Update on Bladder Cancer: What's New in the 2016 WHO Classification of Bladder Tumors and 8th Edition of *AJCC Staging Manual*

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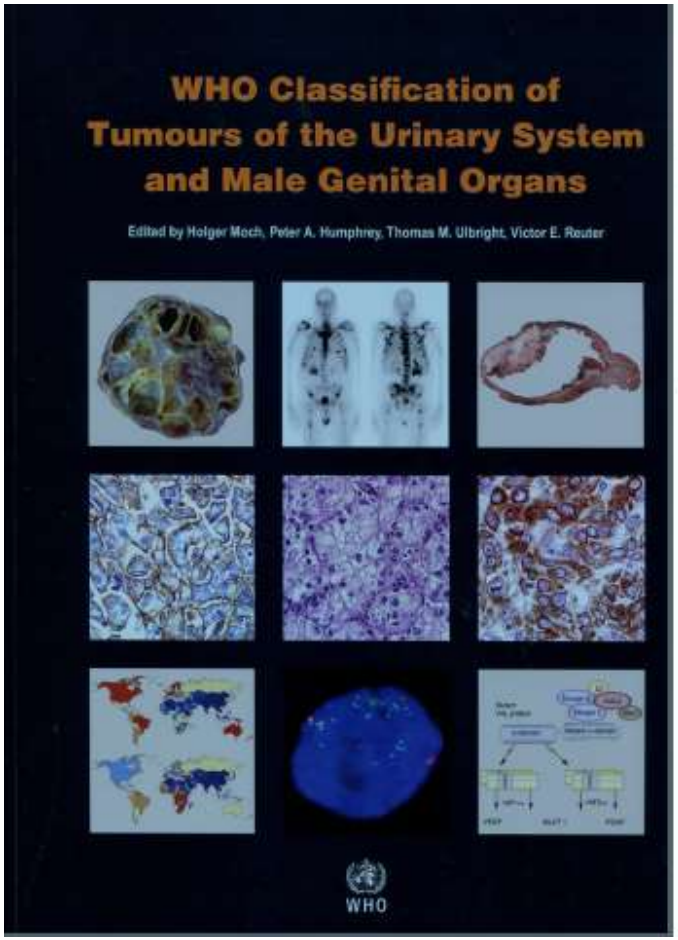
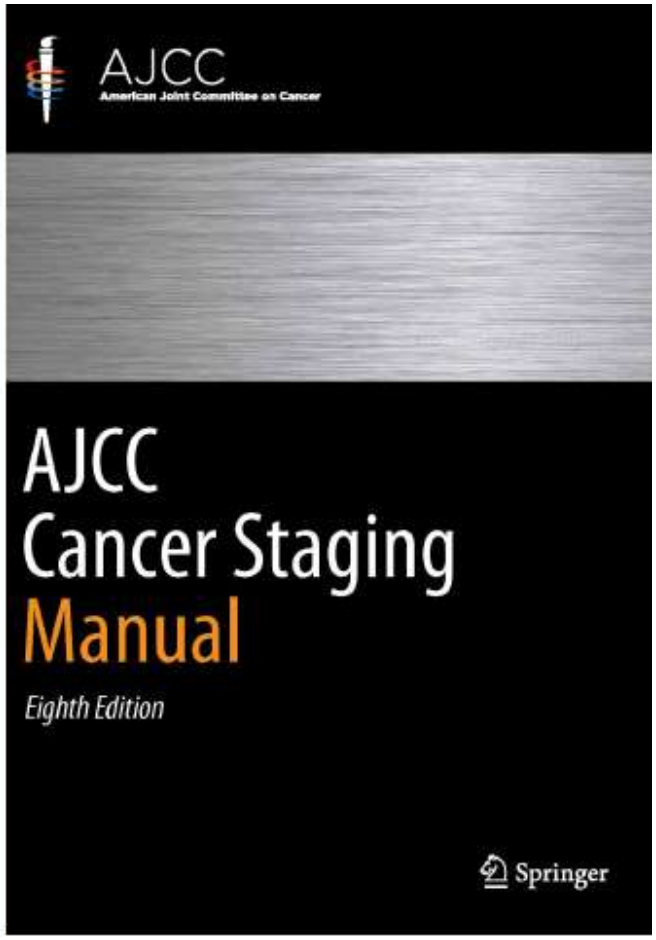
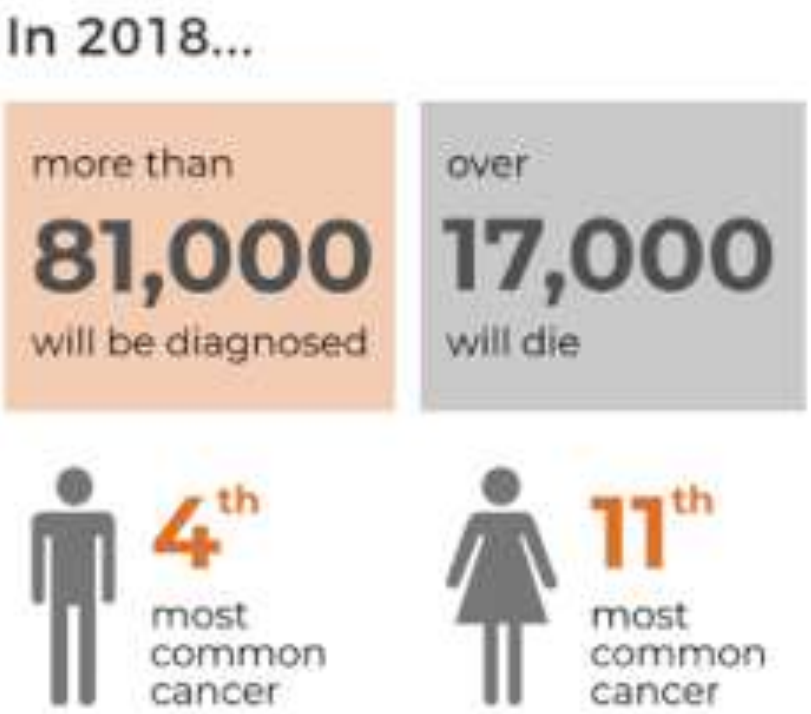




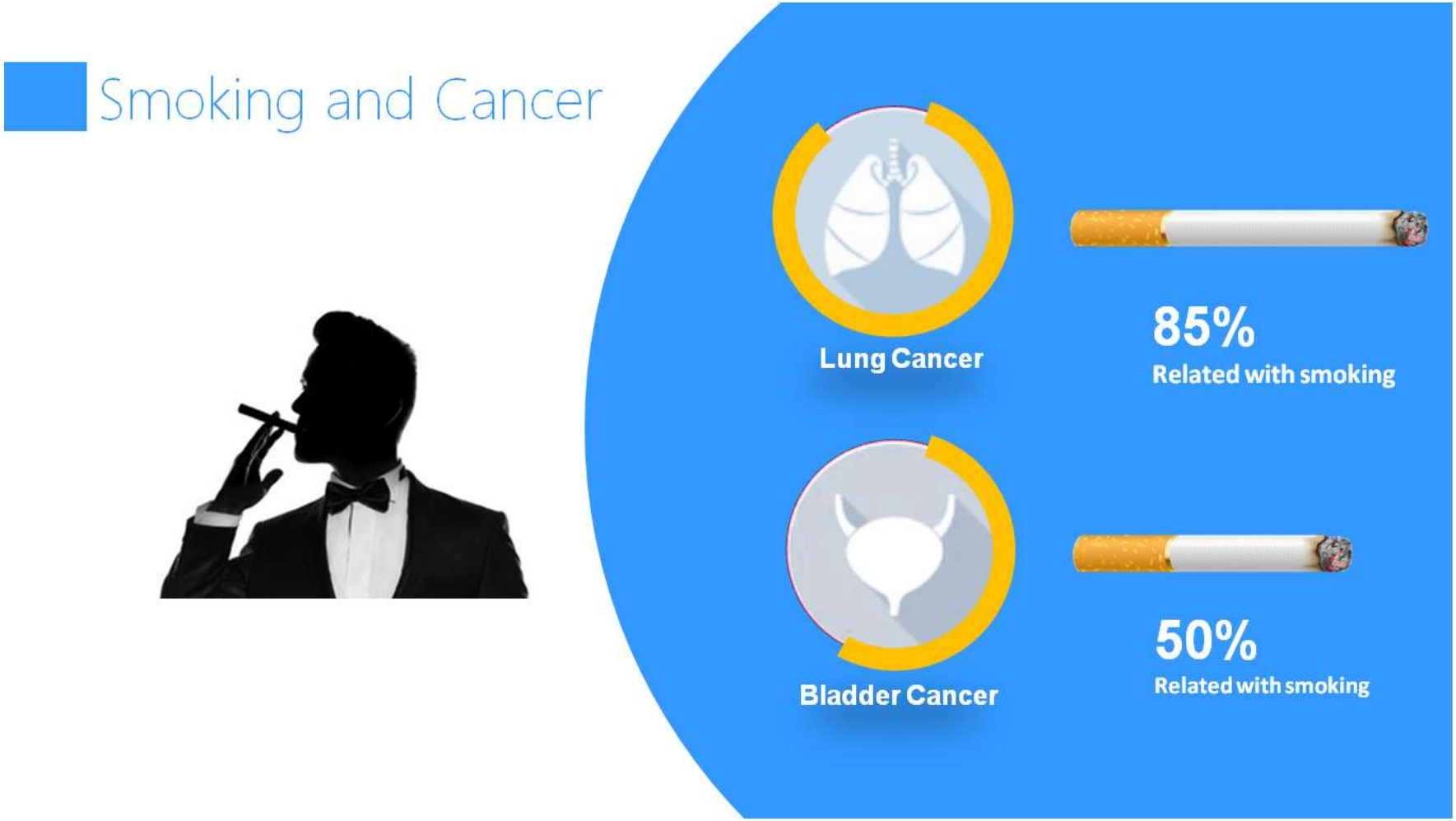
Genitourinary Pathology in 2016…..

Epidemiology



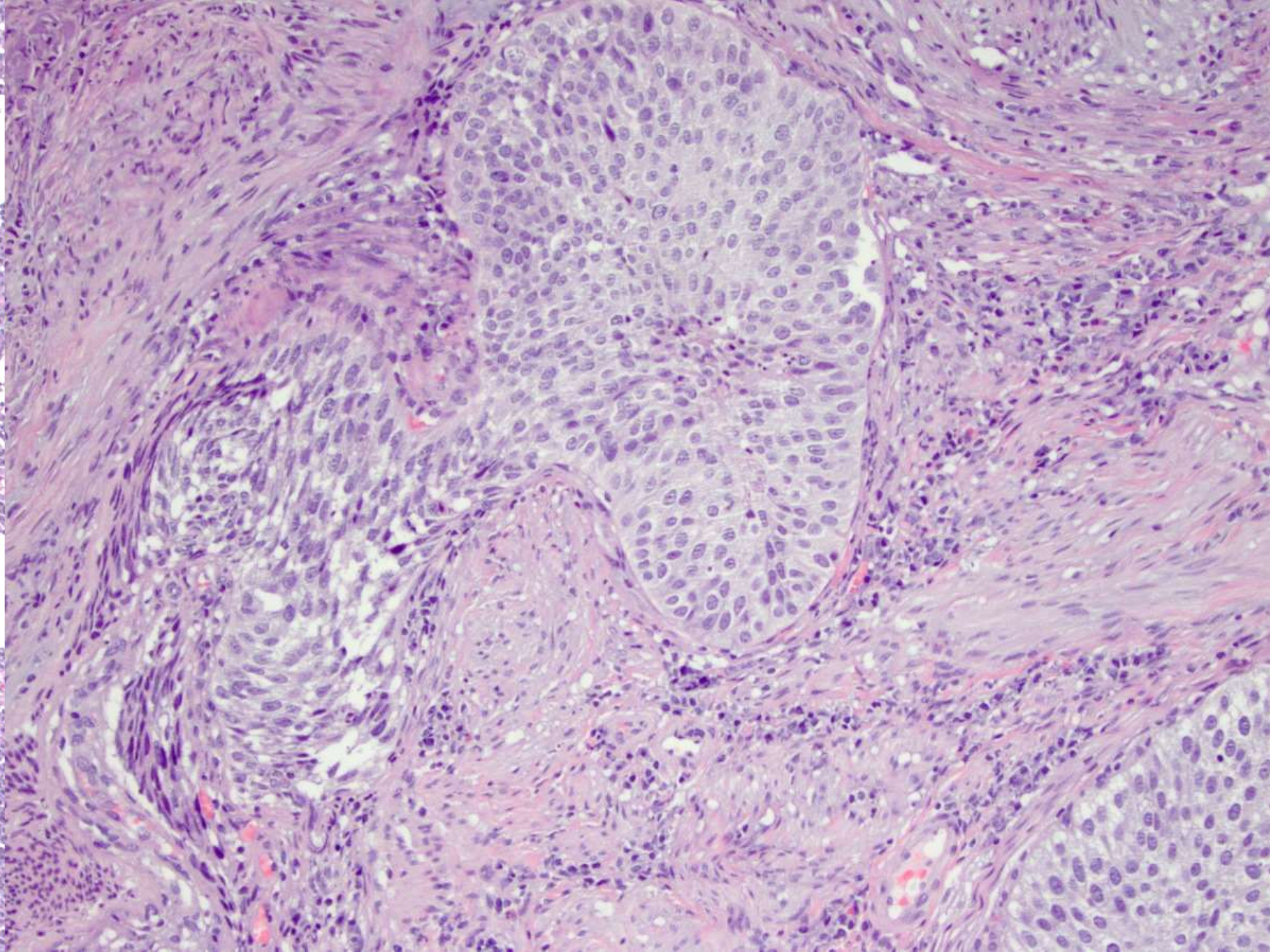
- Due to long natural history of bladder cancer, the prevalence is high (500,000 - 600,000)
- ~$3 billion/year is spent for bladder cancer treatment
- Most expensive cancer to treat!

Incidence of bladder cancer is increasing due to smoking!



Case 1

- A 58 year old male presented with hematuria. On workup was found to have 3 cm polypoid mass involving the anterior bladder wall. The patient underwent transurethral resection.

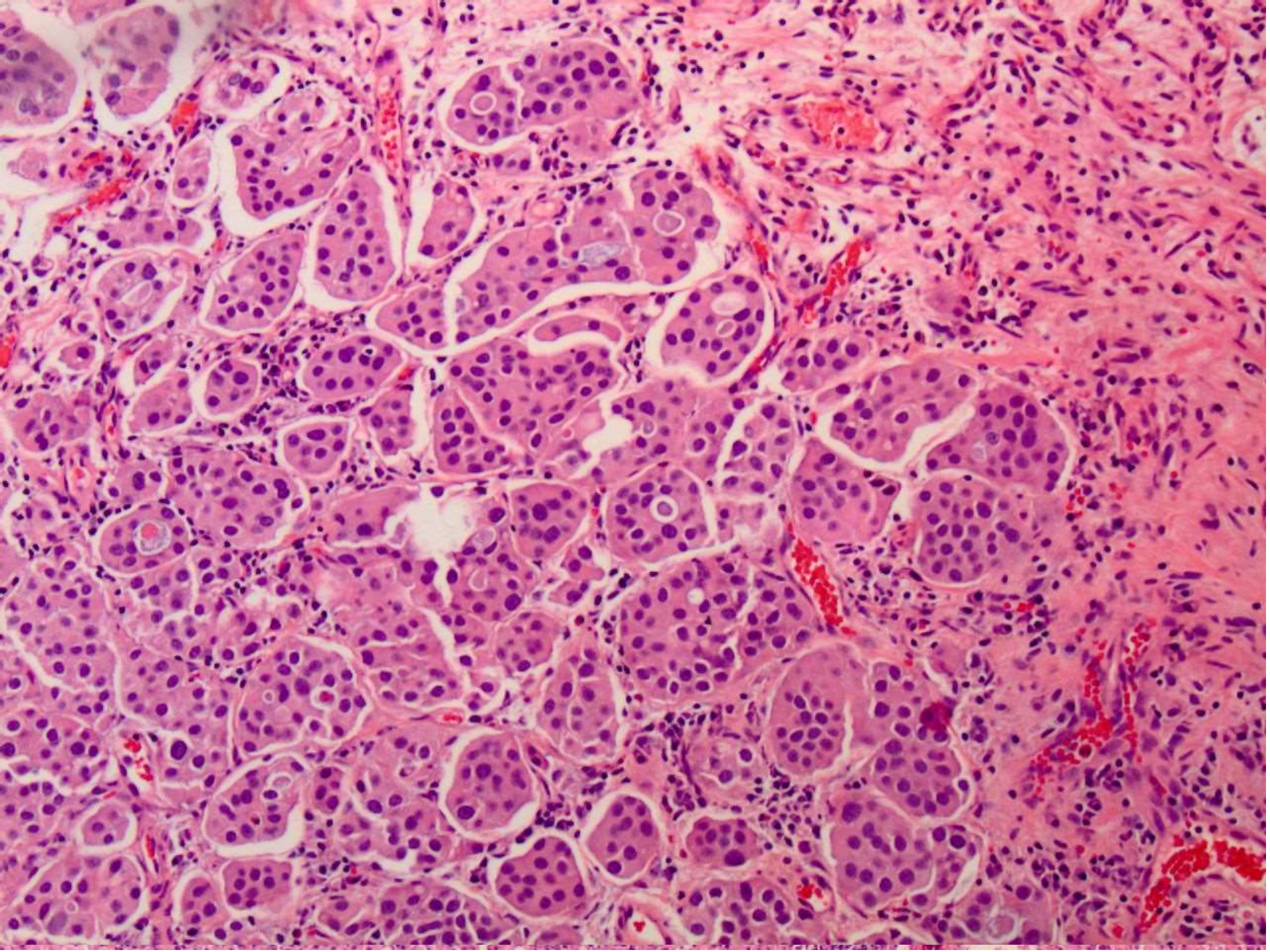


Diagnosis

- Non-invasive low grade urothelial carcinoma with endophytic growth
- Non-invasive high grade urothelial carcinoma with endophytic growth
- Inverted papilloma
- Nested urothelial carcinoma, including large nested

Case 2

- A 65 year old male presented with hematuria and dysuria. On workup was found to have 2 cm mass involving the anterior bladder wall.

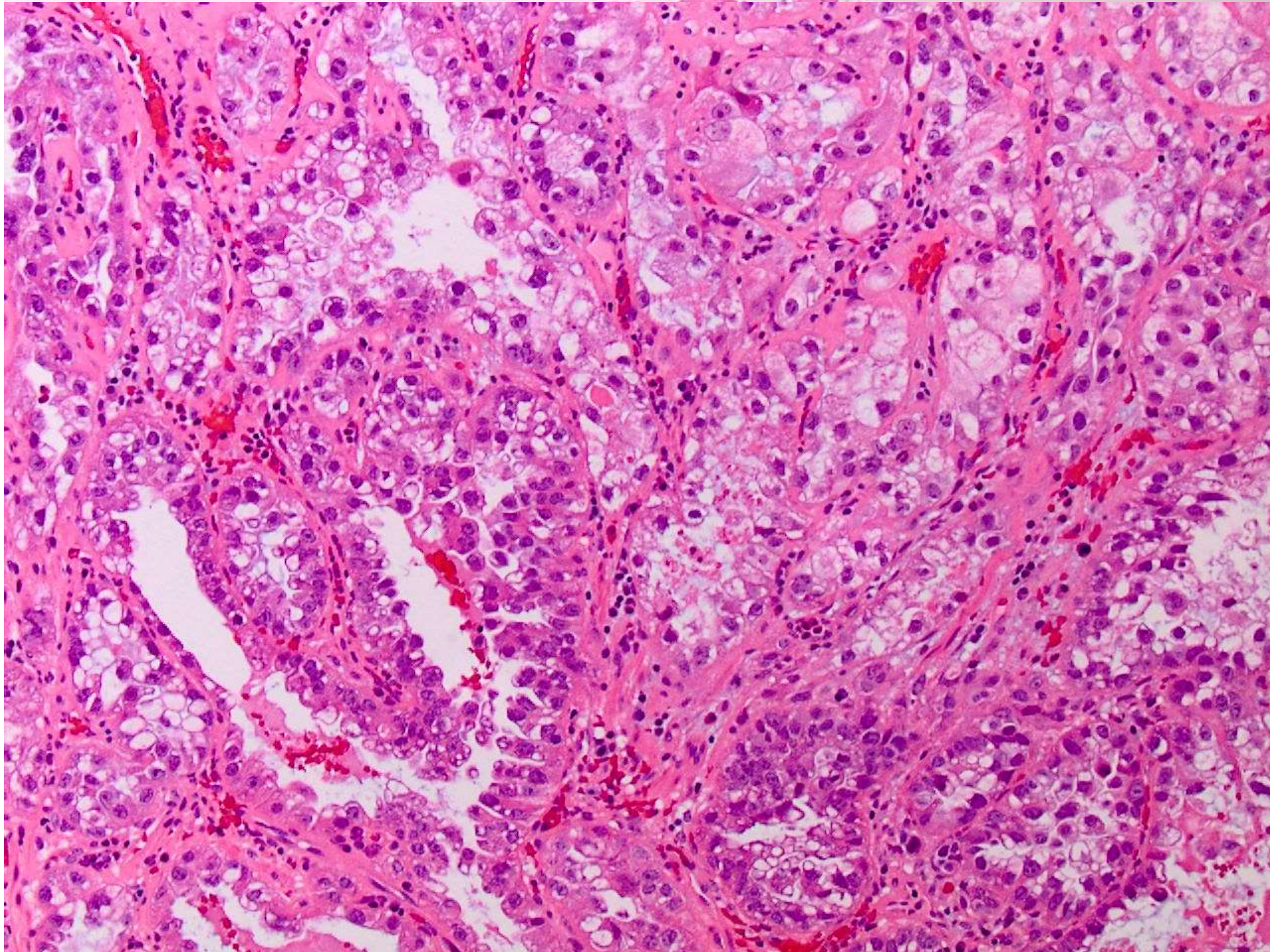


Diagnosis

- Inverted papilloma
- Invasive high-grade urothelial carcinoma
- Nested urothelial carcinoma
- Invasive micropapillary urothelial carcinoma

Case 3

- A 60 year old female presented with hematuria and dysuria. On workup was found to have 2 cm polypoid mass involving the distal urethra.

