Pathology Classification of Bladder Cancer

Matthew Milowsky, MD, FASCO
George Gabriel and Frances Gable Villere Distinguished Professor
Section Chief, Genitourinary Oncology
University of North Carolina at Chapel Hill

UNC | SCHOOL OF MEDICINE

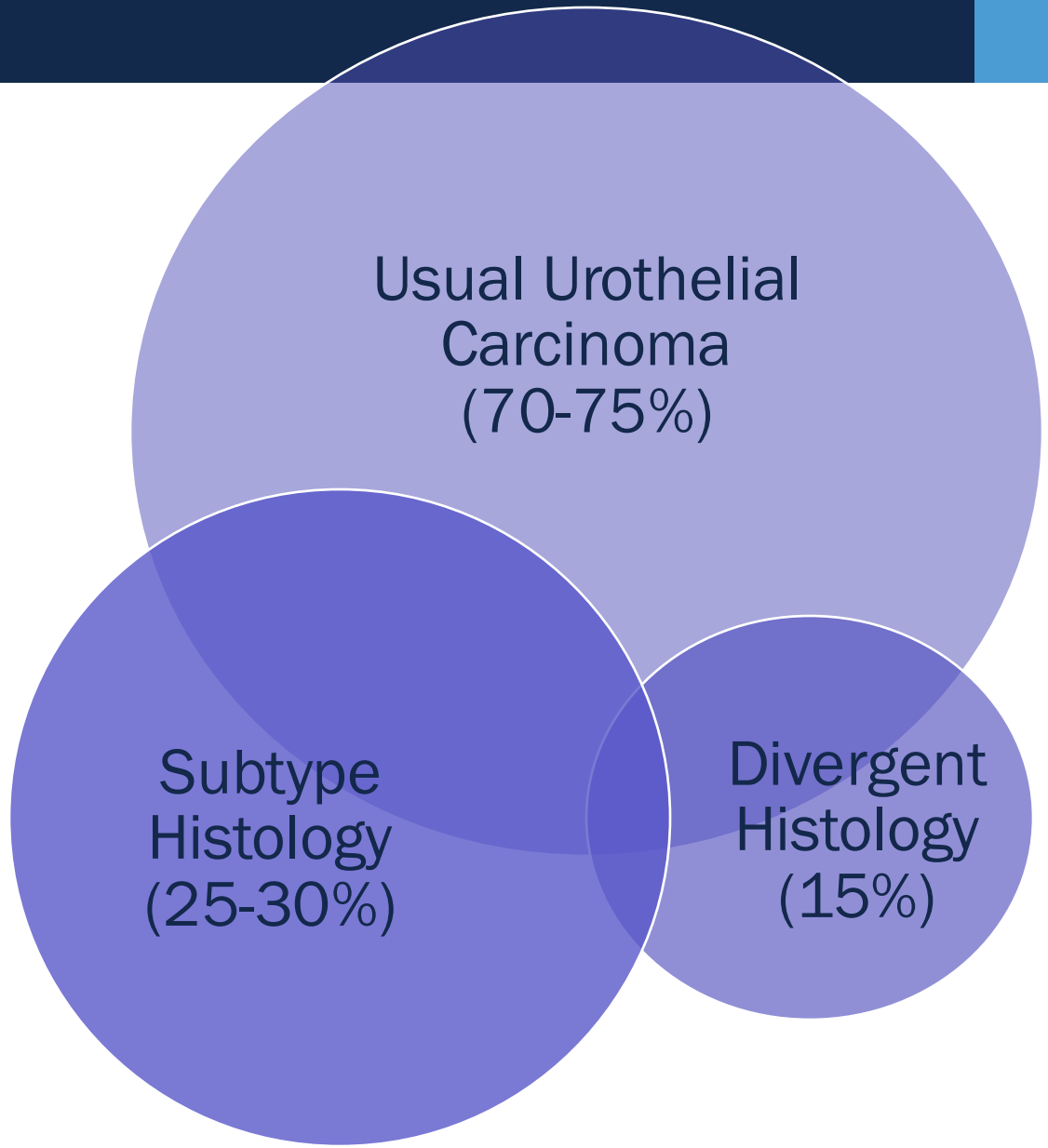
Bladder CA – A heterogeneous disease

UNC SCHOOL OF MEDICINE

- Bladder cancer includes many tumor types:
  - Urothelial (UC) – 90-95% of bladder cancers
  - Squamous cell carcinoma
  - Glandular – primary bladder adenocarcinoma
  - Mesenchymal – sarcoma
  - Others: Urachal, Müllerian, neuroendocrine, hematolymphoid, and melanocytic

Subtypes and Divergence

- Diagnostically challenging, with important prognostic and therapeutic implications
- Both subtype and divergent histology are more likely to present with high pT stage and nodal metastasis
- Different responses to systemic therapy



Importance of Expert Pathology Review

UNC SCHOOL OF MEDICINE

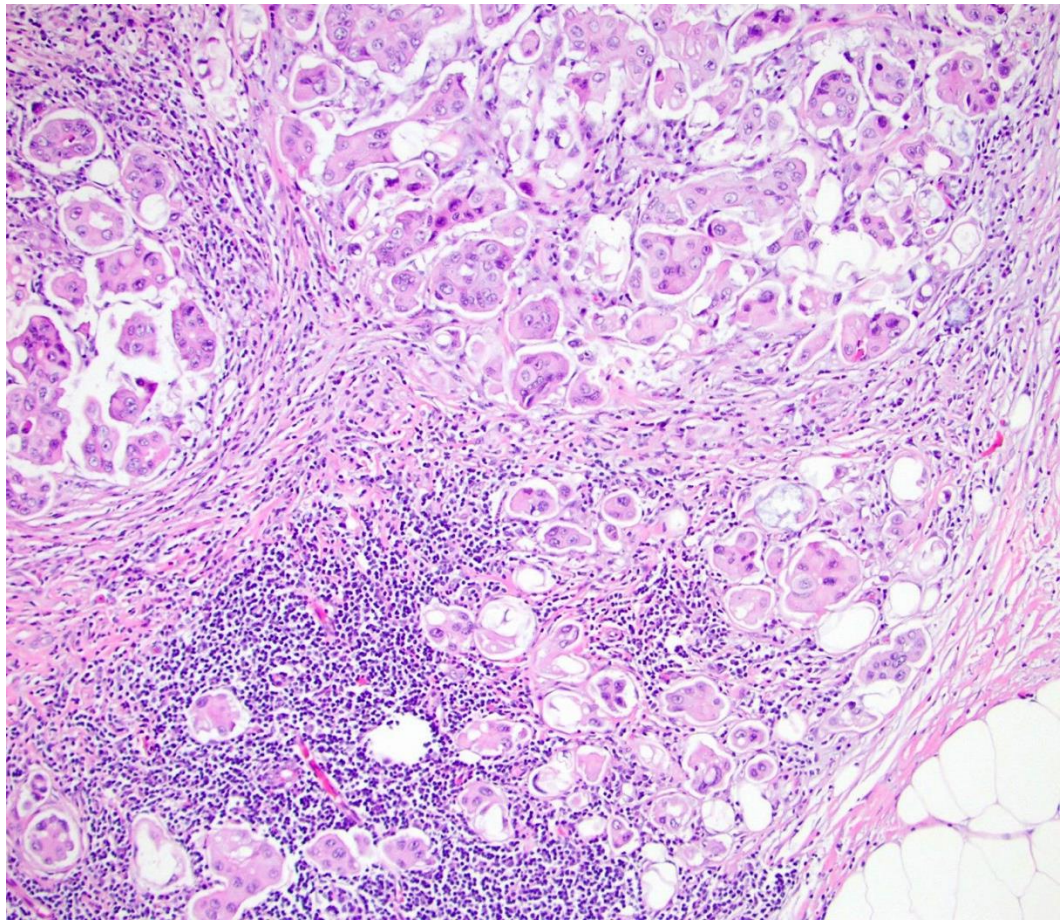
- ~33-44% of subtype/divergent histologies are unrecognized by practicing pathologists
- High interobserver variability when diagnosing subtypes
- NCCN recommends review by experienced GU pathologist in order to confirm:
  - Clinically significant subtype histology
  - Confirming metastatic carcinoma of urothelial origin
  - Clinically discrepant scenarios

