WHO'S WHO IN THE NEW WHO CLASSIFICATION OF UROLOGIC CANCER?

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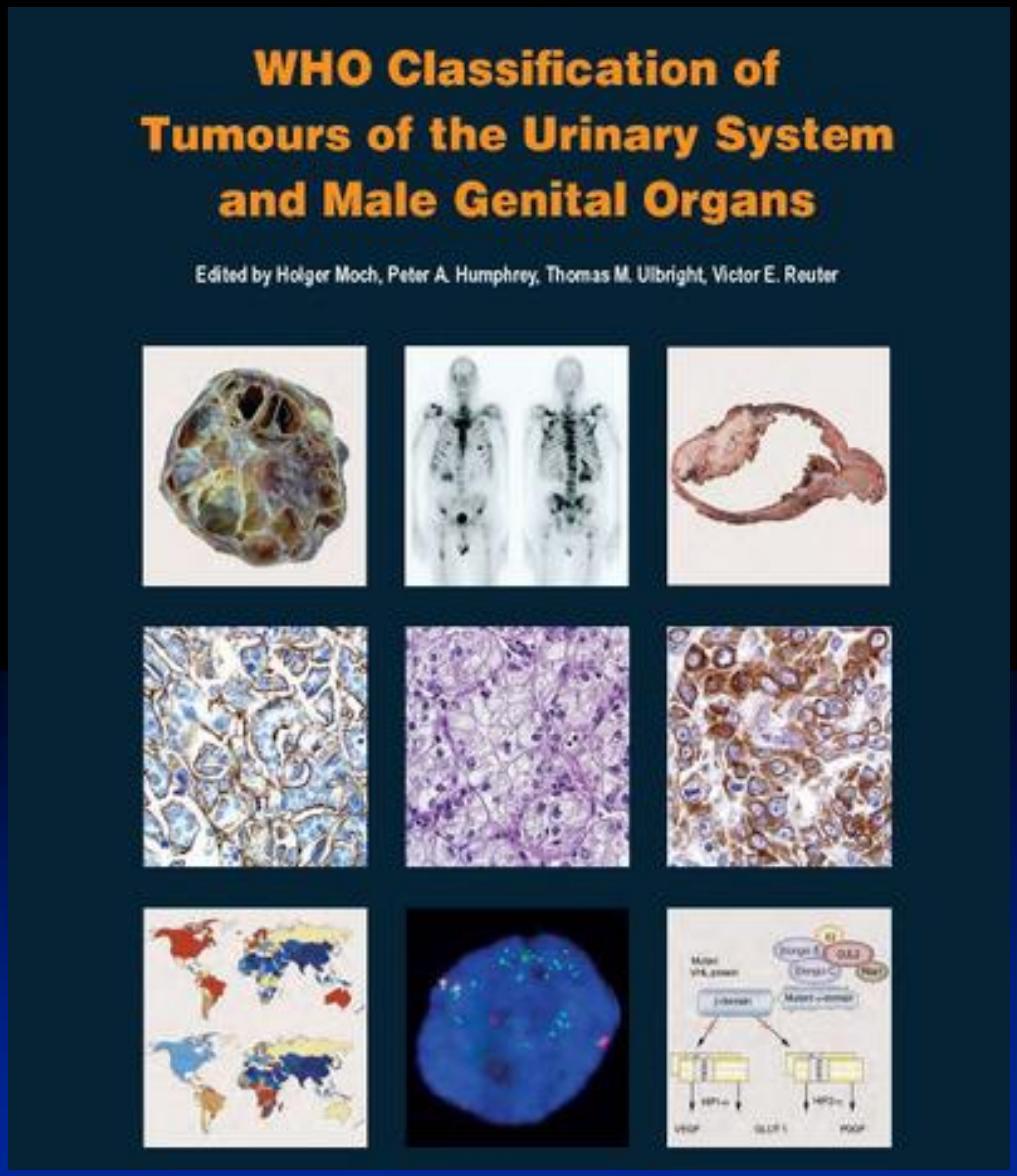
WHO (2015) BLUE BOOK COMMITTEE



- **21 Chapters - Mahul B Amin**
- ***Including Introduction/ Classification chapters :***
  - **Prostate**
  - **Kidney**
  - **Bladder**
  - **Testis**
  - **Penis**

2014: 12 major/new Concepts in the Blue book

PROSTATE CANCER

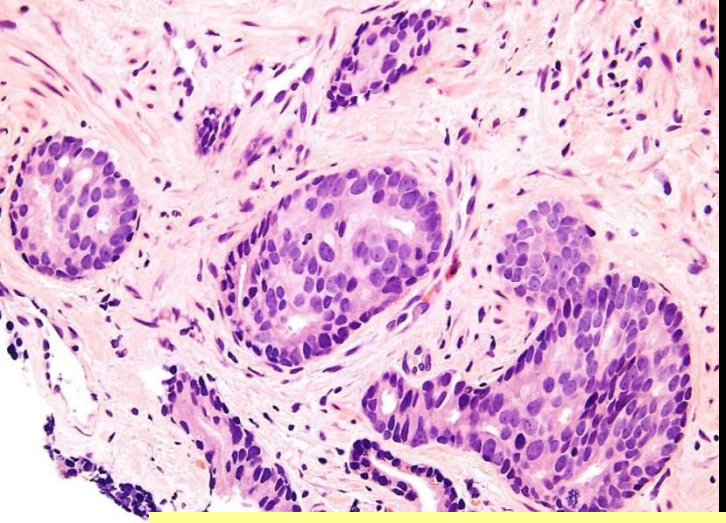
What is new in the WHO 2016:

- **Topic 1:**

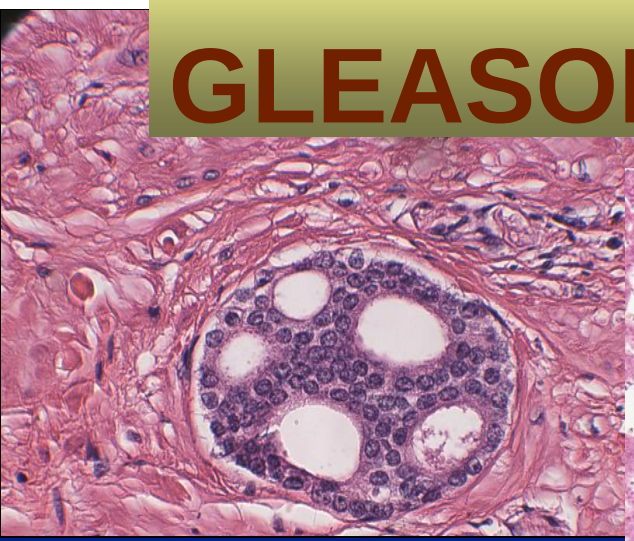
  Grading of prostate tumors

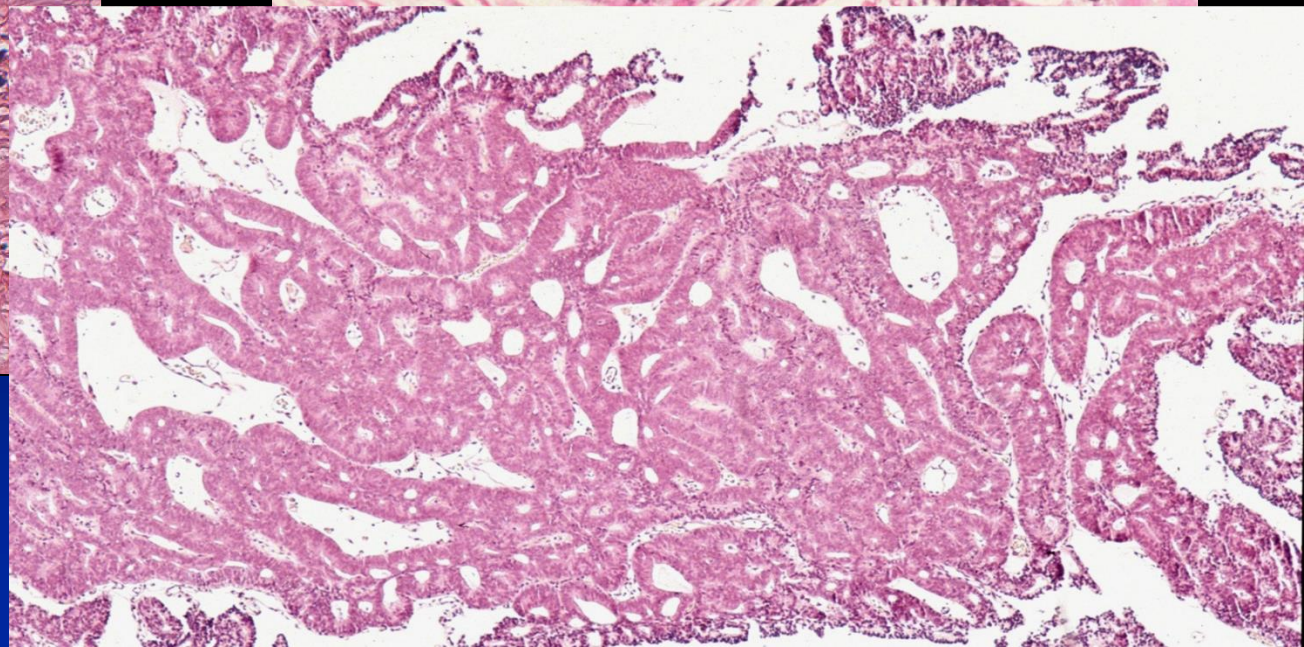
WHO/ISUP 2014 MAJOR RECOMMENDATION

- Report percent pattern 4 Gleason score 7 in both needle biopsies and radical prostatectomies.

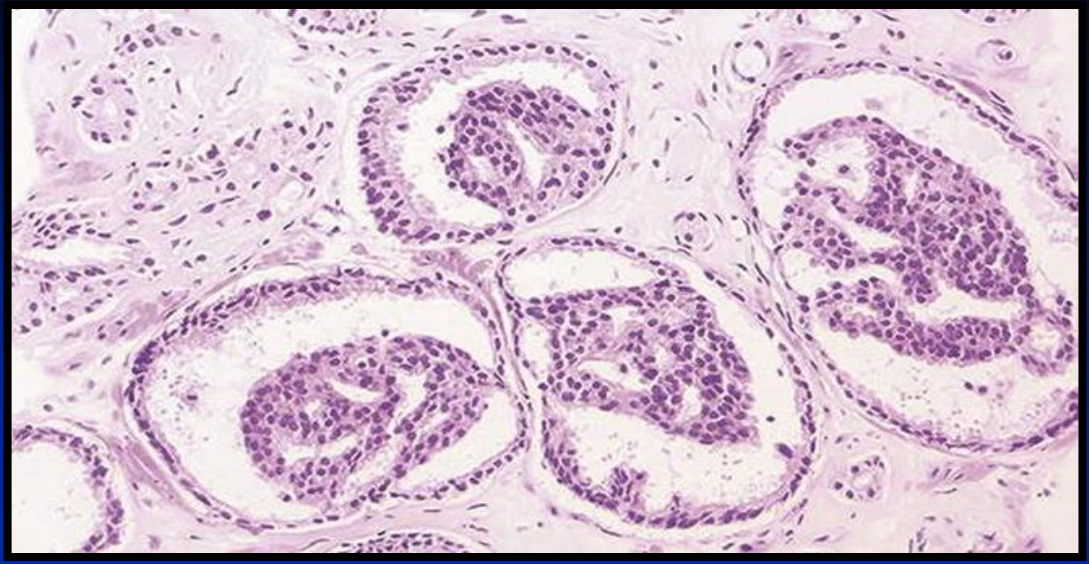


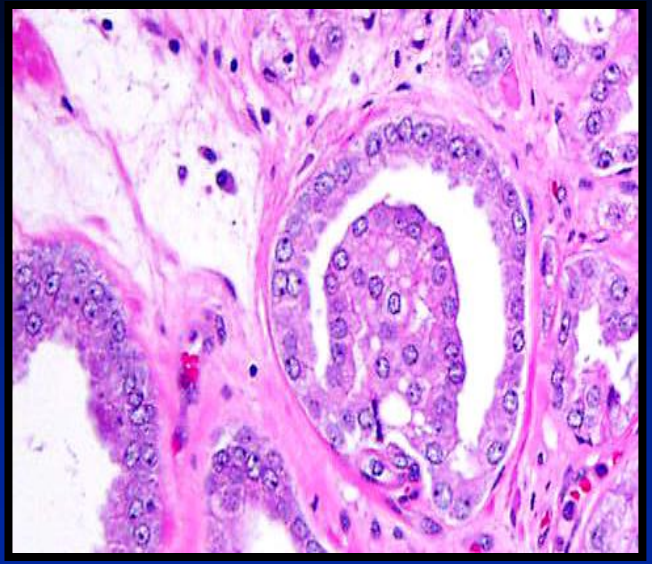
ALL OF THESE ARE NOW GLEASON PATTERN 4





All glomeruloid glands should be graded as Gleason pattern 4 regardless of morphology