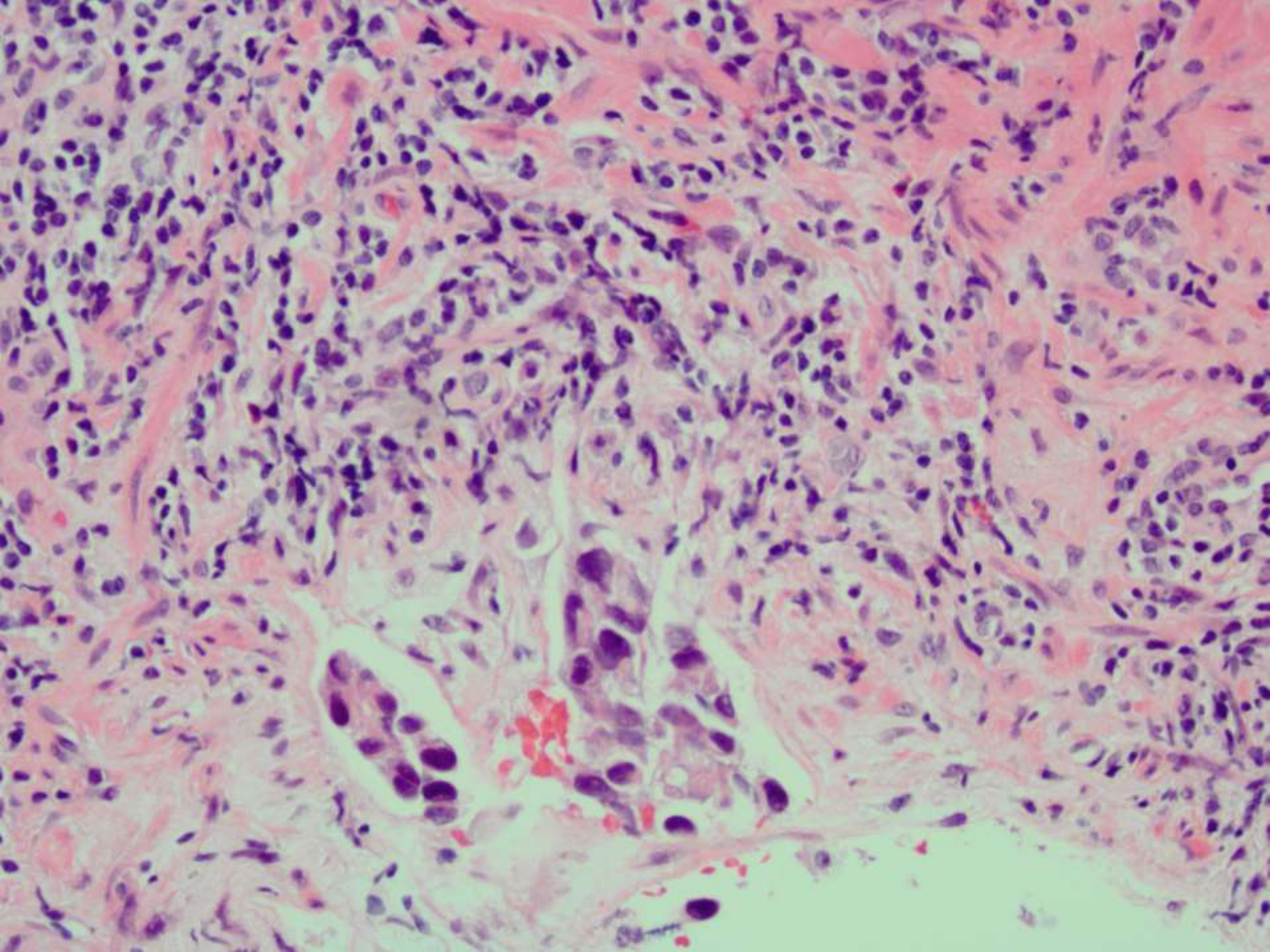


Diagnosis

- Invasive adenocarcinoma, NOS type
- Urachal adenocarcinoma
- Nephrogenic adenoma
- Clear cell adenocarcinoma

Case 4

- A 58 year old male presented with elevated PSA of 8 ng/ml. He underwent an extended prostate biopsy. The right base biopsy showed abnormality which is enclosed for review.



Diagnosis

- Intraductal carcinoma of the prostate
- Prostate adenocarcinoma, Gleason score 5+5=10
- Noninvasive high-grade urothelial carcinoma with spread into prostatic ducts; pTa
- High-grade urothelial carcinoma with spread into prostatic ducts and invasion of prostatic stroma; pT2

Agenda: Discuss Important Changes in Bladder Cancer Classification, Grading, Staging and Reporting

- New/Updated entities

  Divergent differentiation and Variants, Urothelial proliferation of uncertain malignant potential (hyperplasia), Tumors of Mullerian-type

- Classification and Grading

  2004 ISUP grading classification universally adopted

  Molecular taxonomy for classification/prognostication

- Staging

  Substaging tumors invading the lamina propria

  Staging of tumors involving prostatic stroma

WHO Classification of Infiltrating Bladder cancer:

Differences between the 3rd and 4th editions

Third edition

- Infiltrating urothelial carcinoma

With squamous differentiation

With glandular differentiation

With trophoblastic differentiation

- Nested
- Microcystic
- Micropapillary
- Lymphoepithelioma – like
- Lymphoma – like
- Plasmacytoid
- Sarcomatoid
- Giant cell
- Undifferentiated

Fourth edition

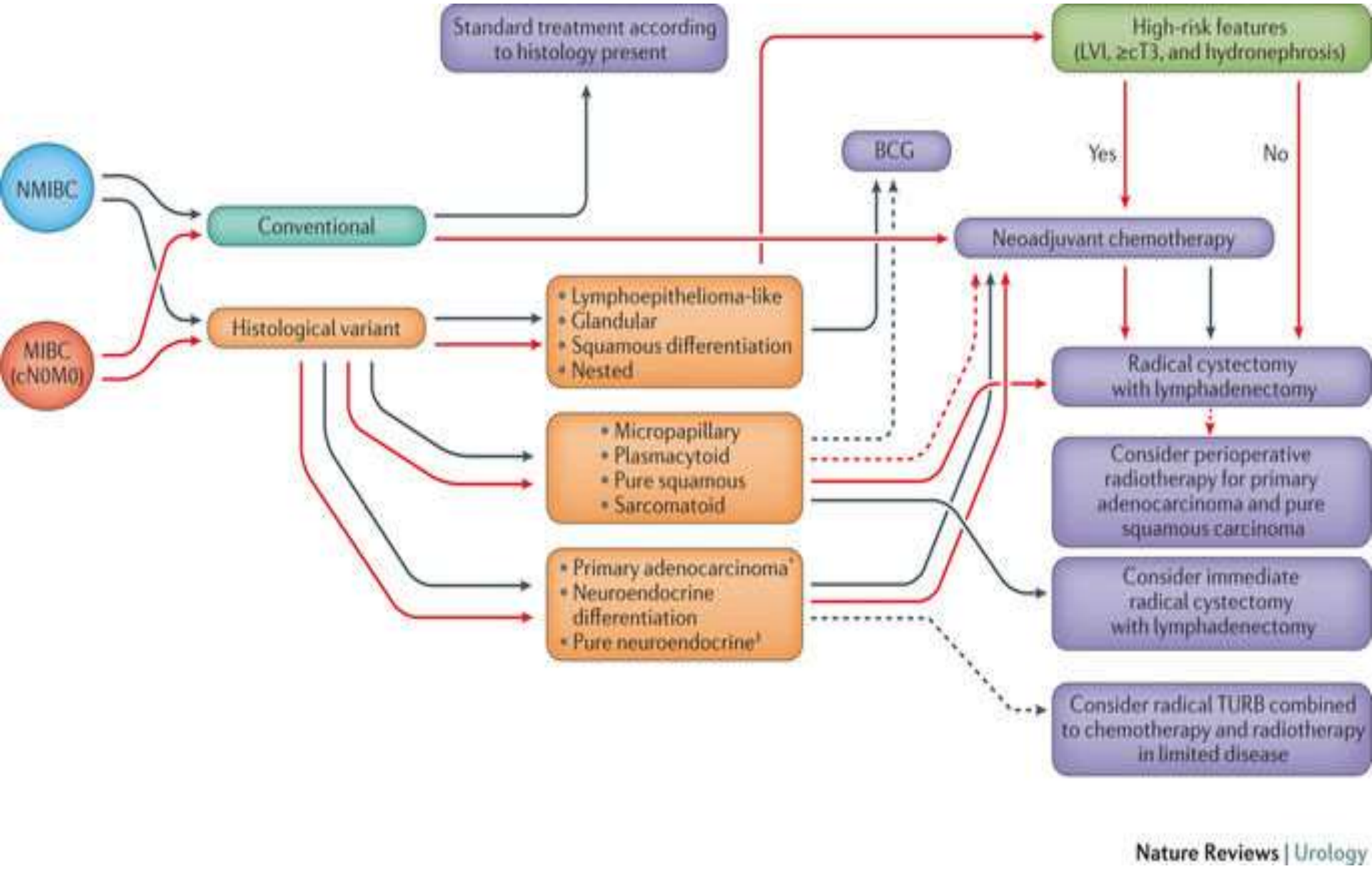
- Infiltrating urothelial carcinoma

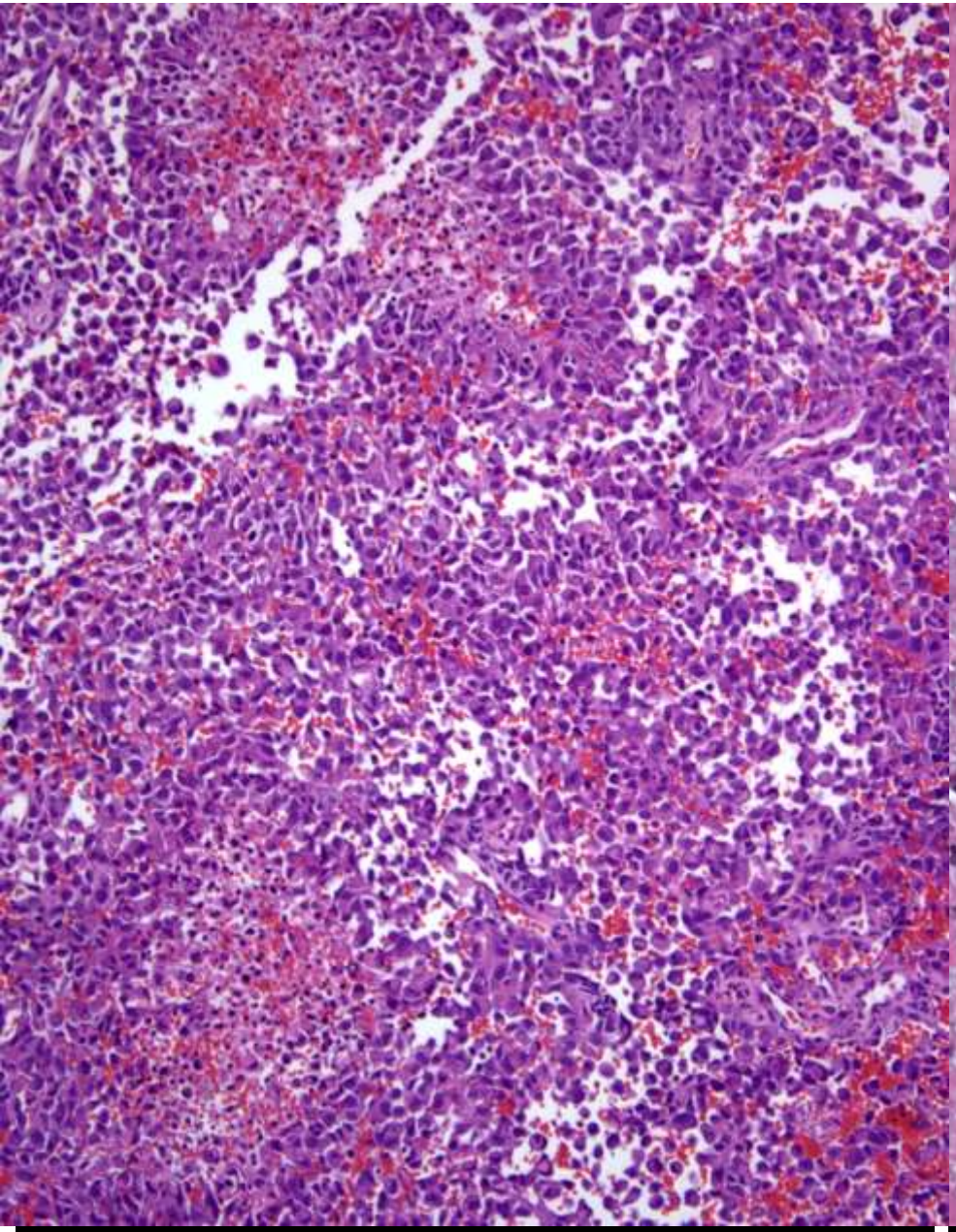
With divergent differentiation

- **Nested, including large nested**
- Microcystic
- Micropapillary
- Lymphoepithelioma – like
- **Plasmacytoid/Signet ring cell/diffuse**
- Sarcomatoid
- Giant cell
- **Poorly differentiated**
- Lipid rich and Clear cell

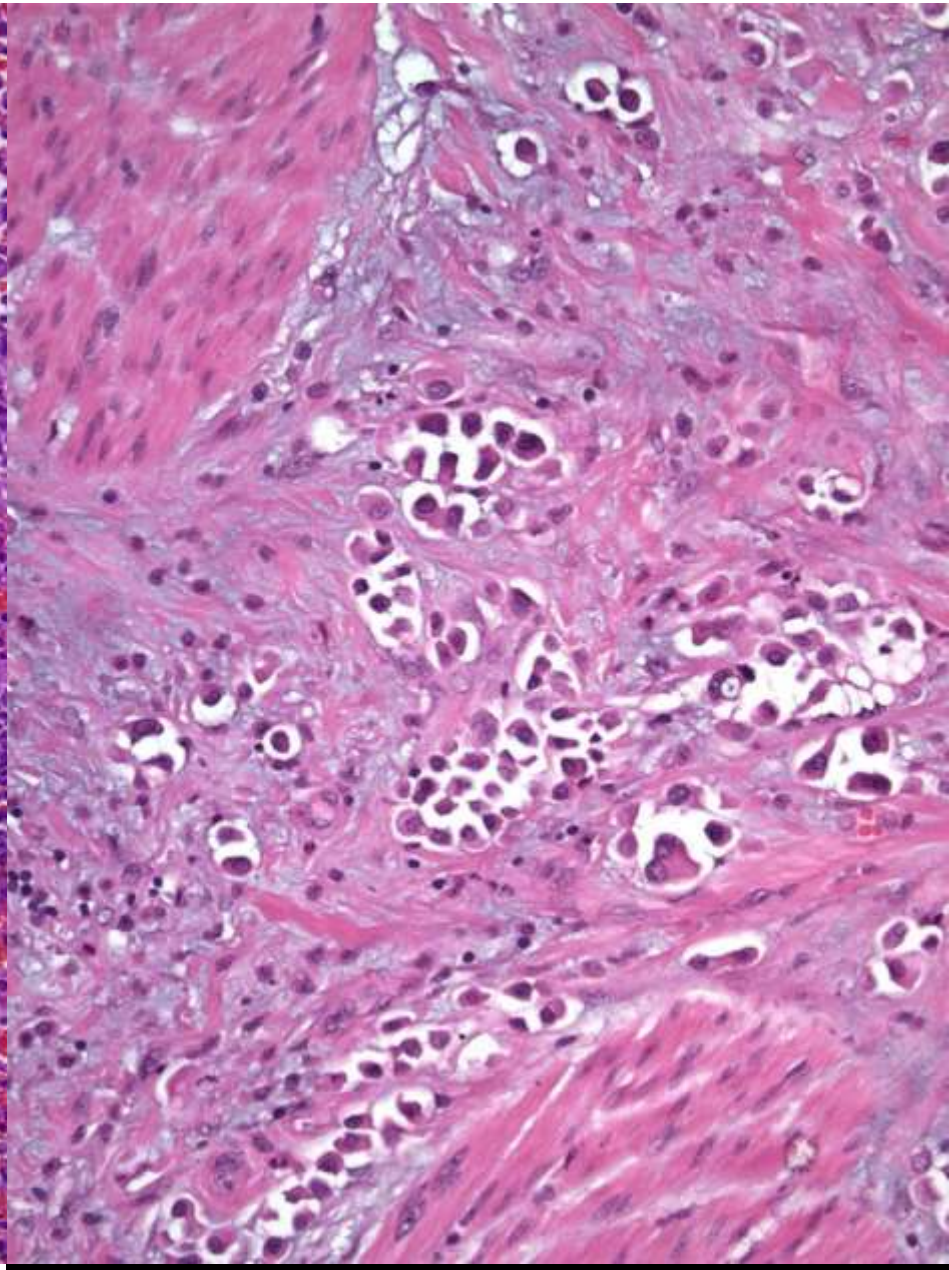
Why it matters to accurately classify Histologic variants?

- Some associated with a different clinical outcome
- Some require different therapeutic approach
- Awareness of certain histologic variants critical in avoiding diagnostic misinterpretations in superficial biopsies
- Distinction of variant histology from metastasis may be difficult when pure
- Variant histology poses higher risk of under-staging in non-muscle invasive (T1) cancer


Standard treatment according to histology present
High-risk features (LVI, ≥cT3, and hydronephrosis)
NMIBC
BCG
Yes
No
Conventional
Neoadjuvant chemotherapy
MIBC (cN0M0)
Histological variant
• Lymphoepithelioma-like
• Glandular
• Squamous differentiation
• Nested
Radical cystectomy with lymphadenectomy
• Micropapillary
• Plasmacytoid
• Pure squamous
• Sarcomatoid
Consider perioperative radiotherapy for primary adenocarcinoma and pure squamous carcinoma
• Primary adenocarcinoma*
• Neuroendocrine differentiation
• Pure neuroendocrine†
Consider immediate radical cystectomy with lymphadenectomy
Consider radical TURB combined to chemotherapy and radiotherapy in limited disease



Dis-cohesive tumor cells in diffuse infiltrative growth



Non-gland/nest-forming, poorly cohesive cells

PLASMACYTOID UROTHELIAL CARCINOMA
(Signet ring cell/diffuse)

Signet ring like cells; No extracellular mucin

Plasmacytoid Urothelial Carcinoma

- Rare highly aggressive variant; often present with extensive spread in peritoneal cavity
- Can be pure or mixed
- Variable # of signet ring cells without extracellular mucin included
- D/D: Plasmacytoma, Signet ring cell carcinoma, metastatic lobular ca and Urothelial carcinoma with rhabdoid features
- Immunohistochemical profile
  - **Pankeratin positive** **- Loss of membranous E-cadherin**
  - **CD 138 expression**
  - **P63 negative, GATA-3 positive**

PLASMACYTOID UROTHELIAL CARCINOMA

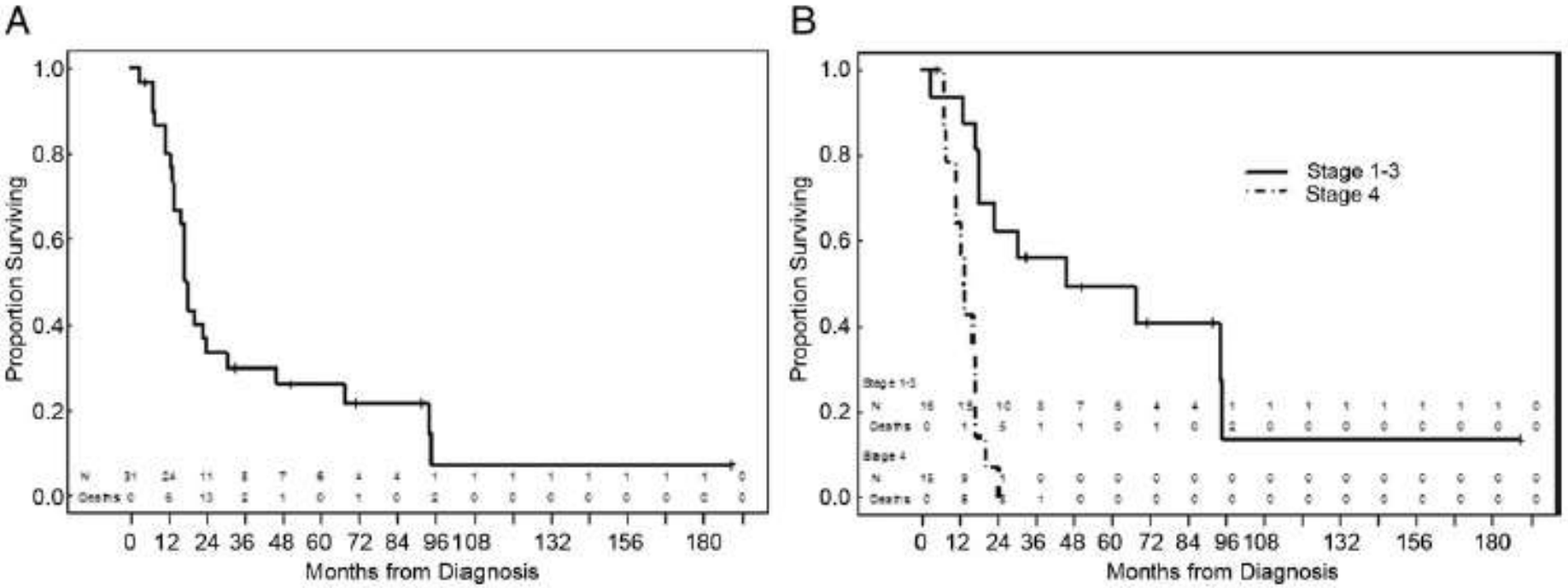


Figure 2. OS. *A*, 17.7 months in all 31 patients. *B*, 45.8 vs 13.4 months for stage I–III vs IV ($p < 0.001$).

