Urothelial Carcinoma WHO 2016

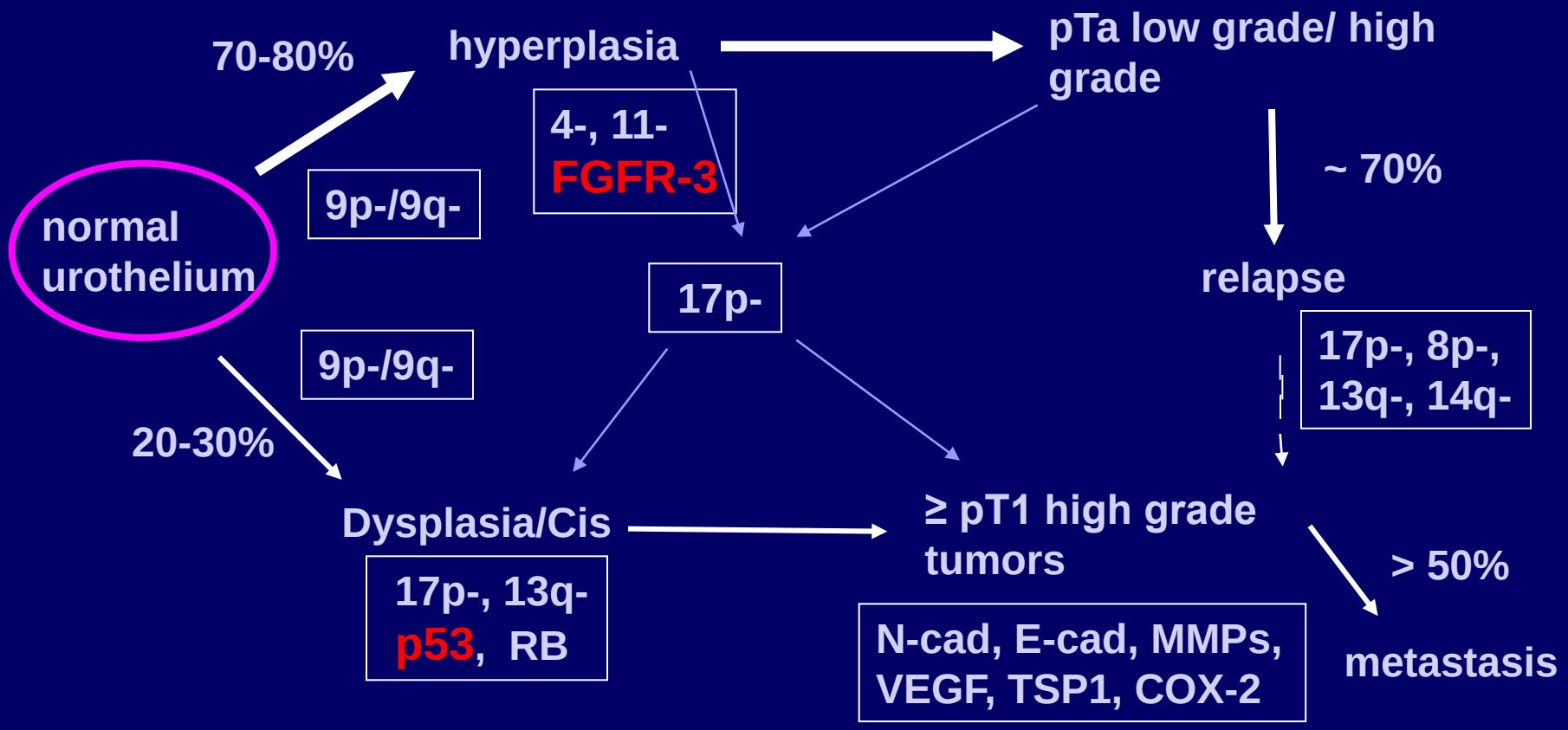
Ph Camparo

Centre de pathologie

Amiens

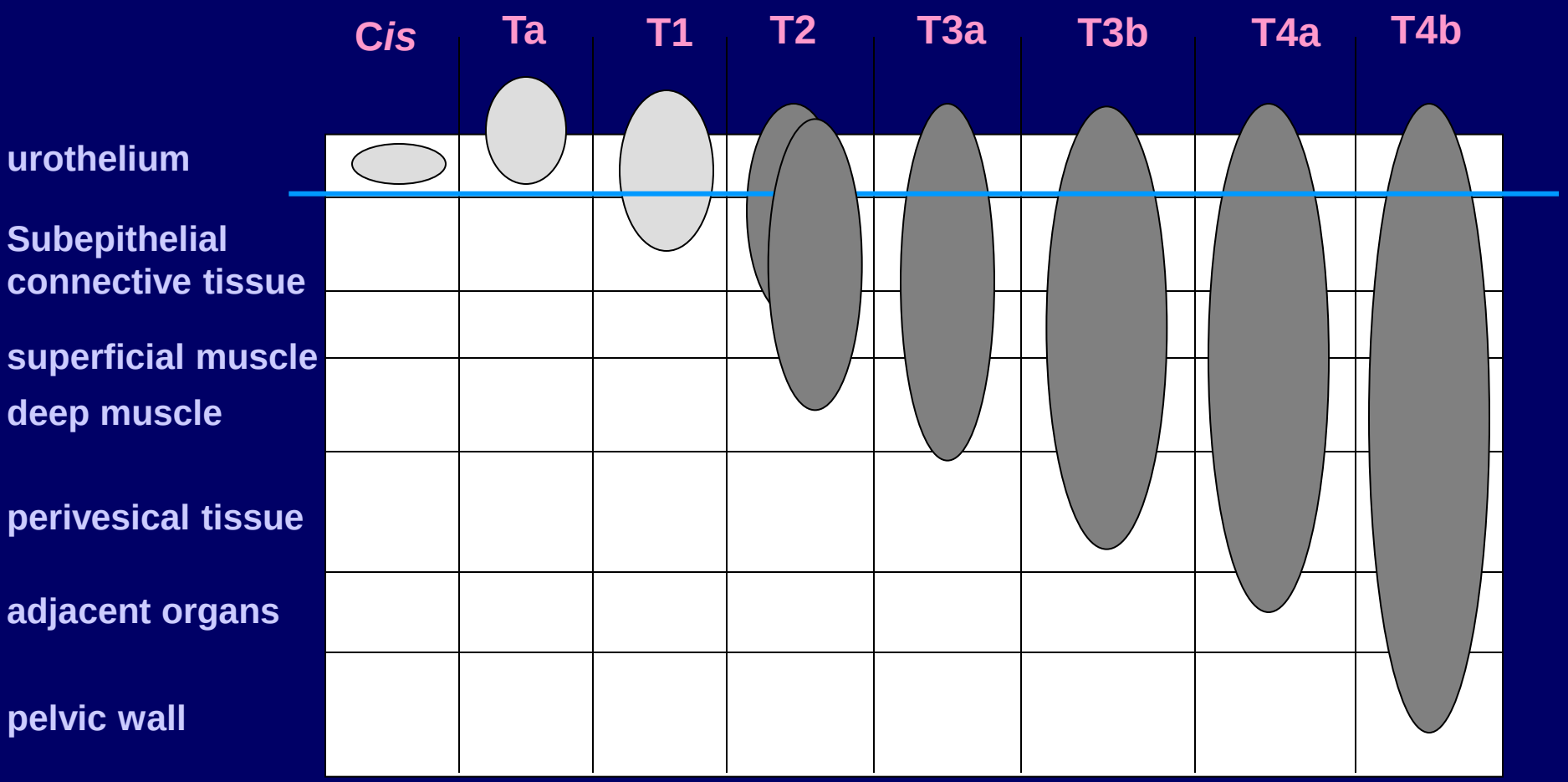
France

Genetic Events Caracterising Bladder Carcinogenesis

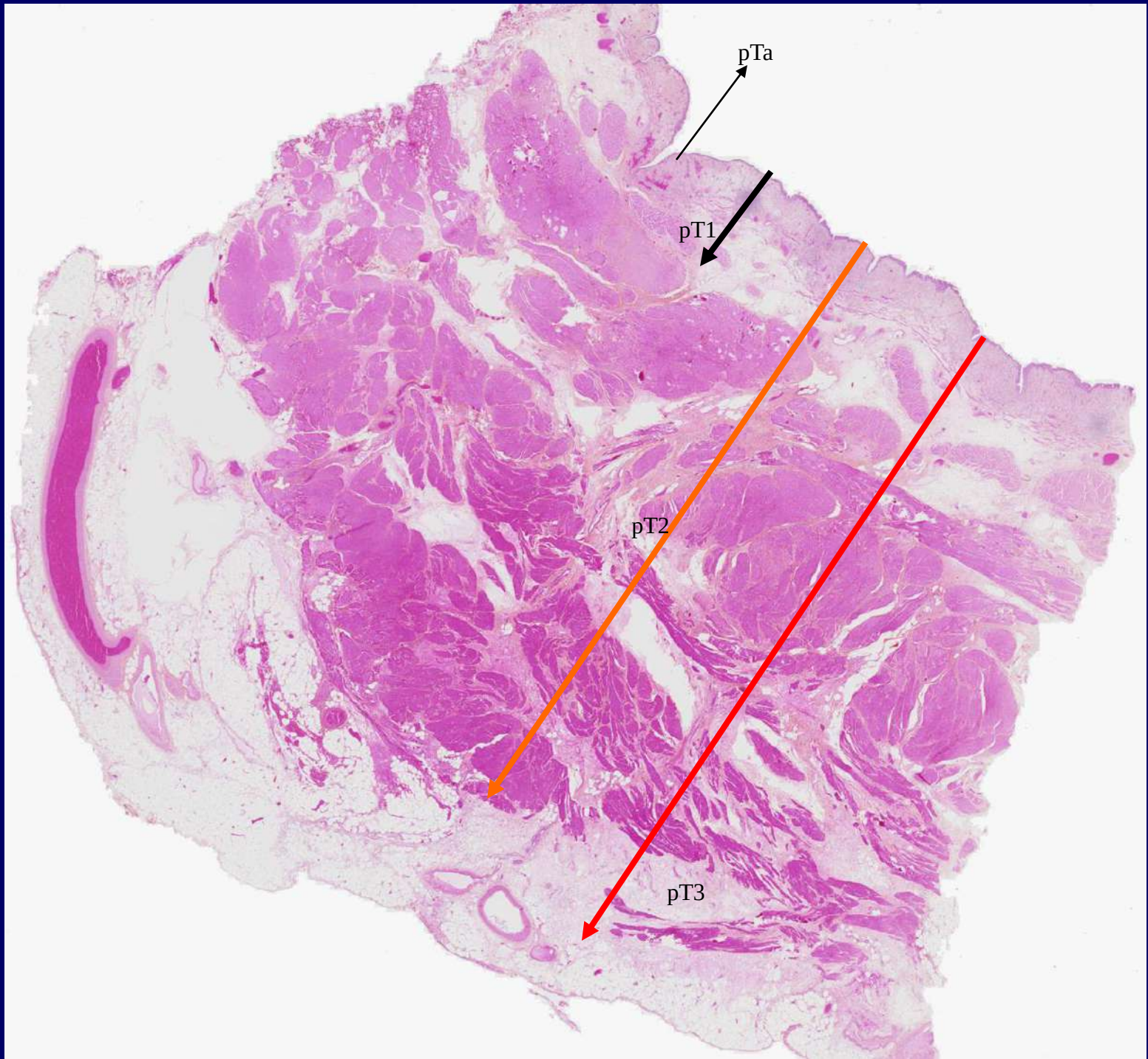


Wu ; Nature Review Cancer 2005

Stages pT



Eble JN SG, Epstein JI, Sesterhenn IA. Tumours of the Urinary System and Male Genital Organs. 2004.


pTa
pT1
pT2
pT3

pTa

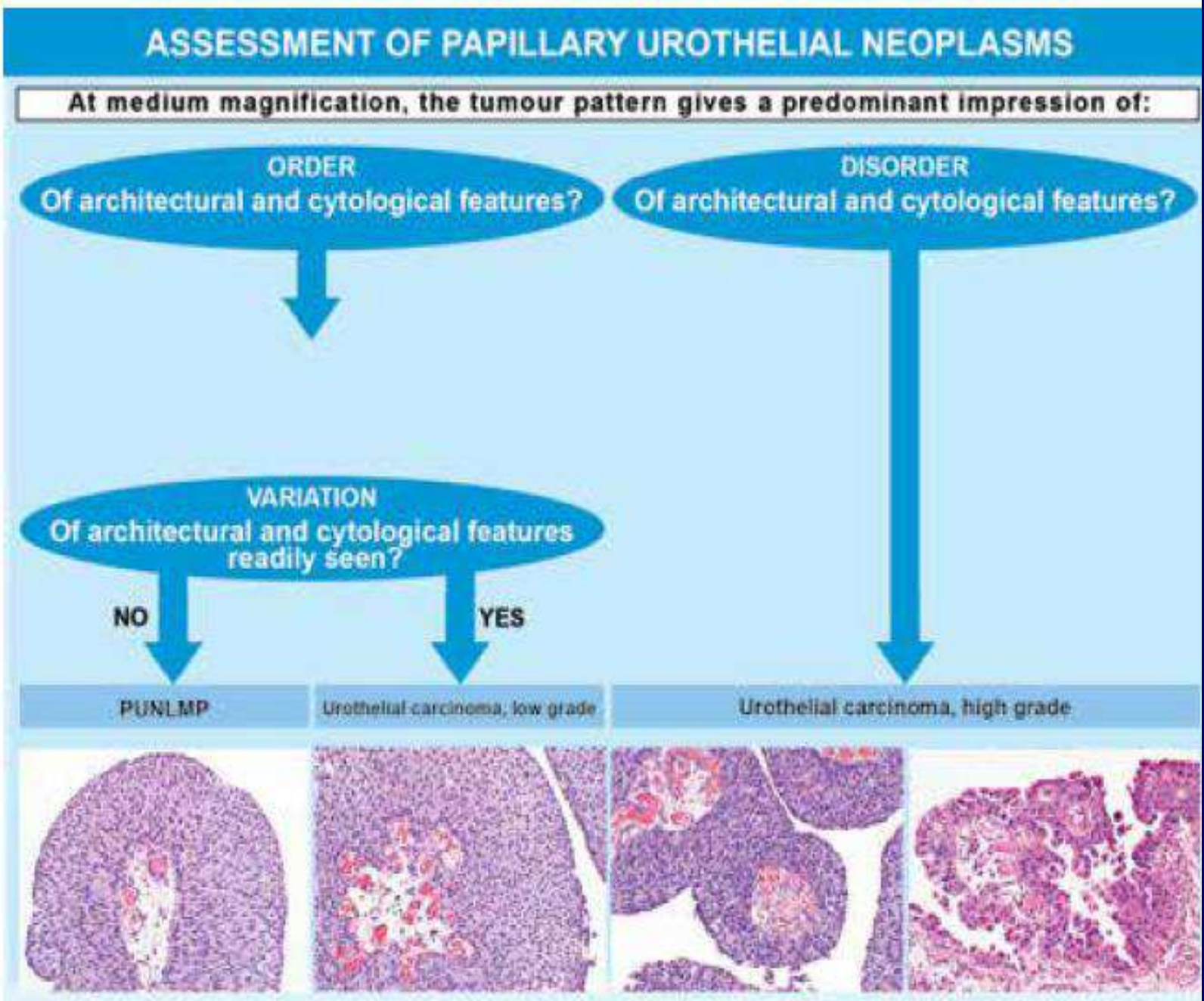
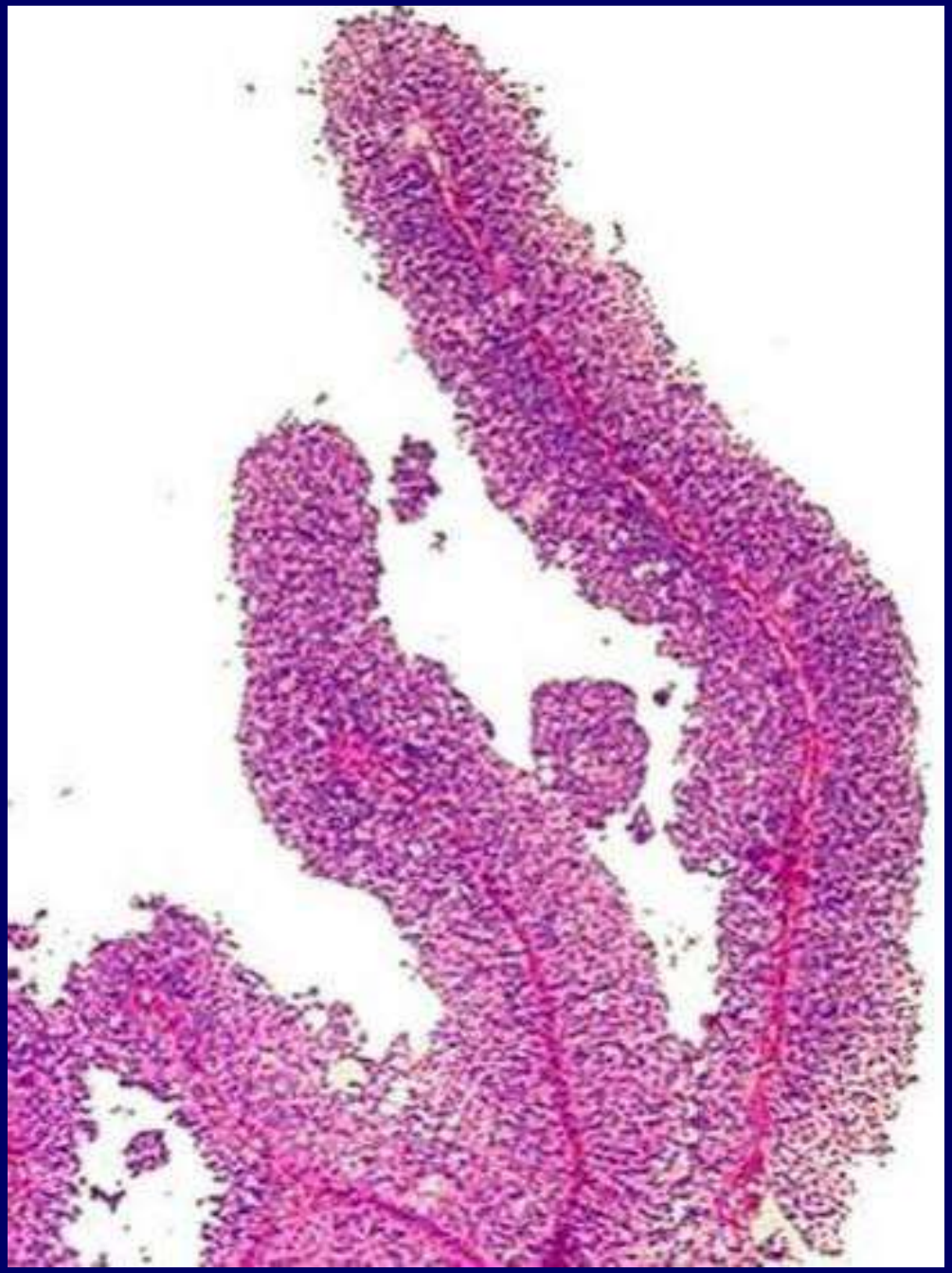


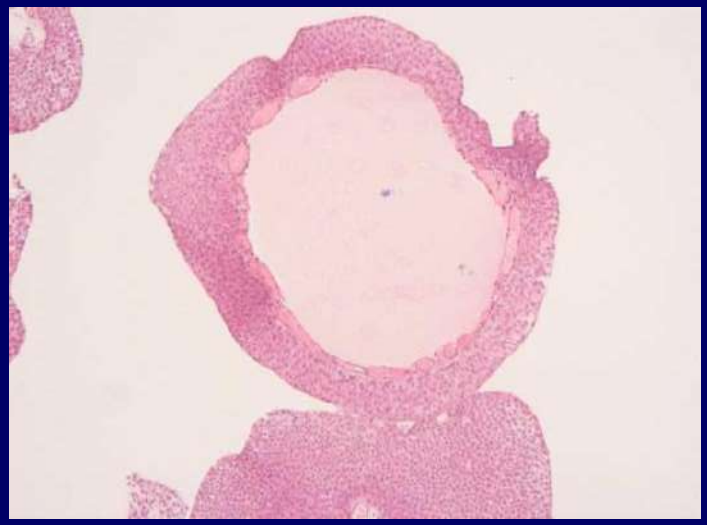
Fig. 2.29 Flow chart of the grading algorithm for papillary urothelial neoplasms.

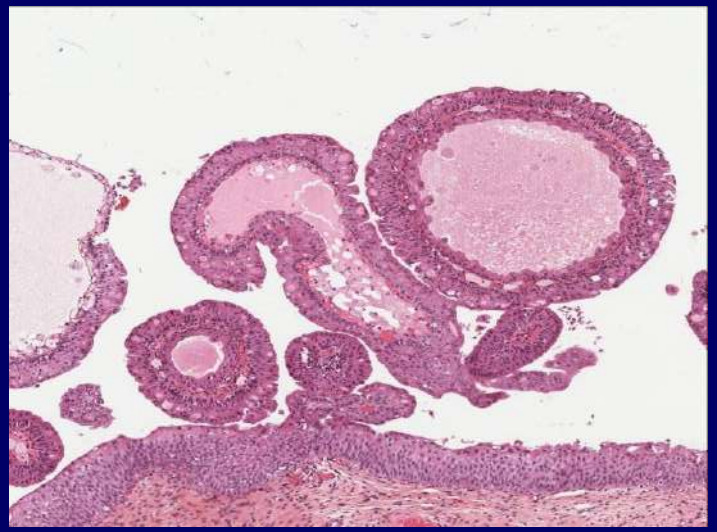
PLUMP



DD : Urothelial papilloma

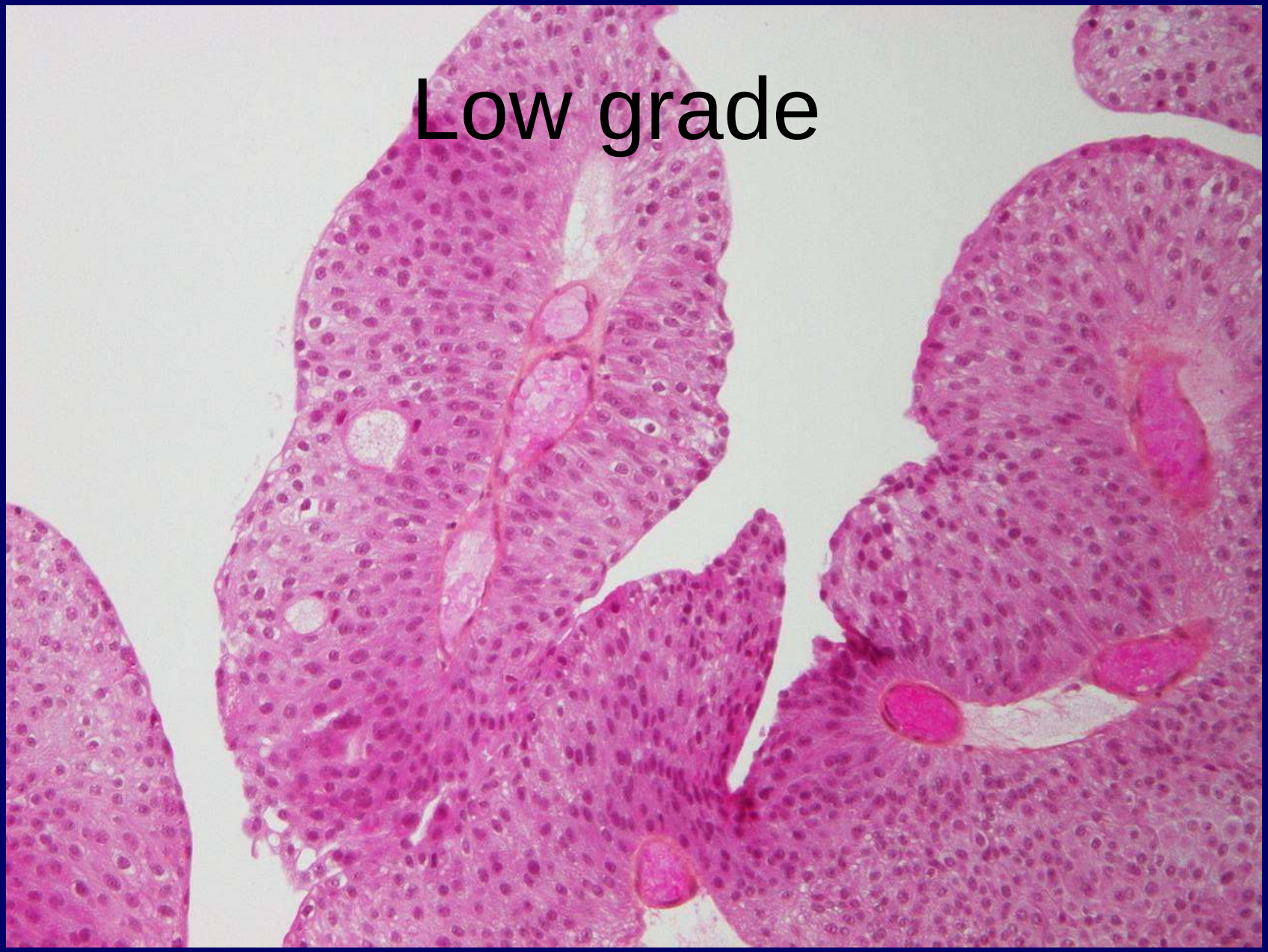
- rare
- benign
- All ages but < 50 ans
- H > F
- Small, unique
- Small thin papillae with no atypia no mitosis no architectural disorder
- Benign

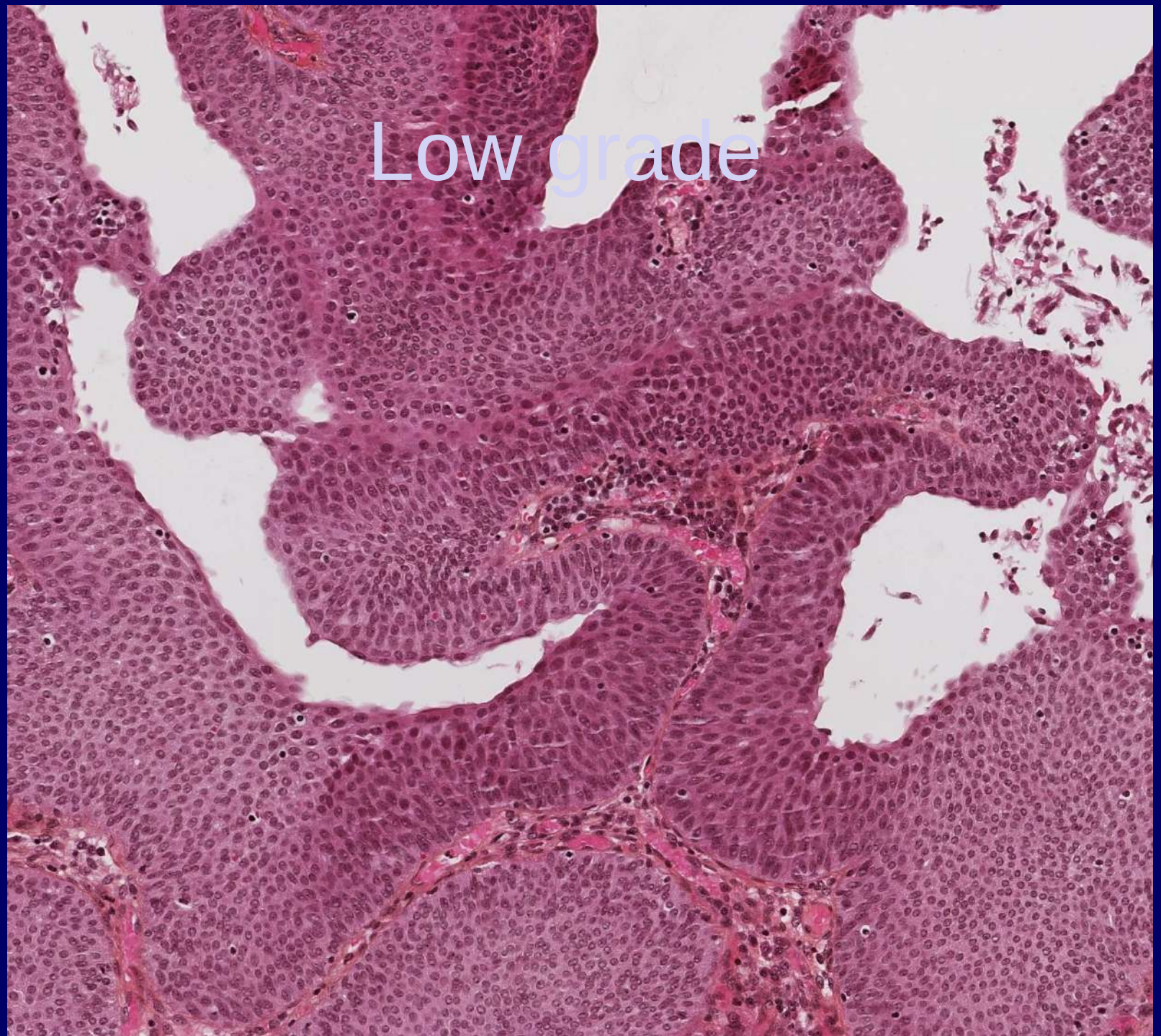




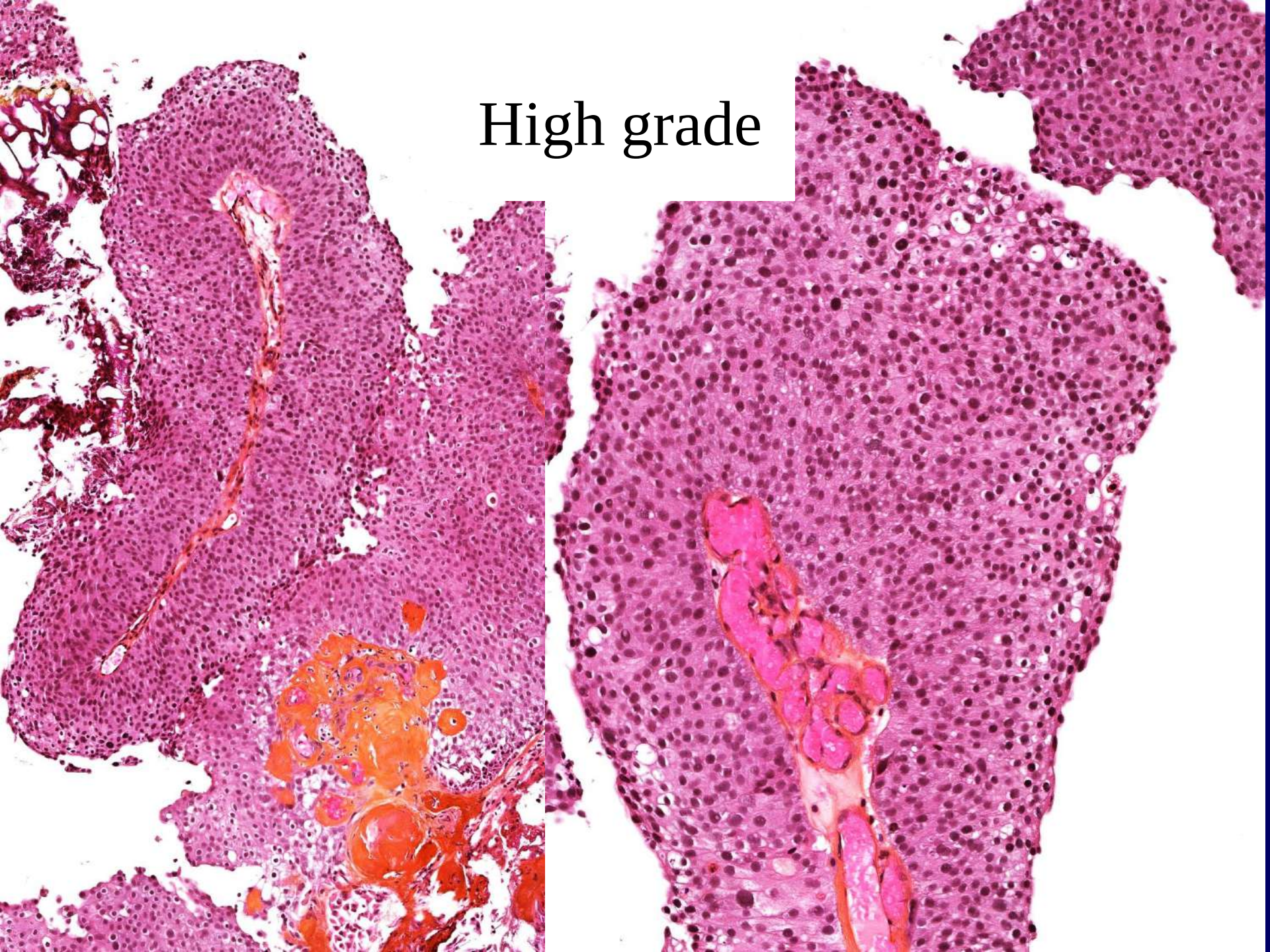
Maggi-Galuzzi C, AJSP 2004

Low grade

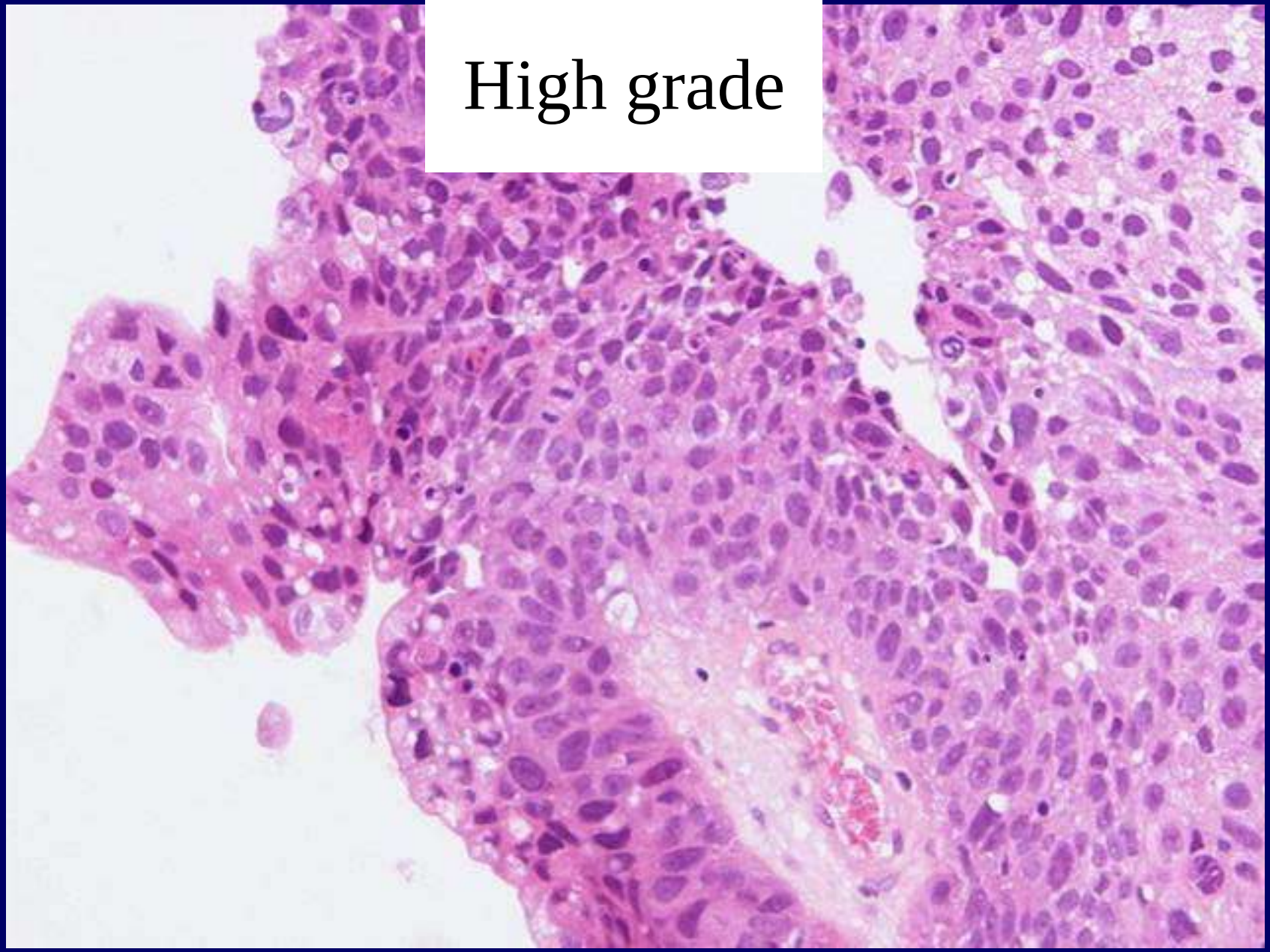


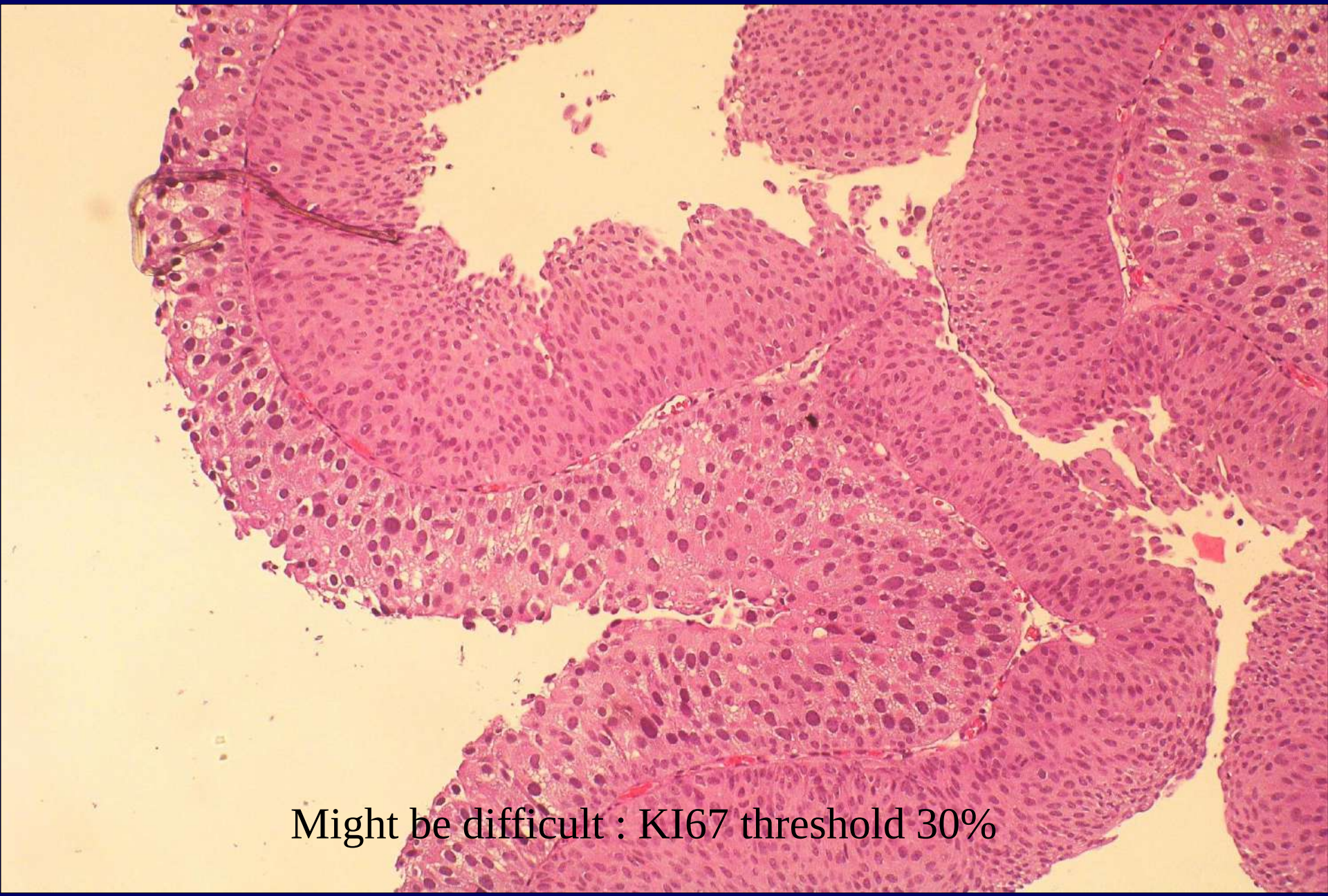

Low grade

High grade



High grade




Might be difficult : KI67 threshold 30%

Recurrences and prognostics

	PUNLMP	NILGC	NIHGC
Recurrence	**6%**	**24%**	**33%**
Death	**0%**	**4%**	**16%**

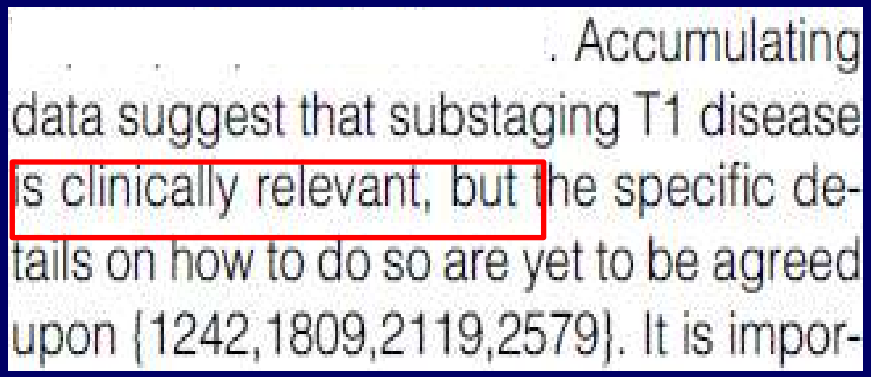
PT1 5 years follow up
Recurrence : 65%
Progression : 35%