Linder BJ, Frank I, Cheville JC, et al. Outcomes Following Radical Cystectomy for Nested Variant of Urothelial Carcinoma: A Matched Cohort Analysis. The Journal of Urology. 2013;189(5):1670-5. PMID: 23142686

Reporting Subtypes and Divergence

UNC SCHOOL OF MEDICINE

- Subtypes and divergence are all considered high grade, independent of cytologic features
  - "Very-high-risk features" per NCCN
- Reporting subtypes provides additional information for subsequent encounters
  - Frozen sections, recurrences
- Subtype histology more frequently identified in lymph node metastases, no matter what amount present in primary tumor



Paner GP, Kamat A, Netto GJ, et al. International Society of Urological Pathology (ISUP) Consensus Conference on Current Issues in Bladder Cancer. Working Group 2: Grading of Mixed Grade, Invasive Urothelial Carcinoma Including Histologic Subtypes and Divergent Differentiations, and Non-Urothelial Carcinomas. Am J Surg Pathol. 2024 Jan 1;48(1):e11-e23. PMID: 37382156.

Rice KR, et aL. Lymph node metastases in patients with urothelial carcinoma variants: influence of the specific variant on nodal histology. Urol Oncol. 2015 Jan;33(1):20.e23-20.e29. PMID: 25047418.

Reporting, Continued

- Recommend reporting the percentage (or semi-quantitative indicator) of subtype histology within a specimen:

Invasive high grade urothelial carcinoma (50%) with micropapillary (30%) and squamous features (20%)

OR

Invasive high grade urothelial carcinoma with focal/extensive squamous features

WHO 2022 Classification

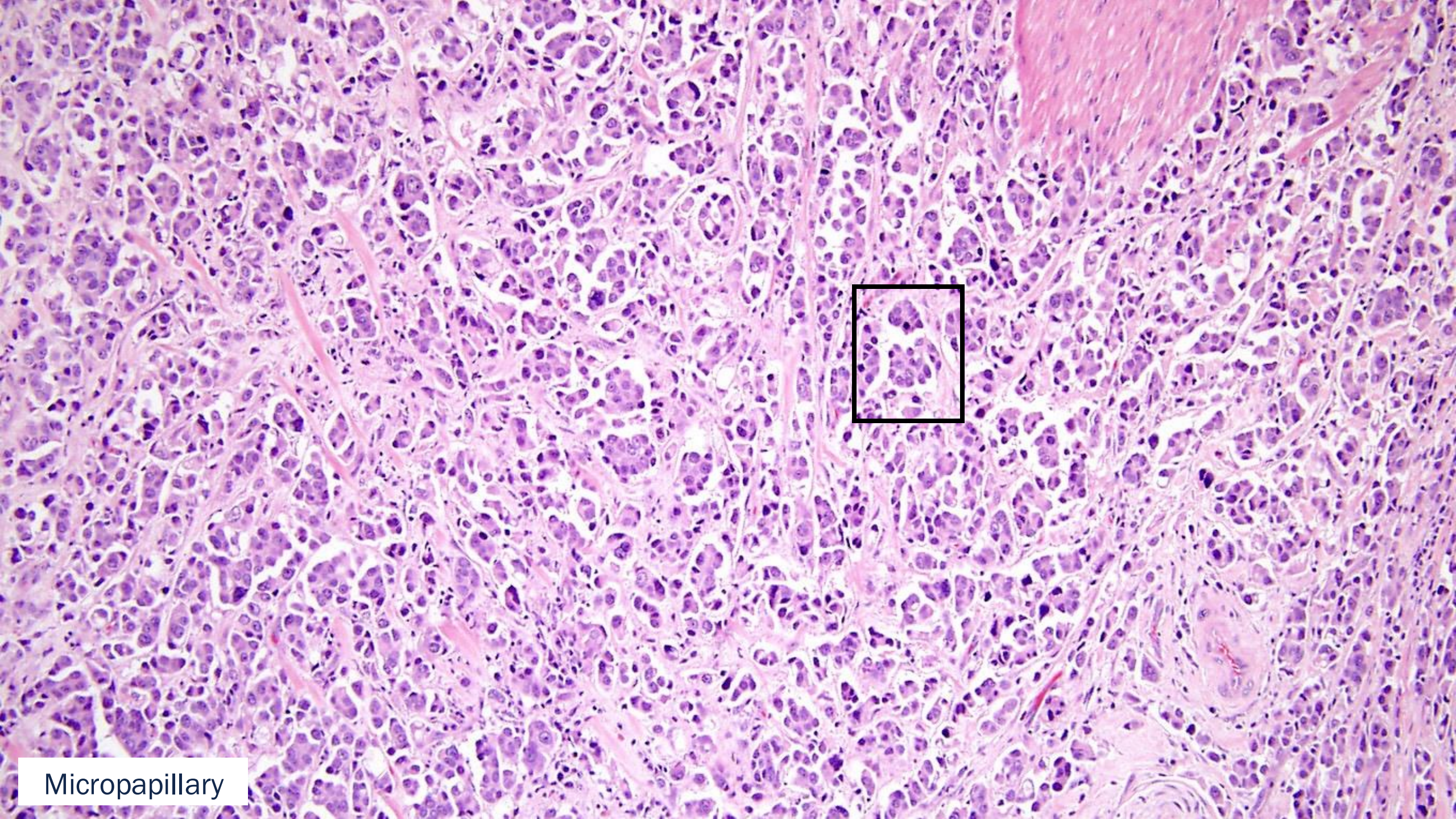
UNC SCHOOL OF MEDICINE

SUBTYPE	ESSENTIAL CRITERIA	DESIRABLE CRITERIA
Nested	Nests of bland cells (superficial portion) or atypical cells (deep portion) in myxoid, focally desmoplastic, or non-reactive stroma	Invasion to the muscularis propria
Tubular and microcystic	Cysts, macrocysts, or large tubular structures in non-reactive or myxoid stroma	Negative IHC for prostate cancer or relevant GYN tumors
Micropapillary	Invasive carcinoma with multiple cell clusters with micropapillary features in cleft-like or lacunar spaces	No morphologically similar tumor in another organ; positive ERBB2; negativity for markers of non-bladder origin
Lymphoepithelioma-like	Invasive carcinoma composed of a syncytial arrangement of cytokeratin-positive cells in a polymorphic inflammatory infiltrate	
Plasmacytoid	Invasive carcinoma composed of single cells, dispersed or in a linear arrangement; absence of extracellular mucin	No morphologically similar tumor in another organ; positive CK; absence of membranous E-cadherin labelling; negative IHC for markers of non-bladder origin
Giant cell	Invasive carcinoma composed of pleomorphic giant cells	Positive CK
Lipid-rich	Invasive carcinoma composed of lipoblast-like, cytokeratin-positive cells	
Clear cell (glycogen-rich)	Invasive carcinoma composed of nests or sheets of clear cells with well-defined cell membranes and voluminous optically clear cytoplasm	No morphologically similar tumor in another organ (RCC); positive for urothelial markers
Sarcomatoid	Tumor cells that are morphologically indistinguishable from sarcoma cells	Positive IHC for urothelial or epithelial markers
Urothelial carcinoma, poorly differentiated	Invasive carcinoma with evidence of urothelial origin by immunohistochemistry	No morphologically similar tumor in another organ

