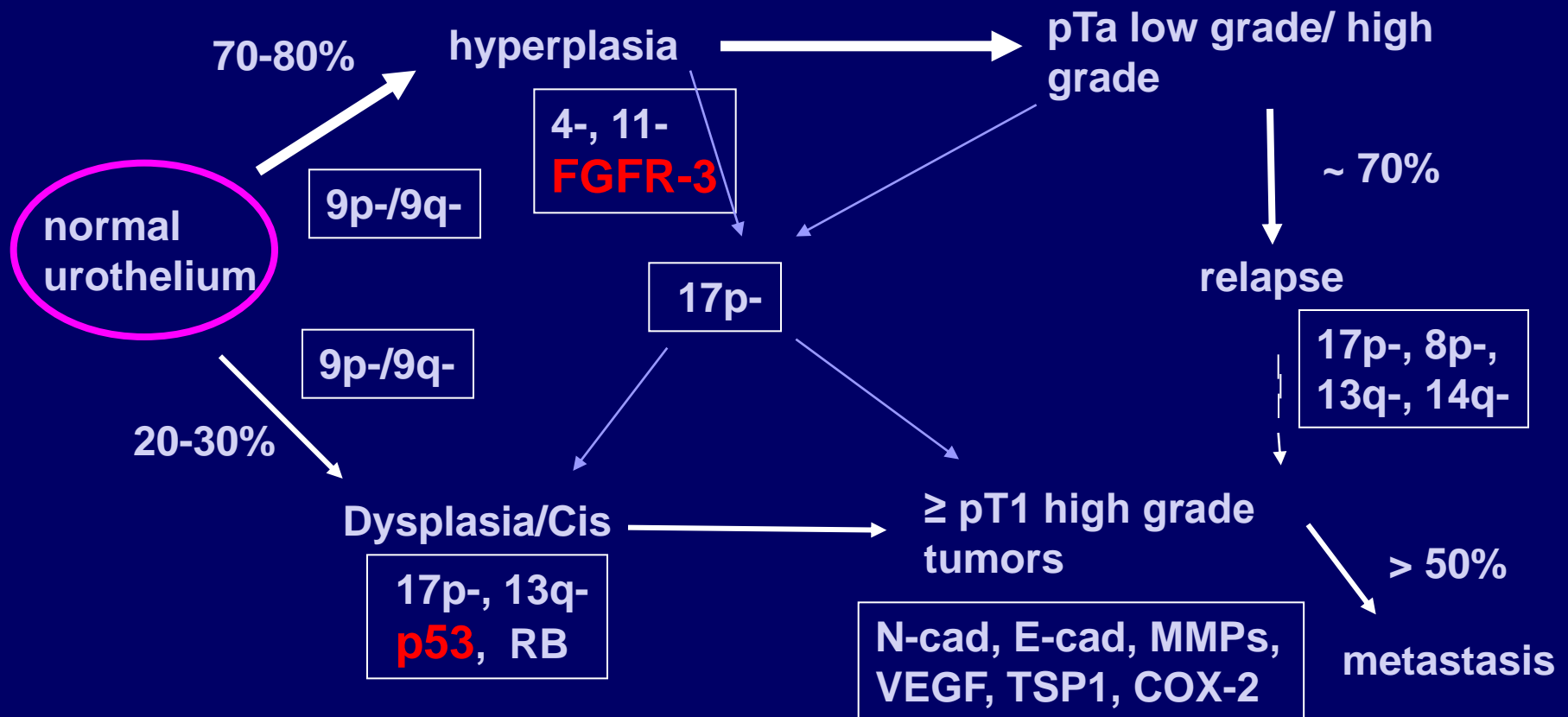


# **Urothelial Carcinoma WHO 2016**

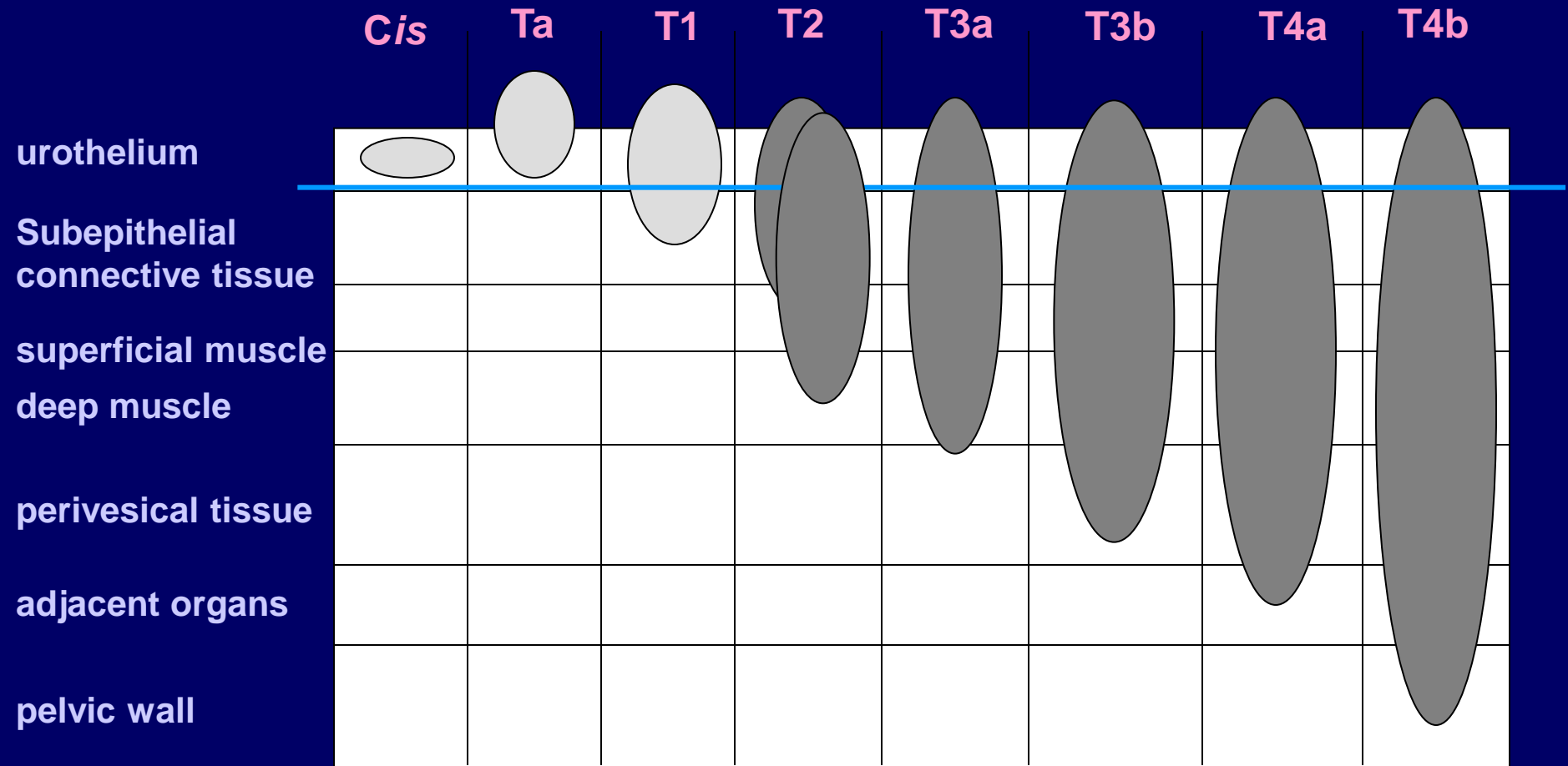
***Ph Camparo***

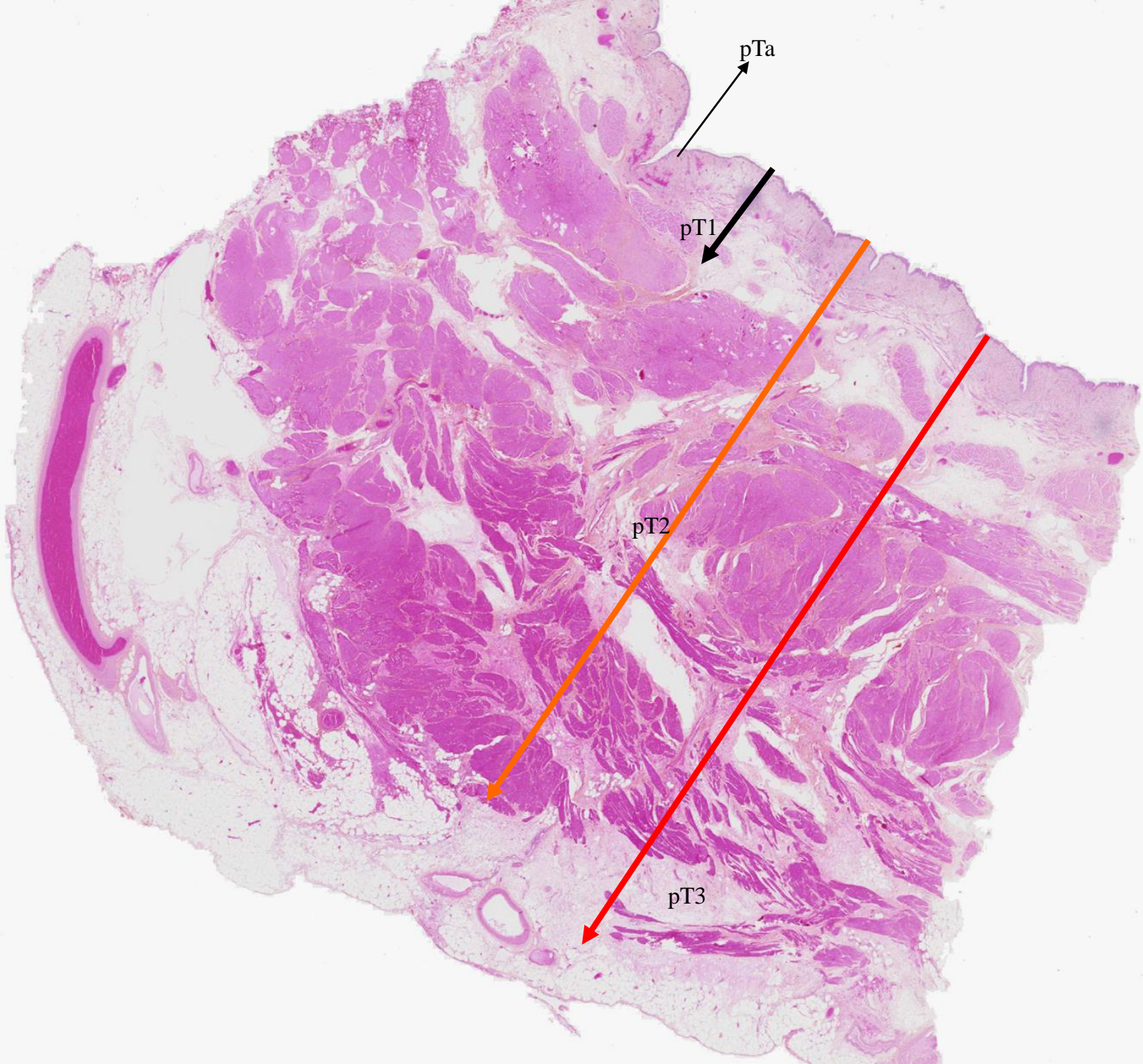
Centre de pathologie  
Amiens  
France

# Genetic Events Characterising Bladder Carcinogenesis



# Stages pT





**pTa**

# ASSESSMENT OF PAPILLARY UROTHELIAL NEOPLASMS

At medium magnification, the tumour pattern gives a predominant impression of:

**ORDER**  
Of architectural and cytological features?

**DISORDER**  
Of architectural and cytological features?

**VARIATION**  
Of architectural and cytological features  
readily seen?

**NO**

**YES**

**PUNLMP**

**Urothelial carcinoma, low grade**

**Urothelial carcinoma, high grade**

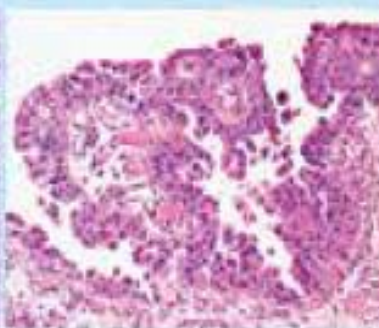
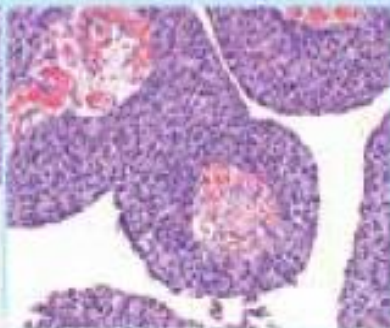
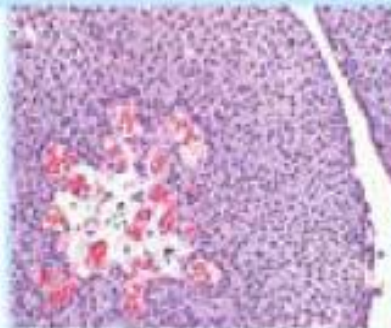
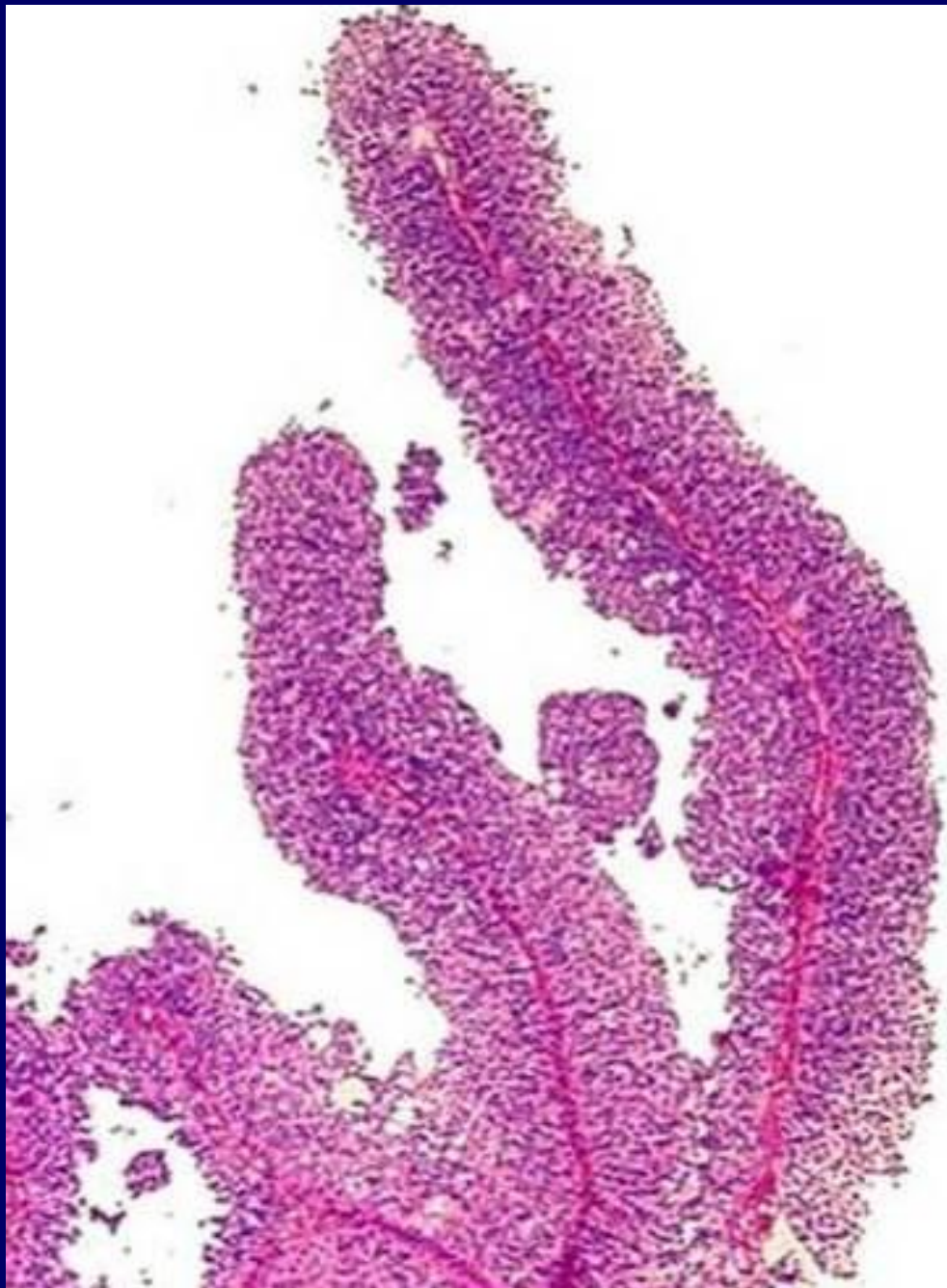


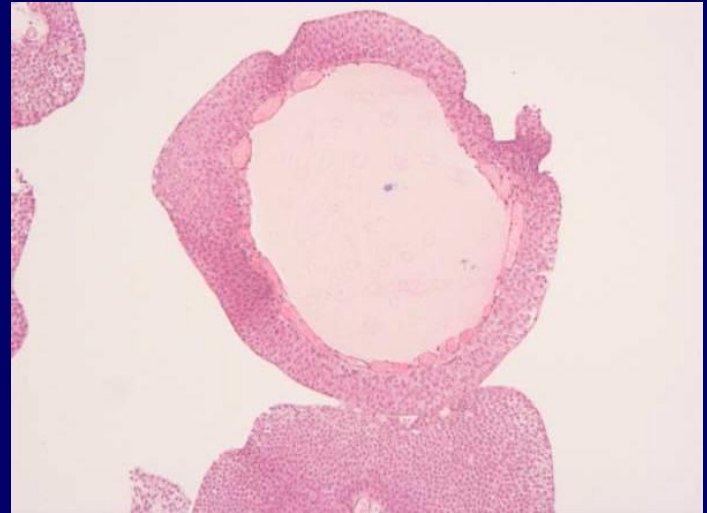
Fig. 2.29 Flow chart of the grading algorithm for papillary urothelial neoplasms.

PLUMP



# DD : Urothelial papilloma

- rare
- benign
- All ages but < 50 ans
- H > F
- Small, unique
- Small thin papillae with no atypia no mitosis no architectural disorder
- Benign

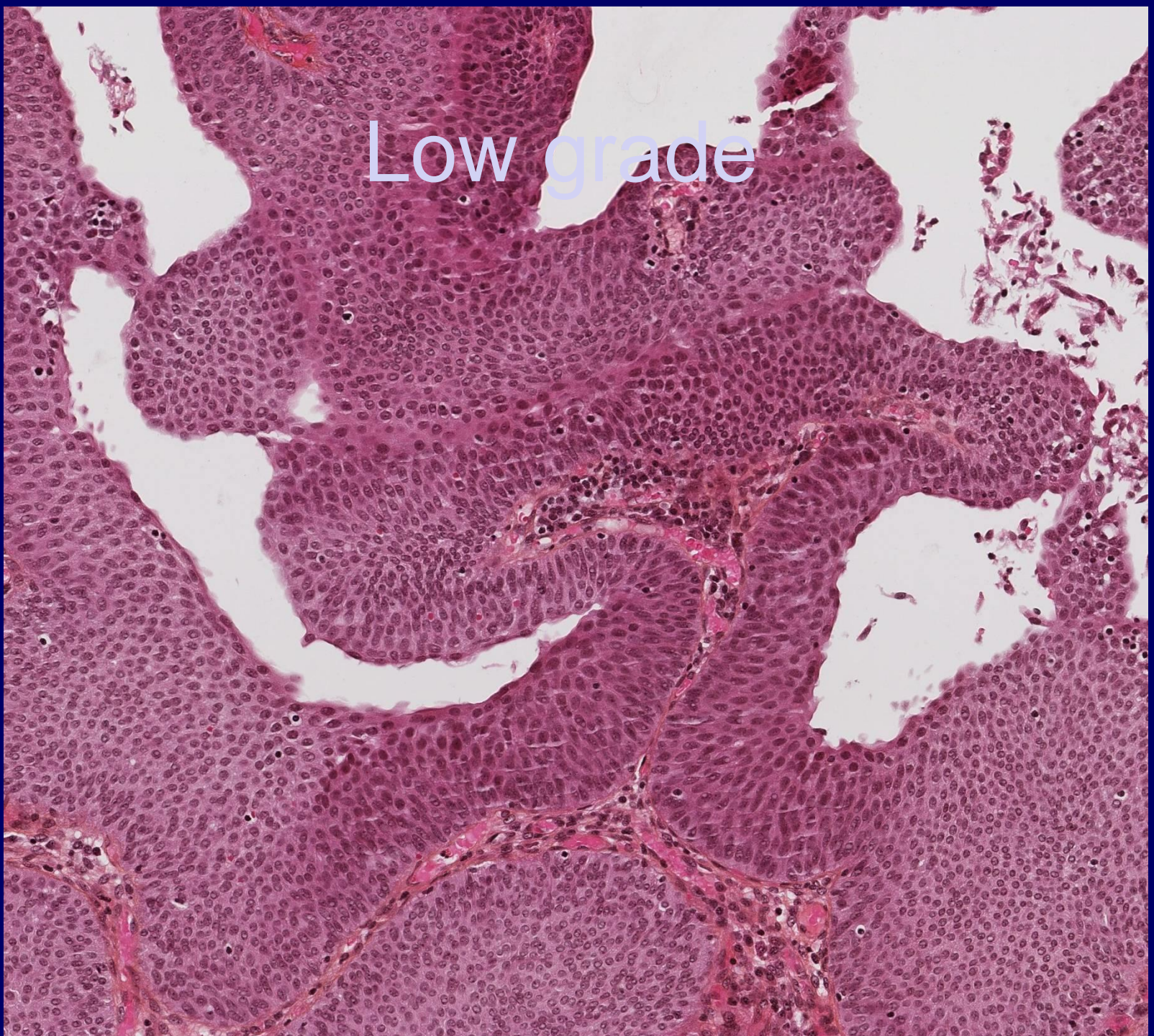




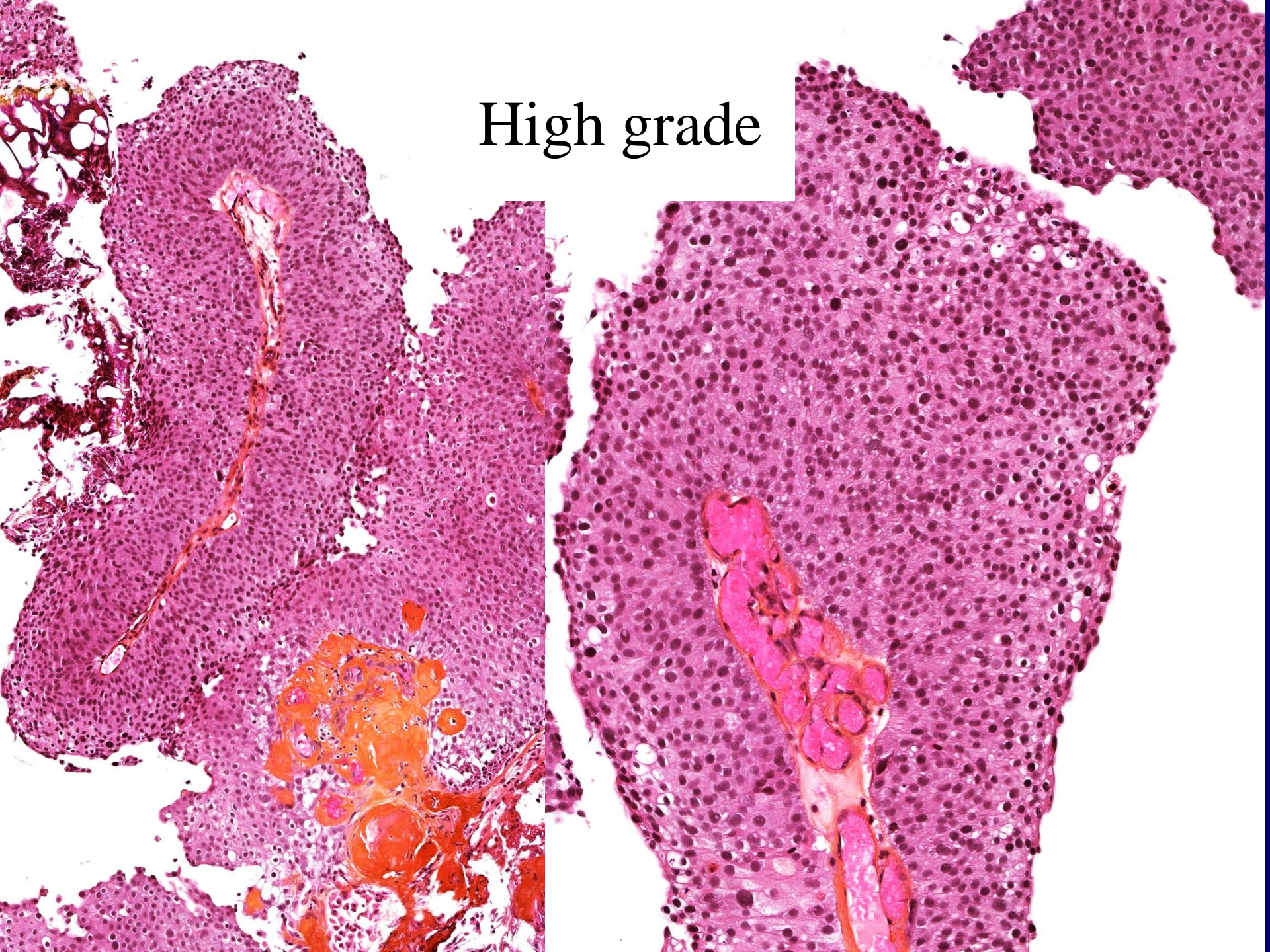
Low grade



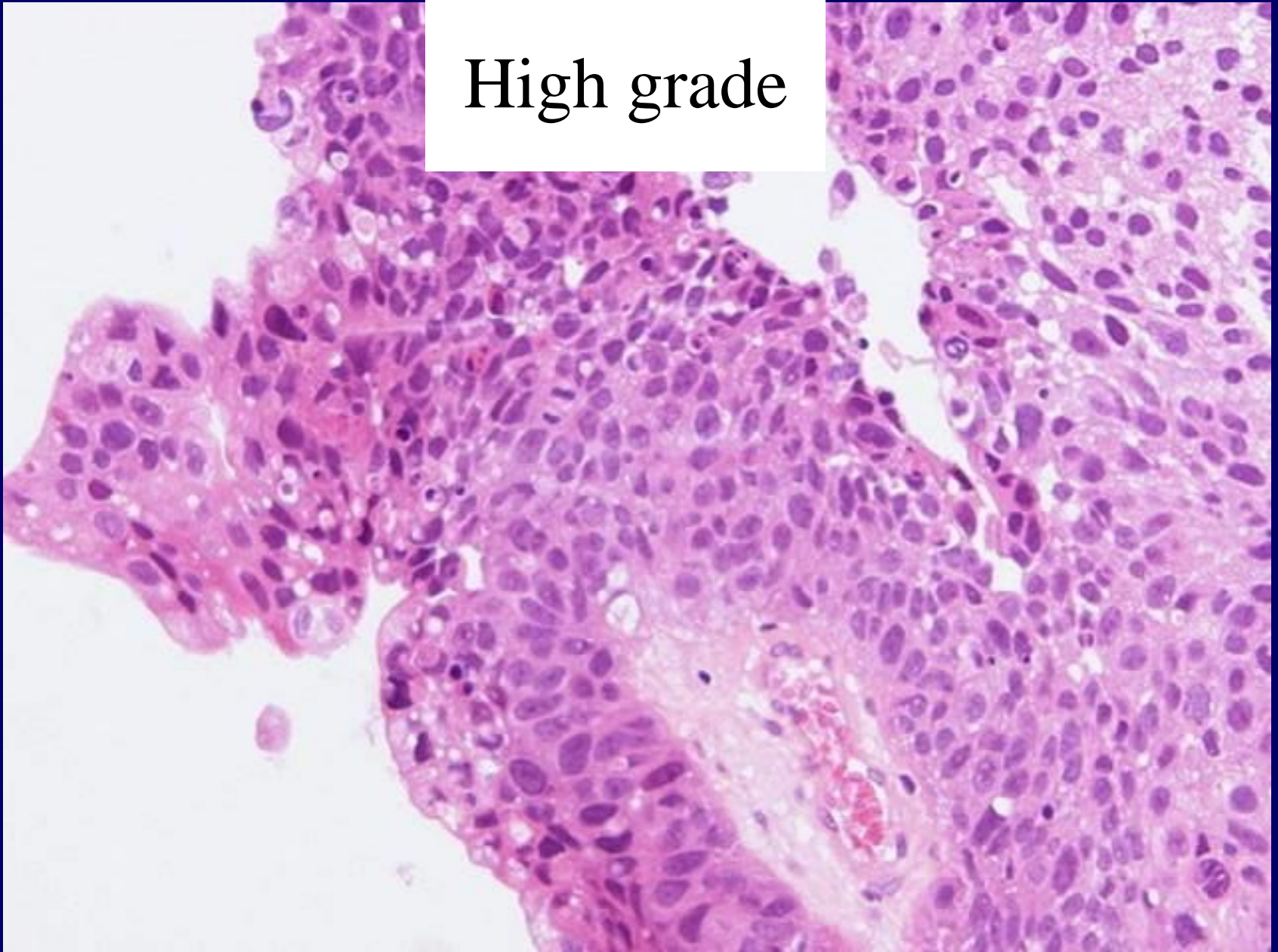
Low grade

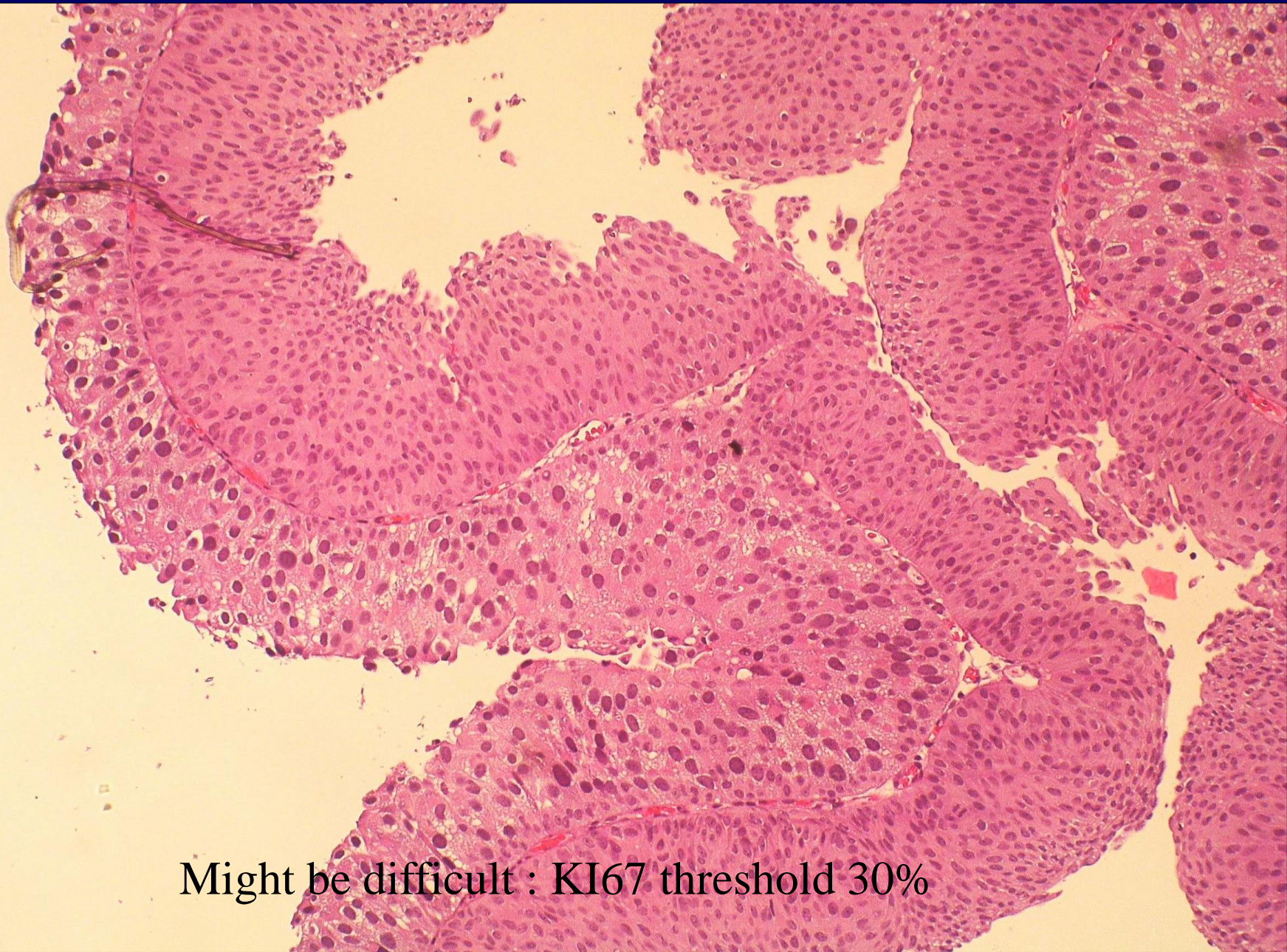


High grade



High grade





Might be difficult : KI67 threshold 30%

# Recurrences and prognostics

	<b>PUNLMP</b>	<b>NILGC</b>	<b>NIHGC</b>
<b>Recurrence</b>	<b>6%</b>	<b>24%</b>	<b>33%</b>
<b>Death</b>	<b>0%</b>	<b>4%</b>	<b>16%</b>