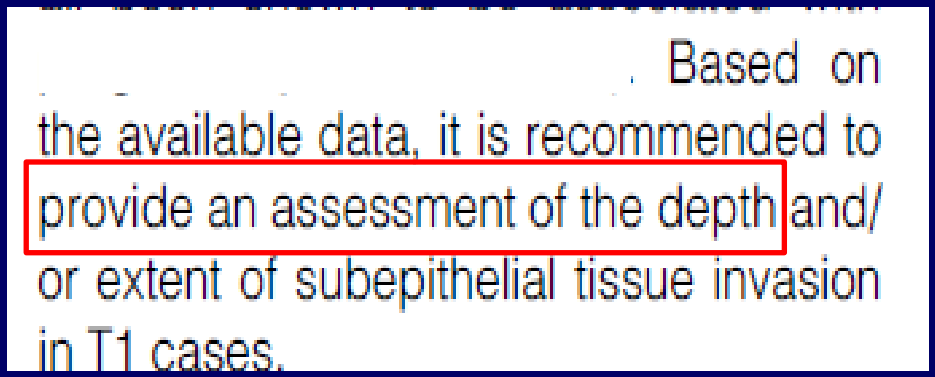
Holmang S et al., J Urol

pT1

Sub-Staging

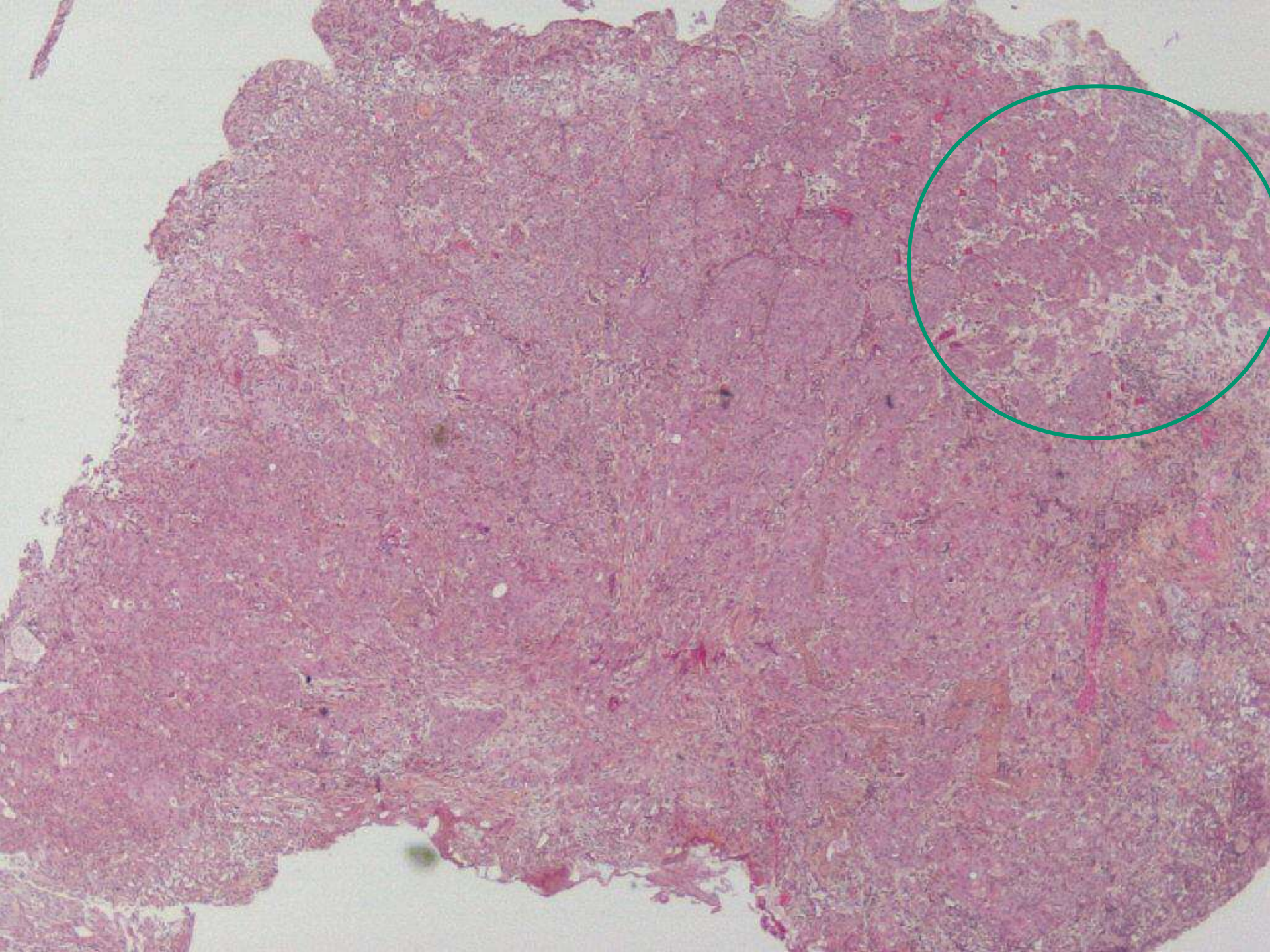
- Substaging pT1 tumors

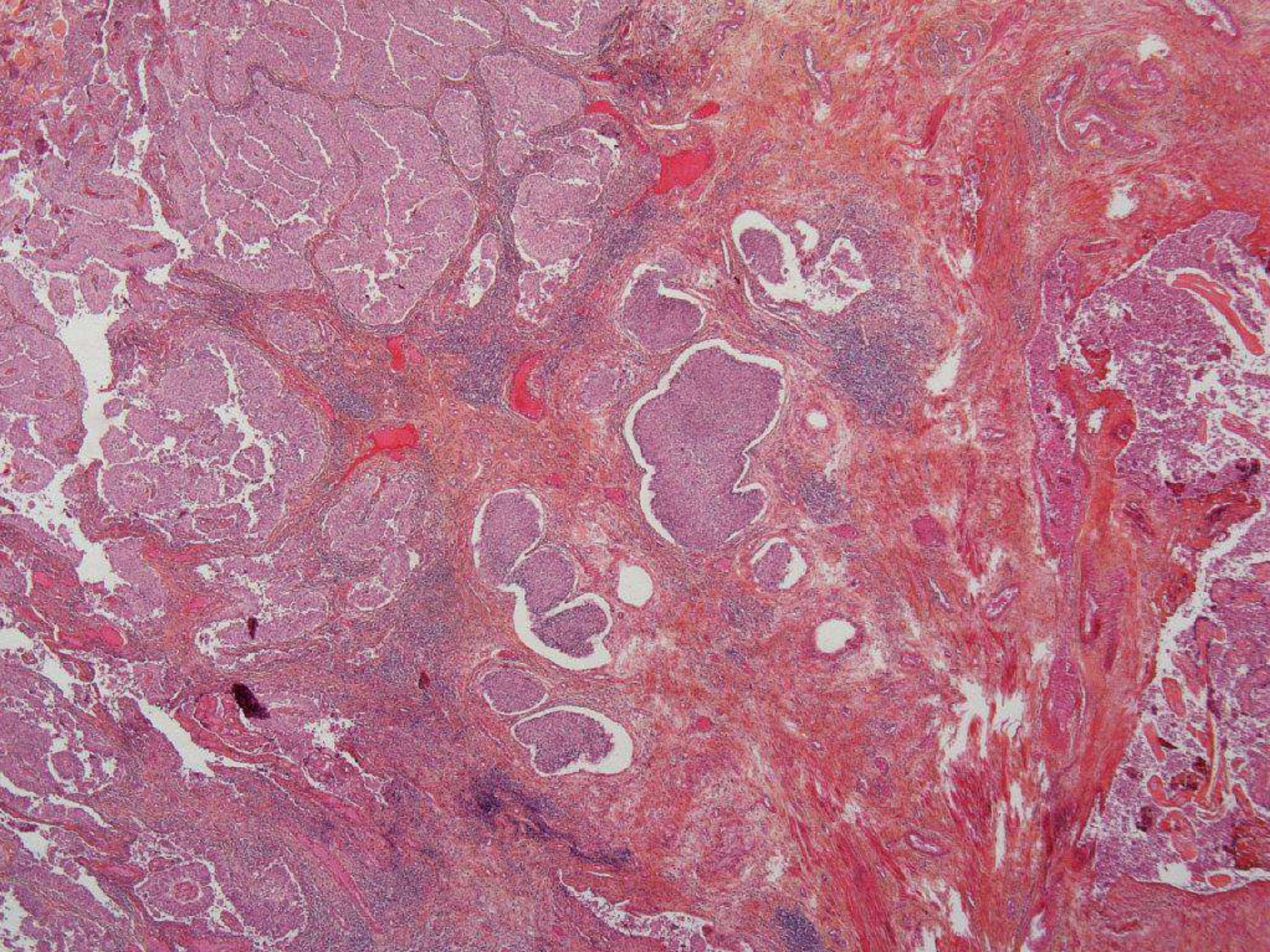

. Accumulating data suggest that substaging T1 disease is clinically relevant, but the specific details on how to do so are yet to be agreed upon {1242,1809,2119,2579}. It is impor-

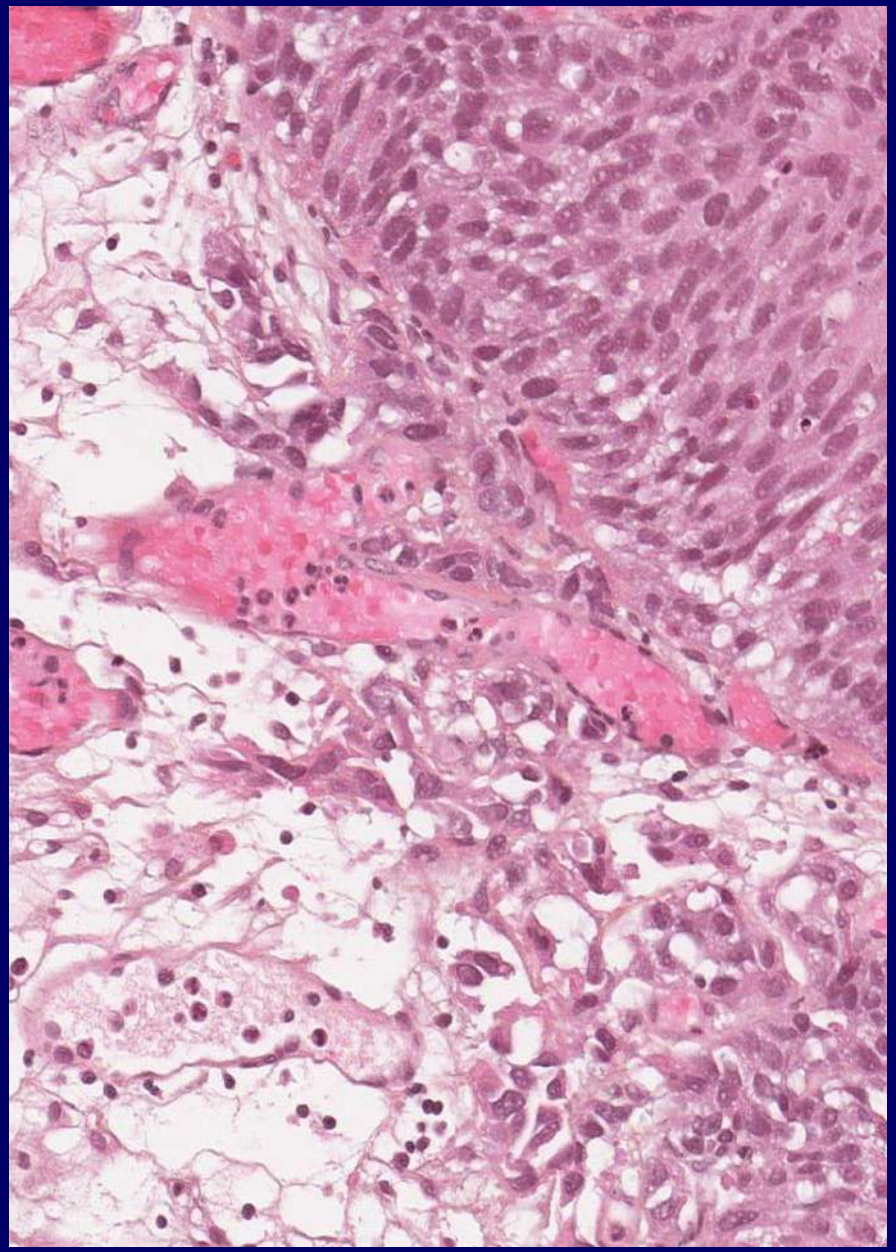

. Based on the available data, it is recommended to provide an assessment of the depth and/or extent of subepithelial tissue invasion in T1 cases.

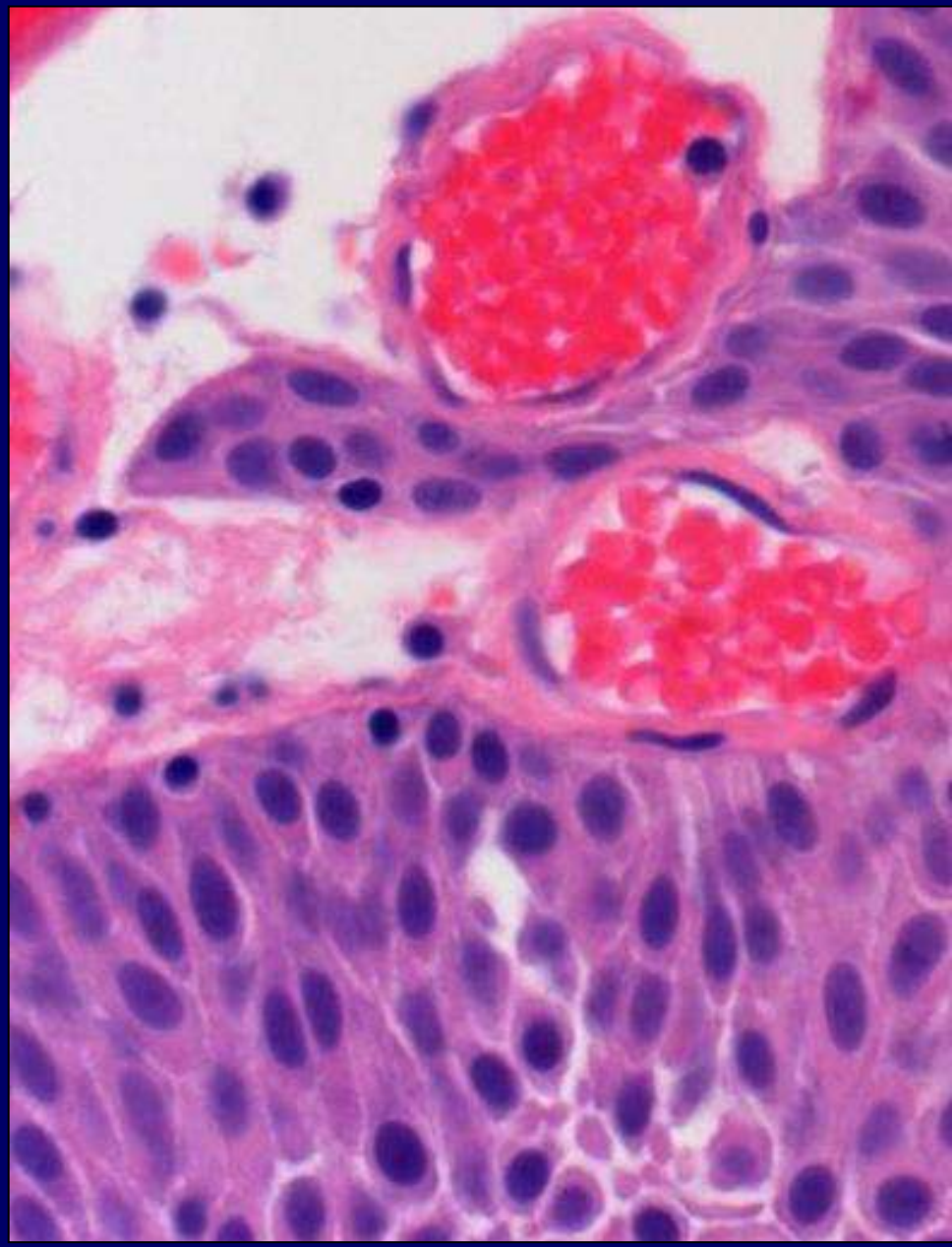
- ICCR (International Collaboration of Cancer Reporting)
  - mm invasion
  - or/and extent
  - and or pT1a/b

WHO 2016









PROGNOSTOC SIGNIFICANCE OF DEPTH OF INVASION IN TRANSURETHRAL RESECTION OF BLADDER SPECIMENS

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

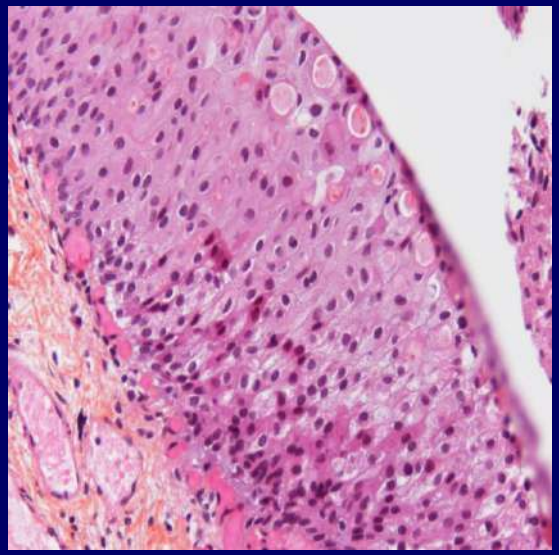
	Recurrences	Progression	Lymph Node +
TADM + (18)	75 %	70 %	40 %
TADM – (82)	37 %	22 %	10 %

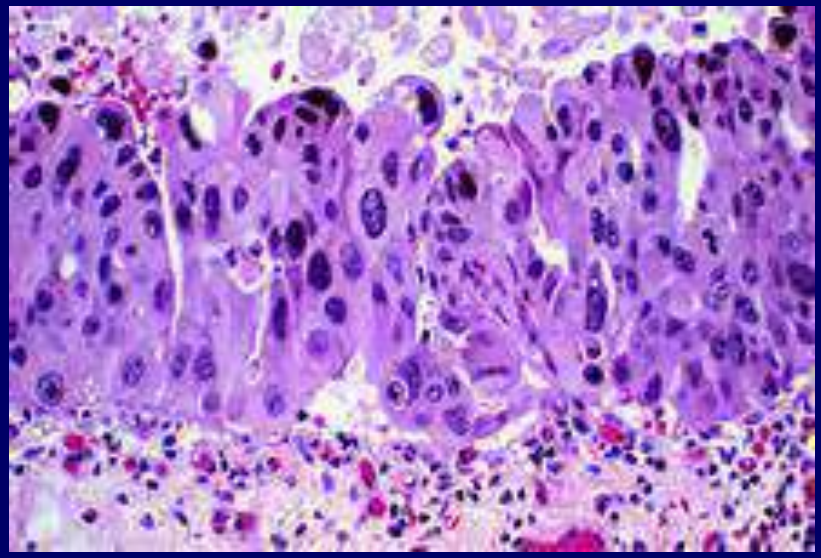
- No current therapeutic impact

Flat lesions

New terminology

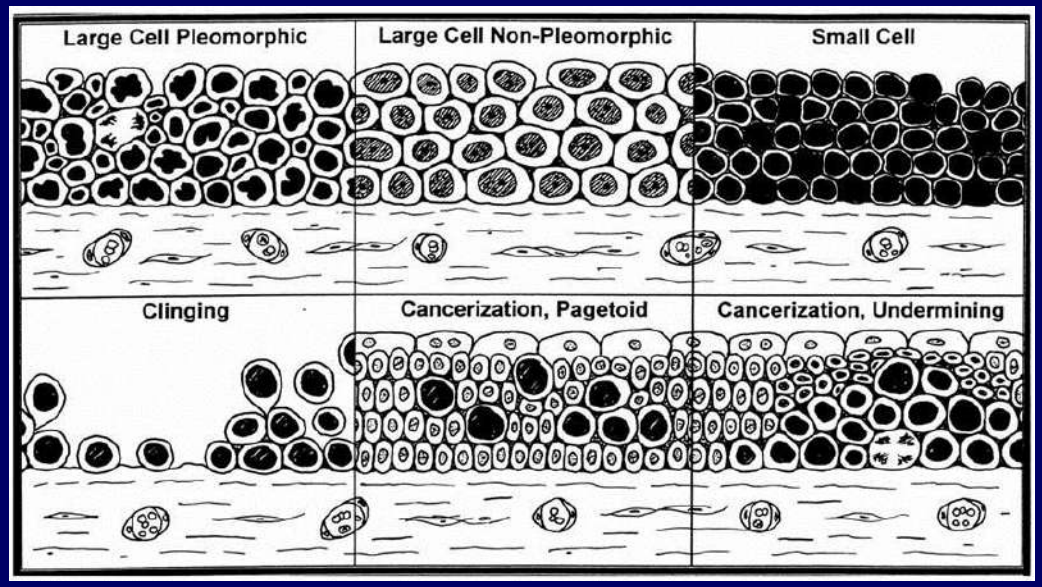
- High grade dysplasia = Carcinoma in situ
- Low grade intraepithelial dysplasia = dysplasia/atypia
- Papillary and flat hyperplasia = urothelial proliferation of uncertain malignant potential

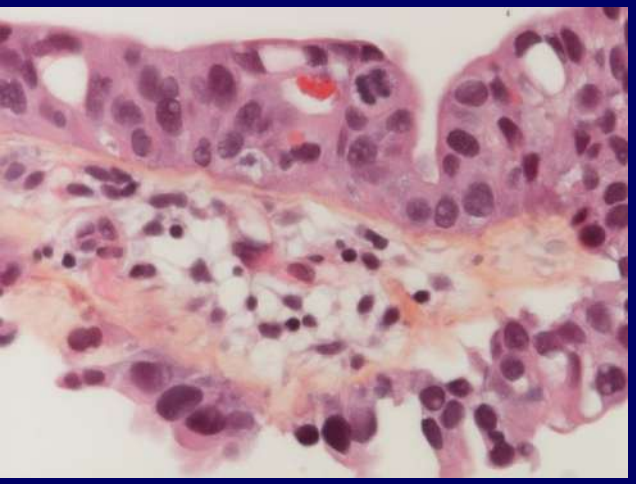




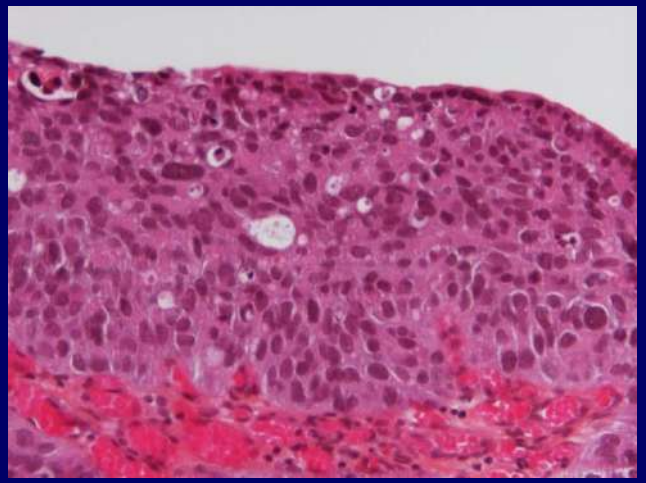
Carcinoma in situ (CIS)

- 3% of bladder tumors
- No infiltration
- malignant
- in 50% of pT1
- In 60% of ≥ pT2

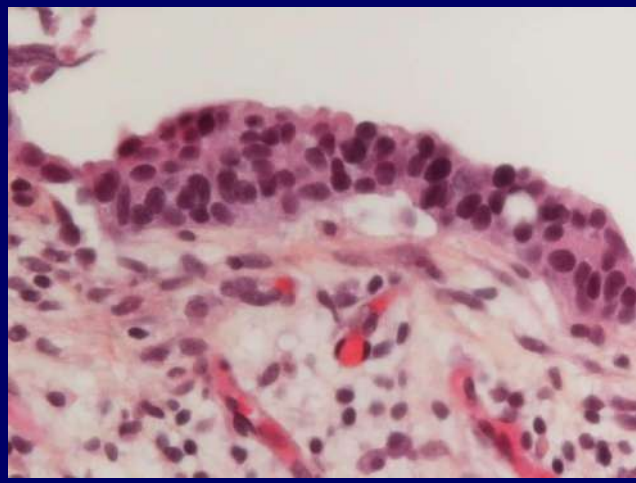




Large cell pleomorphic

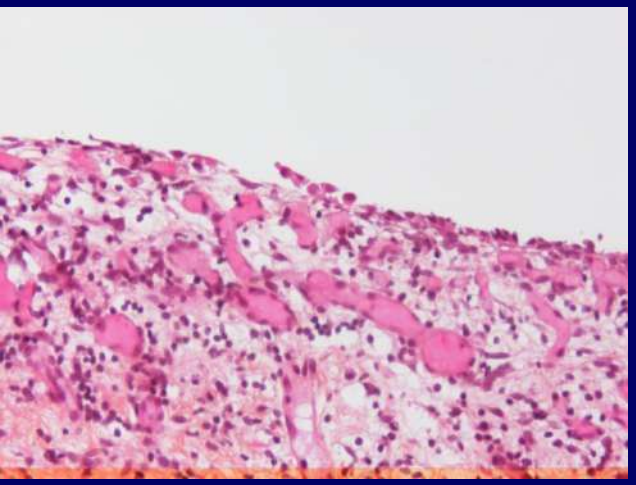


Large cell

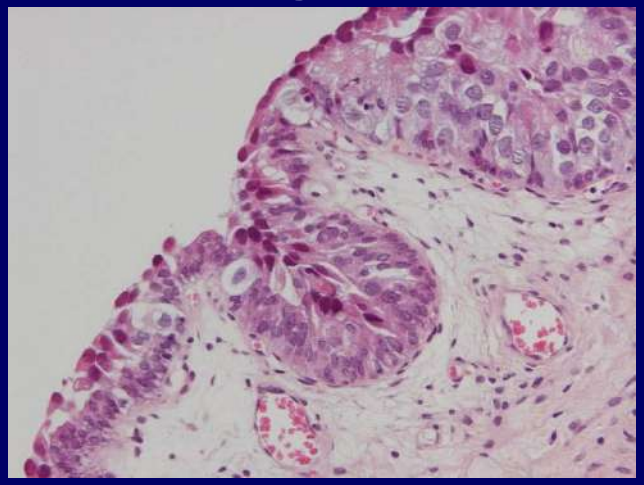


Small cell

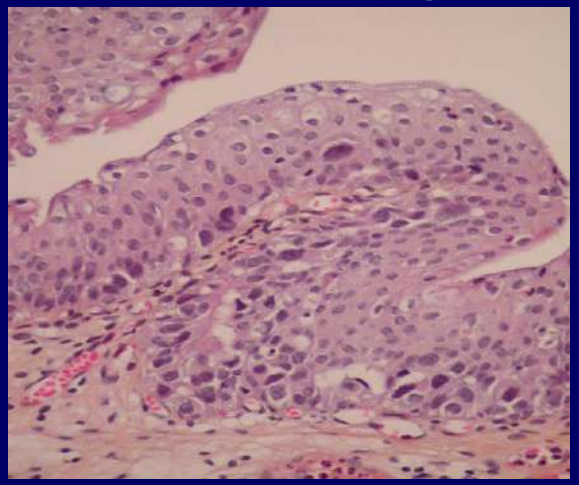
Clinging/denuded



Pagetoid



Undermining



McKenney AJSP 2001

Cis

- Sex ratio H = F

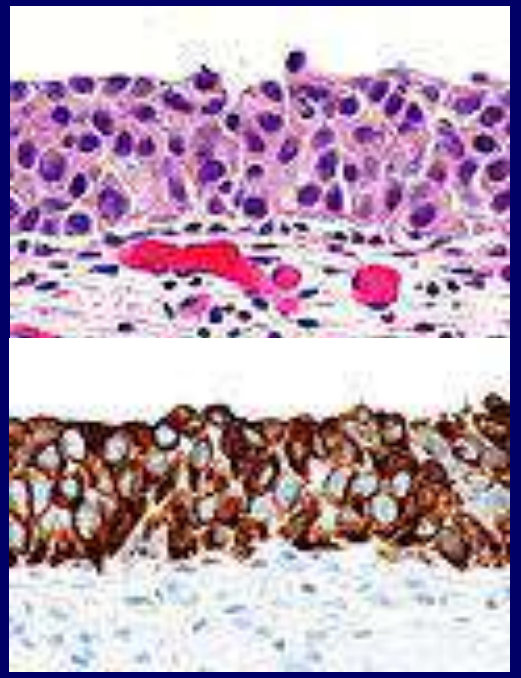
  ↑ risk of urothelial tumor of upper urinary tract RR 2.3

  ↑ risk of recurrence (p=0.045)

  ⬇ OS (p=0.006)

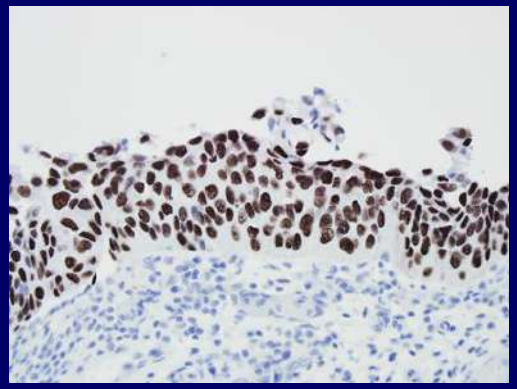
Cis IHC

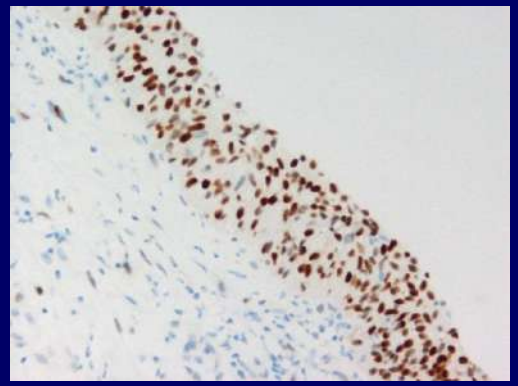
- Diffuse
  - KI 67 +
  - p53 +
  - CK20 +
- Loss of basal CD44 expression



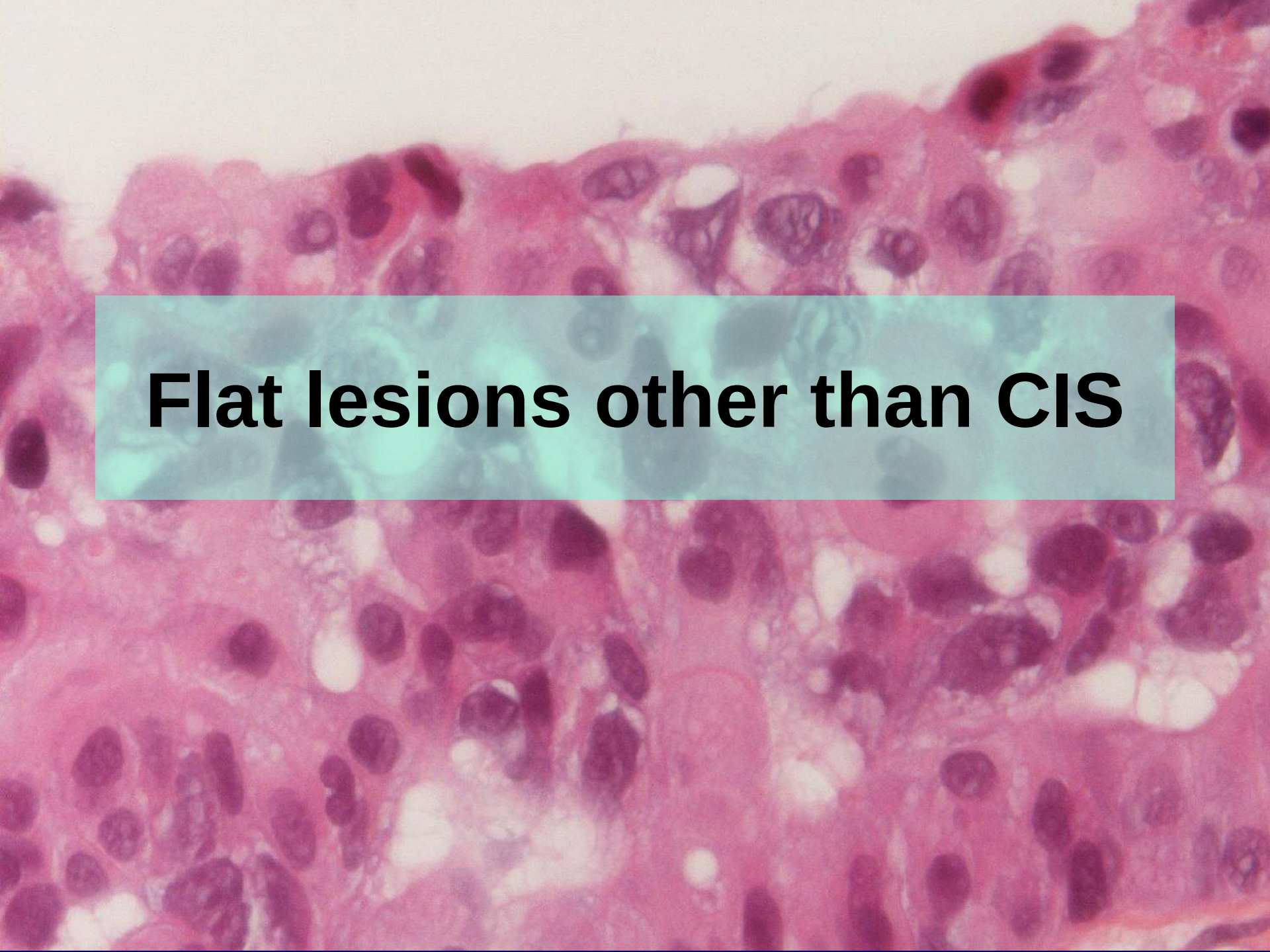
CK20

Ki67





P53



Flat lesions other than CIS

WHO 2016 Classification

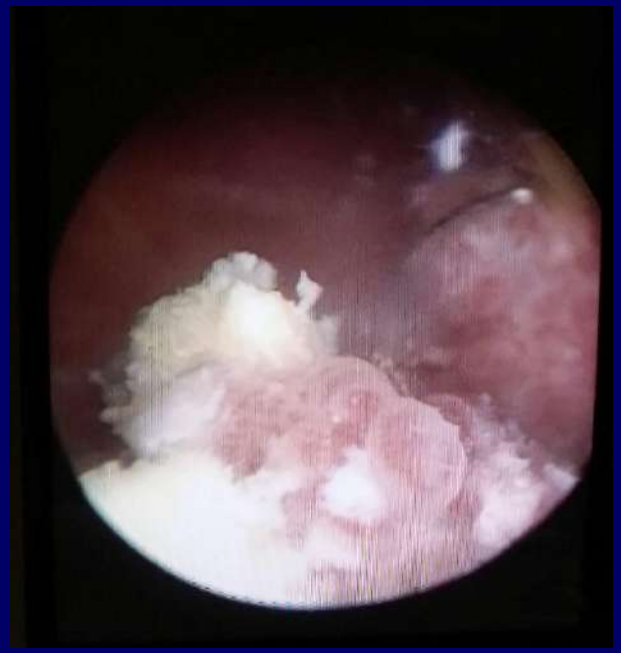
- Metaplasia
  - Squamous with keratinisation/verrucous
  - Glandular /adénoma (tubullous, villous)
- Hyperplasia/ urothelial proliferation of uncertain malignant potential
- Dysplasia