Micropapillary

- 2-5% of all urothelial carcinomas
- Key feature: multiple small nests of tumor within single lacunae
- Any amount of micropapillary in a bladder tumor should be reported
- Less responsive to intravesical therapy (BCG)
- Frequent LVI and lymph node metastases at presentation
- Given the aggressive behavior, NCCN prefers early cystectomy for T1 tumors
- Activating mutations of *ERBB2* or *HER2* amplification more frequently identified in micropapillary subtype compared to conventional UC

Am J Surg Pathol. 2010 Sep;34(9):1367-76. PMID: 20717002.
Urol Oncol. 2022 Jun;40(6):273.e11-273.e20. PMID: 35216892.

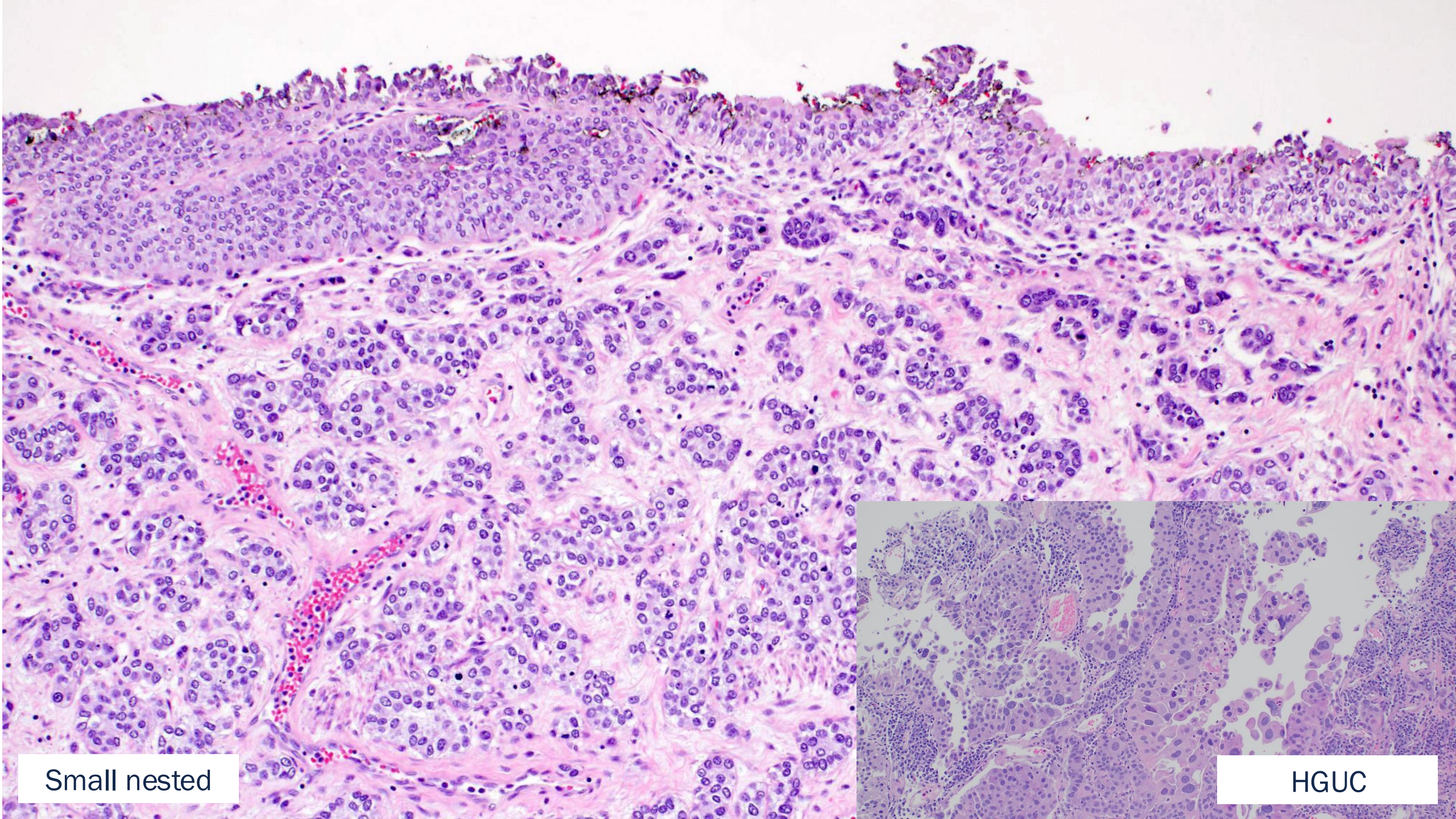

Micropapillary

Nested

UNC SCHOOL OF MEDICINE

- Rare subtype (<1%) of urothelial carcinoma with “deceptively bland” cytology and small round to oval nests of tumor, occasional tubular growth
- Differential diagnosis includes benign entities such as von Brunn nests, nephrogenic adenoma, cystitis cystica, and inverted papilloma
- *TERT* promoter mutations identified in ~80% of nested urothelial carcinomas
- These are high grade tumors
- Some evidence they present at higher stage, but this might be due to underdiagnosis of T1 lesions
- When matched for stage, similar outcomes to conventional urothelial carcinoma

Mod Pathol. 2020 Jun;33(6):1165-1171. PMID: 31932679.