PT1 5 years follow up

Recurrence : 65%

Progression : 35%

**pT1**

# Sub-Staging

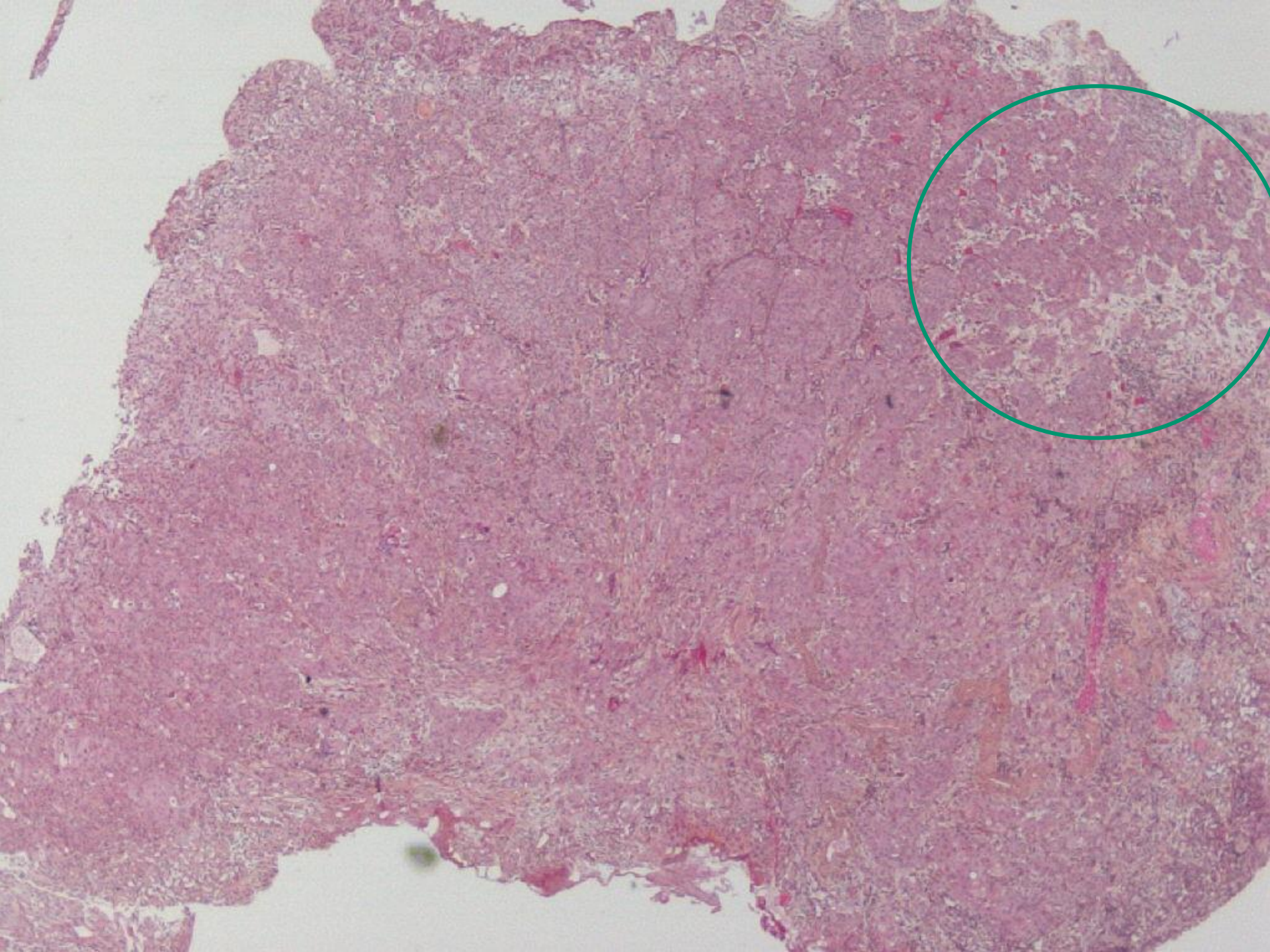
- Substaging pT1 tumors

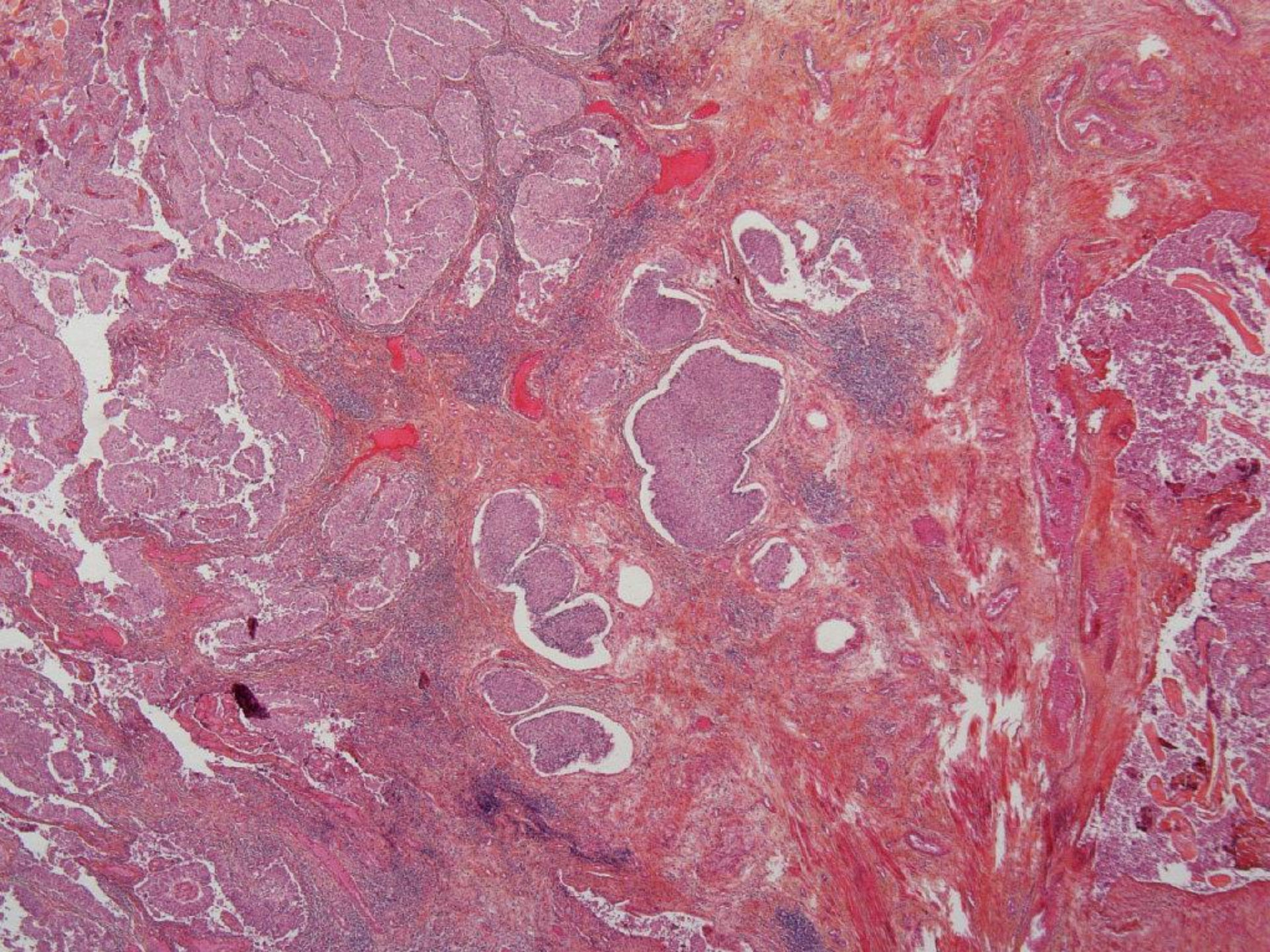
Accumulating data suggest that substaging T1 disease is clinically relevant, but the specific details on how to do so are yet to be agreed upon {1242,1809,2119,2579}. It is impor-

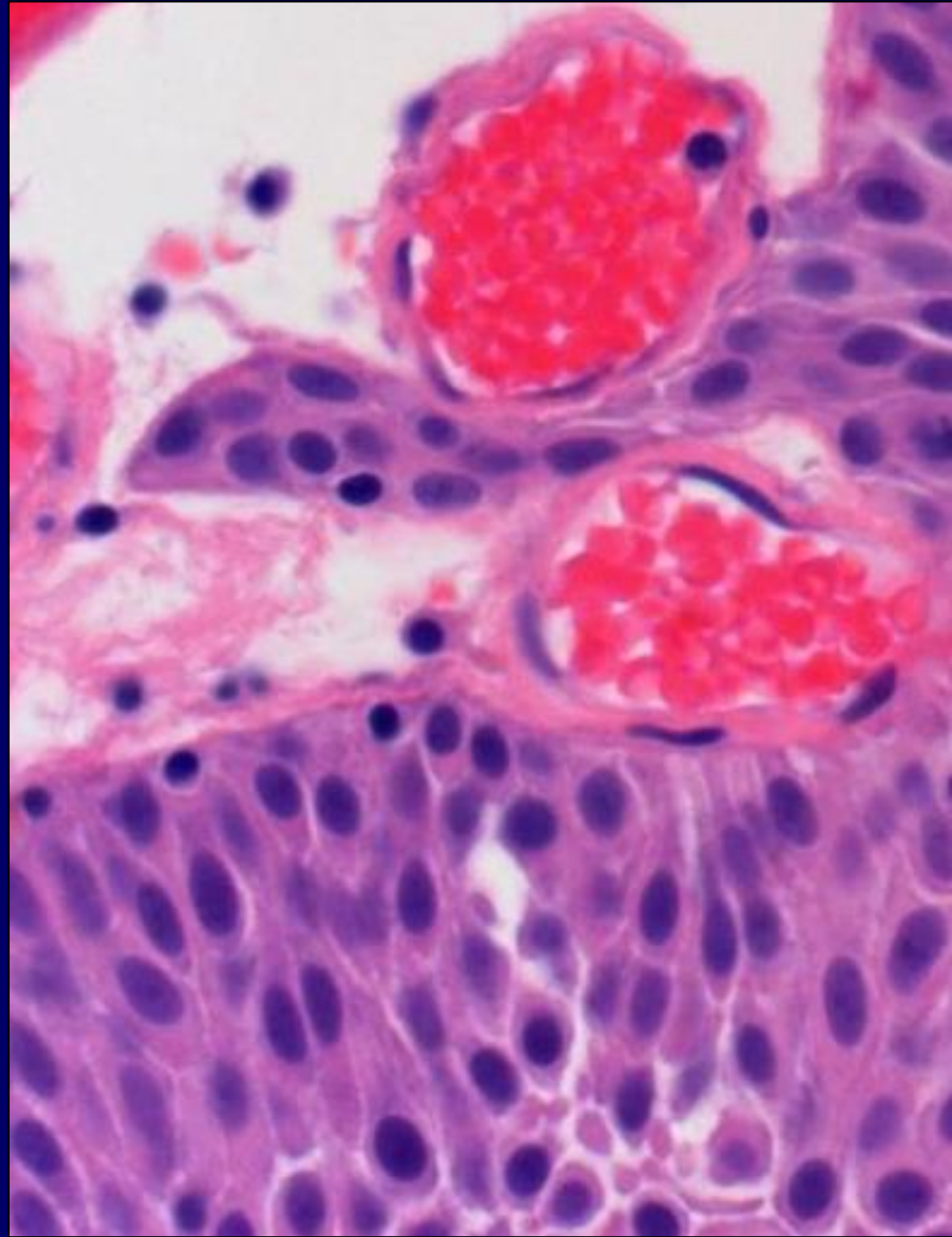
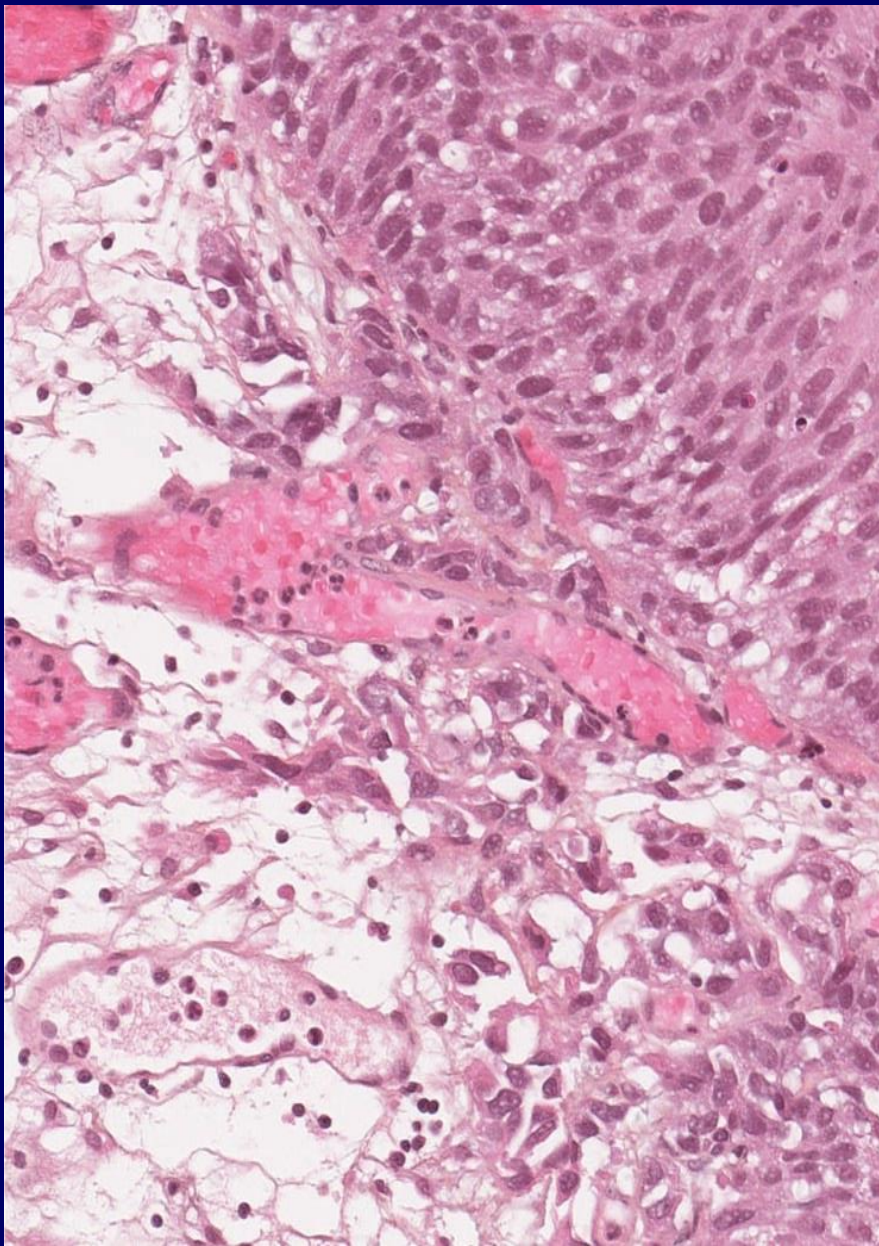
Based on the available data, it is recommended to provide an assessment of the depth and/or extent of subepithelial tissue invasion in T1 cases.

- ICCR (International Collaboration of Cancer Reporting)
  - mm invasion
  - or/and extent
  - and or pT1a/b









# PROGNOSTIC SIGNIFICANCE OF DEPTH OF INVASION IN TRANSURETHRAL RESECTION OF BLADDER SPECIMENS

- USCAP 2016
- 2786 TRUB pT1
- Tumors Adjacent to Detrusor Muscle (TADM).

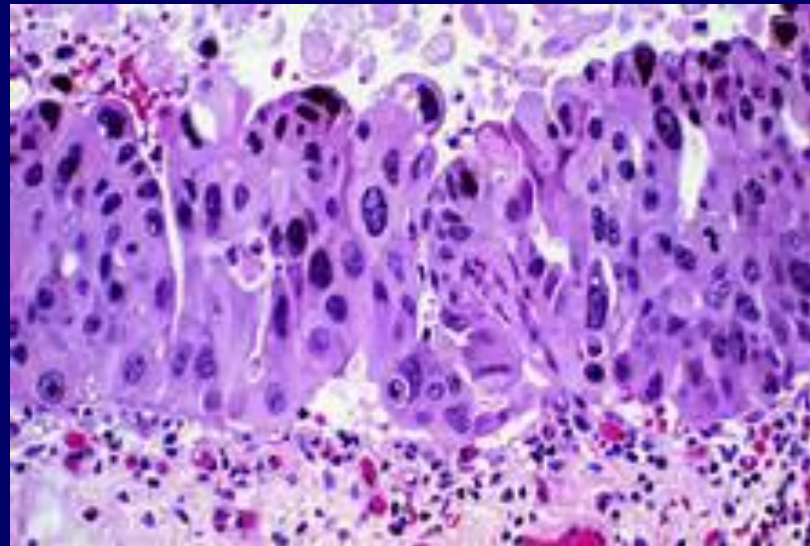
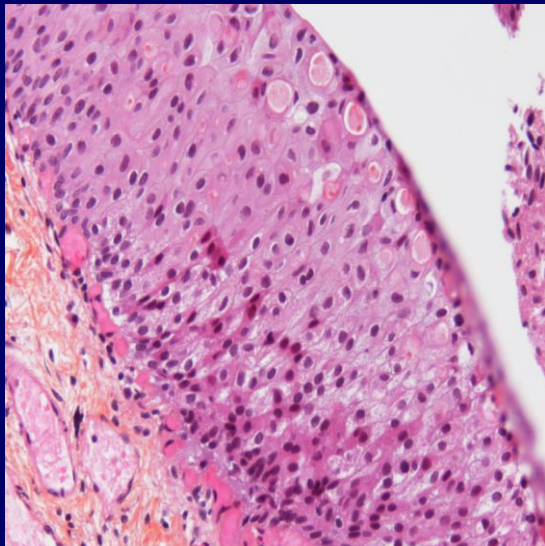
	Recurrences	Progression	Lymph Node +
TADM + (18)	75 %	70 %	40 %
TADM – (82)	37 %	22 %	10 %

- No current therapeutic impact

# Flat lesions

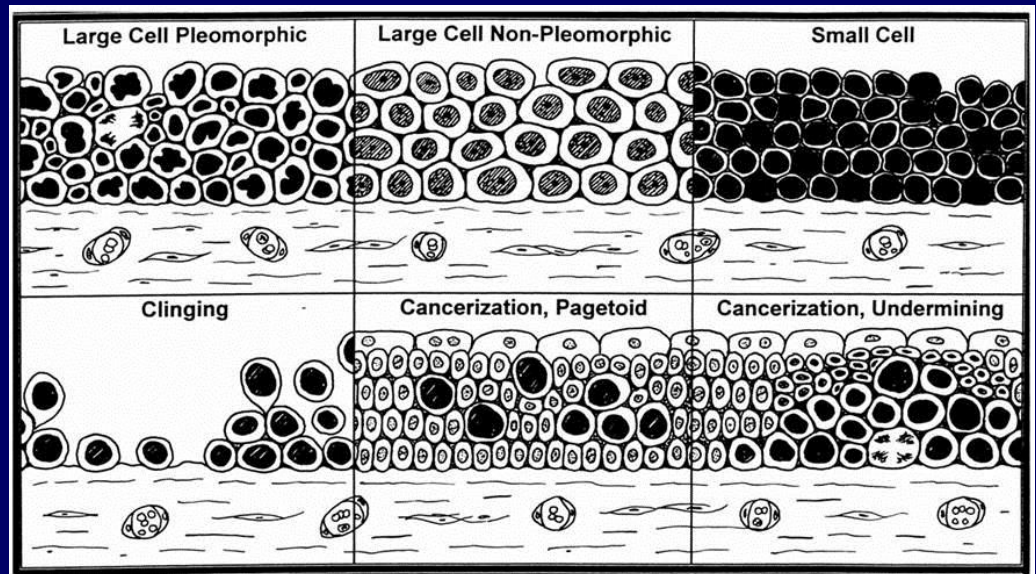
# New terminology

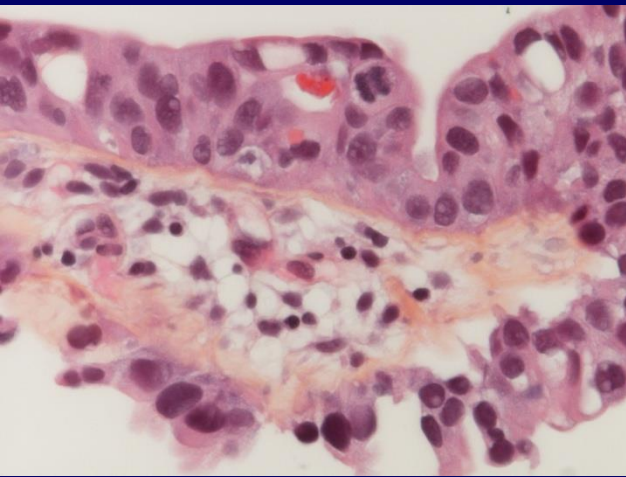
- High grade dysplasia = Carcinoma in situ
- Low grade intraepithelial dysplasia = dysplasia/atypia
- Papillary and flat hyperplasia = urothelial proliferation of uncertain malignant potential



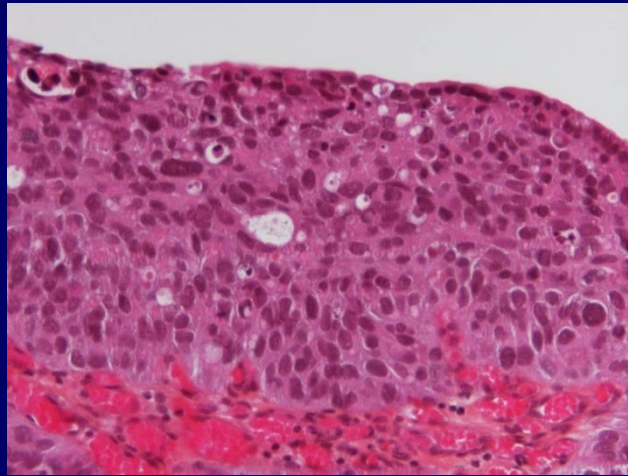
# Carcinoma in situ (CIS)

- 3% of bladder tumors
- No infiltration
- malignant
- in 50% of pT1
- In 60% of  $\geq$  pT2

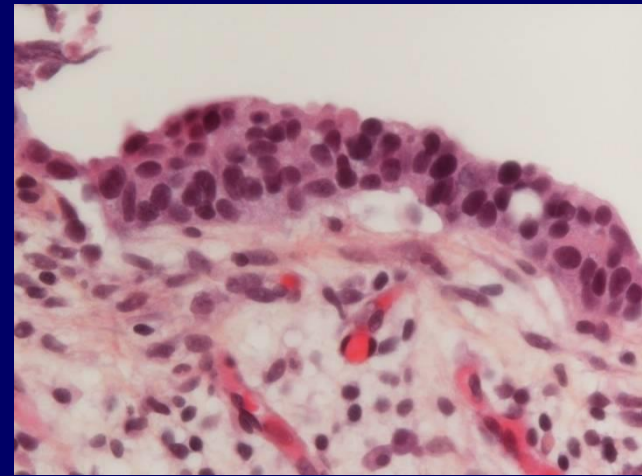




Large cell pleomorphic

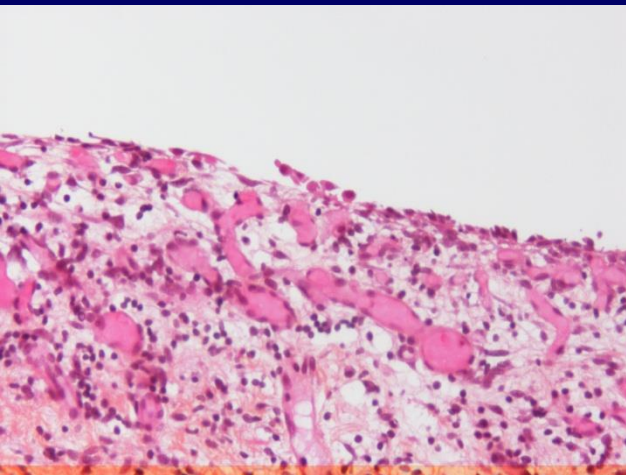


Large cell

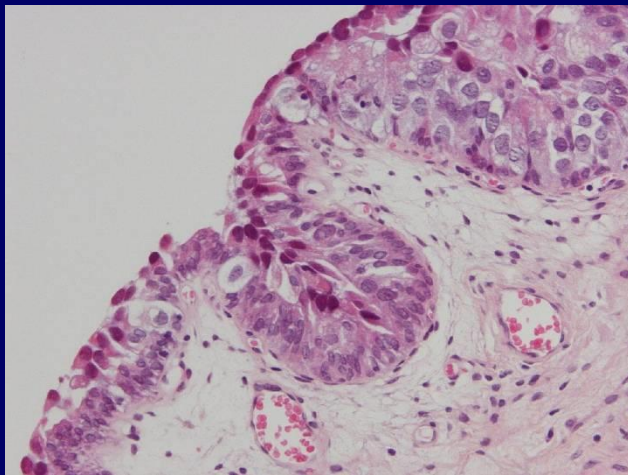


Small cell

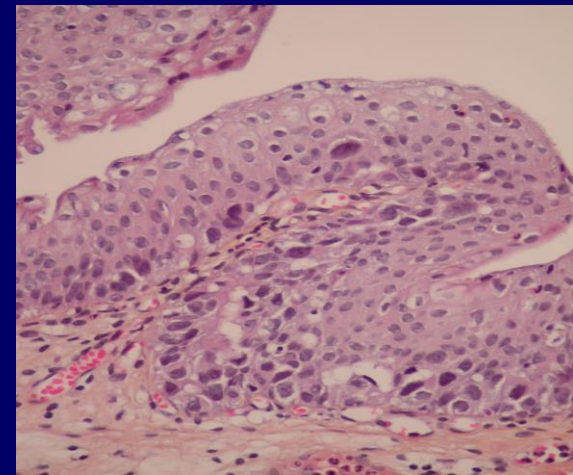
Clinging/denuded



Pagetoid



Undermining





# Cis

- Sex ratio H = F
  - ↑ risk of urothelial tumor of upper urinary tract RR 2.3
  - ↑ risk of recurrence (p=0.045)
  - ↓ OS (p=0.006)

# Cis IHC

- Diffuse

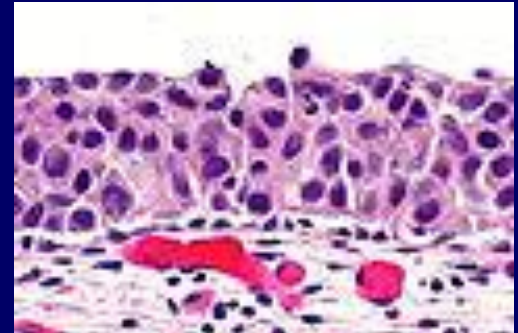
KI 67 +

p53 +

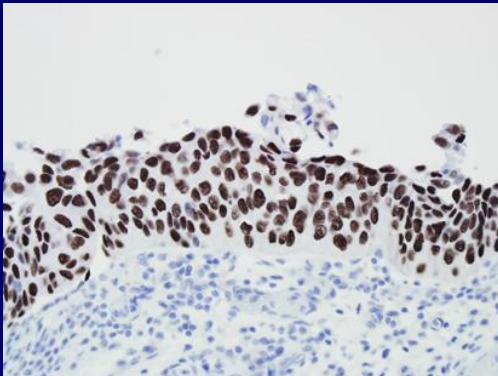
CK20 +

CK20

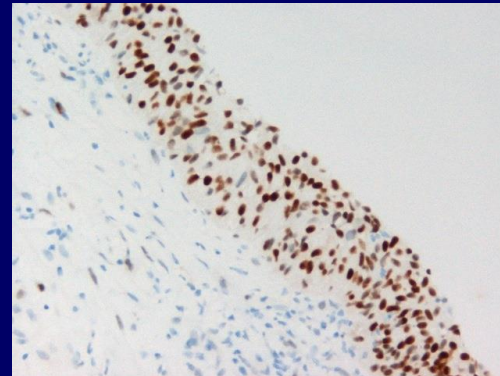
- Loss of basal CD44 expression



Ki67



P53



A histological micrograph showing a cross-section of tissue with a flat lesion. The lesion is characterized by a thickened epithelial layer with numerous cells that have enlarged, hyperchromatic nuclei and some degree of architectural disorganization. The underlying stroma appears relatively normal. A semi-transparent teal box is overlaid on the center of the image, containing the text 'Flat lesions other than CIS'.

# Flat lesions other than CIS

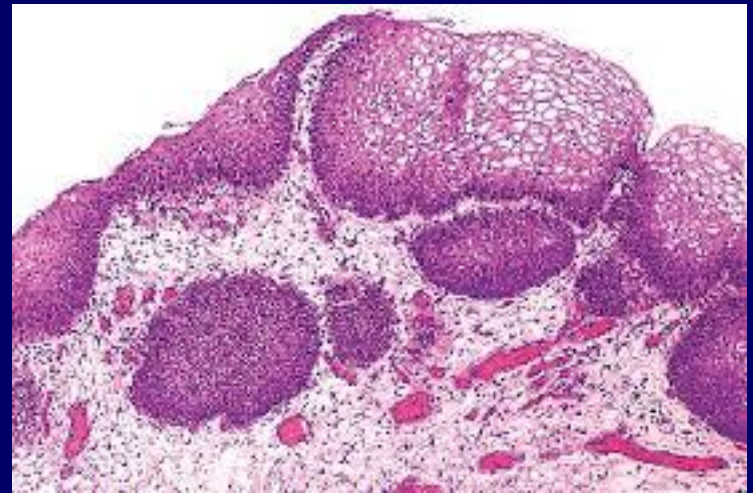
# WHO 2016 Classification

- Metaplasia
  - Squamous with keratinisation/verrucous
  - Glandular /adénoma (tubullous, villous)
- Hyperplasia/ urothelial proliferation of uncertain malignant potential
- Dysplasia

# Metaplasia

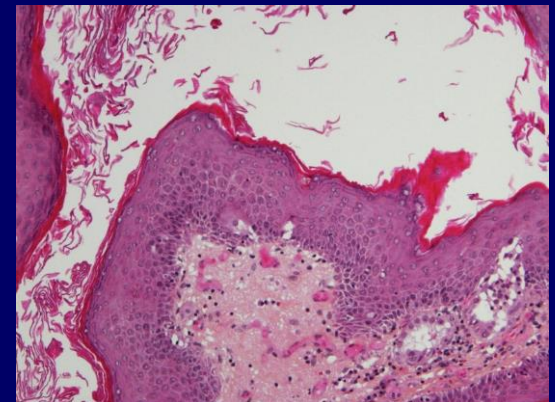
# Squamous metaplasia

- Female predominance
  - Trigonal
  - no keratinisation
- Chronic inflammation
  - Neurologic bladder
- Risk if
  - Male
  - Diffuse metaplasia
  - Inflammation
  - Keratinization



# Keratinization

- M > F
  - inflammation, irritation, lithiasis
  - Immunosuppression
  - Schistosomiasis
- Epidermoid Carcinoma : 62% coexist with keratization
- Keratinisation
  - 12% together with EC
  - 20% will develop cancer



# Glandular metaplasia (GM)

Chronic inflammation (neurologic bladder)

Young male (40 yo) no clinical history

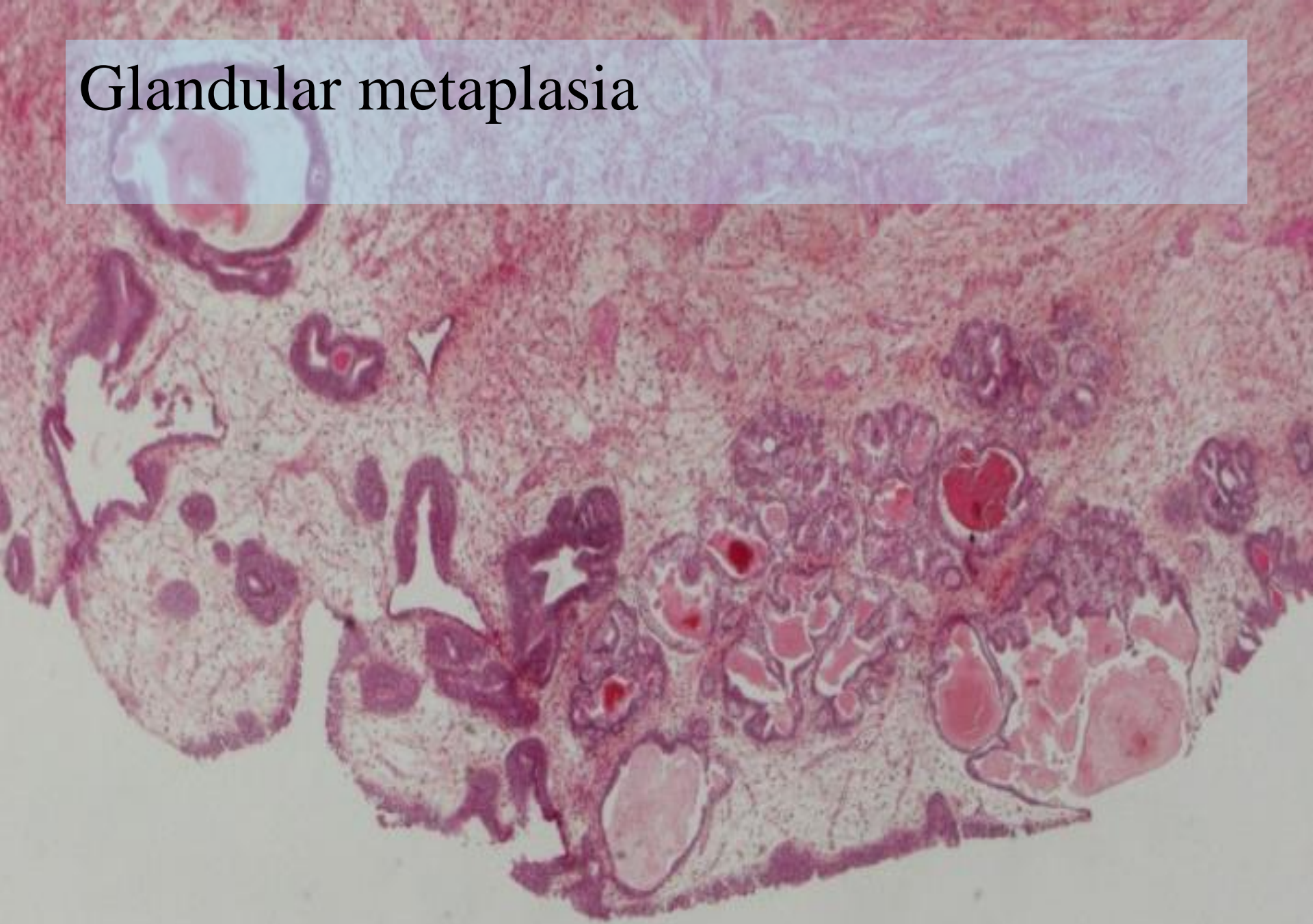
Metaplasia (gastric, colonic)