Metaplasia

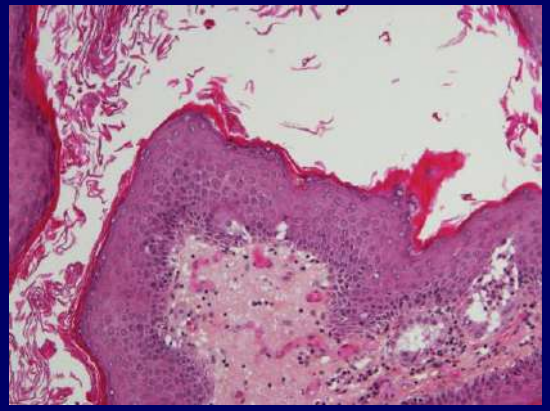
Squamous metaplasia

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

Keratinization



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



Glandular metaplasia (GM)

Chronic inflammation (neurologic bladder)

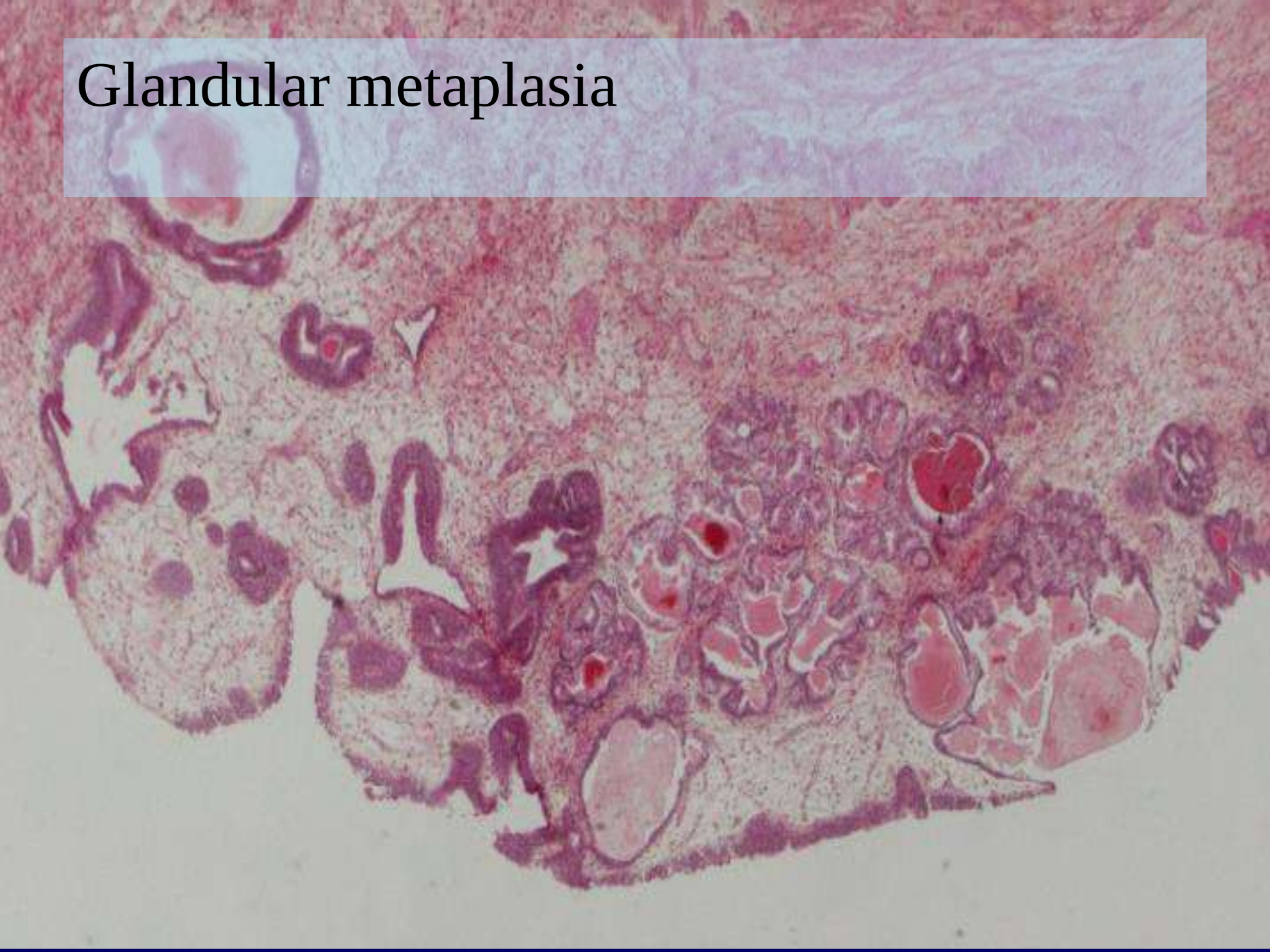
Young male (40 yo) no clinical history

Metaplasia (gastric, colonic)

Differentiation is NOT a prognostic factor

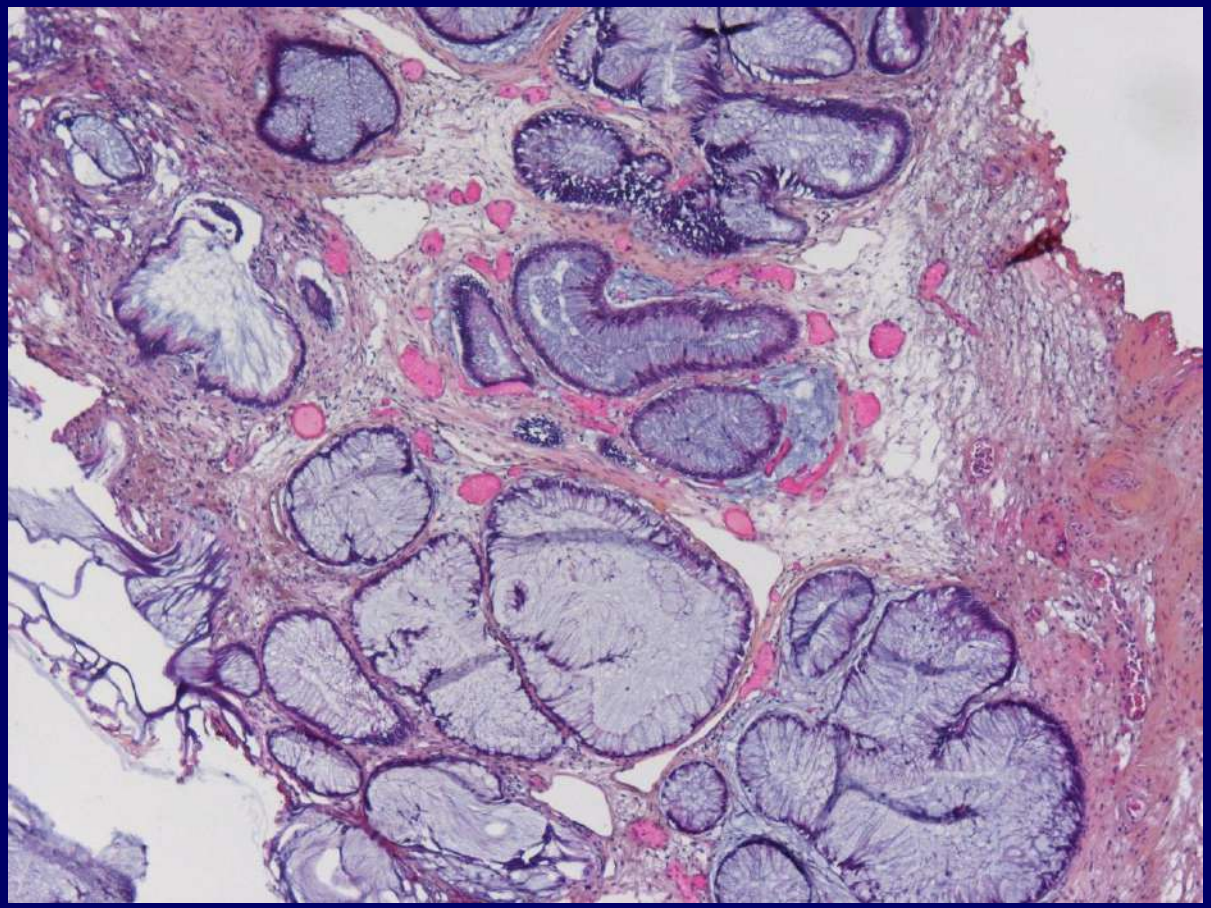
DD : adenocarcinoma

Glandular metaplasia



Glandular metaplasia

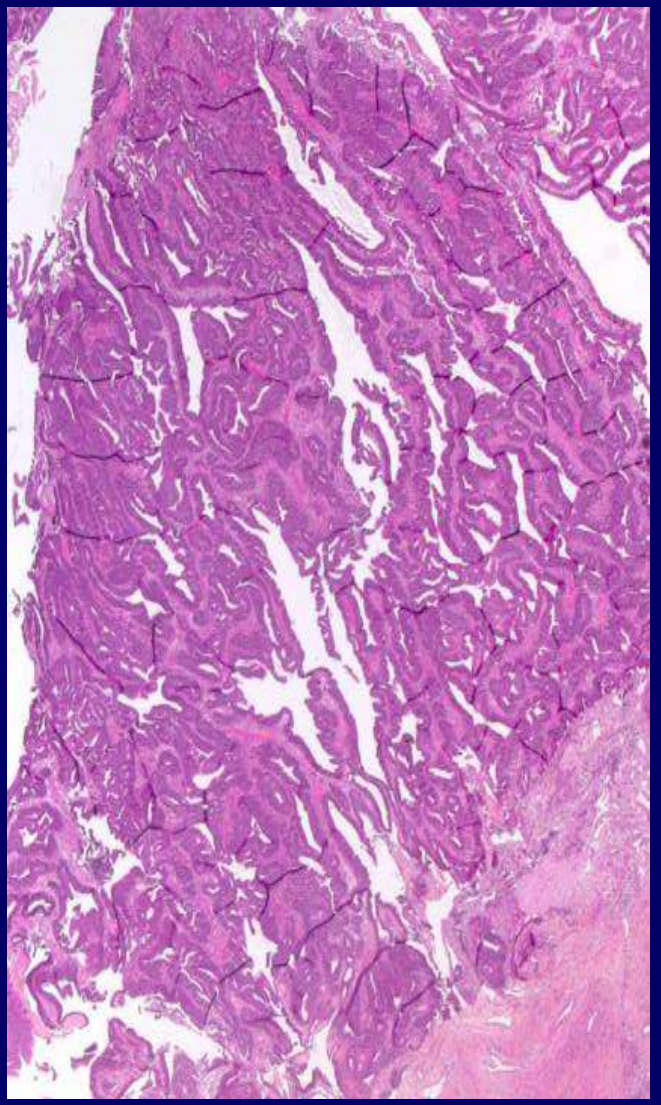
- If mucine production look for ADK



Villous adenoma

- BA +, PAS +
- CK20+, CK7 +/-
- Pronostic good if
  - Isolated
  - Complete excision

- 1/3 association with Adk

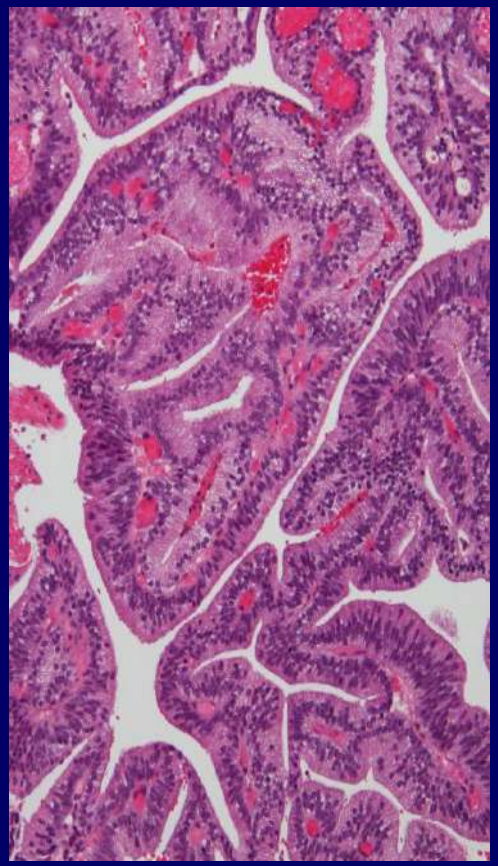


Cheng AJSP 1999

Tubulous adenoma

- Mean 45 yo
- Tubular glands
- Colonic epithelium
- CDX-2+, CK20+, GATA3-, CK7-
- bladder, uretera, uretra

- Association with bladder Adk
- DD : Adk, metastases



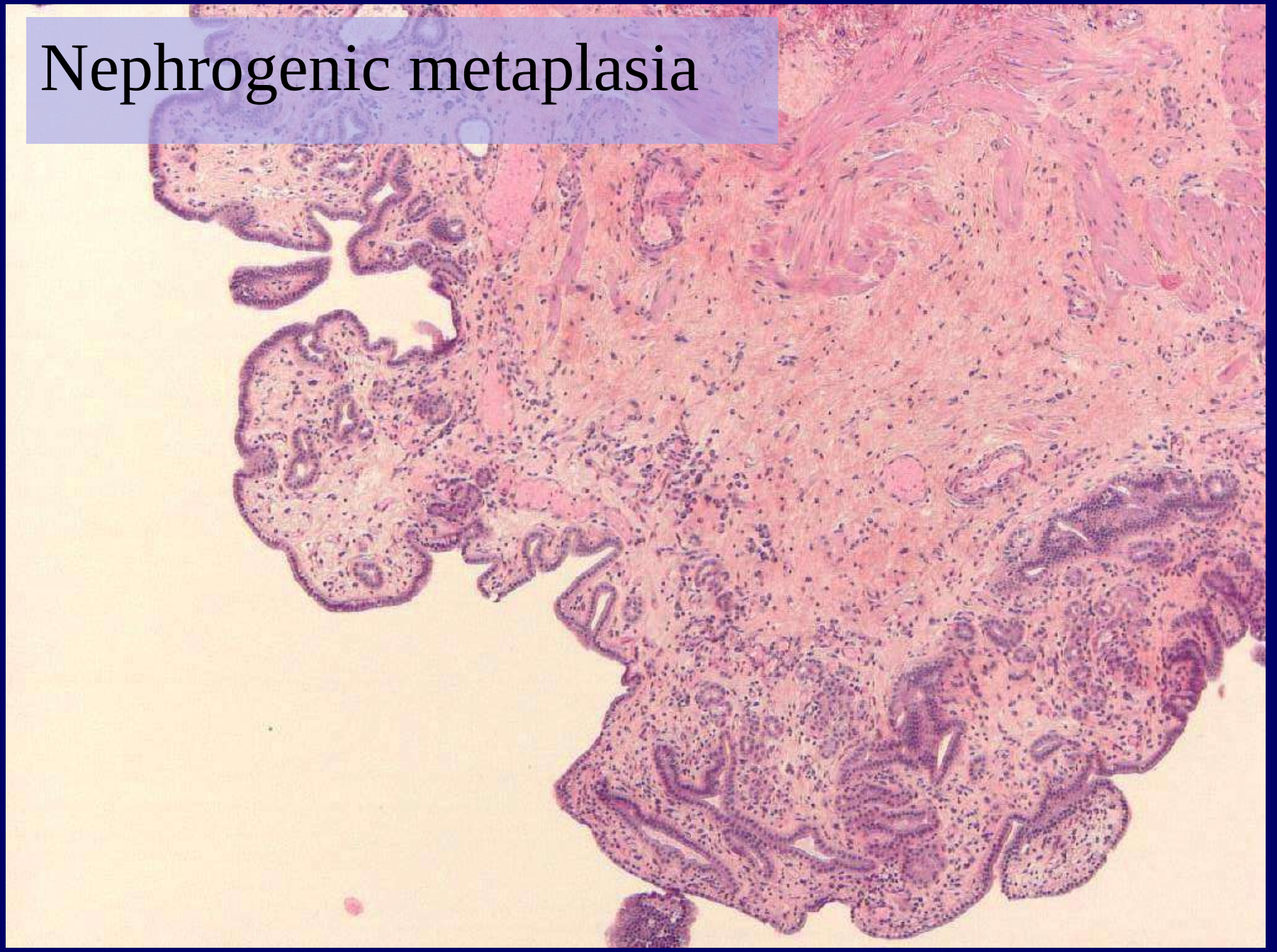
Kao Hum Pathol 2013

Glandular metaplasia

- No mitosis
- No nécrosis
- No single ring cells
- No muscular infiltration

- CAT: watchfull watching
- risk of malignant transformation ≈ 0

Nephrogenic metaplasia



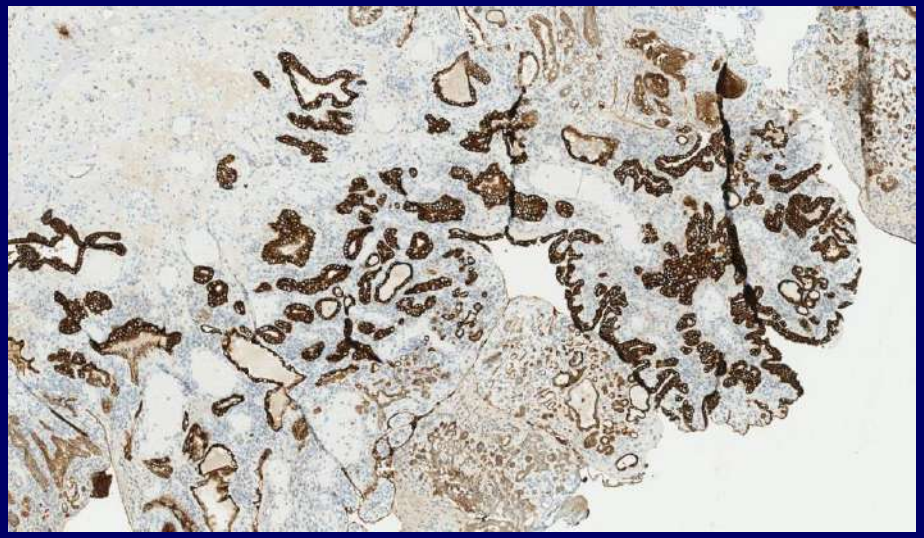
Nephrogenic metaplasia

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

CK7+ Racemase +/-

GATA3- p63 – PSA -

BENIGN

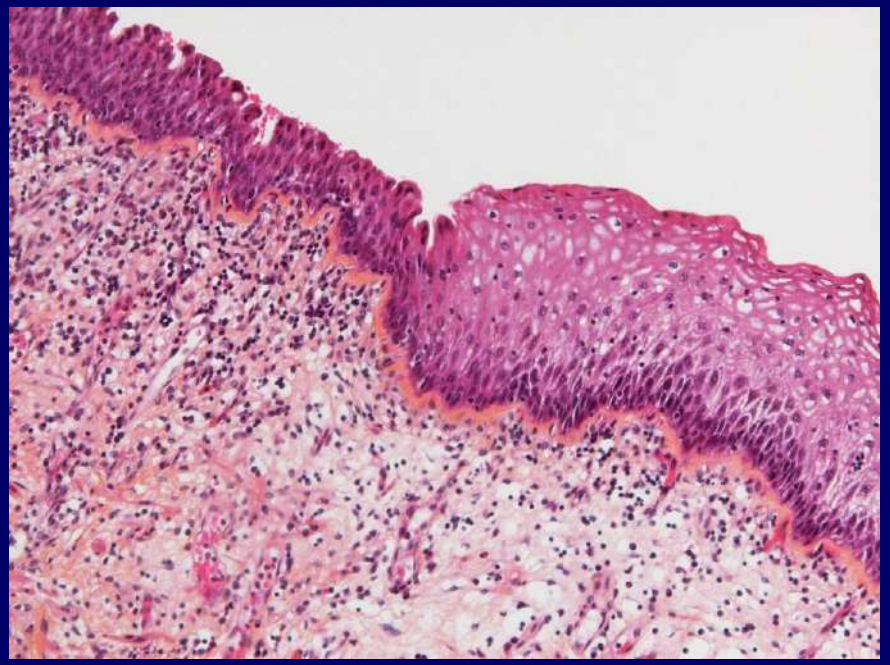


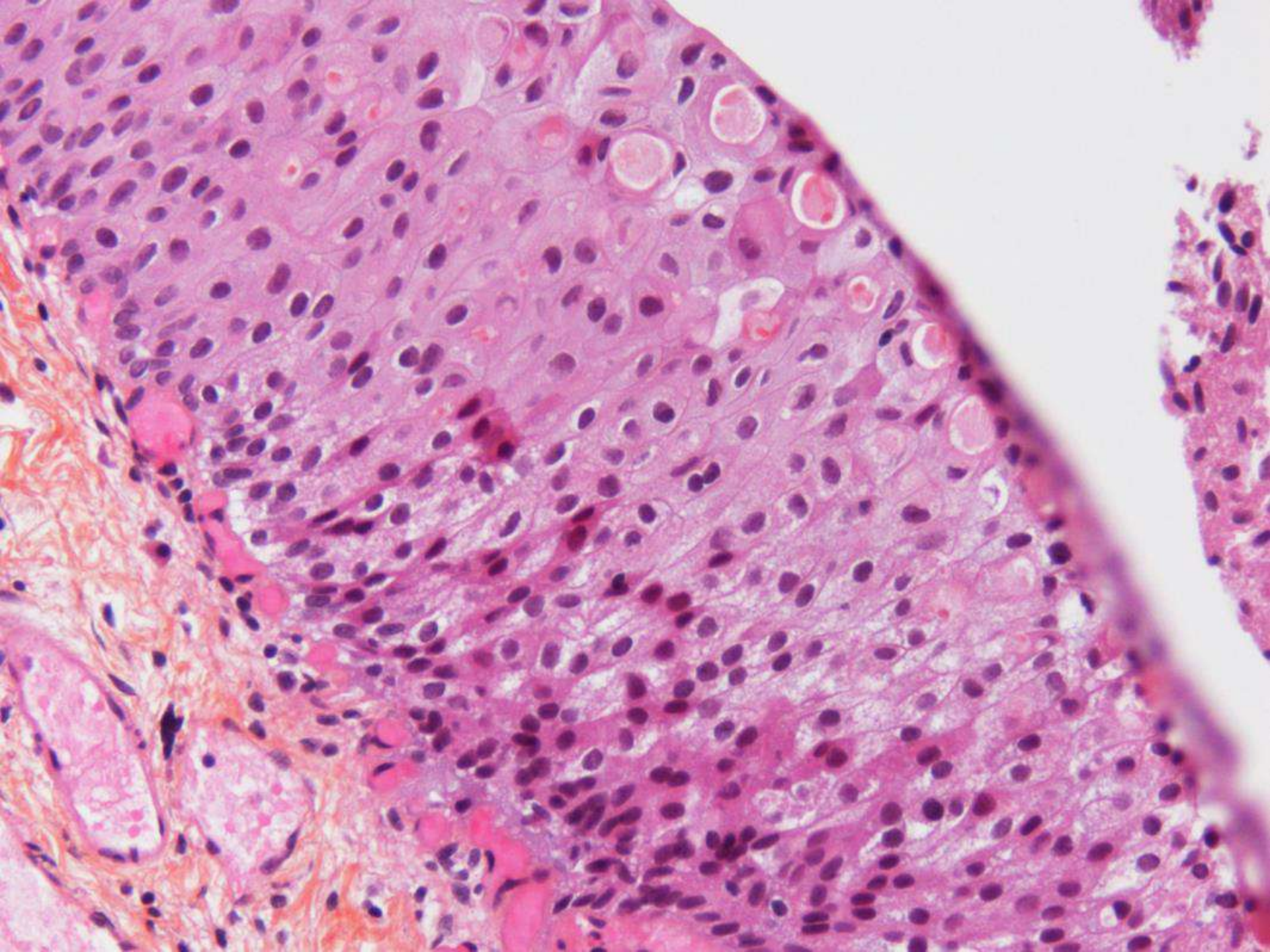
Volmar 2003, Am J Surg Pathol
Hartmann, 2006, Hum Pathol

Urothelial Proliferation of Uncertain Malignant Potential (UPUMP)

UPUMP

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



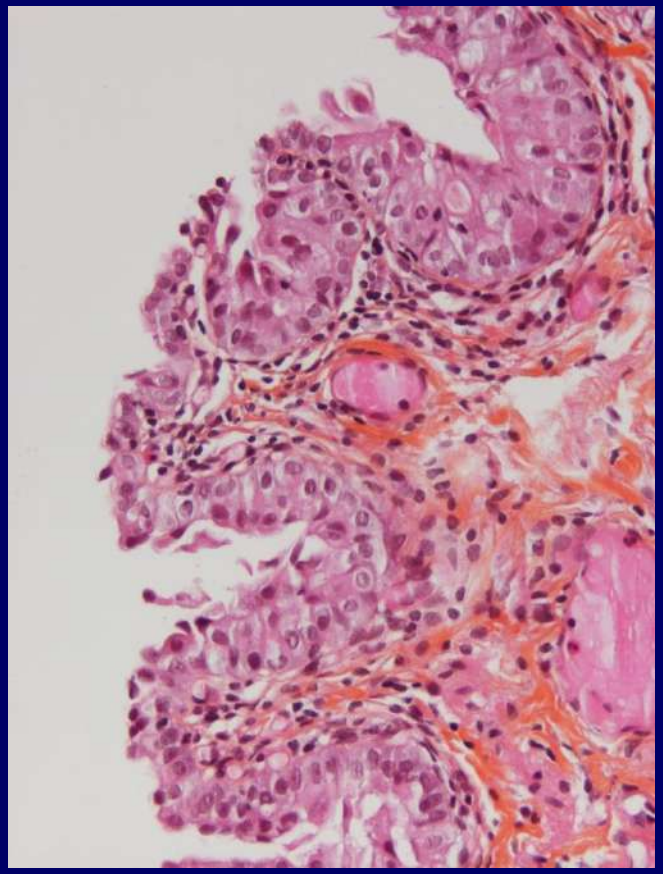


PUPMI papillary with no atypia

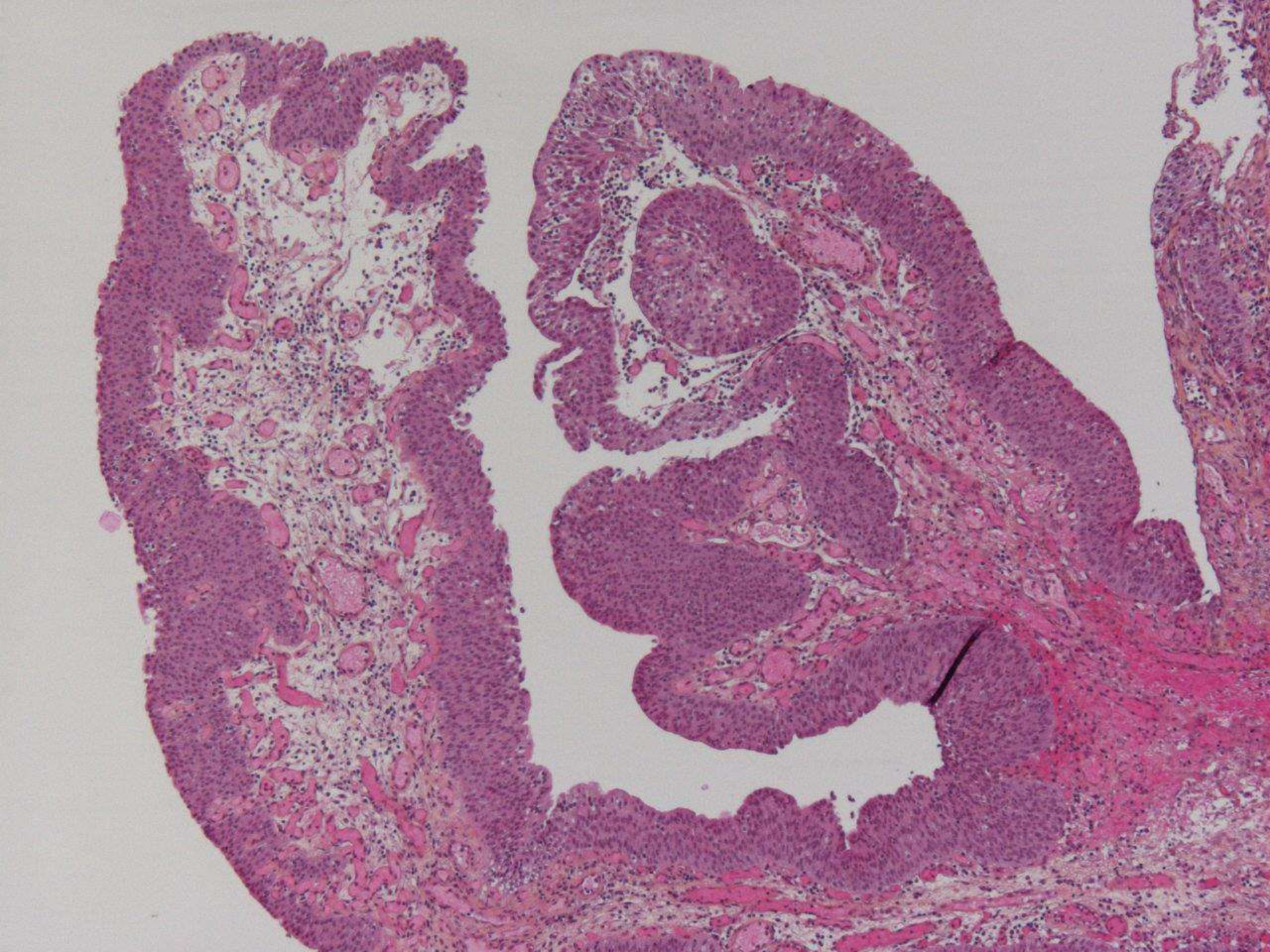
- 1975
- H>F, 50 y.o.

- Normal +/- urothelium
- No atypia

- Association with
  - hematuria
  - pTa BG (60%)

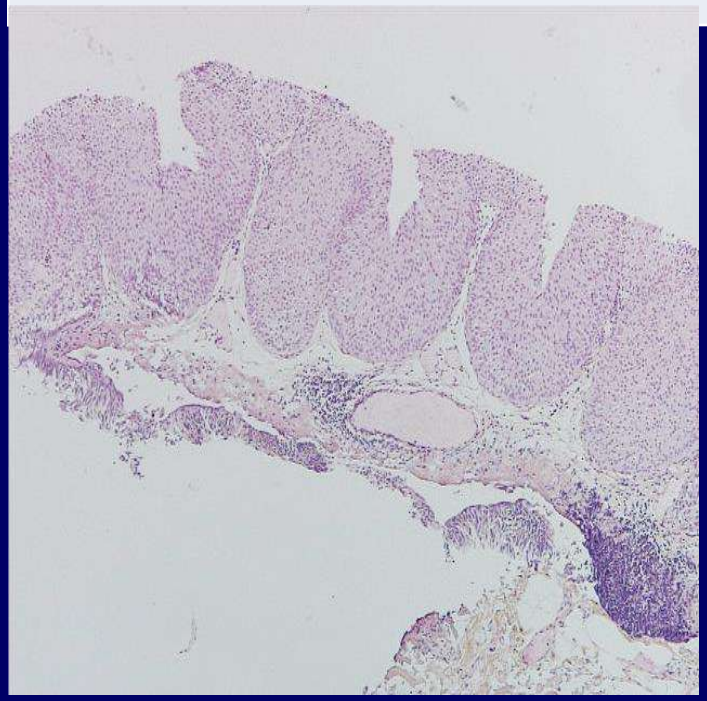


Taylor 1996 AJSP



PUPMI papillary with no atypia

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



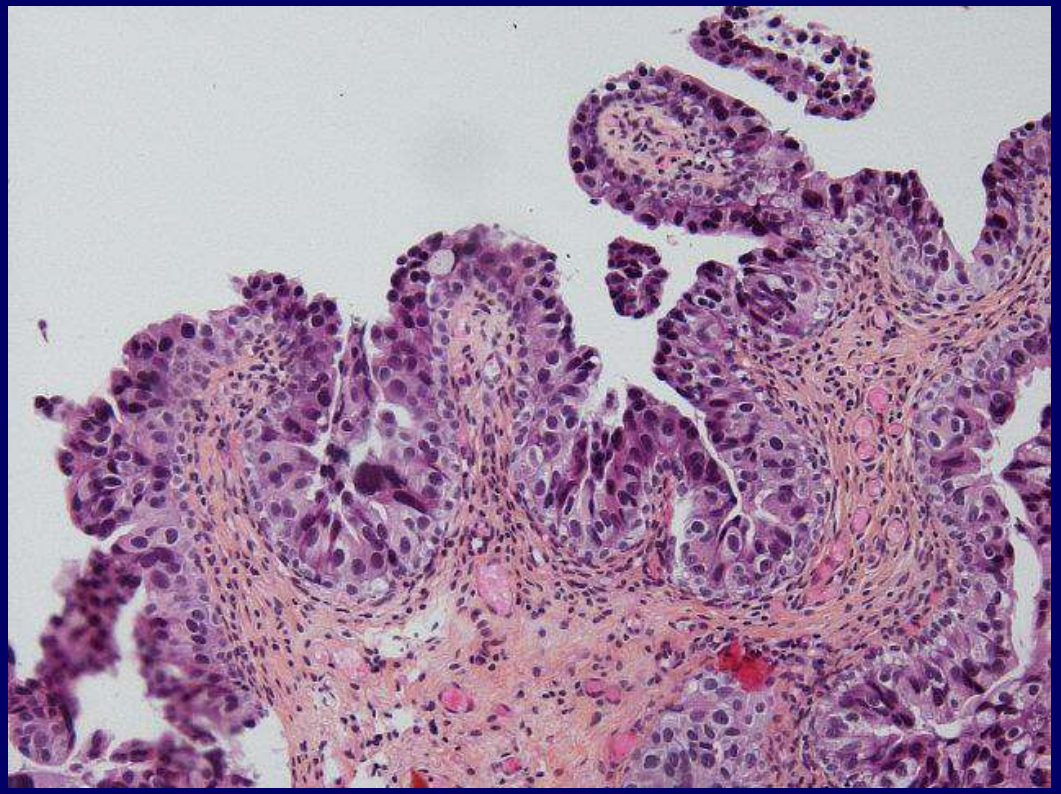
48% developped urothelial carcinoma

Taylor AJSP 1996
Readal, Pathology 2010

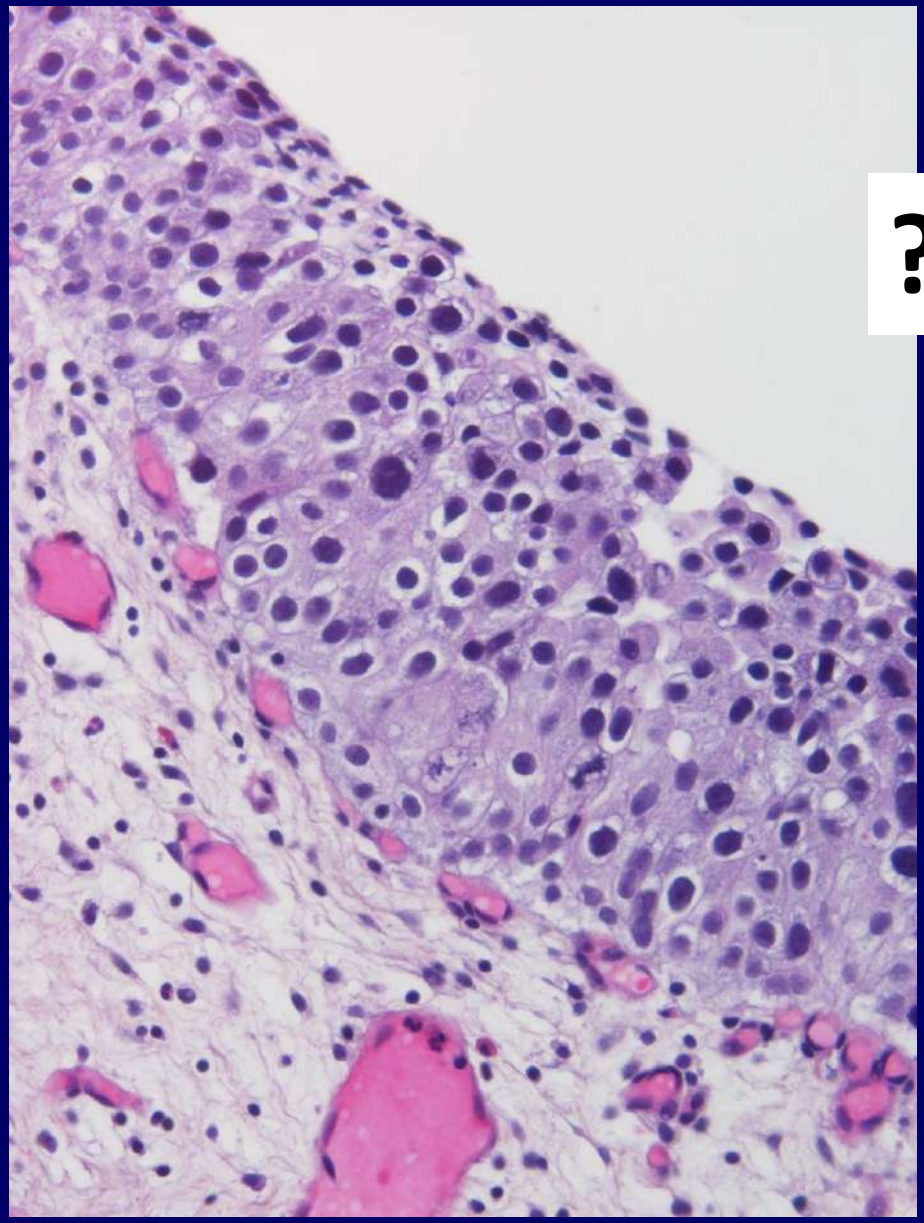
PUPMI papillary with atypia

- Cytologic atypias
- Not enough papillae for pTa

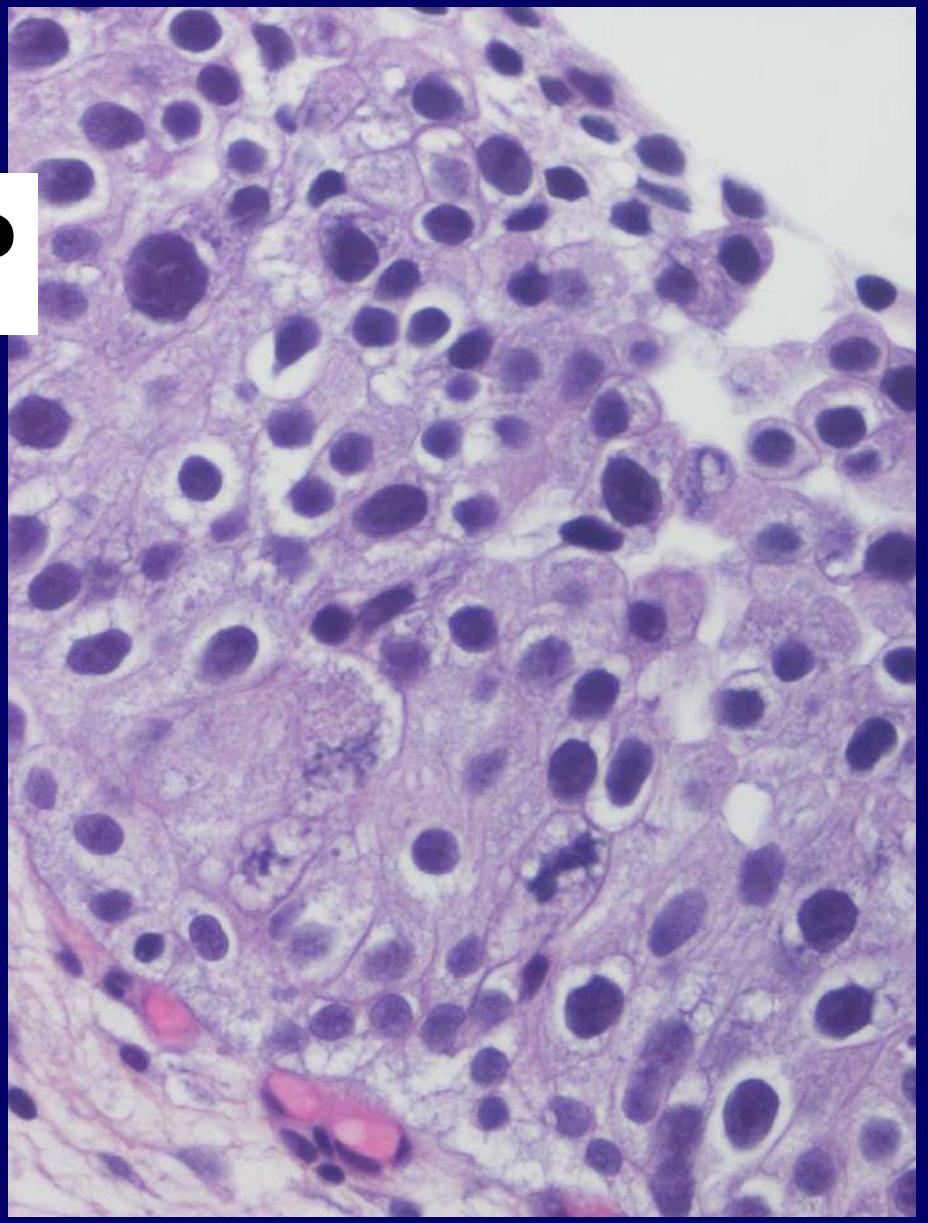
- adults >50 ans
- H> F
- Often association with Cis or previous history of urothelial carcinoma