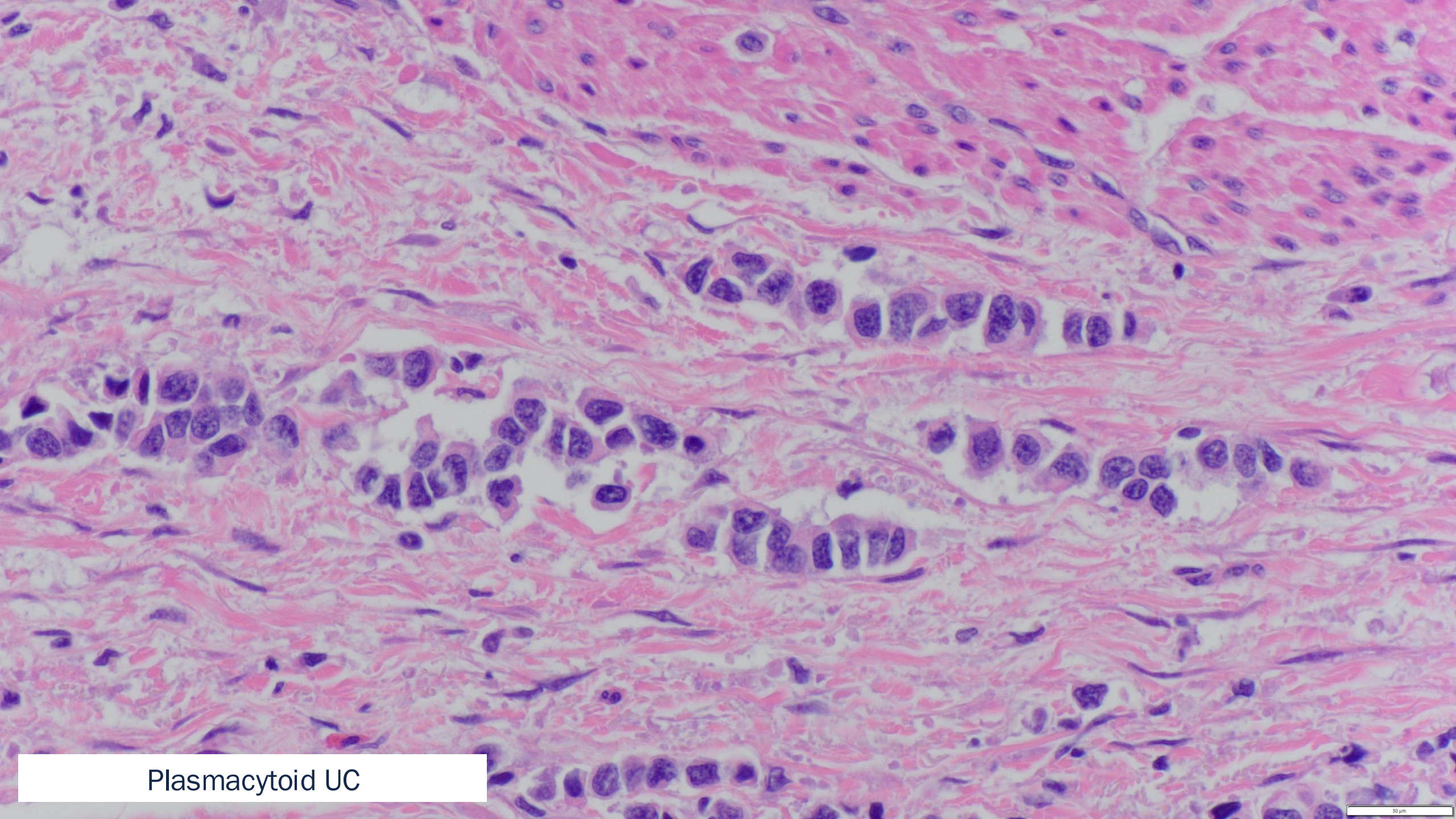

Small nested
HGUC

Plasmacytoid

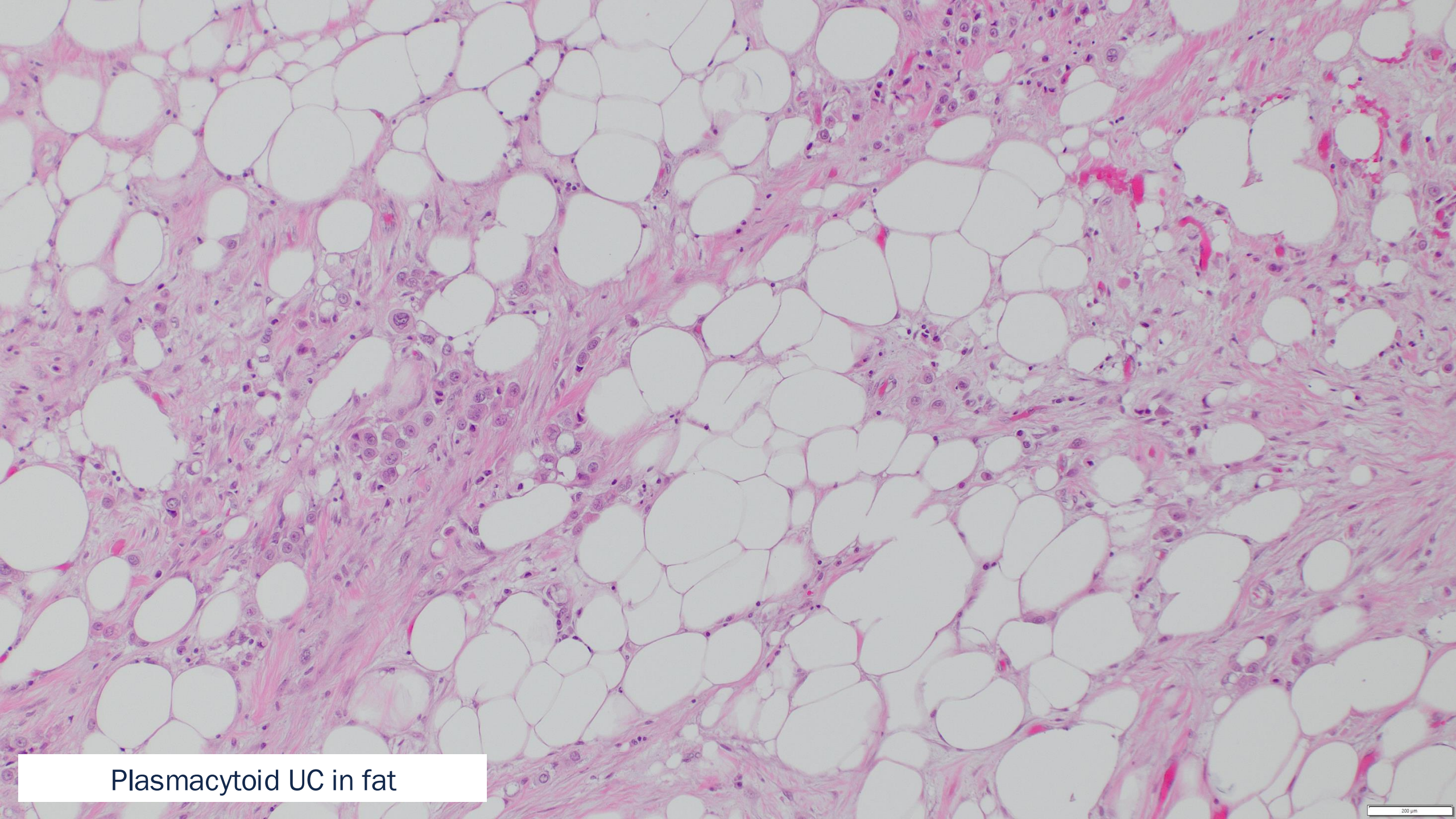
UNC SCHOOL OF MEDICINE

- Relatively rare (1-3%), but important subtype
- Discohesive, single cells with eccentric nucleus embedded in loose or myxoid stroma with minimal stromal reaction
- Differential diagnosis includes inflammation, lobular breast cancer, gastric/signet-ring cell carcinoma, poorly differentiated bladder adenocarcinoma, plasmacytoma, lymphoma, melanoma
- Associated with mutations in *CDH1*, the gene that encodes cell adhesion molecule, e-cadherin
- Aggressive clinical behavior including advanced stage, nodal involvement, may be less sensitive to cisplatin-based chemotherapy, positive margins, peritoneal spread, frequent local recurrence