Differentiation is **NOT** a prognostic factor

DD : adenocarcinoma

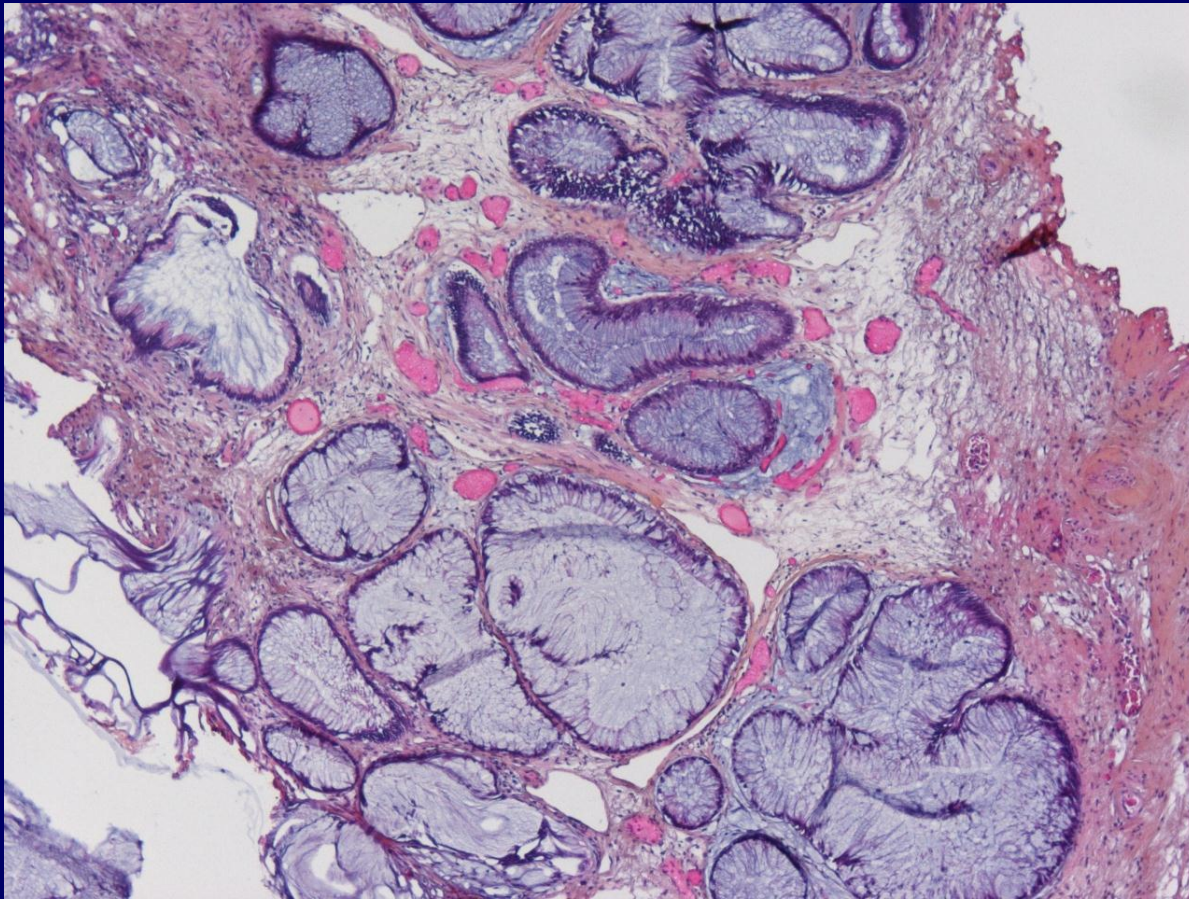


# Glandular metaplasia



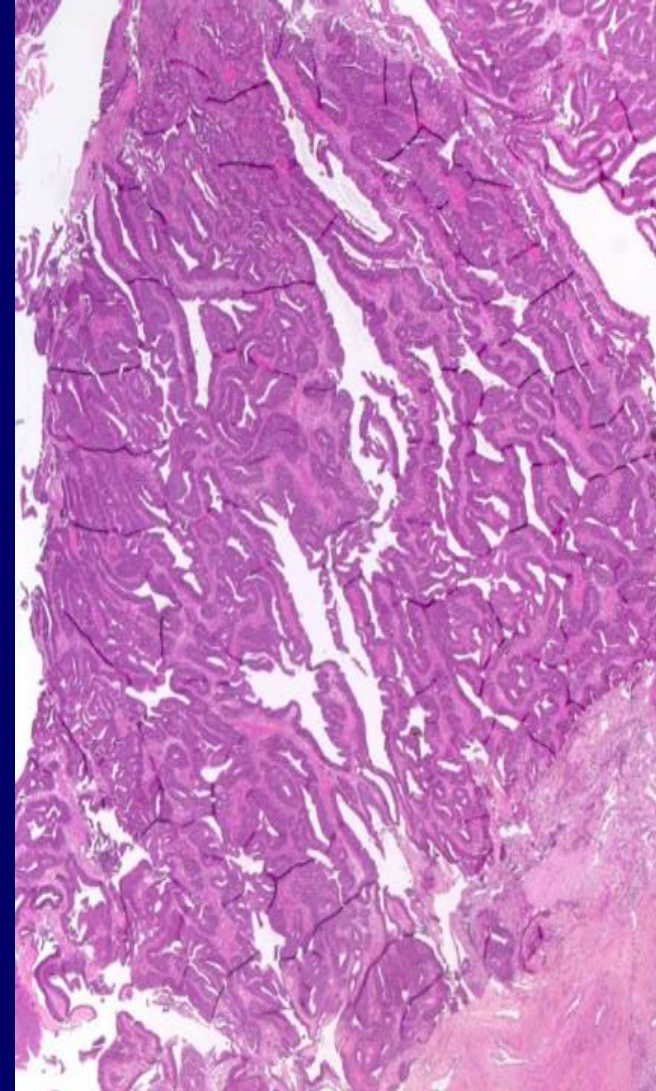
# Glandular metaplasia

- If mucine production look for ADK



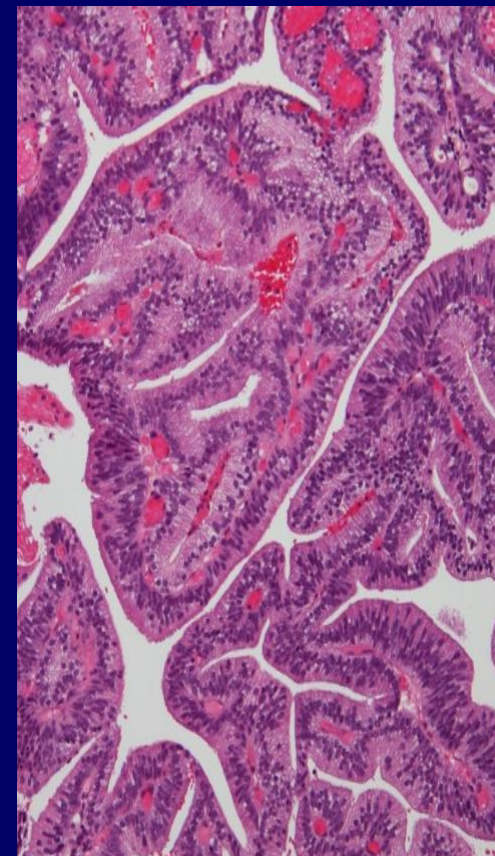
# Villous adenoma

- BA +, PAS +
- CK20+, CK7 +/-
- Prognostic good if
  - Isolated
  - Complete excision
- 1/3 association with Adk



# Tubulous adenoma

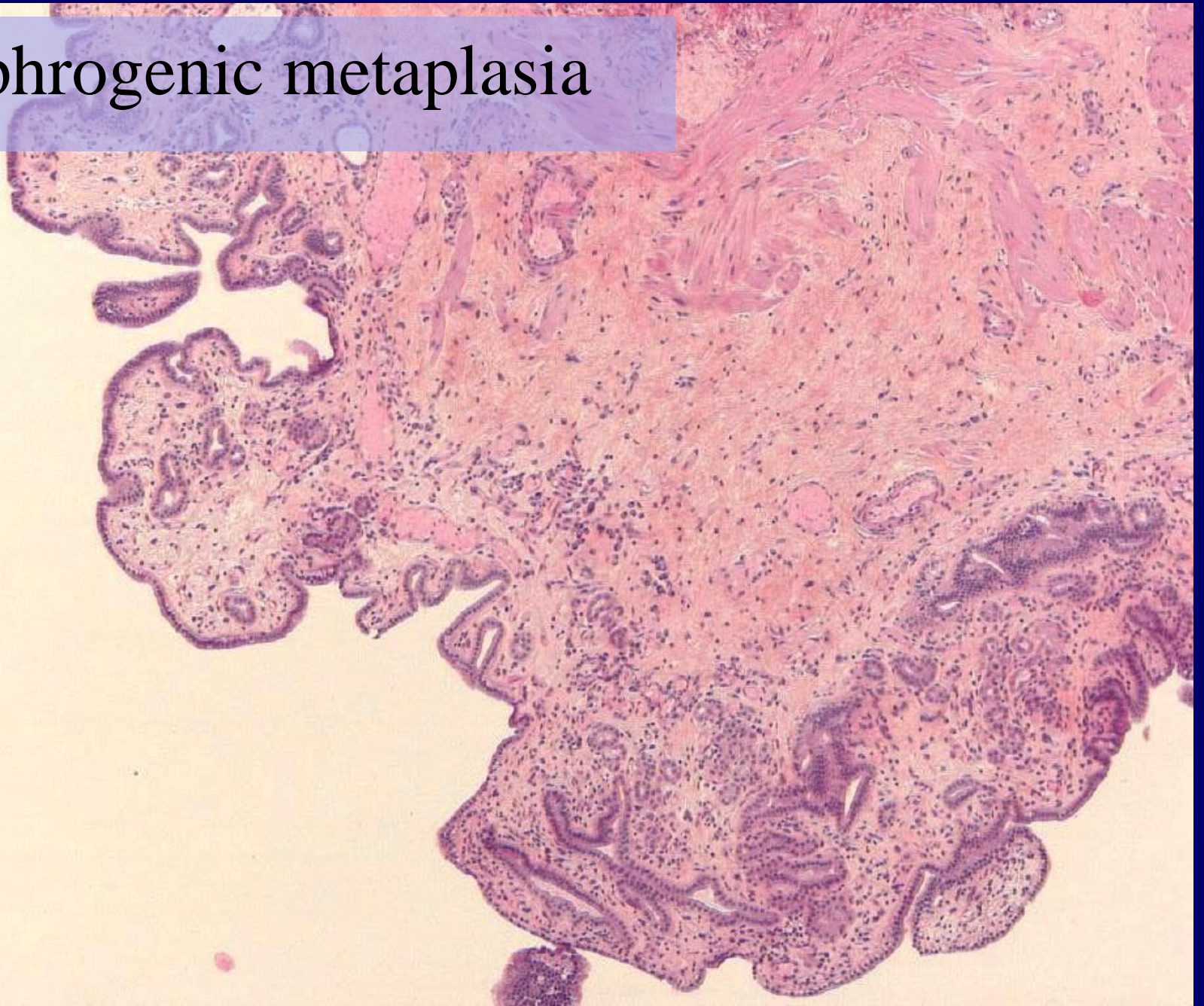
- Mean 45 yo
- Tubular glands
- Colonic epithelium
- CDX-2+, CK20+, GATA3-, CK7-
- bladder, uretera, uretra
  
- Association with bladder Adk
- DD : Adk, metastases



# Glandular metaplasia

- No mitosis
  - No nécrosis
  - No single ring cells
  - No muscular infiltration
- 
- CAT: watchfull watching
  - risk of malignant transformation  $\approx 0$

# Nephrogenic metaplasia



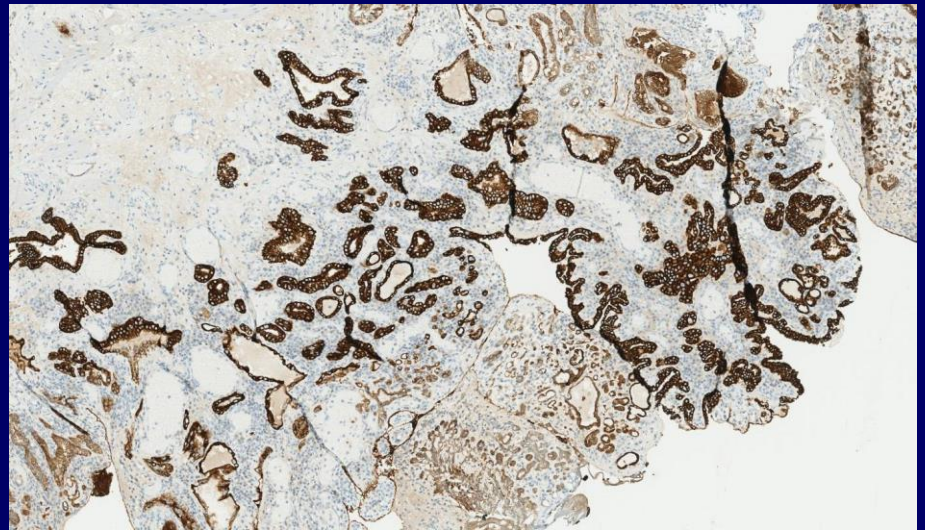
# Nephrogenic metaplasia

- Male predominance
- Previous bladder trauma
- Surgery (60%), lithiasis (14%)

CK7+ Racemase +/-

GATA3- p63 – PSA -

**BENIGN**

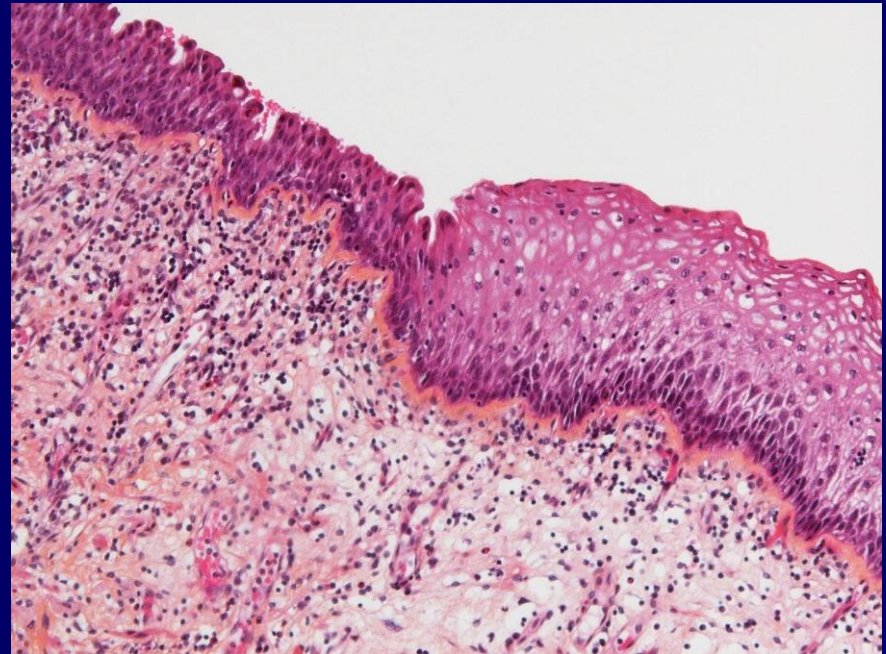


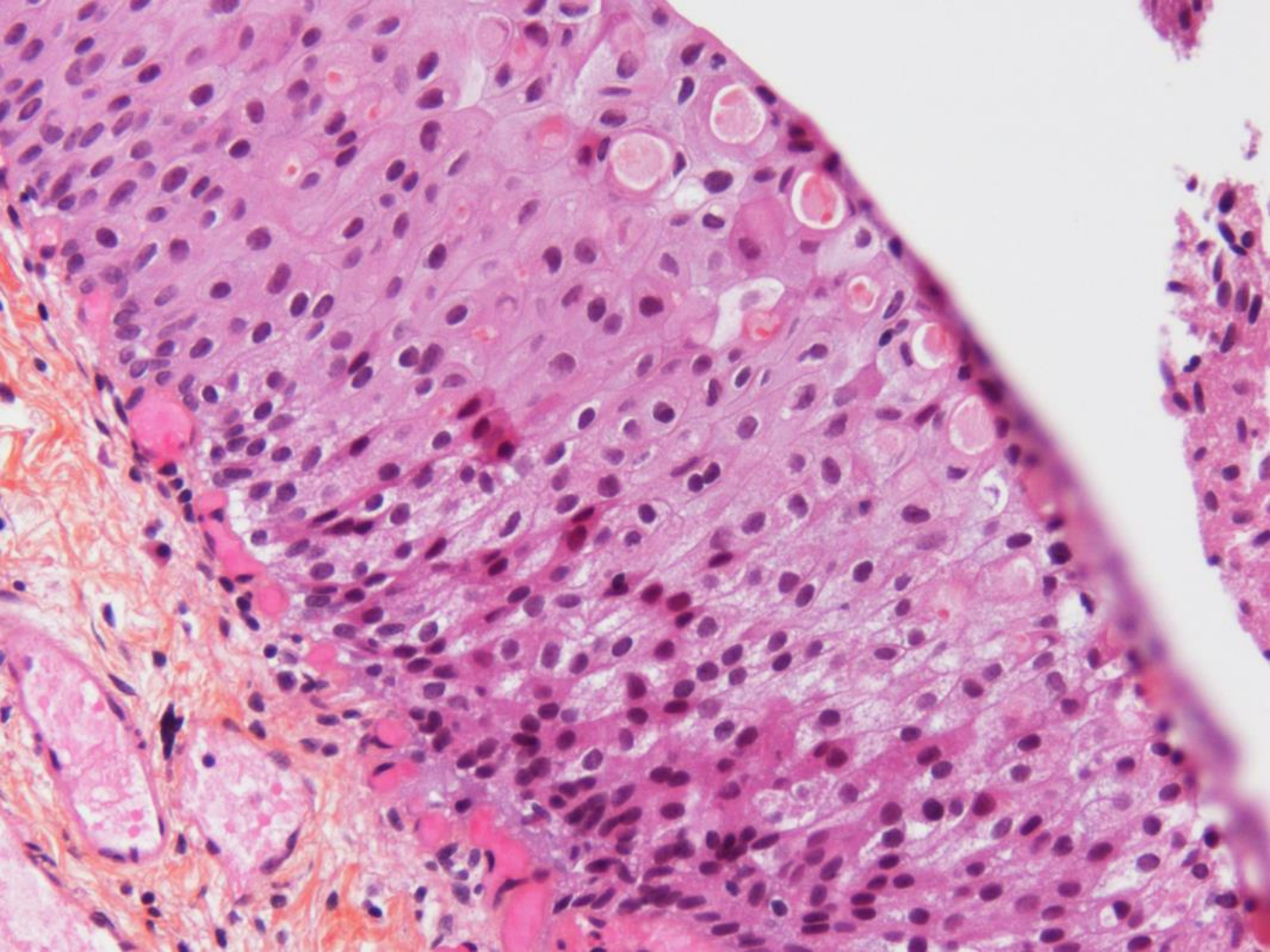
# Urothelial Proliferation of Uncertain Malignant Potential (UPUMP)



# UPUMP

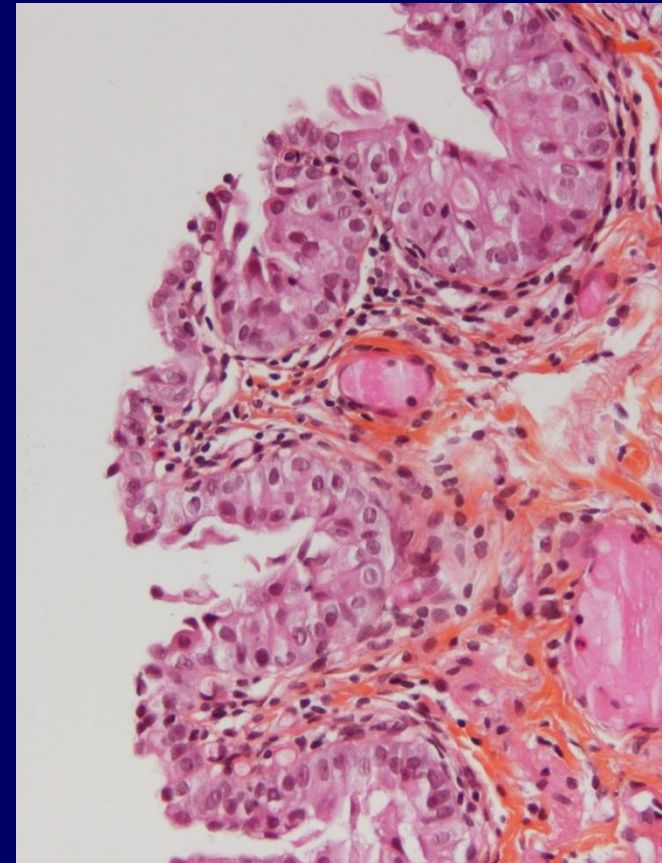
- Under the microscope : real hyperplasia ?
- Few atypia
- No architectural disorder
- Sometimes adjacent to pTa
- Sometimes isolated

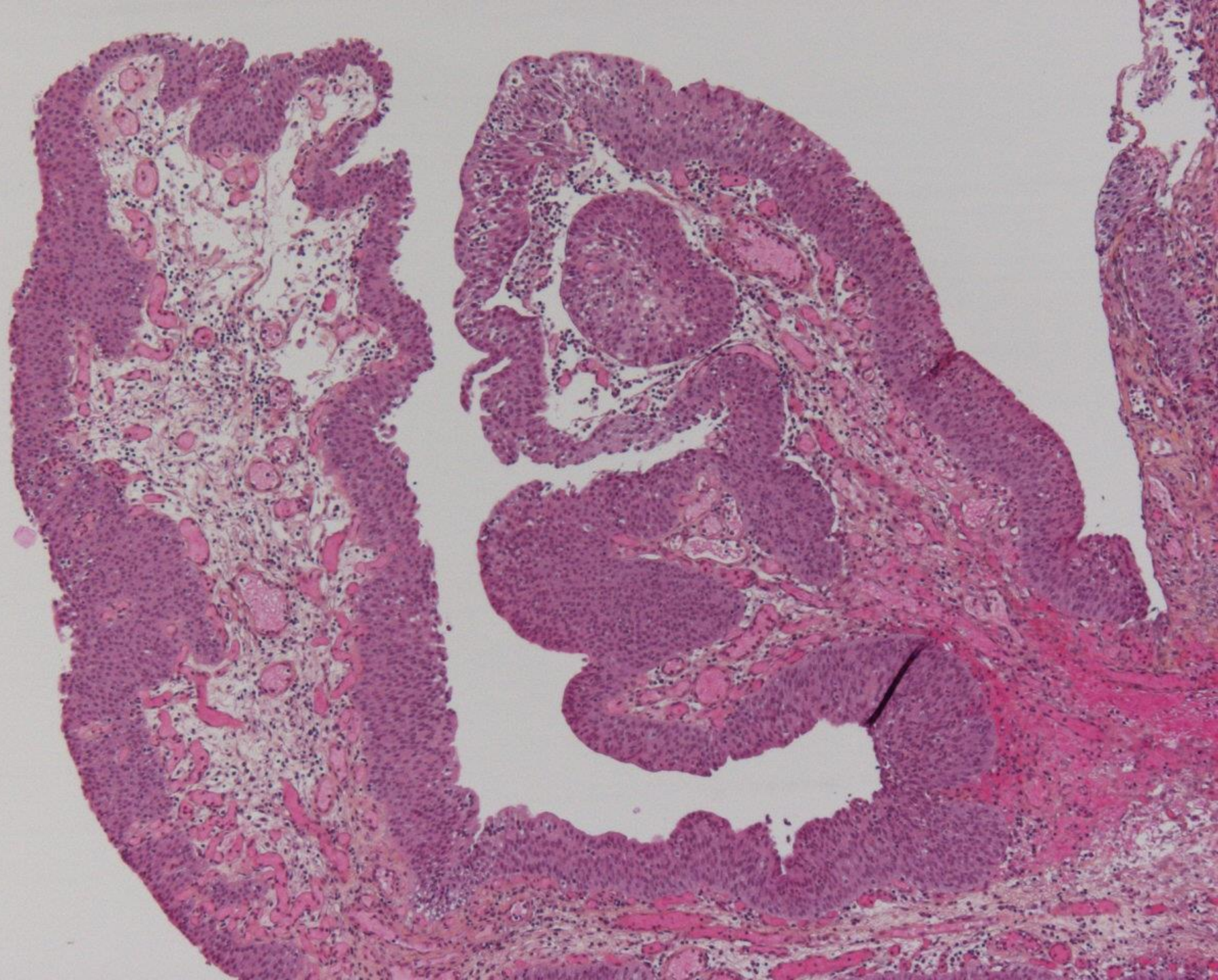




# PUPMI papillary with no atypia

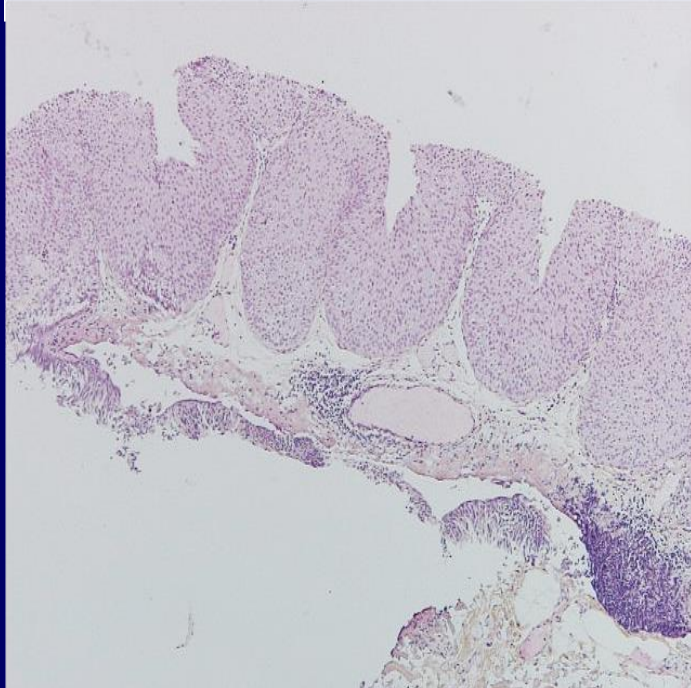
- 1975
- H>F, 50 y.o.
- Normal +/- urothelium
- No atypia
- Association with
  - hematuria
  - pTa BG (60%)





# PUPMI papillary with no atypia

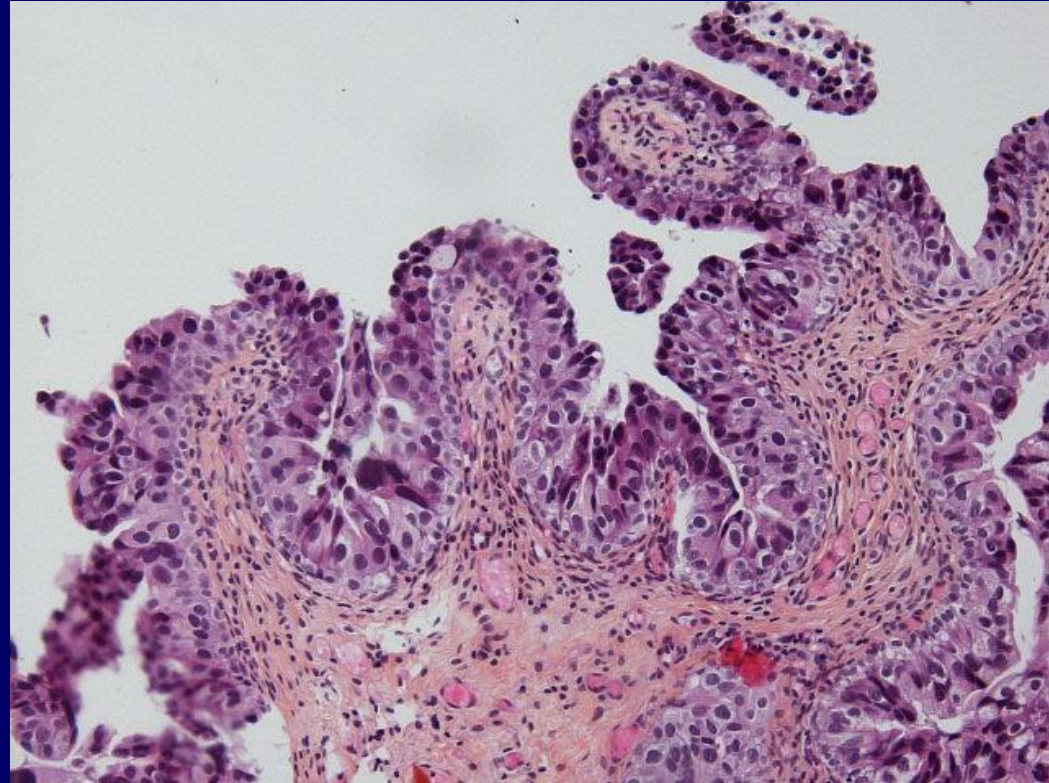
Papillary Hyperplasia Nb of cases	progression
16	4 pTa LG
	3 pTa HG



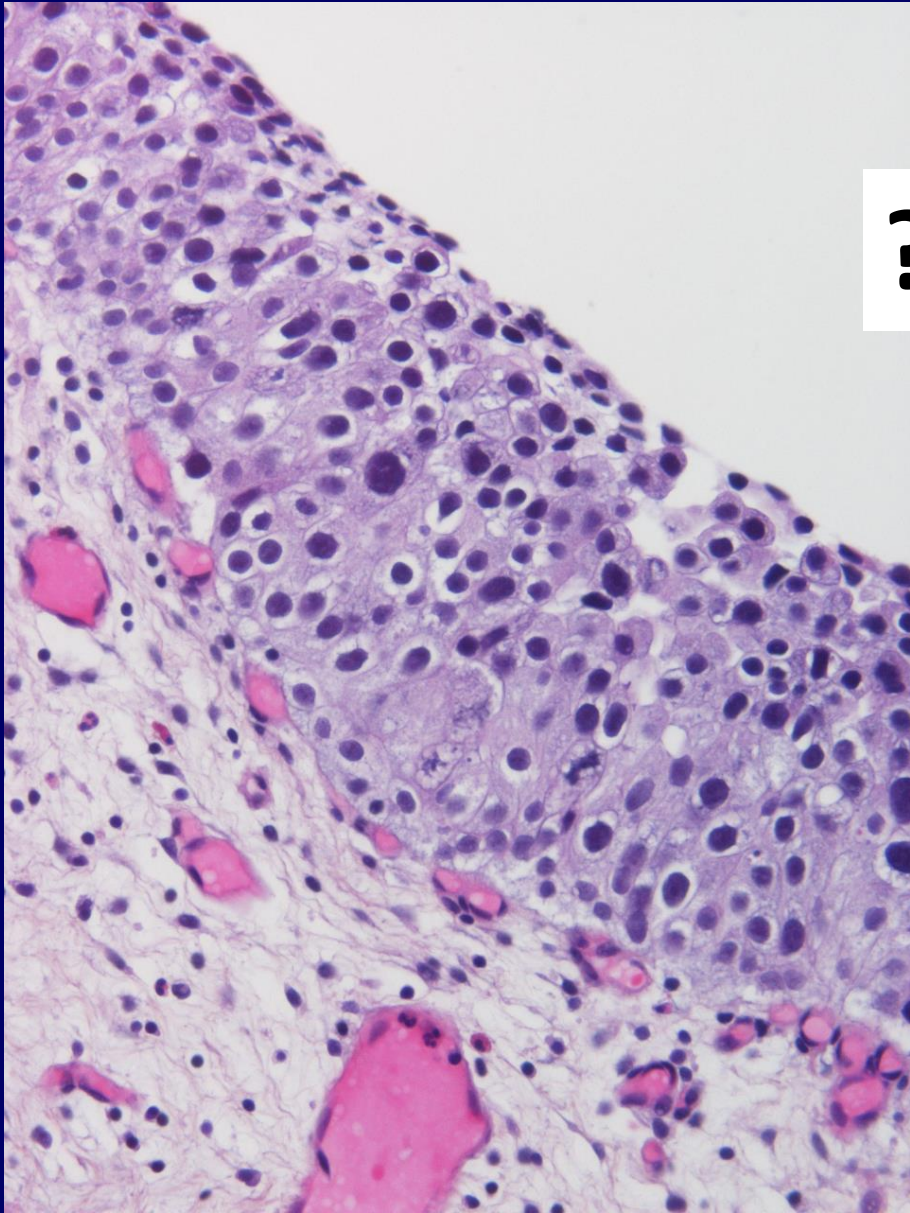
48% developed  
urothelial carcinoma

# PUPMI papillary with atypia

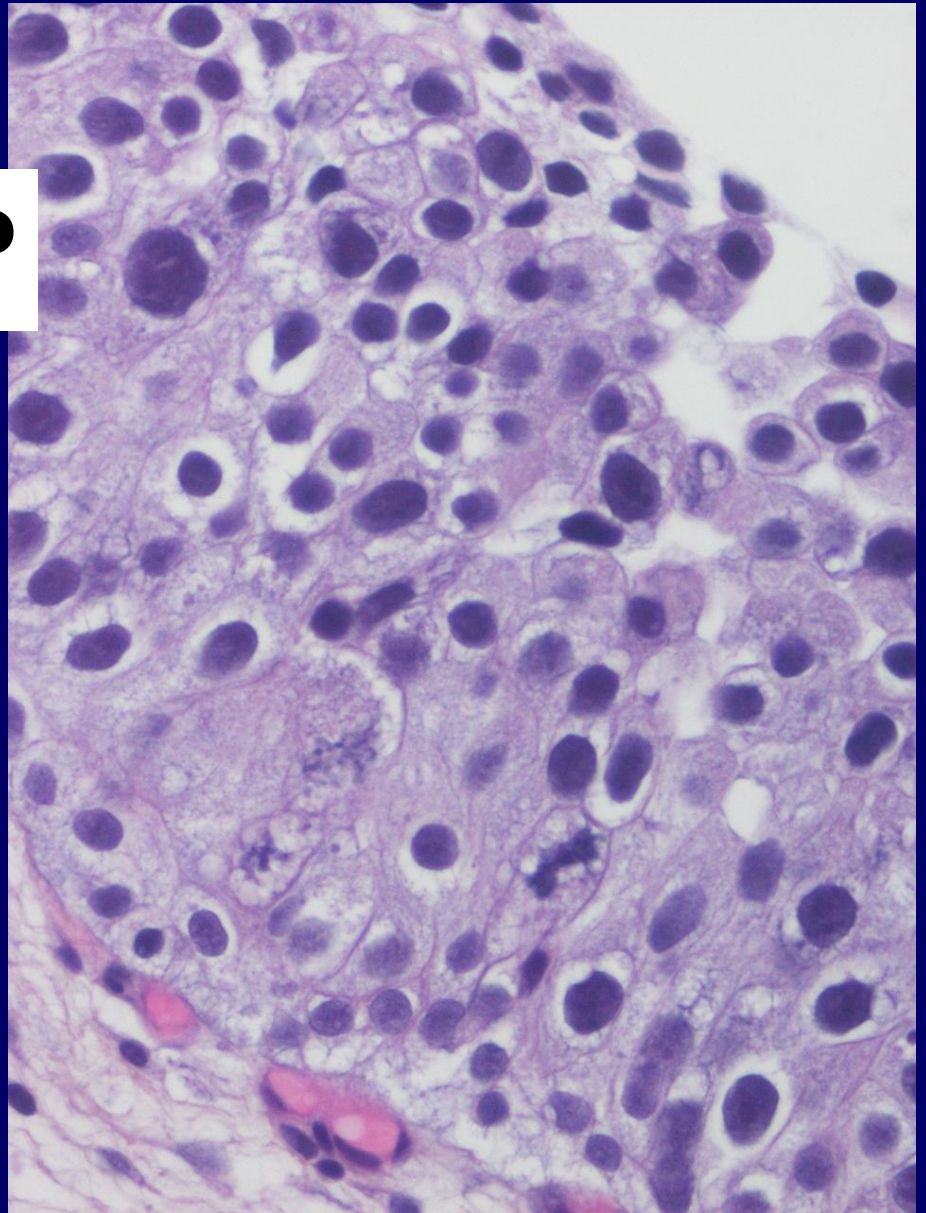
- Cytologic atypias
- Not enough papillae for pTa
- adults >50 ans
- H > F
- Often association with Cis or previous history of urothelial carcinoma



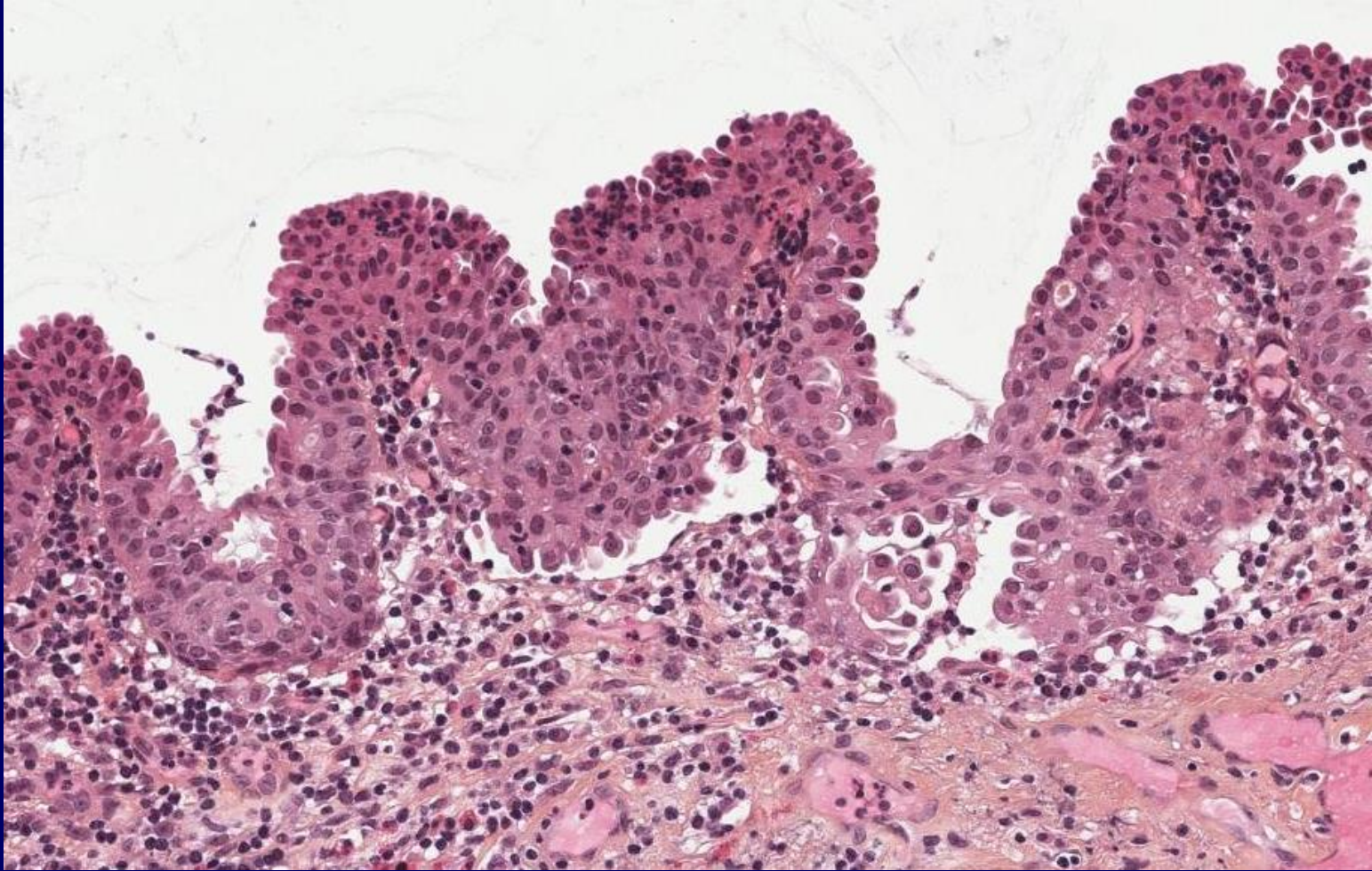
Hungerhuber, 2007, Urology  
Obermann, 2003, J Pathol  
Swierczynski Hum Path 2002