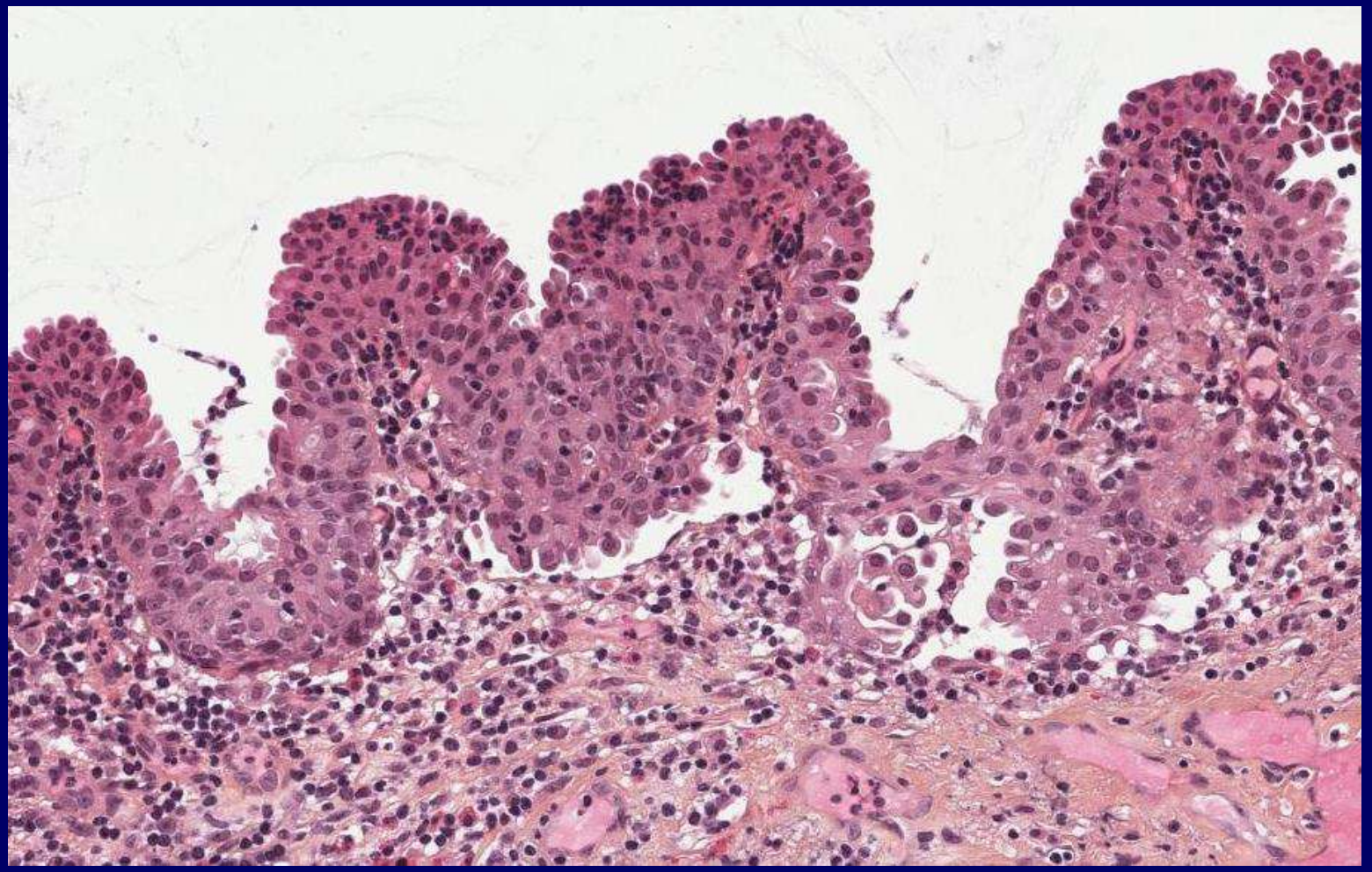
Hungerhuber, 2007, Urology
Obermann, 2003, J Pathol
Swierczynski Hum Path 2002

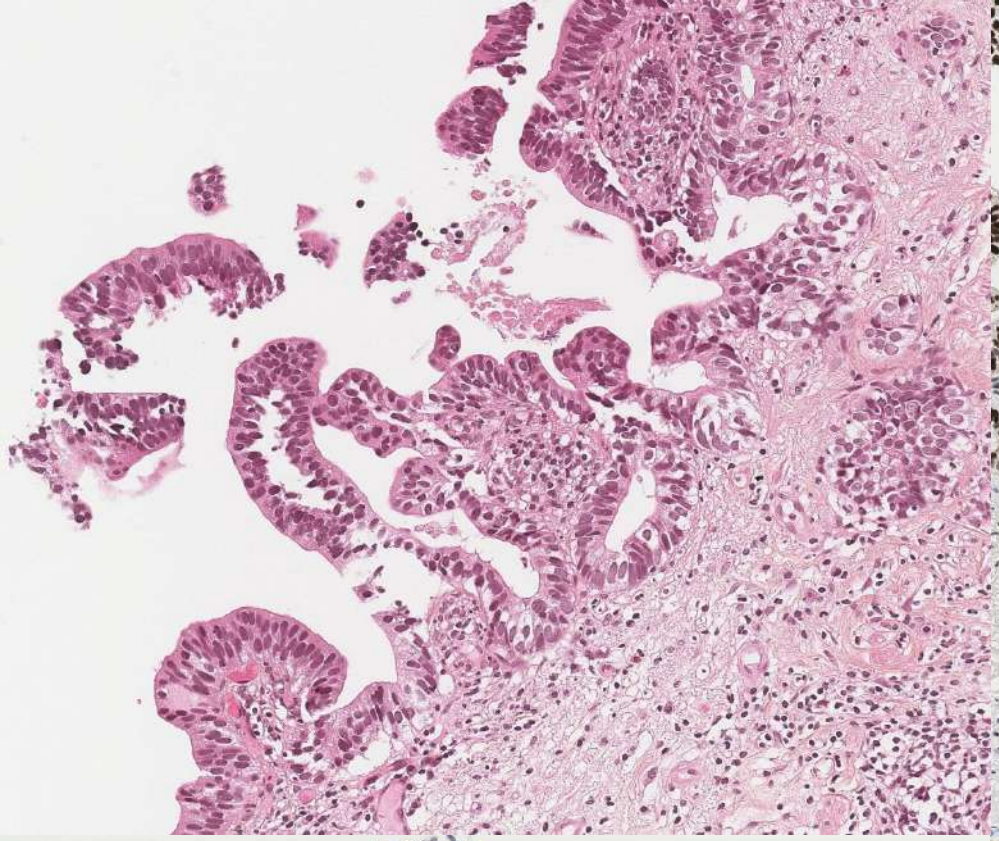


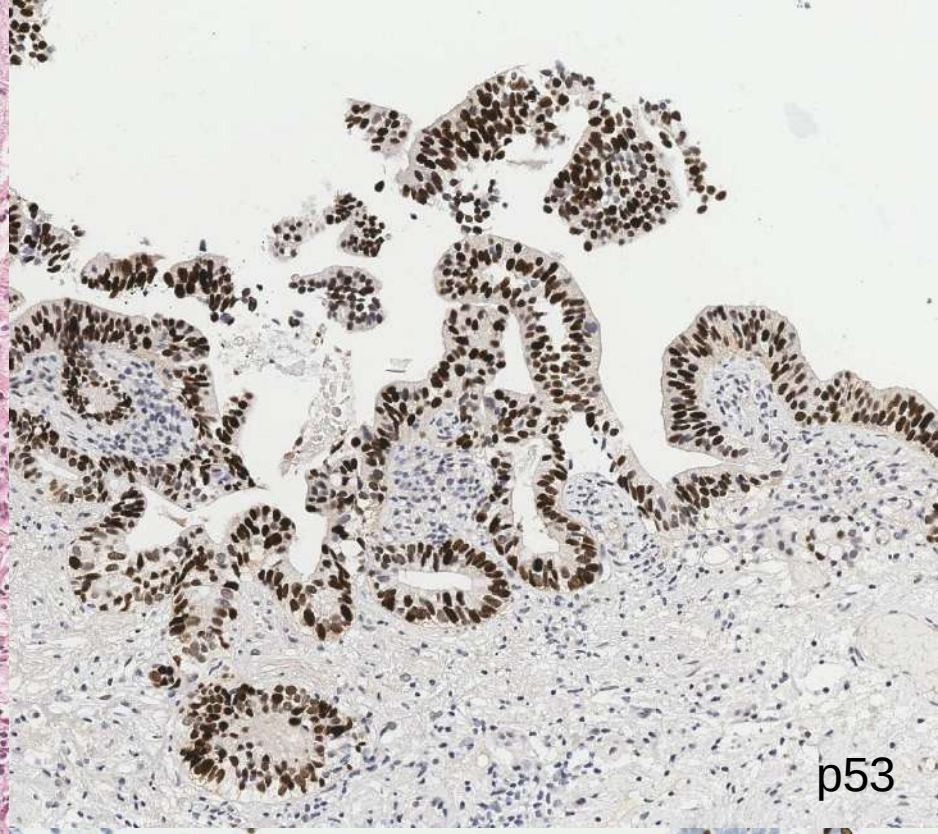
?

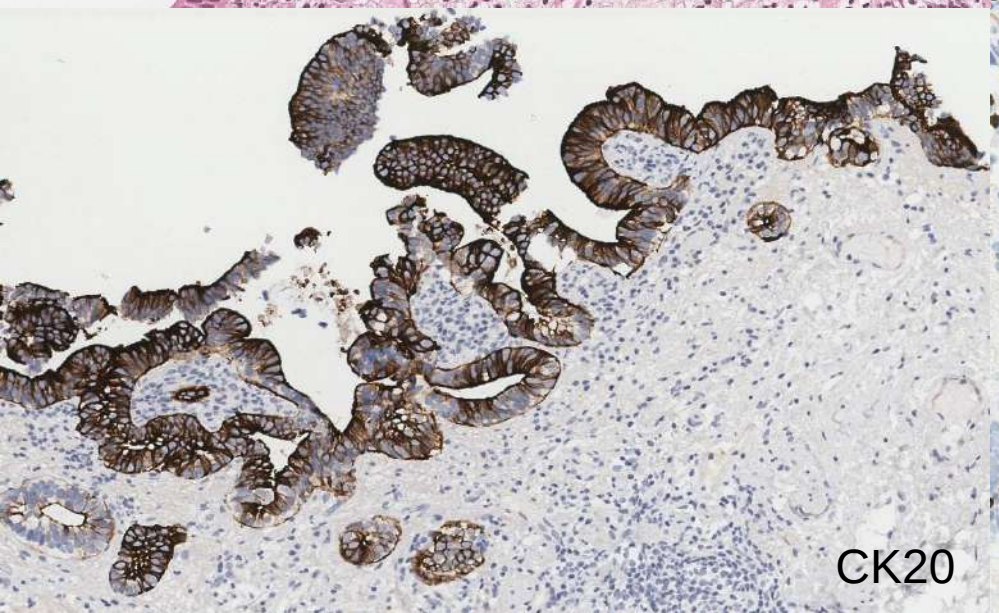


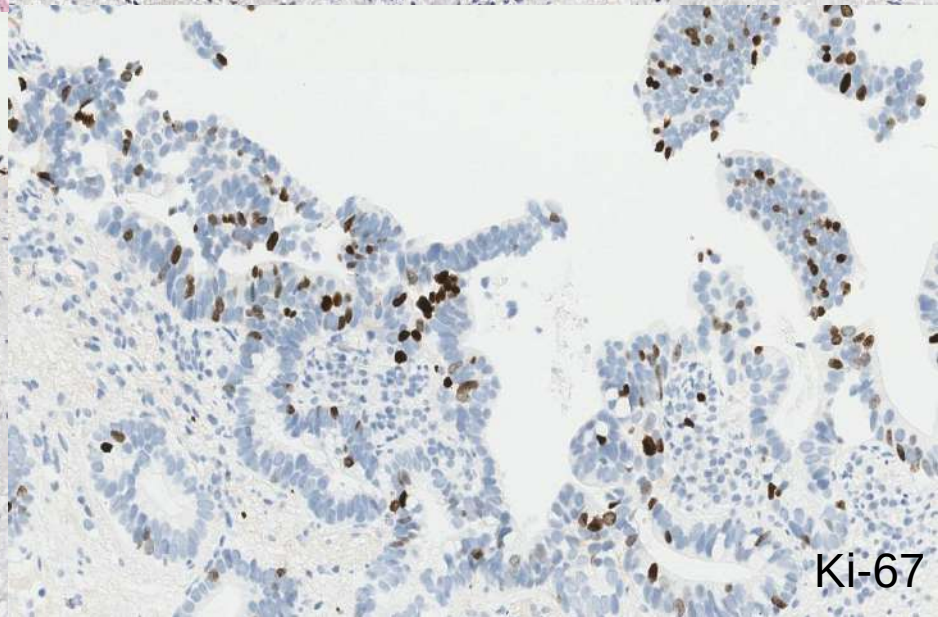
PUPMI with or with no atypia ?






p53


CK20


Ki-67

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 ≥pT1

Swierczynski Hum Path 2002

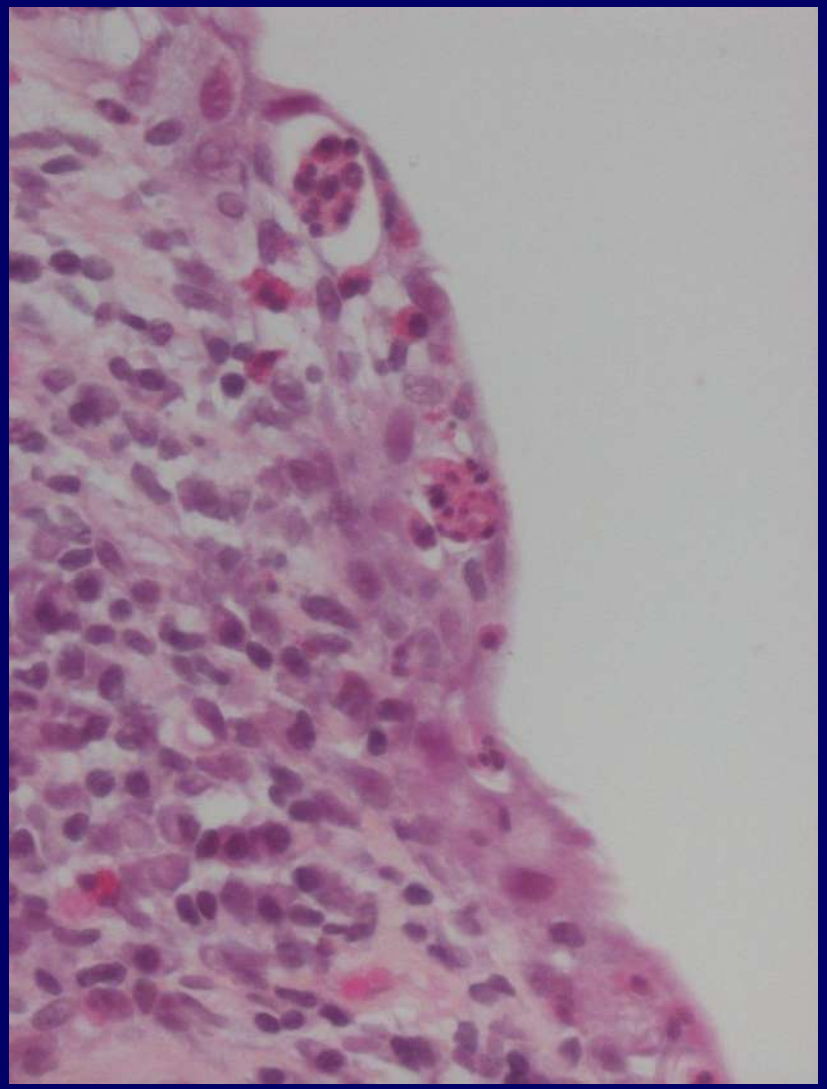
Atypias but not CIS

Reactive atypias

- No precise definition
- Clinical history+++
  TURB, ttt., etc…

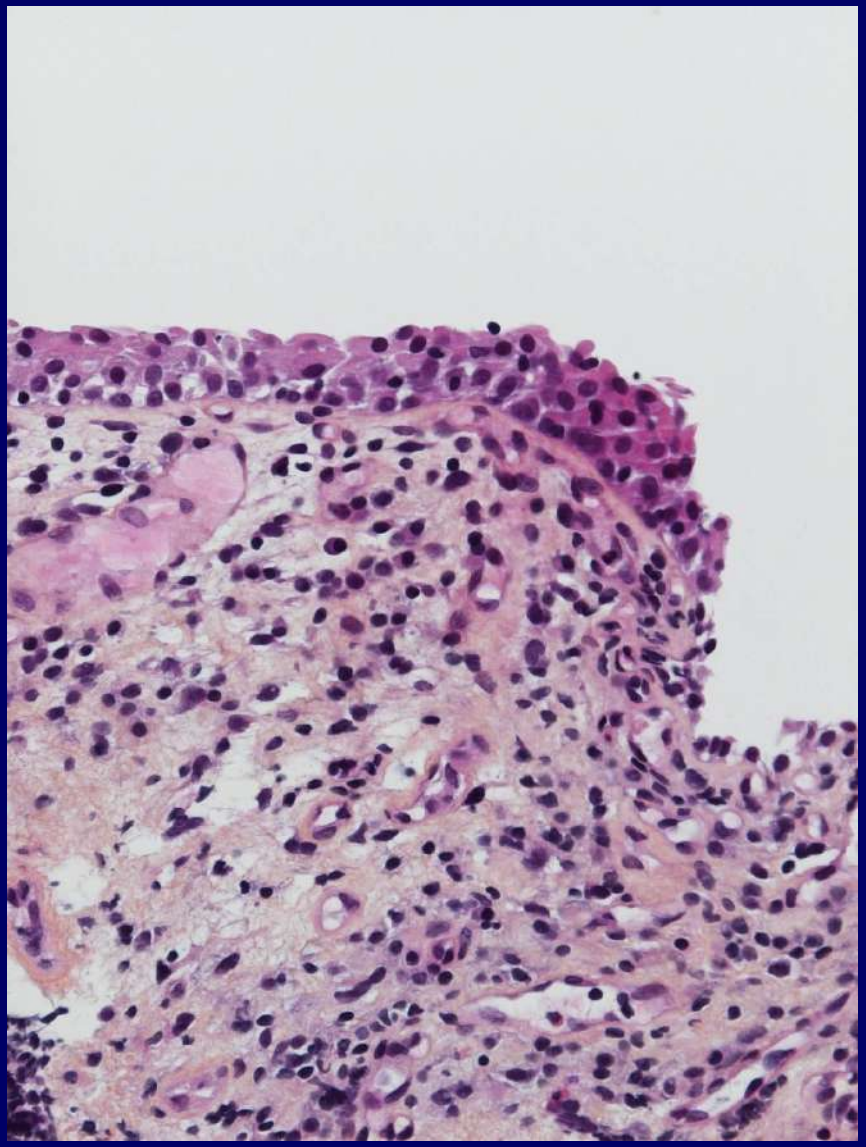
  inflammation mitosis +/-
  denuded areas ?
  → danger (Cis ?)

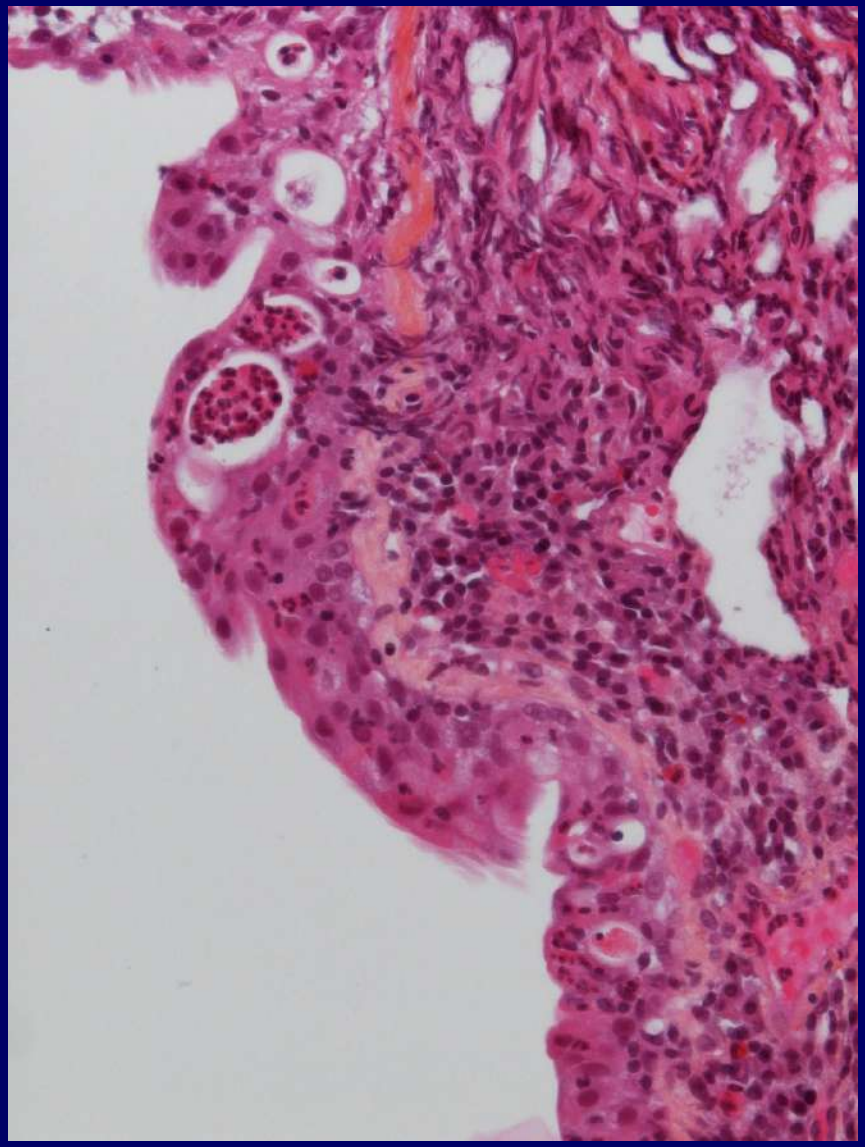
- → Cytology +++ (Cis)



Montironi 2008, Histopathology
Filbeck, 1999, Urology

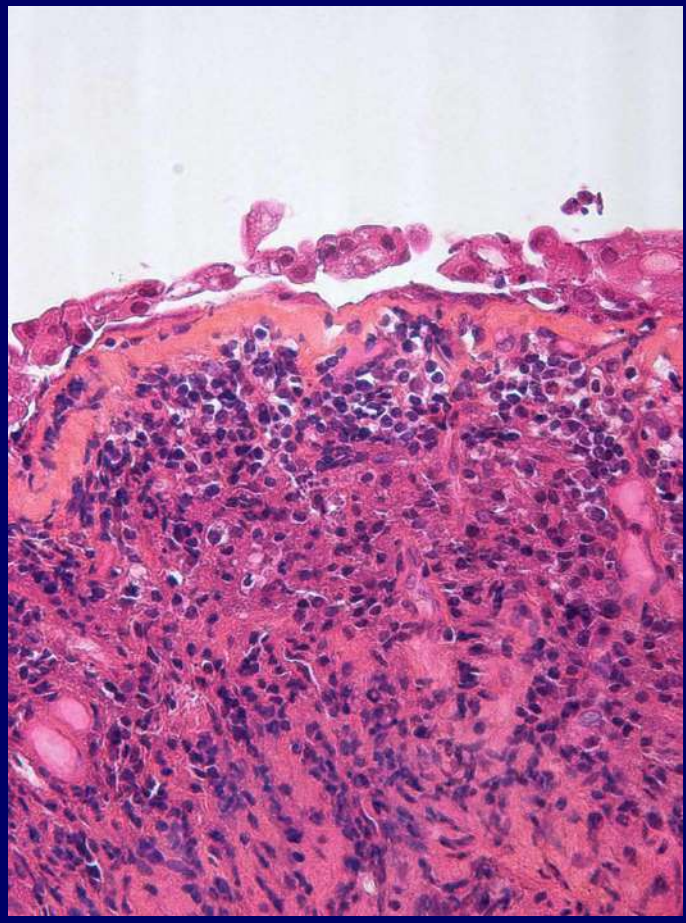
Reactive atypias (clinical history ++)



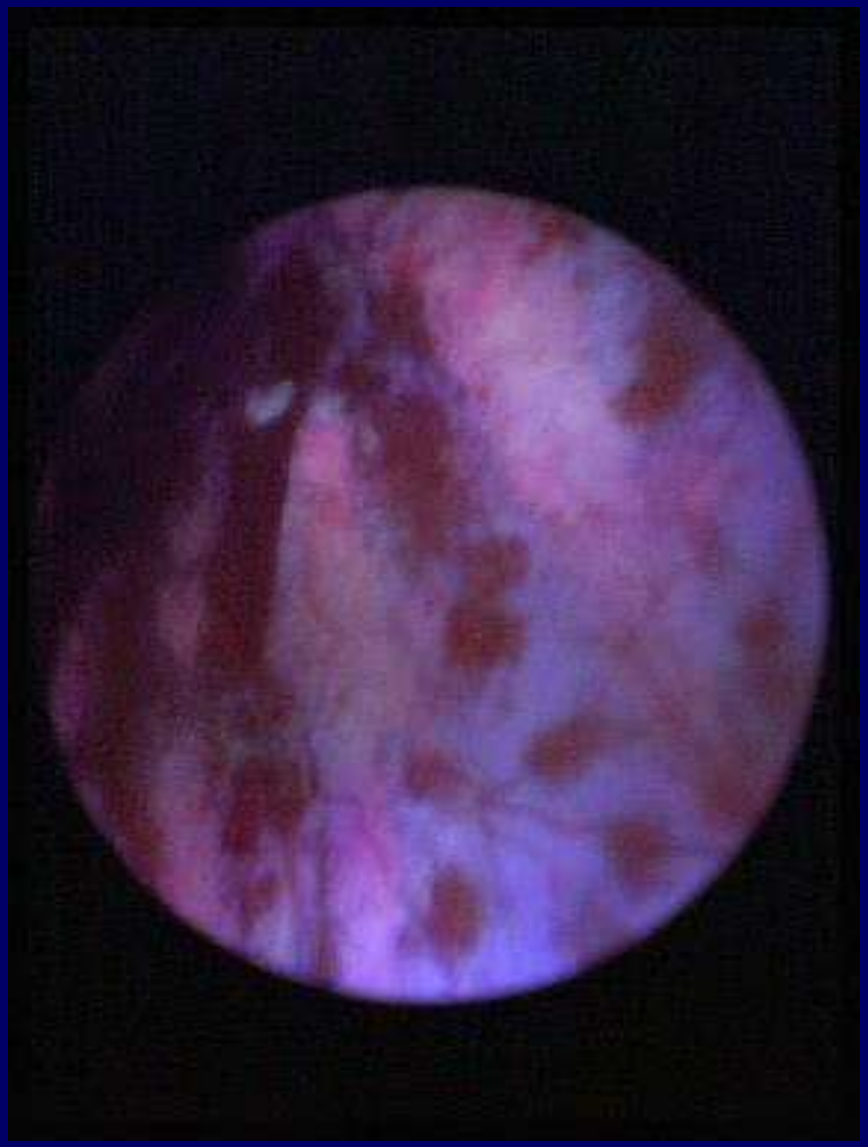


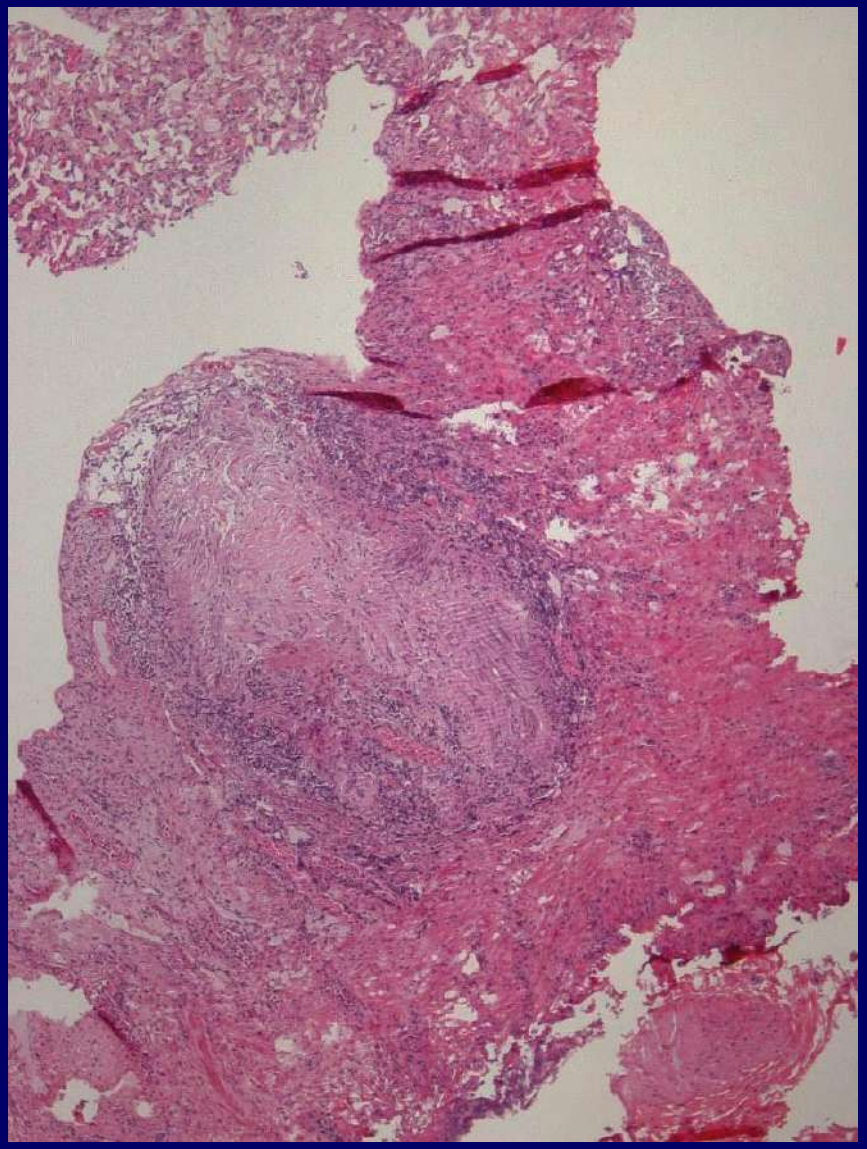
Atypias related to treatment

- Previous medical history+++
  - Irradtiation
  - trauma
    - Catheterims (denuded areas)
  - BCG
    - inflammation
  - Chemotherapie
    - Troncated papillaes