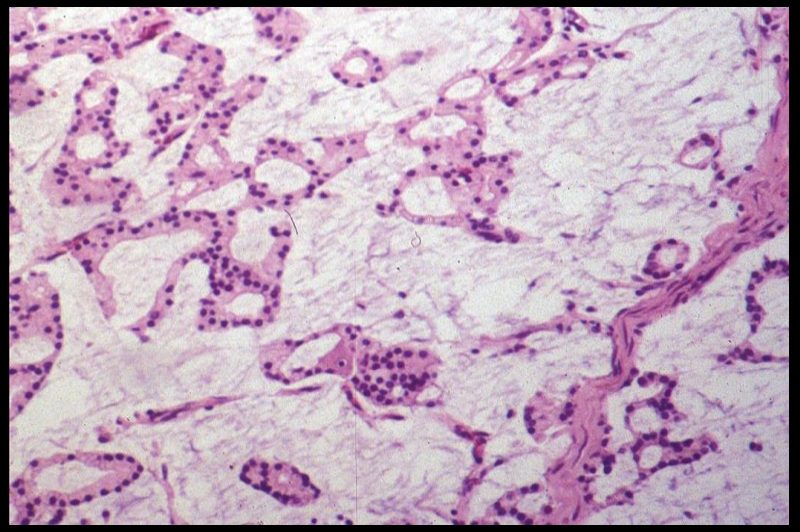
GLEASON GRADING OF VARIANTS OF PROSTATE CANCER

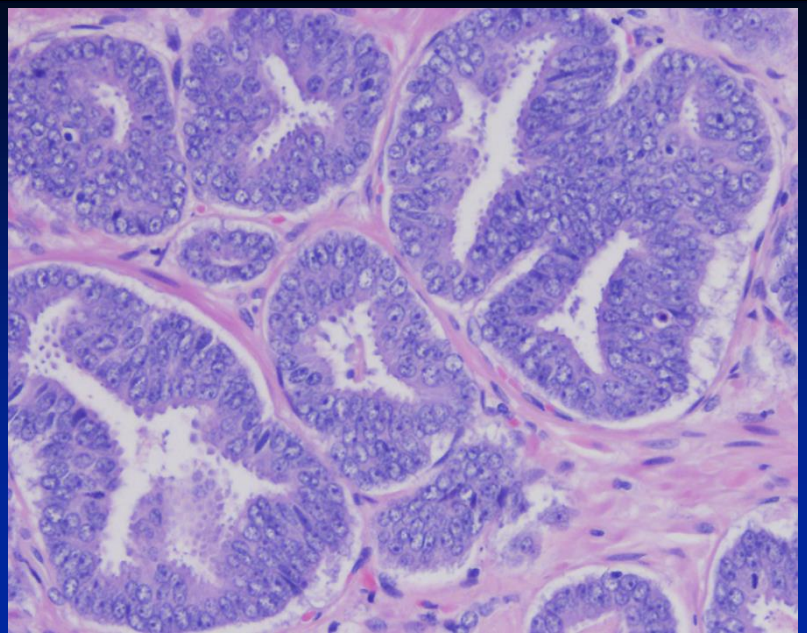
- **Ductal Ca.** - Gleason 4 or 5 (if necrosis)
- **Signet ring cell Ca.** - Gleason 4 or 5
- **Small cell Ca.** - do not grade
- **Sarcomatoid Ca.** - do not grade

GLEASON GRADING OF VARIANTS OF PROSTATE CANCER

NEW

- **Mucinous carcinoma behaves more indolently than previously believed – recommendation: subtract the mucin and grade the tumor – not all mucinous carcinomas are Gleason pattern 4**
- **PIN-like carcinoma is a Gleason pattern 3**





ORIGINAL ARTICLE

The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

Jonathan I. Epstein, MD, Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srigley, MD,‖ Peter A. Humphrey, MD,*

Am J Surg Pathol 2016

Contemporary Gleason Grading of Prostatic Carcinoma

An Update With Discussion on Practical Issues to Implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD, Mahul B. Amin, MD,† Victor E. Reuter, MD,‡ and Peter A. Humphrey, MD, PhD§*

Issues pertaining to implementation in clinical practice

- **reporting of cancer per specimen/cores etc.**
- **reporting of different foci in RP**

Am J Surg Pathol 2017, E Pub ahead of print.

Reporting of Gleason score Prognostic Grade Groups

- Gleason score ≤ 6:
- Gleason score 3 + 4 = 7
- Gleason score 4 + 3 = 7
- Gleason score 8
- Gleason score 9-10

- Grade Group I
- Grade Group II
- Grade Group III
- Grade Group IV
- Grade Group V

Gleason scores can be grouped and range from Grade Group I (most favorable) to Grade Group V (least favorable).

INCORPORTATION OF PROGNOSTIC GROUPS ENDORSED BY THE ISUP (2015) & WHO (2016)

Implications of Reporting of Gleason score Prognostic Grade Groups

Group 1: lowest grade, possible candidates for active surveillance; 20% cases may have higher unsampled grade; makes distinction between Gleason 2+2, 2+3, 3+3 irrelevant

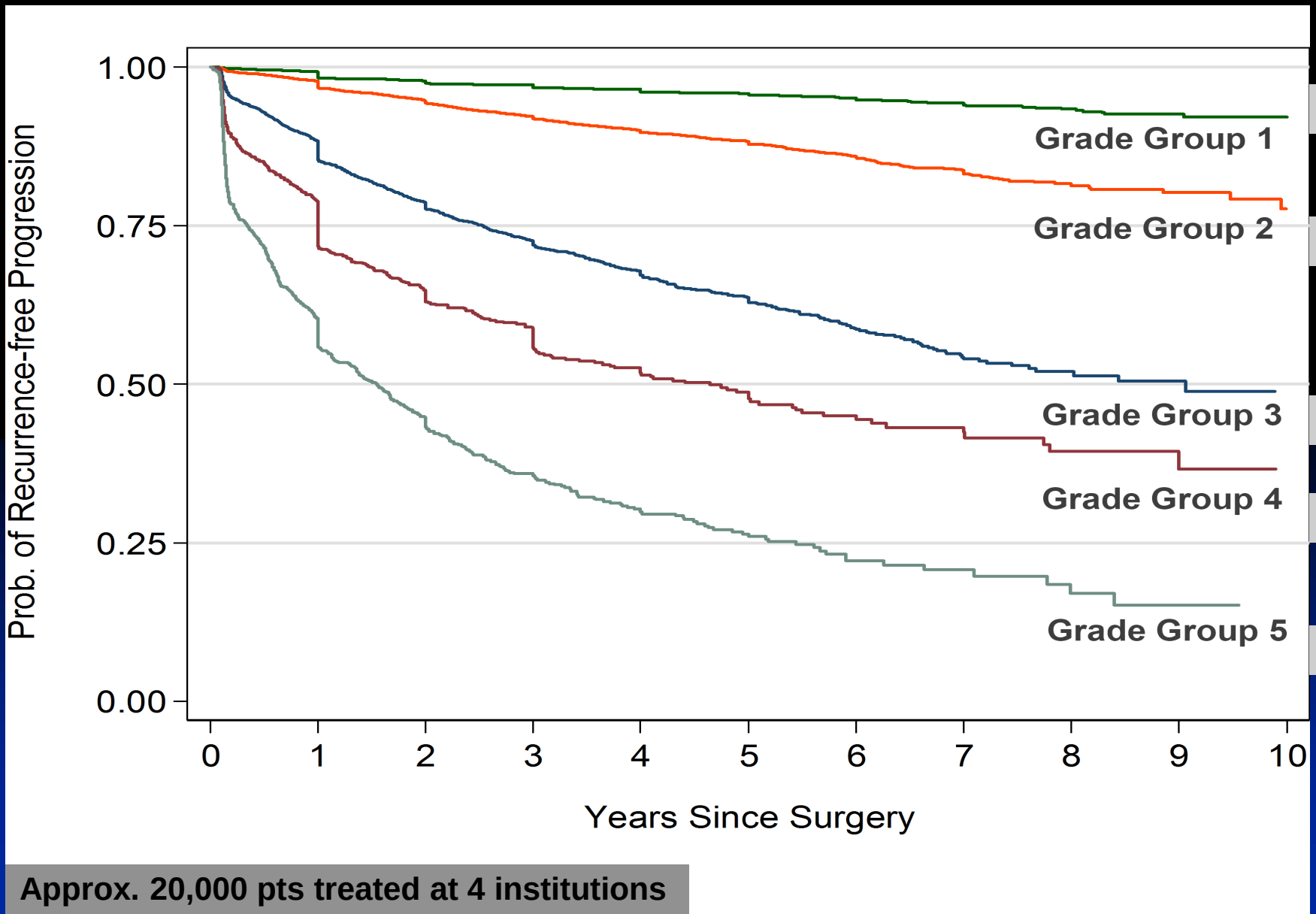
Group 2: Good prognosis, rare metastasis

Group 3: Worst prognosis than Group 2

Group 4: Not nearly considered high-grade, has significantly better prognosis than Group 5

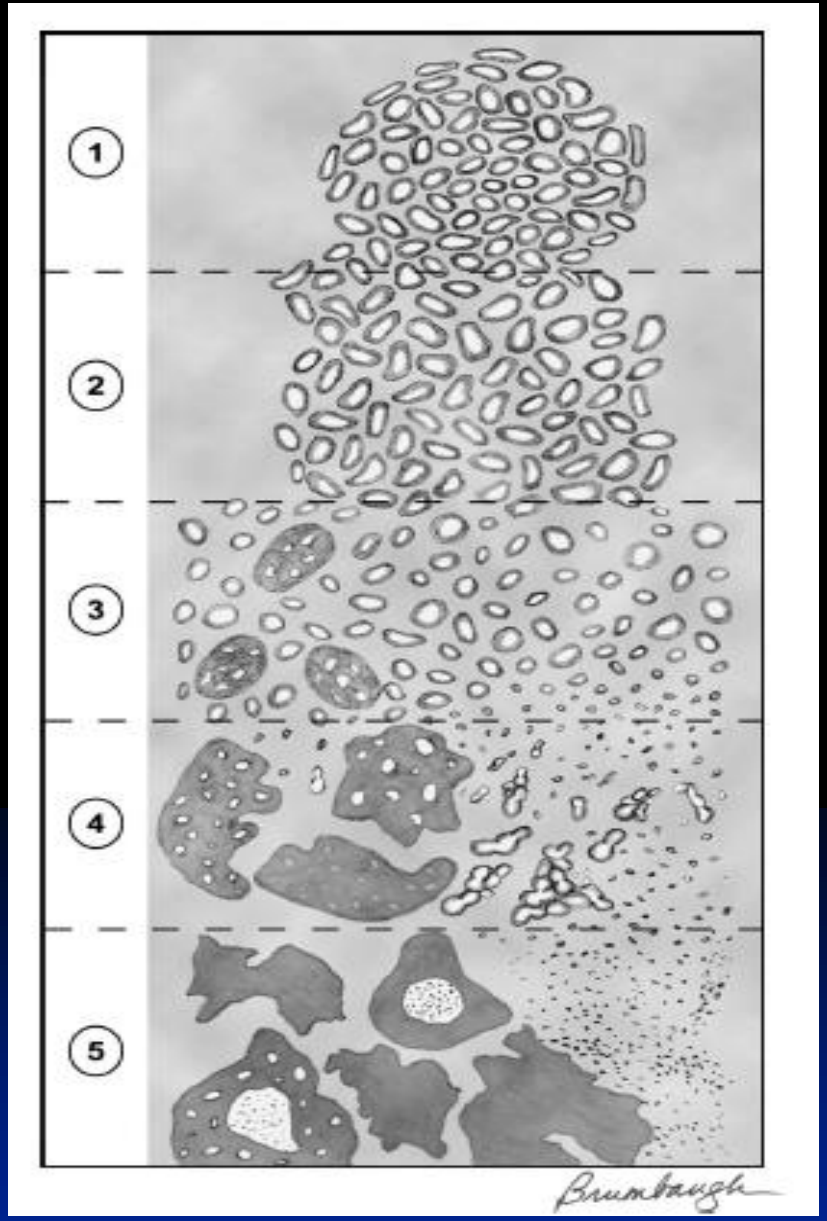
Group 5: Worst prognosis, obviates need to distinguish 4+5, 5+4, 5+5

Probability of recurrence- free progression for different prognostic grade groups