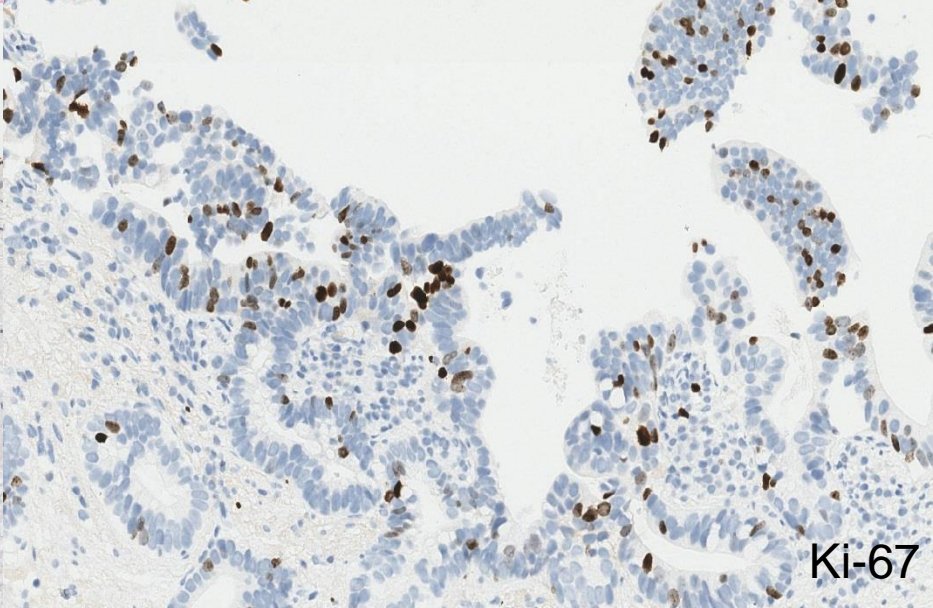
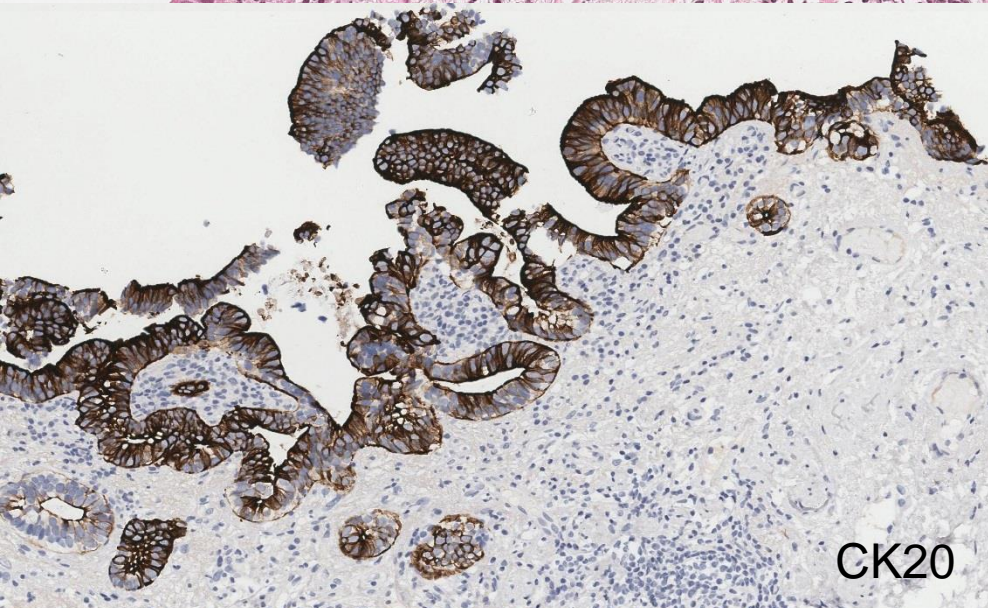
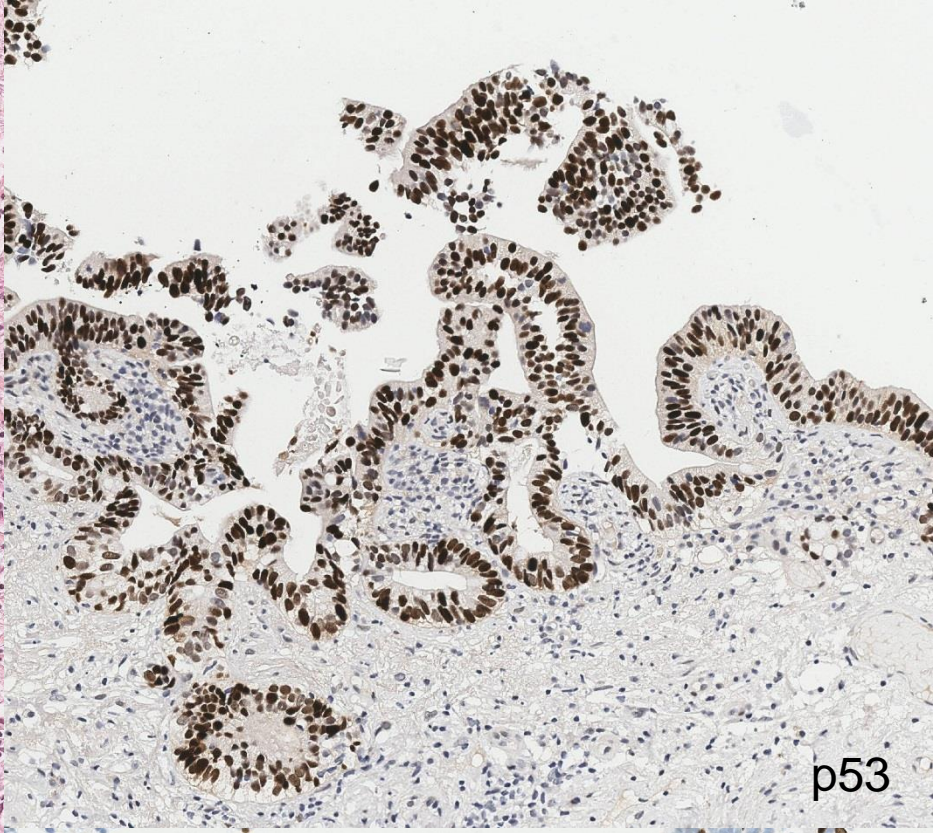
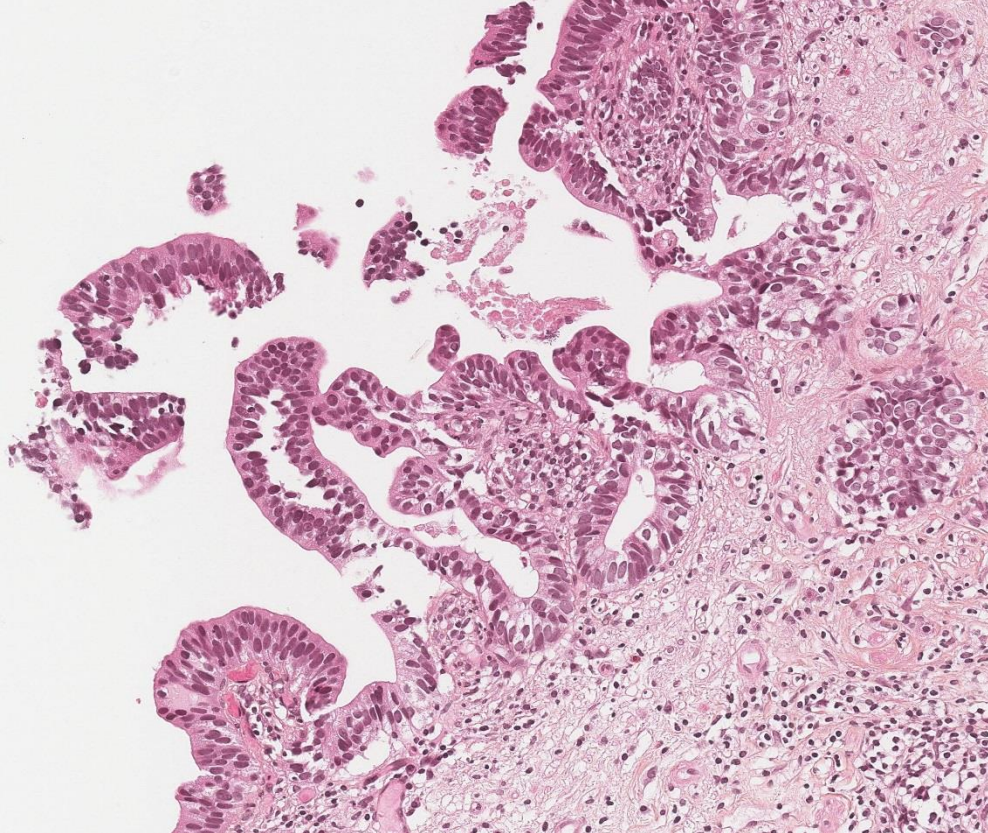
?



# PUPMI with or with no atypia ?







# PUPMI papillary with atypia

PUPMI with atypias	Follow-up 1 year
10	19 recurrences

To be considered as CIS

Histology
1 papilloma
1 pTa low grade
10 pTa high grade
4 Cis
3 $\geq$ pT1

Atypias but not CIS

# Reactive atypias

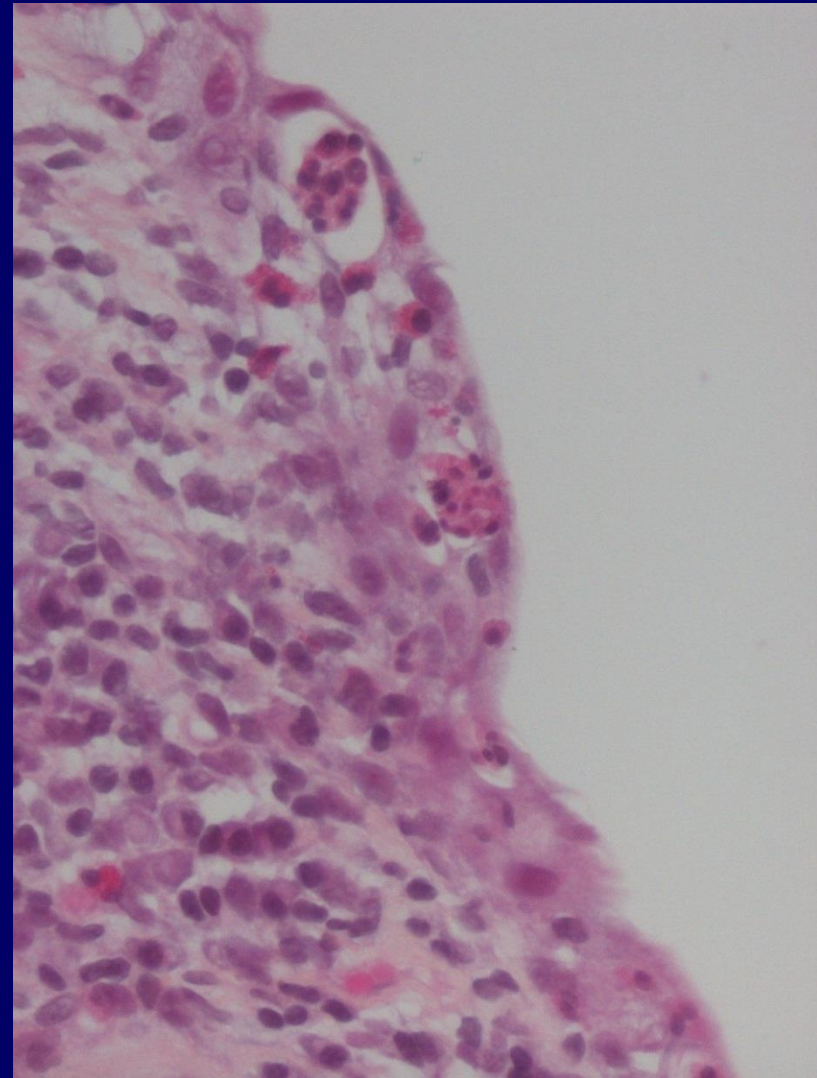
- No precise definition

- Clinical history+++  
TURB, ttt., etc...

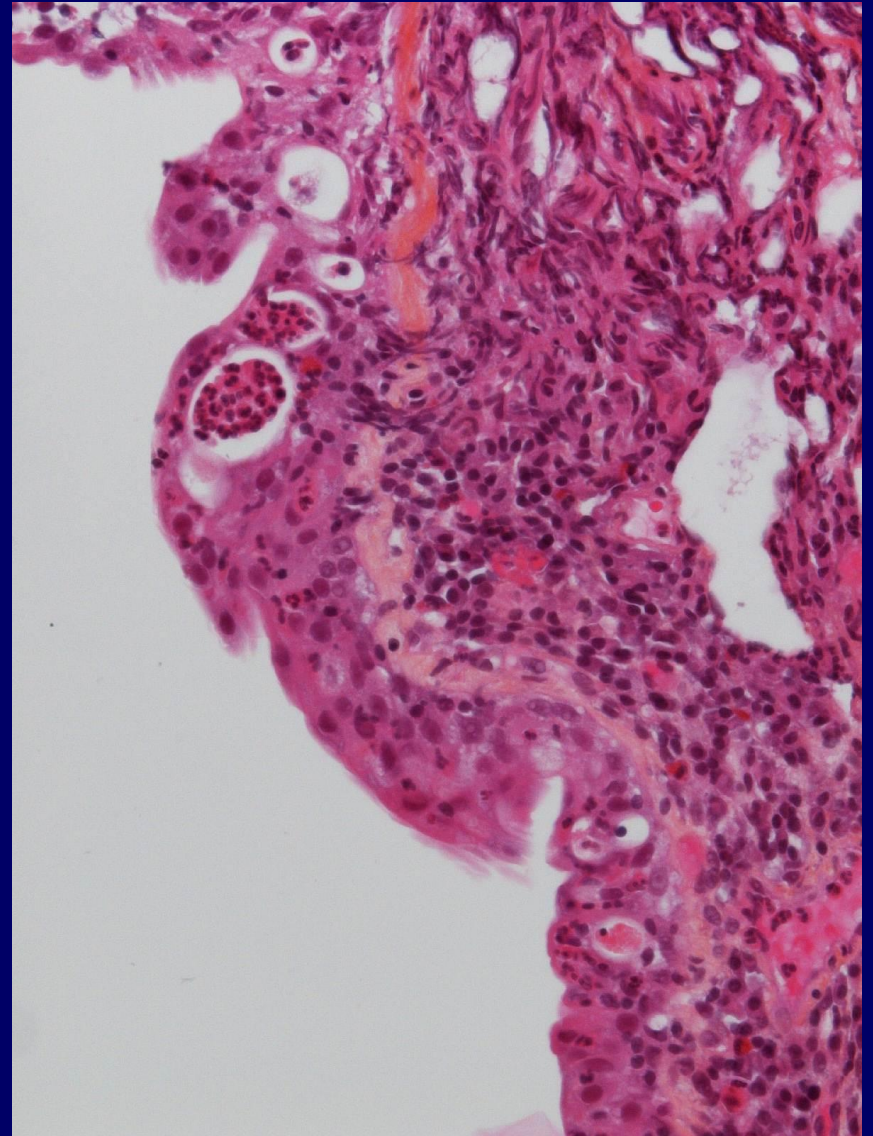
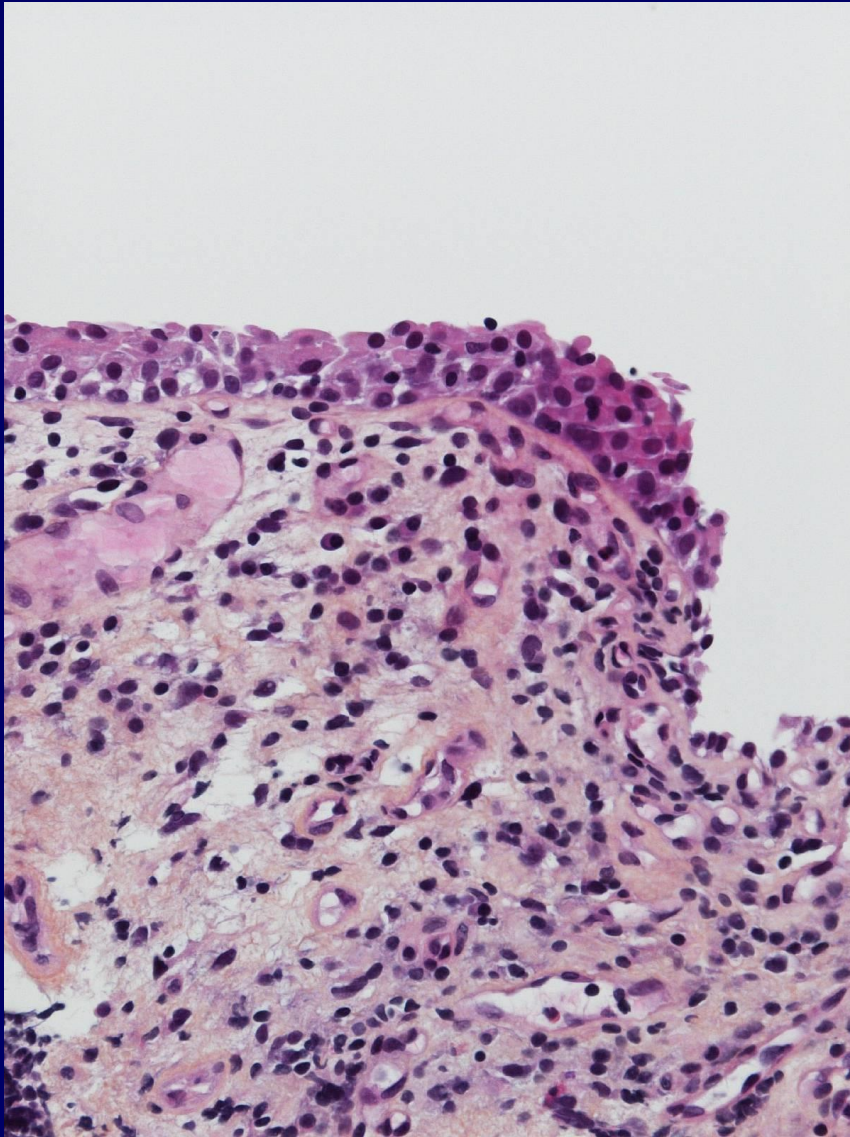
inflammation mitosis +/-  
denuded areas ?

→ danger (Cis ?)

- → Cytology +++ (Cis)

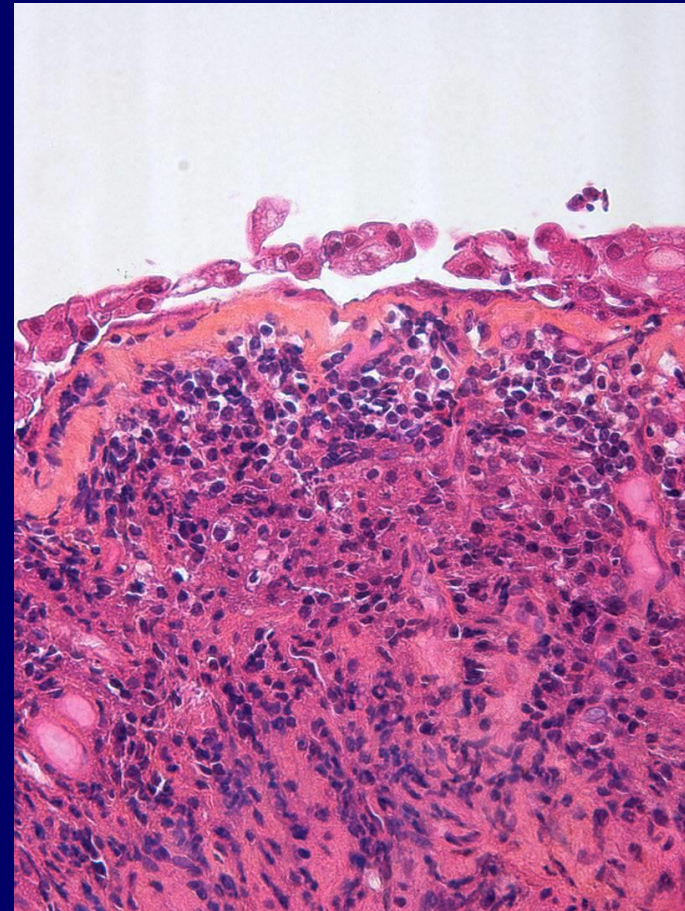


# Reactive atypias (clinical history ++)

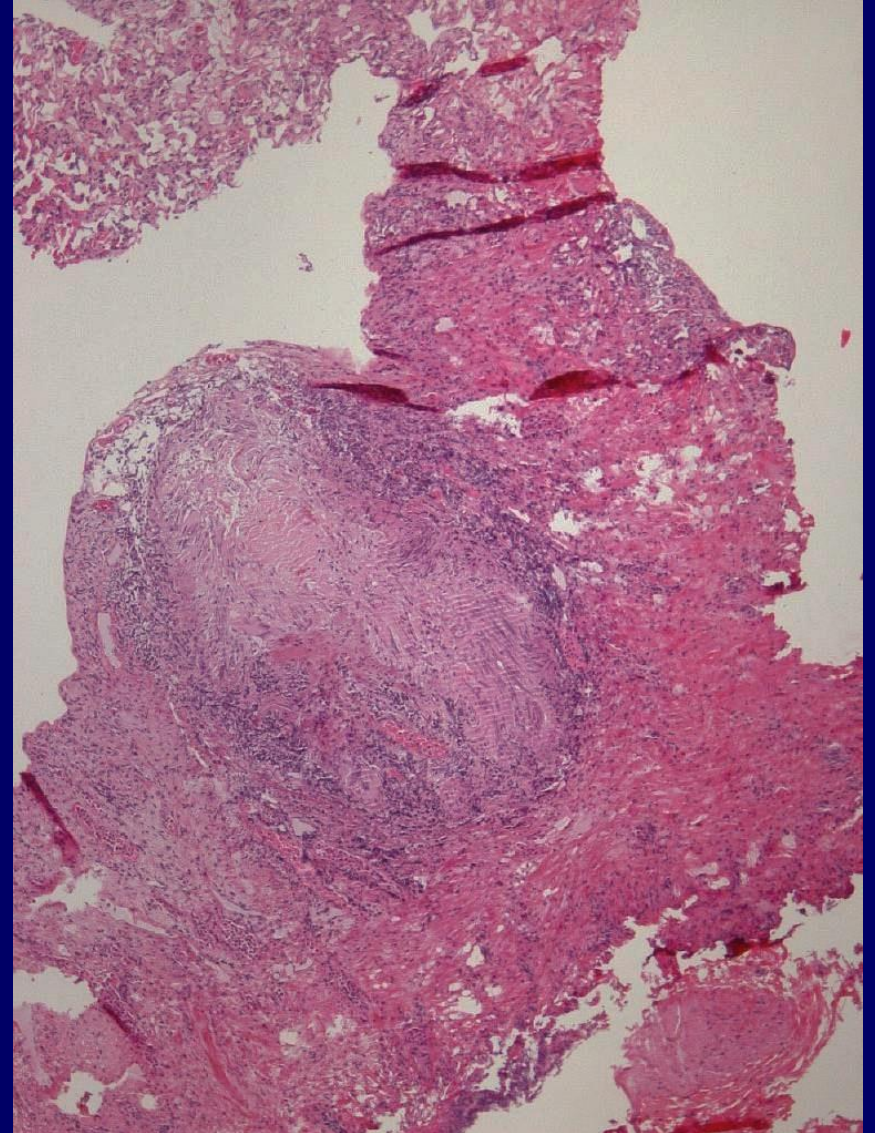
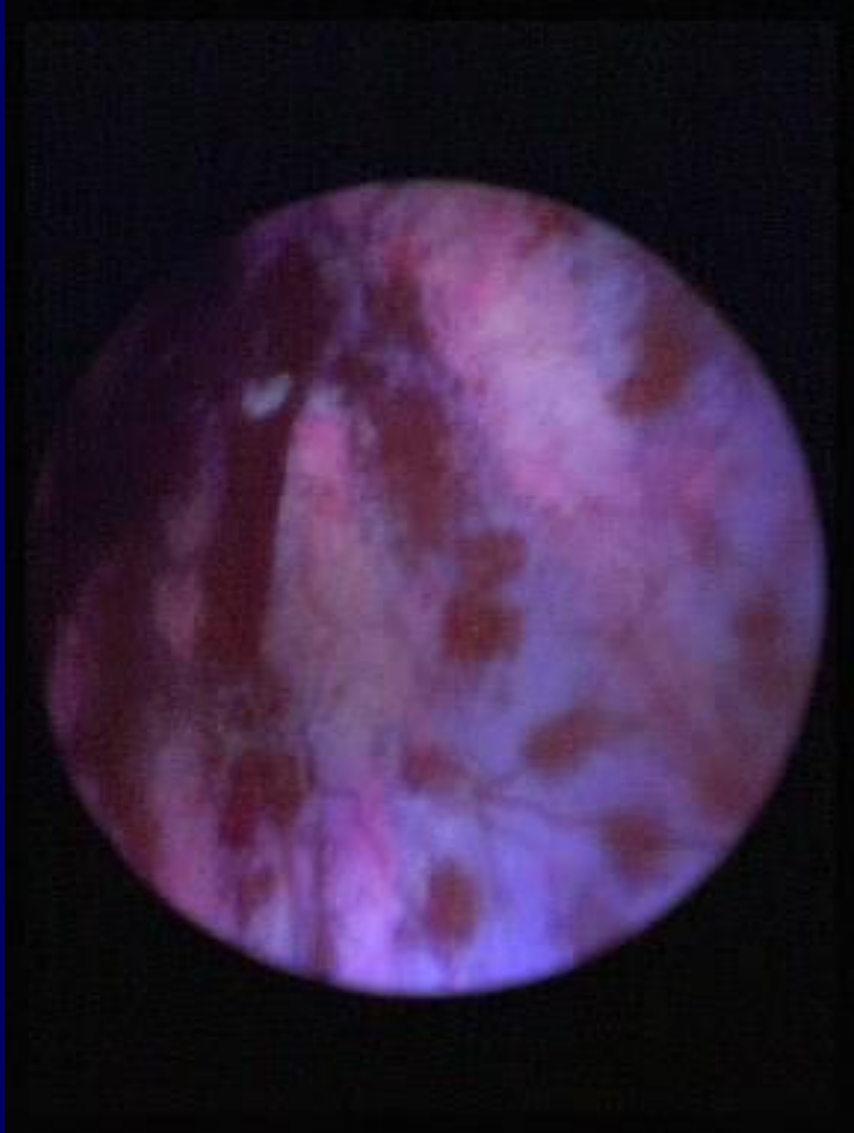


# Atypias related to treatment

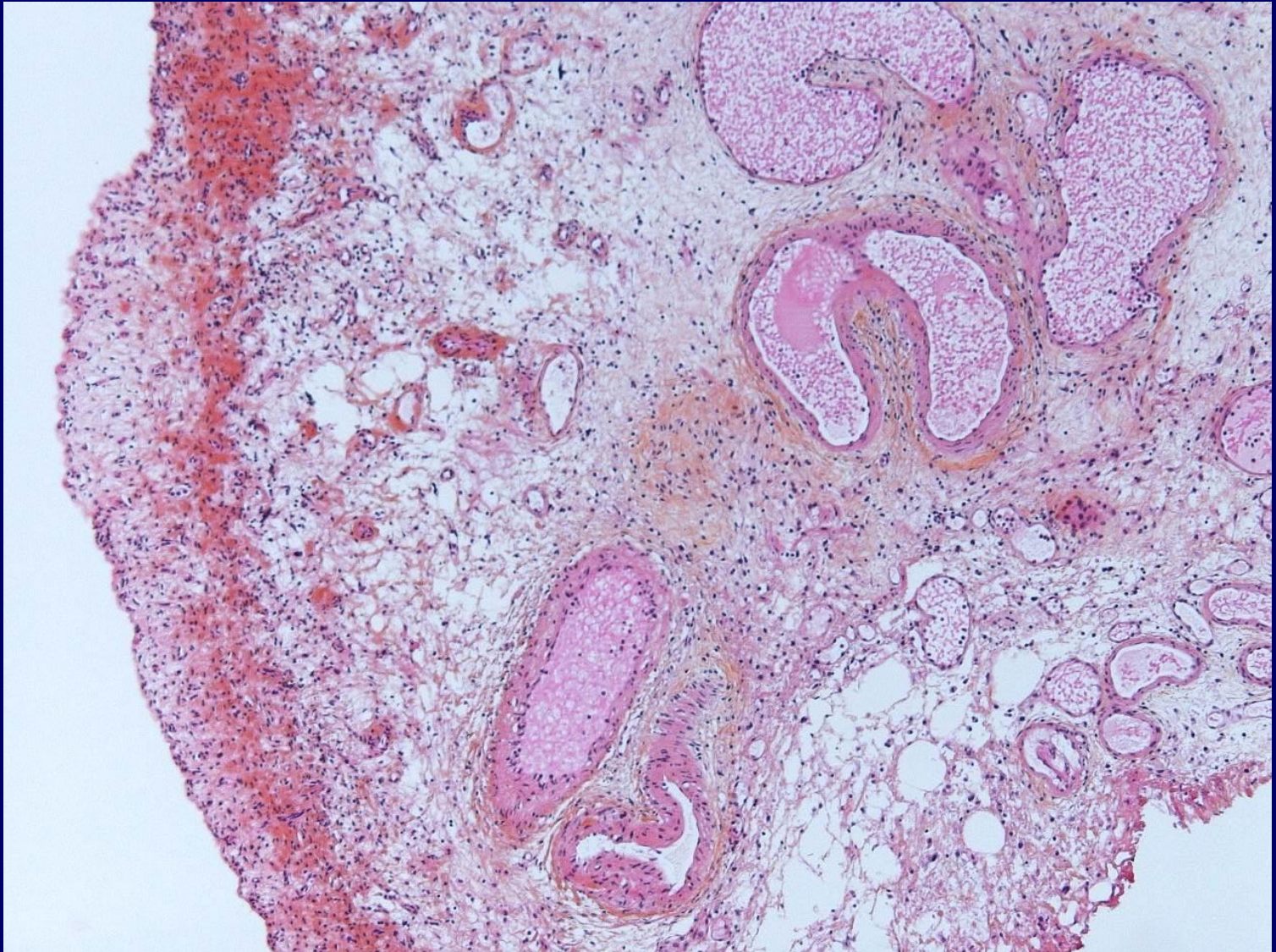
- Previous medical history+++
  - Irradiation
  - trauma
    - Catheterisms (denuded areas)
  - BCG
    - inflammation
  - Chemotherapie
    - Truncated papillae



# Granulomas post BCG therapy

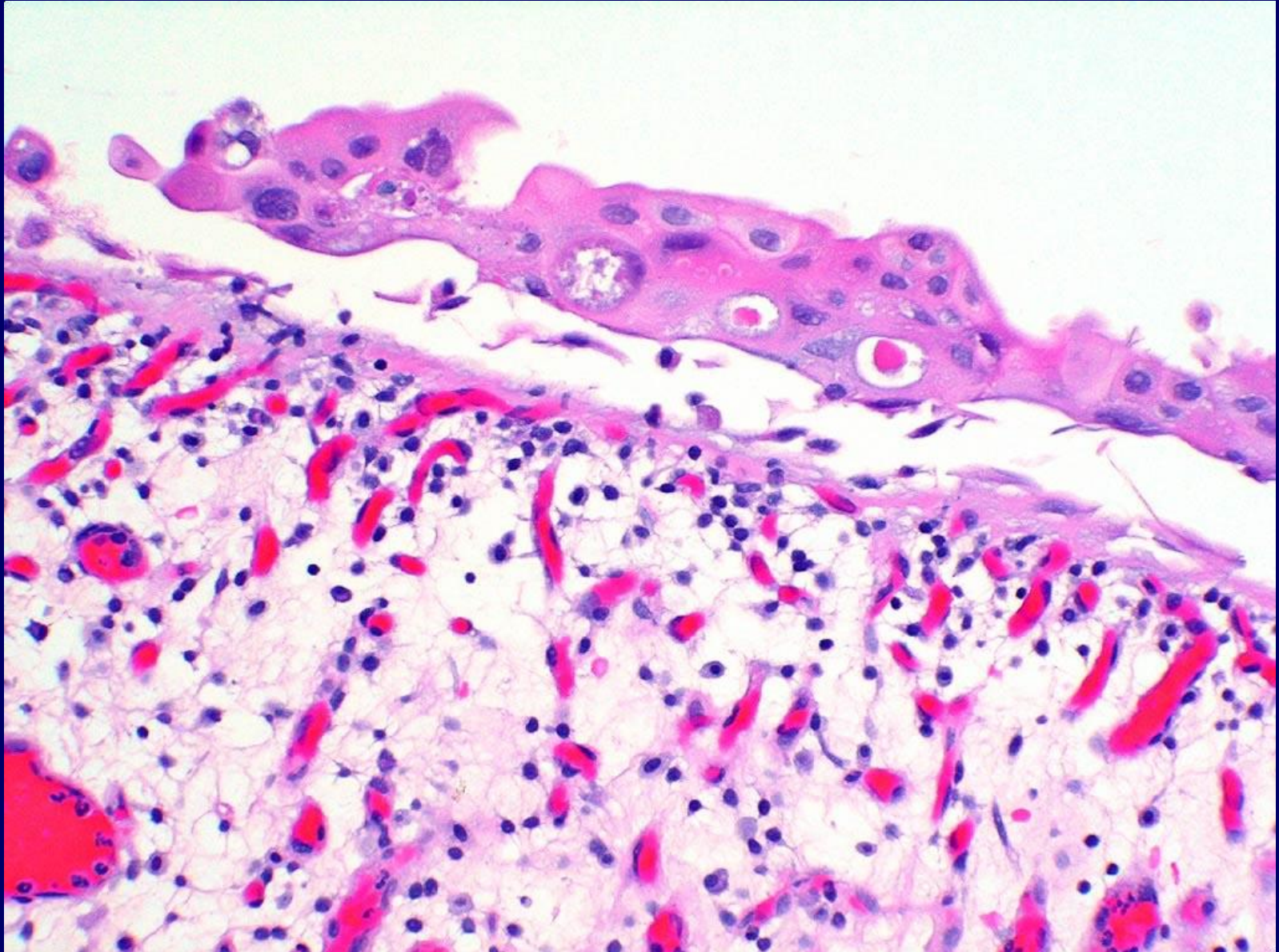


# Atypias related to treatment





# Atypias related to treatment



# Atypia versus dysplasia

Clinical Findings for Patients with Reactive Atypia, Atypia of Unknown Significance, and Dysplasia of the Urinary Bladder