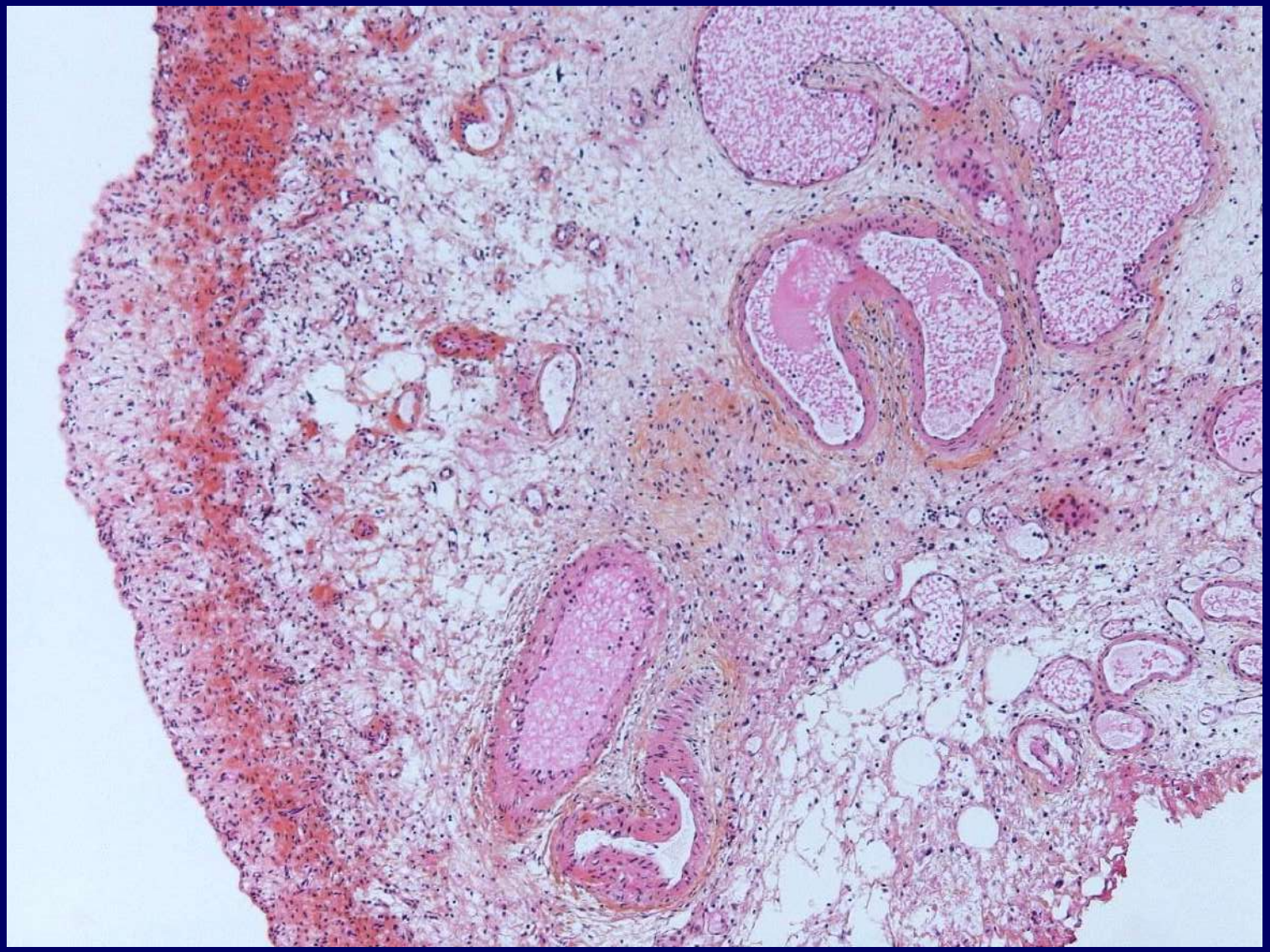


Granulomas post BCG therapy

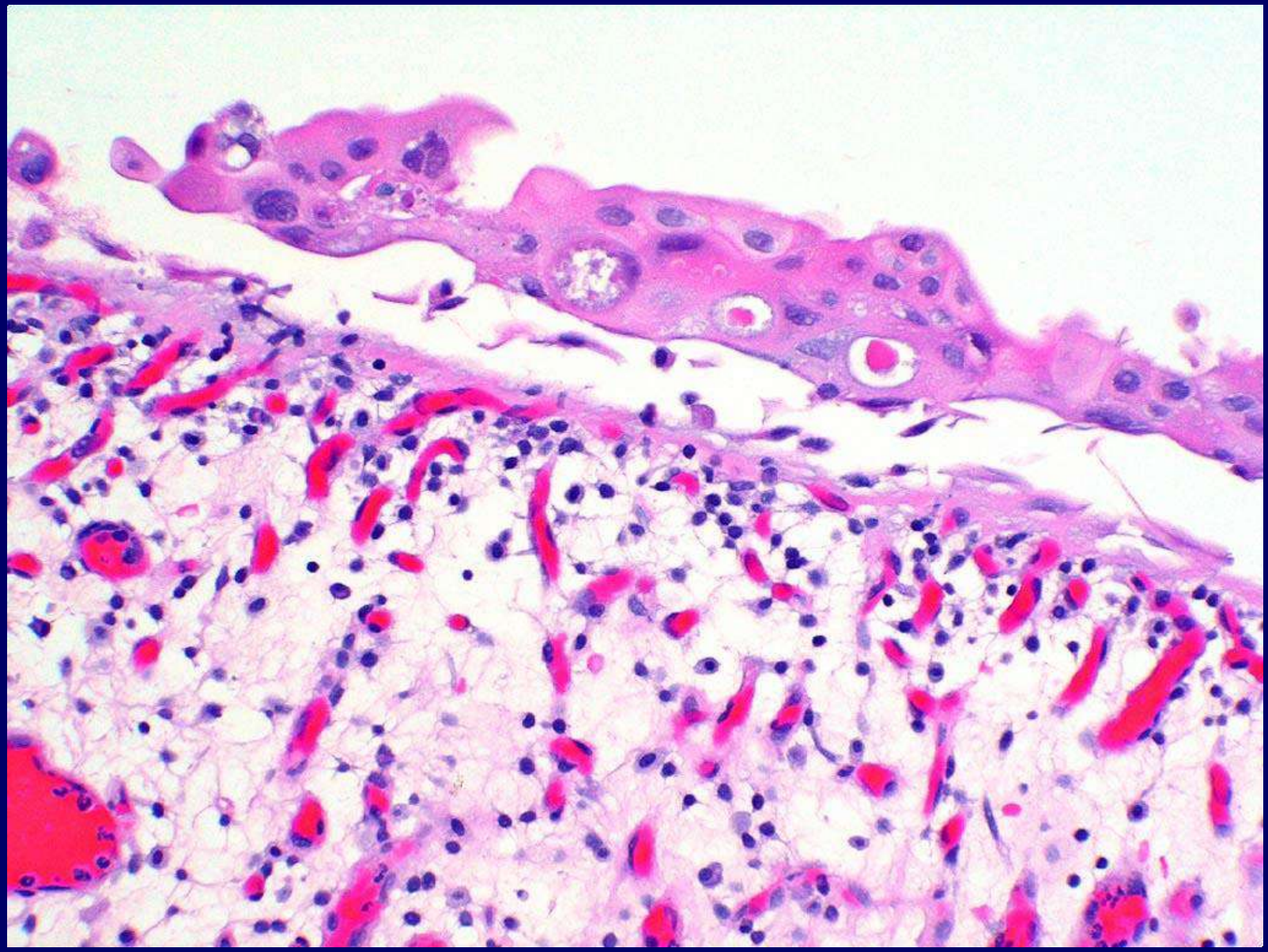




Atypias related to treatment



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	Hematuria or irritative symptoms	Hematuria or irritative symptoms
Major cystoscopic findings	Erythematous/inflamed or suspicious for tumor	Erythematous/inflamed or suspicious for tumor	Erythematous/inflamed or suspicious 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[a]	No adverse outcome[a]	15% developed biopsy-proven cancer progression

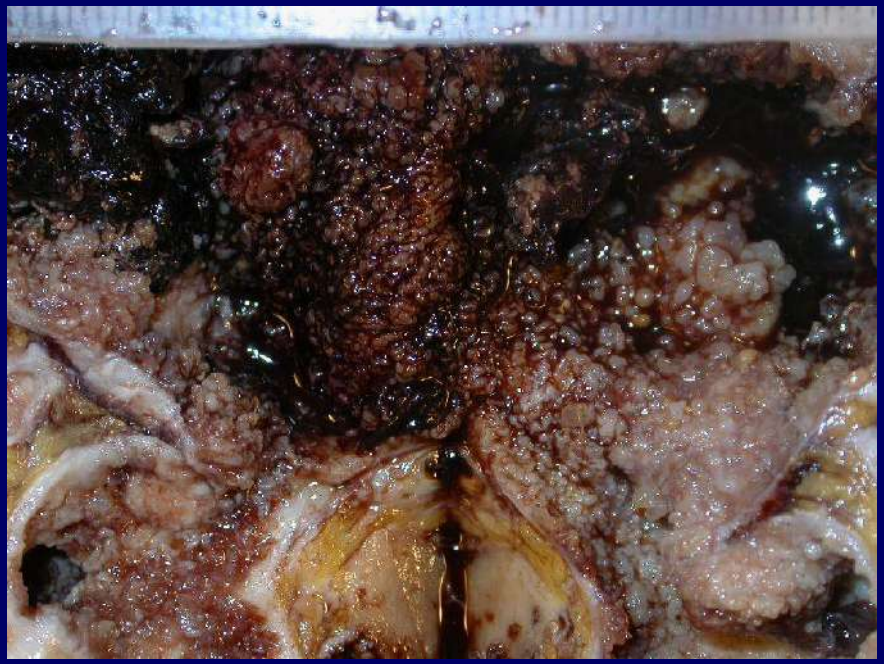
[a] None developed dysplasia, carcinoma in situ, or urothelial carcinoma

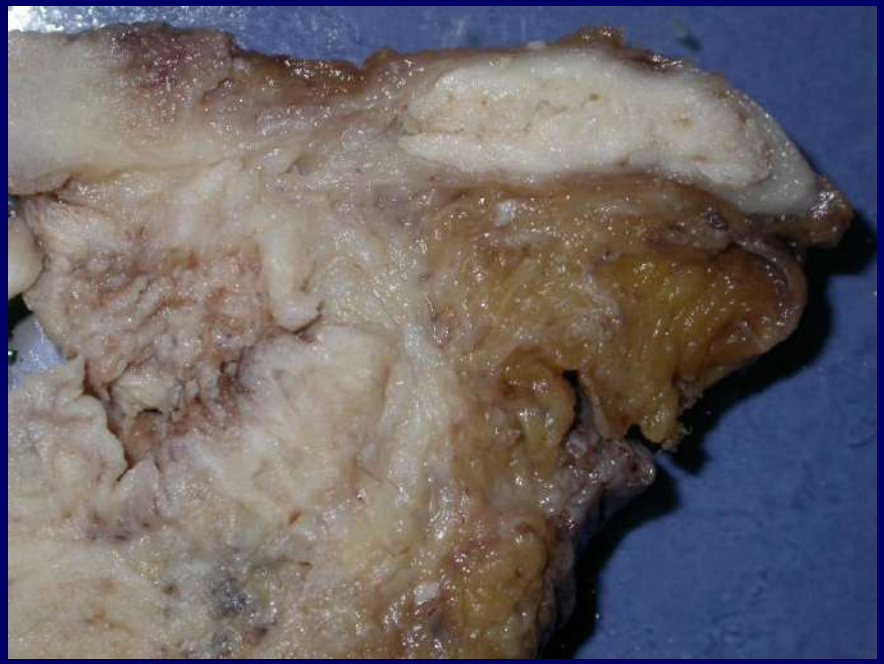
Table 3 Clinical outcomes of patients with atypical urothelial proliferations of the urinary bladder based on the 1998 WHO/ISUP classification

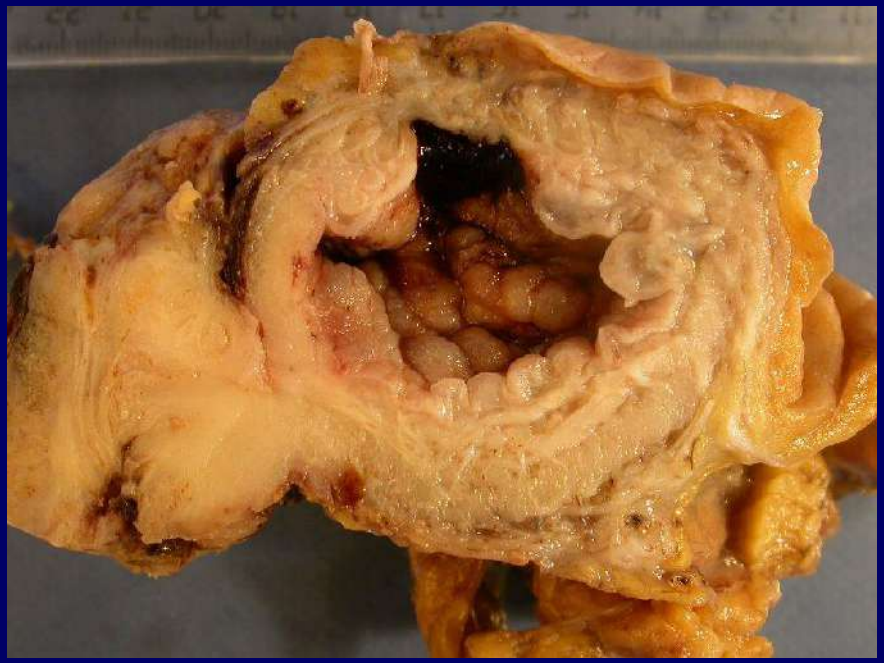
1988 WHO/ISUP classification	Clinical significance
Reactive atypia	None developed dysplasia, carcinoma in situ, or urothelial carcinoma
AUS	None developed dysplasia, carcinoma in situ, or urothelial carcinoma
Dysplasia	14%-19% develop biopsy-proven progression [22,31,34,35]

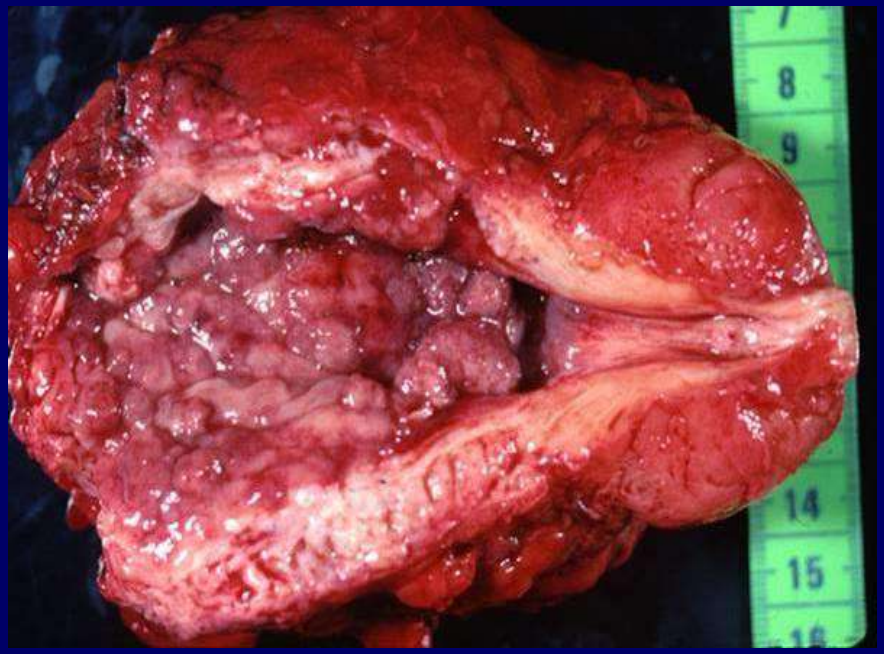
Cheng, 2000, Mod Pathol
Hodges el al. 2010, Hum Path

pT2





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9
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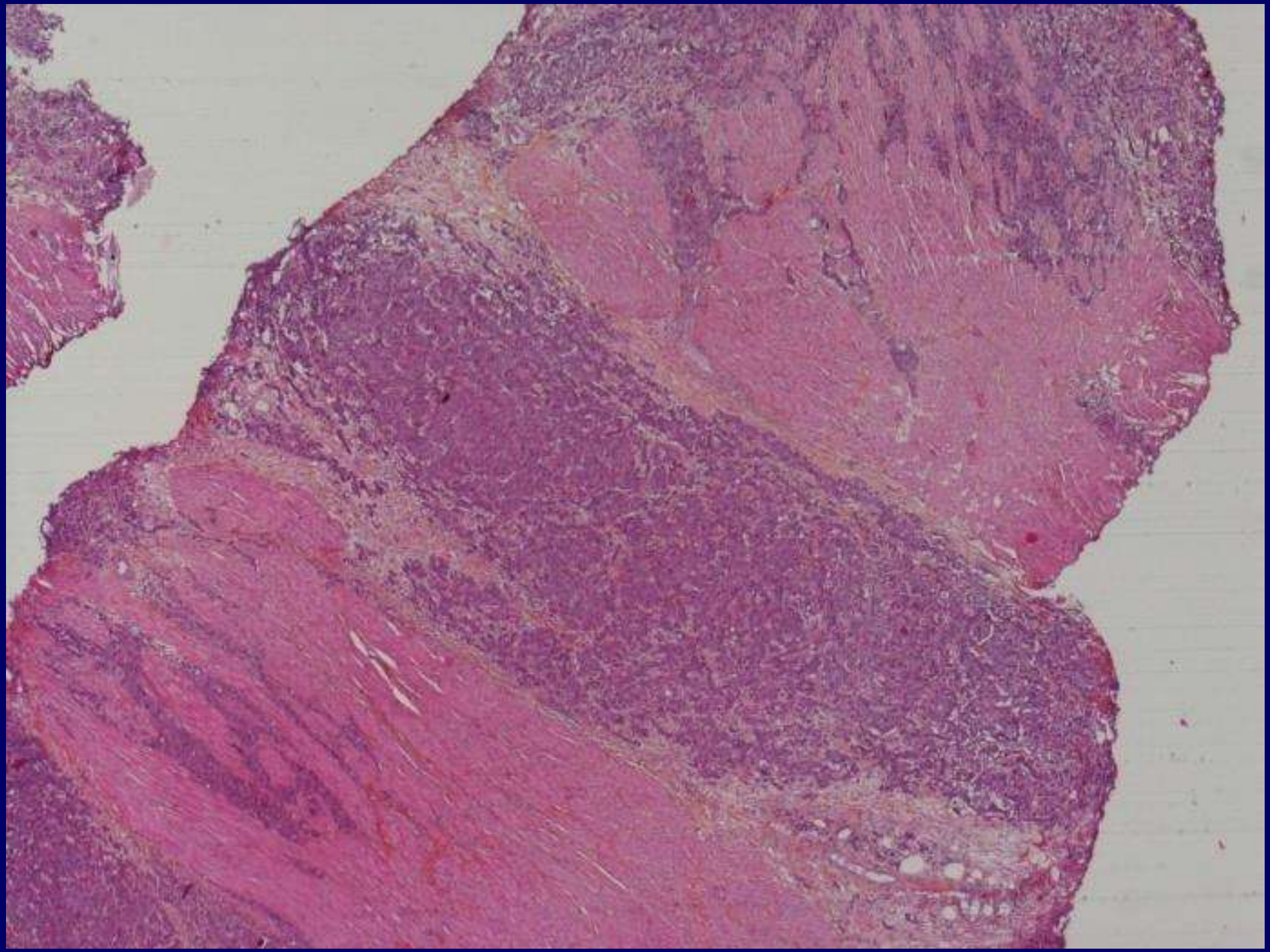
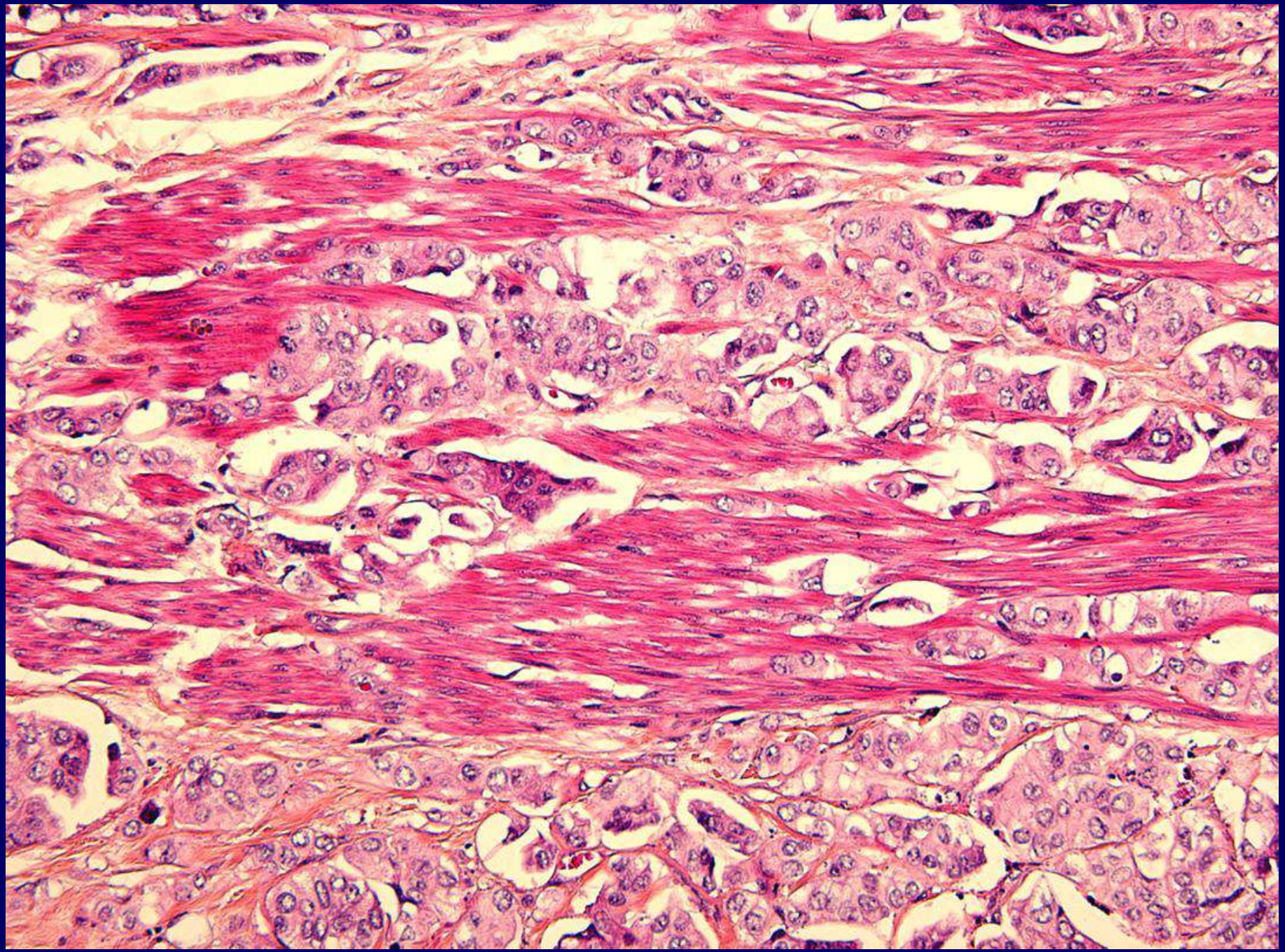




Prognosis (pt2)

Vascular invasion

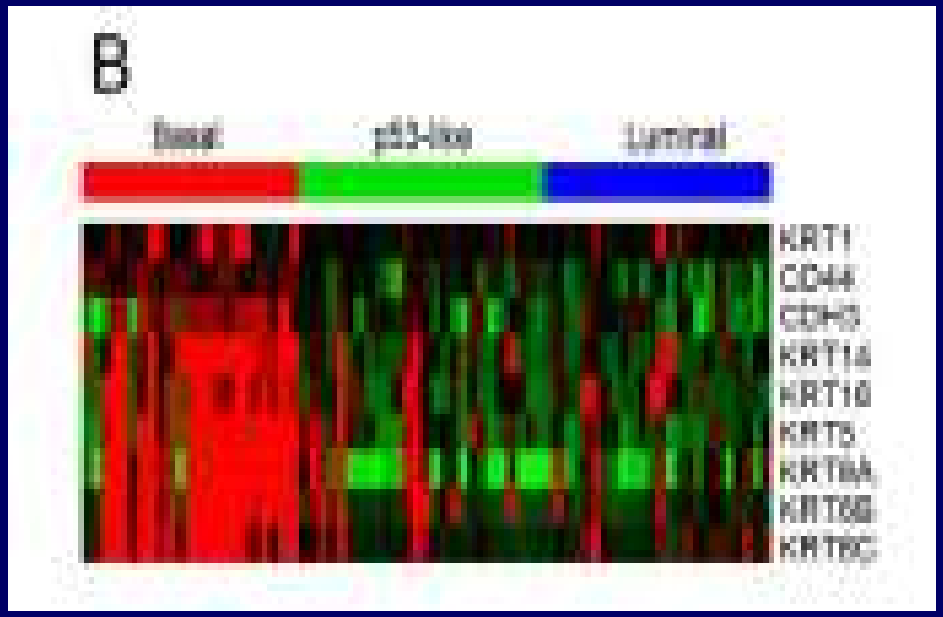
Multifocal CIS

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

Published in final edited form as:
Cancer Cell. 2014 February 10; 25(2): 152–165. doi:10.1016/j.ccr.2014.01.009.

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. Plimack, Jean Hoffman-Censits, Beat Roth, Tiewei Cheng, Mai Tran, I-Ling Lee, Jonathan Melquist, Jolanta Bondaruk, Tadeusz Majewski, Shizhen Zhang, Shanna Pretzsch, Keith Baggerly, Arlene Siefker-Radtke, Bogdan Czerniak, Colin P.N. Dinney, and **David J. McConkey**

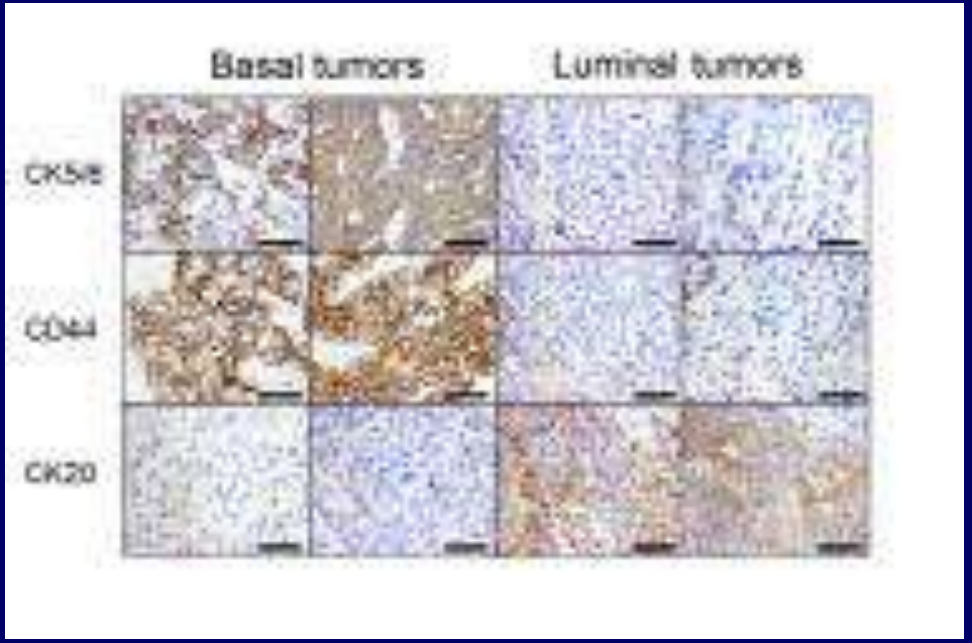


Genotype and immunophenotype close to basal and luminal breast cancer (ER, PPARγ)

Luminal : urothélial differenciation
GATA3, Uroplakin, CK20

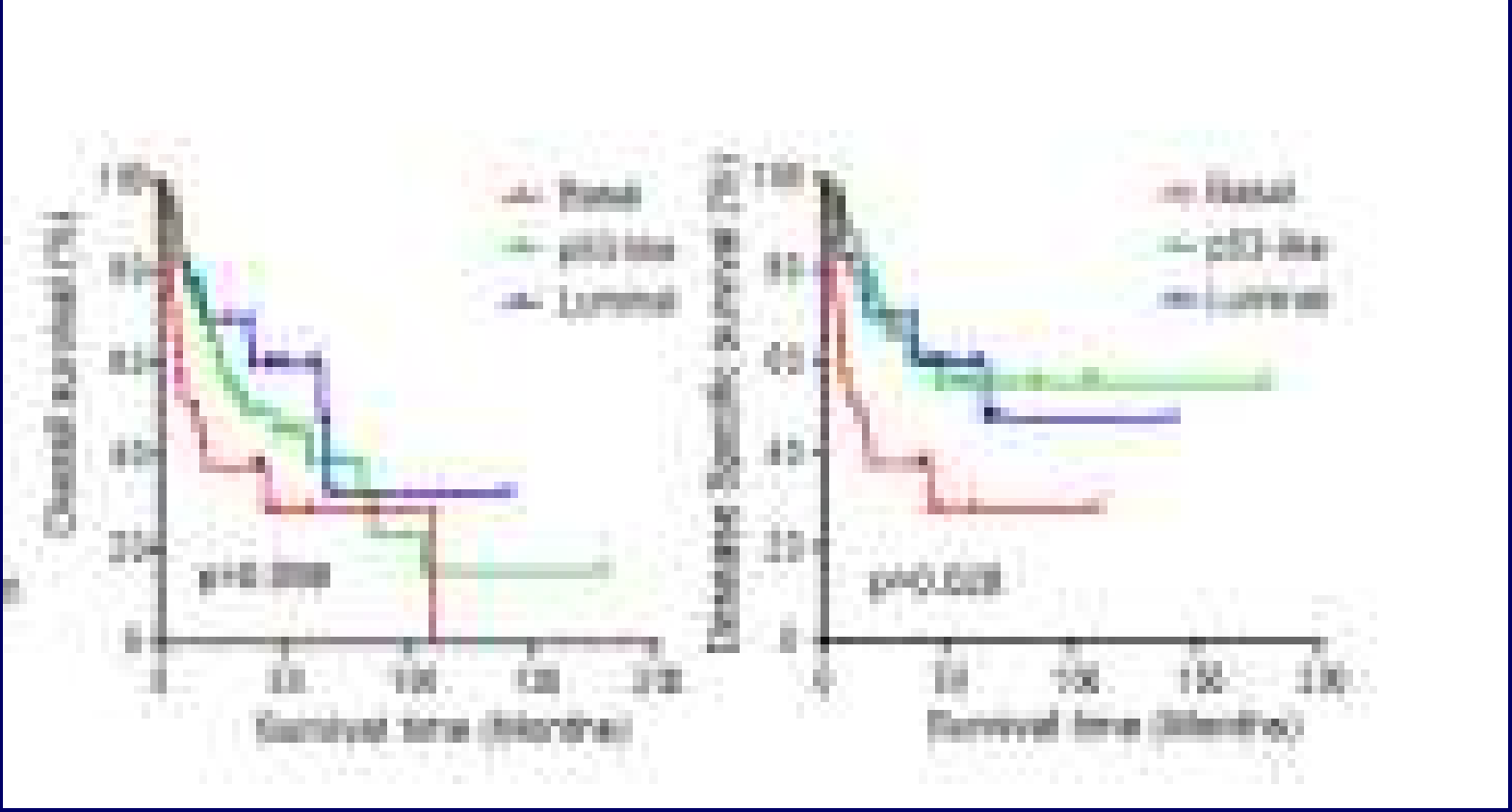
P53-like sub group of luminal has no specific immunphenotype

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



Basal subtype present with squamous or sarcomatoïde phenotype

Basal and luninal have different prognosis
… what pathologist knew from long time !

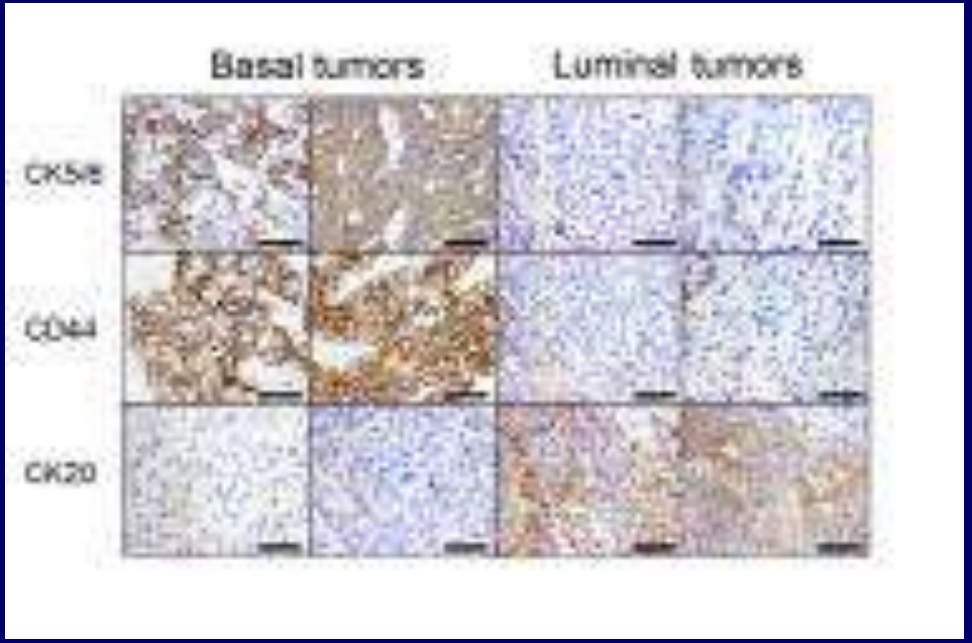


Kaplan-Meier plots of overall survival (p = 0.098) and disease-specific survival (p = 0.028)

Luminal : variable chemosensitivity

P53-like : MVAC resistance

Basal : chemosensitive

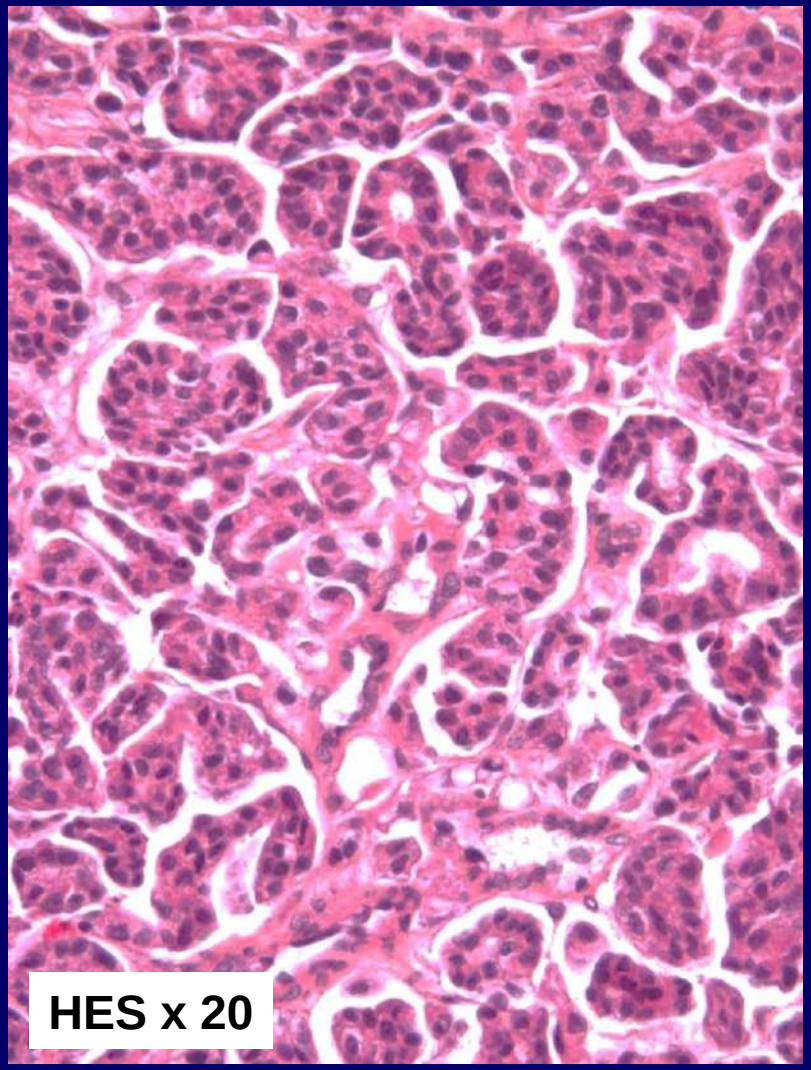


Morphologic variants

Micro Papillary Carcinoma

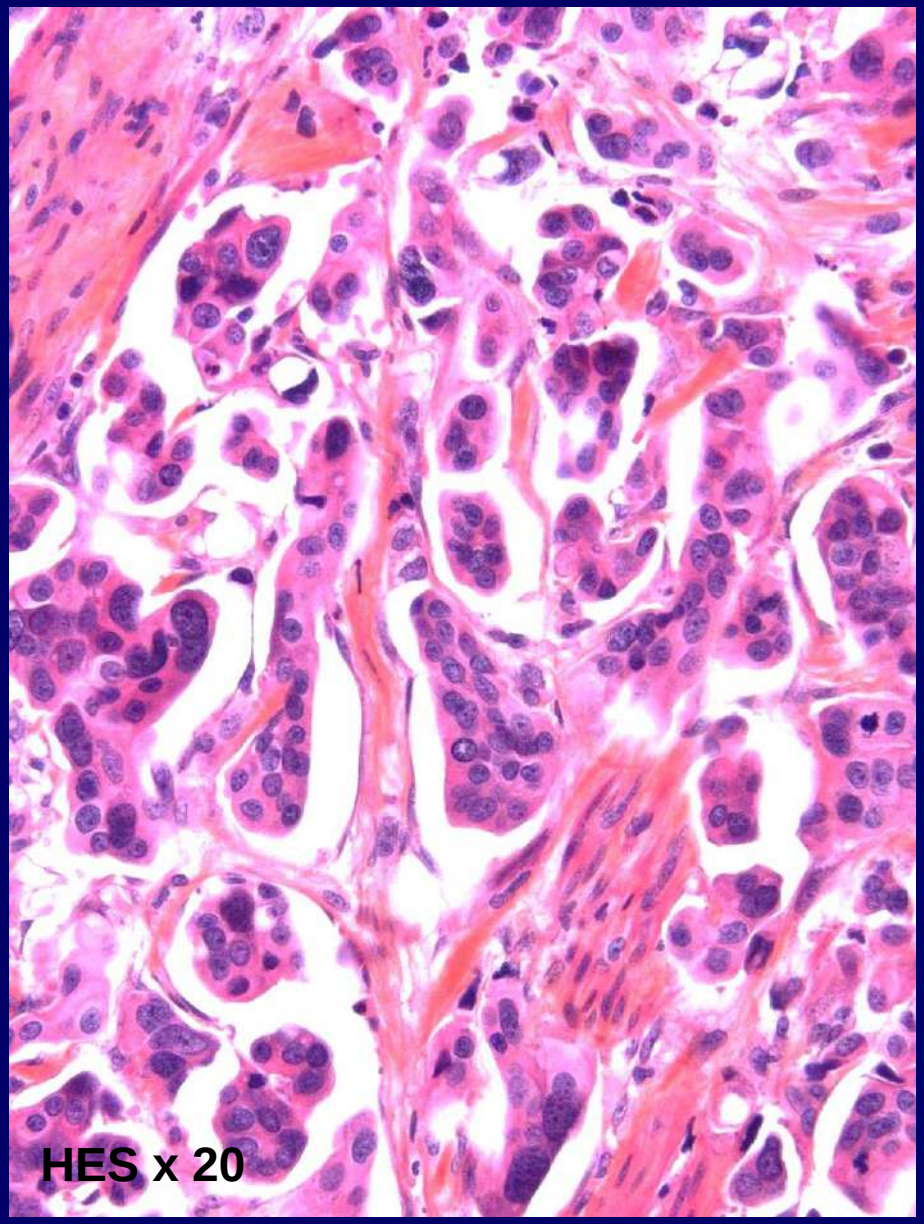
- incidence 0,6 to 2,2%
- M : F = 5 : 1
- papillae
  - 3 to 20 cells
  - nests, balls
  - atypia +/ -
  - mitosis
- fibrovascular core rare