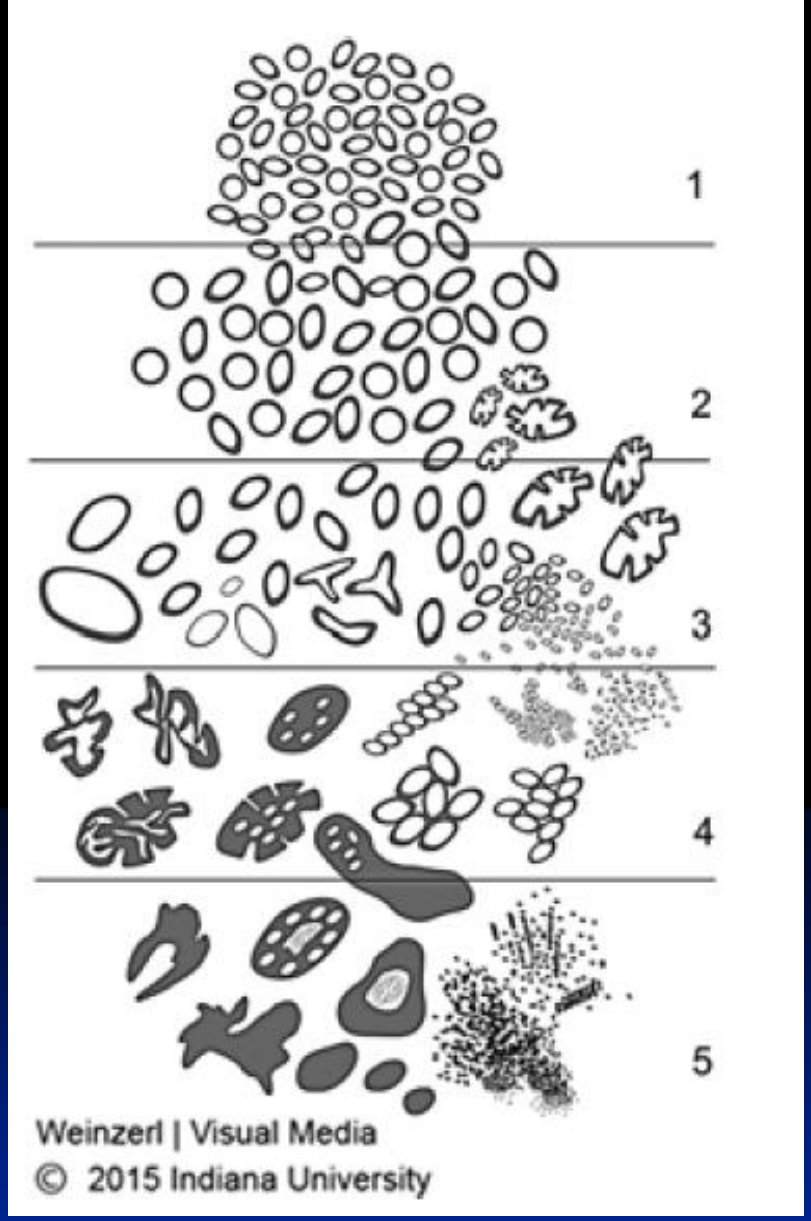


5 yr Biochem Risk free Surv.
97.5 %
93.1%
78.1%
63.3%
48.9 %

Approx. 20,000 pts treated at 4 institutions


1
2
3
4
5

2005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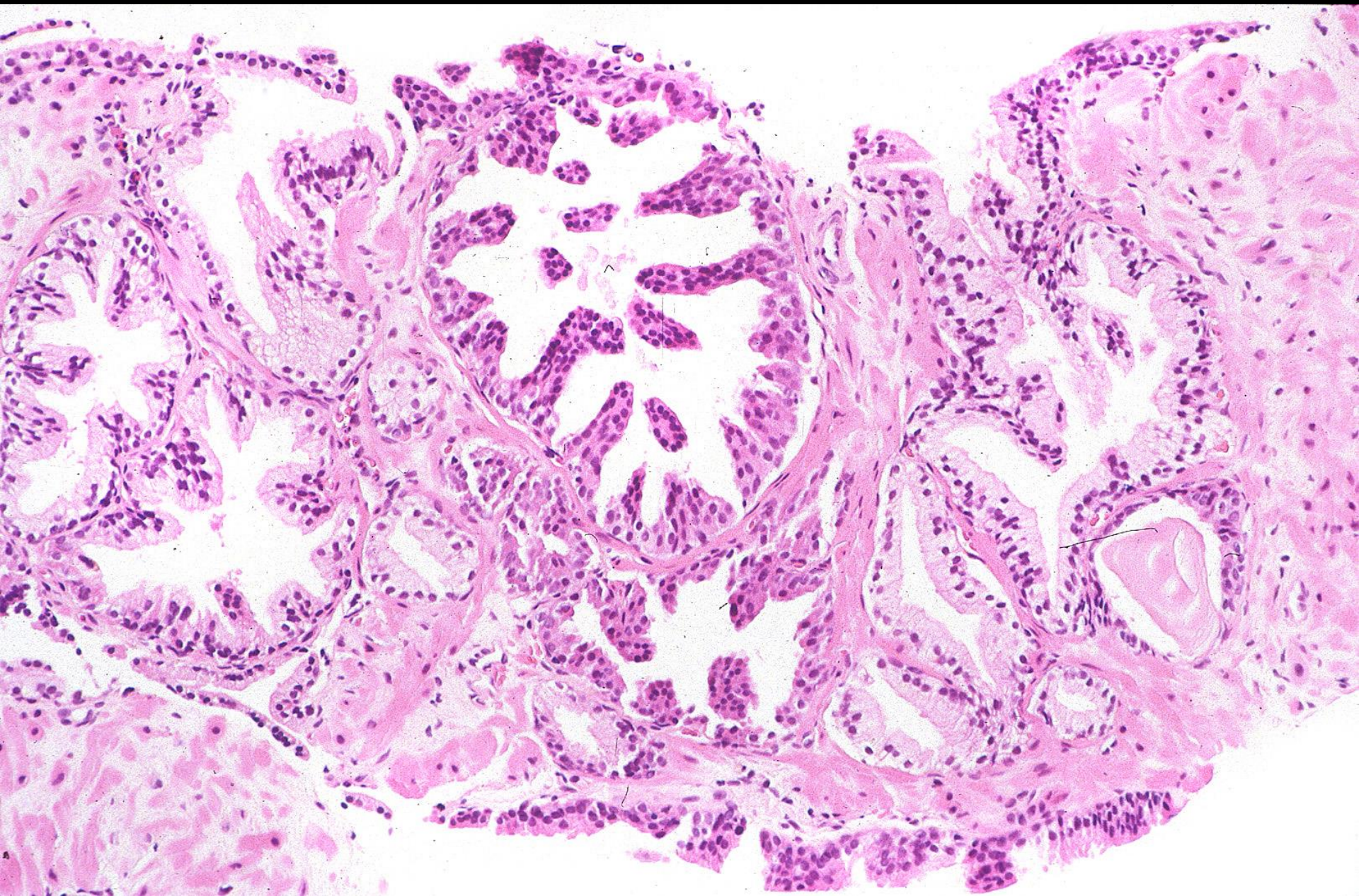
2014

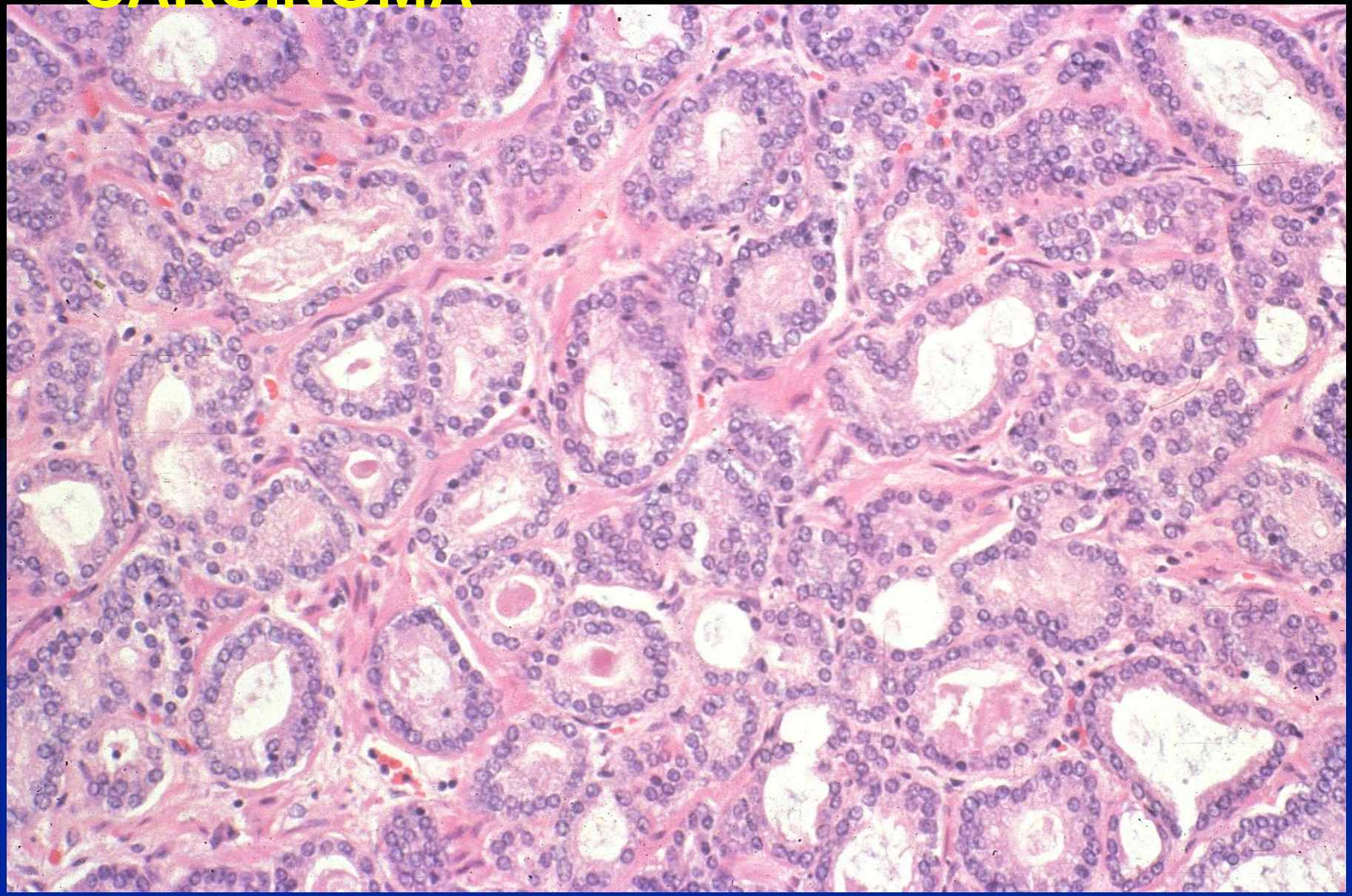
What is new in the WHO 2016:

- Topic 2: Intraductal cancer

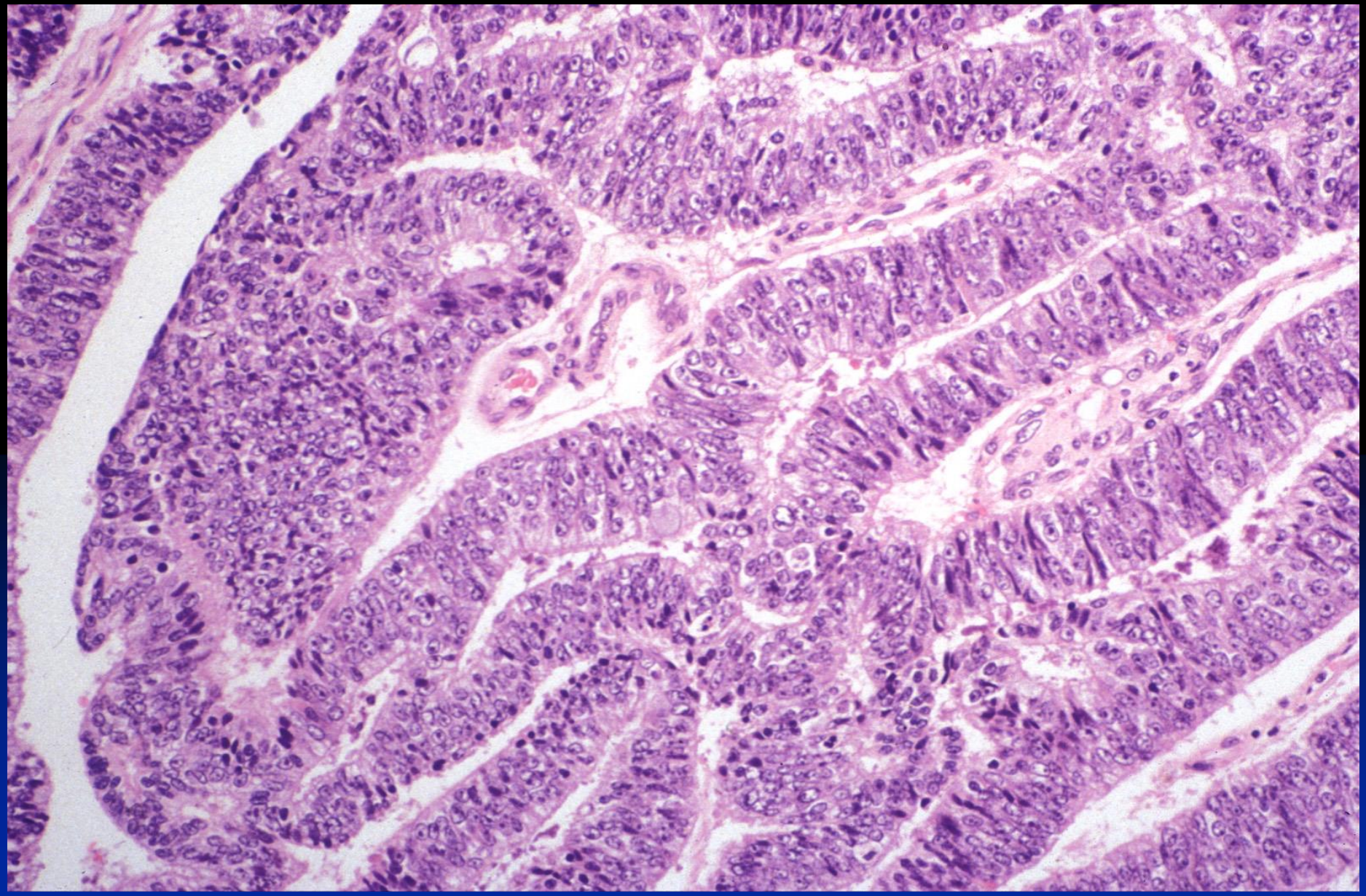
HG-PIN

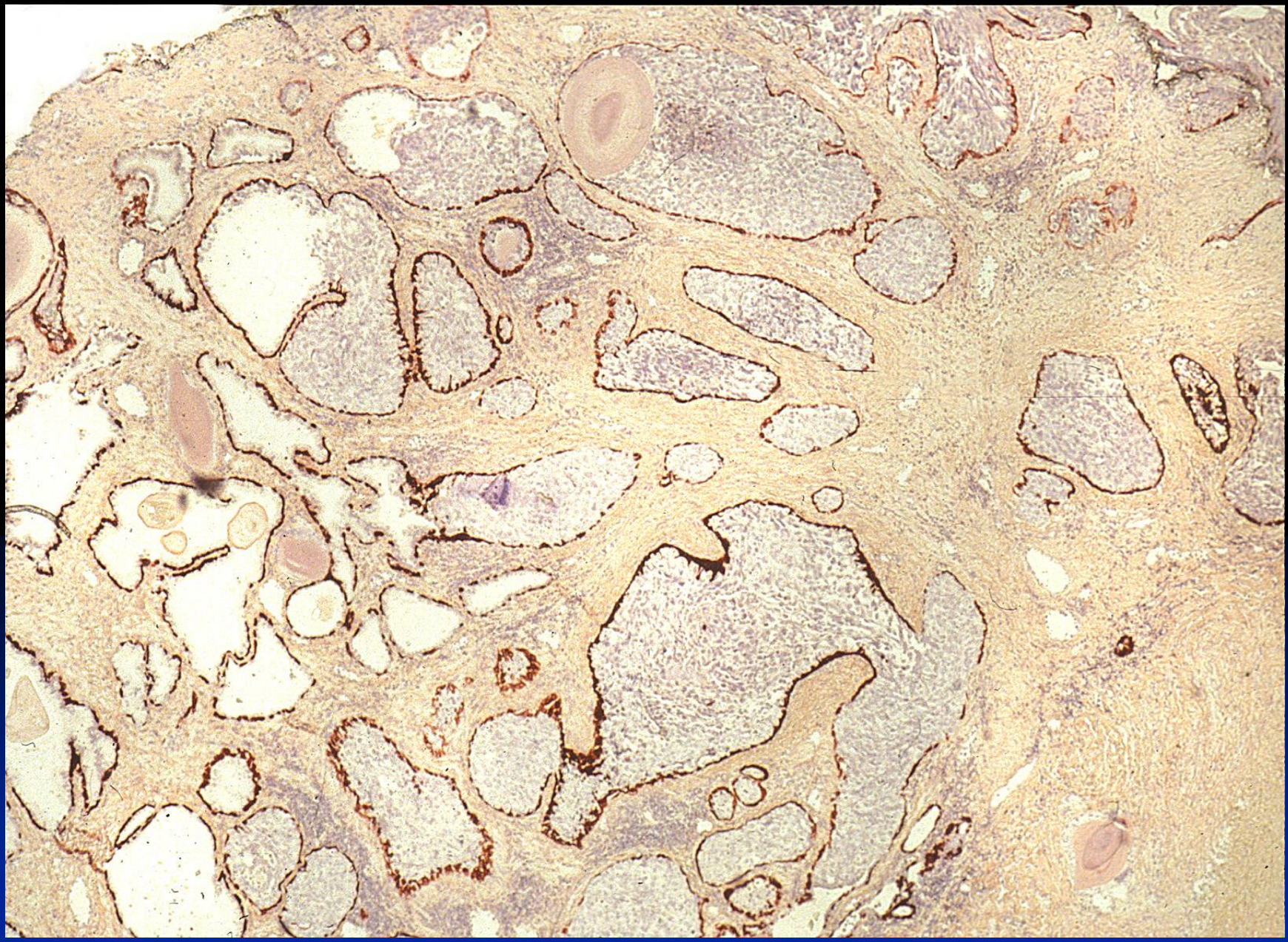


CONVENTIONAL (MICROACINAR) CARCINOMA



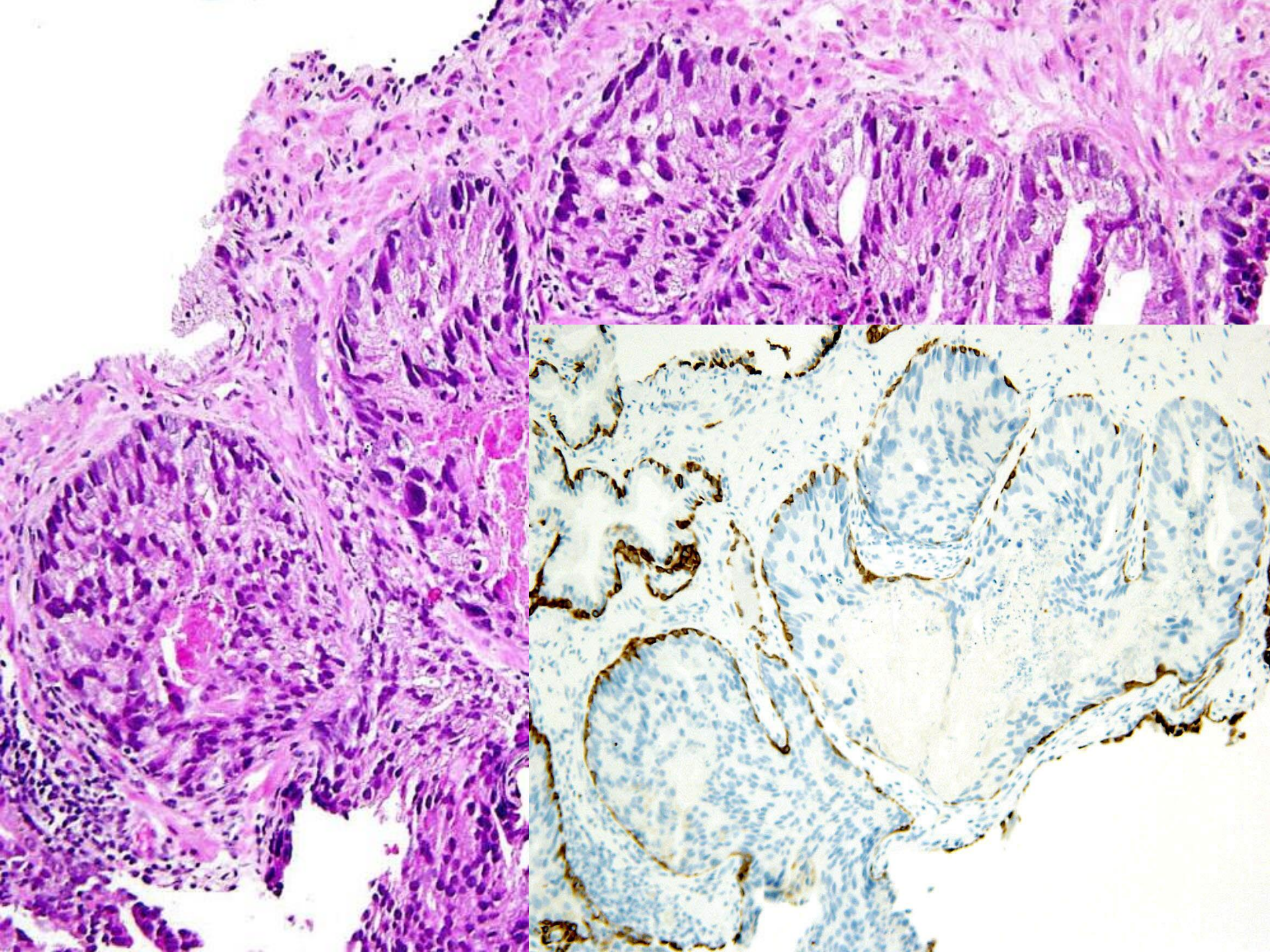
PROSTATIC DUCTAL CARCINOMA





Intraductal Carcinoma of the Prostate

- Late event in P Ca evolution, with intraductal spread of aggressive P Ca and cancerization of preexisting ducts and acini by high-grade P Ca.
- In a minority of cases, may be precursor lesion because in approximately 10% of RP cases following a NBx dx of IDC, IDC in the whole prostate gland is found in pure form, without associated invasive carcinoma