Characteristics	Reactive atypia (n = 25)	Atypia of unknown significance (n = 35)	Dysplasia (n = 26)
Mean age (range), yrs	66 (39-88)	64 (24-80)	69 (50-85)
Male-to-female ratio	4:1	2:1	4:1
Major symptoms	Hematuria or irritative symptoms Erythematous/inflamed or suspicious	Hematuria or irritative symptoms Erythematous/inflamed or suspicious	Hematuria or irritative symptoms Erythematous/inflamed or suspicious
Major cystoscopic findings	for tumor	for tumor	for tumor
Mean follow-up (range), yrs	3.6 (0.1-9.9)	3.7 (0.2-11.4)	3.9 (0.1-13.4)
Clinical outcome	No adverse outcome <sup>a</sup>	No adverse outcome <sup>a</sup>	15% developed biopsy-proven cancer progression

<sup>a</sup> None developed dysplasia, carcinoma in situ, or urothelial carcinoma

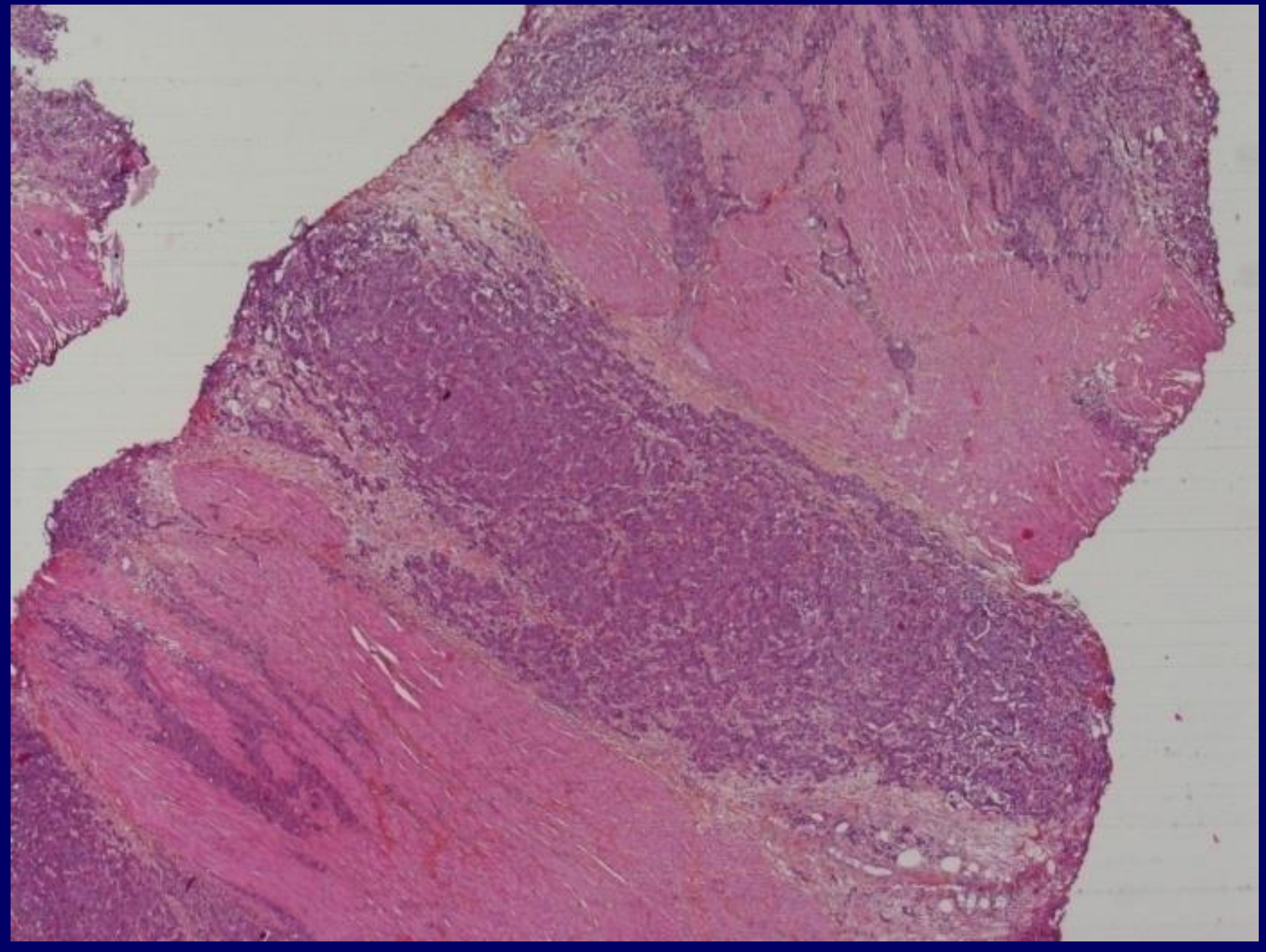
**Table 3** Clinical outcomes of patients with atypical urothelial proliferations of the urinary bladder based on the 1998 WHO/ISUP classification

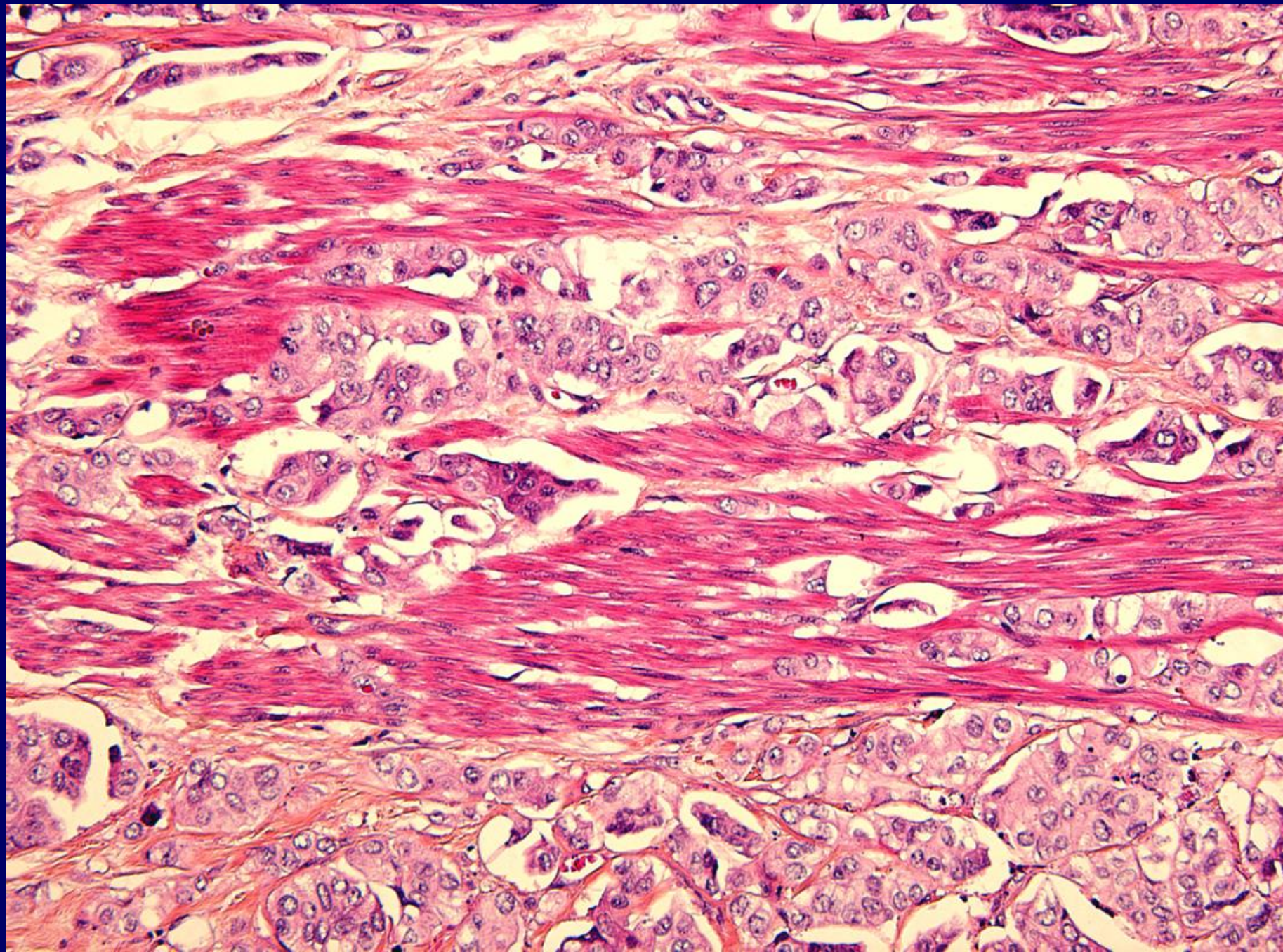
1988 WHO/ISUP classification	Clinical significance
Reactive atypia	None developed dysplasia, carcinoma in situ, or urothelial carcinoma
AUS	None developed dysplasia, carcinoma in situ, or urothelial carcinoma
Dysplasia	14%-19% develop biopsy-proven progression [22,31,34,35]

Cheng, 2000, Mod Pathol  
Hodges et al. 2010, Hum Path

pT2







# Prognosis (pt2)

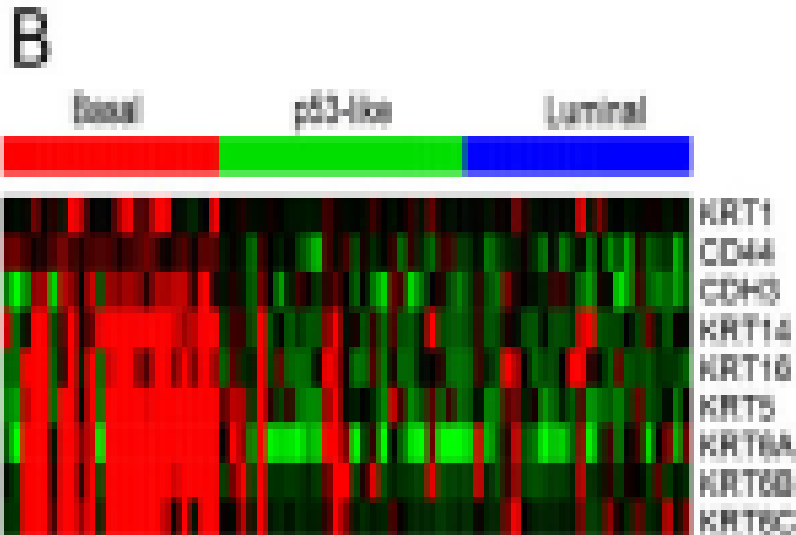
Vascular invasion

Multifocal CIS

Positive surgical margin (ureters and urethra) + (UUT)

## Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy

Woonyoung Choi, Sima Porten, Seungchan Kim, Daniel Willis, Elizabeth R. Pilmack, Jean Hoffman-Censits, Beat Roth, Tiewel Cheng, Mai Tran, I-Ling Lee, Jonathan Melquist, Jolanta Bondaruk, Tadeusz Majewski, Shizhen Zhang, Shanna Pretzsch, Keith Baggerly, Arlene Slefker-Radtke, Bogdan Czerniak, Collin P.N. Dinney, and David J. McConkey



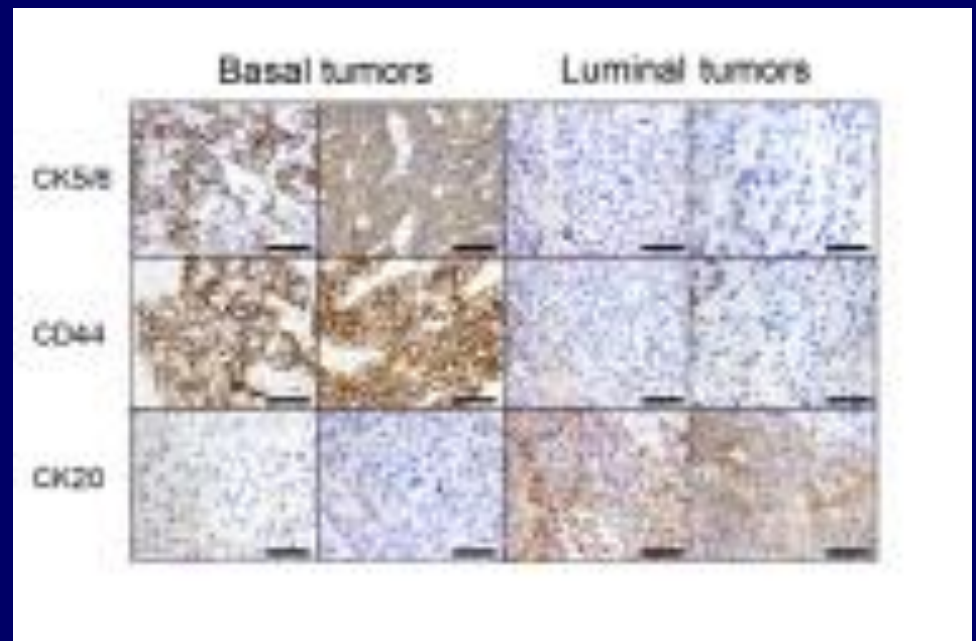
Genotype and immunophenotype close to basal and luminal breast cancer (ER, PPAR $\gamma$ )



Luminal : urothelial differentiation  
GATA3, Uroplakin, CK20

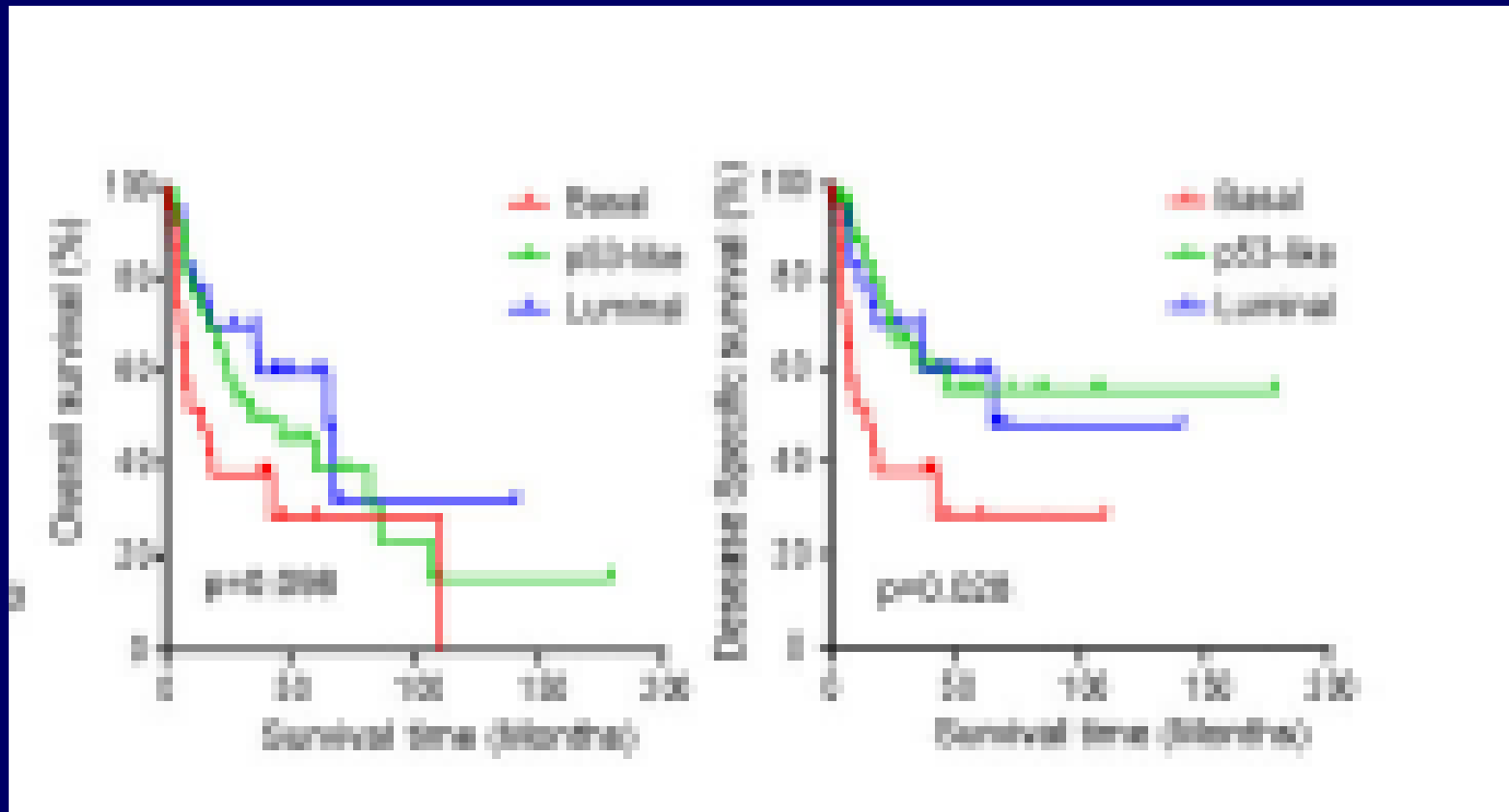
P53-like sub group of  
luminal has no specific  
immunphenotype

Basal : basal and stem cell  
differentiation p63 CK5-6,  
CK14, CD44



Basal subtype present with squamous or sarcomatoïde  
phenotype

Basal and luminal have different prognosis  
... what pathologist knew from long time !

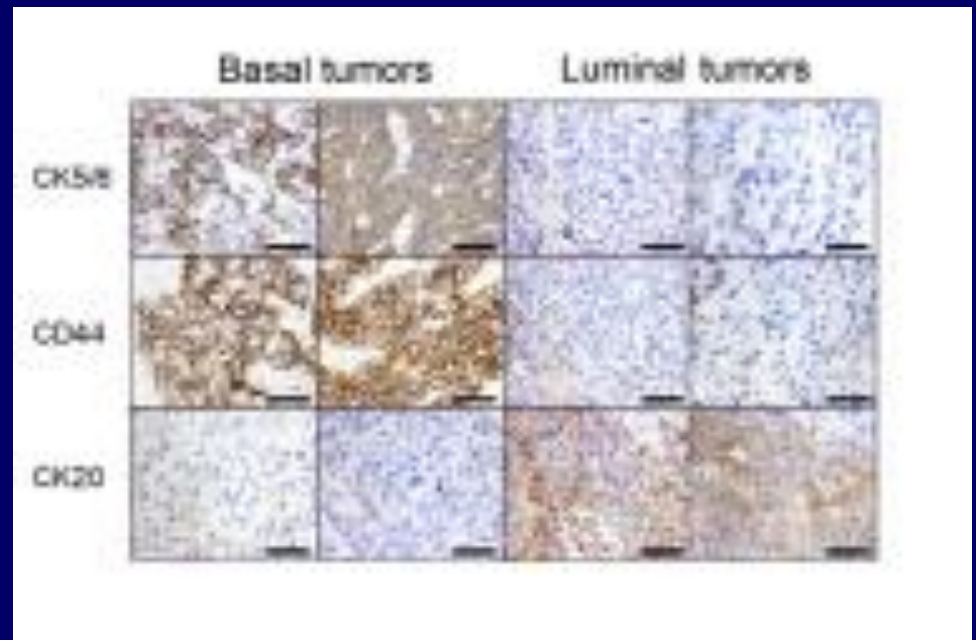


Kaplan-Meier plots of overall survival (p = 0.098) and disease-specific survival (p = 0.028)

Luminal : variable  
chemosensitivity

P53-like : MVAC resistance

Basal : chemosensitive

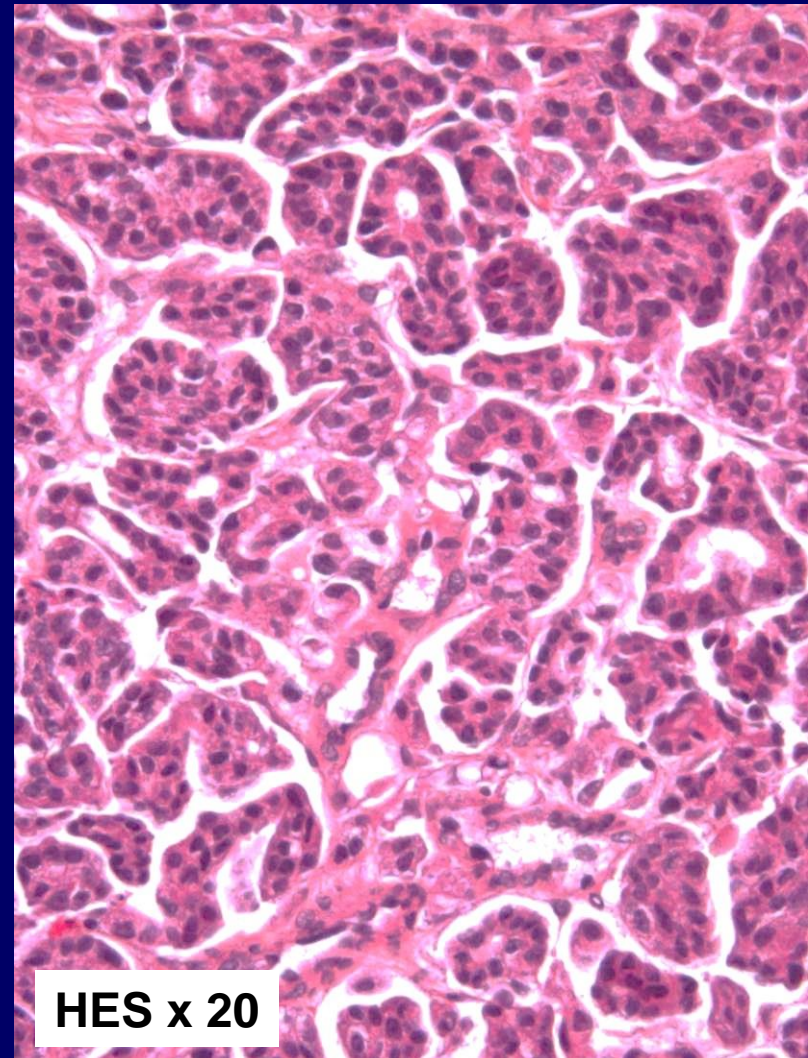


# Morphologic variants

# Micro Papillary Carcinoma

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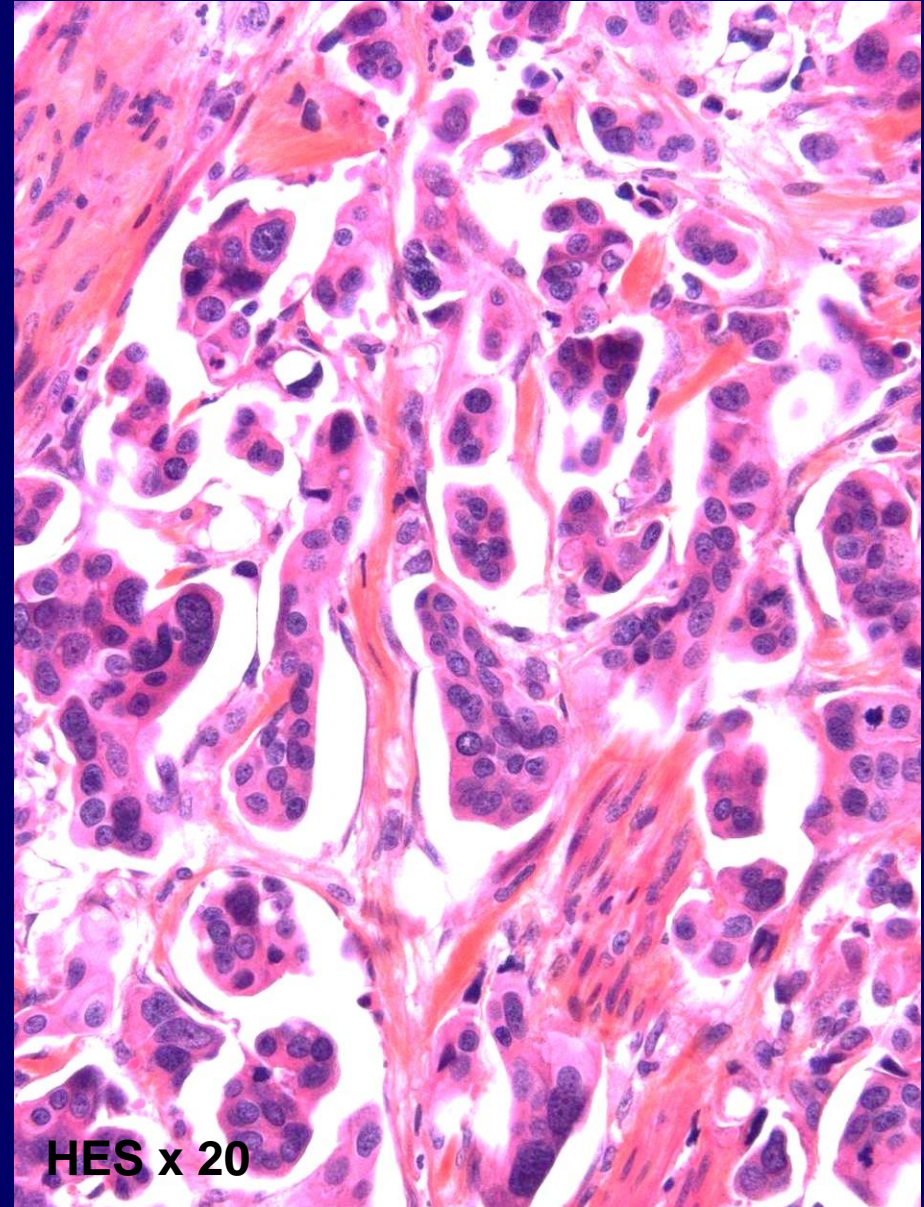
- incidence 0,6 to 2,2%
- M : F = 5 : 1
- papillae
  - 3 to 20 cells
  - nests, balls
  - atypia +/-
  - mitosis
- fibrovascular core rare
- few inflammation



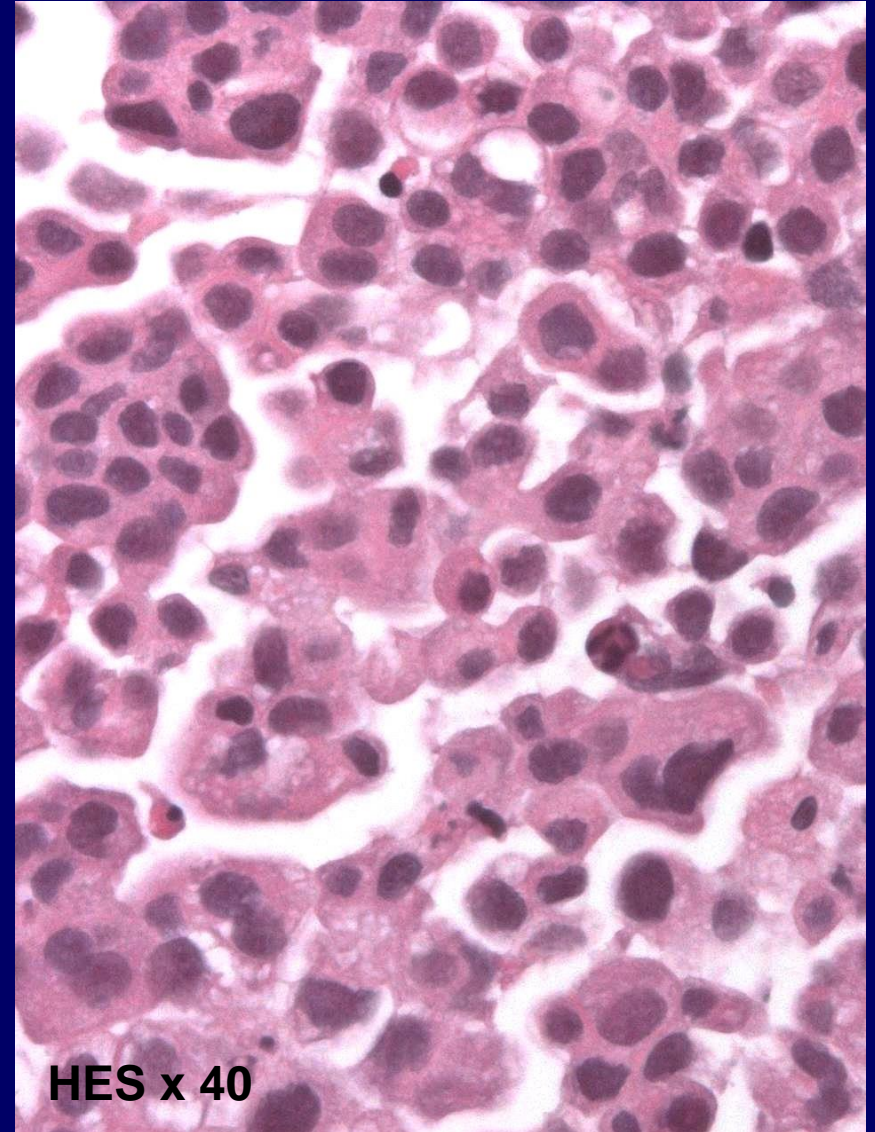
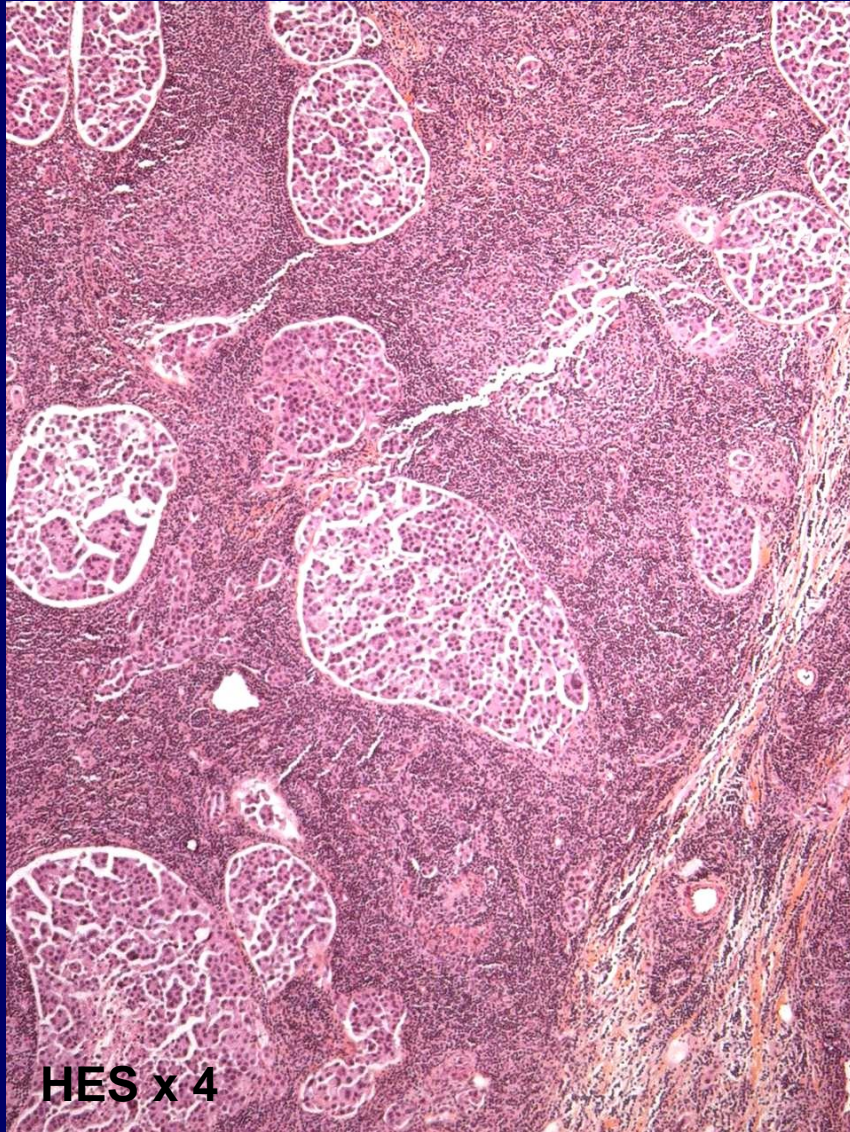
# MPC Histology

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- mimic vascular invasion
- not overestimate

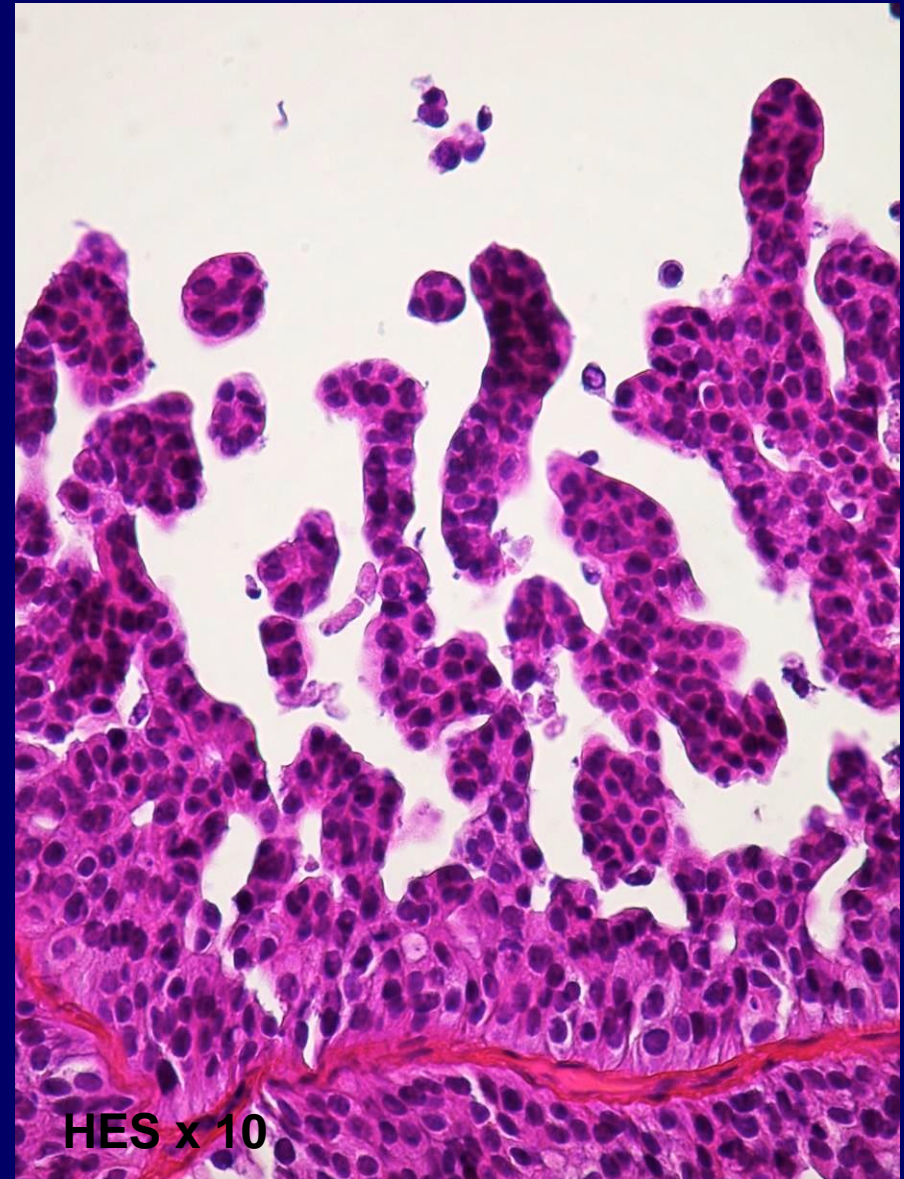


# Lymph node metastasis: common



# Superficial Non Invasive Variant

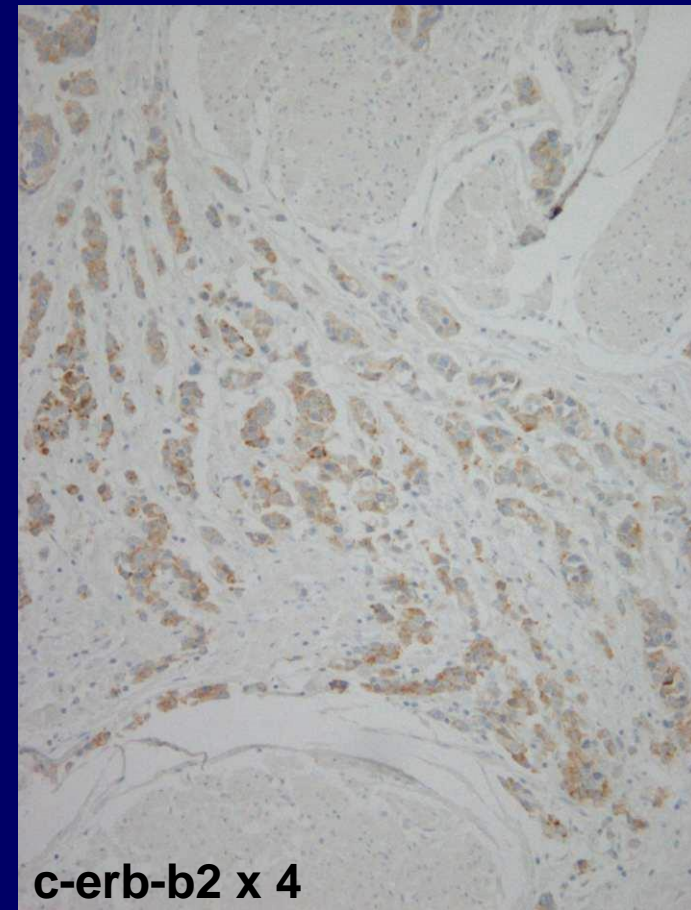
- superficial MPC be sure of presence of muscle in case of biopsy
- associated with *Cis*
  - ( $> 50\%$ )