- few inflammation

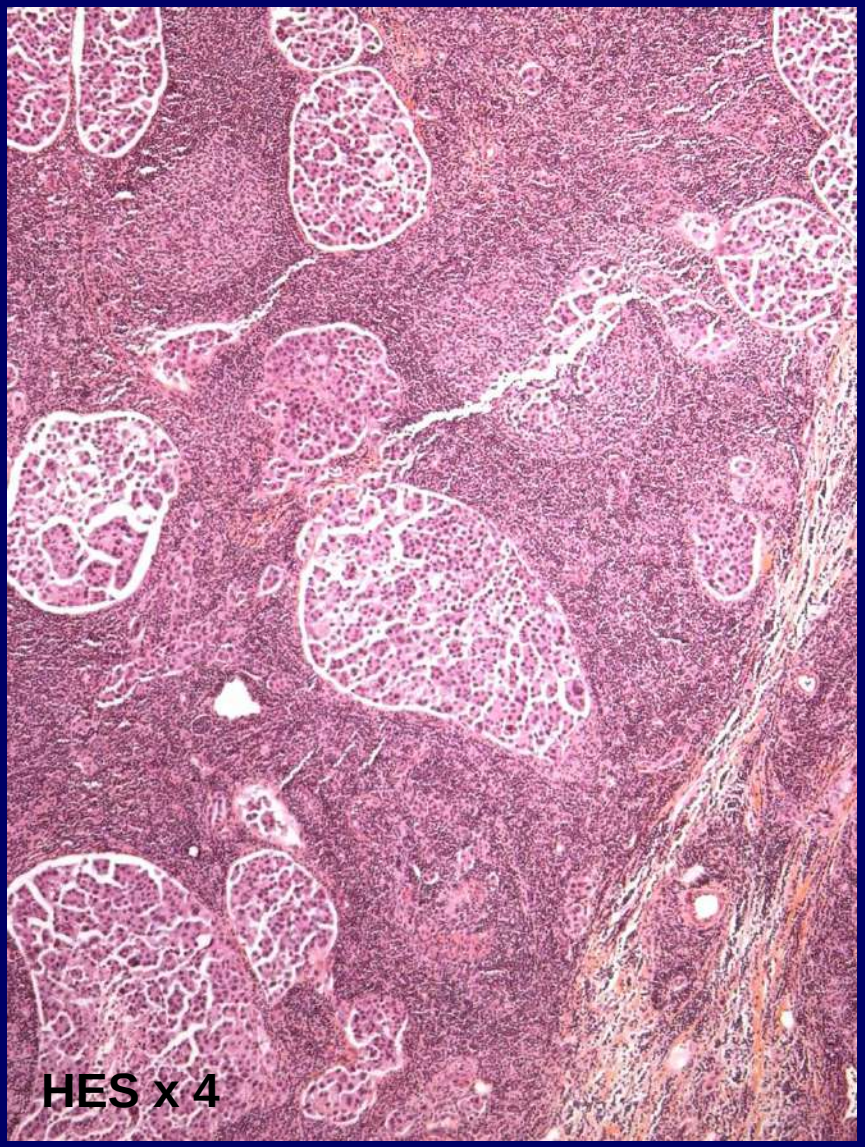


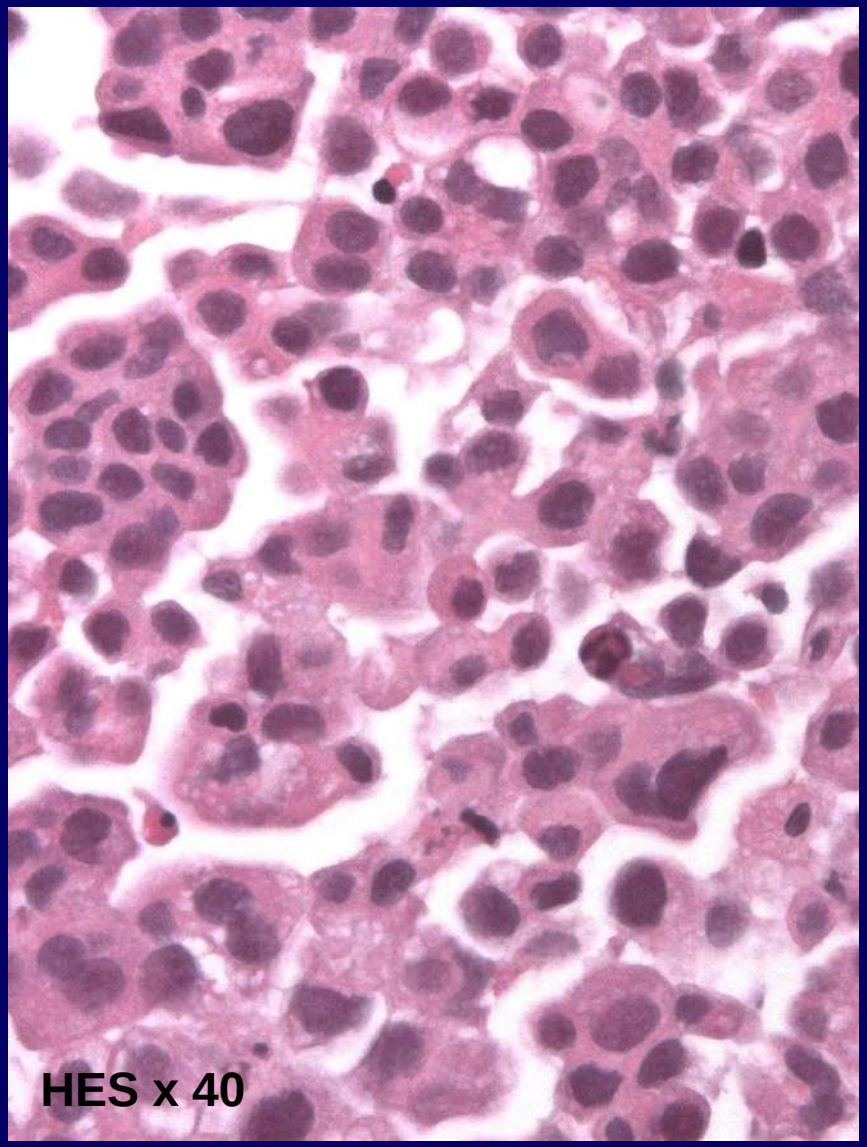
MPC Histology

- mimic vascular invasion
- not overestimate



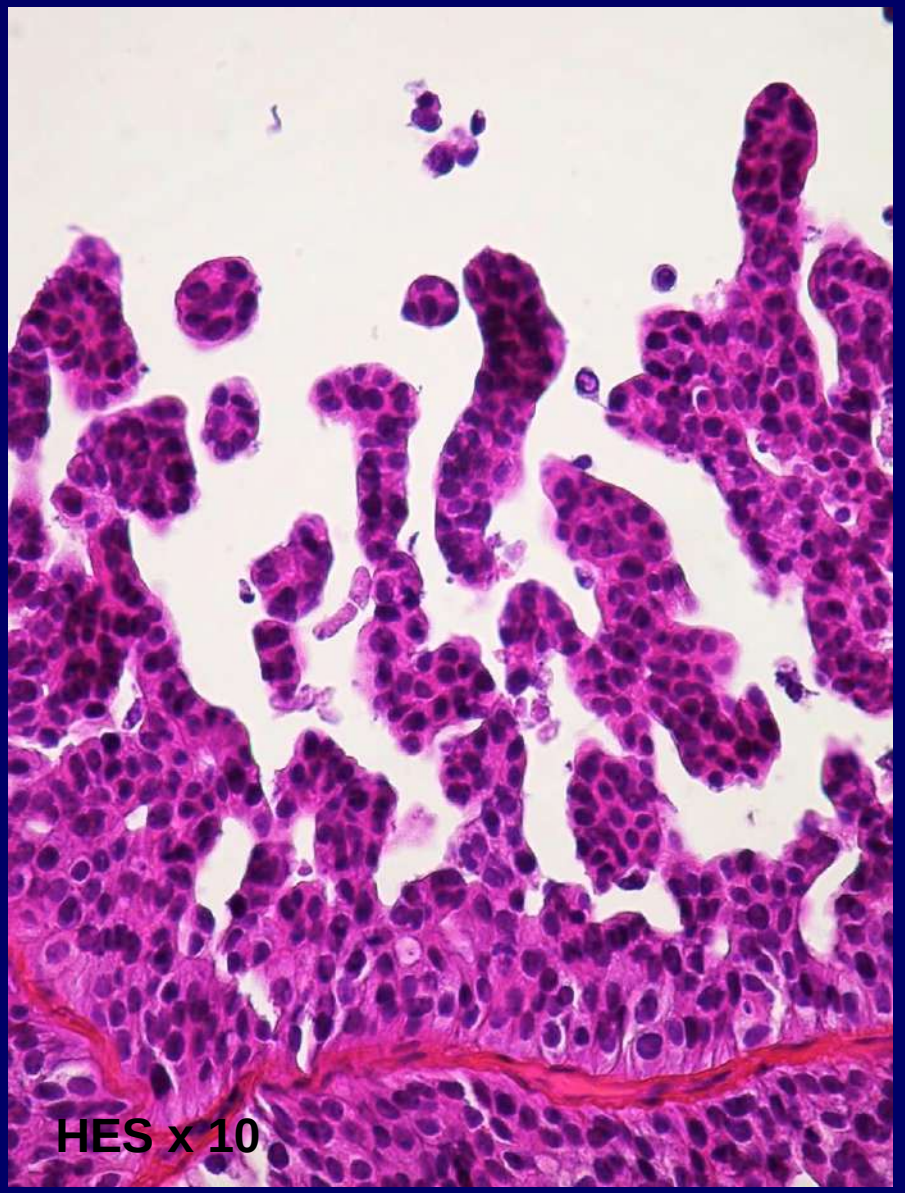
Lymph node metastasis: common





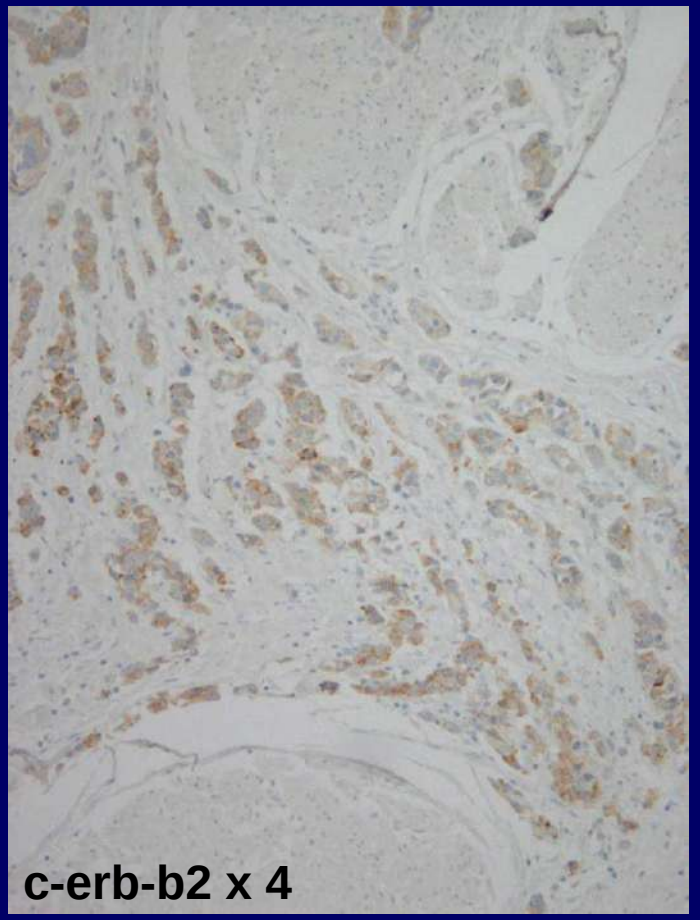
Superficial Non Invasive Variant

- superficial MPC be sure of presence of muscle in case of biopsy
- associated with C*is*
  - (> 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%



c-erb-b2 x 4

Latif 2004, Eur J Cancer
de Pinieux 2004, Virchow
Comperat 2007, ECP

Treatment

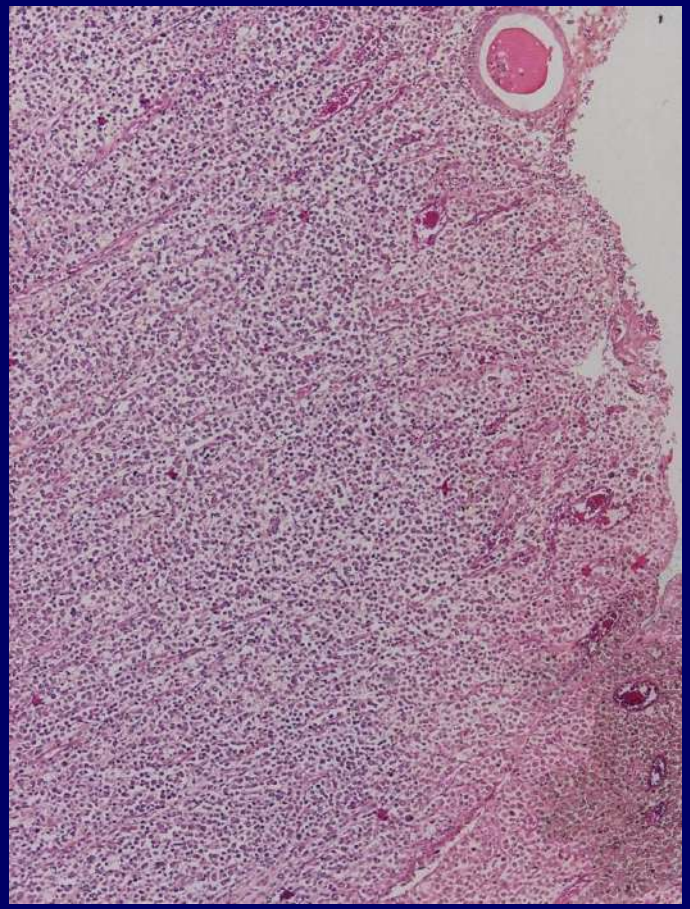
- BCG therapy inefficient in superficial forms (pTa, pT1)
  - cystectomy if pT1 ?
- c-erb-b2 expression
  - Herceptin ?
- educate urologist
  - repeat biopsies if no muscle

Kamat 2007, J Urol

Plasmacytoid UC

- unusual
- M : F = 2:1
- DD
  - lymphoma
  - multiple myeloma

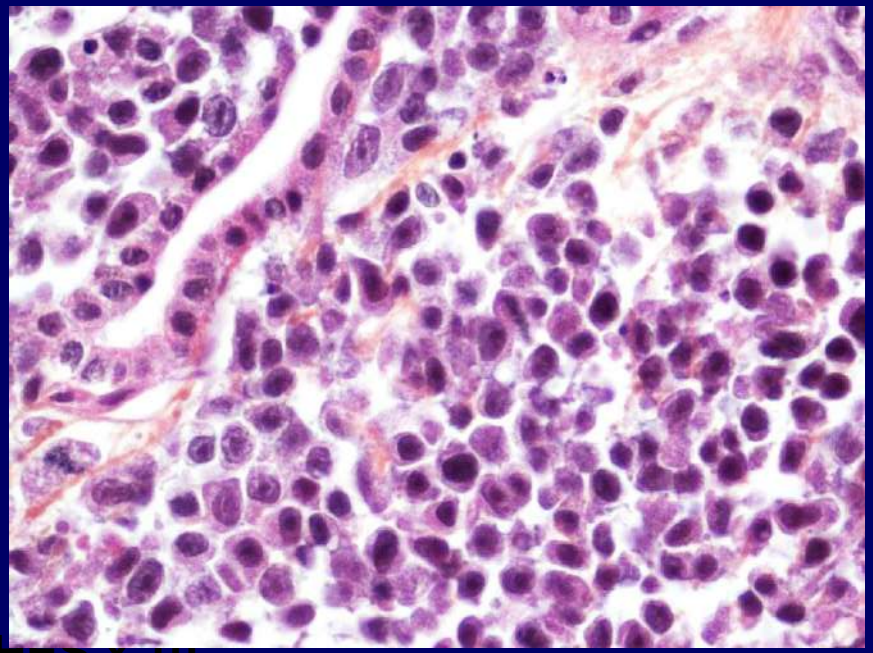
- epithelial markers + (CK7+)
  - CD45-, HMB-45 -, PS100 -



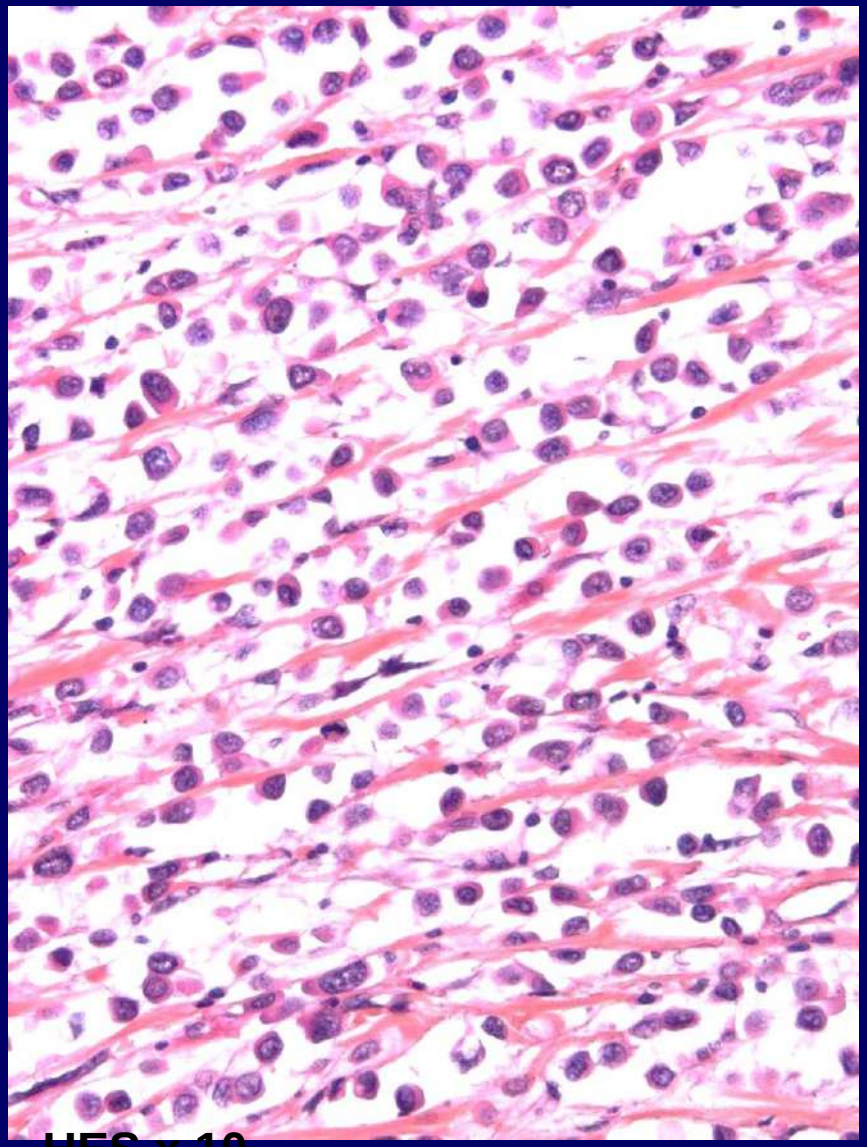
Zuckerberg 1991; Am J Surg Pathol
Zhai 2007, Arch Pathol Lab Med

Plasmacytoid UC

Luminal phenotype
Loss of E-Cadherine expression



HES x 10

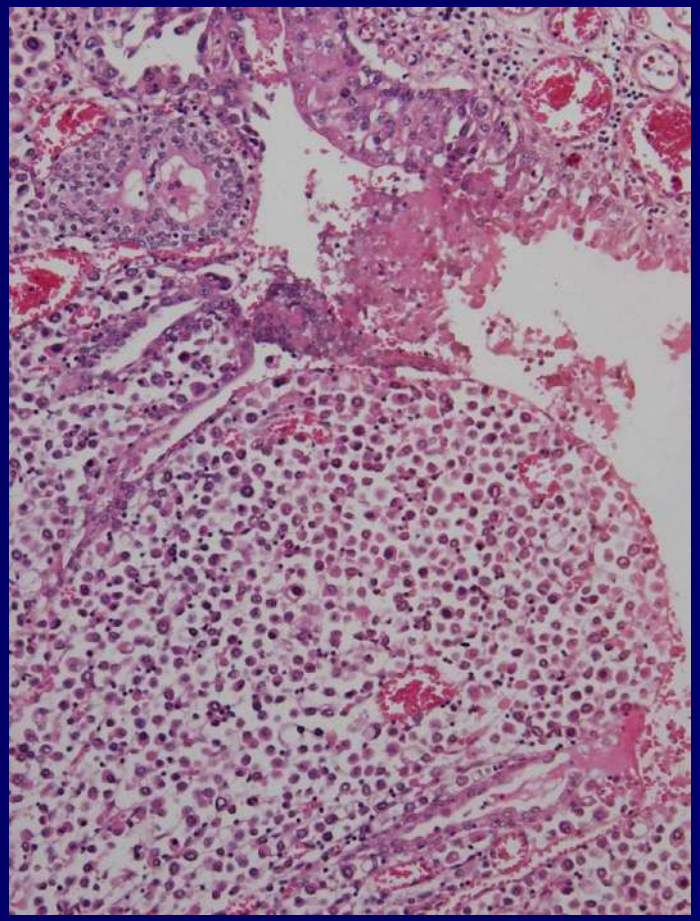


HES x 10

Plasmacytoid UC

- association with
  - high grade UC
  - sarcomatoid carcinoma

- prognosis related to stage
- clinical outcome poor
- overall survival ~ 23 month

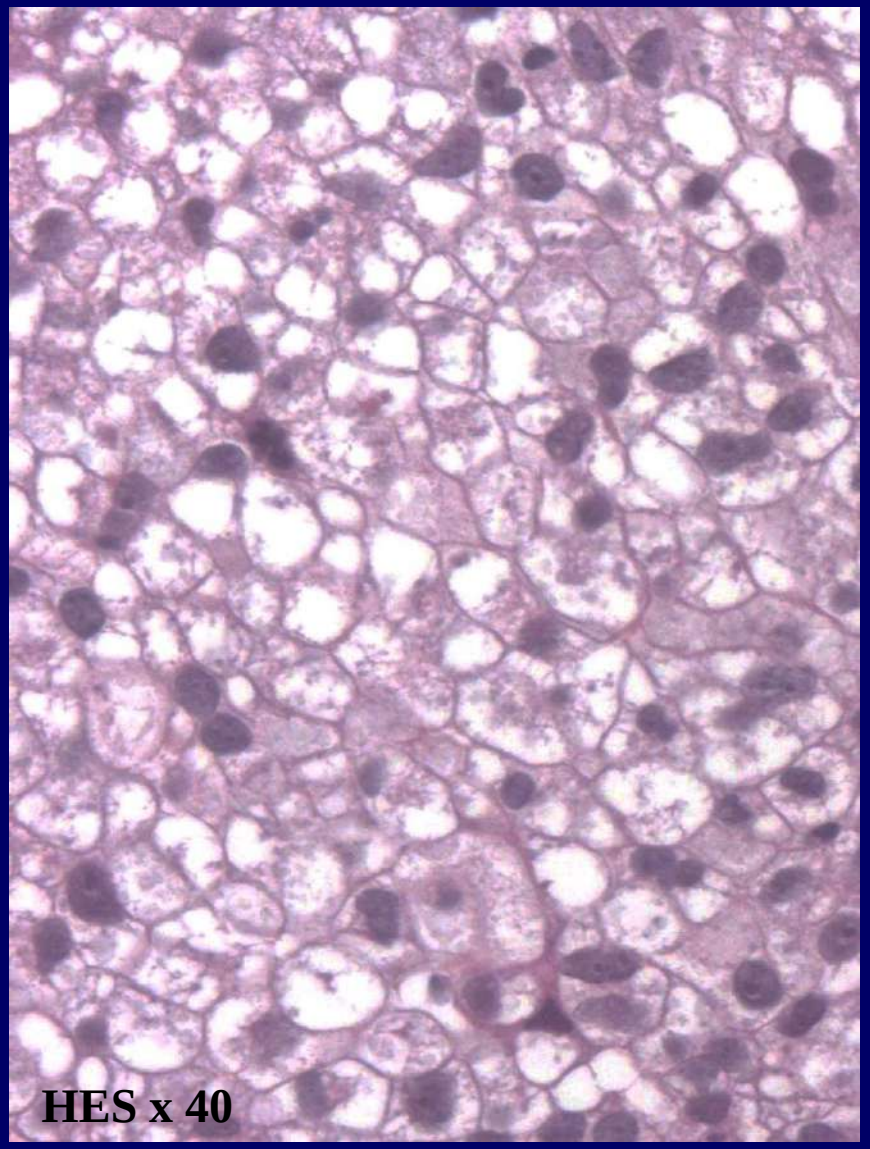


Tamboli 2000; Mod Pathol

Clear Cell Carcinoma

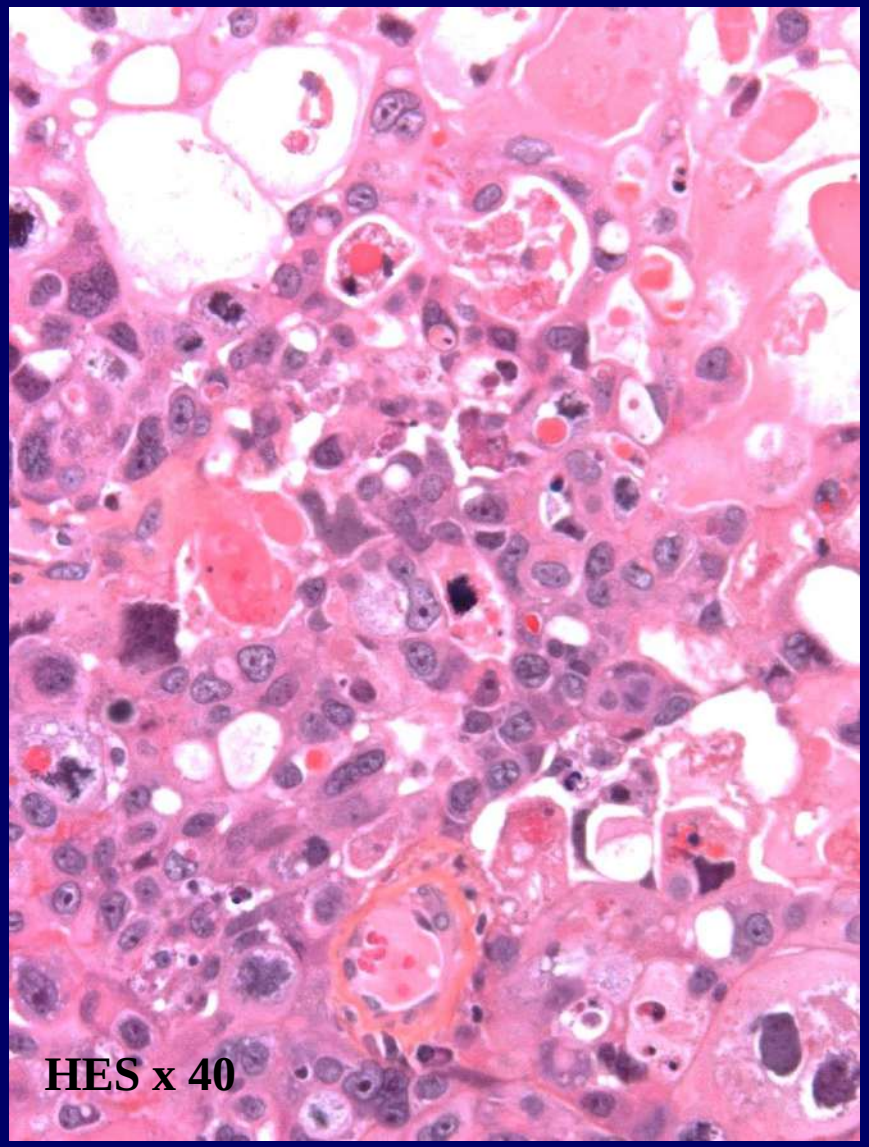
- aboundant glycogene
- CK7 +

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



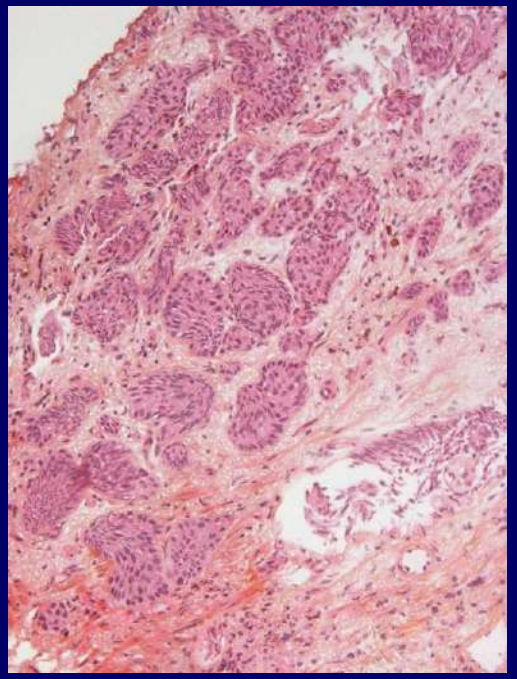
Large Cell Tumors/ undifferentiated UC

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



Nested Carcinoma

- male predominance (H/F= 4/1)
- age ~ 65a
- rare
- often associated with high grade UC

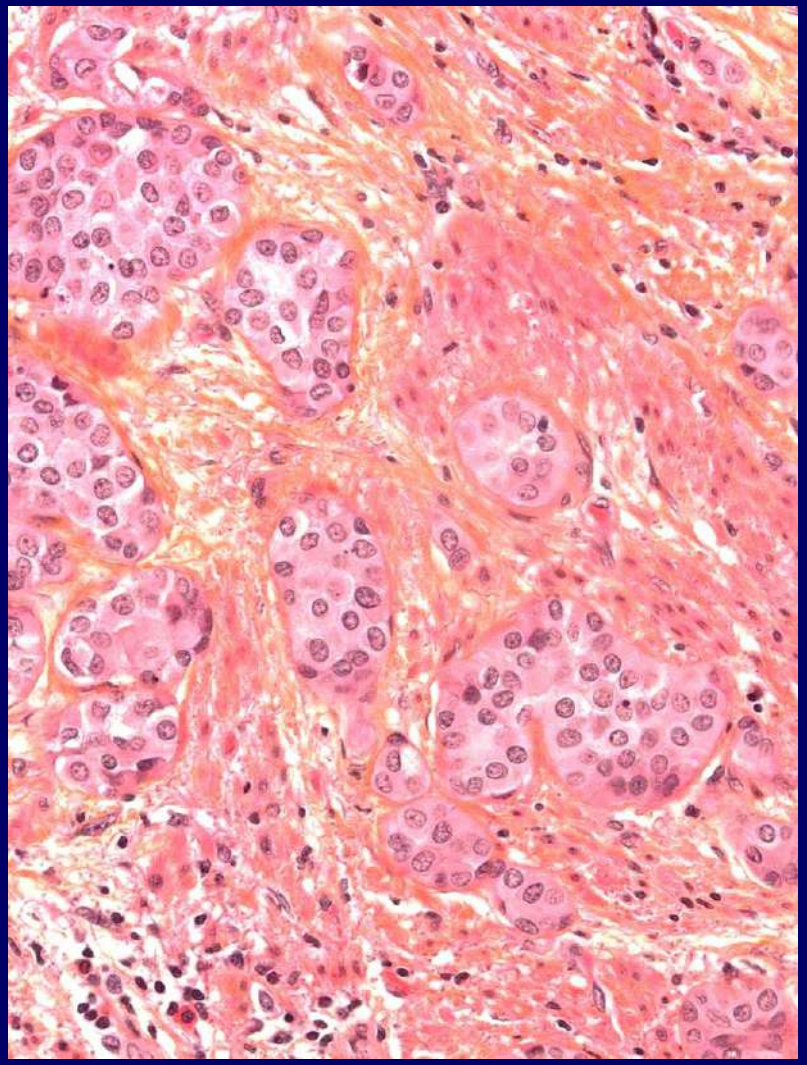


- grossly no specific findings
- association with flat and papillary tumors possible

Volmar 2003, Am J Surg Patho
Amin, 1994, Am J Surg Pathol
Drew 1996, Mod Patholl

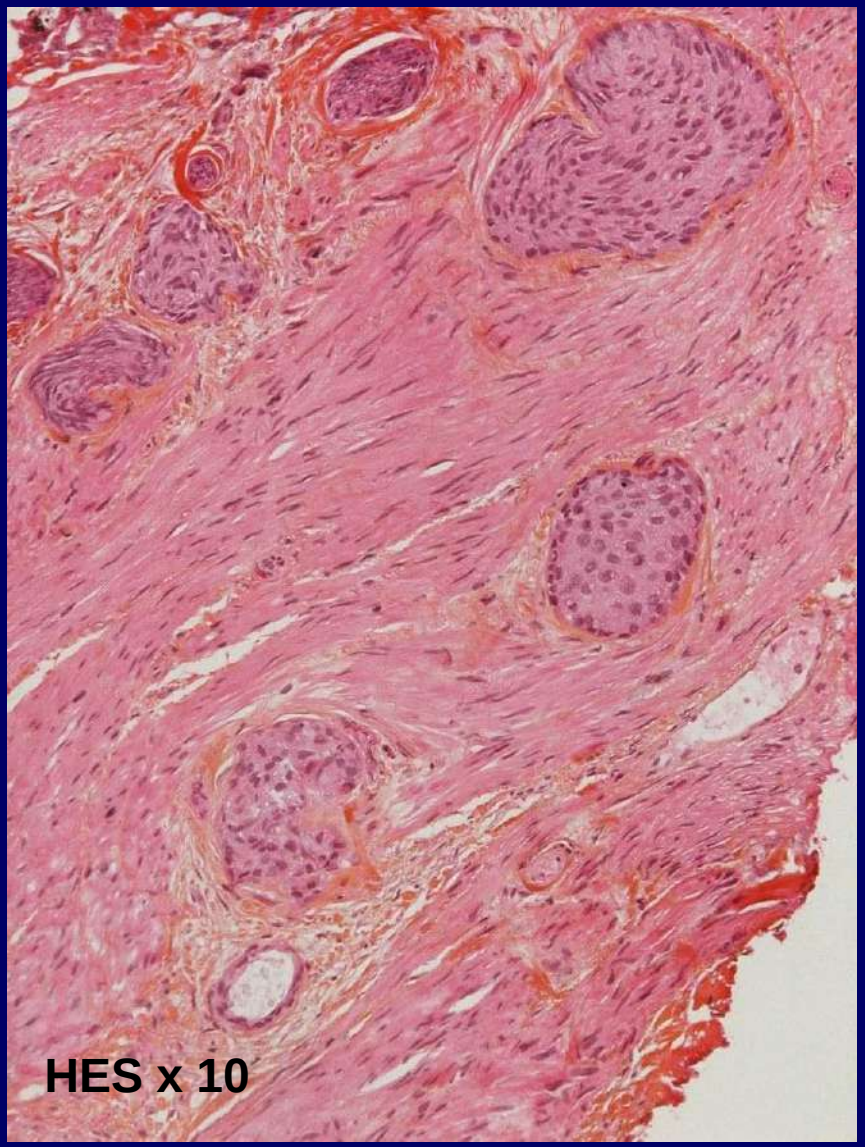
NC Histology

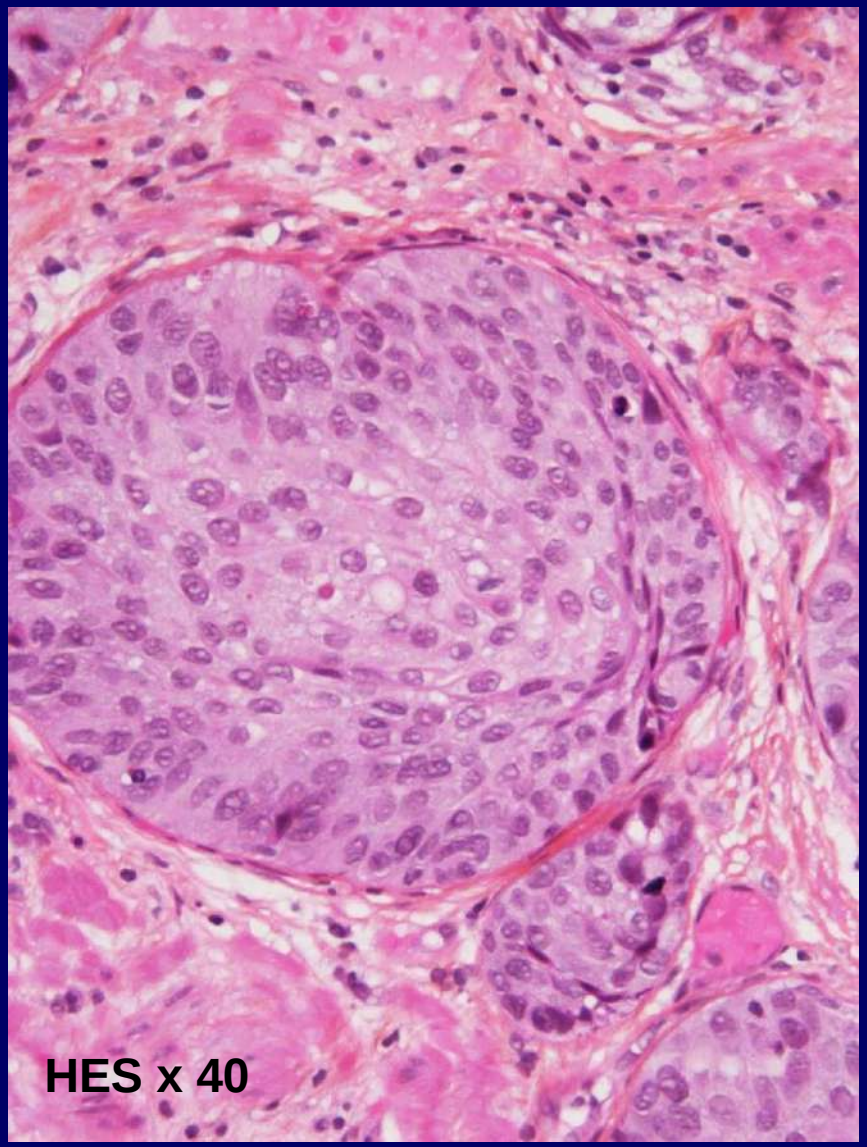
- discrete nests
- bland cytologic appearance
- mimics von Brunn nests
- few mitosis
- few atypia
- sometimes confluent
- relatively well delimited