Nat Genet. 2016 Apr;48(4):356-8. PMID: 26901067



Plasmacytoid UC

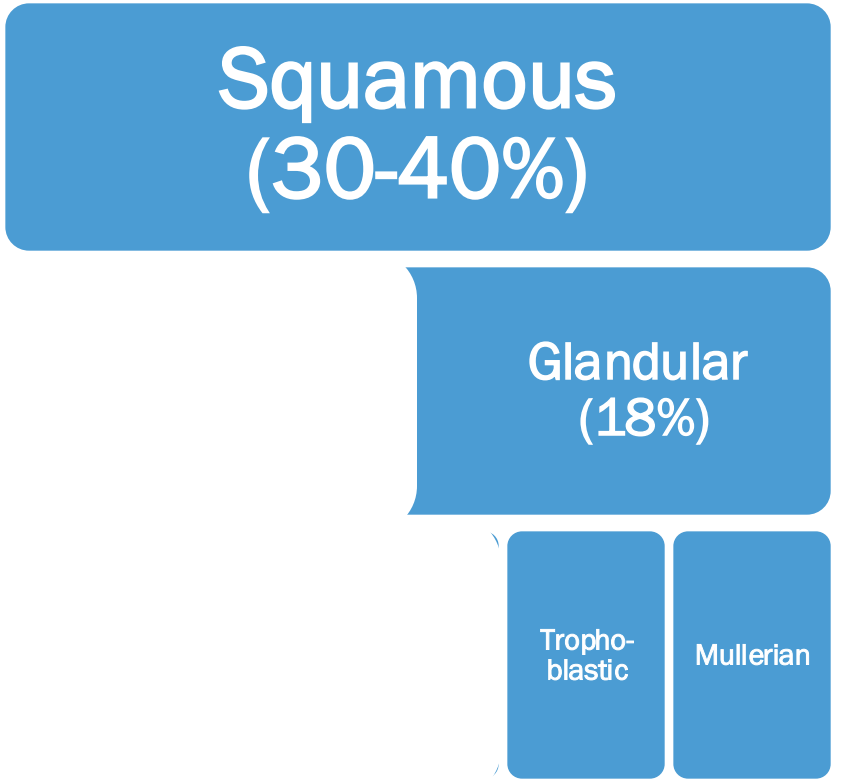


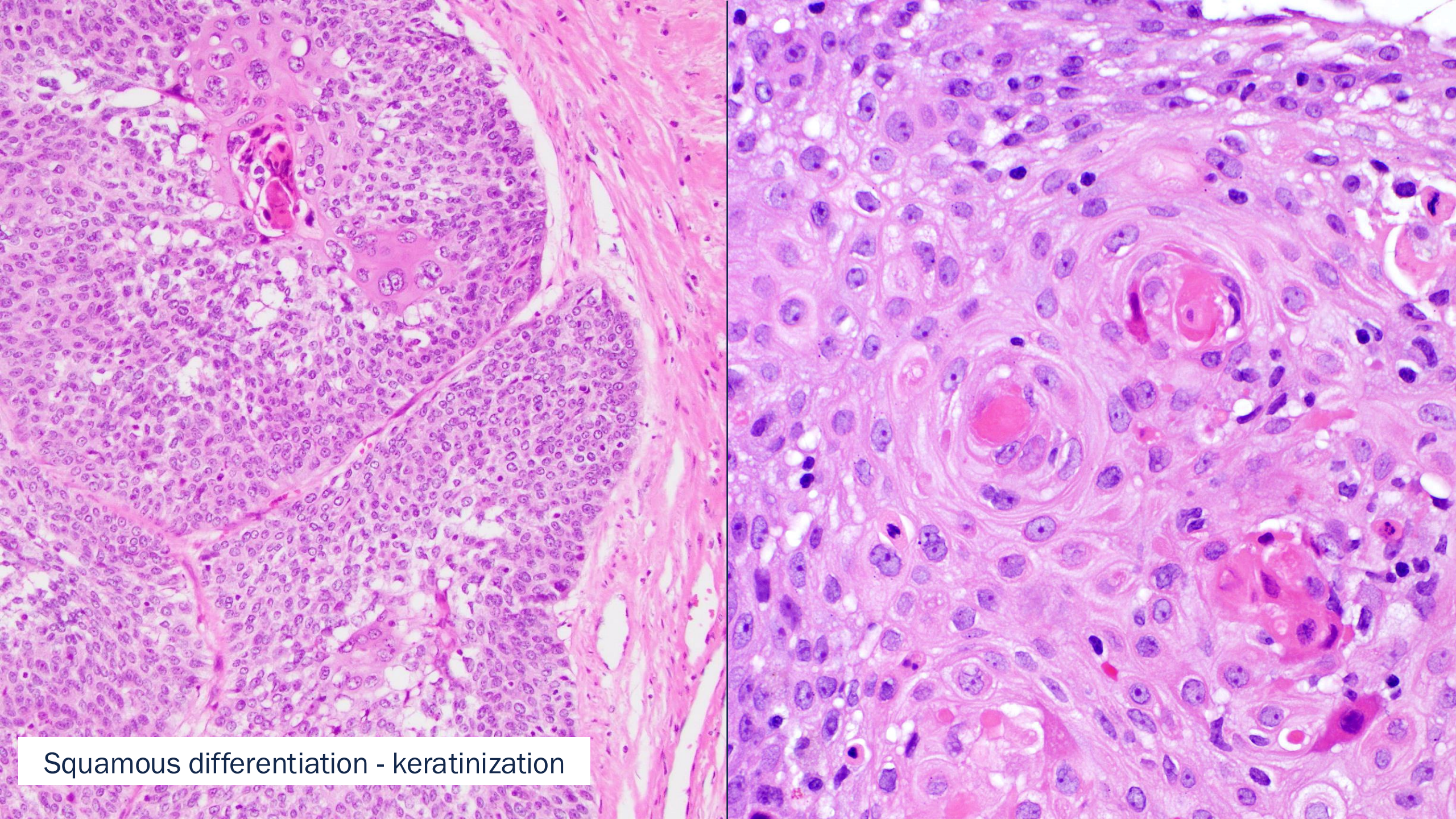
Plasmacytoid UC in fat

Divergent Differentiation

UNC SCHOOL OF MEDICINE

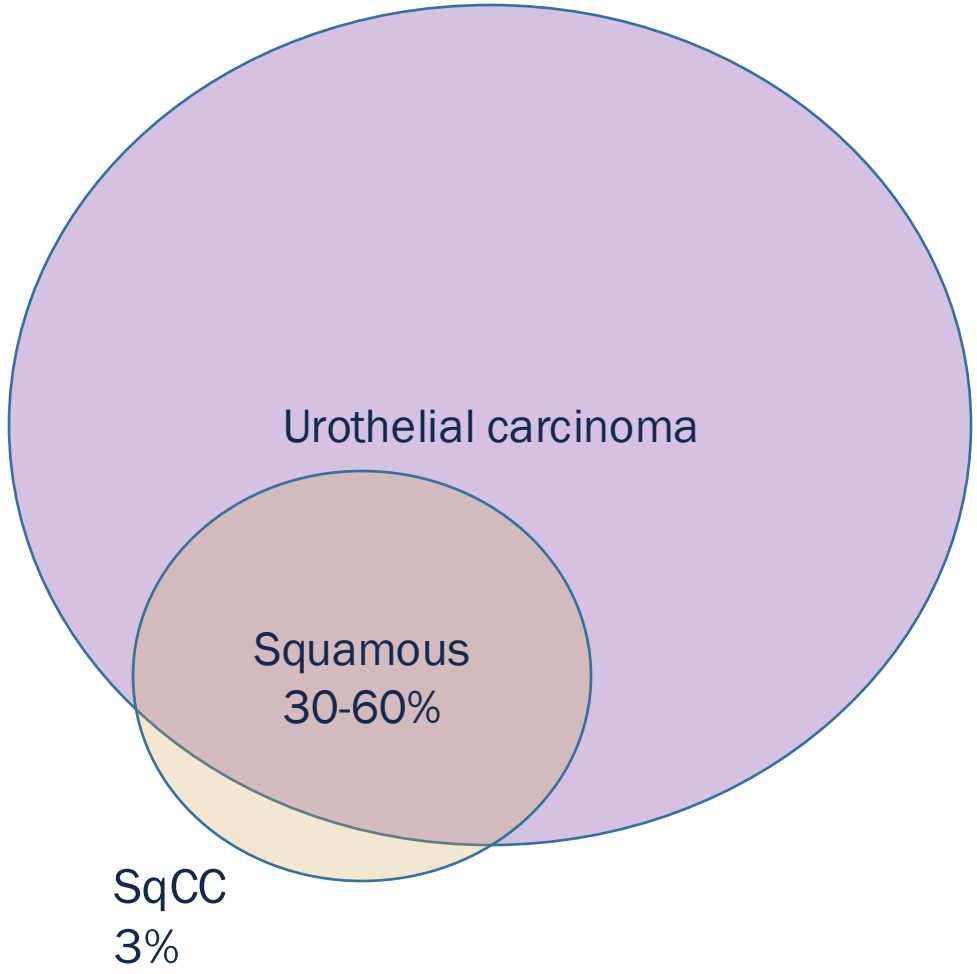
- Because divergent histology resembles another non-urothelial cell of origin, it raises a complex differential diagnosis
- Must be distinguished from pure versions of those tumors arising in the bladder, and from secondary/metastatic origin