Dayyeni F et al. J Urol. 2013; 189(5): 1656-1661

“Deceptively Bland” Carcinomas

Invasive urothelial carcinomas described as “deceptively bland” and “underdiagnosed”

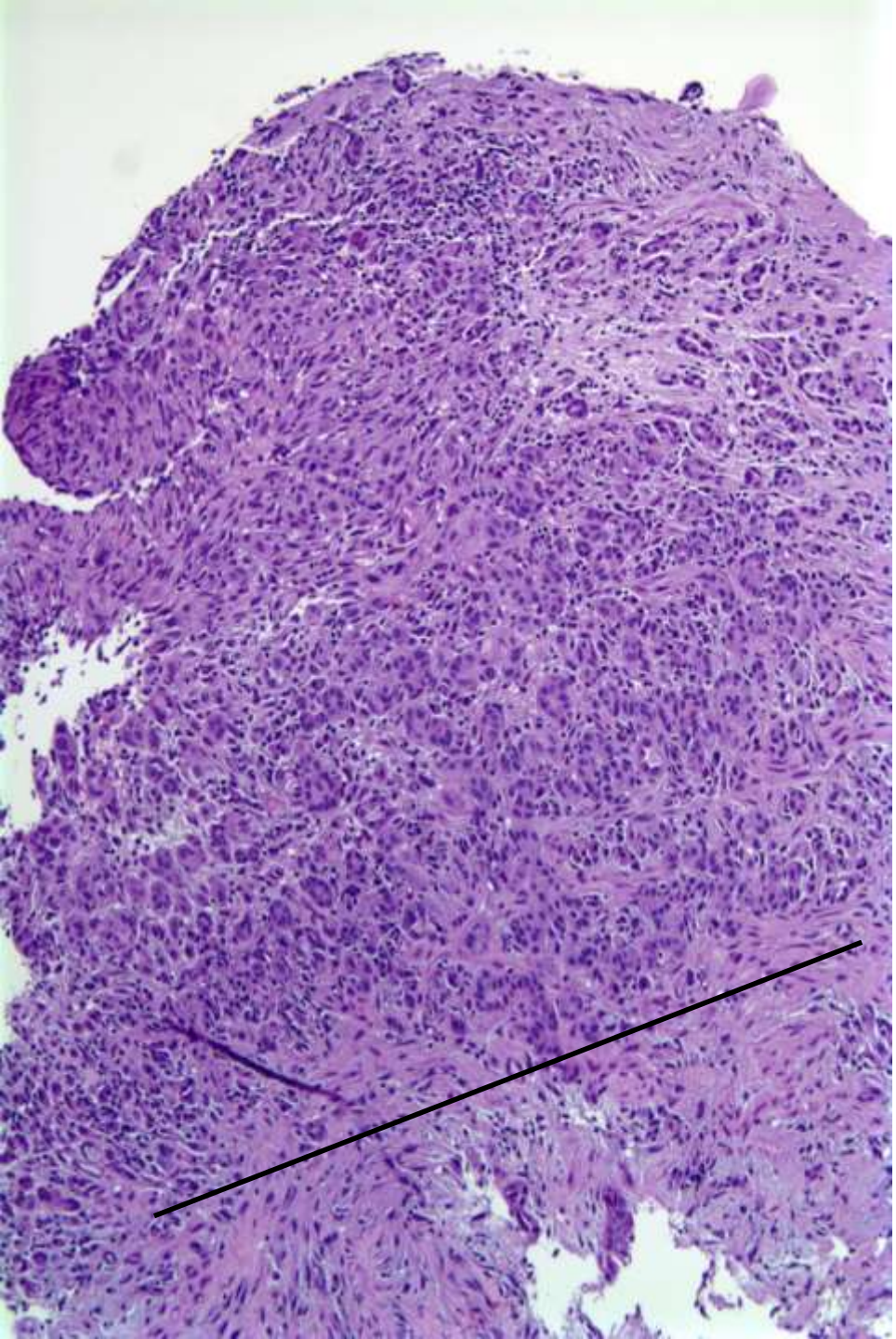
- Nested Carcinoma, including large nested
- Tubular Carcinoma
- Microcystic Carcinoma

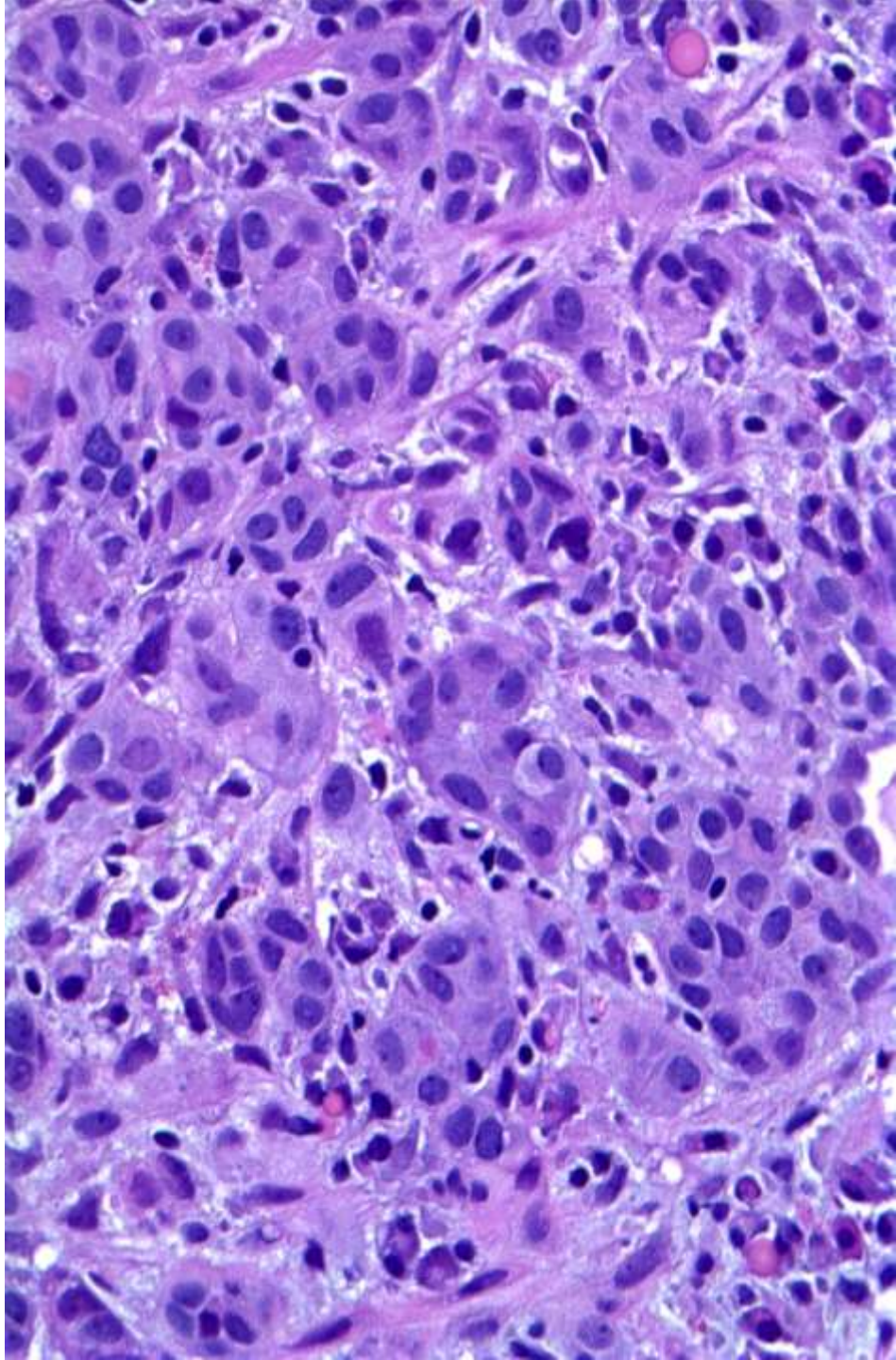
Nested Urothelial Carcinoma

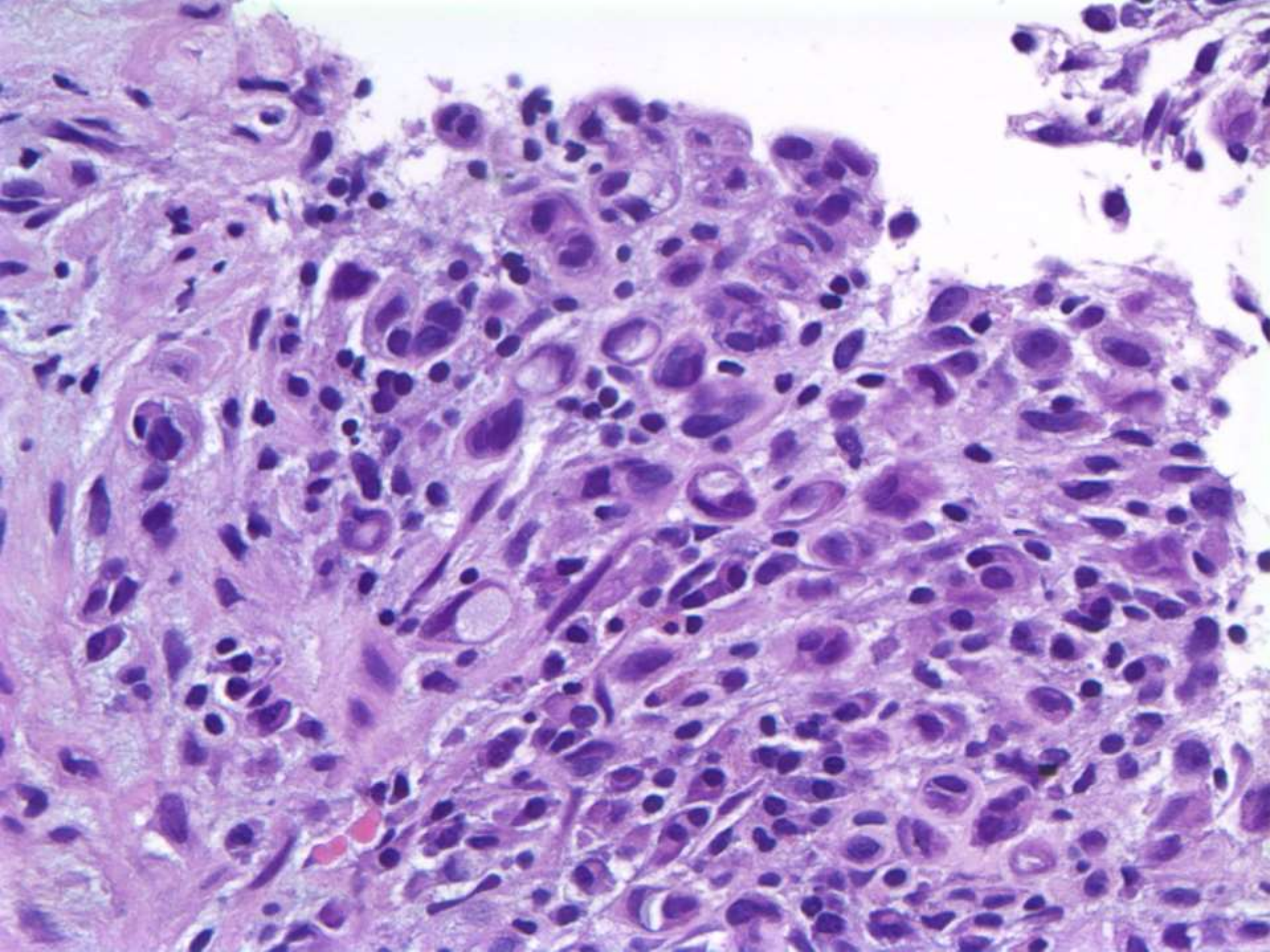
Nested Urothelial Carcinoma

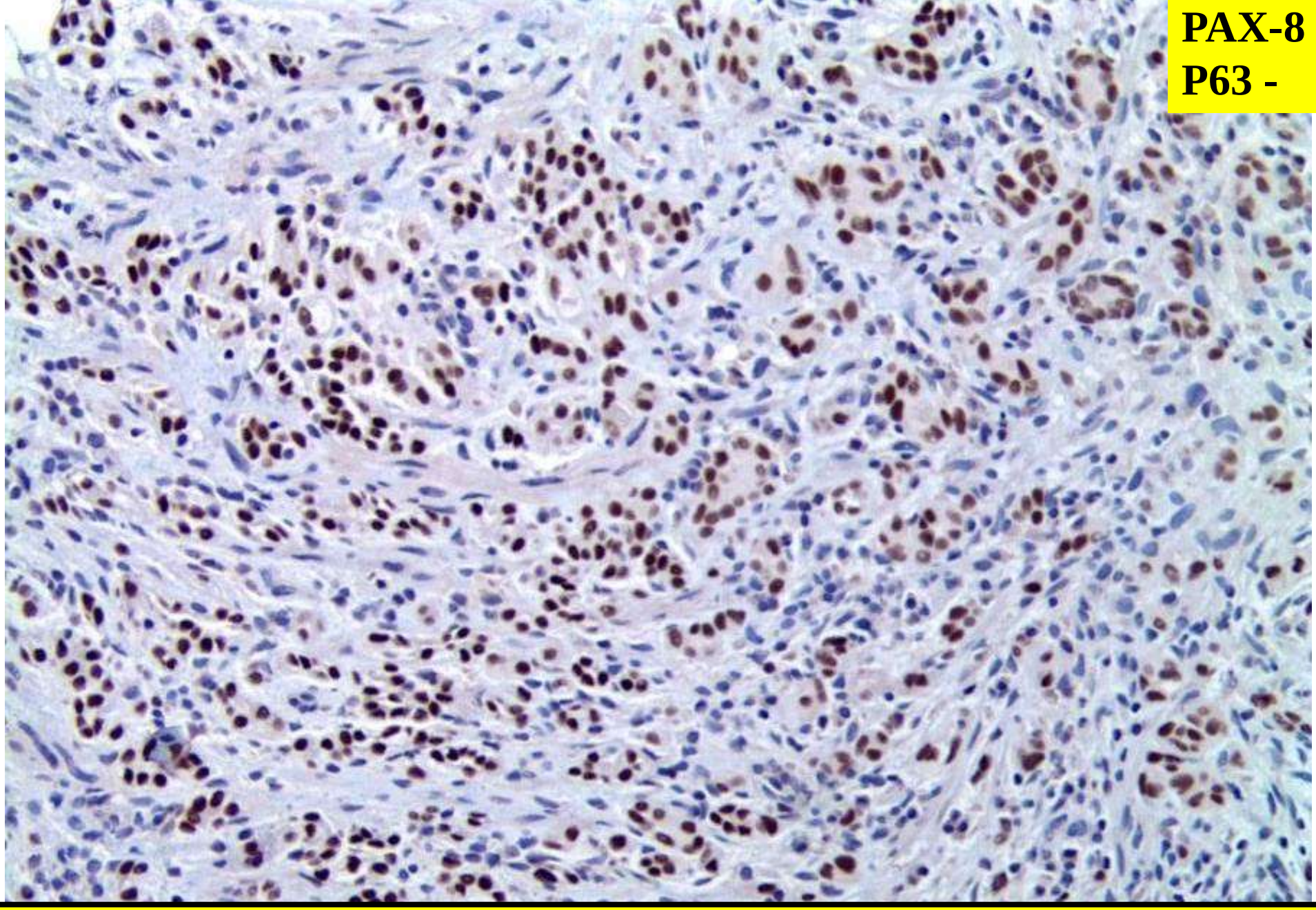
- 30 nested urothelial carcinoma
- A component of conventional UC was present in 60% of cases
- Mixture of nests, cordlike, cystitis cystica and tubular growth patterns frequently present
- Immunophenotype (CK7/20, p63, HMWCK 903) identical to usual UC
- Nested UC associated with advanced disease and metastasis, compared to pure conventional UC ($p<0.001$) regardless of whether nested UC was pure or mixed (nested with conventional components)

Wasco M, Shah RB *et al*, *Hum Pathol*, 41(2): 163-71









Nephrogenic Adenoma with Nested Features

“Deceptively Bland” Carcinomas

- **Differential Diagnosis**
  - Proliferative Von Brunn nests
  - Nephrogenic adenoma

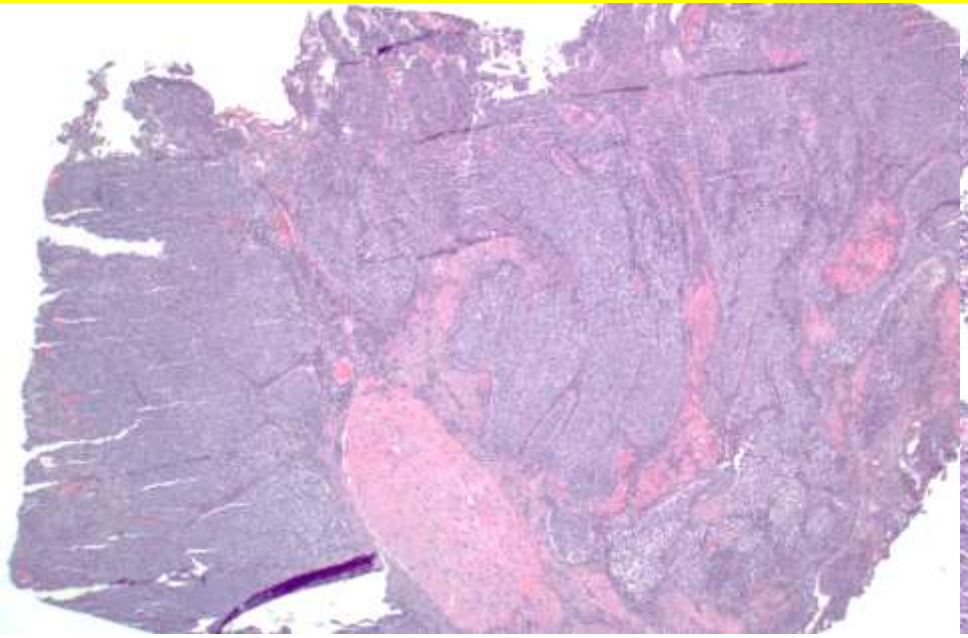
Disorderly/Haphazard proliferation of nests in superficial biopsy should prompt one to consider Nested carcinoma