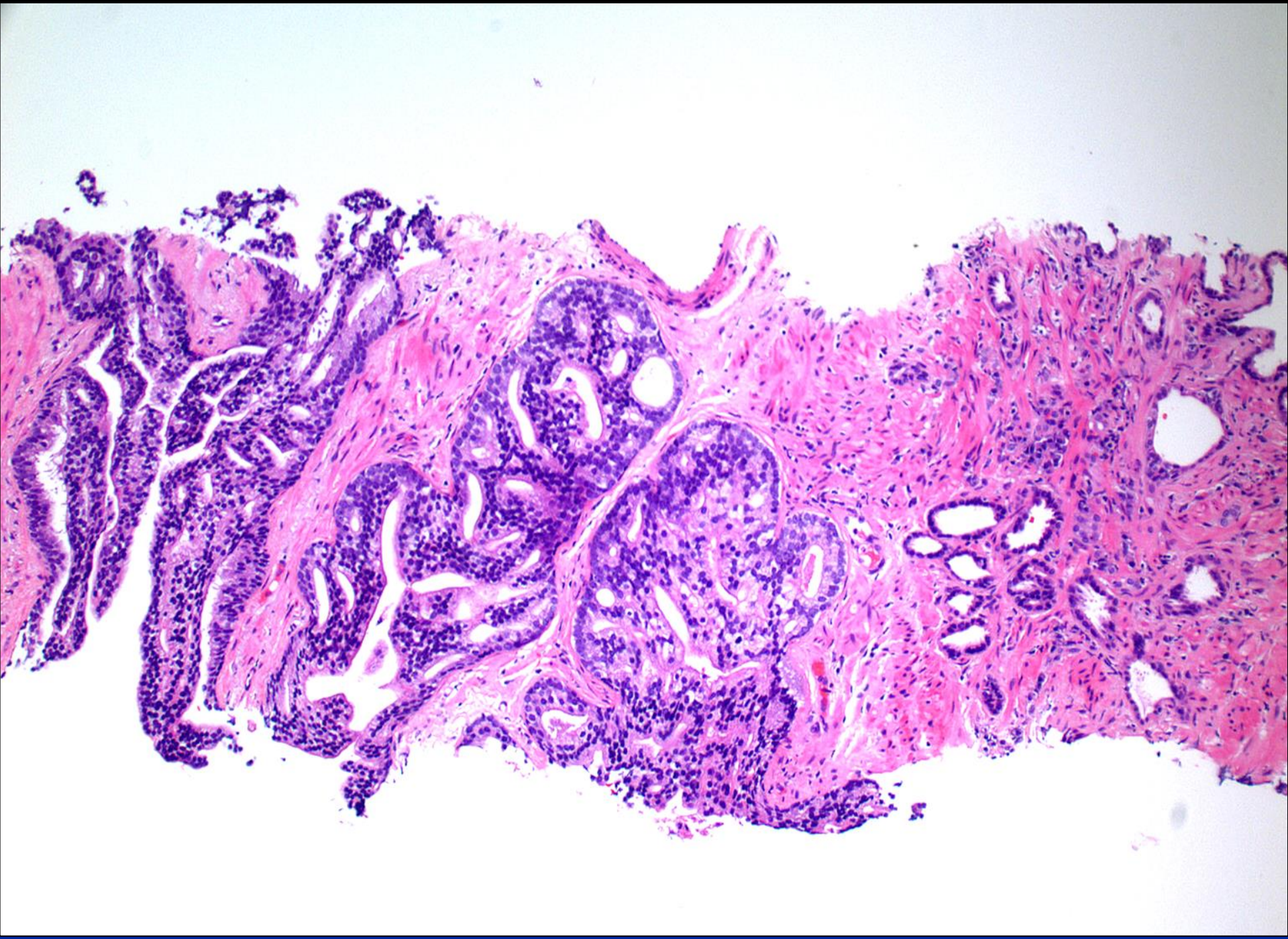
Intraductal Carcinoma of the Prostate

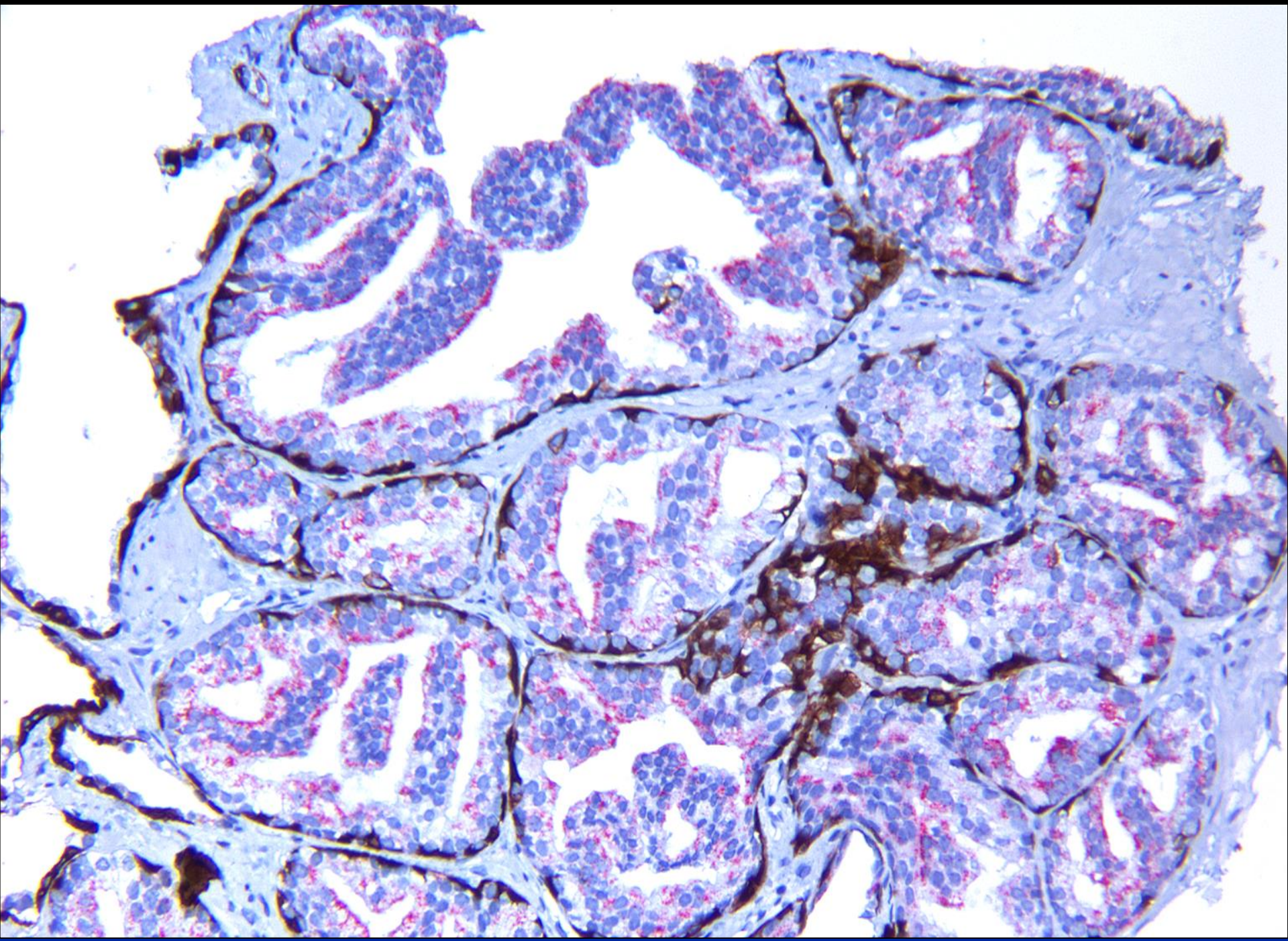
Criteria

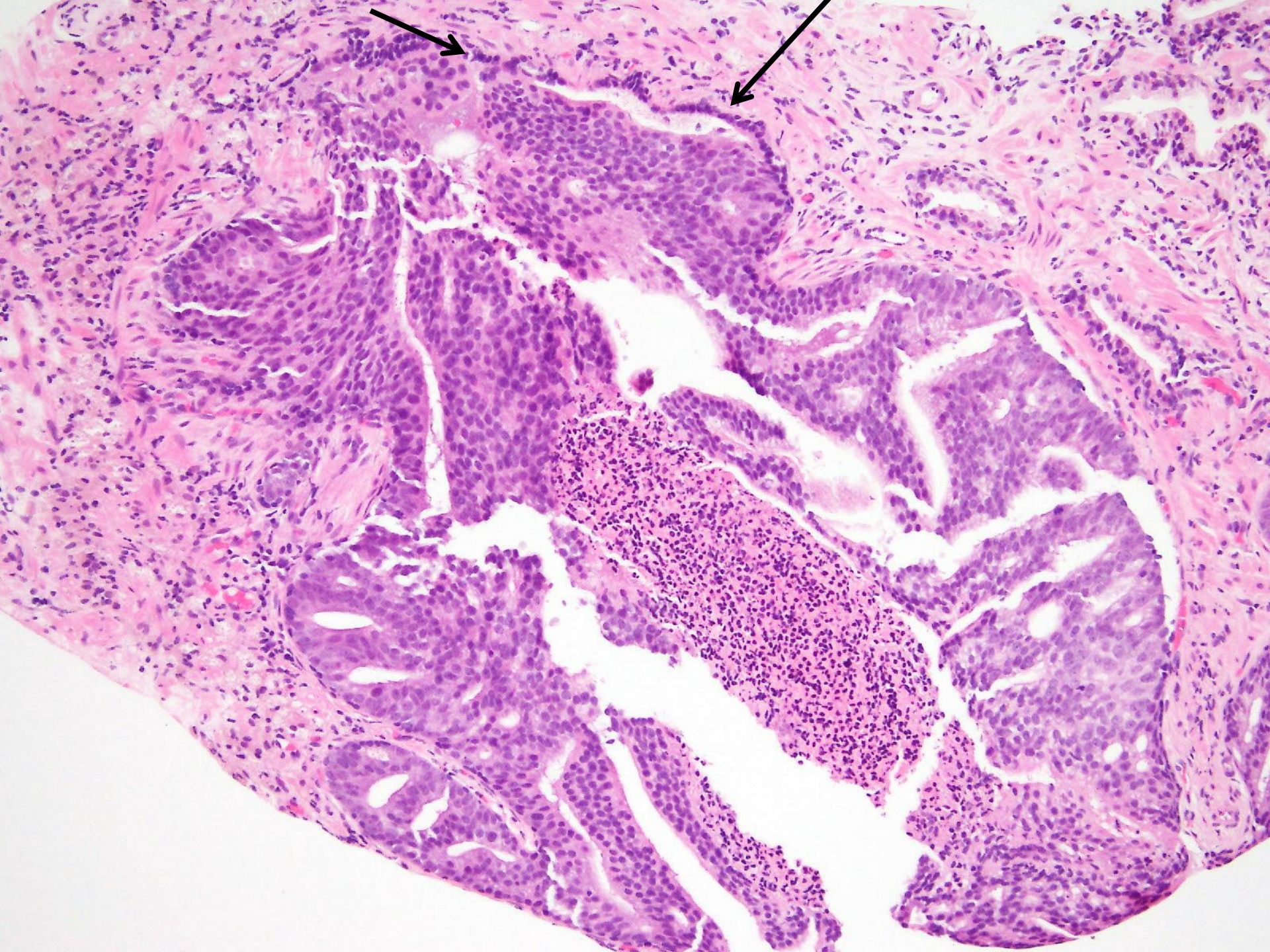
- Marked expansile growth of atypical cells
  - Large cribriform/solid architecture
  - occasionally spans the width of the core

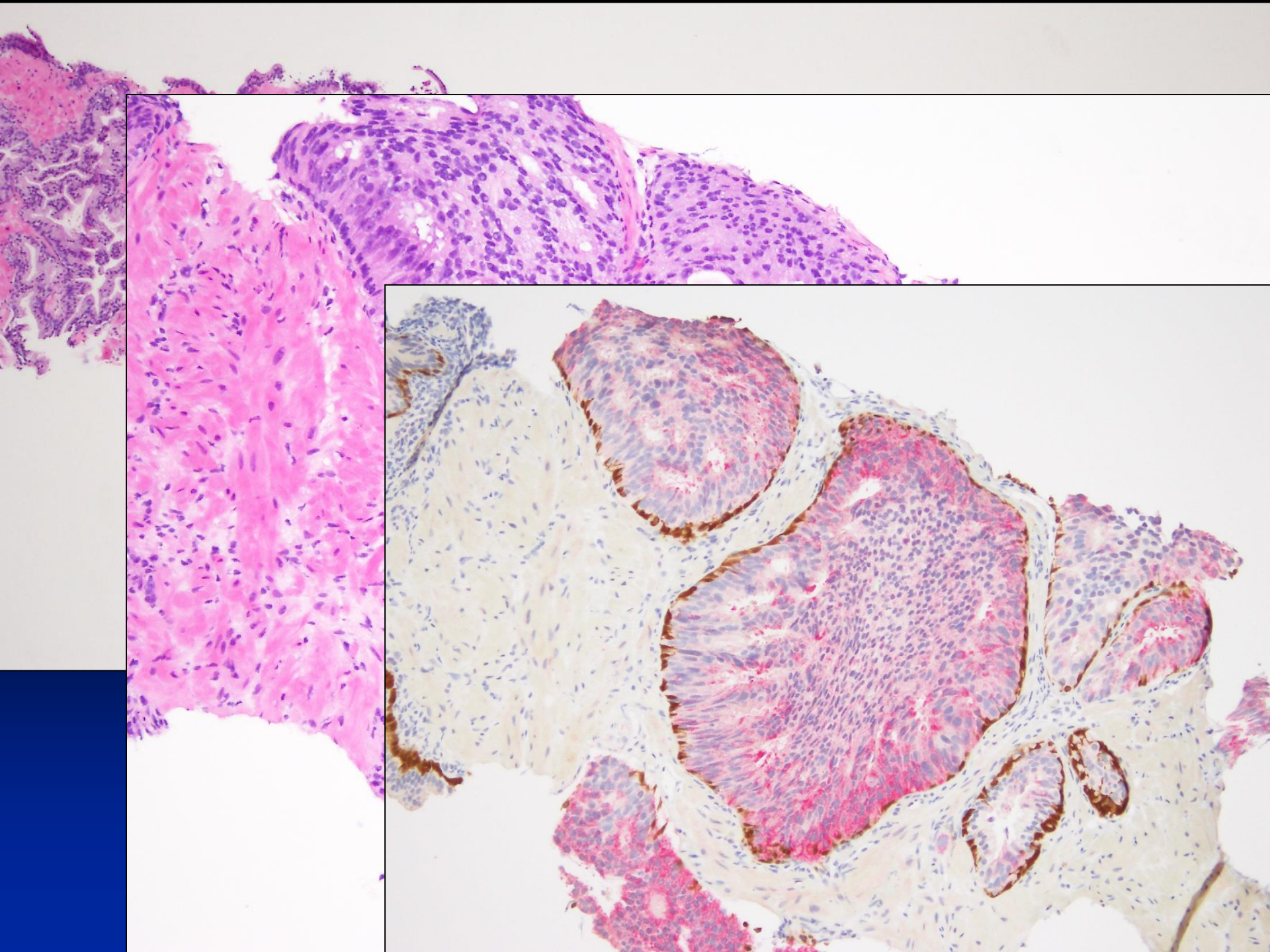
- Lesion within native prostate glands
  - Basal cell layer at least partially preserved
  - Complete or partial involvement of involved glands