  - Colorectal adenocarcinoma invading bladder
  - Cervical squamous cell carcinoma involving bladder
- May not be possible on histopathology alone
- Often with major treatment differences so distinction is critical




Squamous differentiation - keratinization

Squamous Differentiation

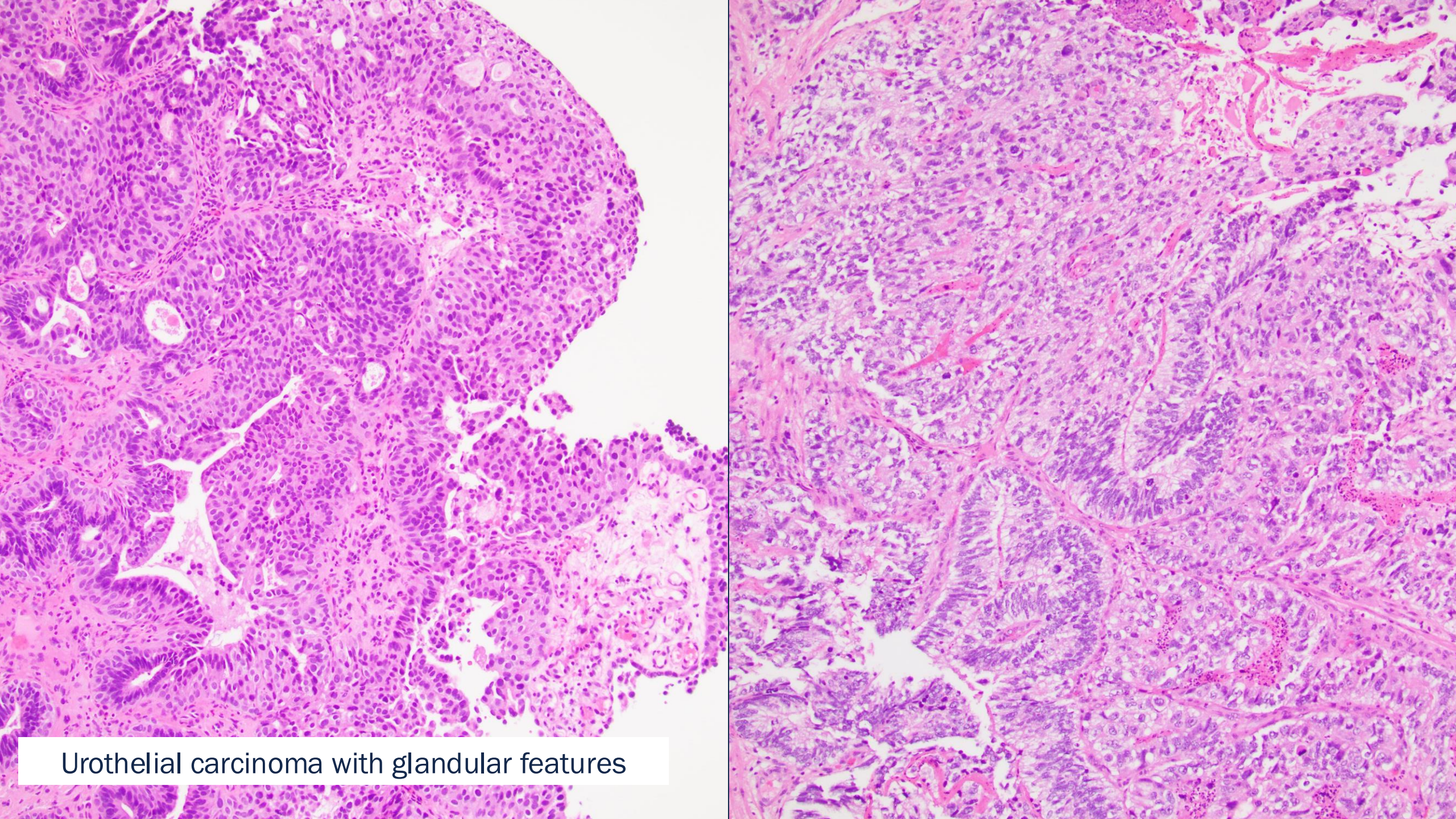
- Urothelial carcinoma with squamous features: ~50%
- Pure squamous cell carcinoma: 3%
- Can also have secondary involvement from a gynecologic or lower anogenital site
  - hrHPV to evaluate