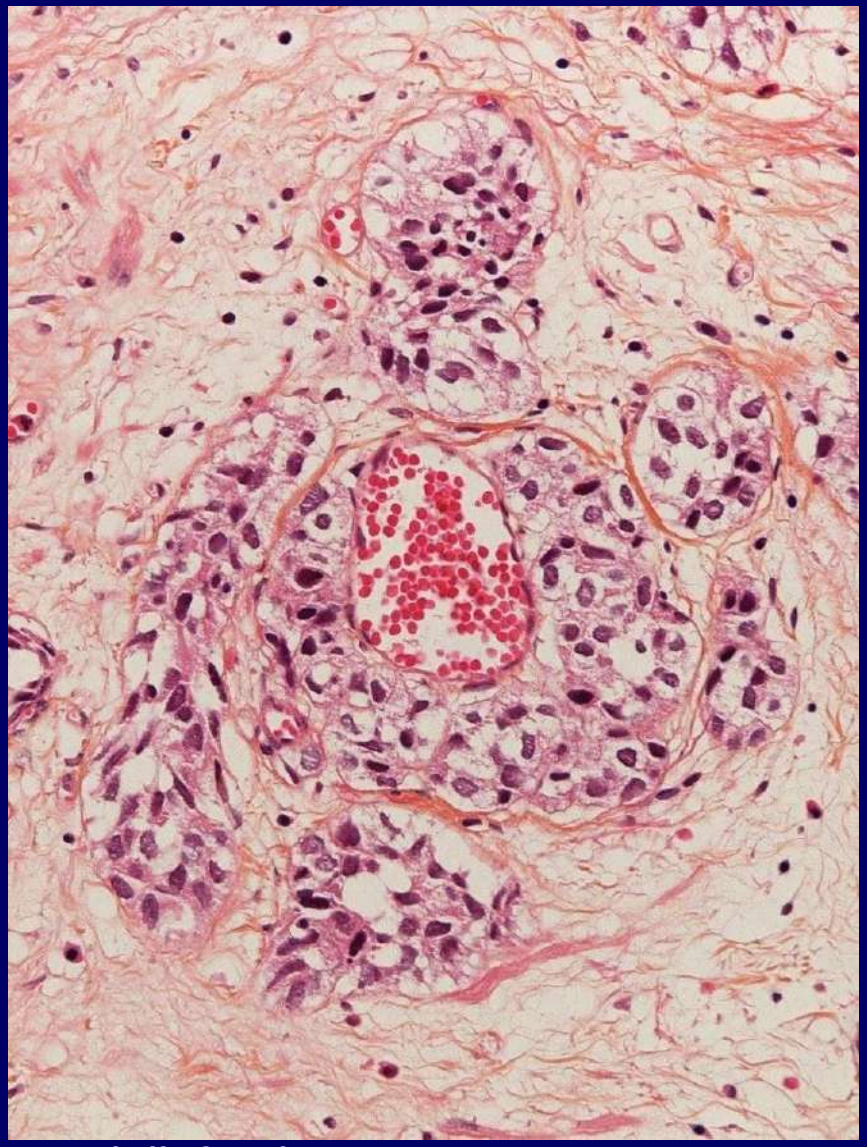
HES x 20

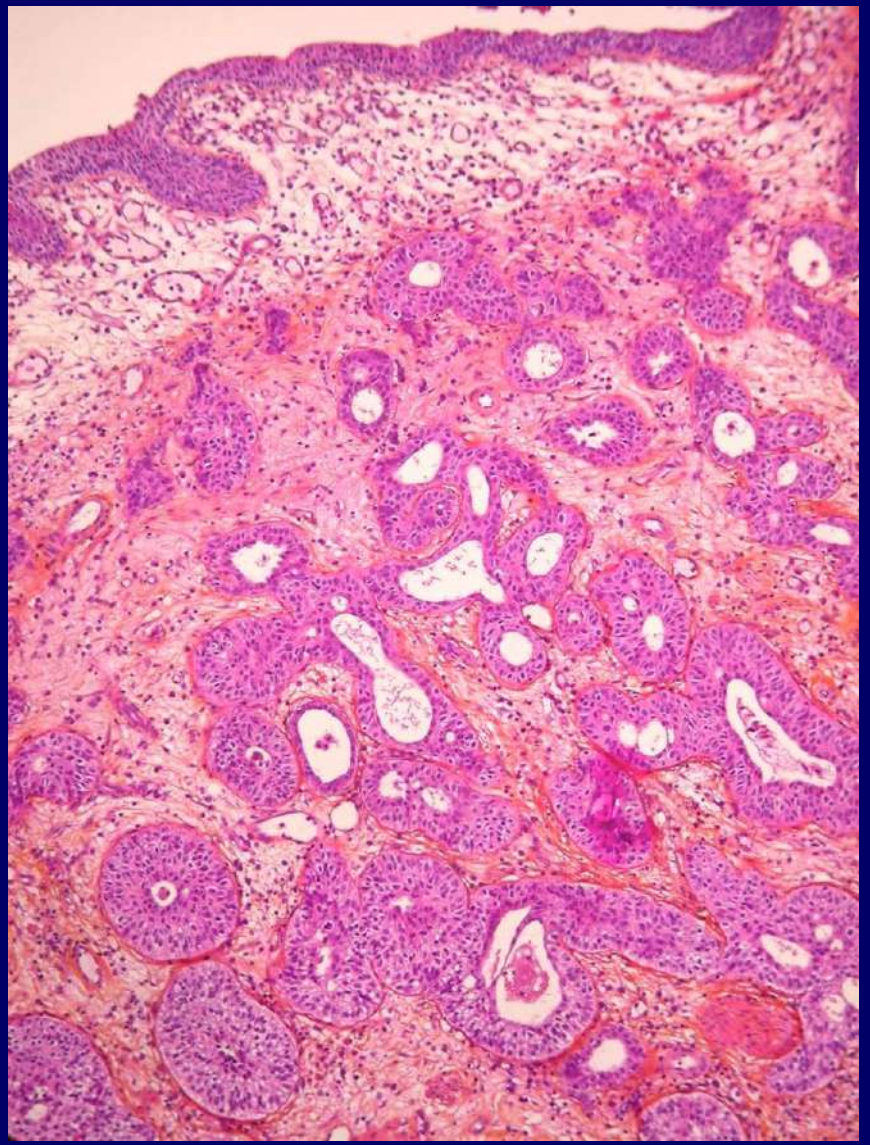
Histology of NC





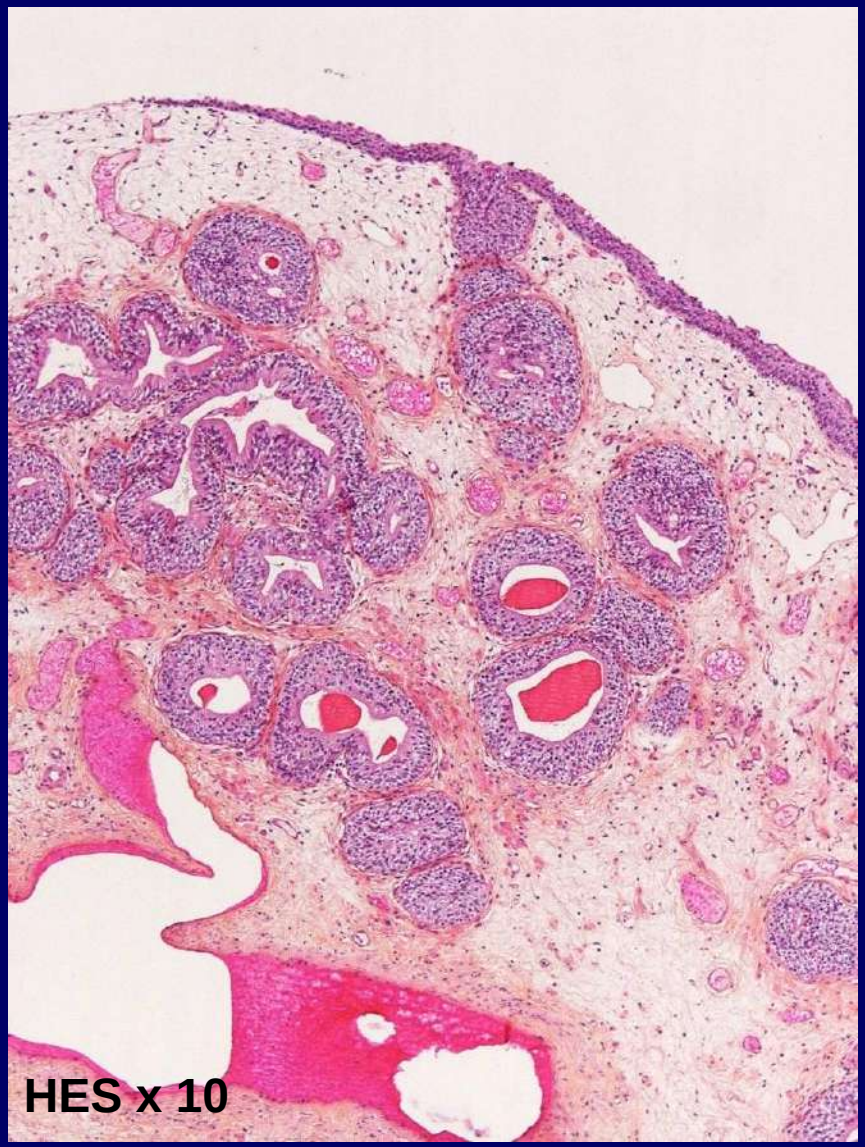
Tubular or cystic differentiation of NC

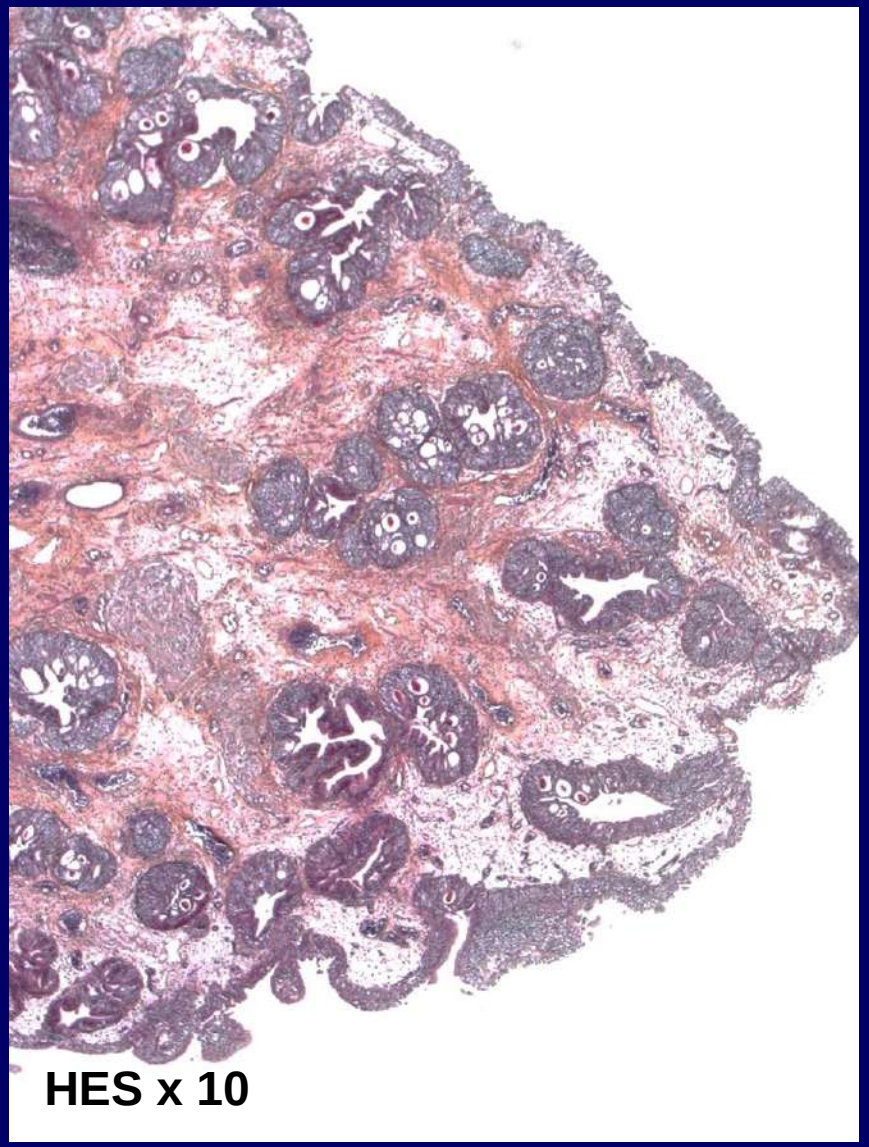




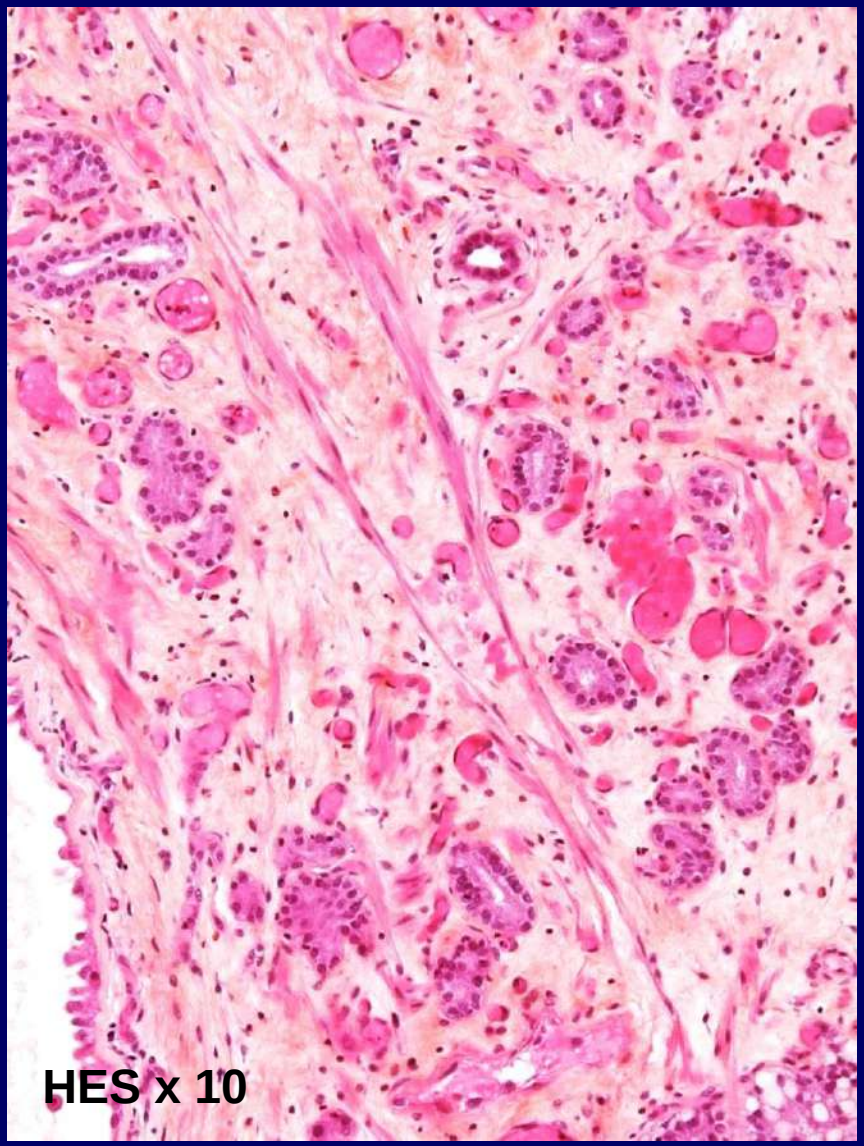
Dr. Viellefond

Diferential Diagnosis : Von Brunn Nests

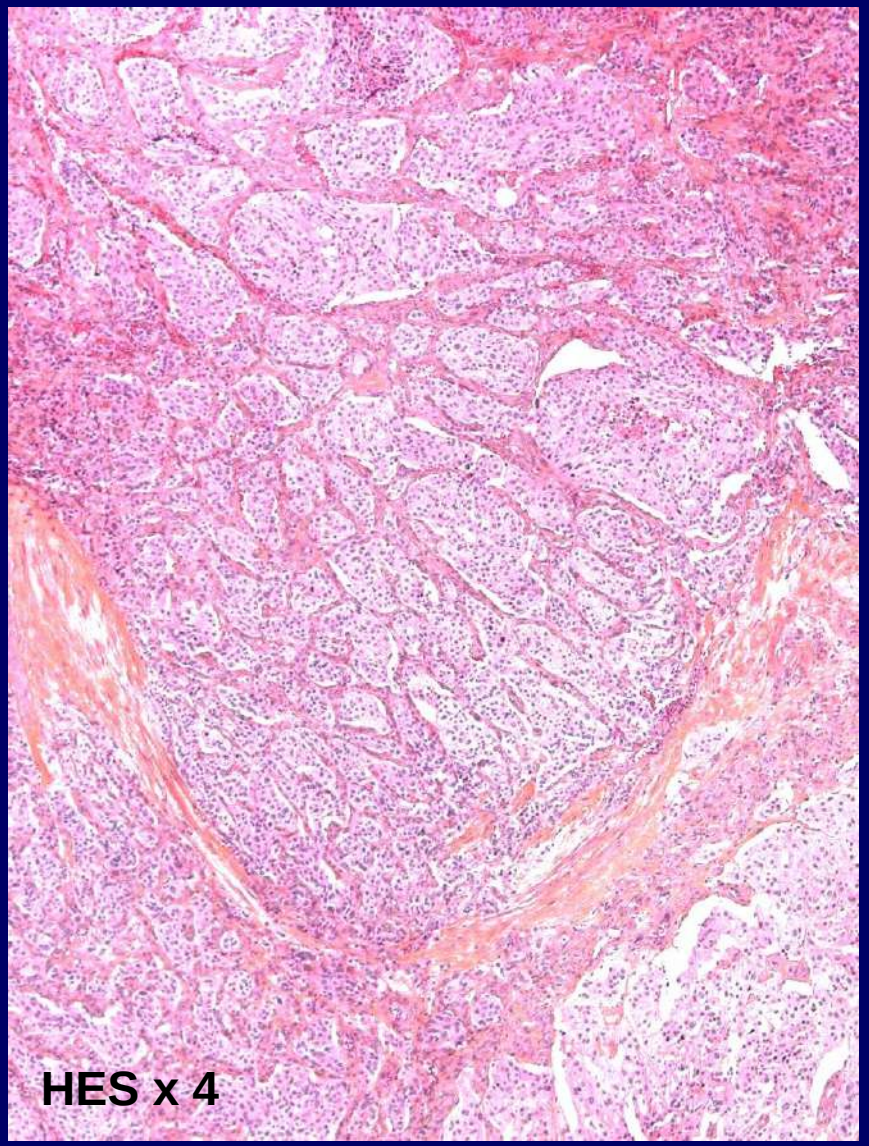




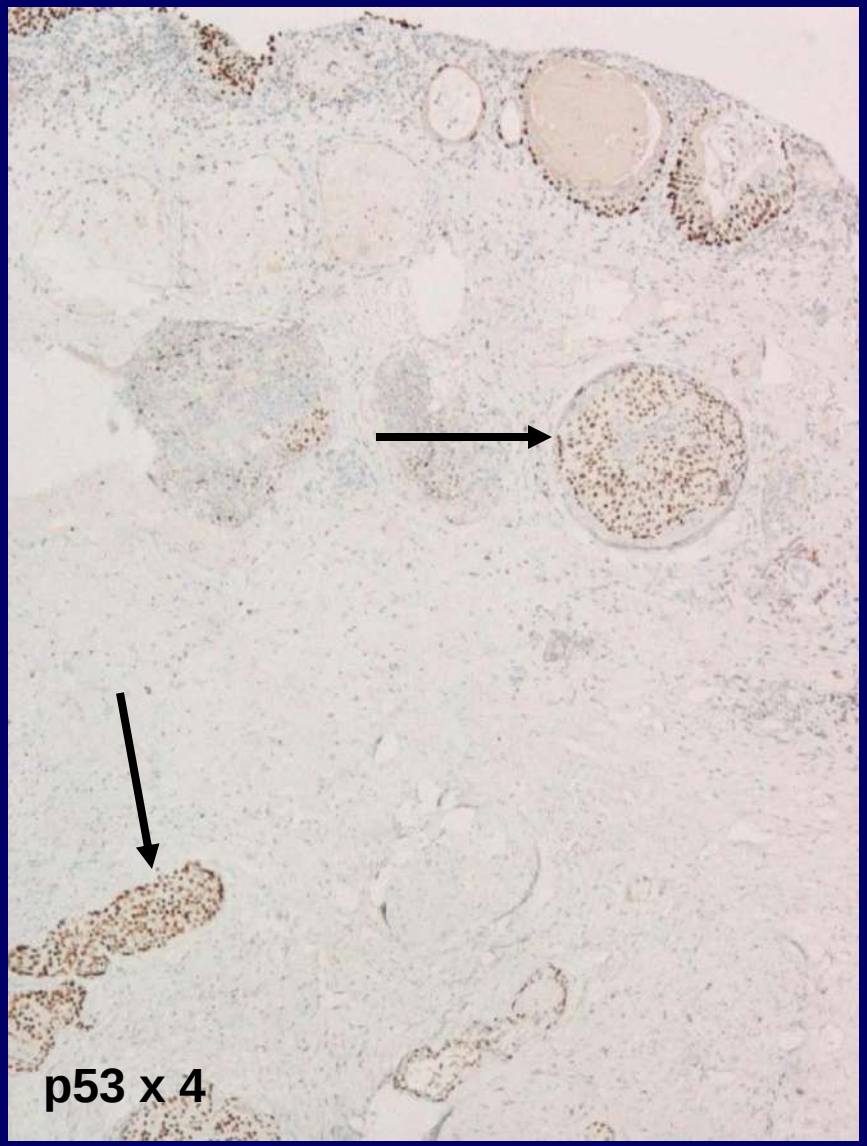
Nephrogenic Adenoma

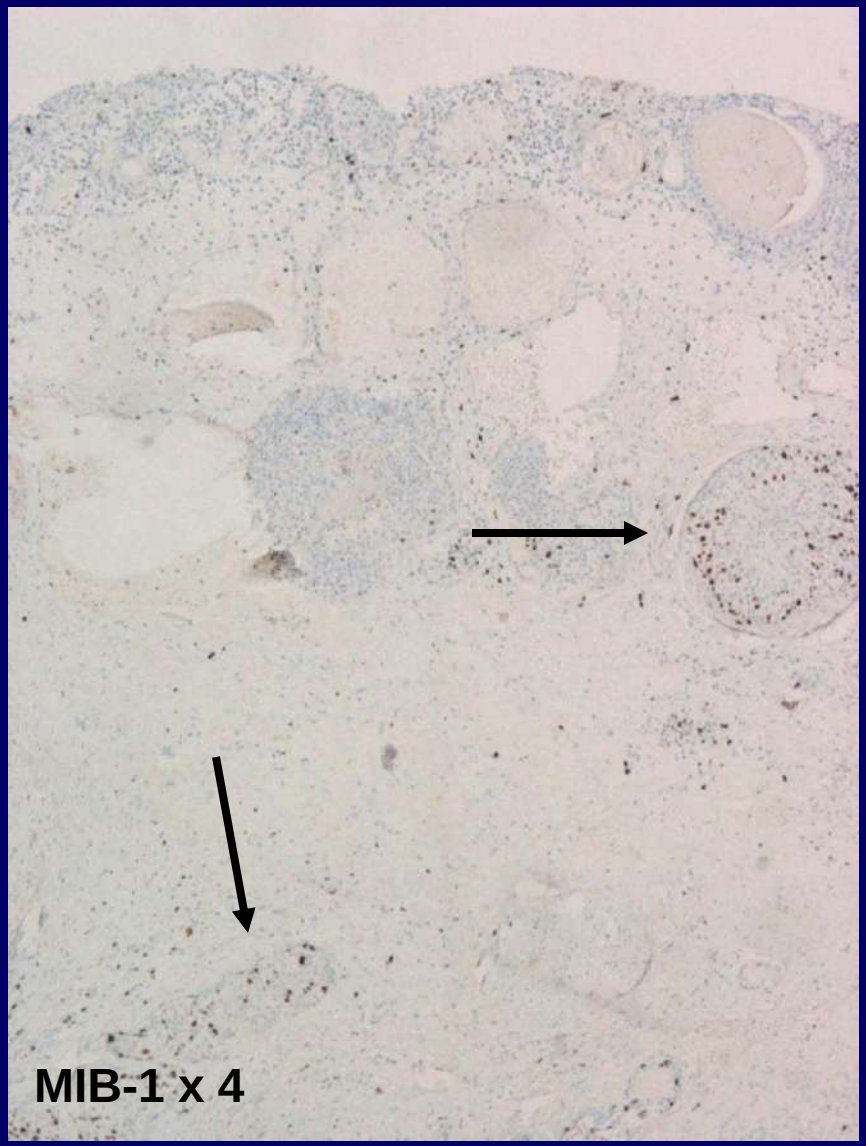


Paraganglioma



Immunohistochemistry



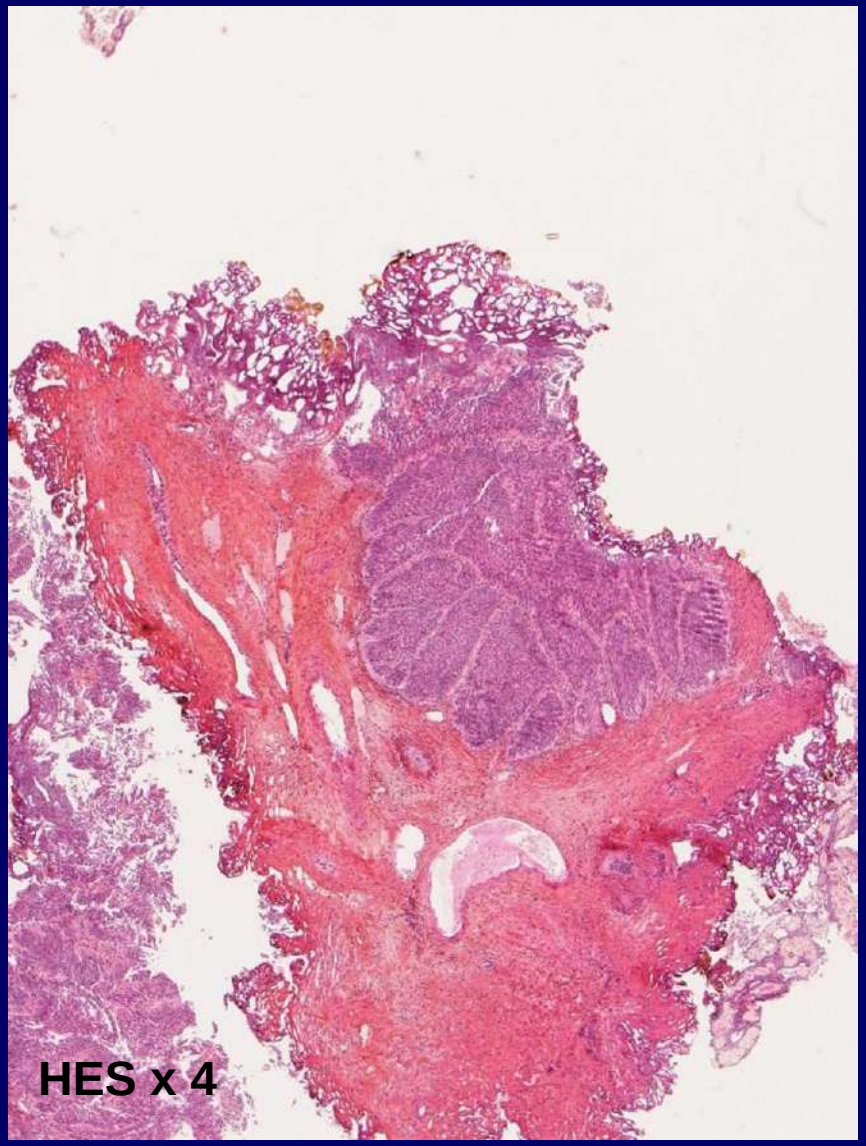


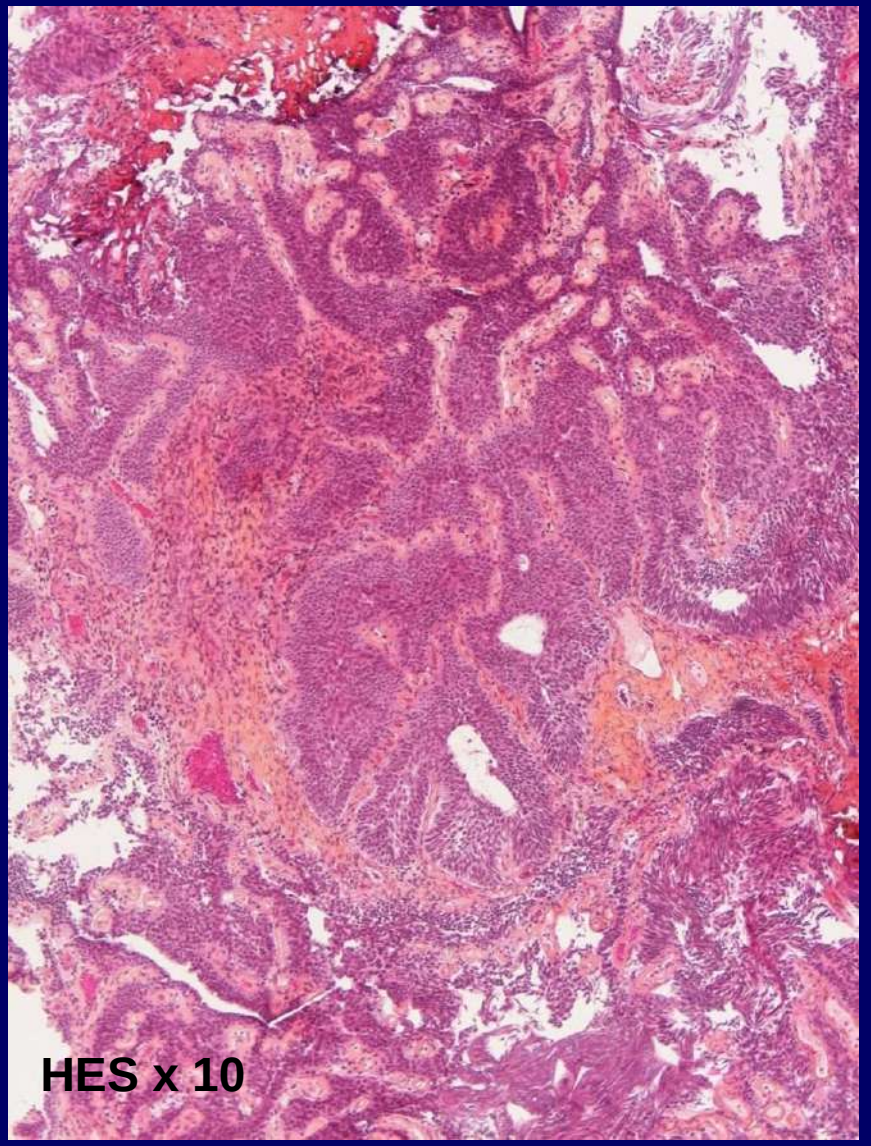
Nested Carcinomas

- OS : mean 30 months
- danger
  - Underestimate ++
  - or overestimate

- if no muscle
  - new biopsies

Inverted Papilloma-like Growth



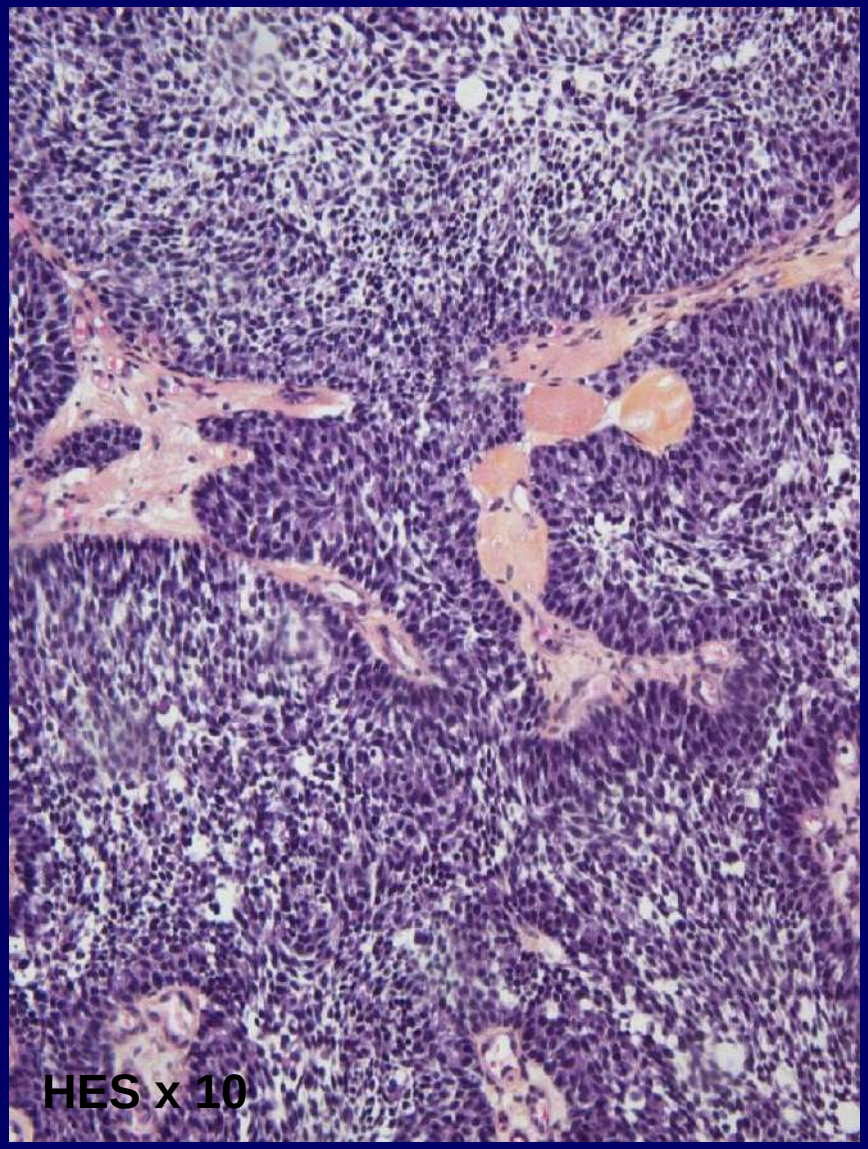


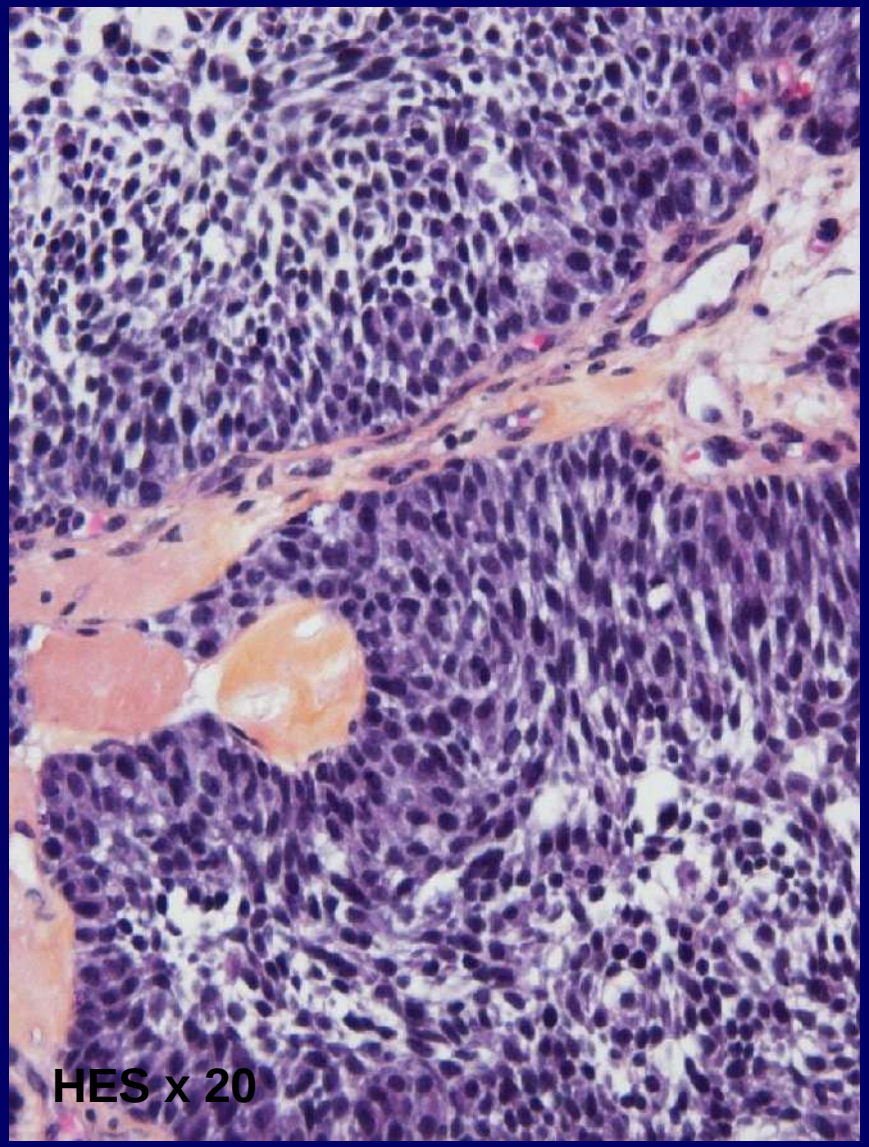
Inverted Papilloma-like Growth

- 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

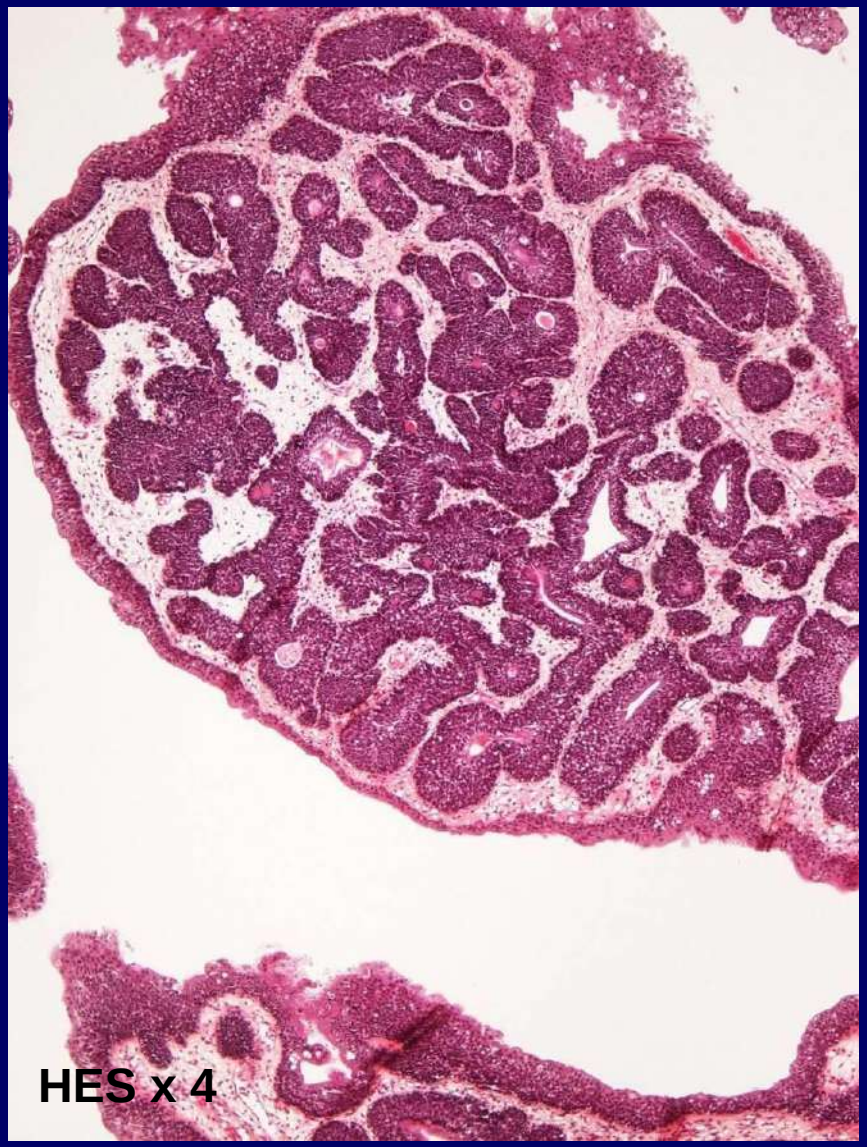
Amin 1997; Am J Surg Pathol
Lopez-Beltran 1996, Hum Pathol