- Prominent cytologic atypia, mitoses, comedonecrosis may be present

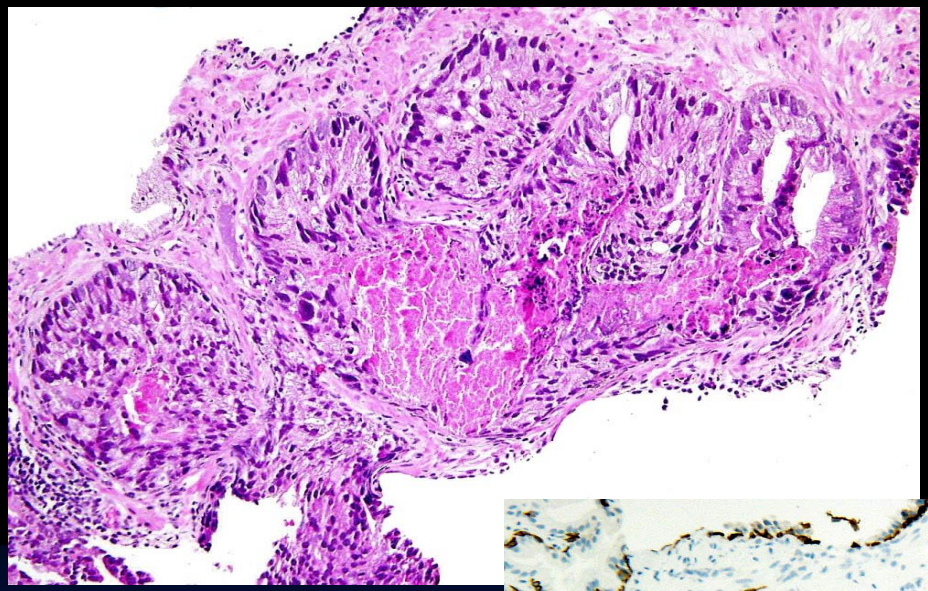


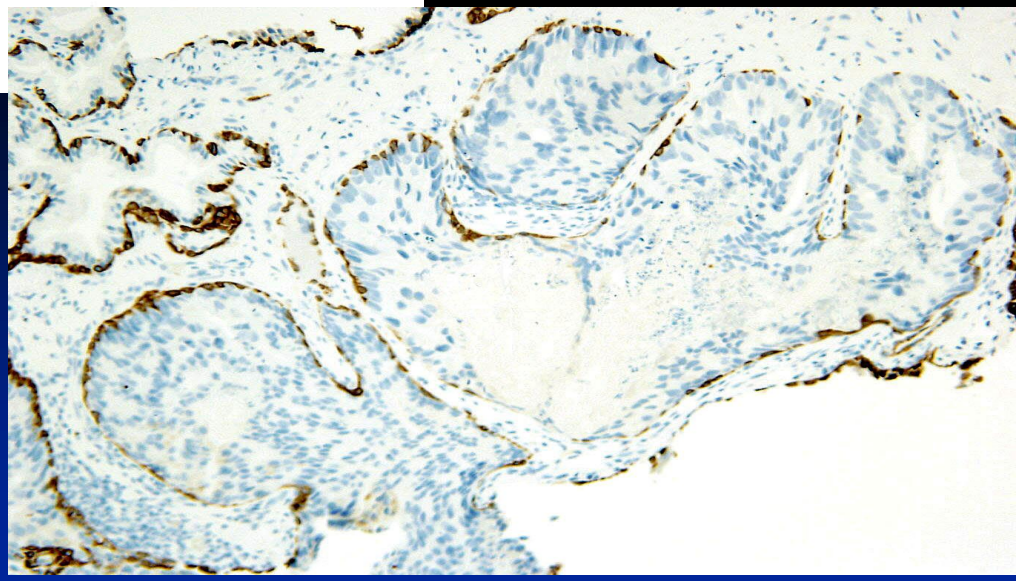






Grading of Intraductal Prostate cancer



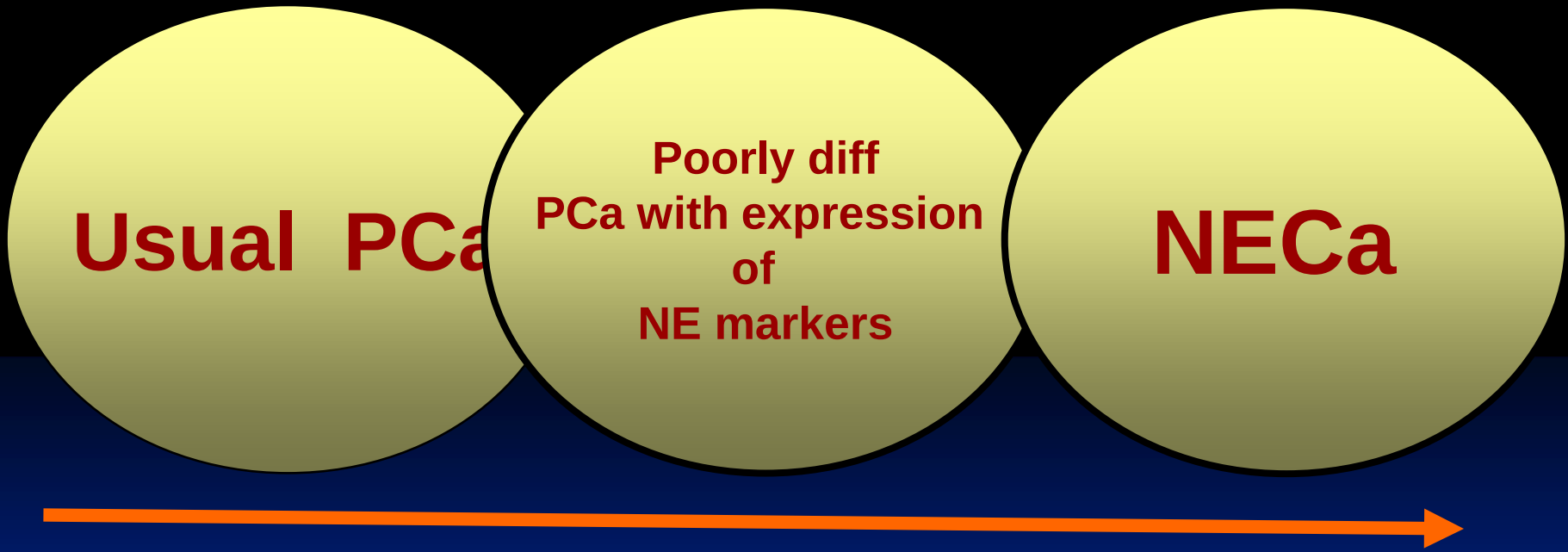


Pure Intraductal Carcinoma Should not be Graded

What is new in the WHO 2016:

- **Topic 3:** Classification of neuroendocrine differentiation in prostate

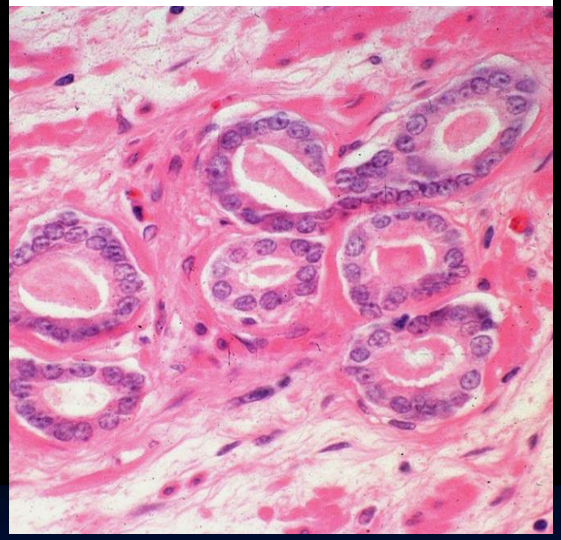
PCa with neuroendocrine differentiation



- How do we characterize lesions along this spectrum
- At what point in this continuum is the NE marker expression clinically significant ?

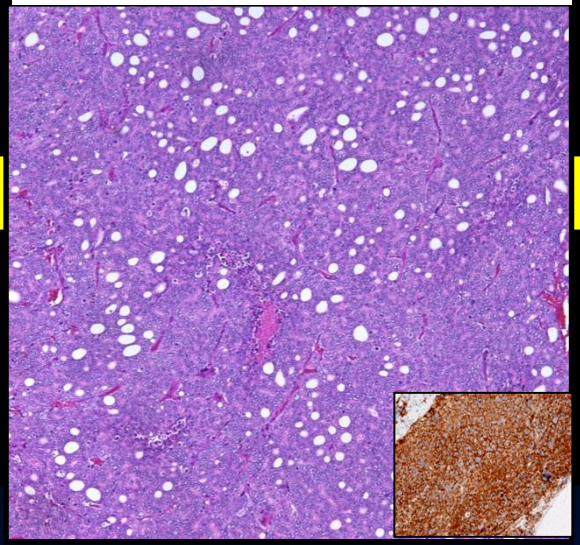
EMERGENCE OF NE PHENOTYPE WITH MOLECULAR CORRELATES

USUAL PCA



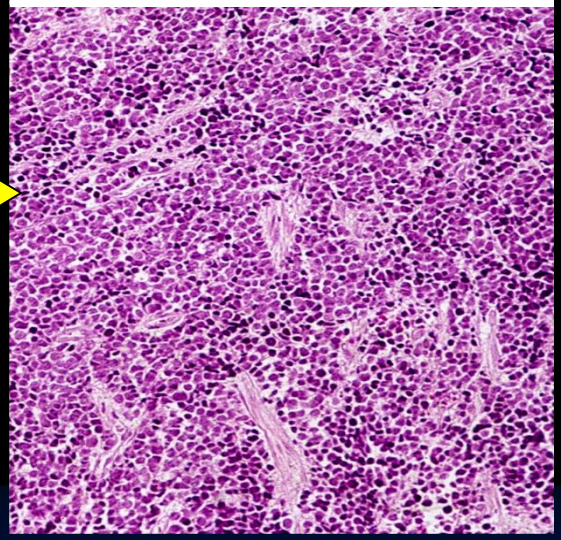
AR++
PSA++
REST++
MYC Amplif -/+
TMPRSS2- ERG -/+
PTEN Loss -/+

PCA with NED



AR -/+
PSA-/+
REST low
MYC Amplif -/+
TMPRSS2- ERG -/+
PTEN Loss -/+
↑anti-apoptotic factors & neuronal genes

SMALL CELL CA



AR -
PSA -
REST -
MYC Amplif -/+
AURKA Amplif -/+
Rb Loss -/+
↑neuronal genes

CLASSIFICATION OF TUMORS ALONG

Proposed Morphologic Classification of Prostate Cancer with Neuroendocrine Differentiation

Epstein*, Amin*, Beltran, Lotan Mosquera,

Reuter, Robinson, Troncoso, Rubin

**** co-first authors***

Am J Surg Pathol (2014)

PROSTATE CANCER FOUNDATION

Accelerating the world's most promising research

Proposed Morphologic Classification of Prostate Cancer with Neuroendocrine Differentiation

Epstein , Amin, Beltran, Lotan Mosquera, Reuter, Robinson, Troncoso, Rubin

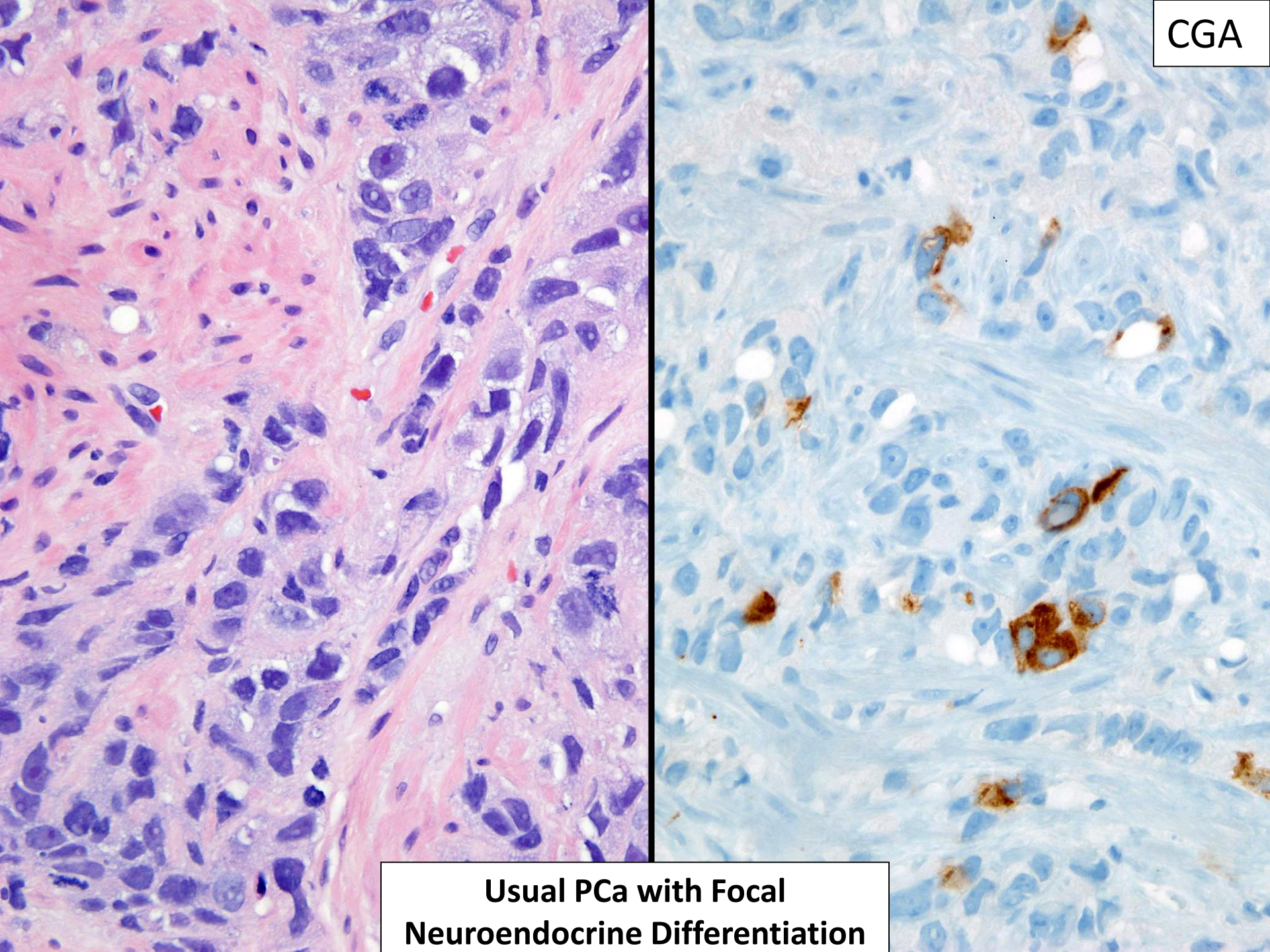
Am J Surg Pathol (2014)