Squamous: Clinical Implications

UNC SCHOOL OF MEDICINE

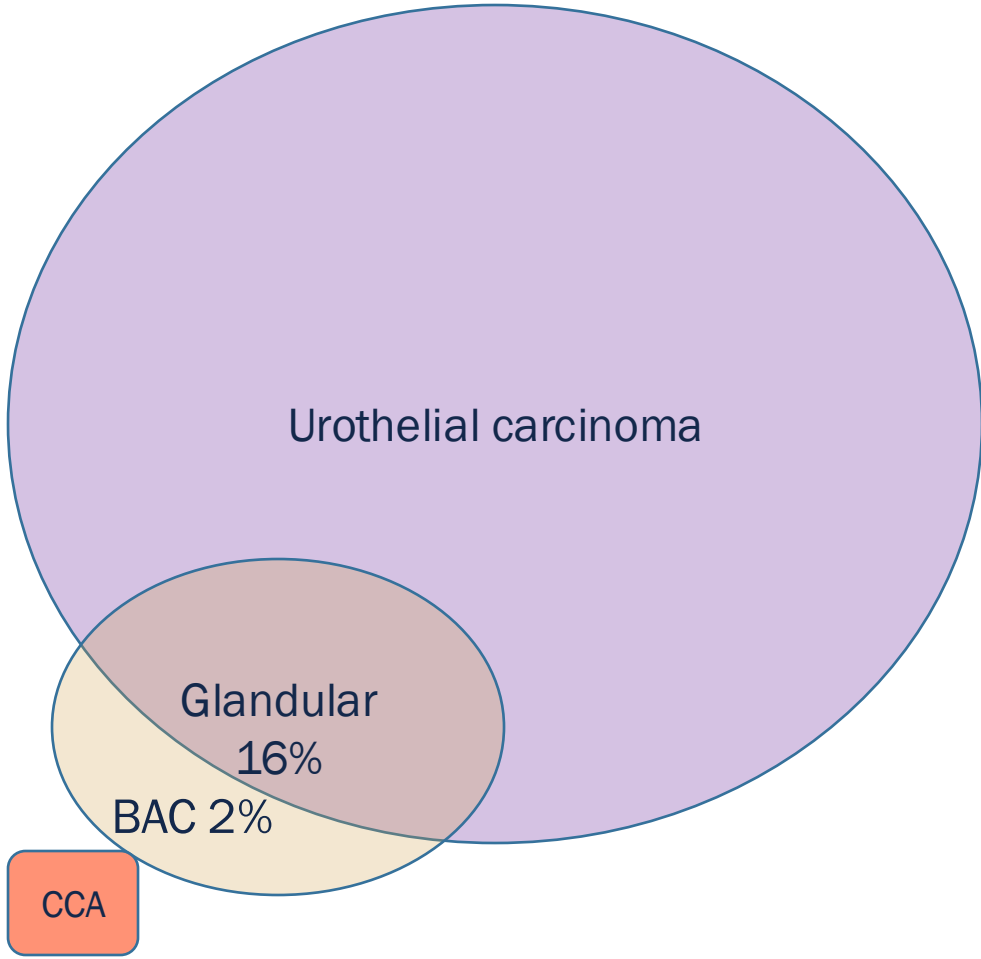
- Pure squamous cell carcinomas of the bladder appear to be less responsive to conventional chemotherapy
  - Important to identify any urothelial component, invasive or non-invasive
  - Unknown what percentage of squamous divergence may drive differential treatment response