# MPC and Prognostic Markers

- Alteration of different metabolic pathways
  - cell cycle (p53)
  - mitosis (Aurora A)
  - mitosis (MIB-1)
  - apoptosis (survivin)
- Luminal phenotype
- c-erb-b2 expression : 70%



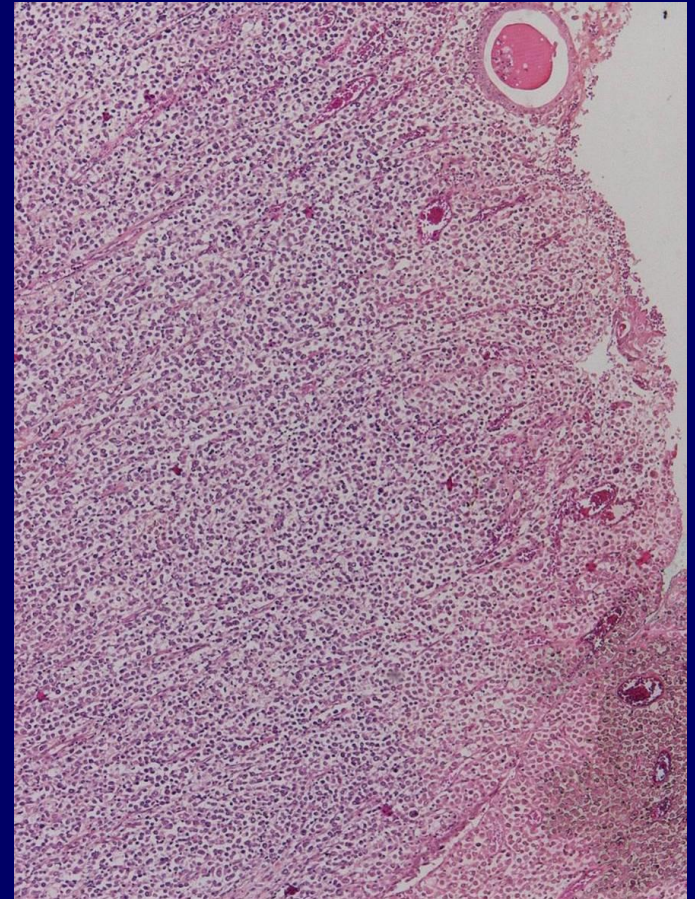
# Treatment

---

- BCG therapy inefficient in superficial forms (pTa, pT1)
  - cystectomy if pT1 ?
- c-erb-b2 expression
  - Herceptin ?
- educate urologist
  - repeat biopsies if no muscle

# Plasmacytoid UC

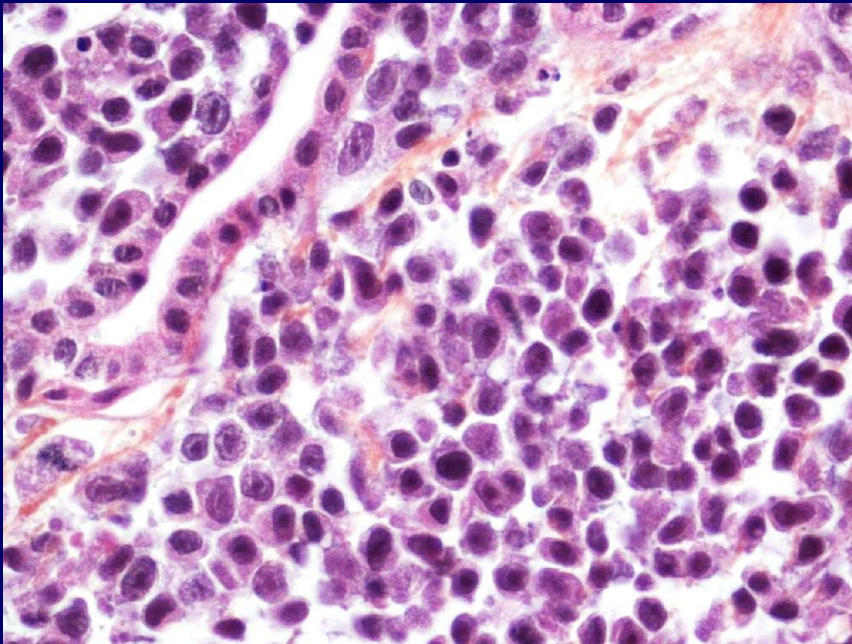
- unusual
- M : F = 2:1
- DD
  - lymphoma
  - multiple myeloma
- epithelial markers + (CK7+)
  - CD45-, HMB-45 -, PS100 -



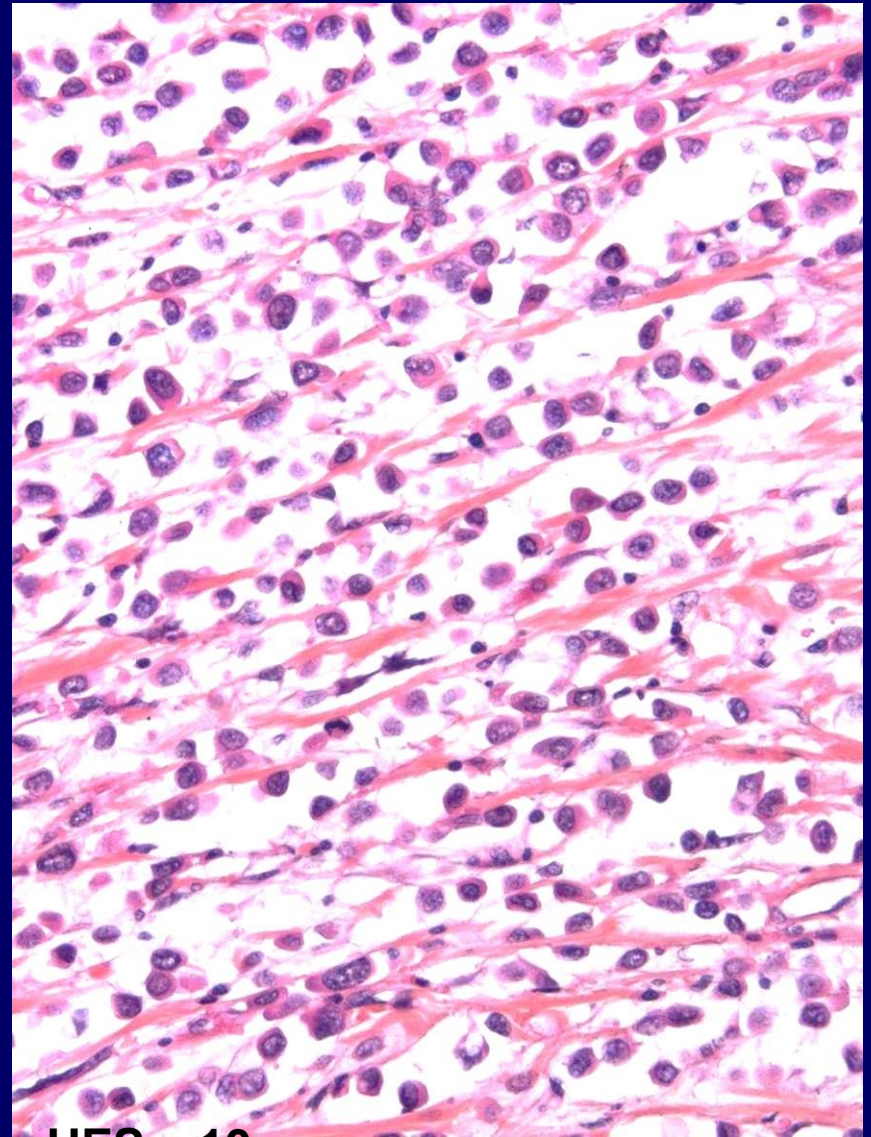
# Plasmacytoid UC

Luminal phenotype

Loss of E-Cadherine expression



HES x 10

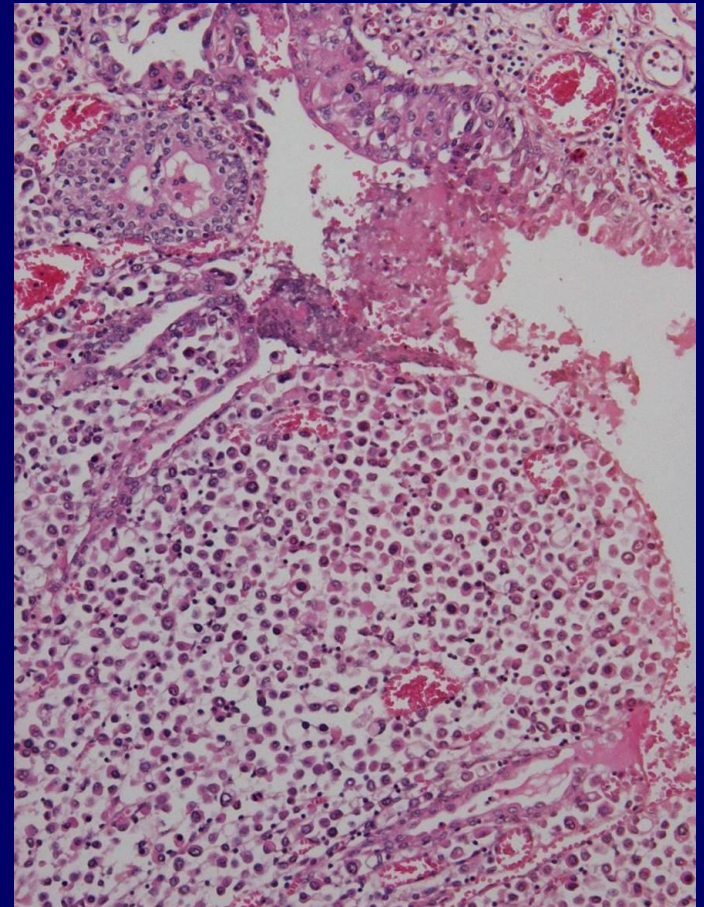


HES x 10

# Plasmacytoid UC

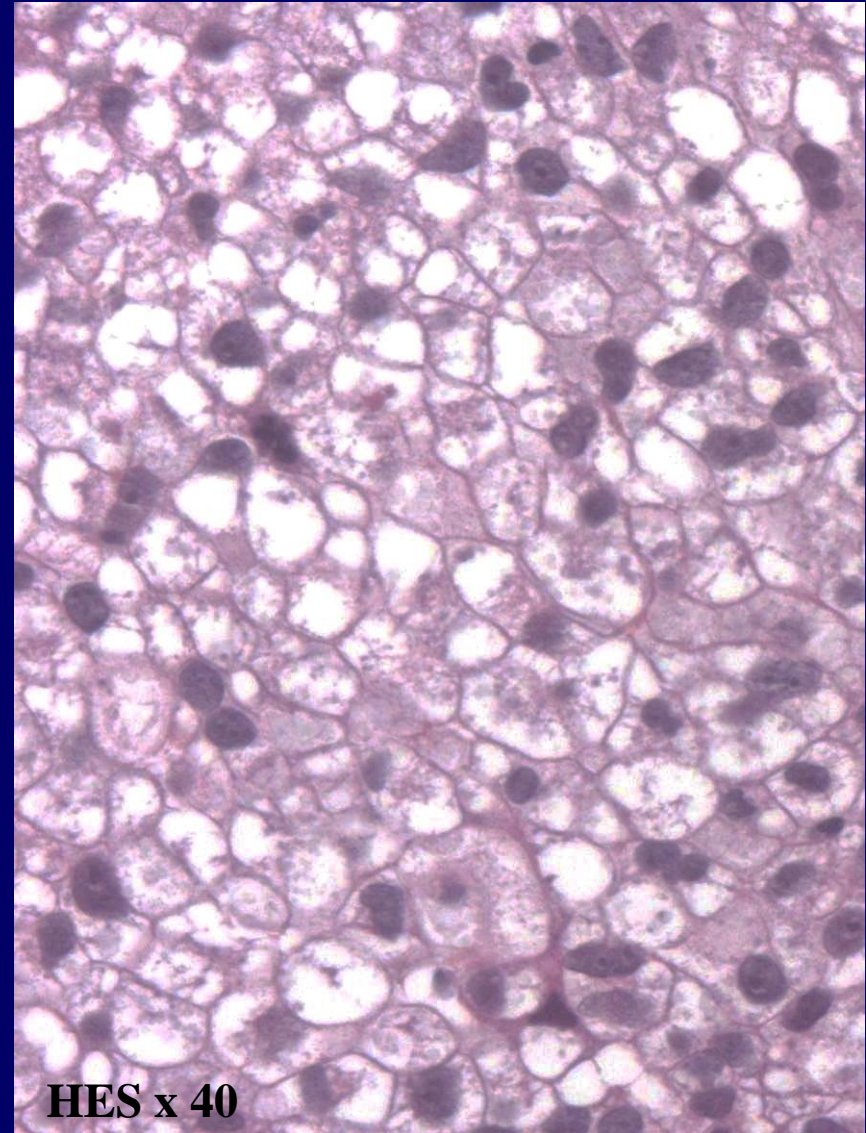
---

- association with
  - high grade UC
  - sarcomatoid carcinoma
- prognosis related to stage
- clinical outcome poor
- overall survival ~ 23 month



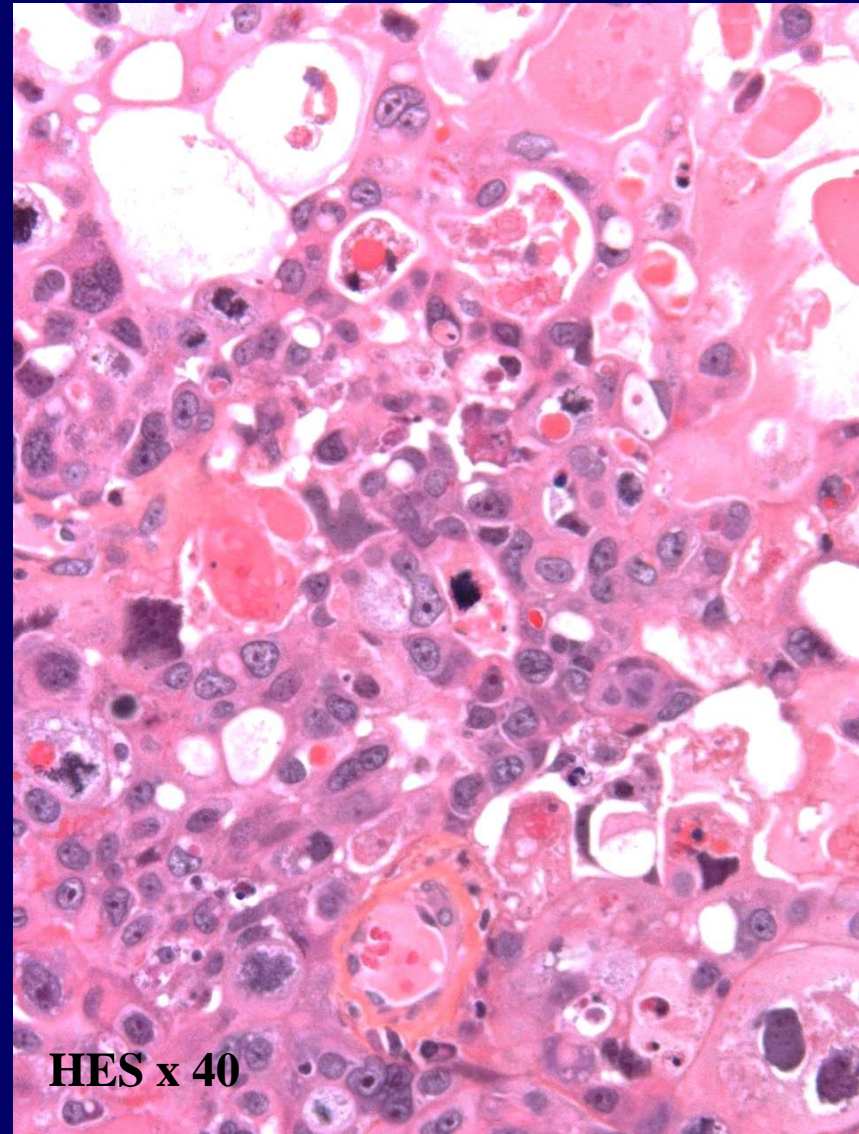
# Clear Cell Carcinoma

- abundant glycogene
- CK7 +
- DD:
  - CCC kidney (CD10)
  - paraganglioma (PS100, Chromo A)
  - clear cell adenocarcinoma



# Large Cell Tumors/ undifferentiated UC

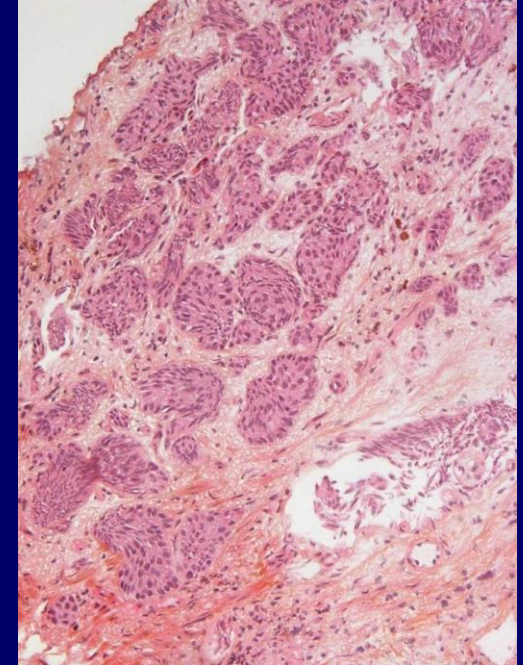
- poor differentiation
- poor prognosis
- DD, lung, prostate...
- pure cases rare



# Nested Carcinoma

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- male predominance (H/F= 4/1)
- age ~ 65a
- rare
- often associated with high grade UC
- grossly no specific findings
- association with flat and papillary tumors possible

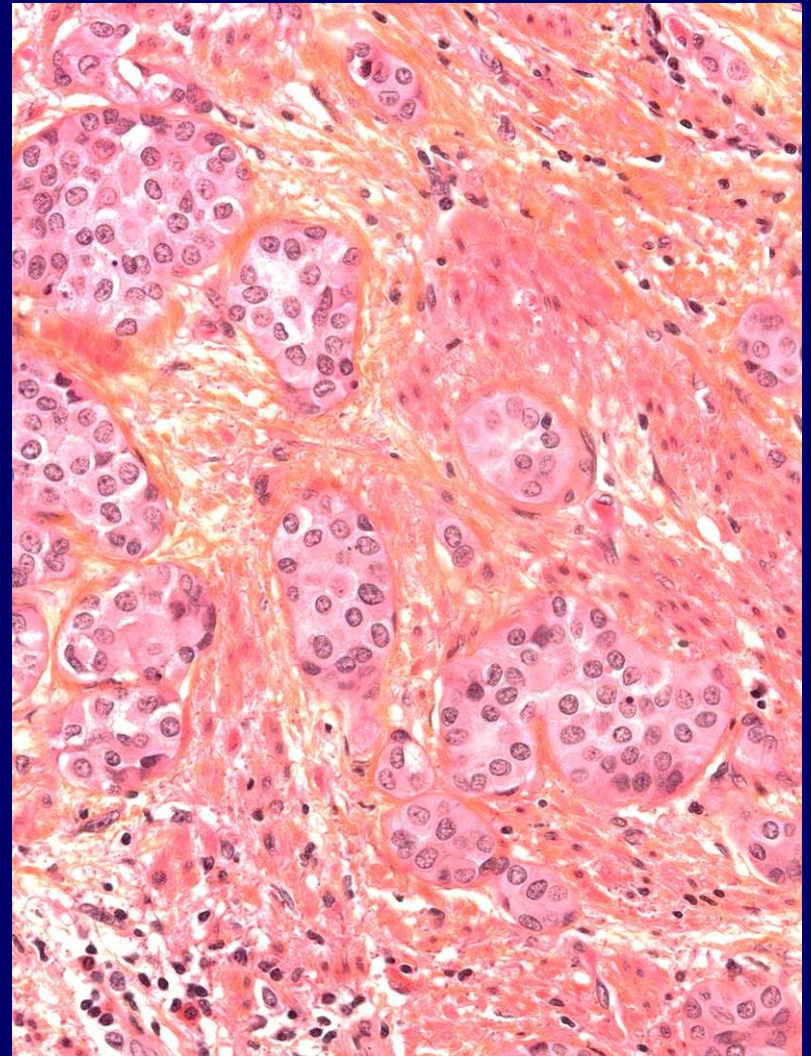




# NC Histology

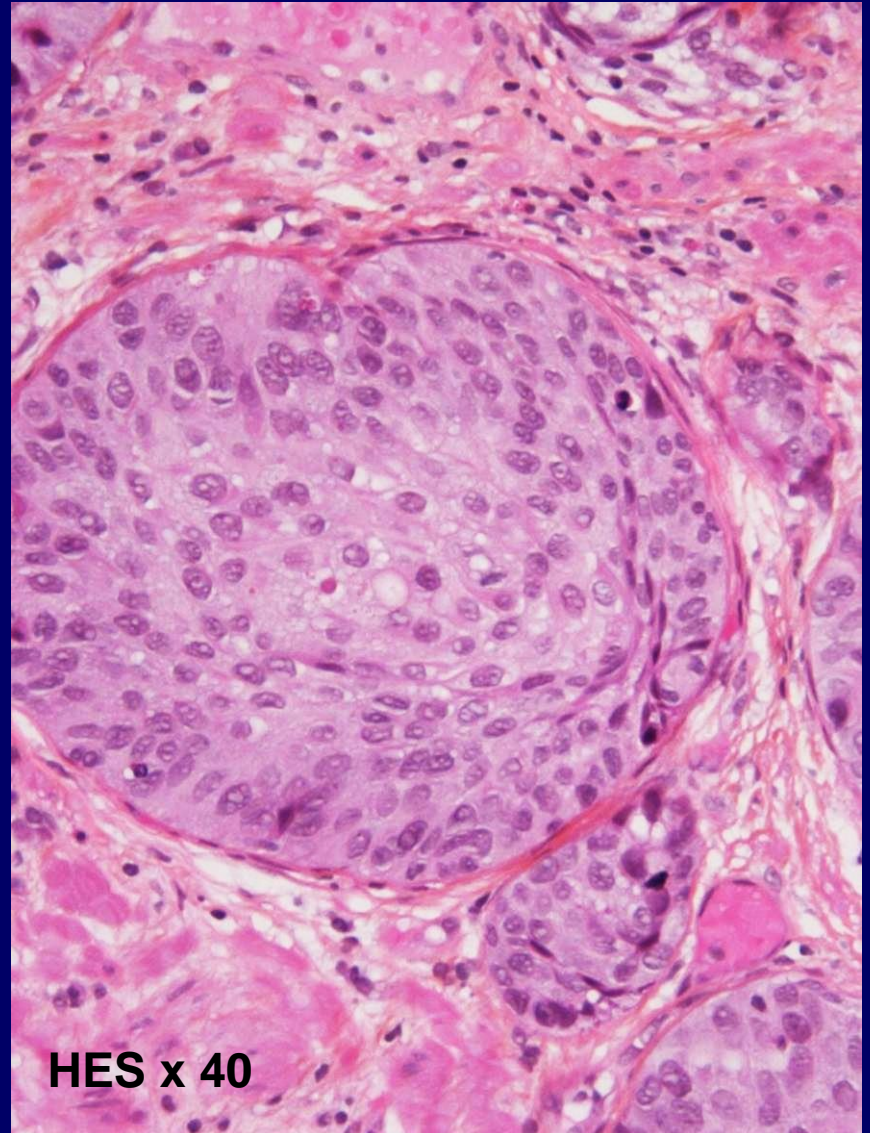
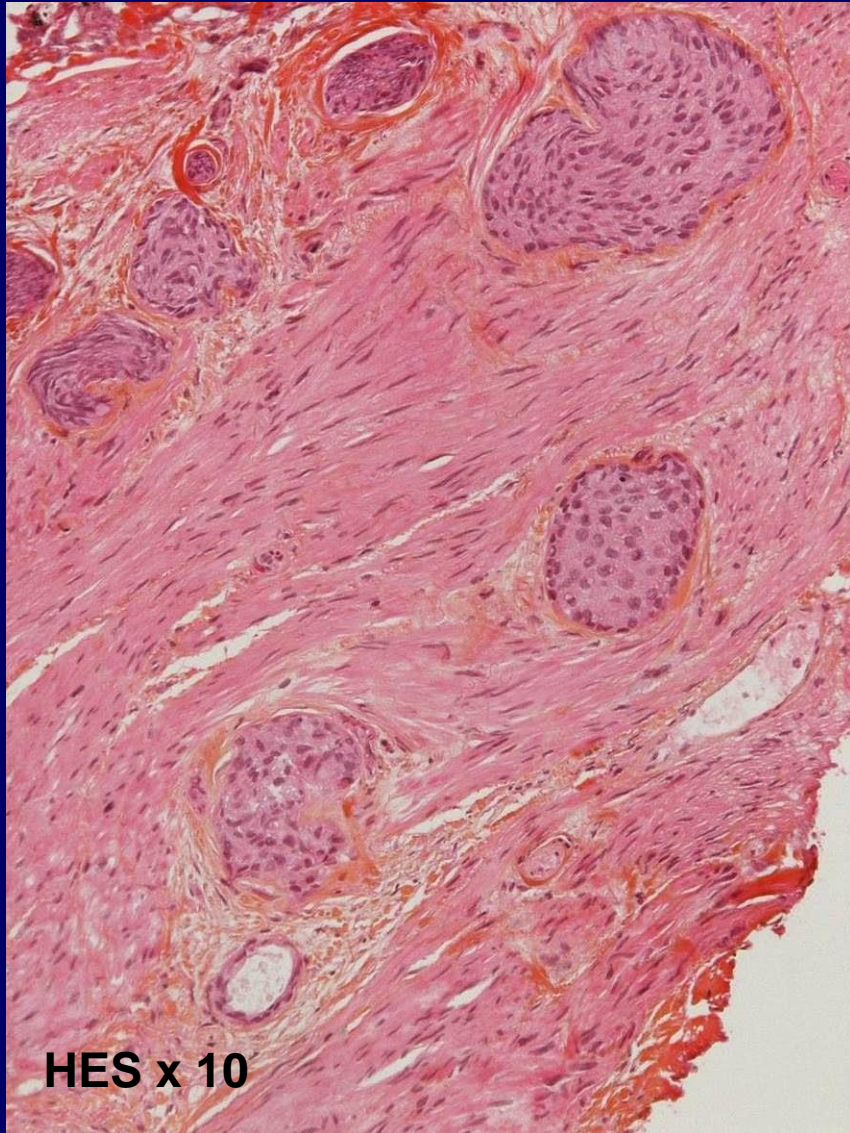
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- discrete nests
- bland cytologic appearance
- mimics von Brunn nests
- few mitosis
- few atypia
- sometimes confluent
- relatively well delimited

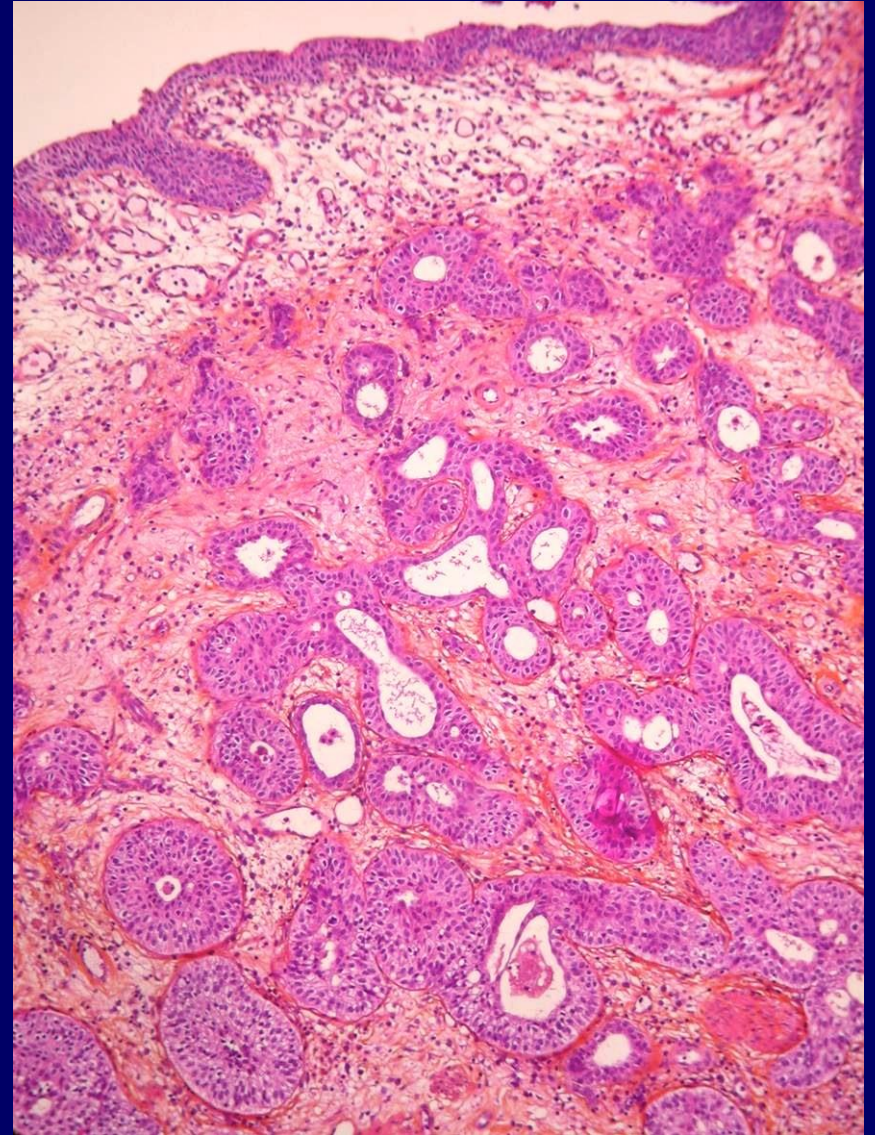
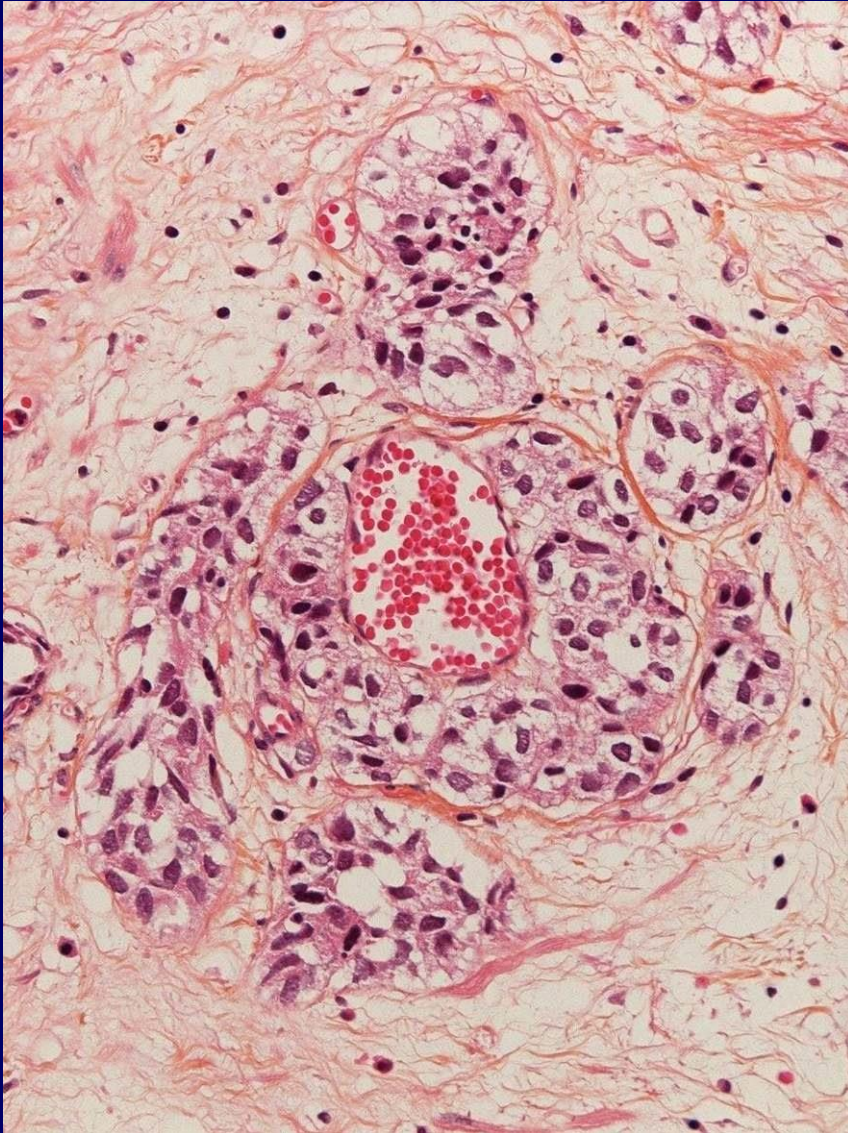