PCF 2013 Classification for PCa with Neuroendocrine Differentiation

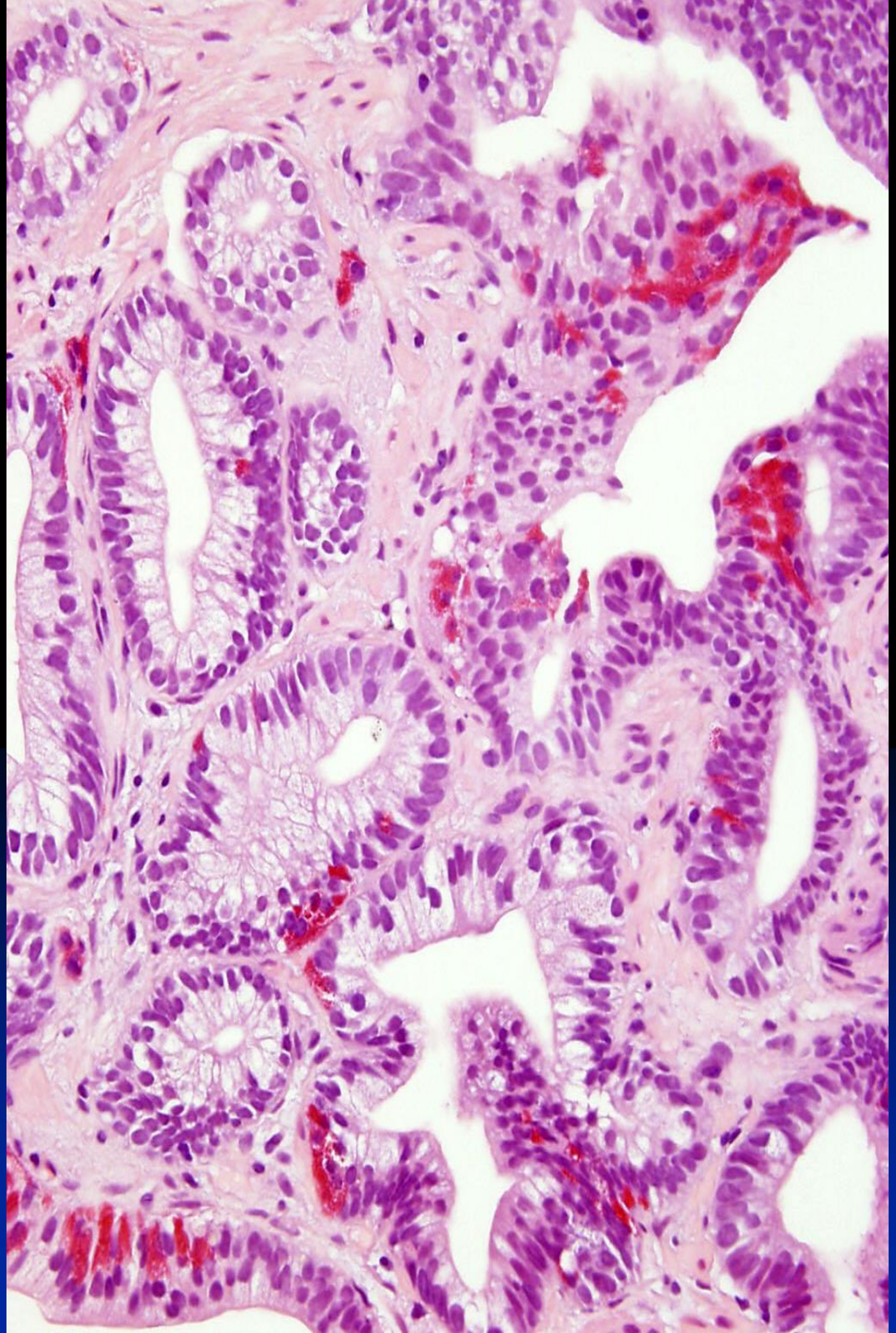
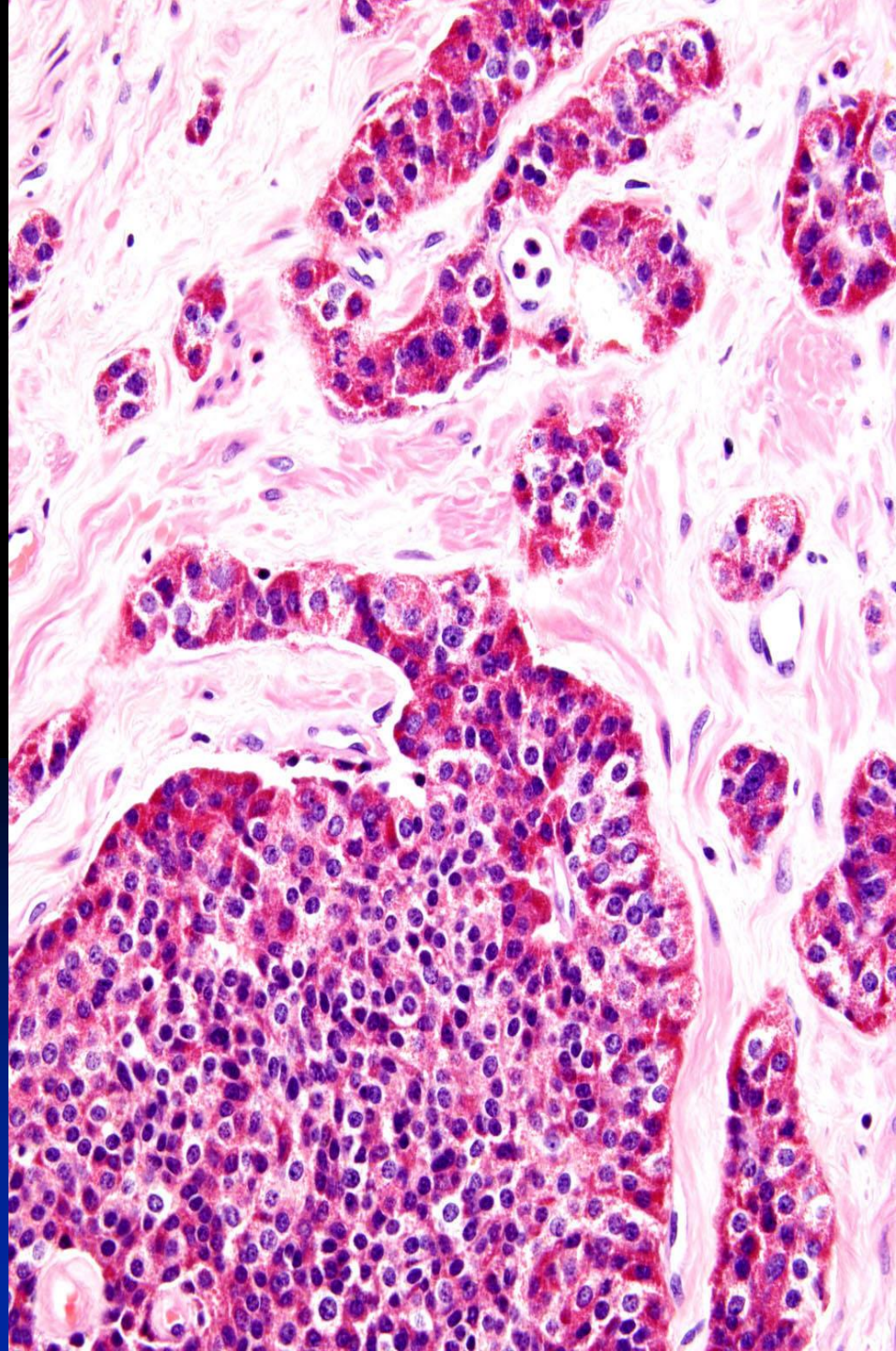
- **Usual PCa with Neuroendocrine (NE) Differentiation**
- **PCa with Paneth Cell NE Differentiation**
- **Carcinoid Tumor**
- **Small Cell NE Carcinoma**
- **Large Cell NE Carcinoma (LCNEC)**
- **Mixed (Small or Large Cell) NE Carcinoma - Acinar Adenocarcinoma**
- ***PCa with overlap features of small cell and acinar adenocarcinoma – Provisional Category***
- ***Castration resistant PCa with small cell carcinoma-like clinical features – Clinical Category***

Usual PCa with NE Differentiation

- **Definition:** Morphologically typical, usual acinar or ductal adenocarcinoma of the prostate in which NE differentiation is demonstrated by immunohistochemistry alone