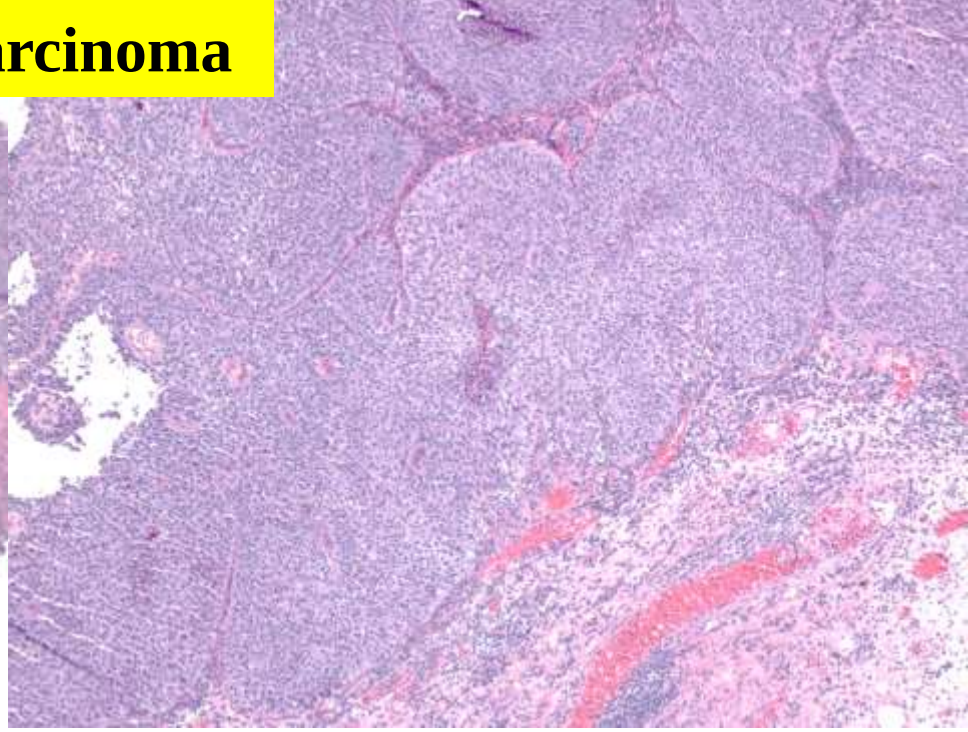
Large Nested urothelial carcinoma

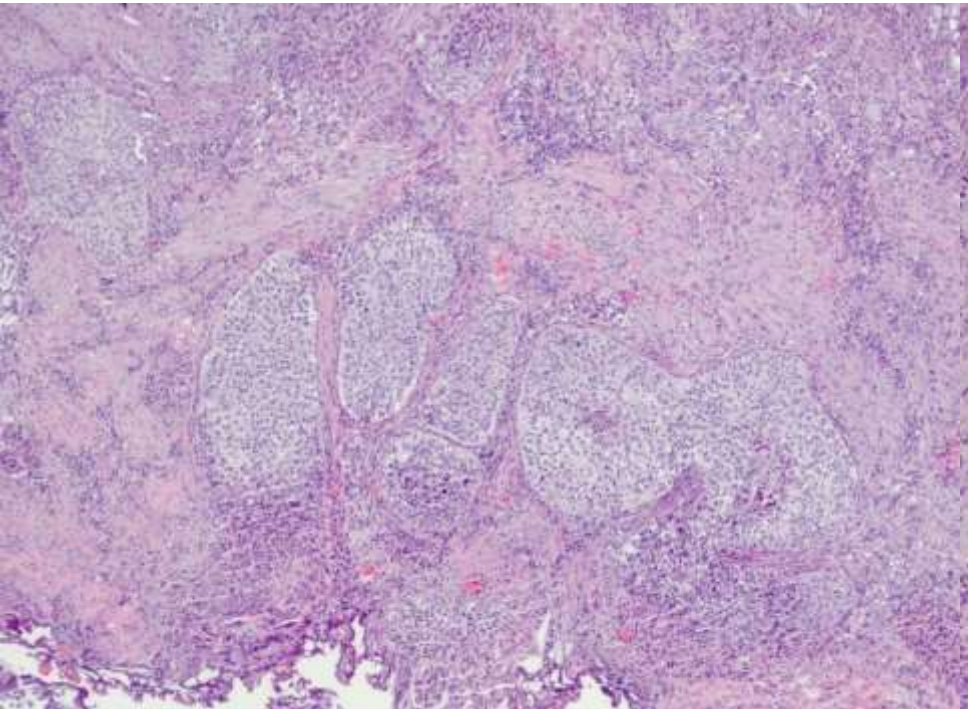
D/D: Non-invasive urothelial carcinoma with prominent inverted growth pattern

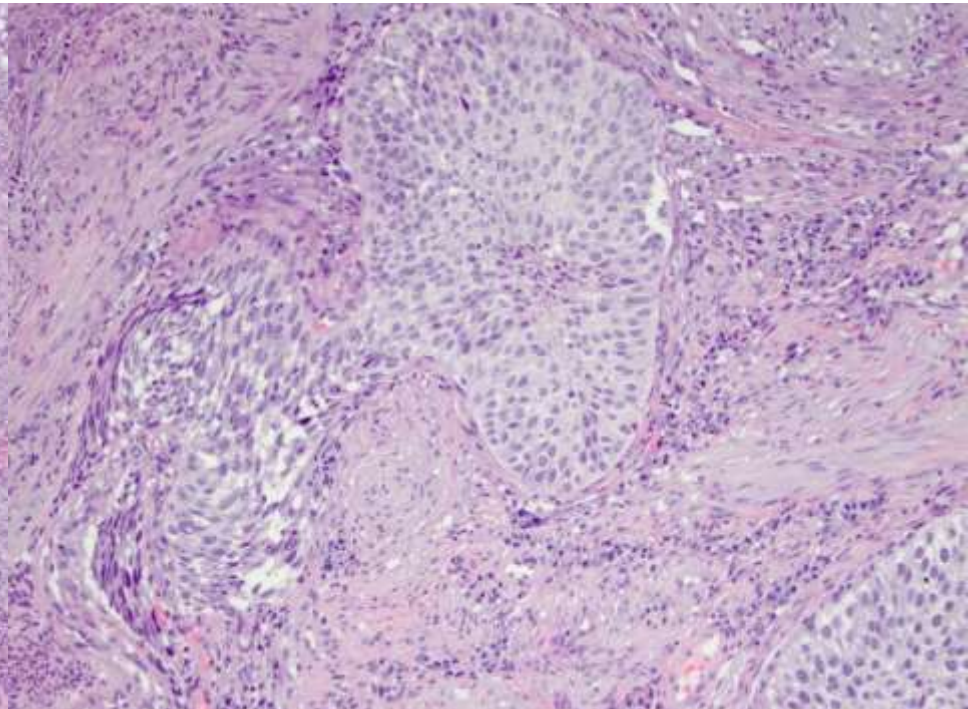
- Muscularis propria invasion
- Irregularly infiltrating nests
- Stromal reaction

Case 4: Large Nested urothelial carcinoma





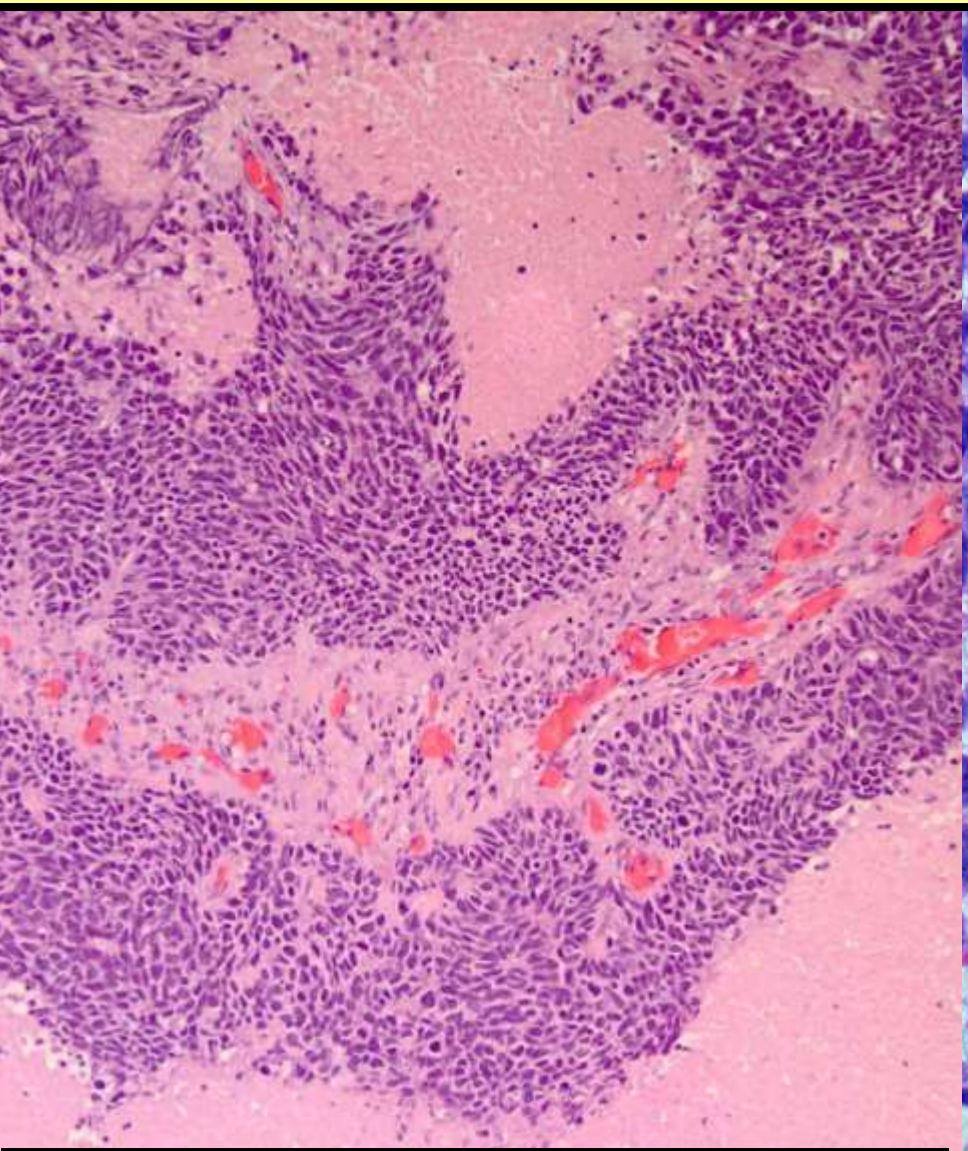




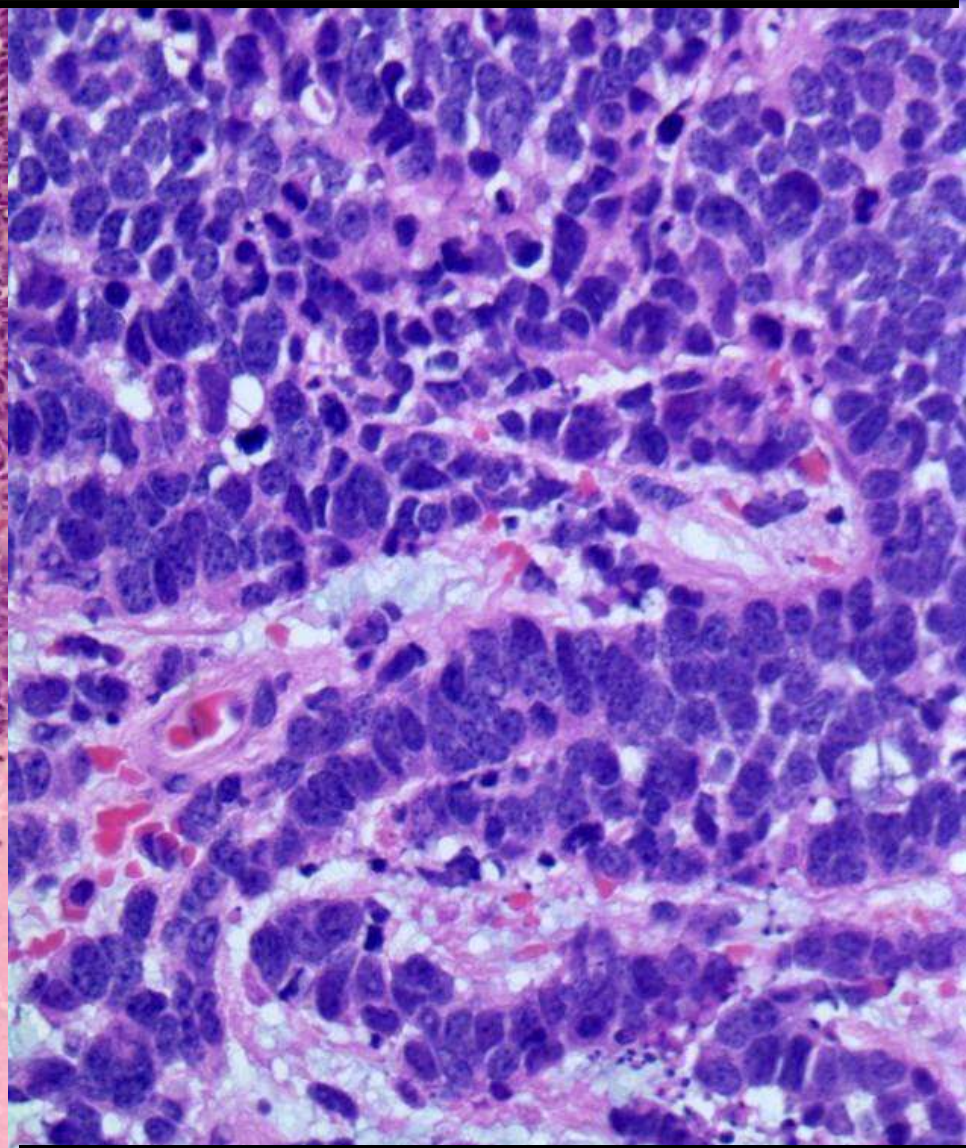
Neuroendocrine Tumors

- Well-differentiated NE neoplasm (Carcinoid)
- Small Cell Carcinoma
- Large Cell NE Carcinoma

Pure Small Cell Carcinoma



Sheets/Nests of cells with scant cytoplasm and high N:C ratio



Chromatin finely stippled; inconspicuous nucleoli

Small cell carcinoma

- Male predisposition 5:1
- Conventional urothelial component common (50%)
- Chromogranin/Synaptophysin positivity >60%
- CD56 is the most sensitive marker
- Dot-like positivity for cytokeratin
- TTF1 positive ~40%
- High Ki-67 index (>80%)
- Systemic disease with 5 year survival of 8 to 40%
- Tumor responds to platinium based chemotherapy

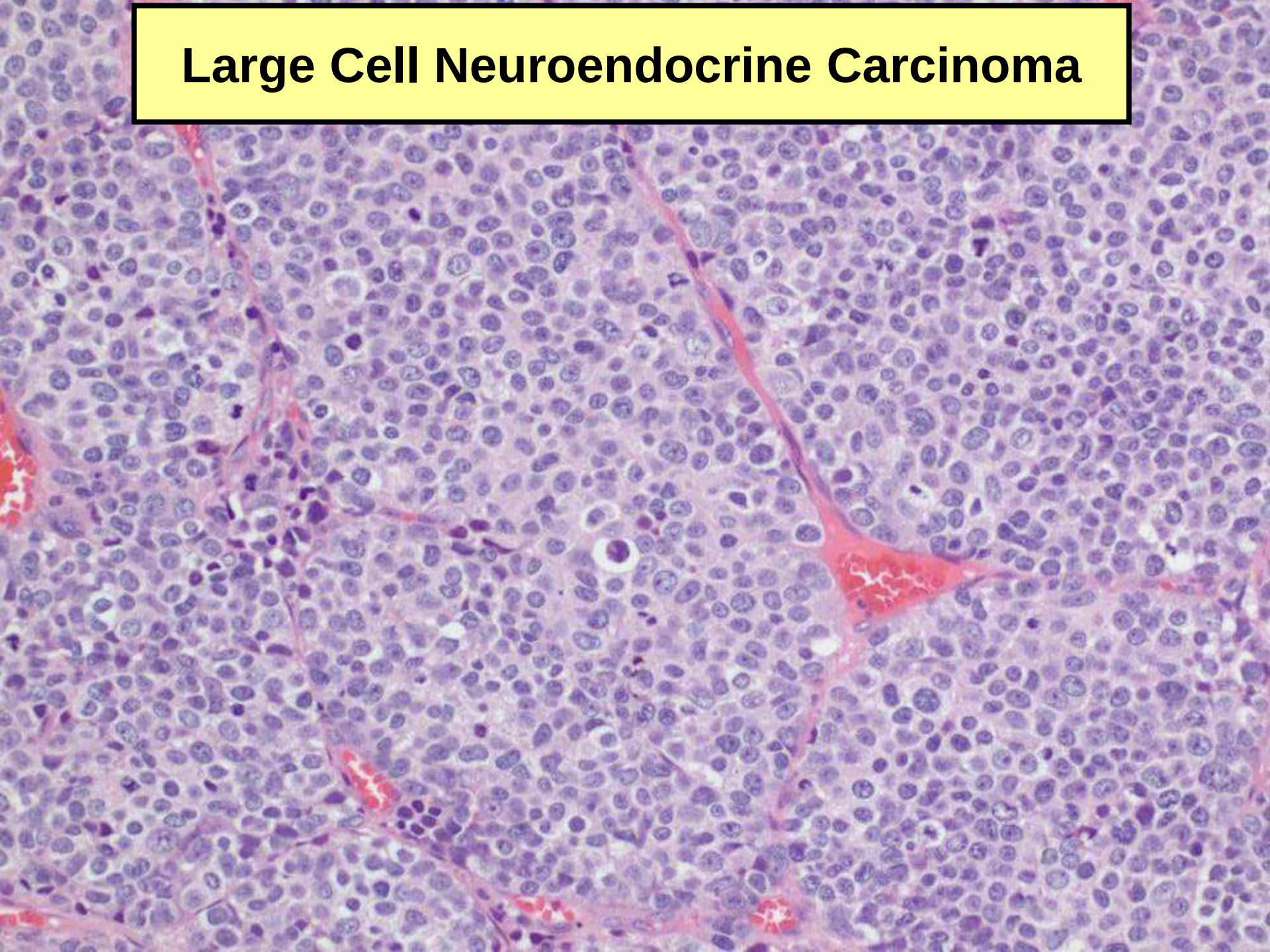
Small cell carcinoma

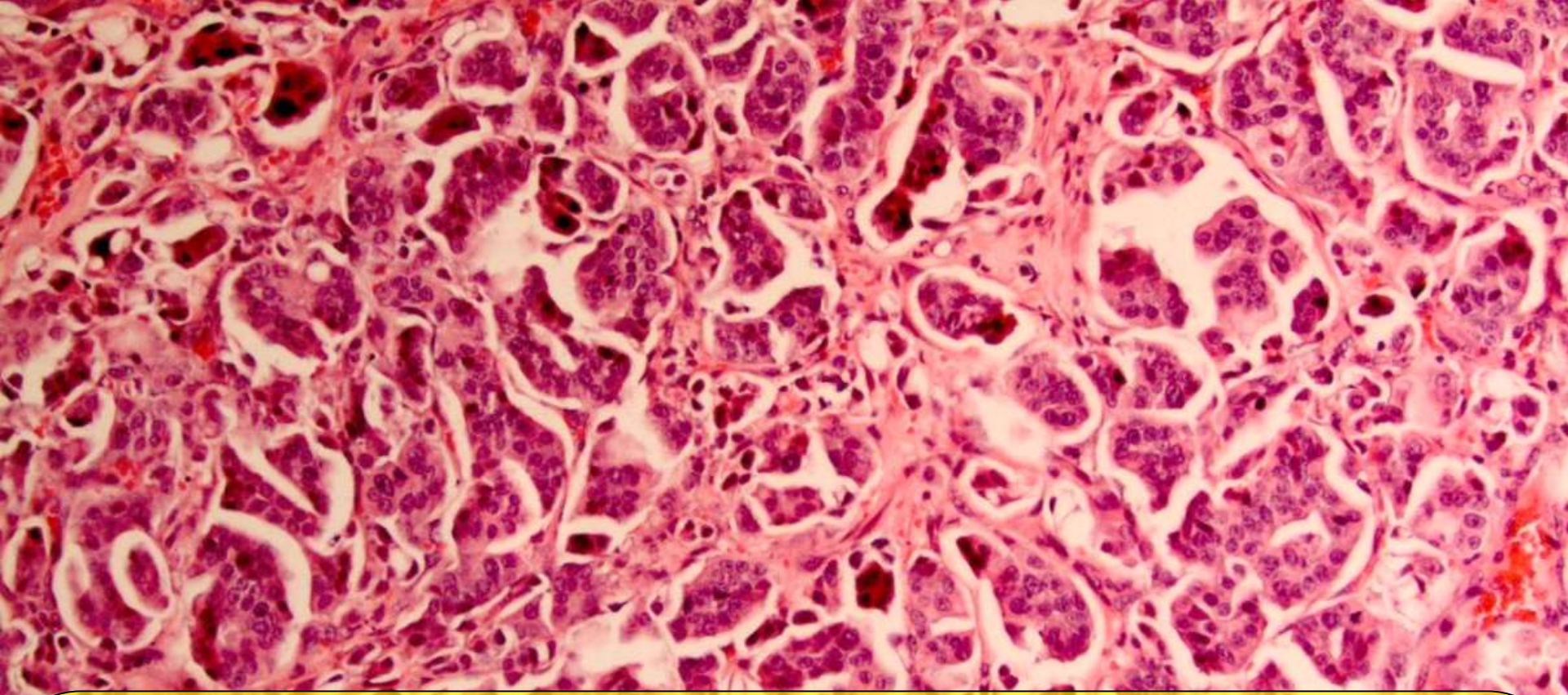
D/D:

- Poorly differentiated carcinoma
- High grade lymphoma
- Solid alveolar rhabdomyosarcoma

! Important to rule out these differentials in absence of positivity for neuroendocrine markers

Large Cell Neuroendocrine Carcinoma





"Slender, delicate filiform processes or tight papillary clusters reminiscent of papillary serous carcinoma of ovary"

Male predominance

Tumors with similar morphology described at other sites

Conventional Treatment Approach

- Several published studies independently reported high stage presentation with frequent nodal metastasis
- On TURBT
  - If: pT1 (no invasion of muscularis propria) with Micropapillary morphology, re-staging biopsies performed with intravesical BCG therapy

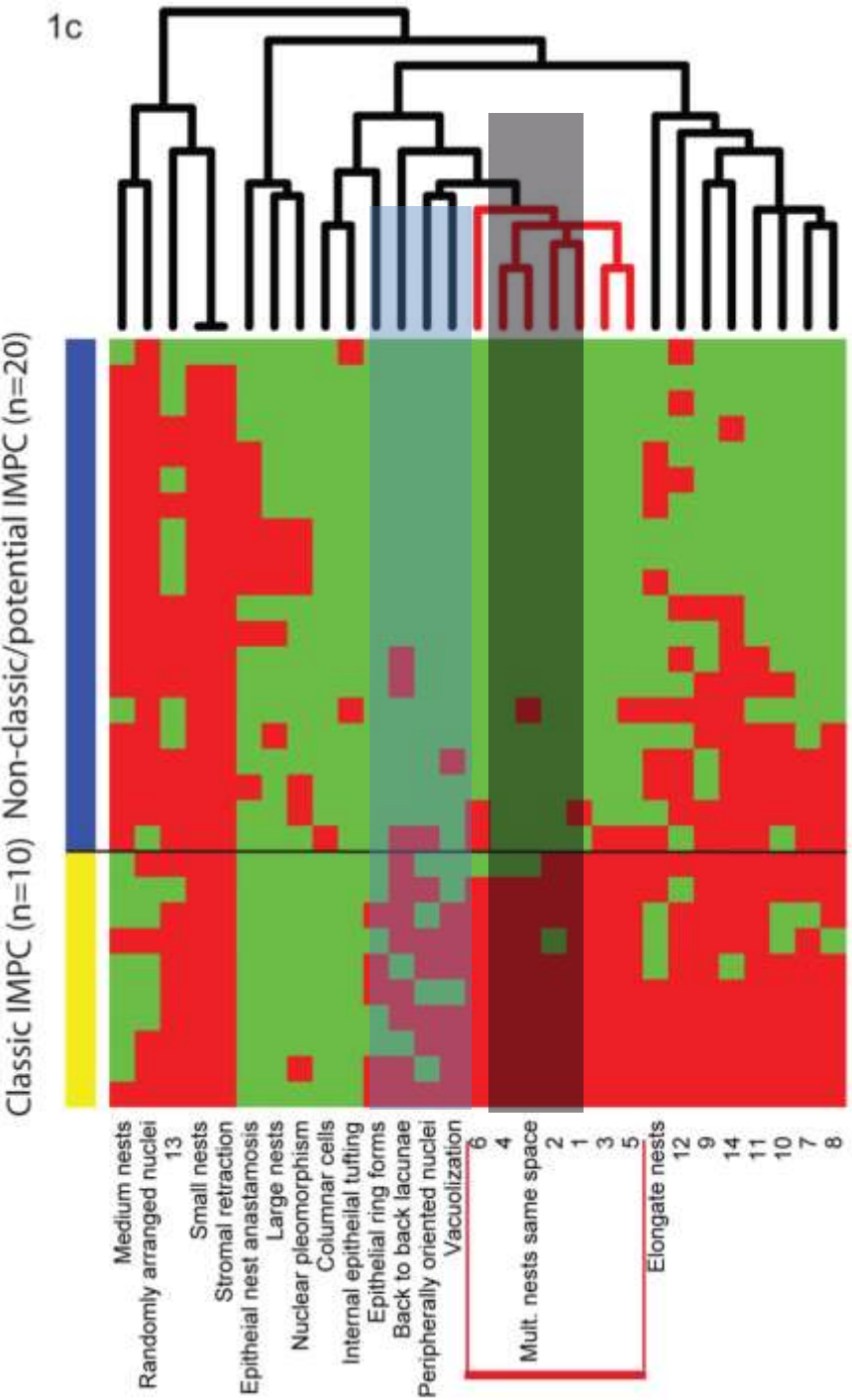
J Urol 2006; 175: 881-885

The Case for Early Cystectomy in the Treatment of Nonmuscle Invasive Micropapillary Bladder Carcinoma

Ashish M. Kamat,*,† Jason R. Gee,‡ Colin P. N. Dinney,§ H. Barton Grossman,‖ David A. Swanson,¶ Randall E. Millikan, Michelle A. Detry,‡ Tracy L. Robinson‡ and Louis L. Pisters††**

From the Departments of Urology (AMK, JRG, CPND, HBG, DAS, TLR, LLP), Genitourinary Medical Oncology (REM), and Biostatistics and Applied Mathematics (MAD), The University of Texas M. D. Anderson Cancer Center, Houston, Texas

- 44 nonmuscle invasive Micropapillary carcinoma
- Not responsive to intravesical BCG therapy
- Surgery offered the best chance of cure
- Some US centers treat T1 micropapillary urothelial carcinomas aggressively with cystectomy
- For pathologists strict diagnostic criteria warranted to avoid over interpretation



Interobserver Reproducibility Study of Micropapillary carcinoma:

Sangoi et al, AJSP 2010

- Overall agreement
  - Moderate (kappa: 0.54)
- 10 “classic” MP cases
  - 93% [130 of 140: 10 cases x 14 reviewers] diagnosed as micropapillary
- 20 “non-classic” MP cases
  - Marked variability

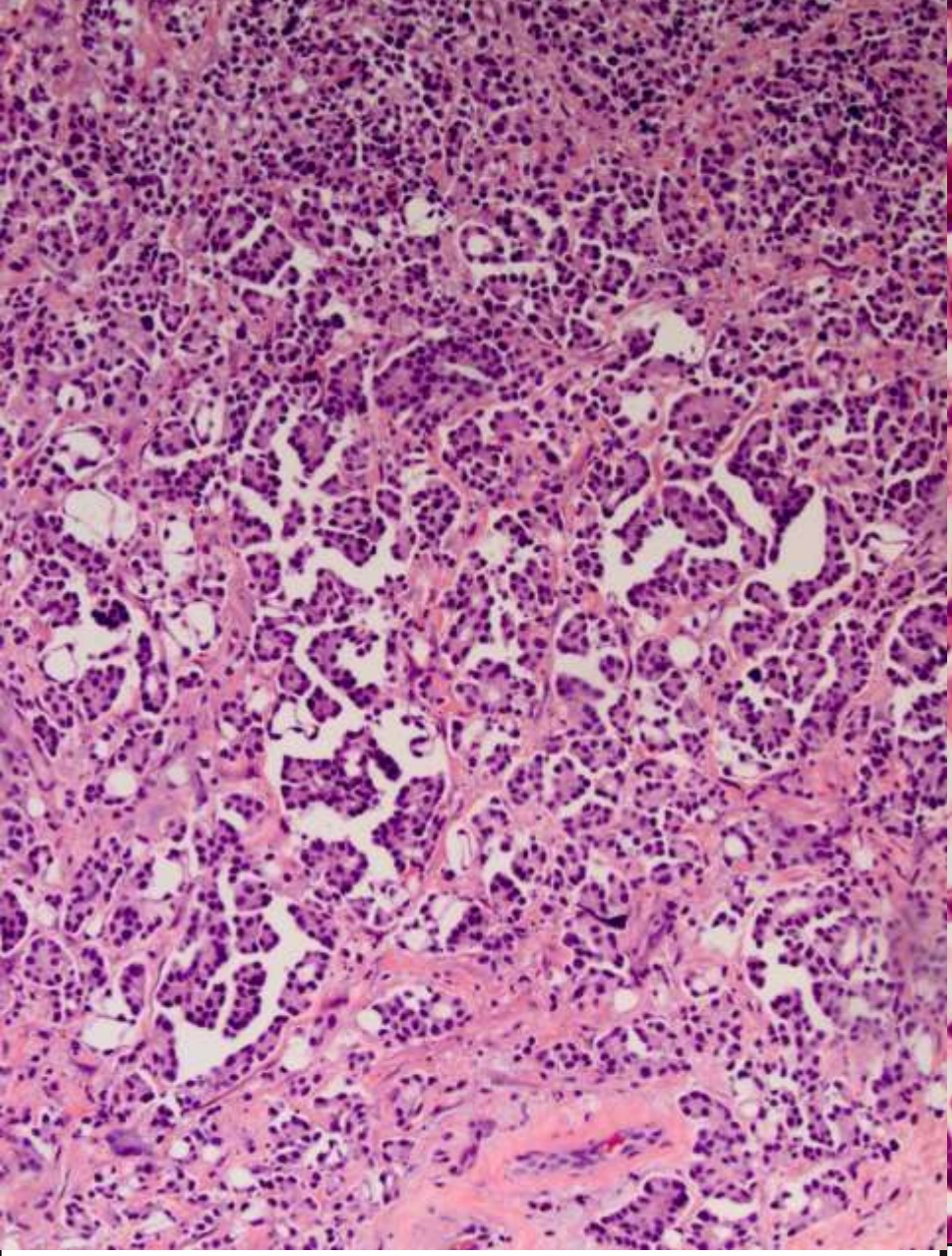
Recommended Restricted Criteria

Major feature

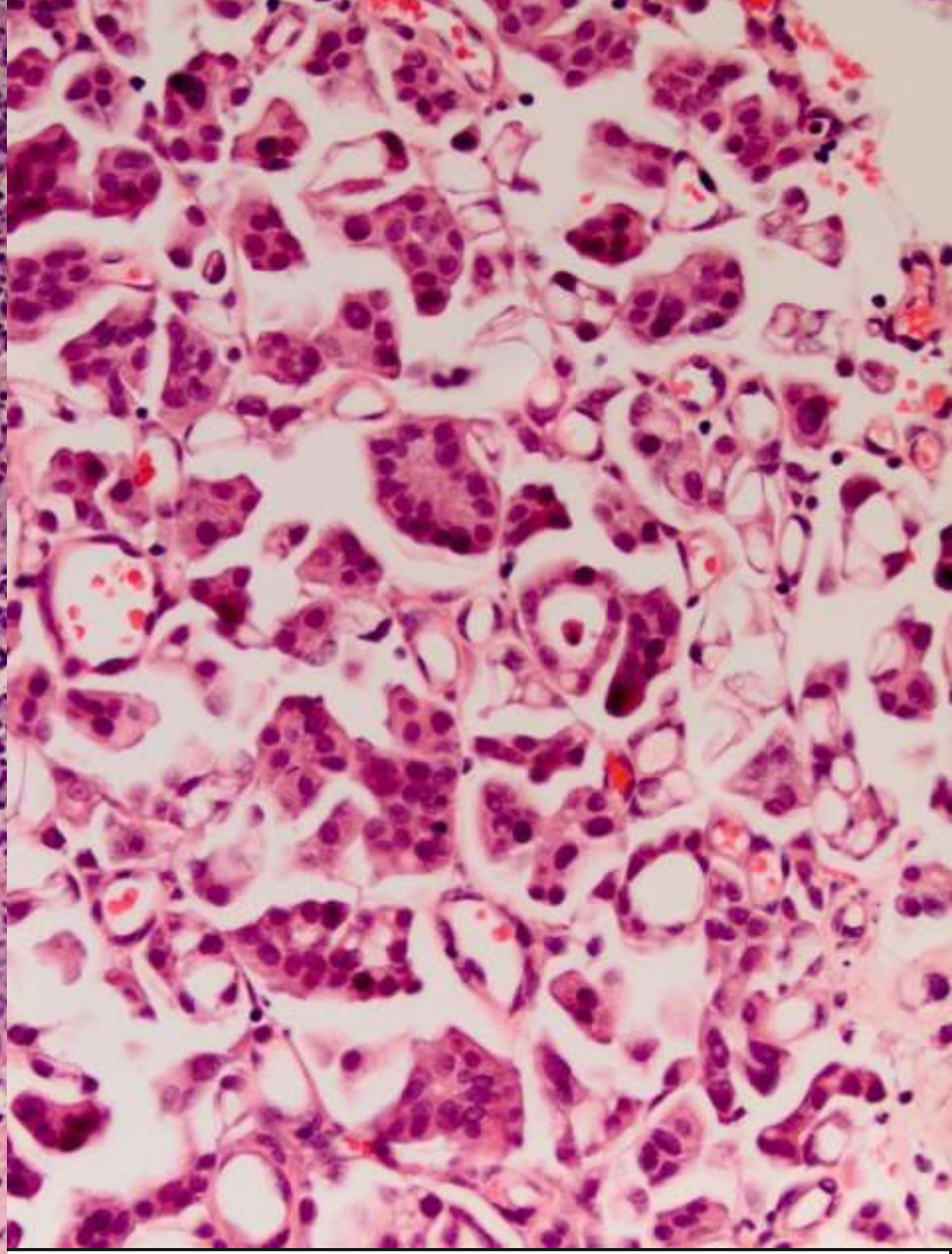
- Multiple small nests in same lacunar space

Frequently seen features

- Epithelial ring forms
- Back to back lacunae
- Peripheral nuclei
- Cytoplasmic vacuolization

