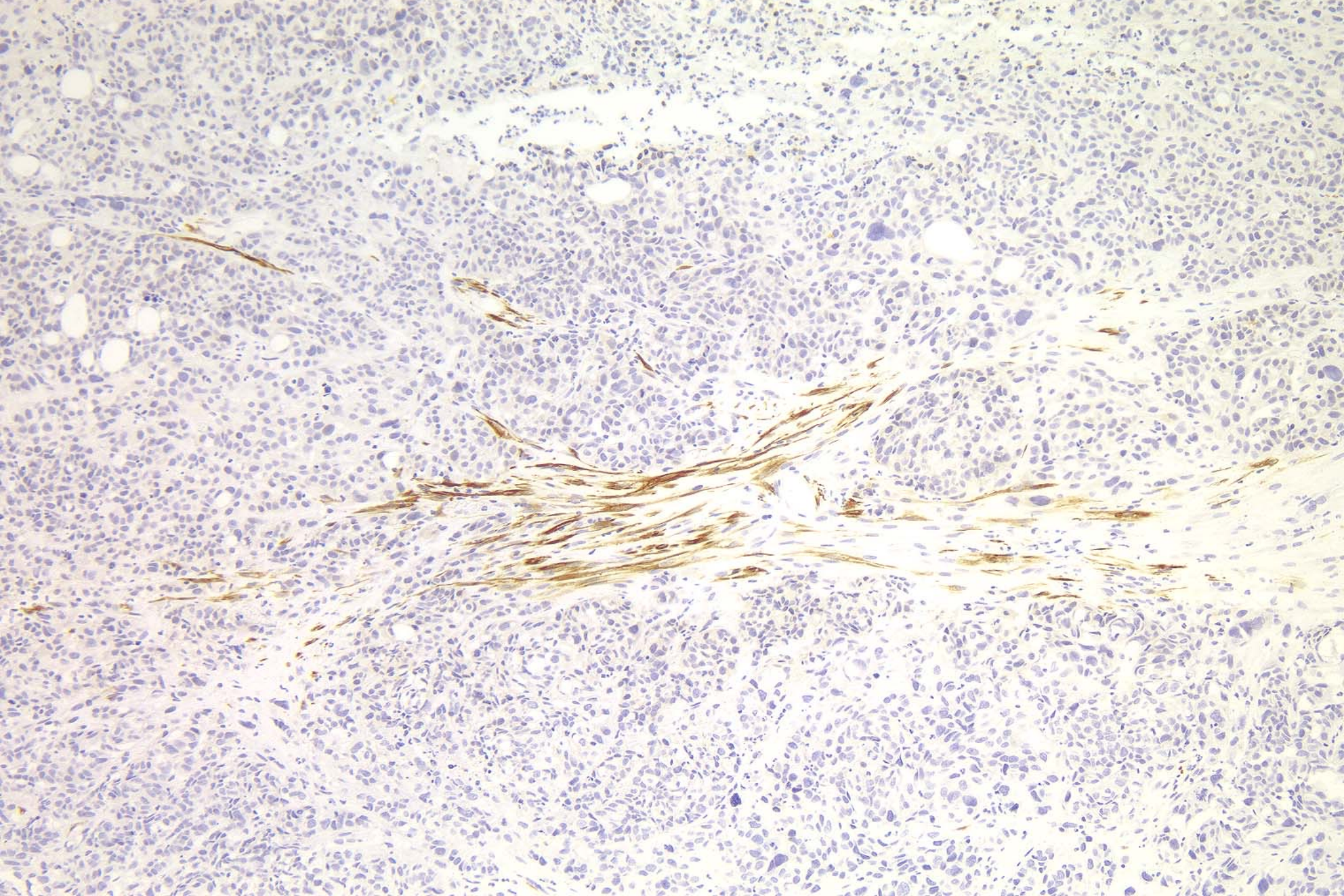


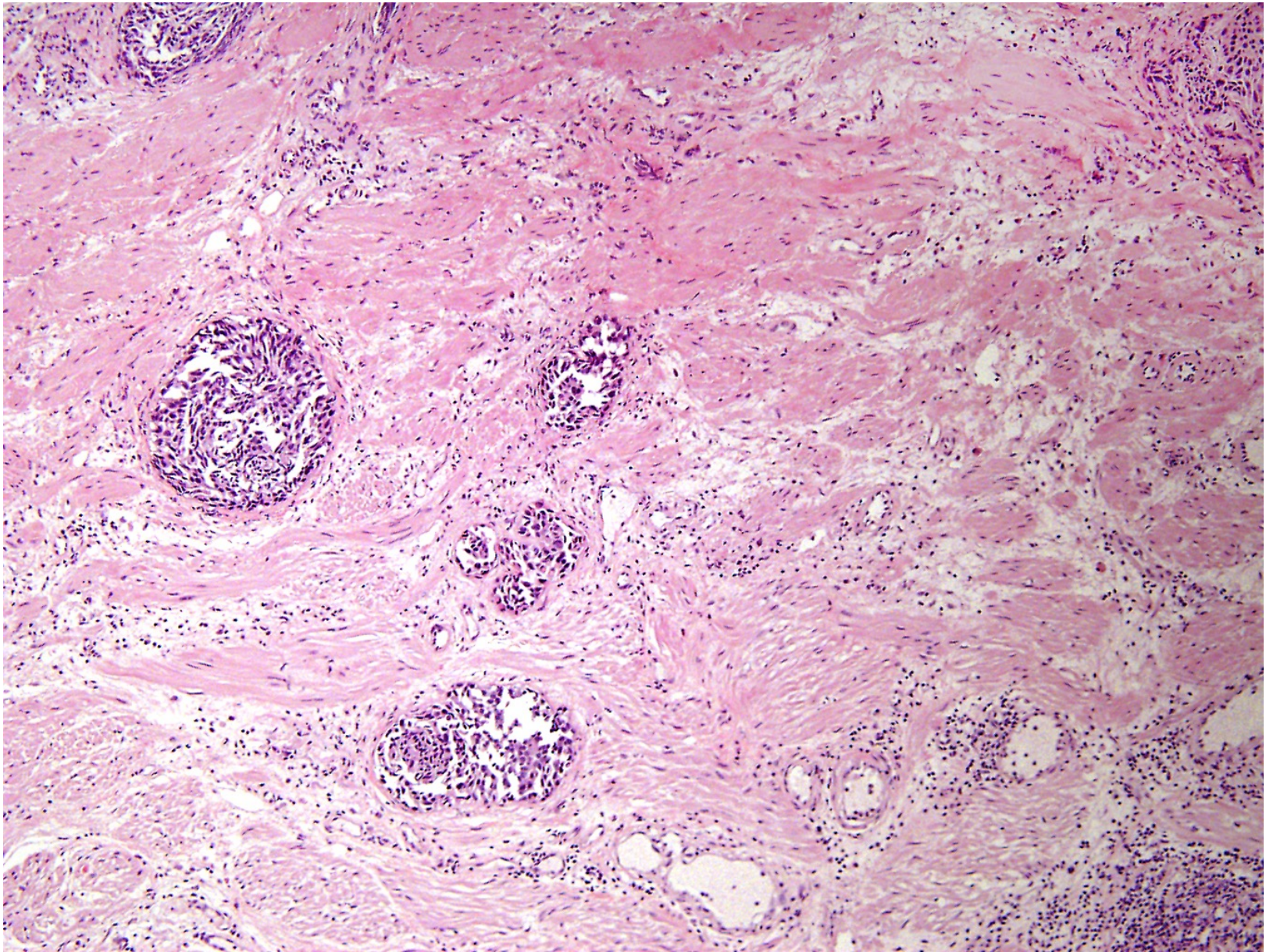
CK



Desmin







Trigon

## CONCLUSIONS

- Bladder cancer represents a major clinical and health cost burden
- Accurate WHO/ISUP grading based on detailed histologic criteria is critical for PGx and management of NMIBC
- Staging issues remain a challenge in TURBT

Thank You !



**UAB** MEDICINE