Inverted Papilloma-like Growth

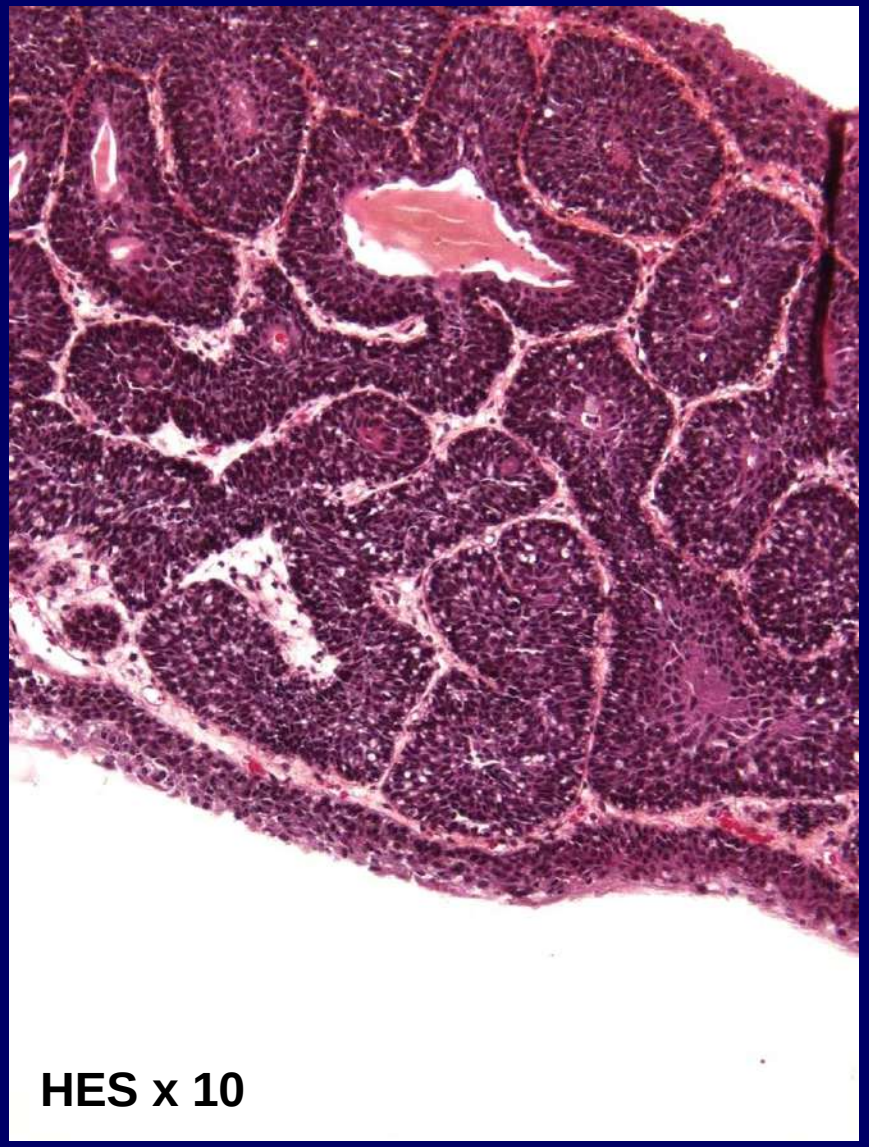




DD : Inverted Papilloma



HES x 4

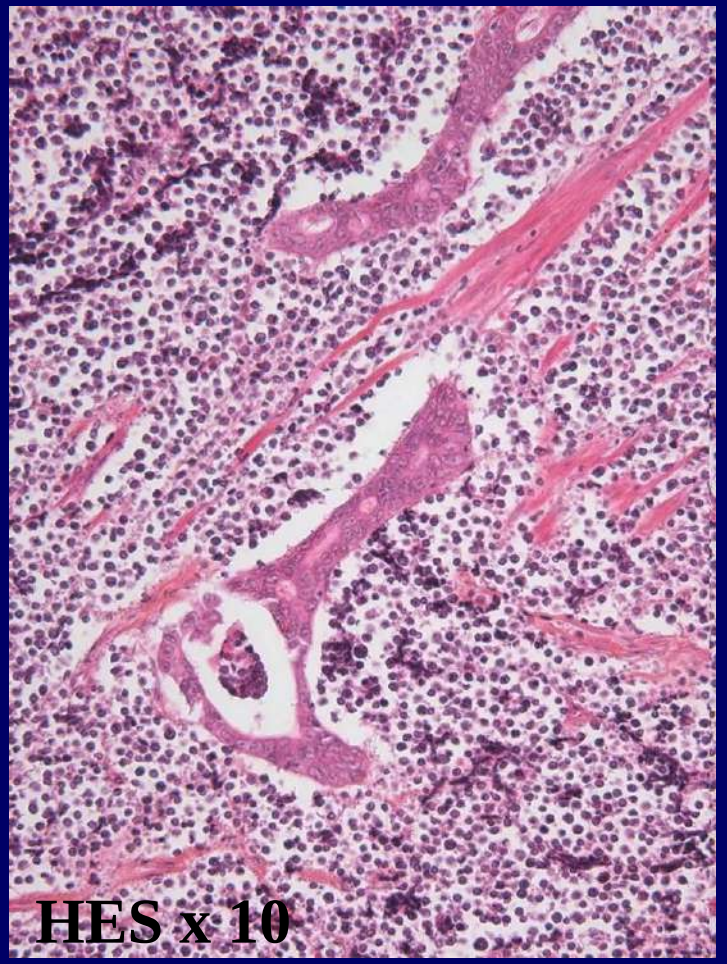


HES x 10

Lymphoepithelioma-like UC

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

- Immunotherapy ?



Lopez-Beltran 20

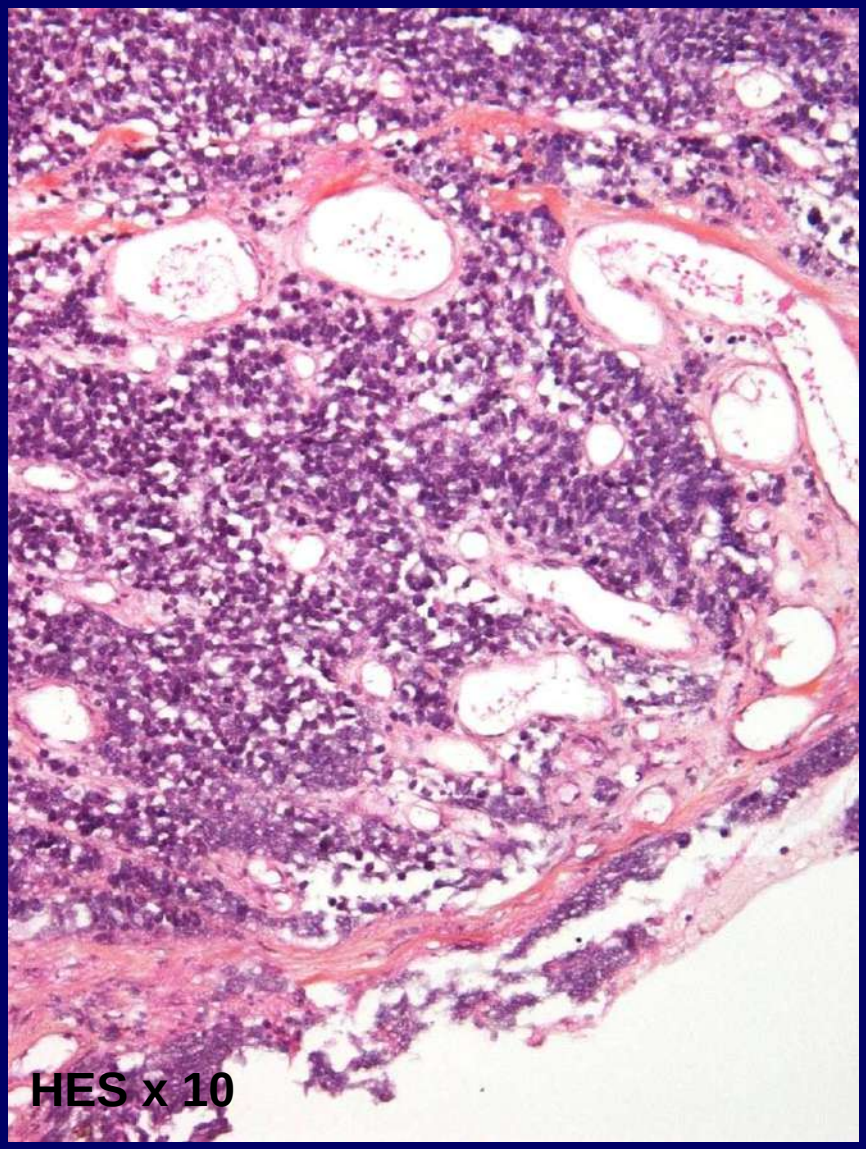
Small Cell (neuro endocrine) Carcinoma (SCC)

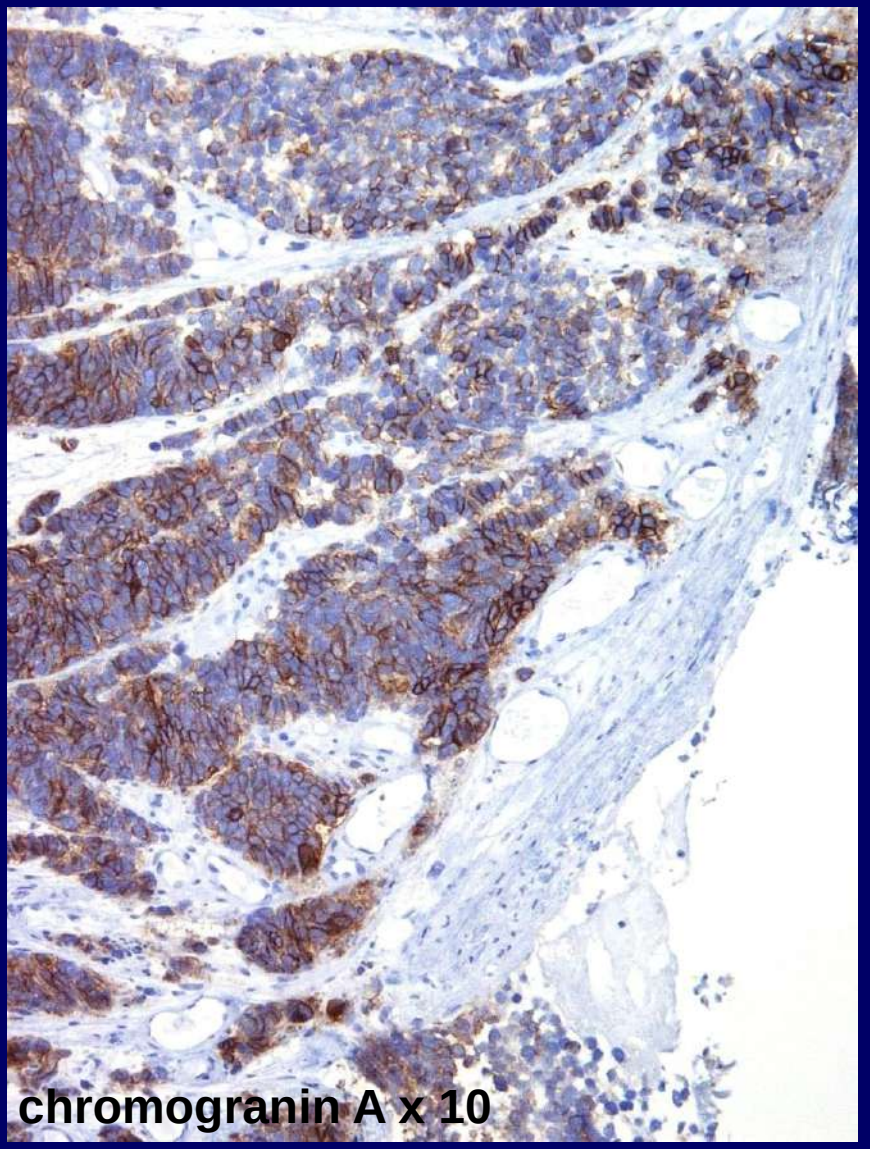
- rare
- highly aggressive
- coexistence with other tumor types common

- origin?
  - expression of cytokeratins → urothelial origin
  - Cheng *et al.* →identical allelic loss patterns in UC and SCC

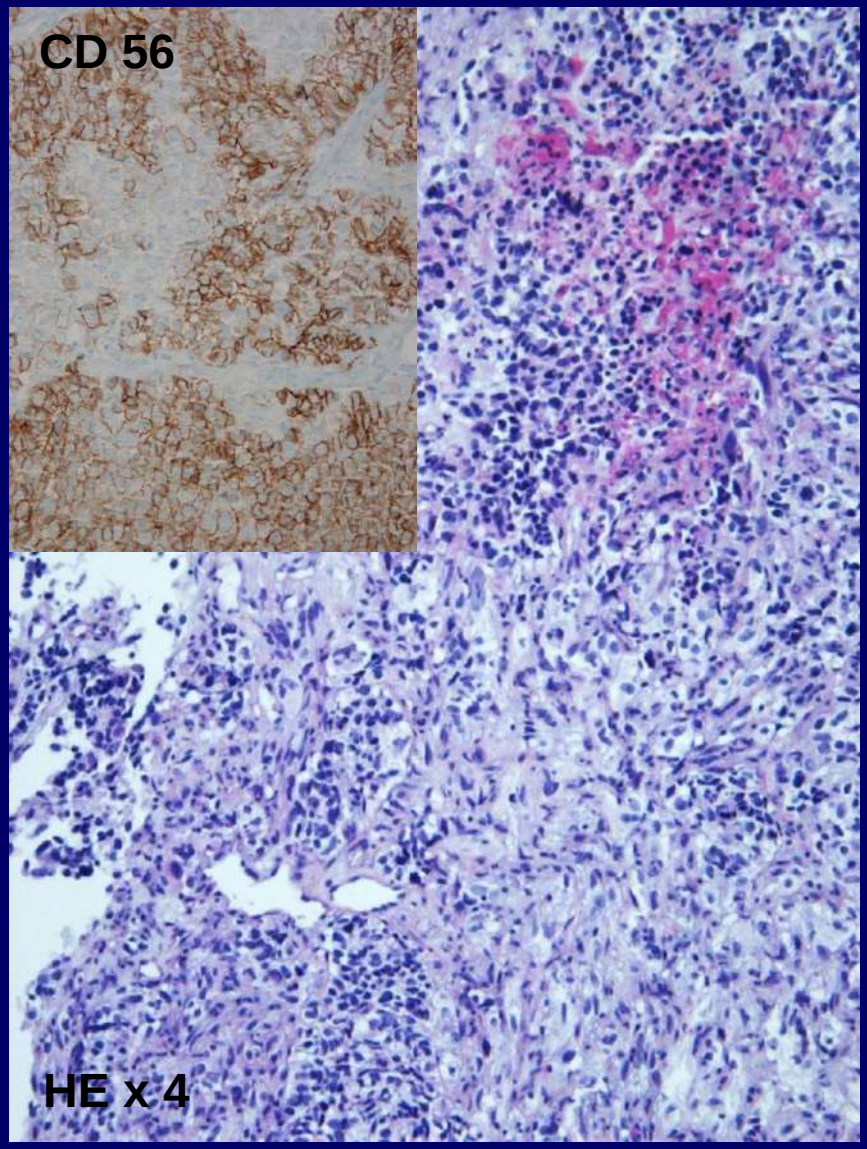
Cheng 2004, Clin Cancer Res

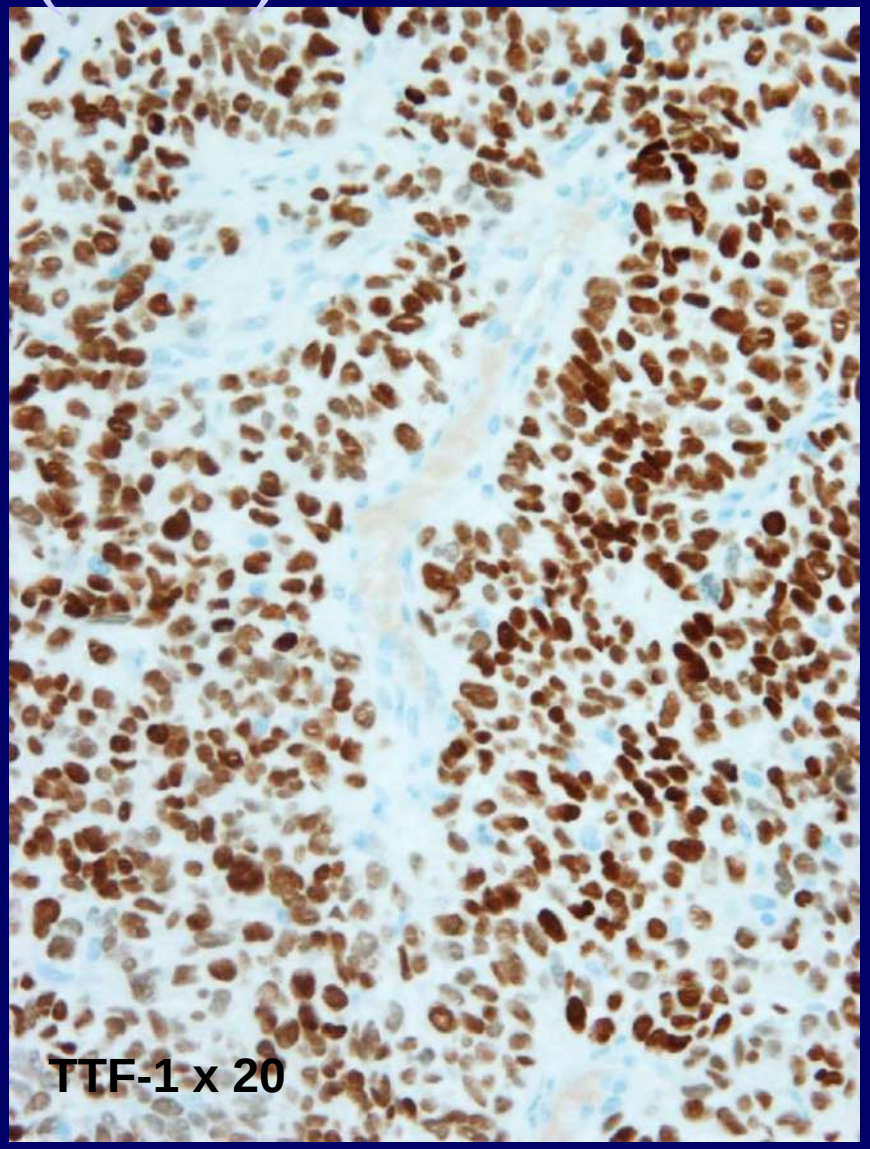
Small Cell Carcinoma (SCC)


HES x 10

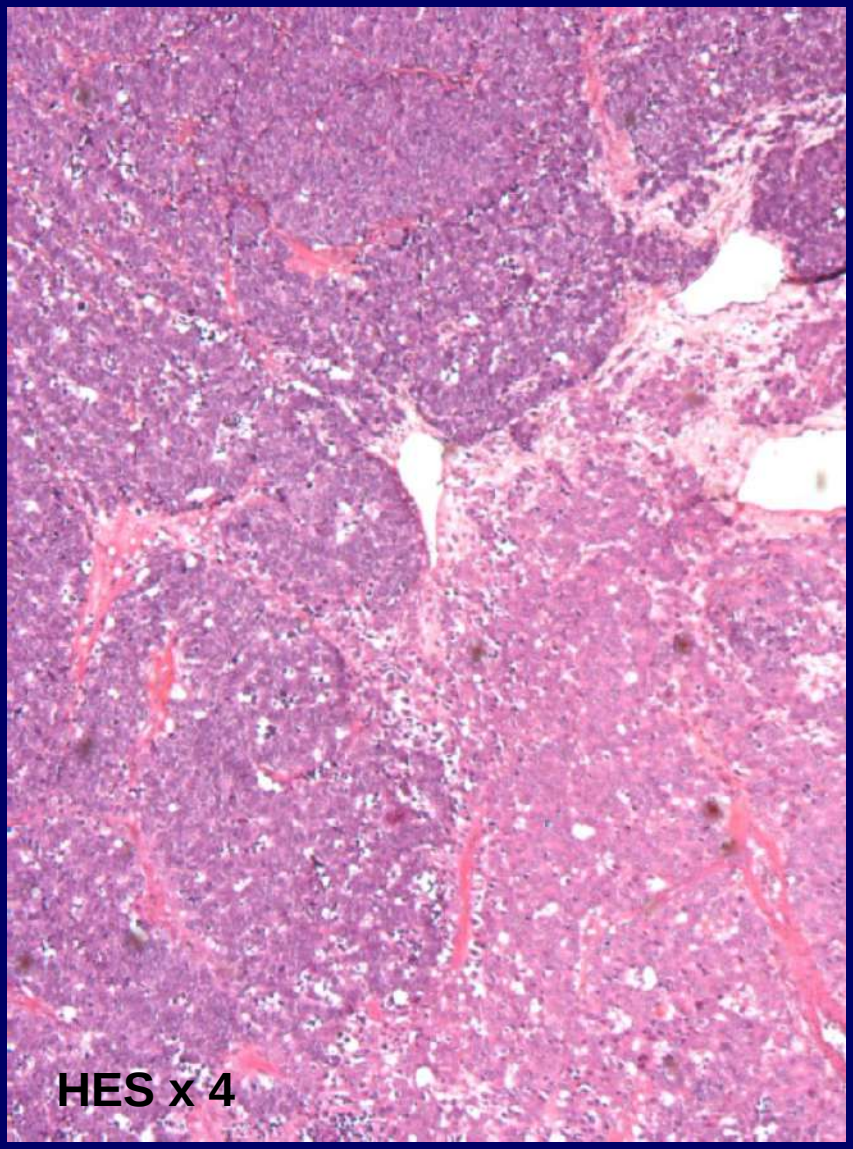

chromogranin A x 10

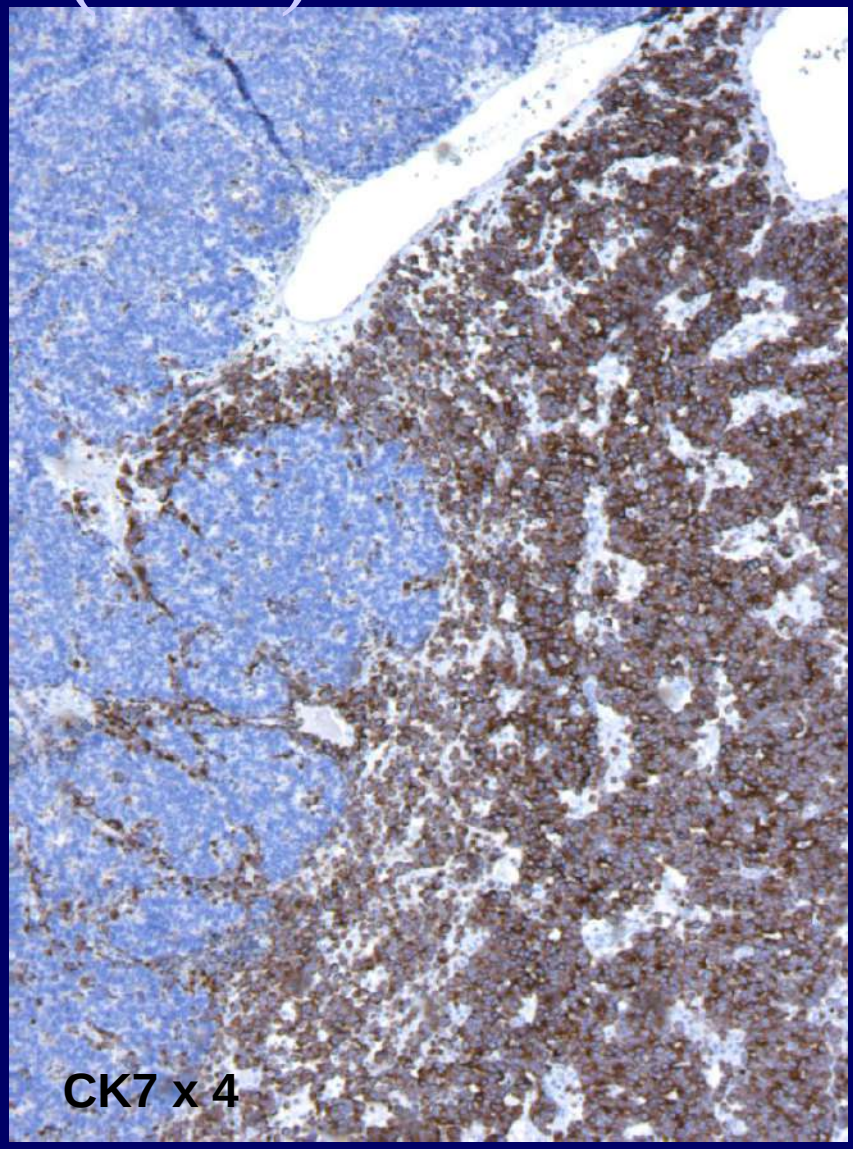
Small Cell Carcinoma (SCC)





Small Cell Carcinoma (SCC)





Small Cell Carcinoma (SCC)

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

Eble 2004, WHO

Small Cell Carcinoma (SCC)

- prognosis
  - very poor
  - correlation with stage
  - often association with paraneoplastic syndromes

  - Chemotherapy if pure or dominant
    - cisplatin and etoposide ? no consensus nor recommandations
  - surgery

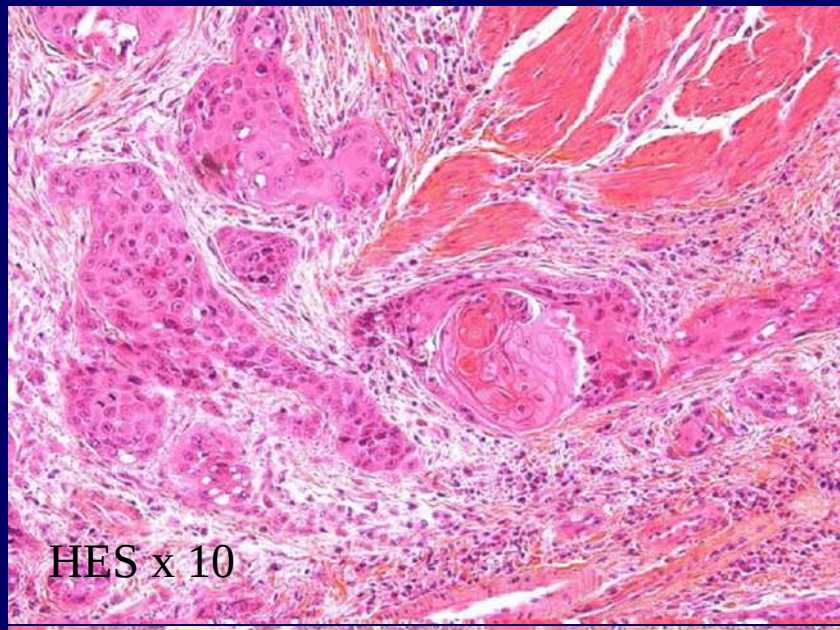
    →same results

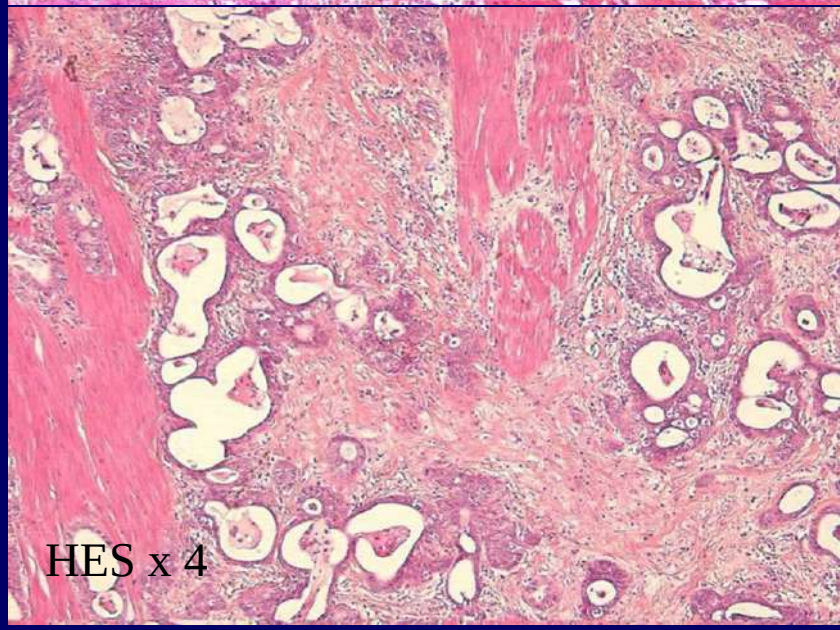
Cheng 2004; Cancer

Squamous or Glandular Differentiation

- consider as squamous cell carcinoma or adenocarcinoma only if pure forms

- squamous component
  - 20%
  - more aggressive than UC
- glandular differentiation
  - less common
  - 6%

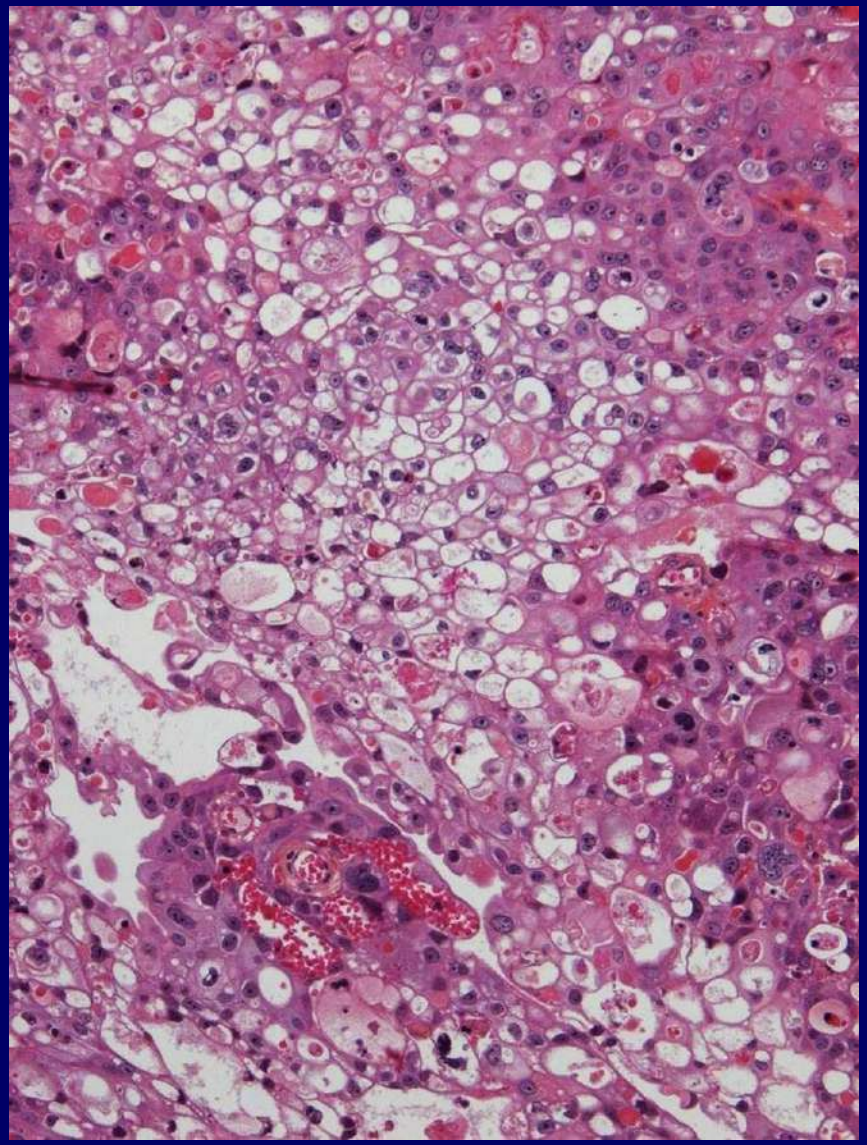




Lopez-Beltran 2006, Hum Pathol

Lipid Rich Variant

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



Leroy 2007; Am J Surg Pathol

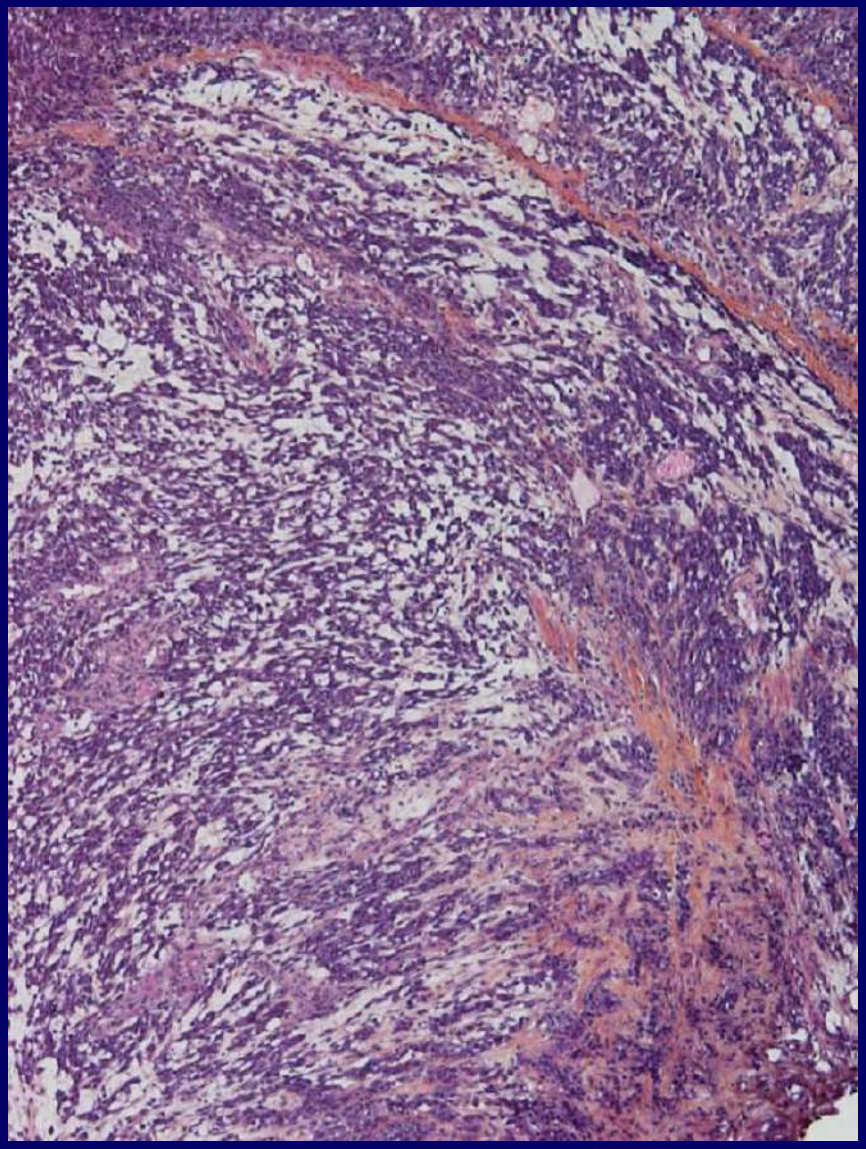
Sarcomatoid UC

- heterologous elements
  - osteosarcoma
  - chondrosarcoma
  - rhabdomyosarcoma
  - leiomyosarcoma
- EMA +
- p63 +

} urothelial component

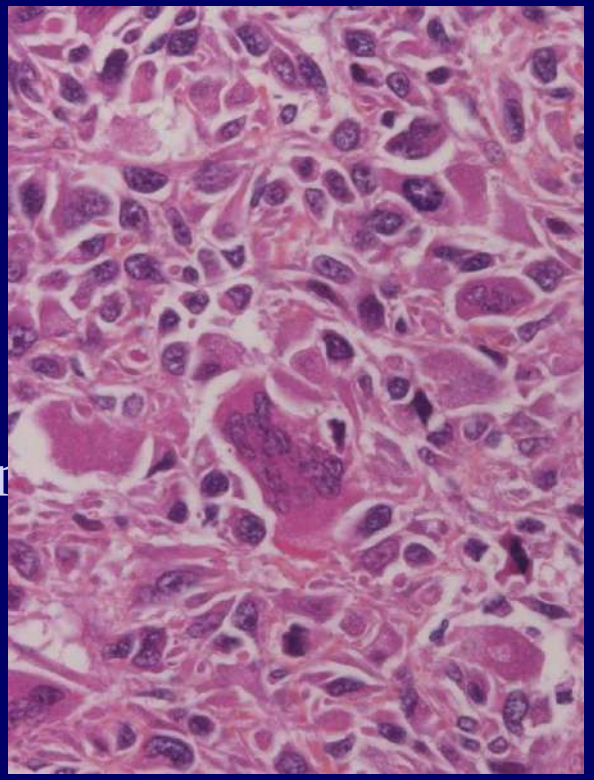
- PS100 +
- vimentin +

} mesenchymal component



UC with stromal reactions

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



Lopez-Beltran 1996, Pathol Pract Res

Conclusion

- 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 +++

Lopez-Beltran 2007; BJU