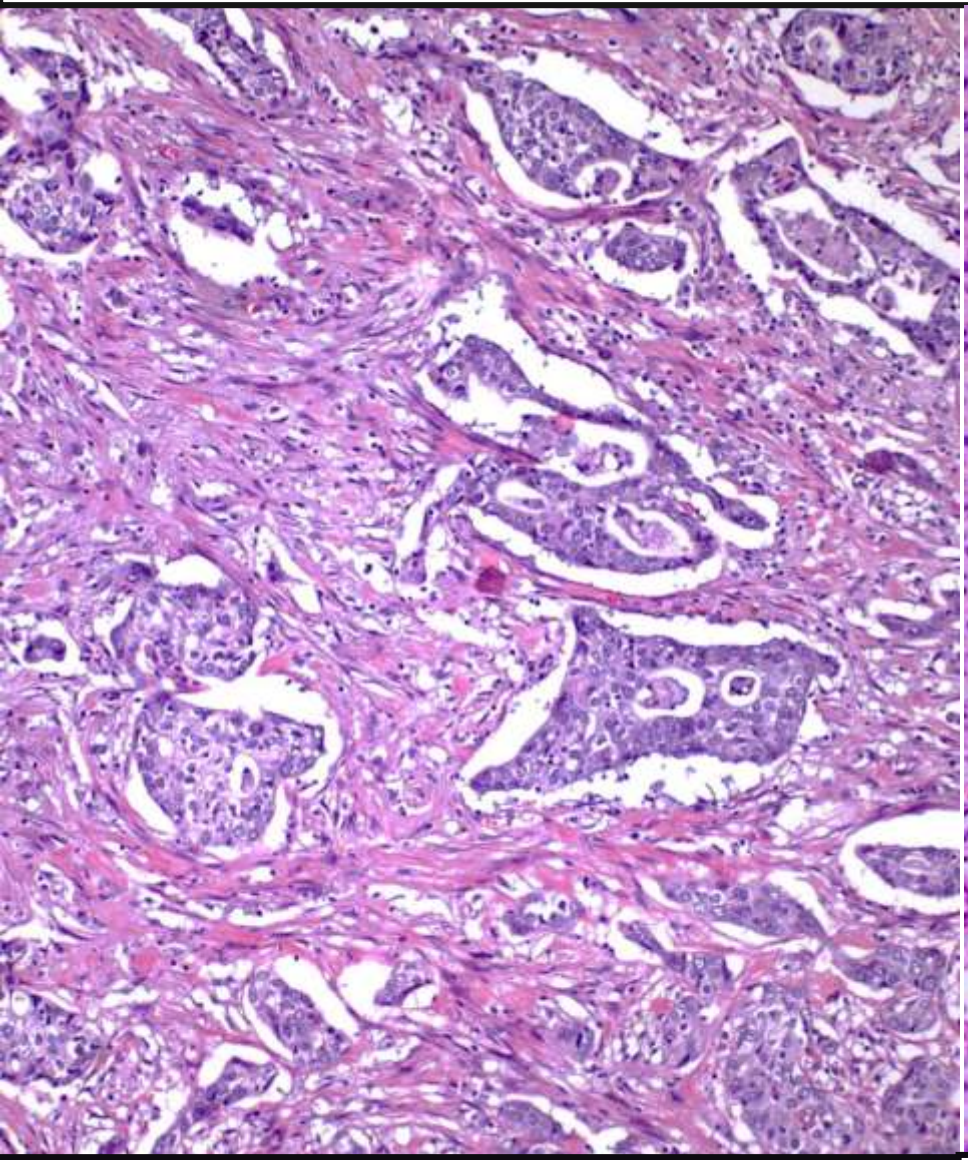


Multiple nests in same lacunar space

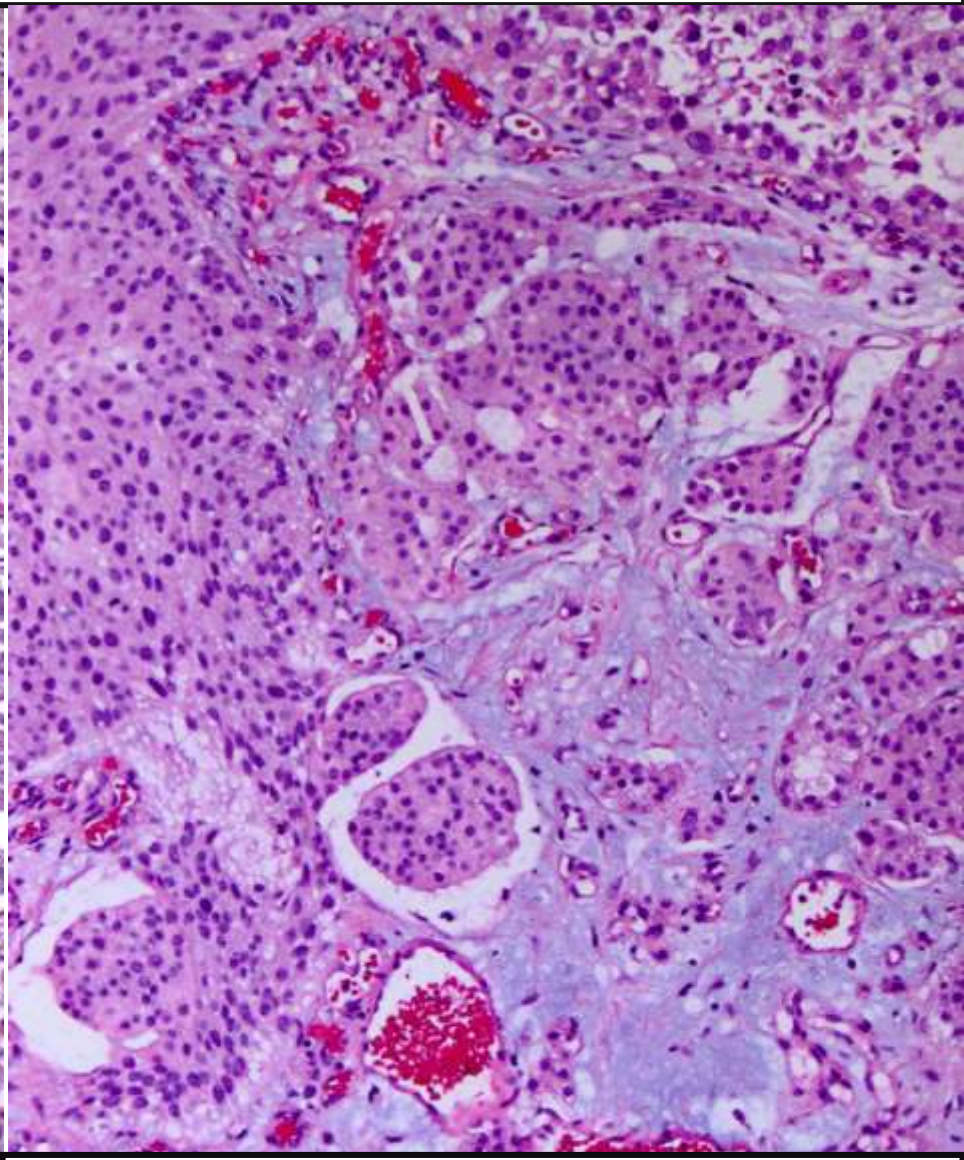


Epithelial ring forms and back-to-back lacunae

NOT Micropapillary

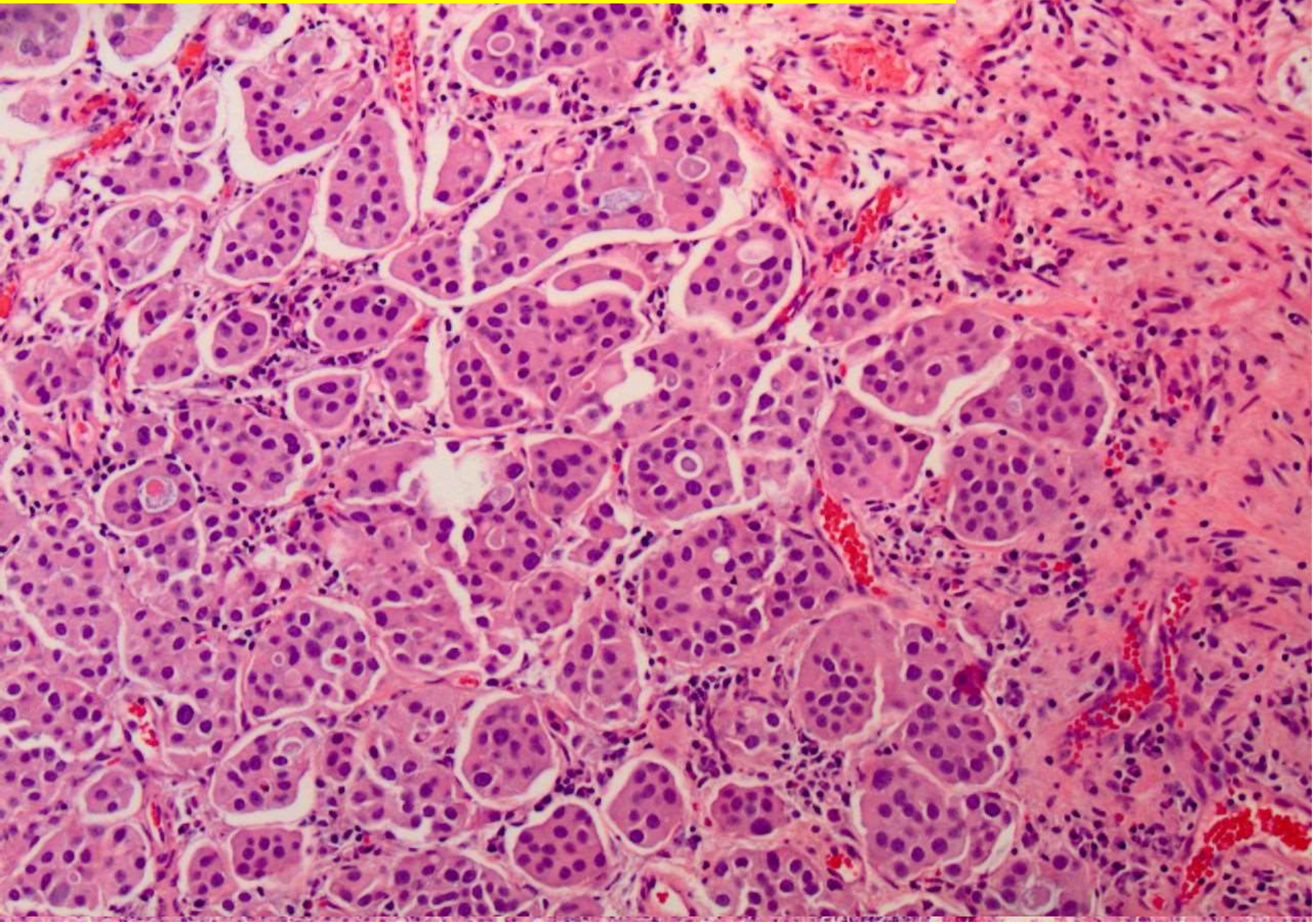


Large nests (> 5 cells across narrowest width)

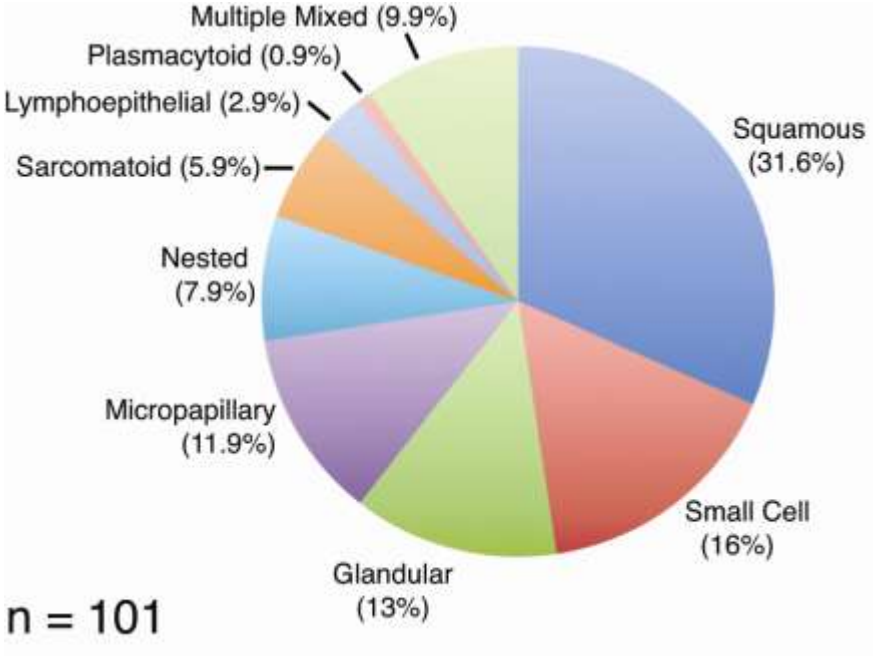


Epithelial confluence and branching

Case 2: Invasive high-grade urothelial carcinoma



Variant histologic differentiation in urothelial carcinoma (UC) is under-recognized in community practice: Impact of mandatory central pathology review



- Variant histologic differentiation was not reported by the referring institution in 44% of cases with variant histology at central review, of which 47% were extensive
- Increased awareness required

Shah RB *et al*, Urologic Oncology: Seminars and Original Investigations, 2012

WHO Classification of Non-invasive Urothelial Neoplasias: Differences between the 3rd and 4th editions

Third edition

Noninvasive urothelial neoplasias

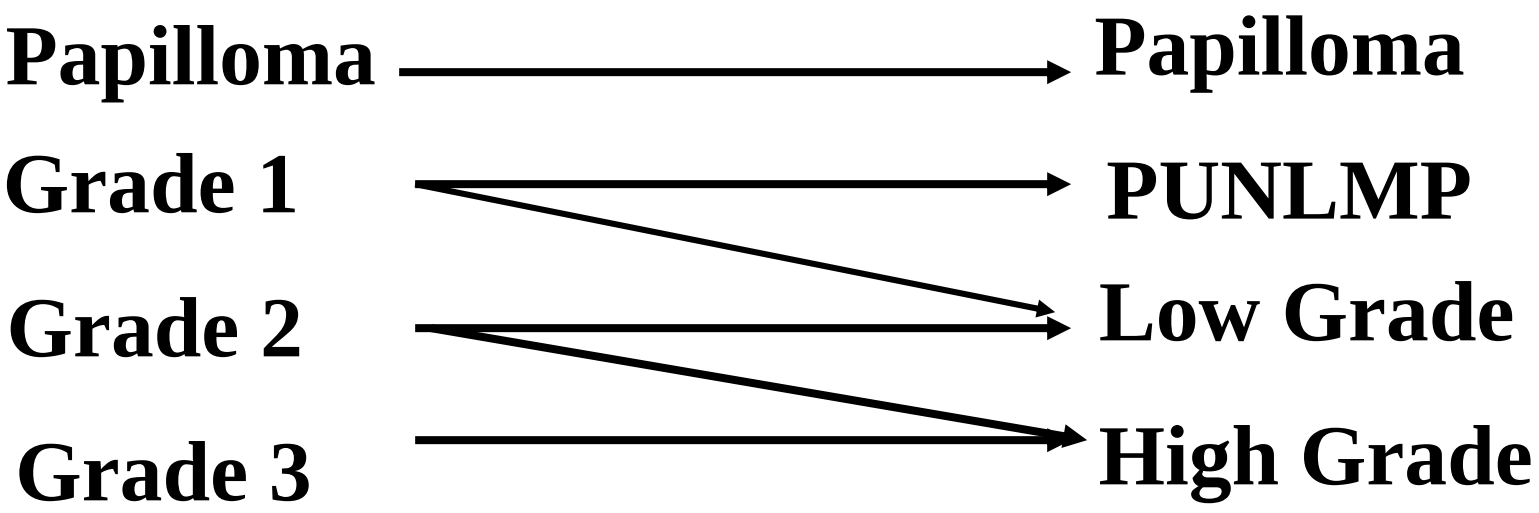
- Urothelial carcinoma in situ
- Papillary urothelial carcinoma, low grade
- Papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma

Fourth edition

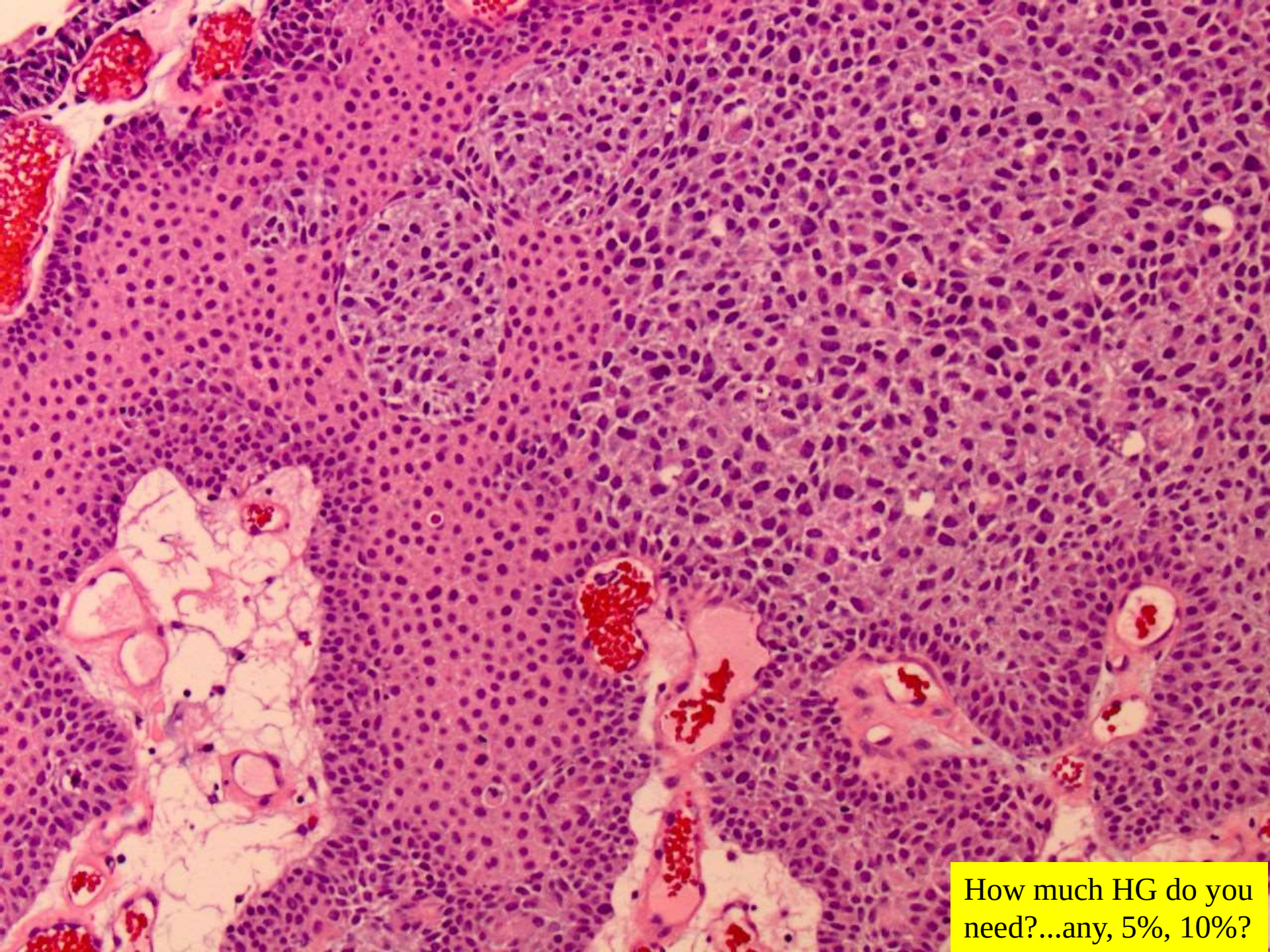
Noninvasive urothelial neoplasias

- Urothelial carcinoma in situ
- Papillary urothelial carcinoma, low grade
- Papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
- **Urothelial proliferation of uncertain malignant potential (hyperplasia)**
- **Urothelial dysplasia**

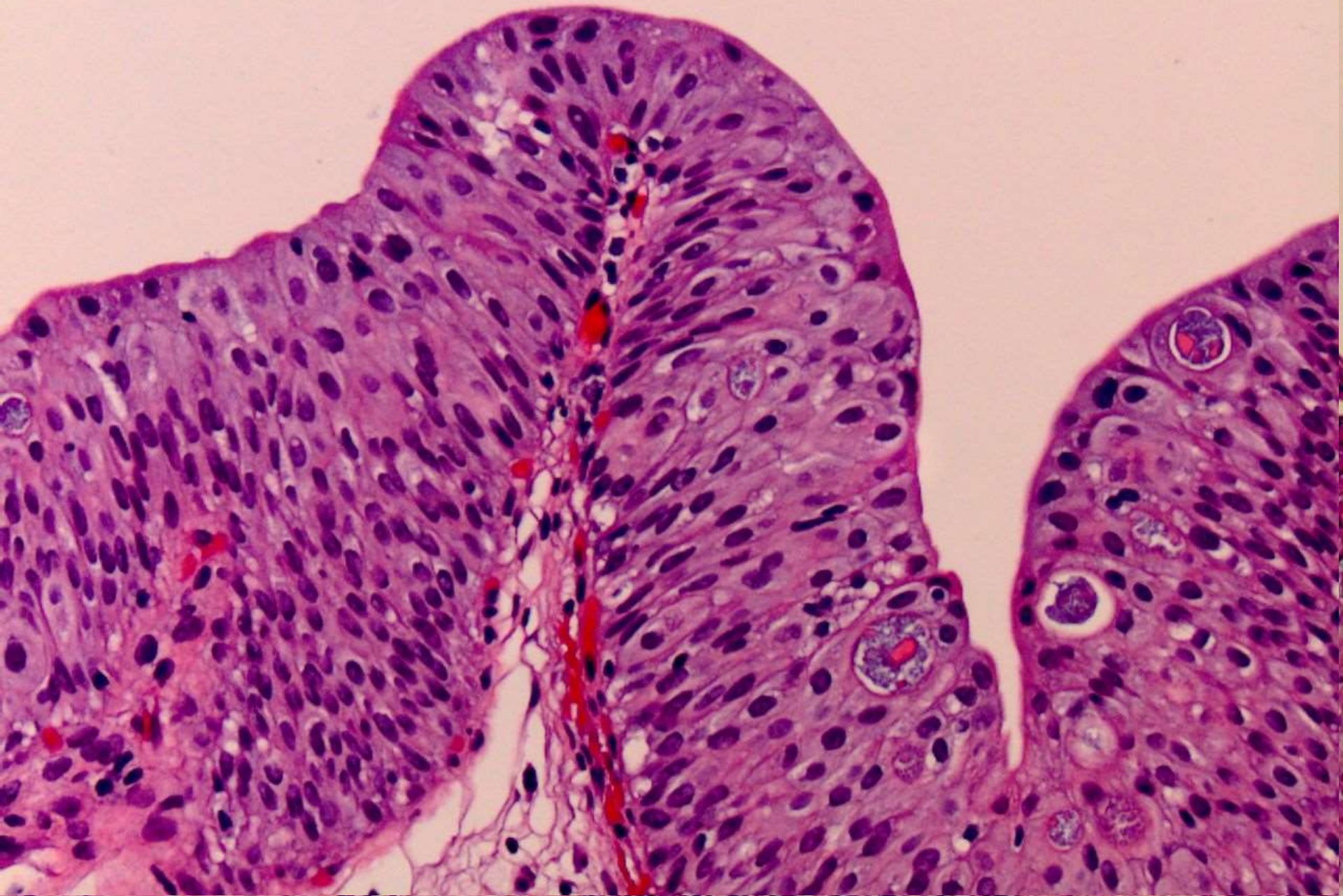
Histological Comparison of Grading Systems for Papillary Urothelial Tumors



- Eliminates Grade 1 UCC category which is not cancer
- Better stratifies high grade UCC for intravesical BCG
- Removes ambiguity of 5 grades by pathologists:
  Grade 1, 1-2 (?), 2, 2-3 (?), 3
- Higher % classified High grade


How much HG do you need?...any, 5%, 10%?

Tent-shaped broader folds, lack of well defined delicate fibrovascular cores, Hyperplastic epithelium but benign cytology



PAPILLARY UROTHELIAL PROLIFERATION OF UNCERTAIN MALIGNANT POTENTIAL (UPUMP)

~~Urothelial hyperplasia~~

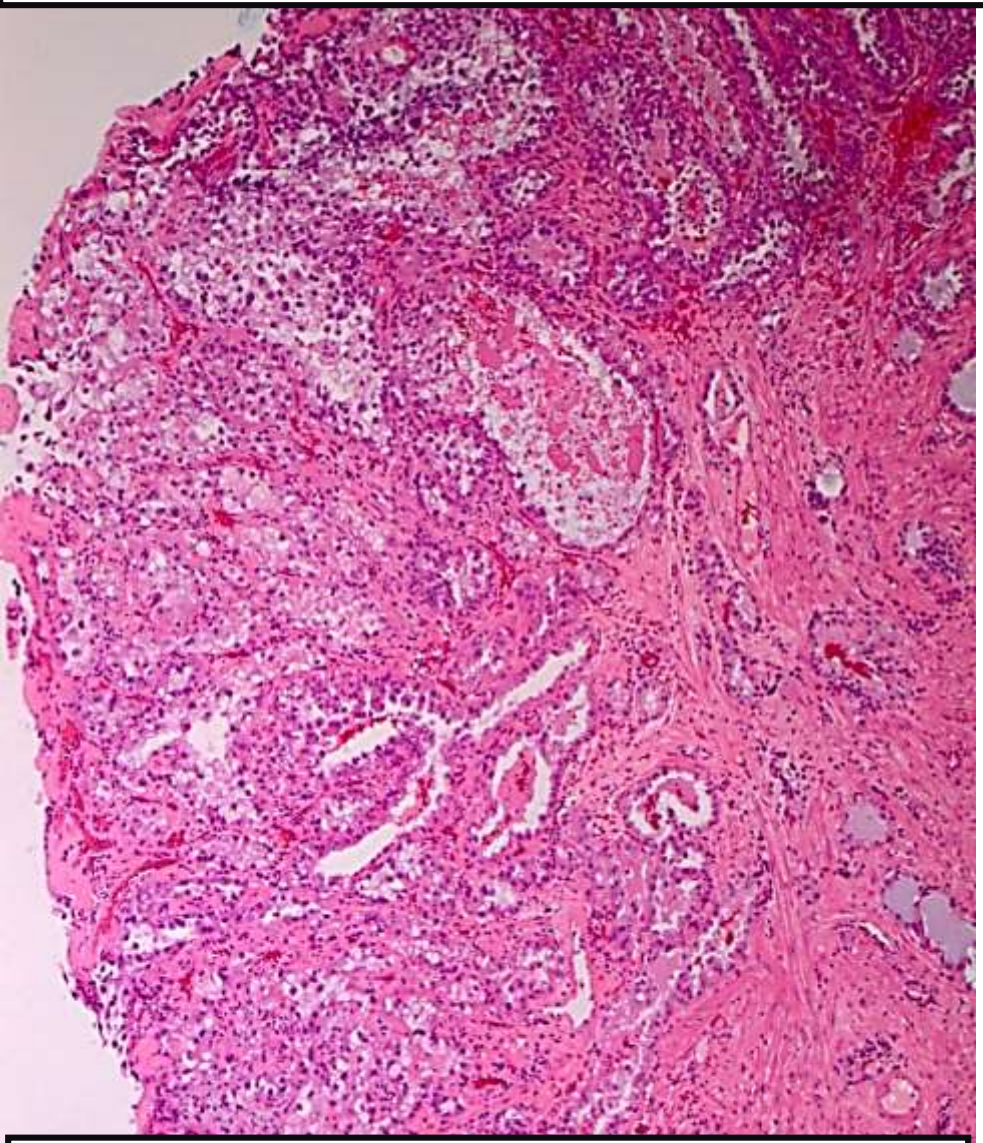
- Thickened urothelium with minimal or no cytological atypia
- Undulations but no true papillary fronds
- Most frequent in patients with history of prior carcinoma or adjacent to papillary lesions
- Likely lateral extension ("shoulder lesion") of a papillary neoplasm
- May be seen de novo and in this setting the clinical relevance unknown