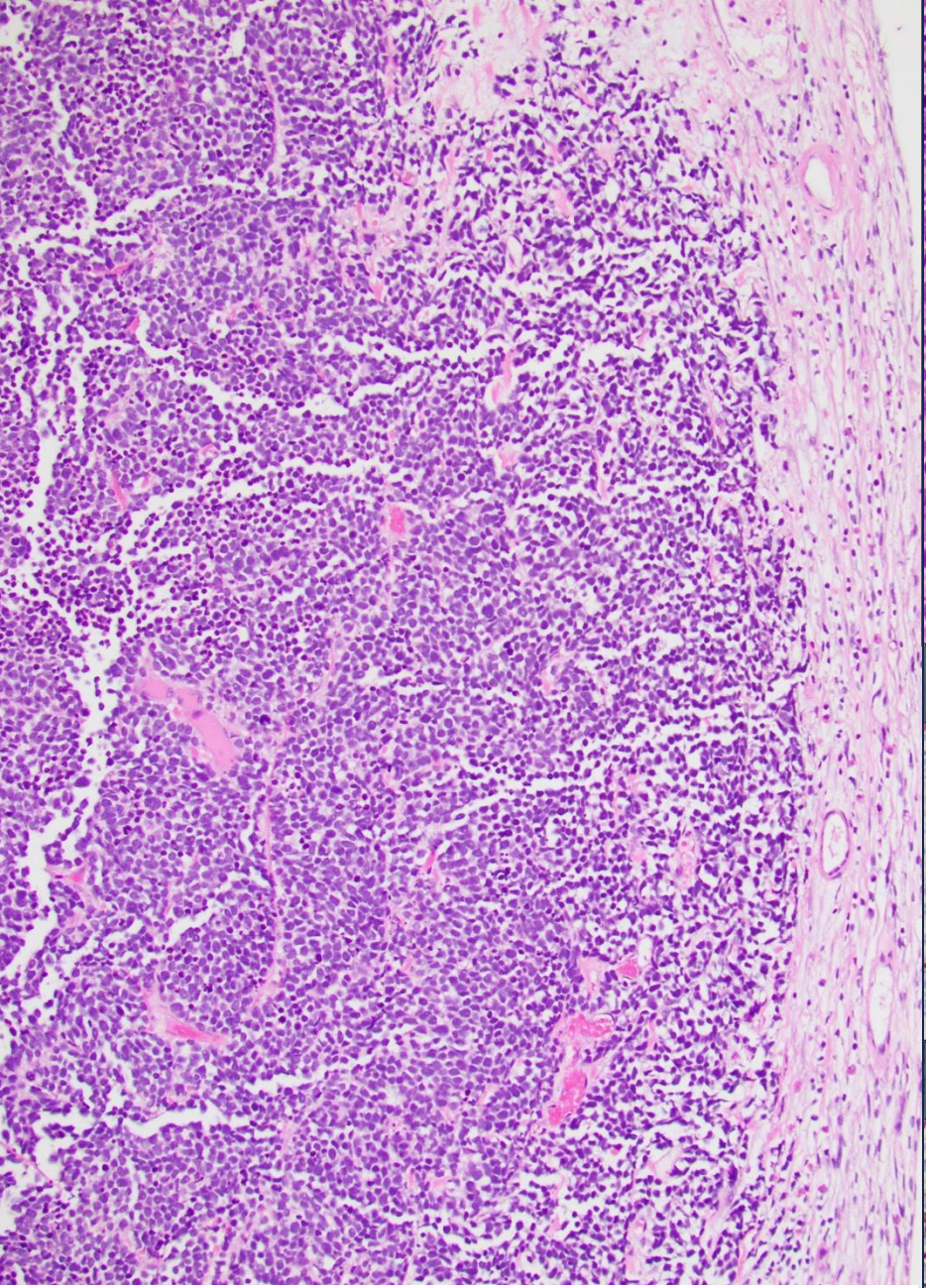


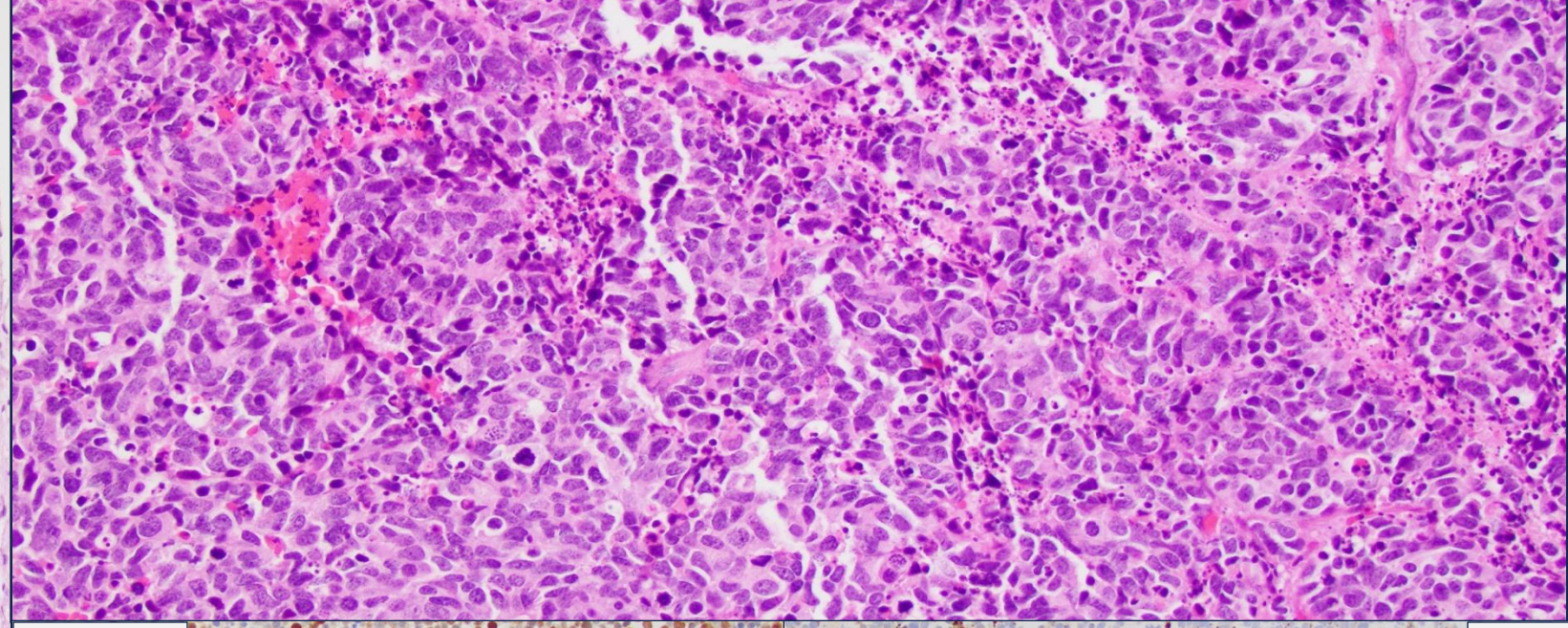
Urothelial carcinoma with glandular features

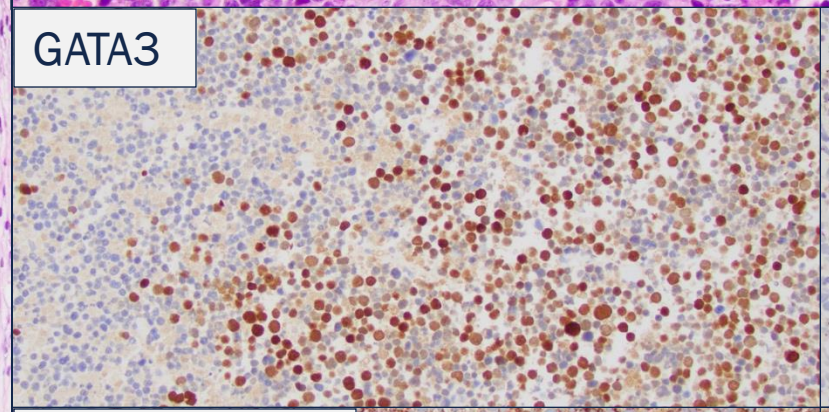
Glandular Differentiation

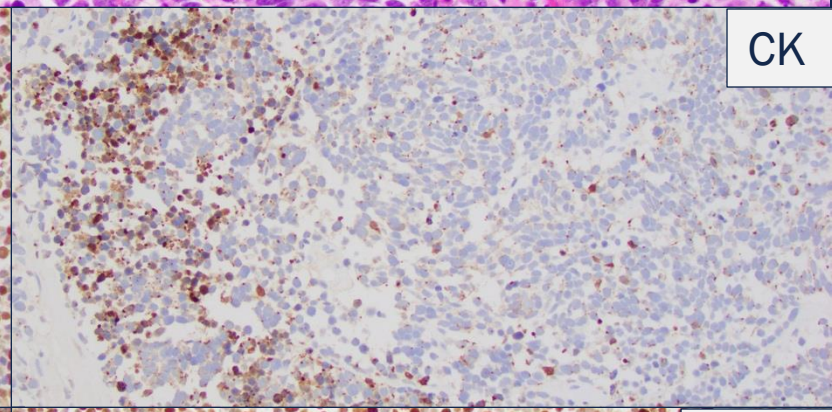
- Less common than squamous
  - Urothelial carcinoma with glandular features: 16%
  - Pure bladder adenocarcinoma: 2%
  - Clear cell adenocarcinoma: <1%
- Unclear prognostic significance, but broader differential diagnosis

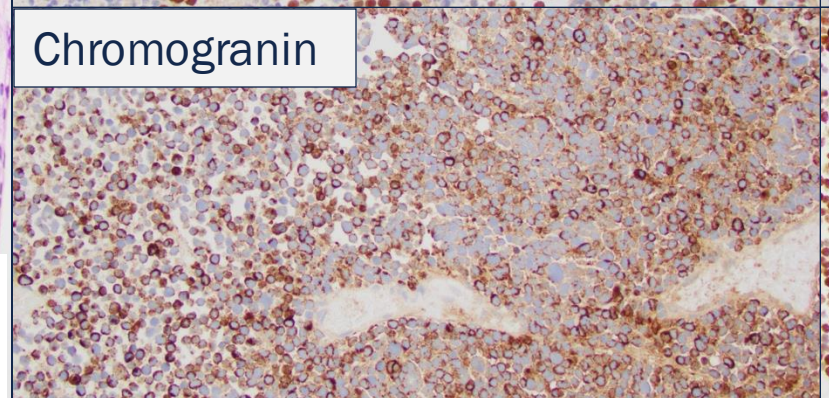


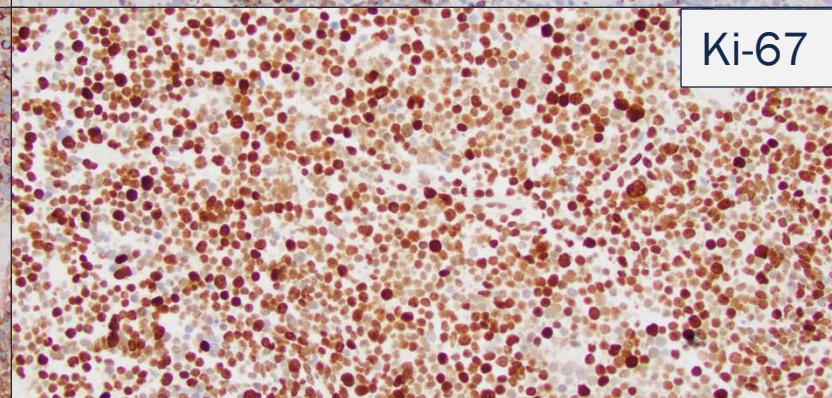












Small cell carcinoma/
high grade neuroendocrine carcinoma

Small Cell: Clinical Implications

UNC SCHOOL OF MEDICINE

- Neuroendocrine carcinoma exhibits divergence from urothelial to neuronal type cells
  - ~50% admixed with other subtypes or divergence
- Overall poor prognosis with worse OS and DSS compared to conventional urothelial carcinoma
- Non-durable response to cisplatin plus etoposide

Conclusion

UNC SCHOOL OF MEDICINE

- More research on histologic subtypes and divergent differentiation is needed
- Only select subtypes discussed today with even less known about the others due to rarity
- We have a lot of work ahead of us to understand the molecular underpinnings of subtype histology and the association with prognosis and therapeutic interventions

A special thank you to Dr. Sara Wobker

UNC SCHOOL OF MEDICINE

SARA ELIZABETH WOBKER, MD, MPH
ASSOCIATE PROFESSOR
DIRECTOR OF SURGICAL PATHOLOGY
DIRECTOR OF GENITOURINARY PATHOLOGY