HES x 20

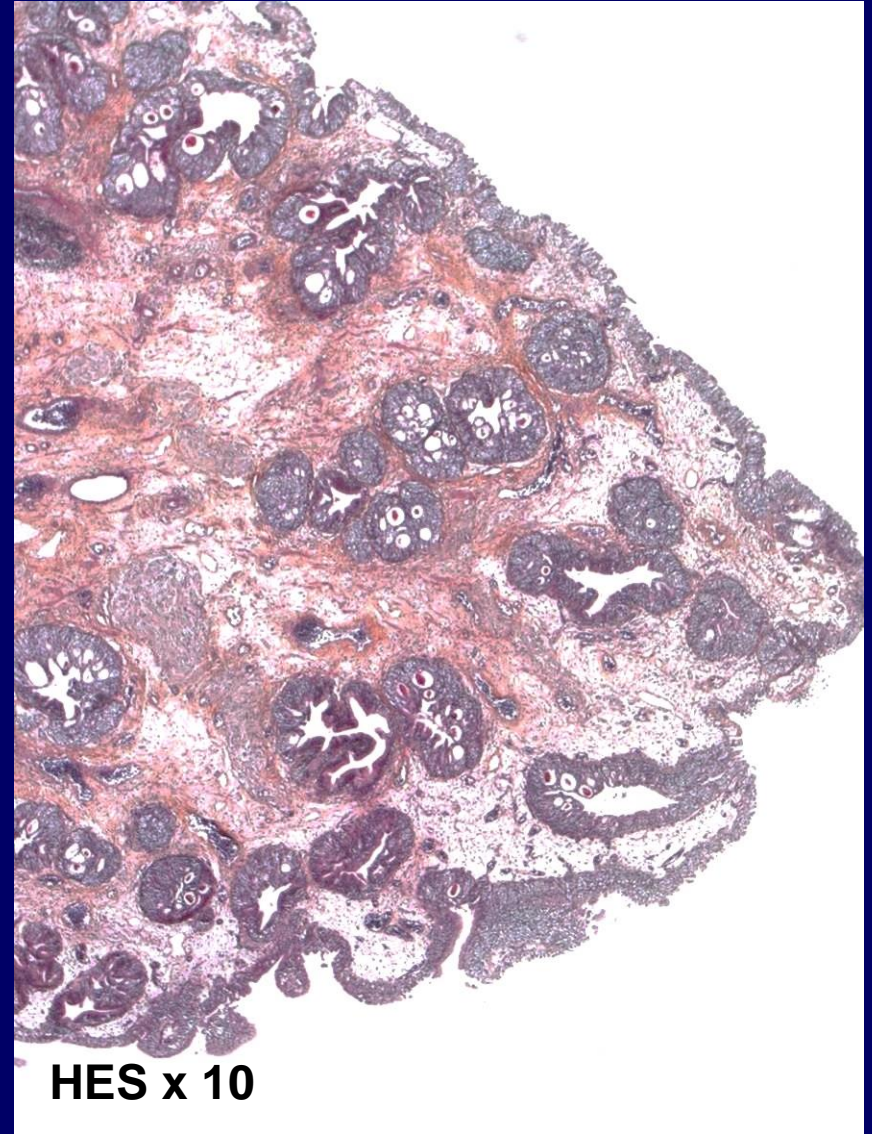
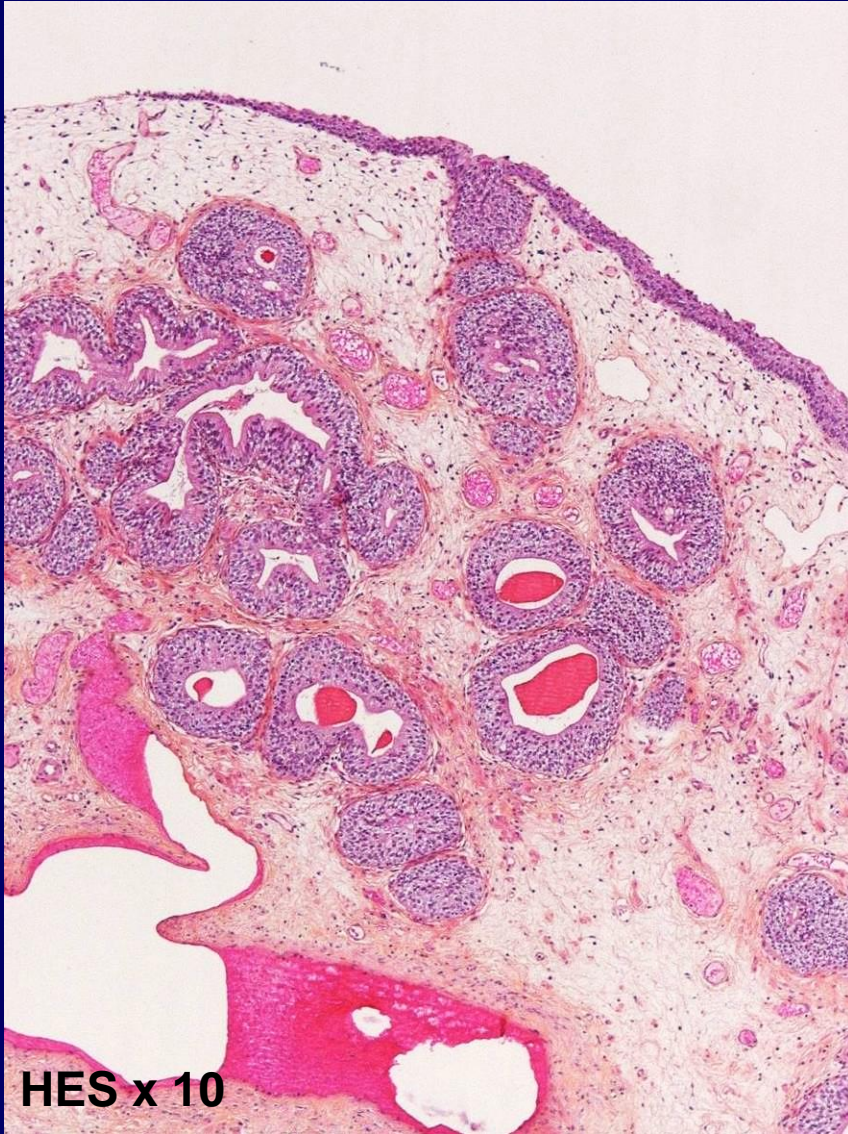
# Histology of NC



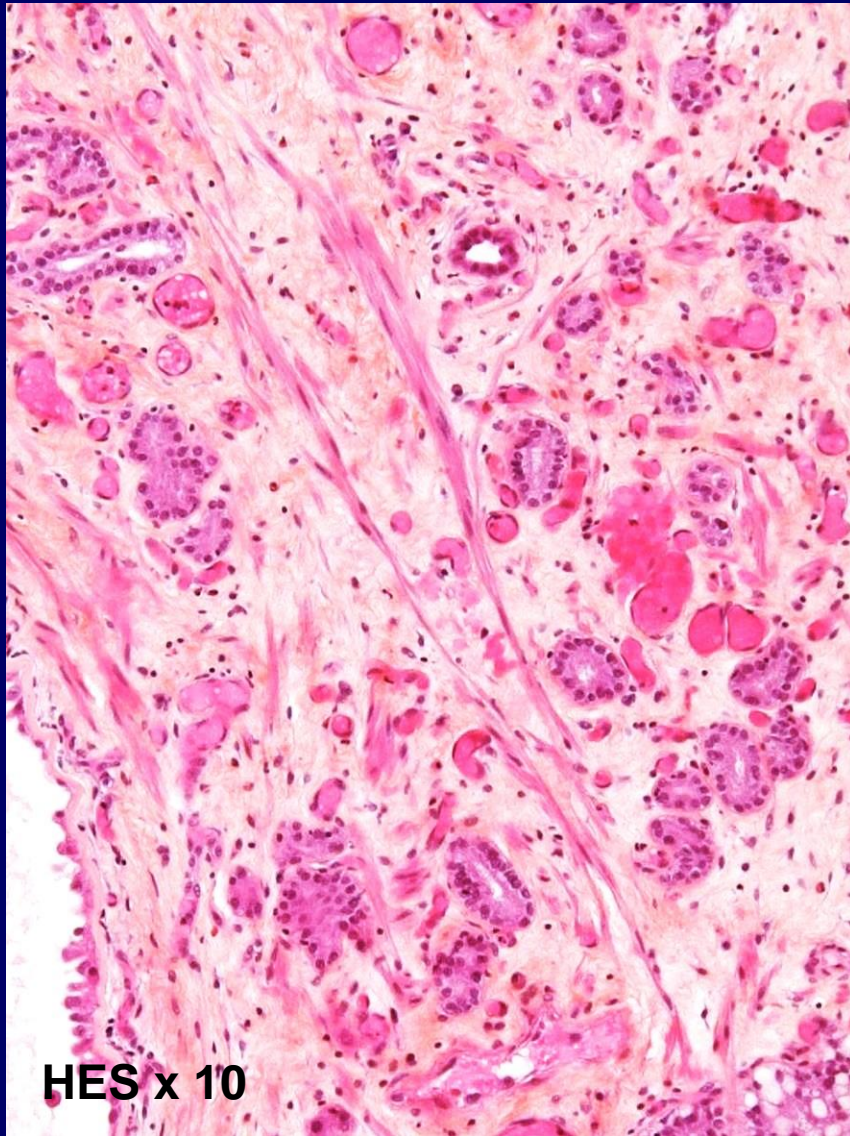
# Tubular or cystic differentiation of NC



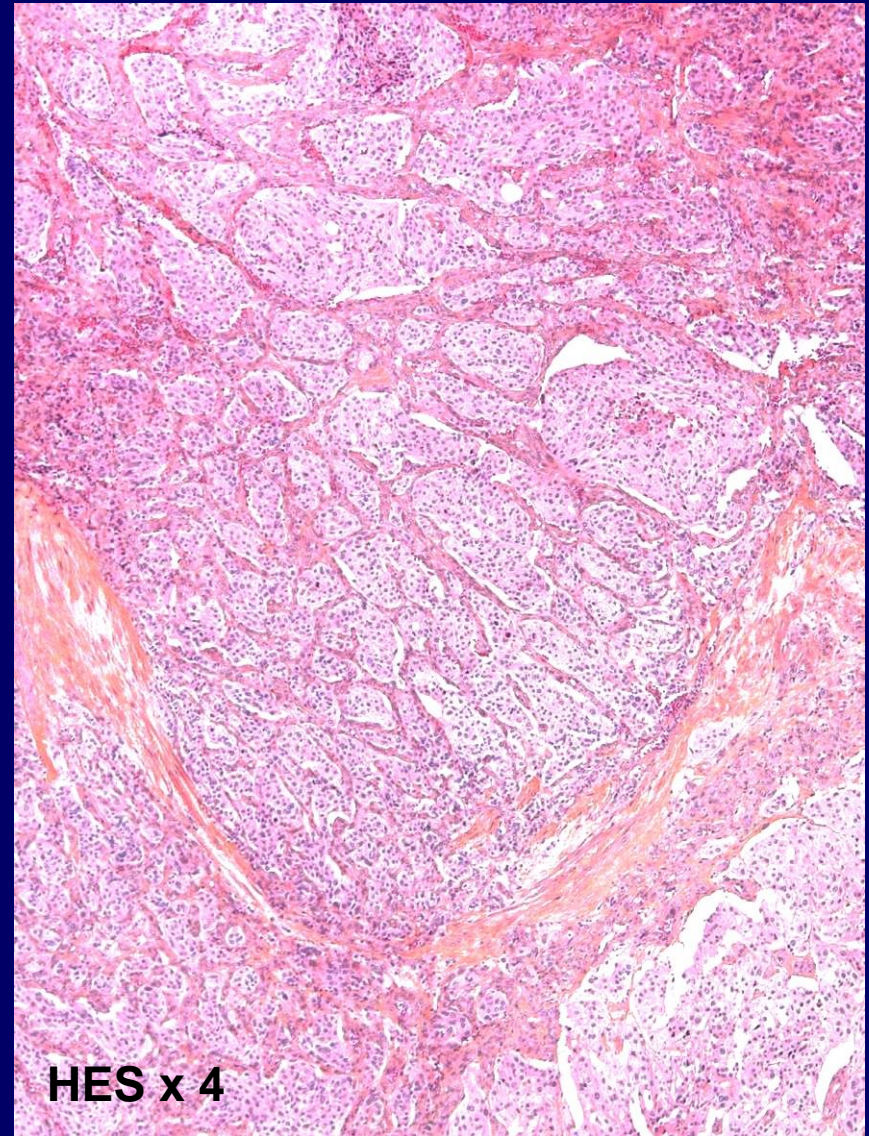
# Diferential Diagnosis : Von Brunn Nests



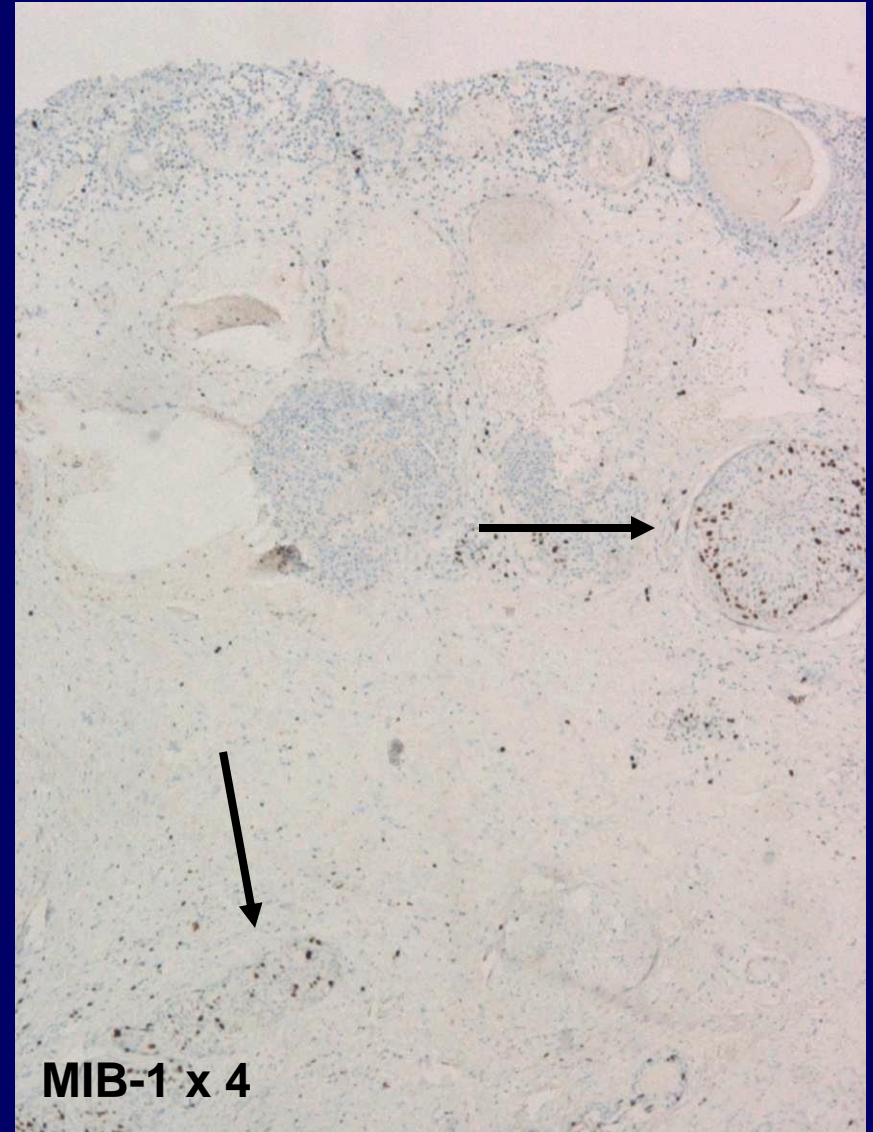
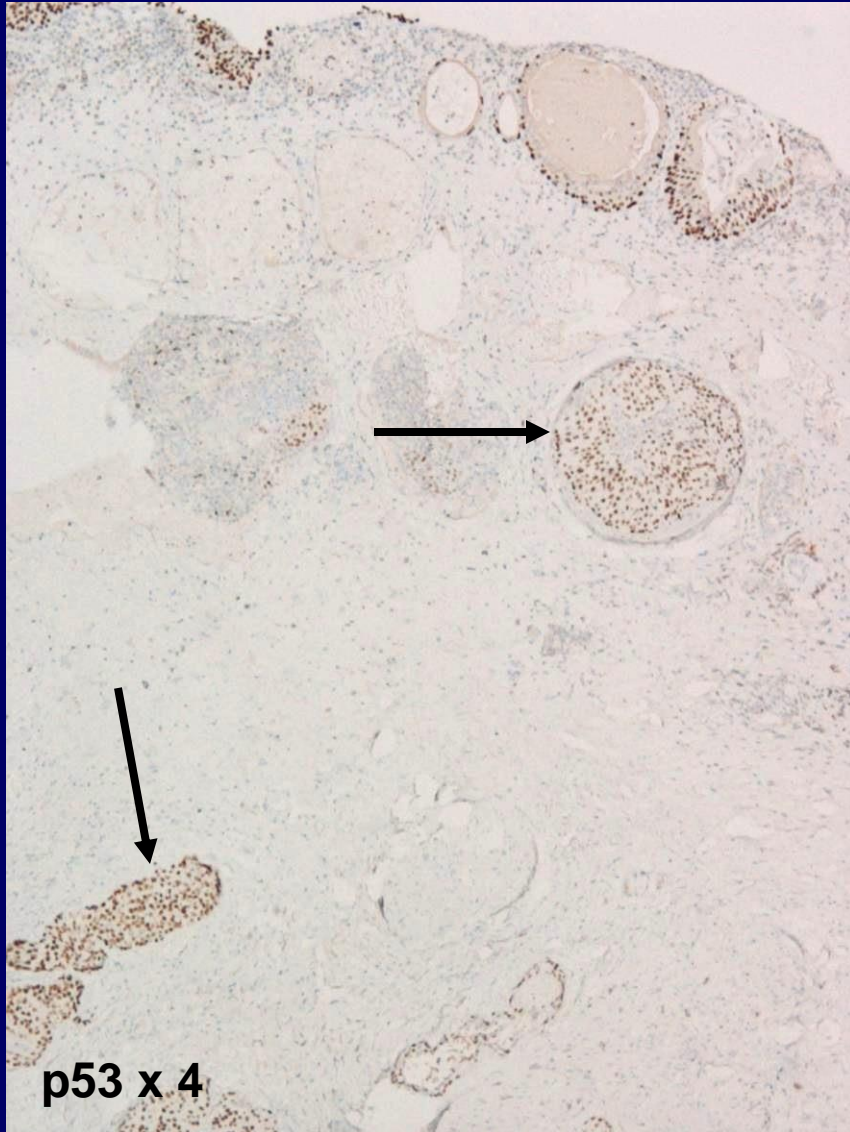
# Nephrogenic Adenoma



# Paraganglioma



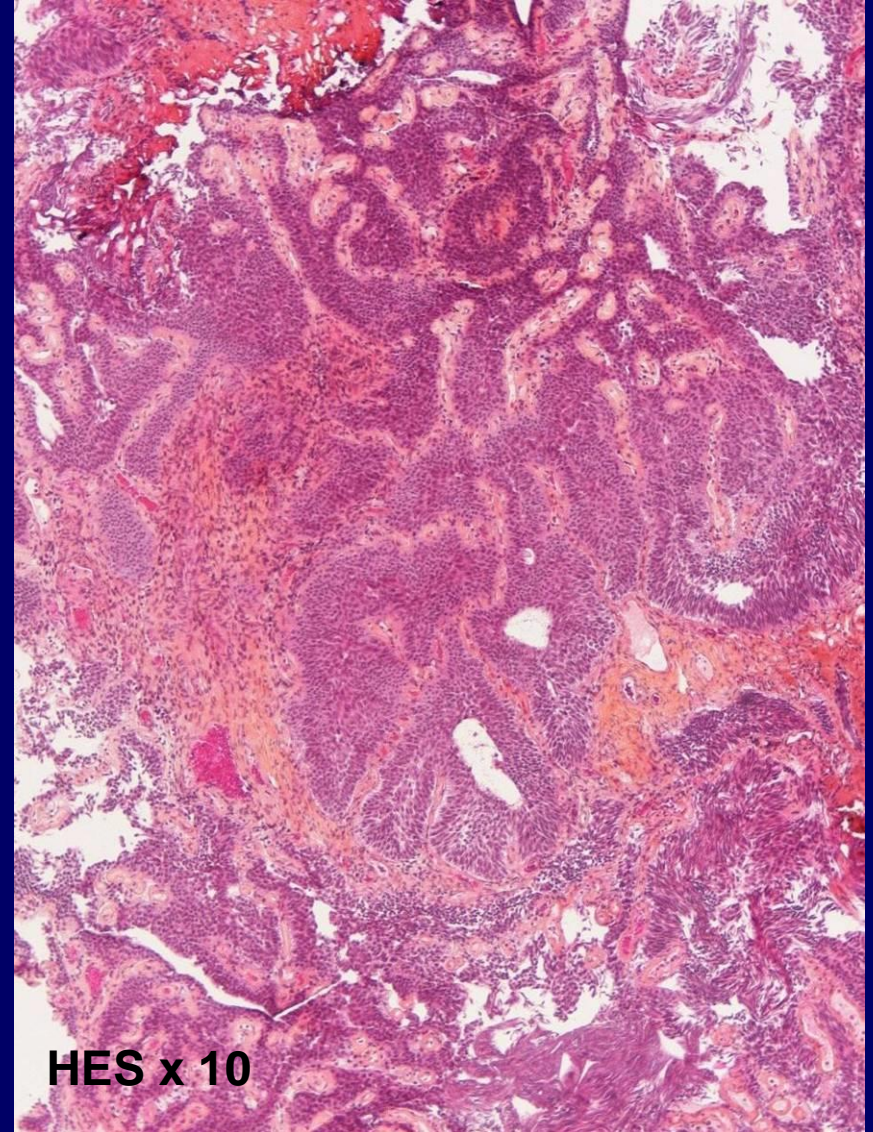
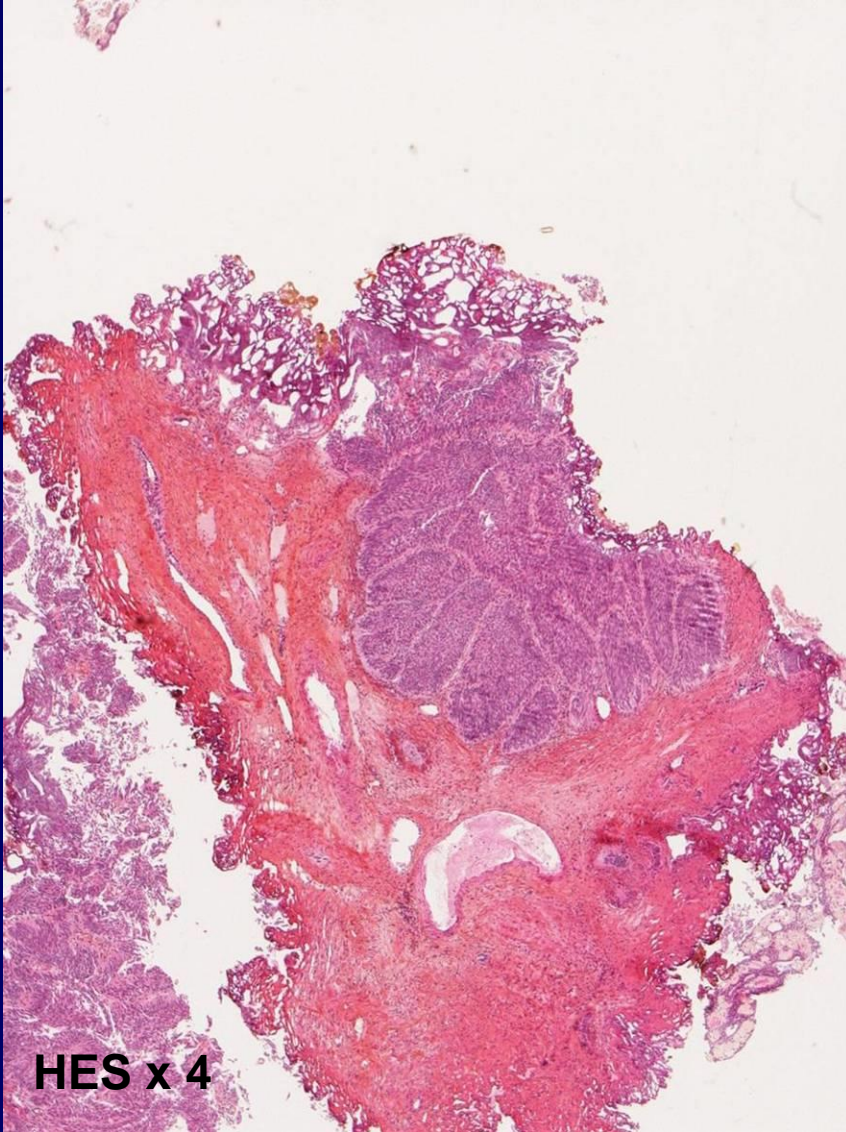
# Immunohistochemistry



# Nested Carcinomas

- OS : mean 30 months
- danger
  - Underestimate ++
  - or overestimate
- if no muscle
  - new biopsies

# Inverted Papilloma-like Growth



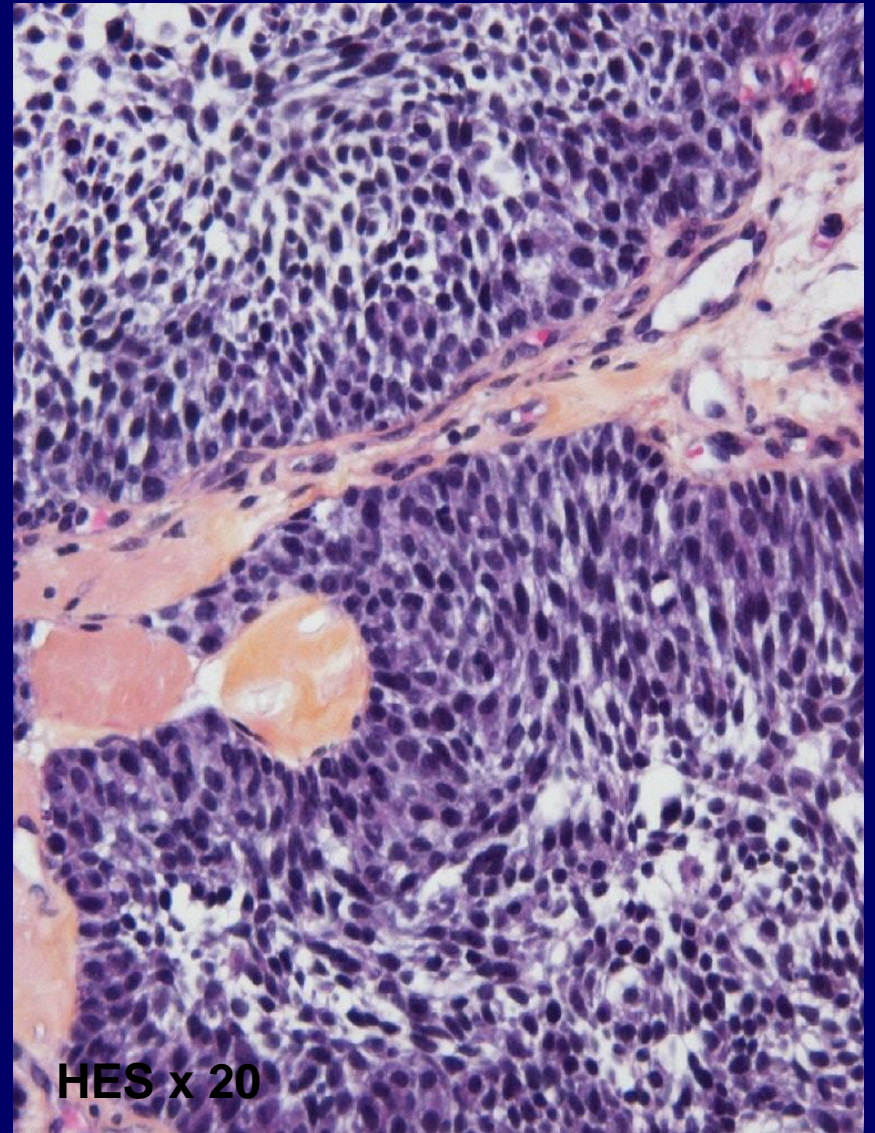
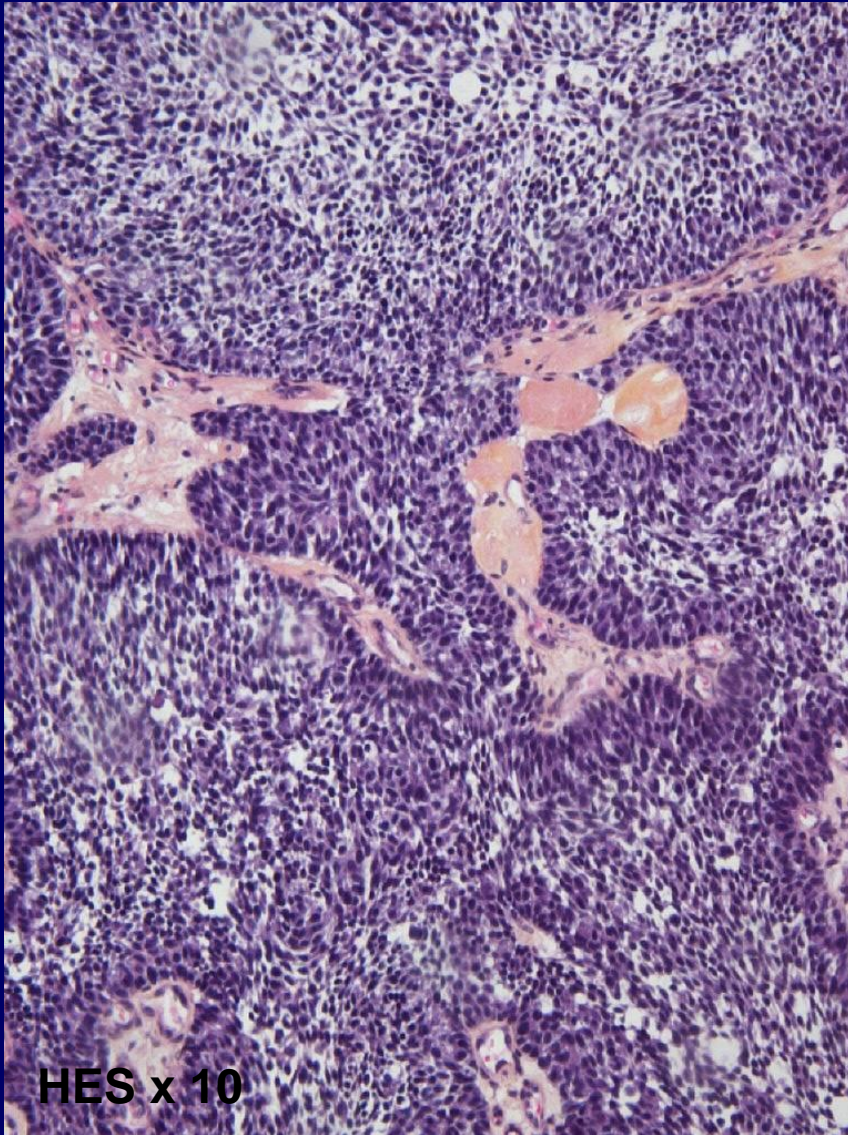


# Inverted Papilloma-like Growth

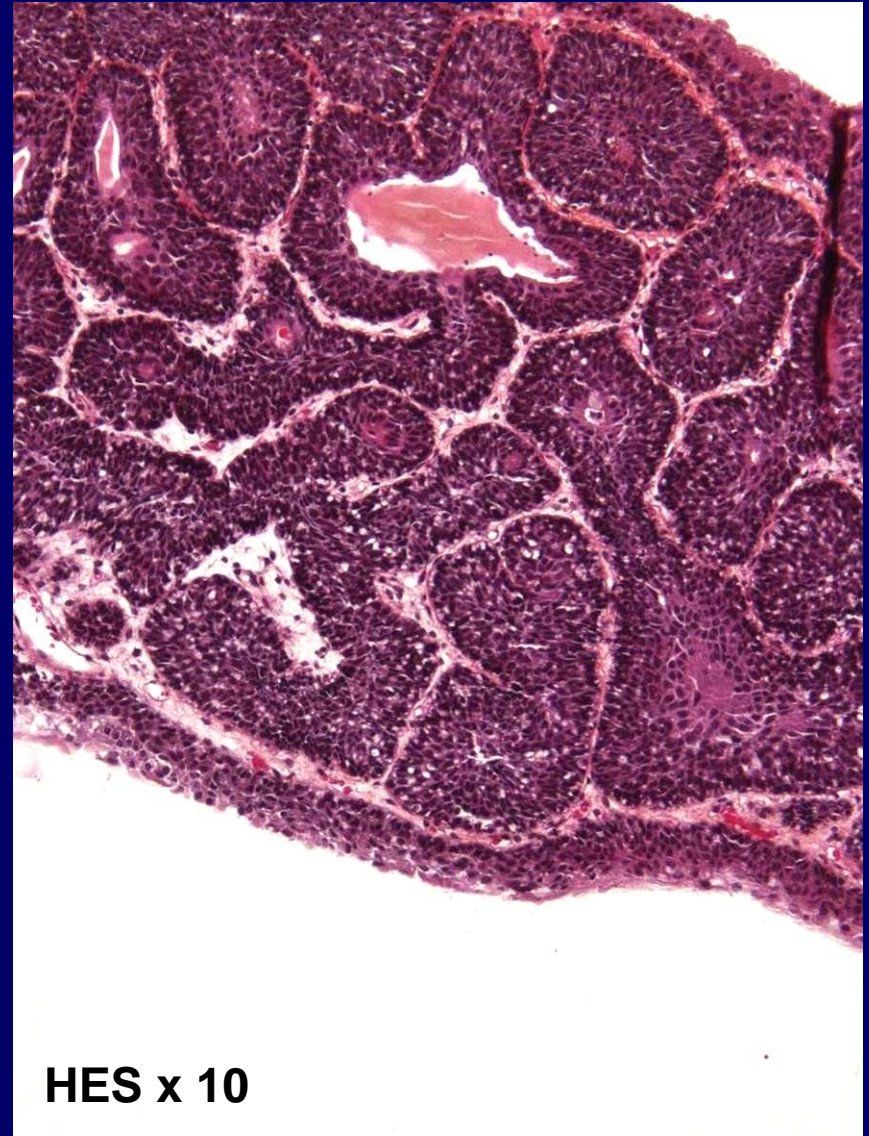
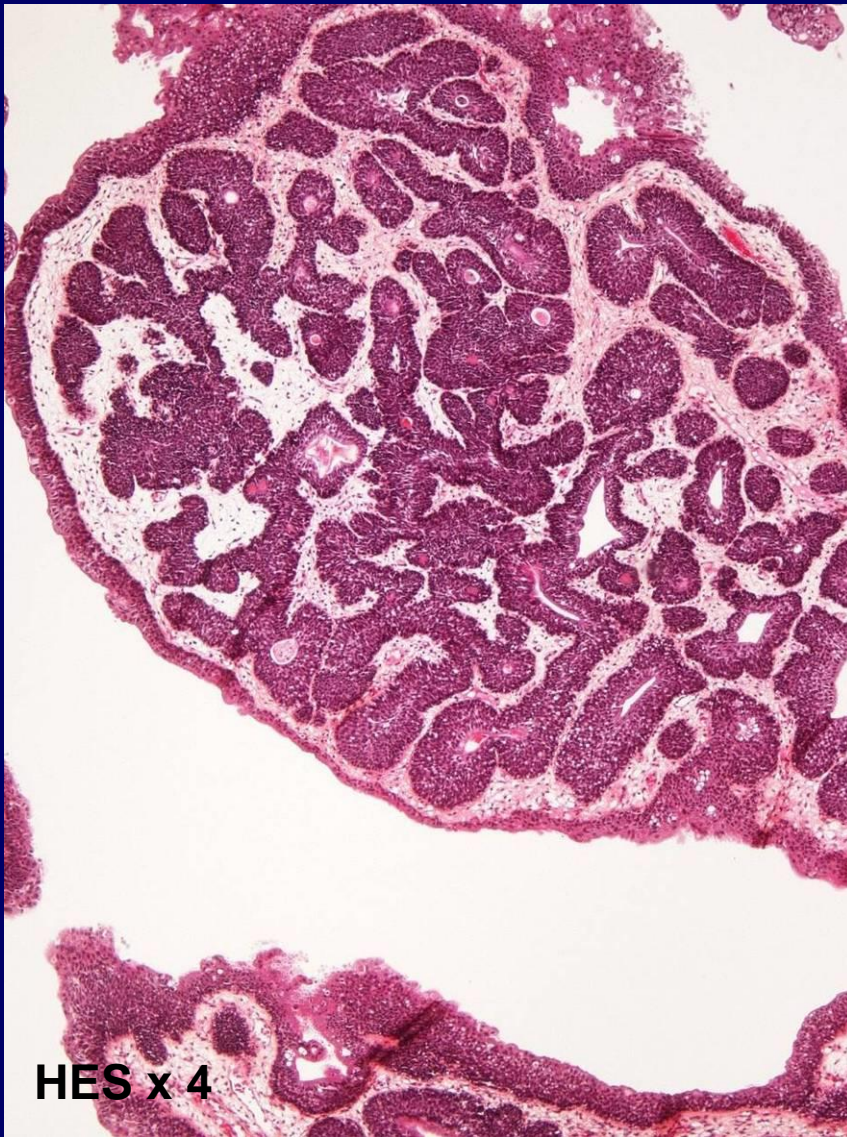
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- distinction from inverted papilloma
- difficult to assess invasion +++++
- variants with both components (papillary and inverted) possible
- Malignant
  - mitosis
  - MIB-1, p53
  - thick columns
  - solid areas
  - distinction high grade/low grade

# Inverted Papilloma-like Growth



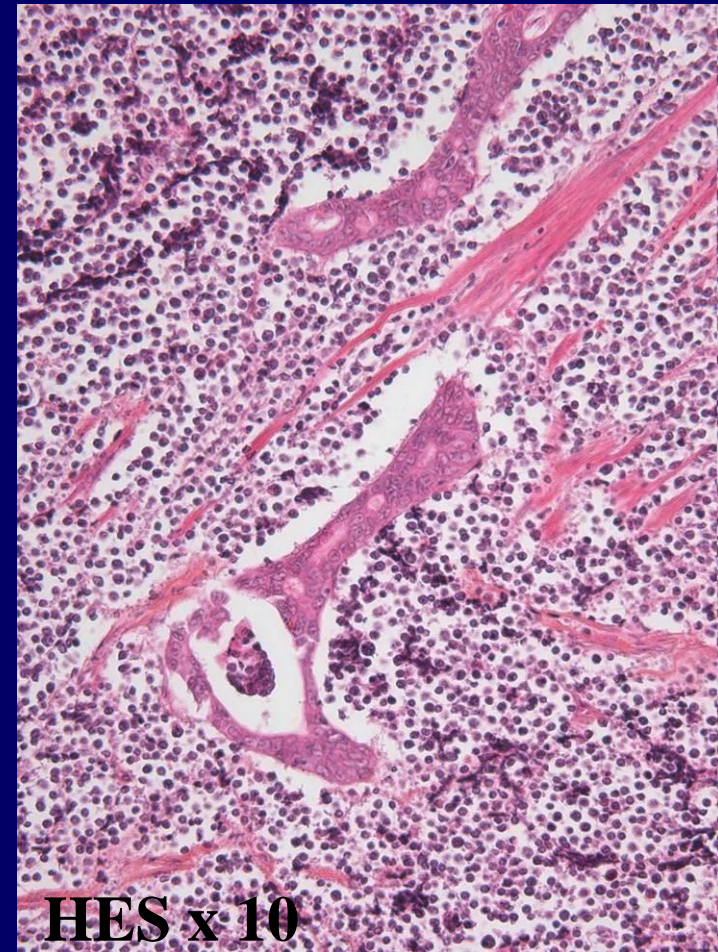
# DD : Inverted Papilloma



# Lymphoepithelioma-like UC

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- resembles UNC
- proeminent lymphoid infiltrate
- *Cis* +/-
- CK7+, CK8+
  - highlights epithelial origin
- lymphocytes
  - mixed population of B and T cells
  - EBV –
  
- Immunotherapy ?