  High incidence of chromosome 9 deletions and lesser but significant FGFR3 abnormality
- Potential to confuse it with PUNLMP
- Overuse/misuse must be avoided

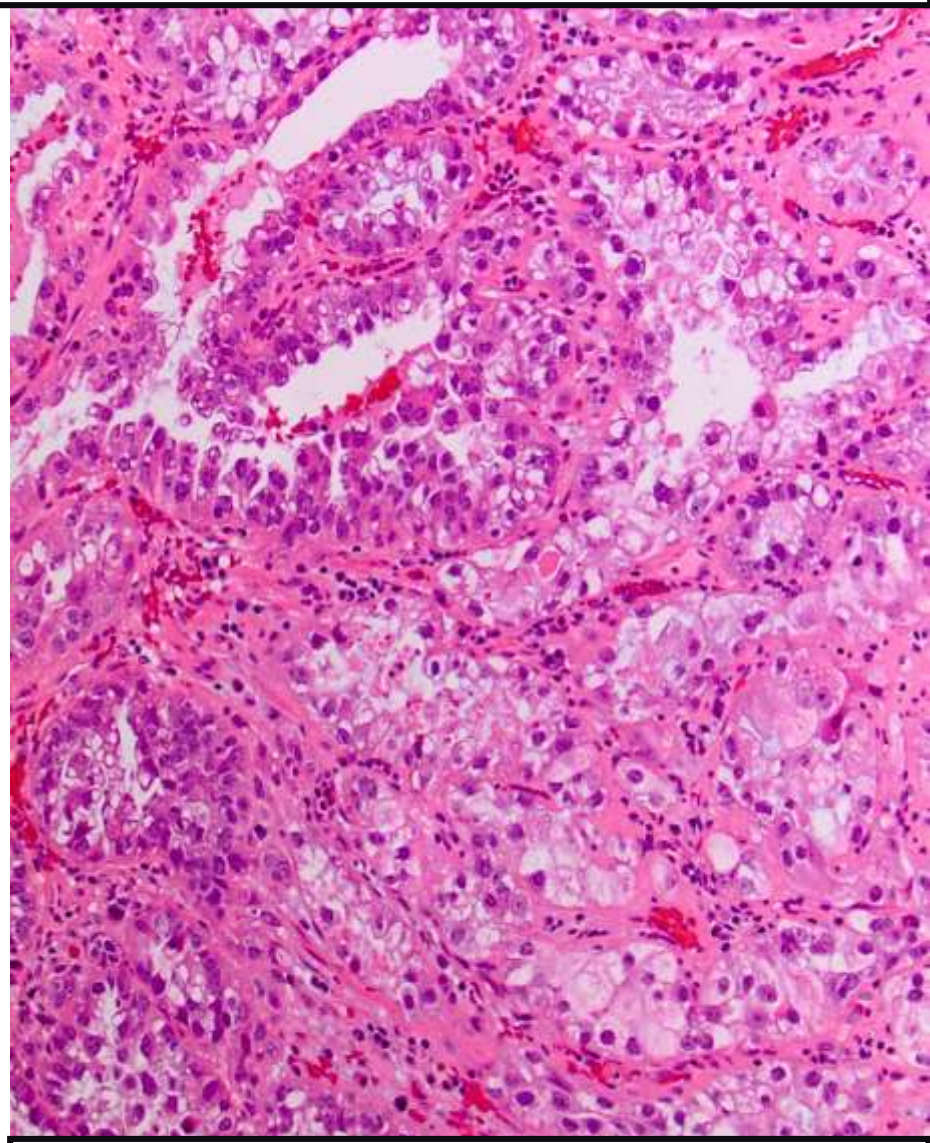
MULTIPLE FACES OF ADENOCARCINOMA OF THE UROTHELIAL TRACT

Bladder	Urachus	Mullerian
Enteric features predominate	Enteric features predominate	**Clear cell and endometrioid features predominate**
Mixed histology common	Mixed histology less common	**Mixed histology rare**
Arises from surface urothelium	Arises from Urachal epithelium	**Arises from Mullerian rests within or outside bladder**
Standard bladder staging	Staging varies depending on site of urachal involvement	Not well defined

CASE 3: CLEAR CELL ADENOCARCINOMA



Tubulocystic and papillary patterns



Clear cytoplasm, Hobnailing

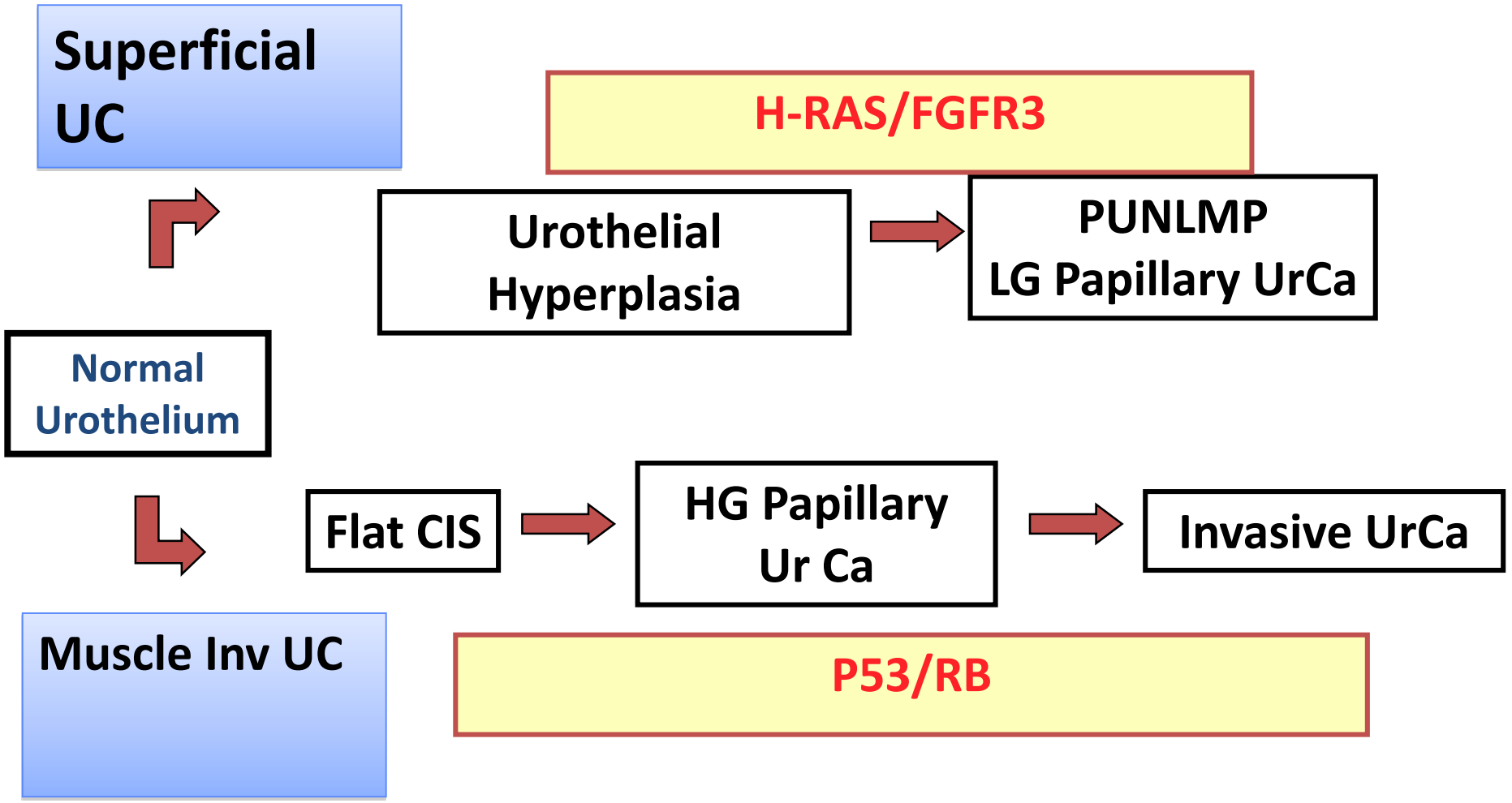
Immunohistochemical markers in D/D

	NA	Clear cell Adenoca	UCC	PCA
PAX2/8	+	+	-	-
AMACR	+	+	-/+	+
GATA3	-	-	+	-
PSA	-	-	-	+
Basal markers	-	-	+	-

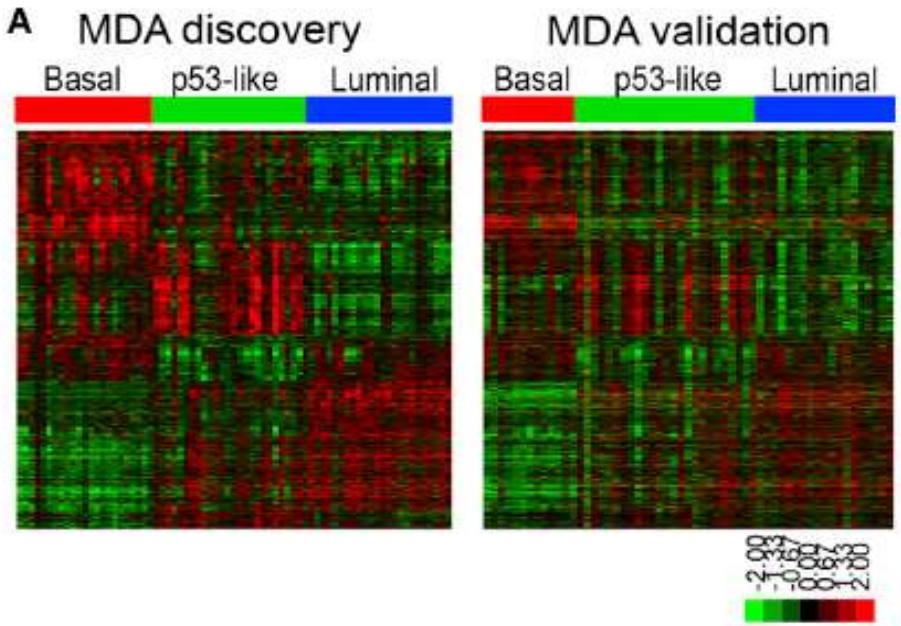
Nephrogenic adenoma; UCC=Urothelial carcinoma, PCA=prostate adenoca

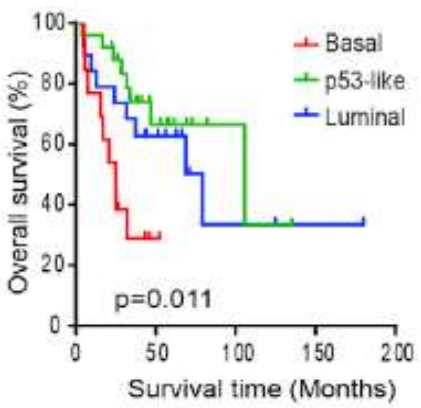
Urothelial Carcinoma

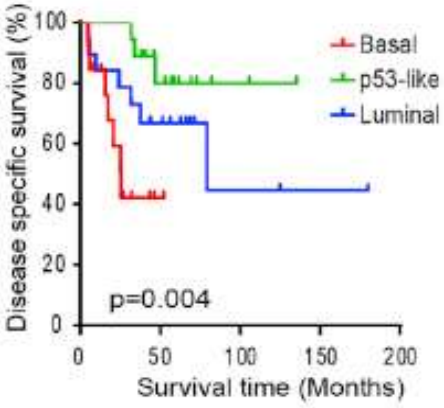
Two Divergent Molecular Pathways

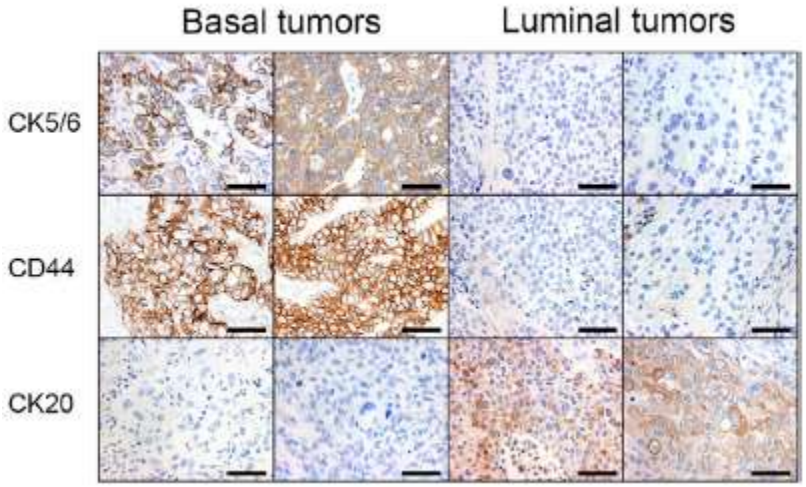


MOLECULAR CLASSIFICATION OF BLADDER CANCER









Choi et al, Cancer cell, 2014

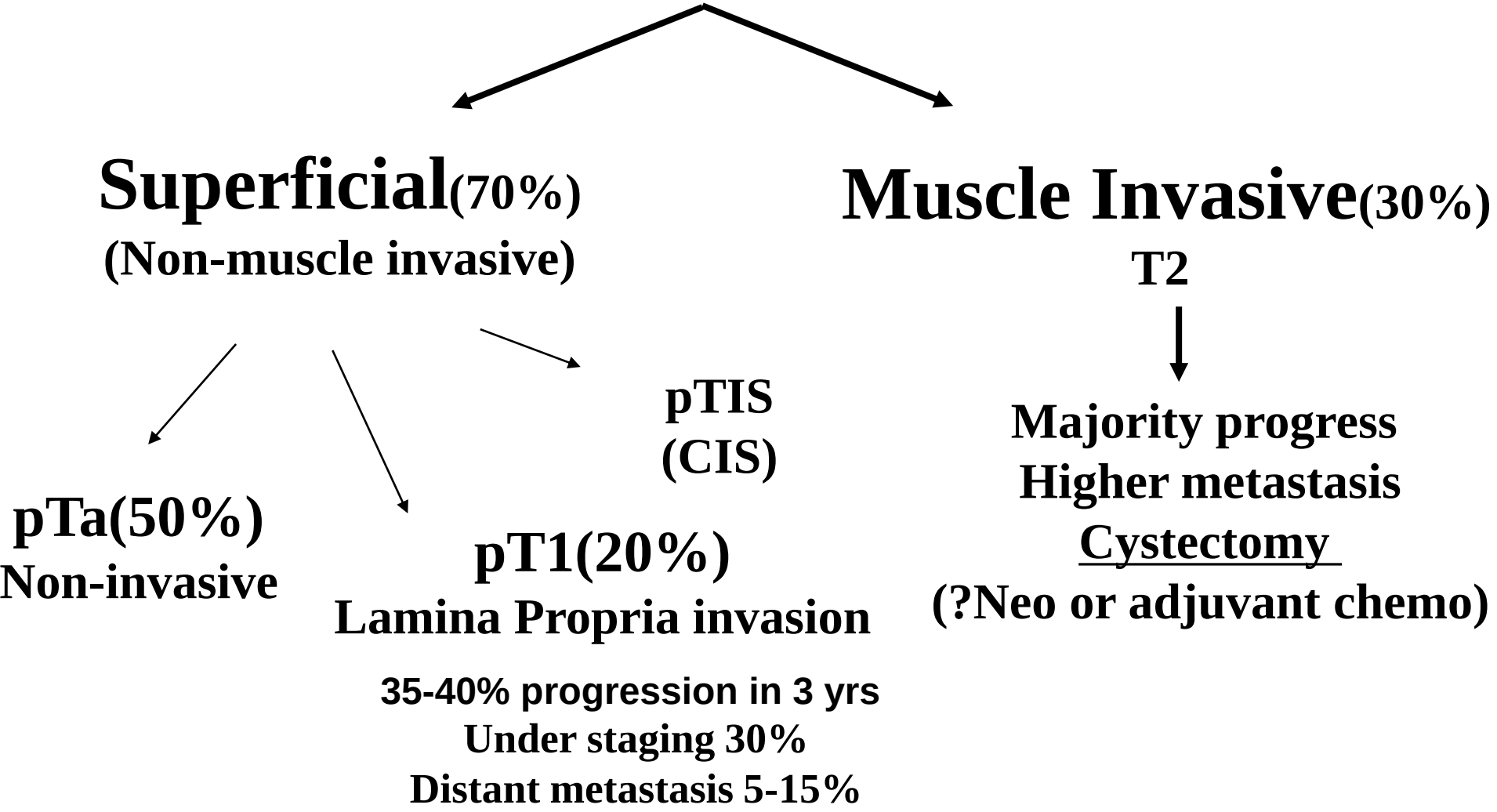
Basal type: p63 activation, squamous diff, clinically aggressive but sensitive to neoadjuvant chemotherapy

Luminal type: activating FGFR3 mutations

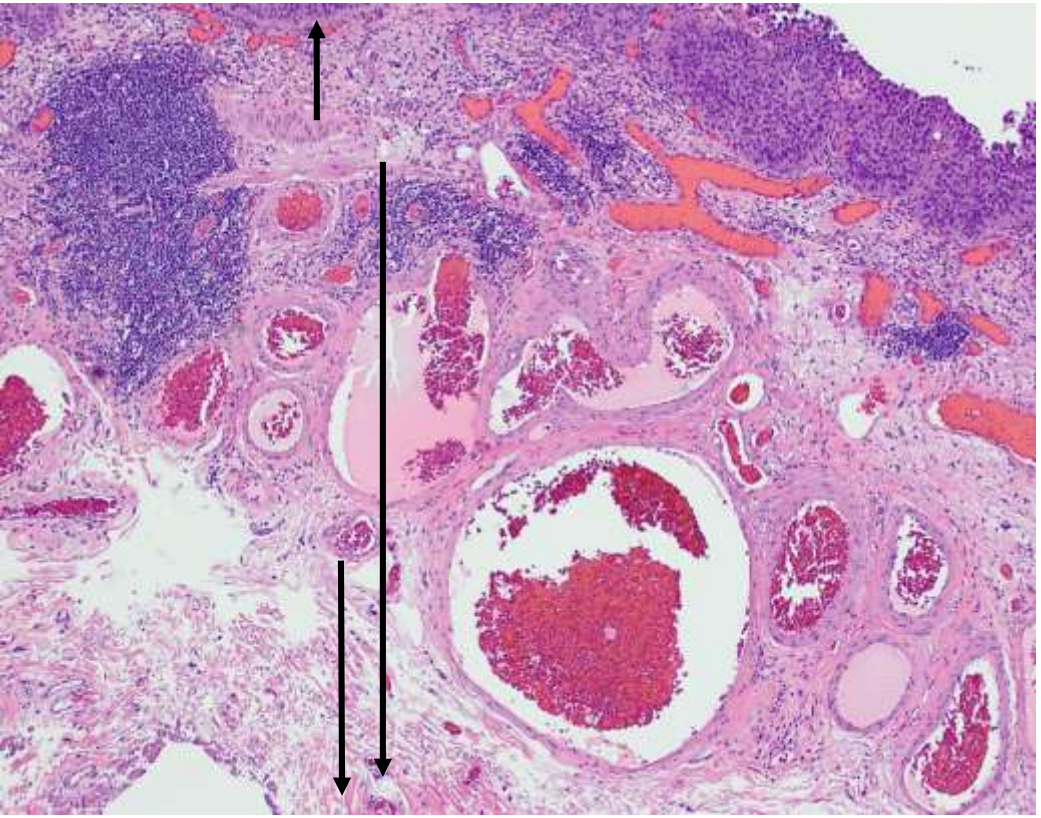
P53 type: wildtype TP53 expression, resistance to neoadjuvant MVAC

Clinical trial (COXEN) by SWOG

Pathologic Staging of Urothelial Carcinoma



Substaging of pT1 disease



- AJCC Level of Evidence: II
- Numerous subcategories proposed

- Above (T1a) or below (T1b) muscularis mucosae

- Beyond the venous plexus (T1c)

- Microinvasive (T1m) vs more deeply invasive (T1e)

- The method of T1 substaging not optimized

- Inherent lack of orientation of the specimen due to fragmentation and tangential sectioning
- Muscularis mucosae and venous plexus landmarks often not present

European Association of Urology

Bladder Cancer

A New and Highly Prognostic System to Discern T1 Bladder Cancer Substage

Bas W.G. van Rhijn [a,b,], Theo H. van der Kwast [c,d], Sultan S. Alkhateeb [a], Neil E. Fleshner [a], Geert J.L.H. van Leenders [d], Peter J. Bostrom [a], Madelon N.M. van der Aa [b], David M. Kakiashvili [a], Chris H. Bangma [b], Michael A.S. Jewett [a], Alexandre R. Zlotta [a,e]*

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Microinvasive (T1m) vs Advanced disease (T1e)

Table 3 – Direct comparison of the two T1 substaging systems used in the present study: T1a/T1b/T1c [10] and T1m/T1e [26] *

	T1a	T1b	T1c	Total
T1m	38	2	–	40
T1e	43	16	35	94
Total	81	18	35	134

T1m = a single focus of lamina propria invasion ≤0.5 mm (within one high-power field, objective ×40); T1e = specimens showing a >0.5-mm lamina propria invasion or multiple microinvasive areas; T1a = lamina propria invasion above the muscularis mucosae–vascular plexus; T1b = lamina propria invasion at the level of the muscularis mucosae–vascular plexus; T1c = lamina propria invasion beyond the muscularis mucosae–vascular plexus.

Substage according to the new system (T1m and T1e) was user-friendly, possible in 100% of cases, and very predictive of T1 bladder cancer behavior

Substaging of pT1 disease

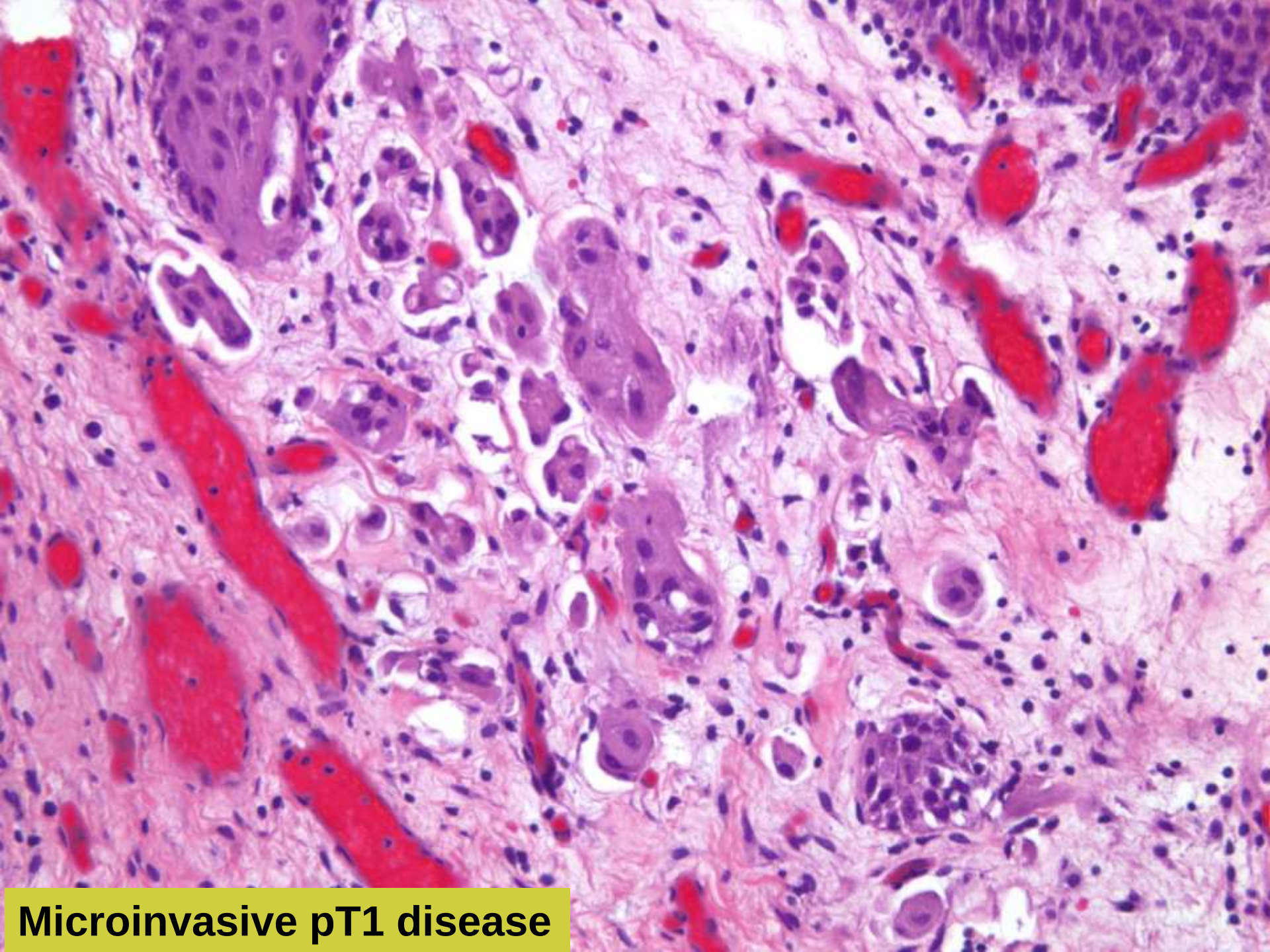
- Microinvasive vs. Advanced pT1 disease
- Microinvasive disease

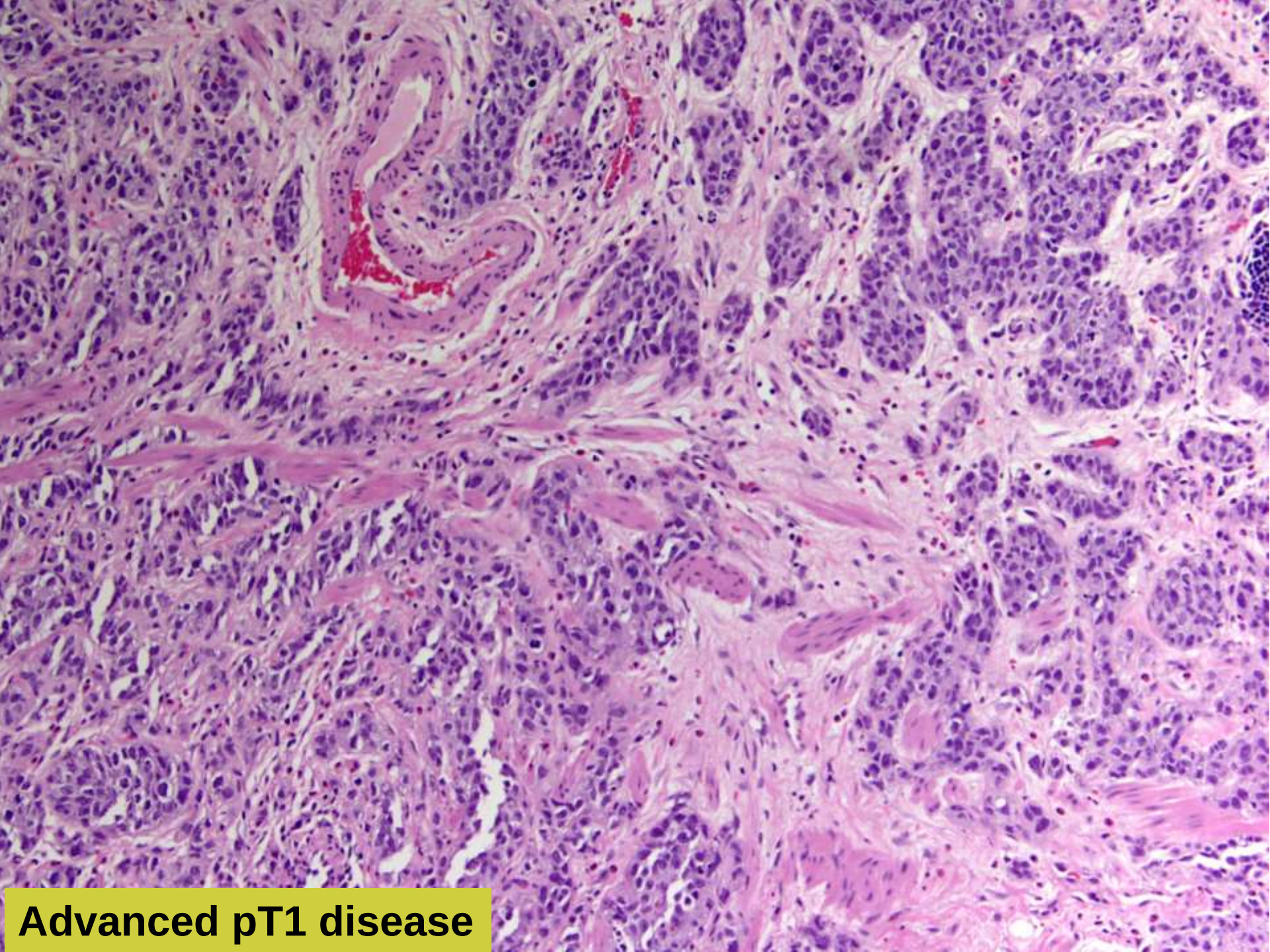
    1) Invasive tumor <1 high power in content

    2) Greatest invasive tumor diameter of 1 mm

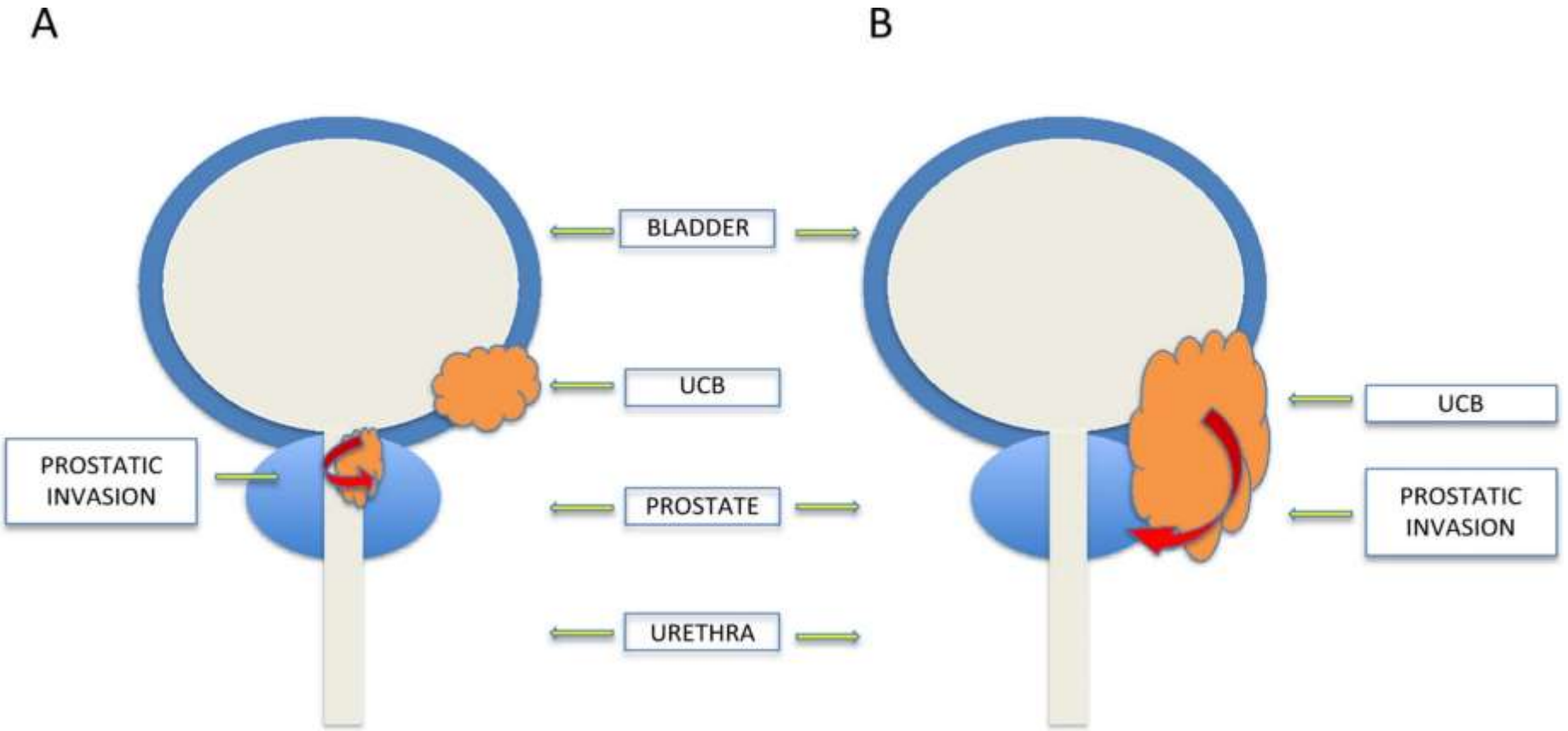
    3) Invasive tumor above the muscularis mucosae extending to a depth of 2 mm or less

- Microinvasive disease has better outcome than Advanced pT1 disease
- Recommended to categorize pT1 disease using one of the above methods


Microinvasive pT1 disease


Advanced pT1 disease

INVASION OF URETHRA AND BLADDER TUMORS IN PROSTATIC STROMA



Prostatic stromal invasion via Subepithelial invasion (Urethral surface or prostatic duct) pT2

Prostatic stromal invasion via Transmural or Extravesical route pT4

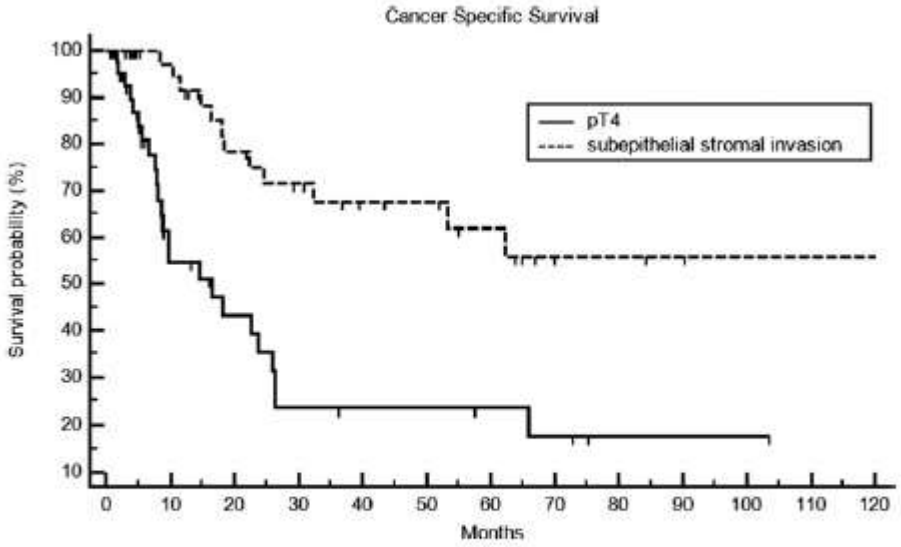


Figure 2. Kaplan-Meier curves for CSS between pT4a and SSI (HR 0.28, 95% CI 0.14–0.55, p <0.001).

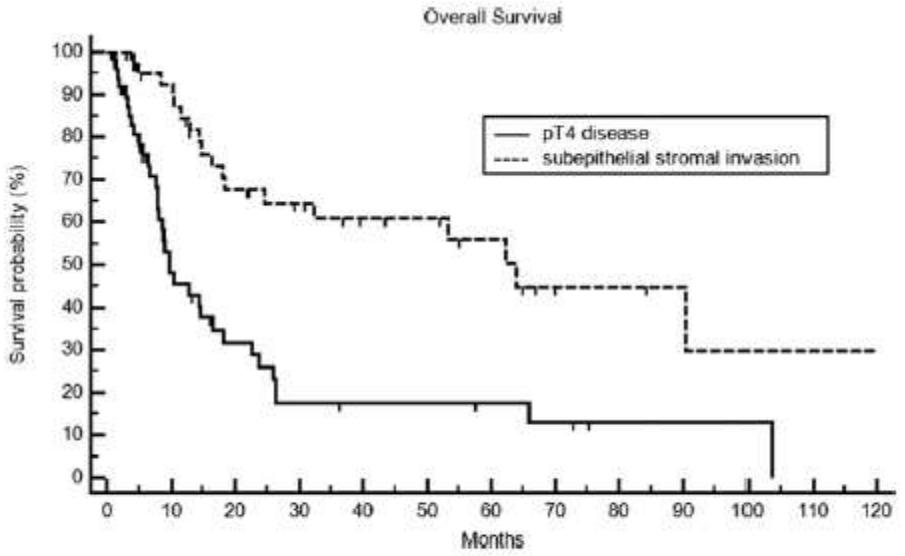
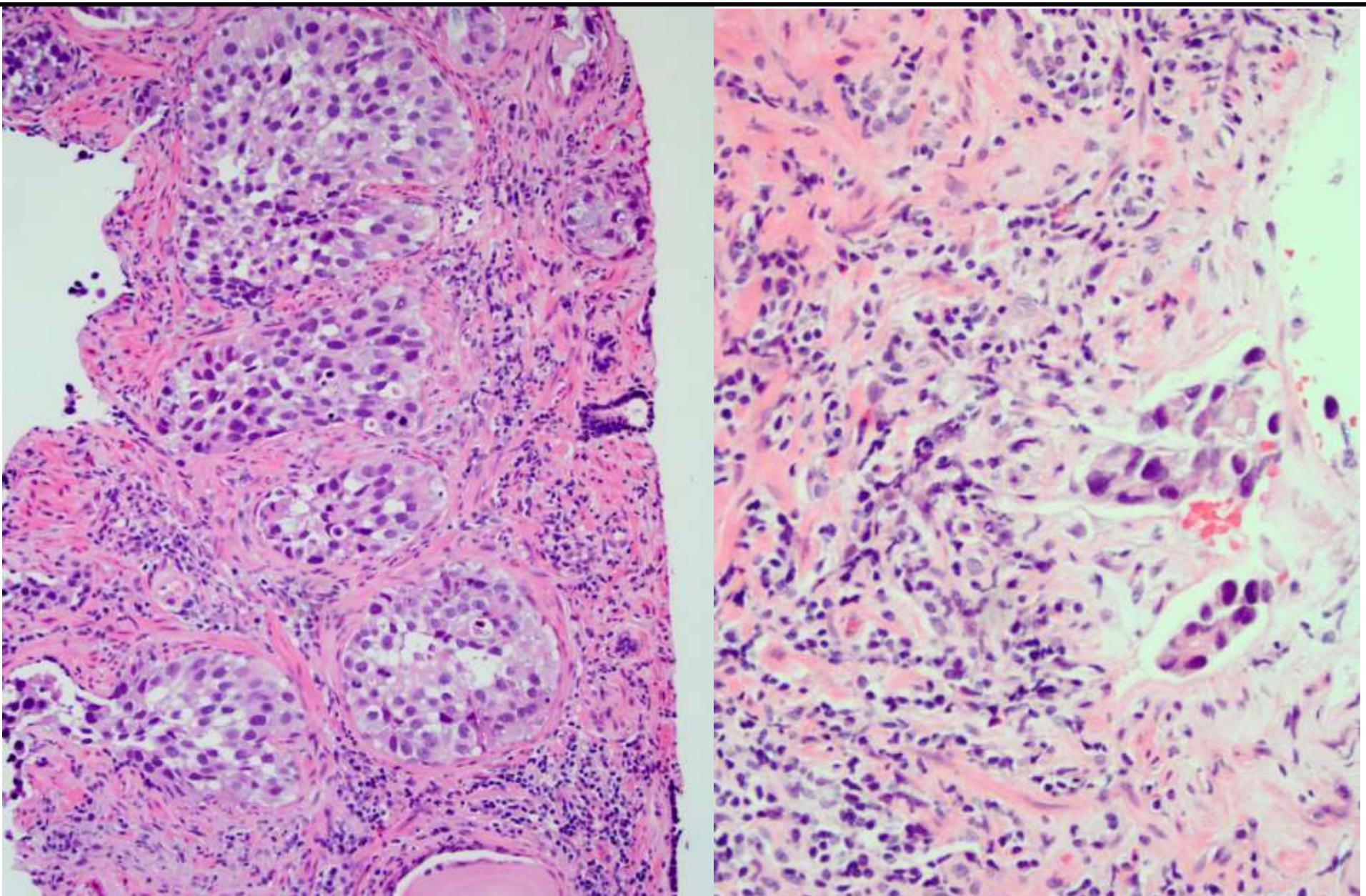


Figure 3. Kaplan-Meier curves for OS between pT4a and SSI (HR 0.33, 95% CI 0.19–0.57, p <0.0001).

Patel AR et al, J Urol, (189) 53-58, 2013

CASE 4: HIGH-GRADE UCC WITH SPREAD INTO PROSTATIC DUCTS AND INVASION OF STROMA; pT2



Take Home Messages

- Recognize many faces of Urothelial carcinoma
- Nested, Micropapillary, Small cell and Plasmacytoid: UC variants to worry about in small biopsies
- Document in the report, including % if not pure
- 2004 WHO classification of non-invasive urothelial tumors has been universally adopted
- Better understanding of genomic profile of bladder cancer is likely to further improve therapeutic targeting

Take Home Messages

- An assessment of the depth and/or extent of subepithelial tissue invasion in T1 cases is recommended
- Prostatic stromal invasion is staged differently depending on subepithelial (T2) versus transmural invasion (T4)


thank you so much