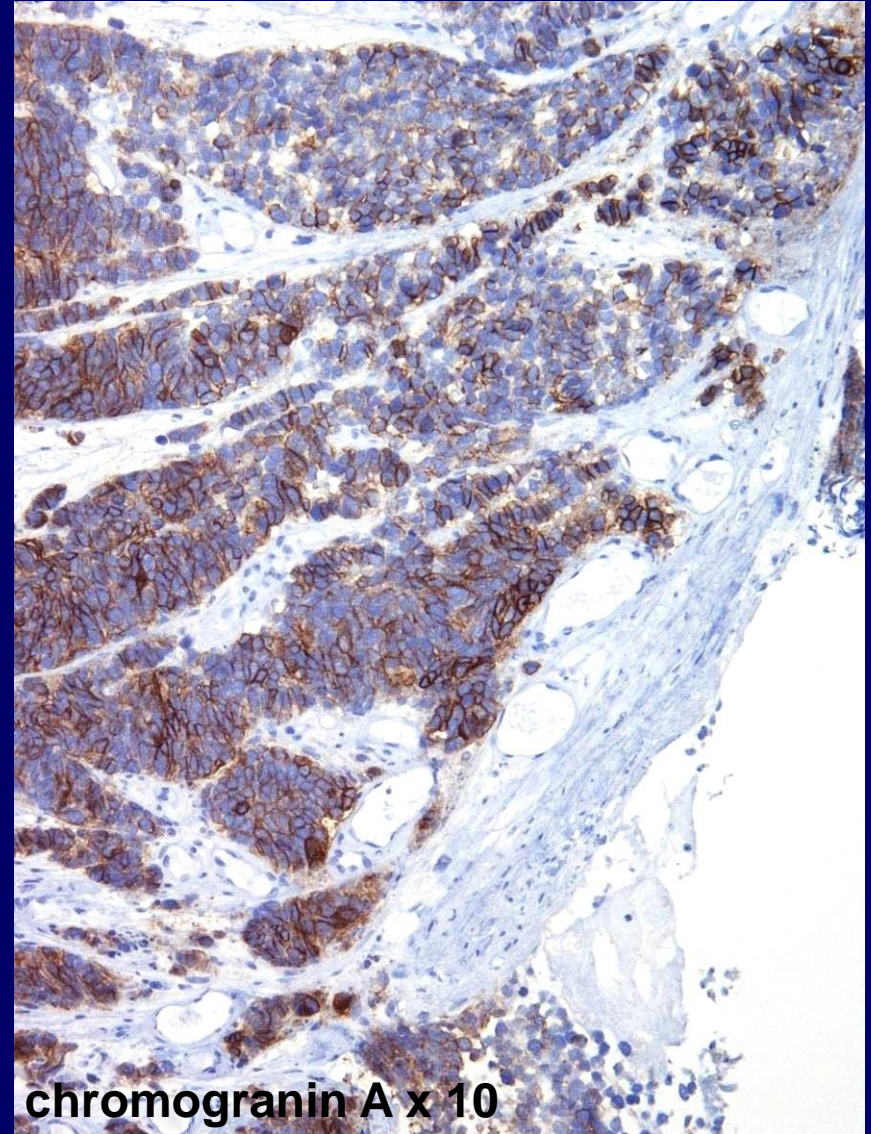
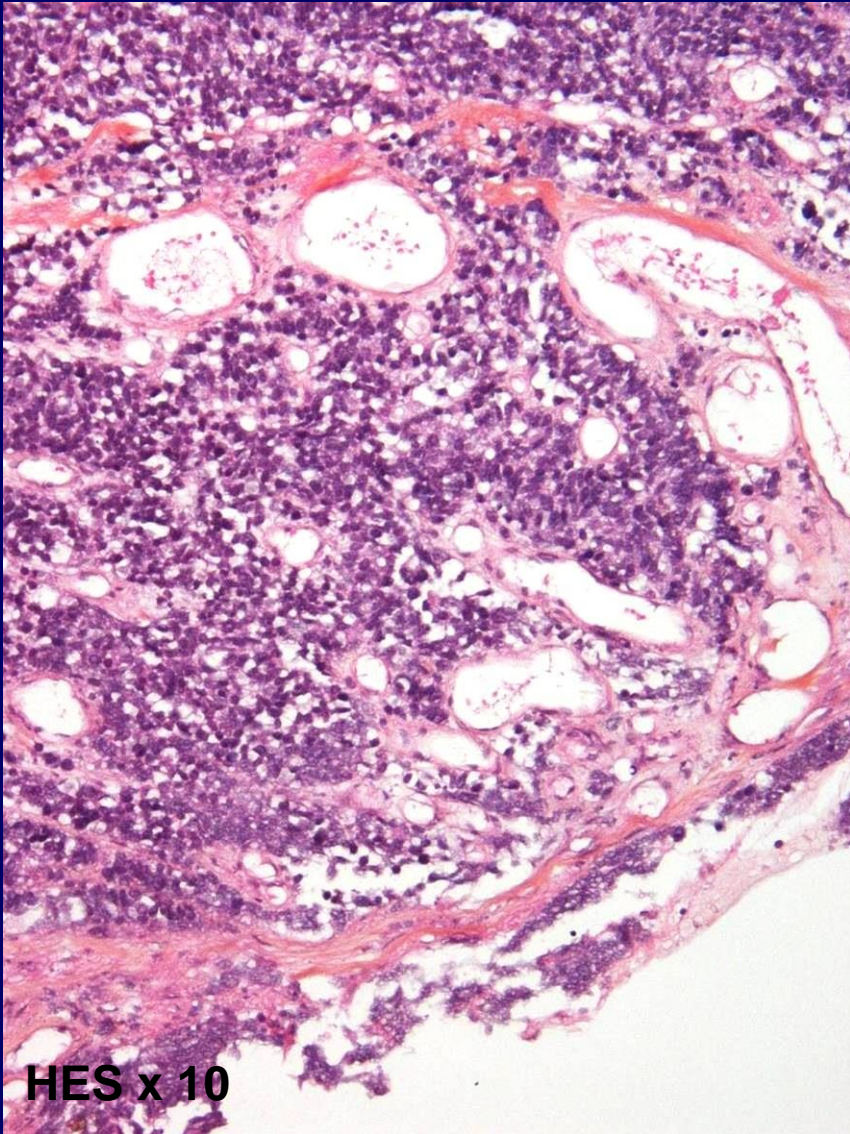


# Small Cell (neuro endocrine) Carcinoma (SCC)

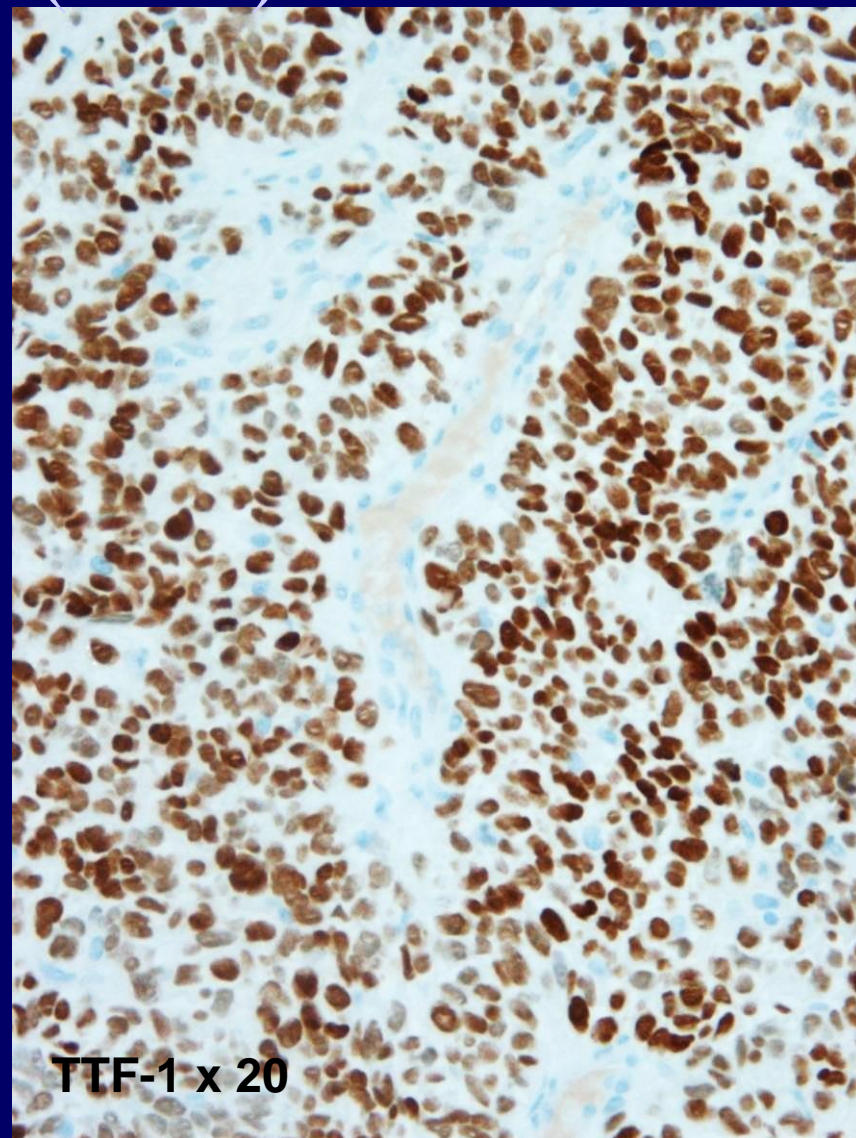
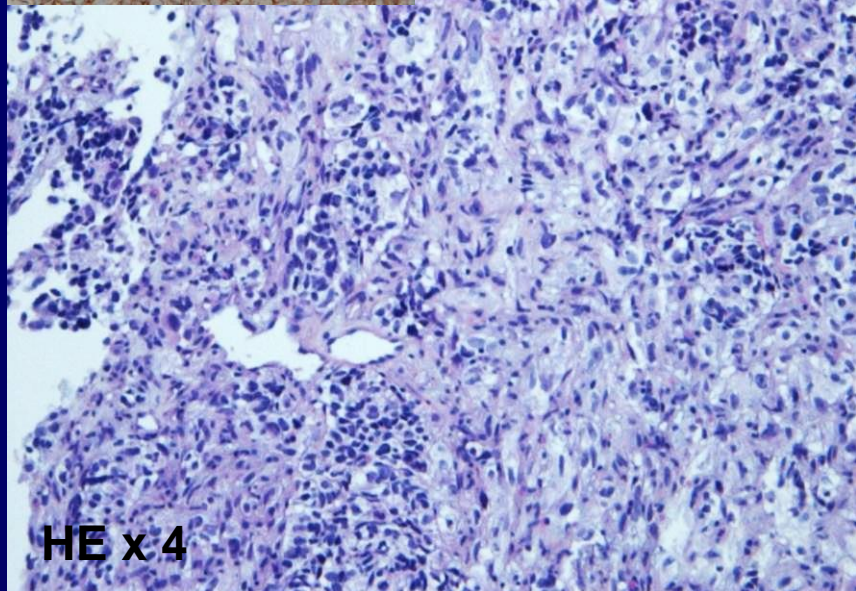
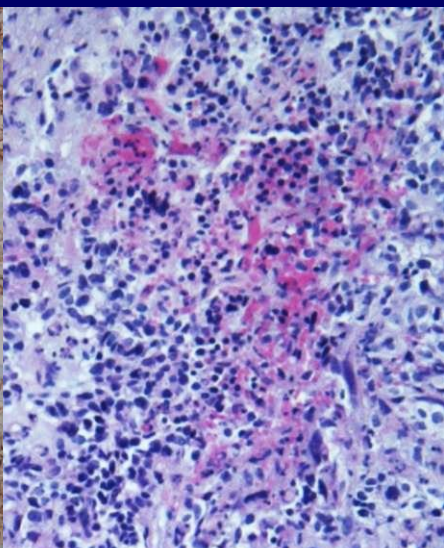
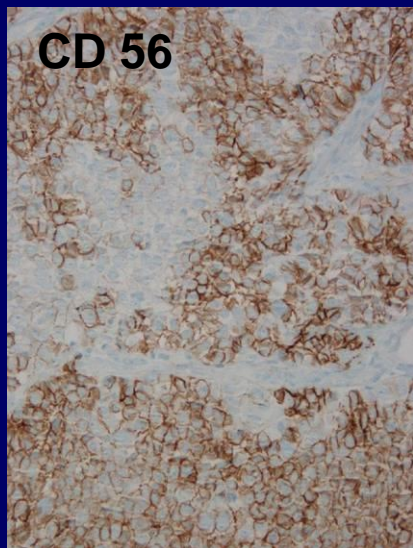
---

- rare
- highly aggressive
- coexistence with other tumor types common
- origin?
  - expression of cytokeratins → urothelial origin
  - Cheng *et al.* → identical allelic loss patterns in UC and SCC

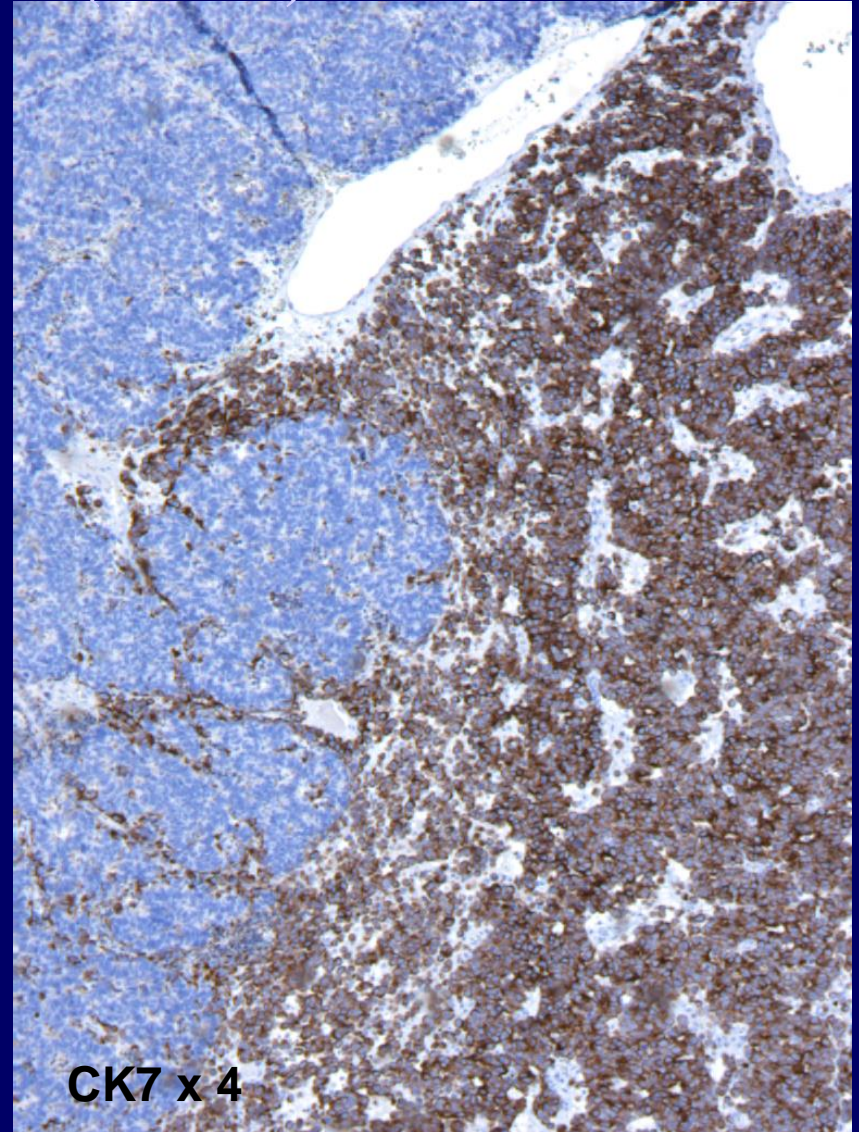
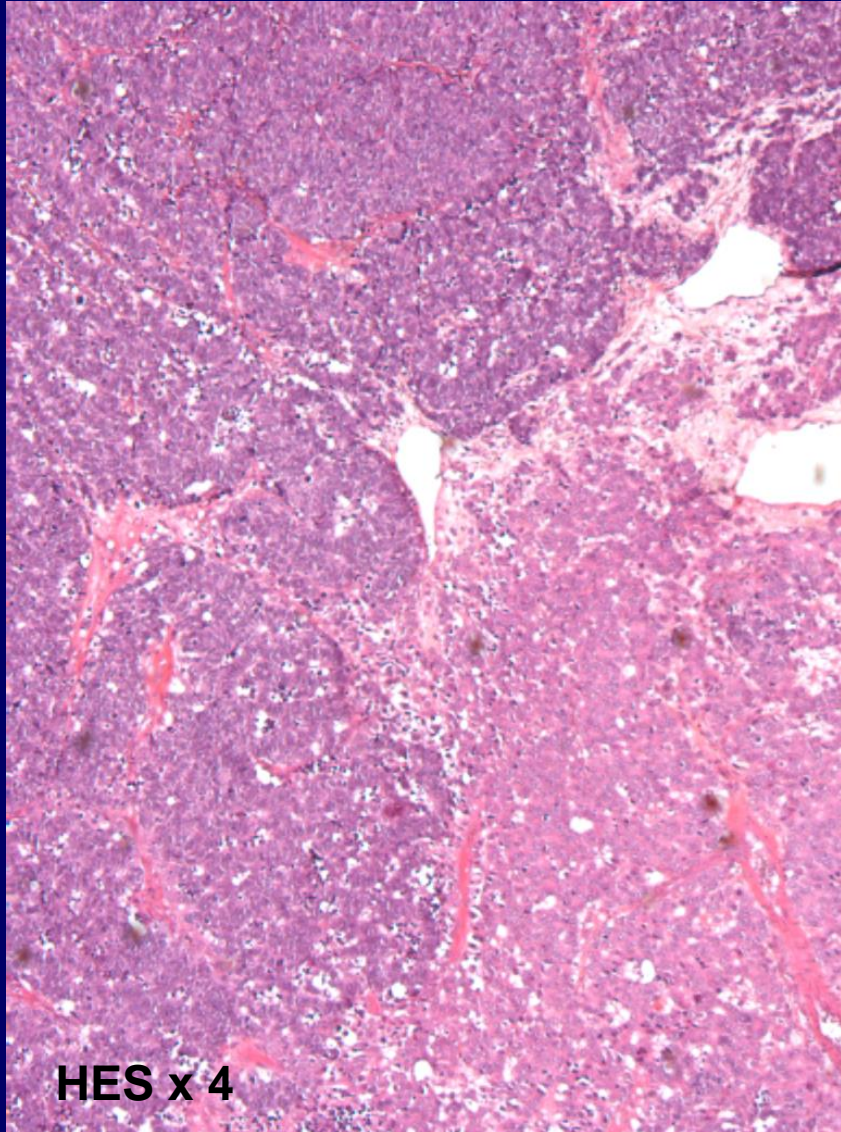
# Small Cell Carcinoma (SCC)



# Small Cell Carcinoma (SCC)



# Small Cell Carcinoma (SCC)





# Small Cell Carcinoma (SCC)

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- immunohistochemistry
  - CK +
  - chromogranin A +/-
  - NSE +
  - synaptophysin +/-
  - CD56 +/-
  - TTF-1 +/- (exclude other origin)

# Small Cell Carcinoma (SCC)

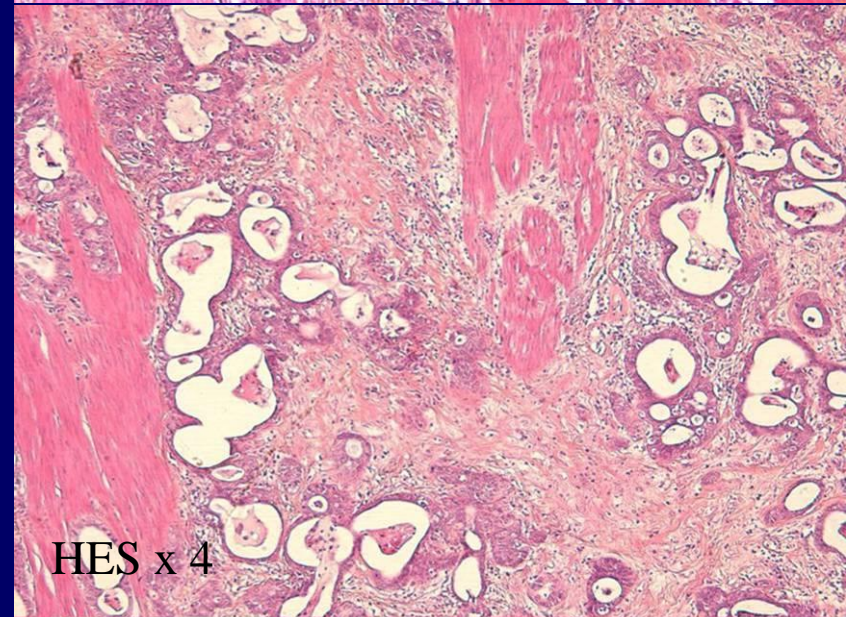
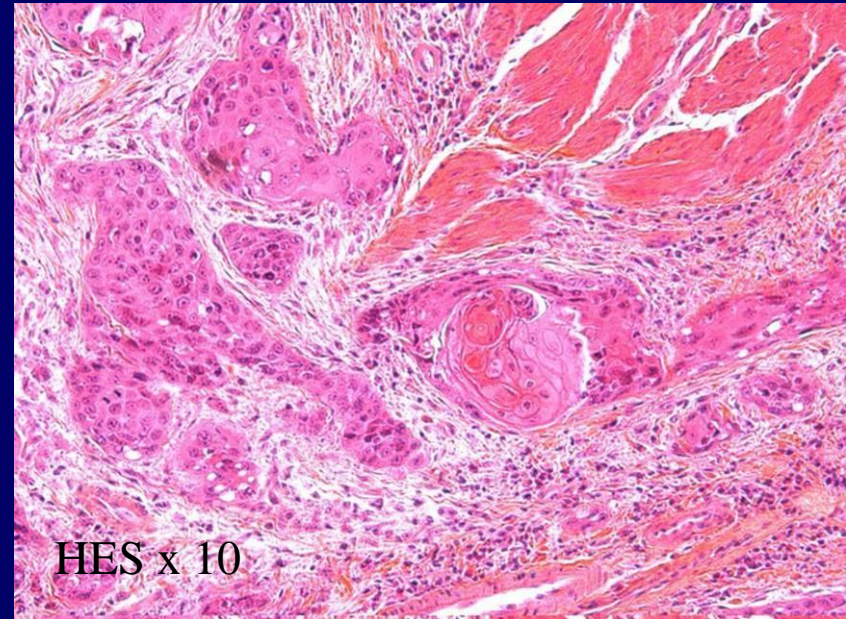
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- prognosis
  - very poor
  - correlation with stage
  - often association with paraneoplastic syndromes
  - Chemotherapy if pure or dominant
    - cisplatin and etoposide ? no consensus nor recommendations
  - surgery
    - same results

# Squamous or Glandular Differentiation

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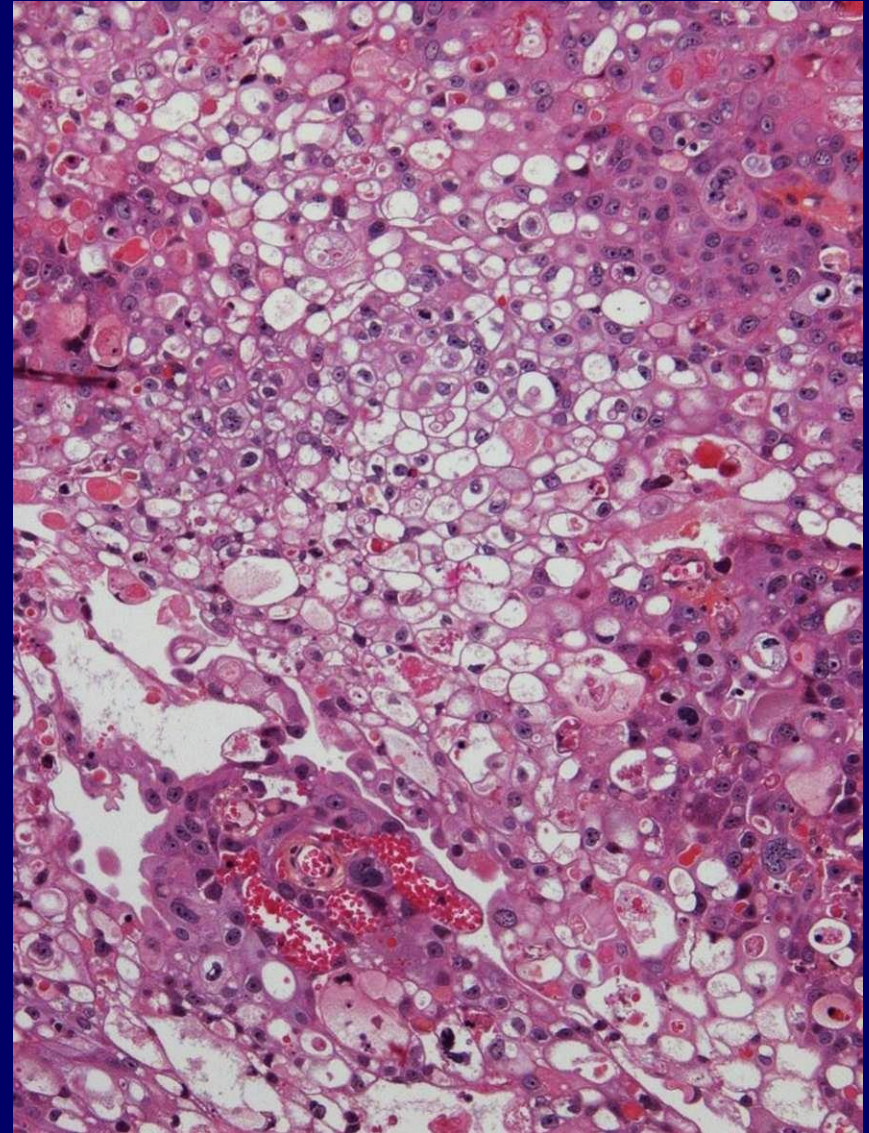
- consider as squamous cell carcinoma or adenocarcinoma only if pure forms
- squamous component
  - 20%
  - more aggressive than UC
- glandular differentiation
  - less common
  - 6%



# Lipid Rich Variant

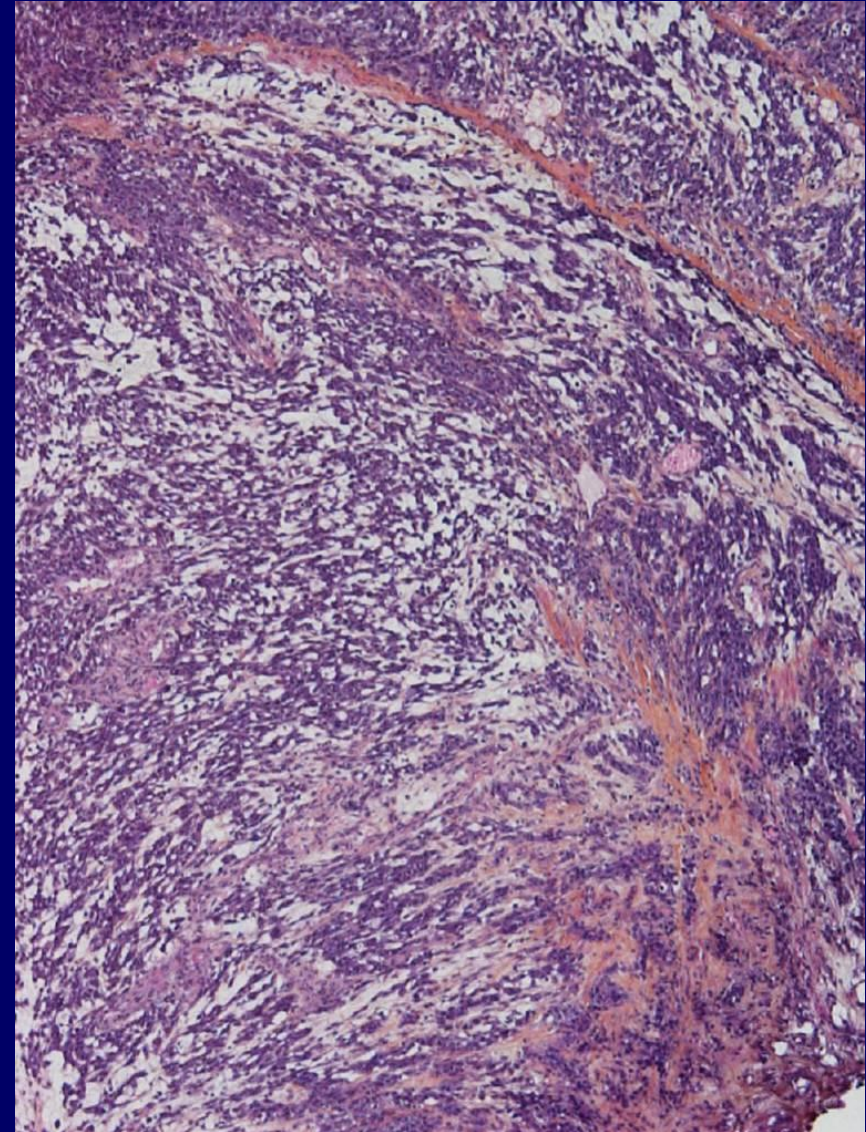
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- focally or patchy
  - associated with other patterns
- DD
  - liposarcoma
  - signet ring cell carcinoma
- CK 7 +
- EMA +
- PS 100 –
- poor prognosis



# Sarcomatoid UC

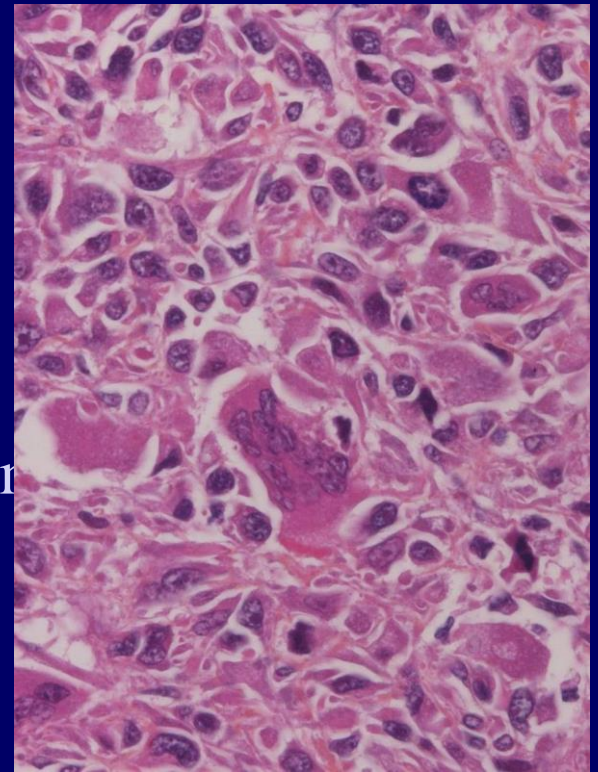
- heterologous elements
    - osteosarcoma
    - chondrosarcoma
    - rhabdomyosarcoma
    - leiomyosarcoma
  - EMA +
  - p63 +
  - PS100 +
  - vimentin +
- } urothelial component
- } mesenchymal component



# UC with stromal reactions

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- pseudosarcomatous stroma,
- osseous or cartilaginous metaplasia,
- osteoclastlike giant cells,
- prominent lymphoid infiltrate
- tendency to metastazise
- inflammatory response common
- inflammation sign of good clinical outcome
- giant cell host response?



# Conclusion

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- UC with aberrant differentiation
  - more aggressive biologically
  - tend to present more advanced stage
    - rapid growth and high mitotic index
- accurate diagnosis important for patient management
  - precise in report +++