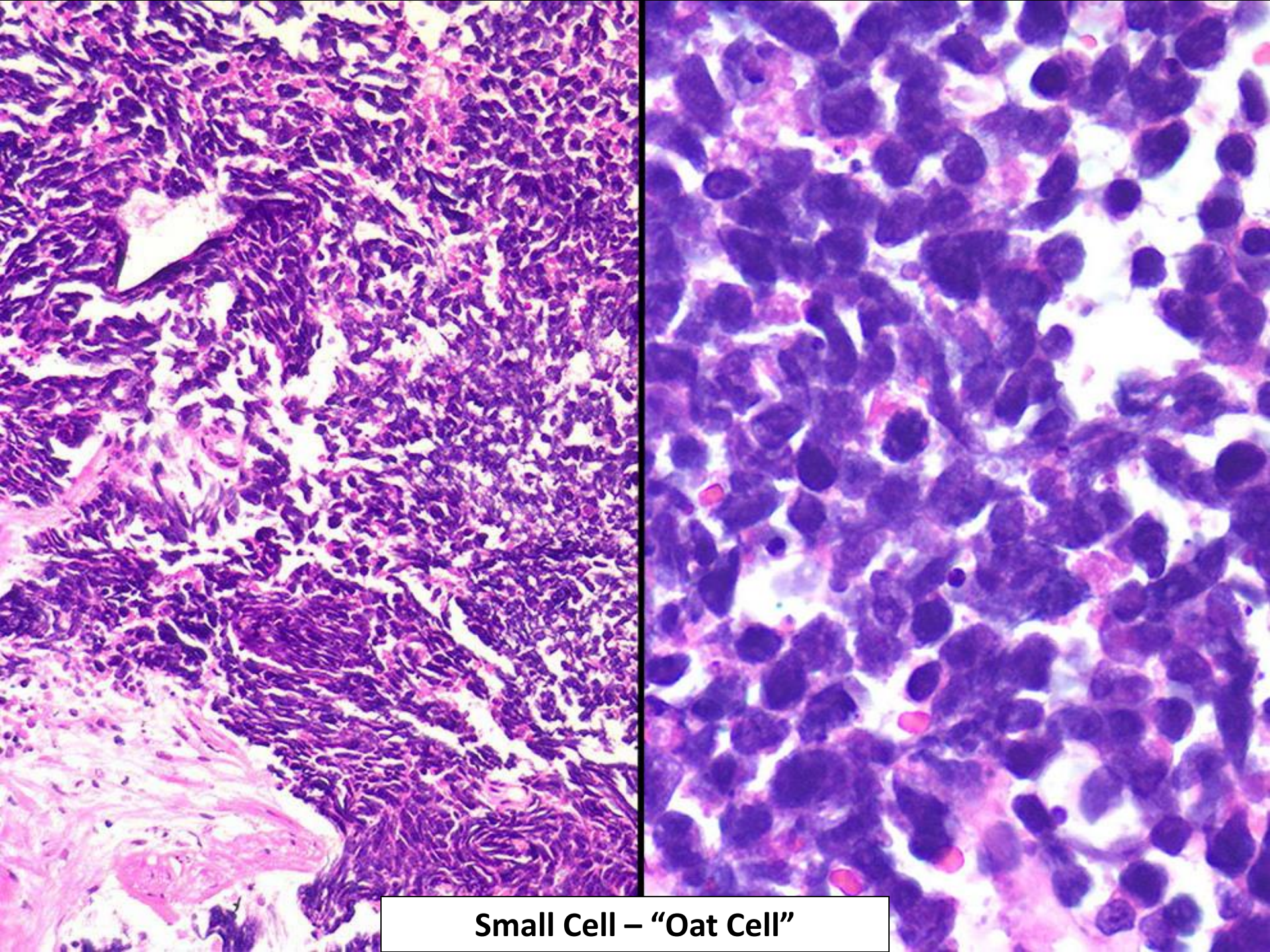


Usual PCa with Focal Neuroendocrine Differentiation

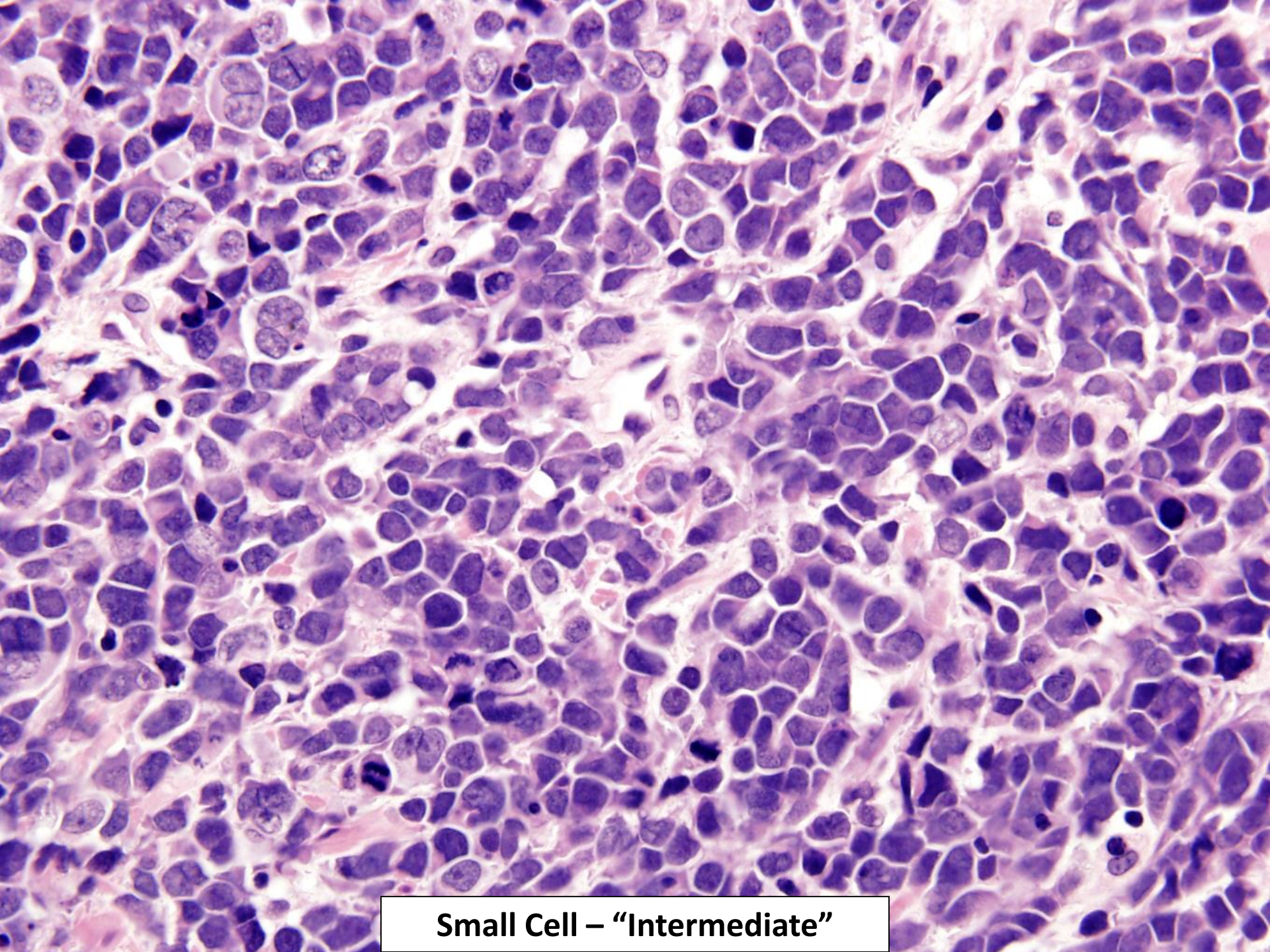



Carcinoid Tumor - WDNET

- **Definition: A well differentiated NE tumor occurring primarily in the prostate gland, showing the classic morphology of carcinoid tumor at other sites such as the lung, but which is not closely associated with usual prostate carcinoma or which does not arise from the urethra or extend from the bladder**
- **In younger patients, screening for stigmata of MEN may be considered**

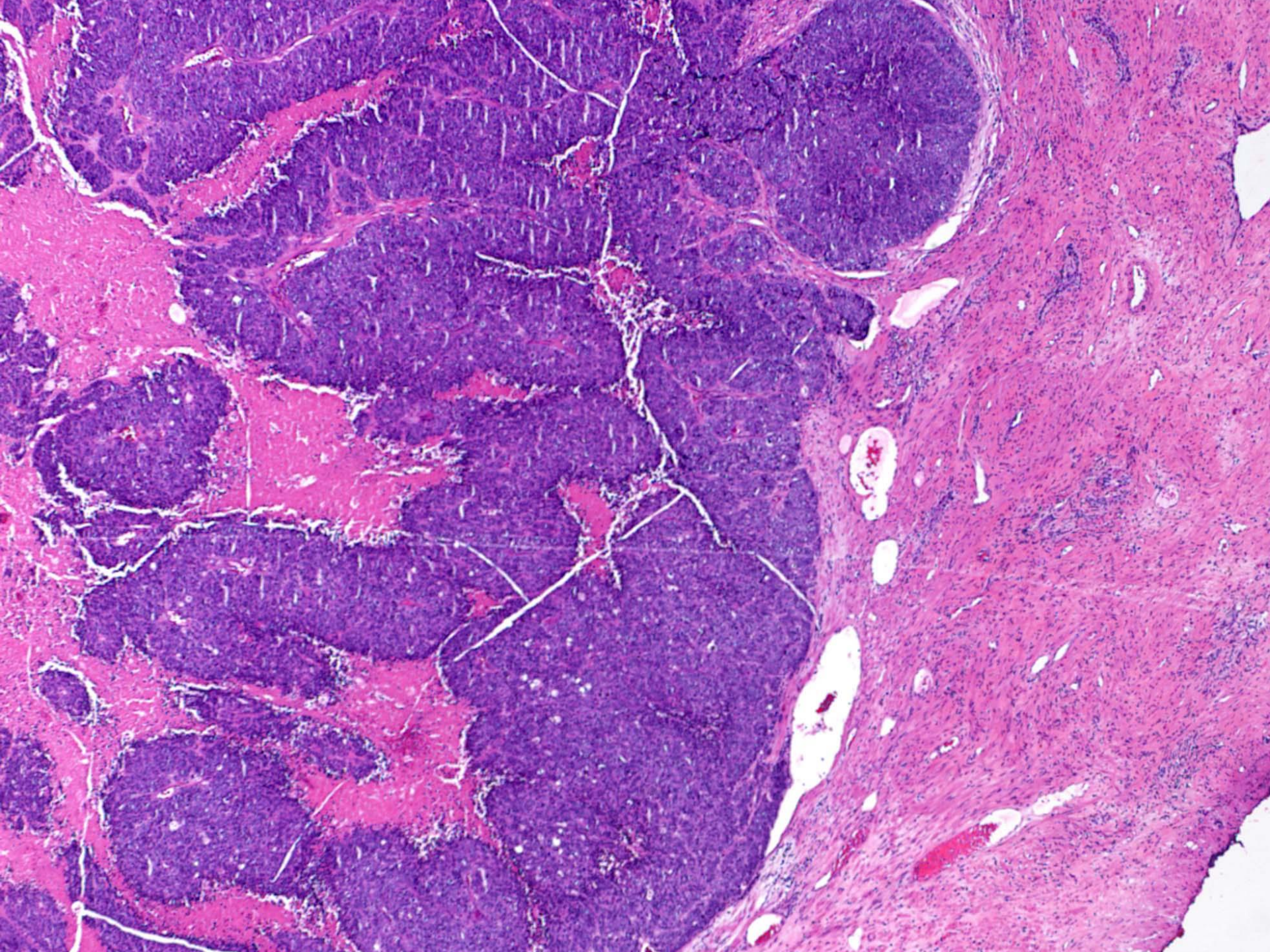


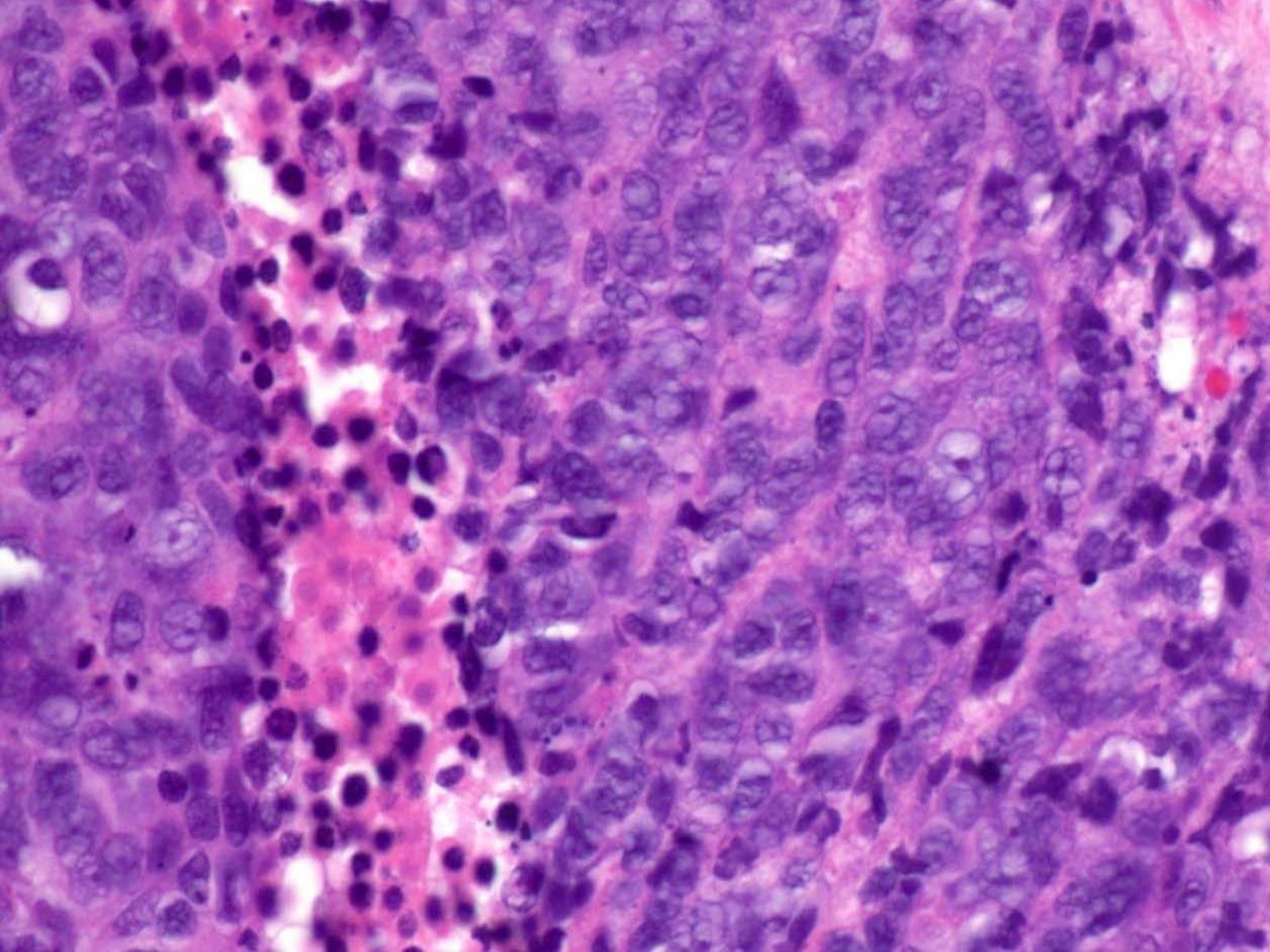
Small Cell – “Oat Cell”


Small Cell – “Intermediate”

Large Cell NE Carcinoma

- **Definition:** High grade tumor with
  - NE architecture (organoid nests, palisading, rosettes, trabeculae, sheets)
  - Non-small cell NE carcinoma cytology (prominent nucleoli, vesicular clumpy chromatin and/or large cell size and abundant cytoplasm)
  - Expression of at least one neuroendocrine marker (excluding neuron specific enolase)





KIDNEY CANCER

What is new in the WHO 2016:

- **Topic 4:**

  Classification of renal tumors

Will be covered tomorrow.

What is new in the WHO 2016:

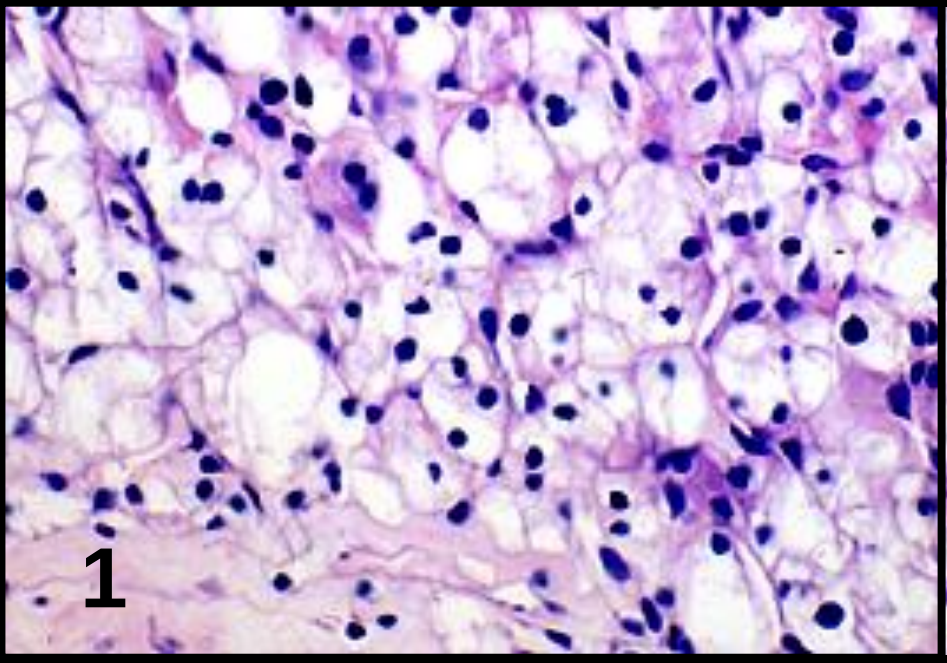
- **Topic 5:**

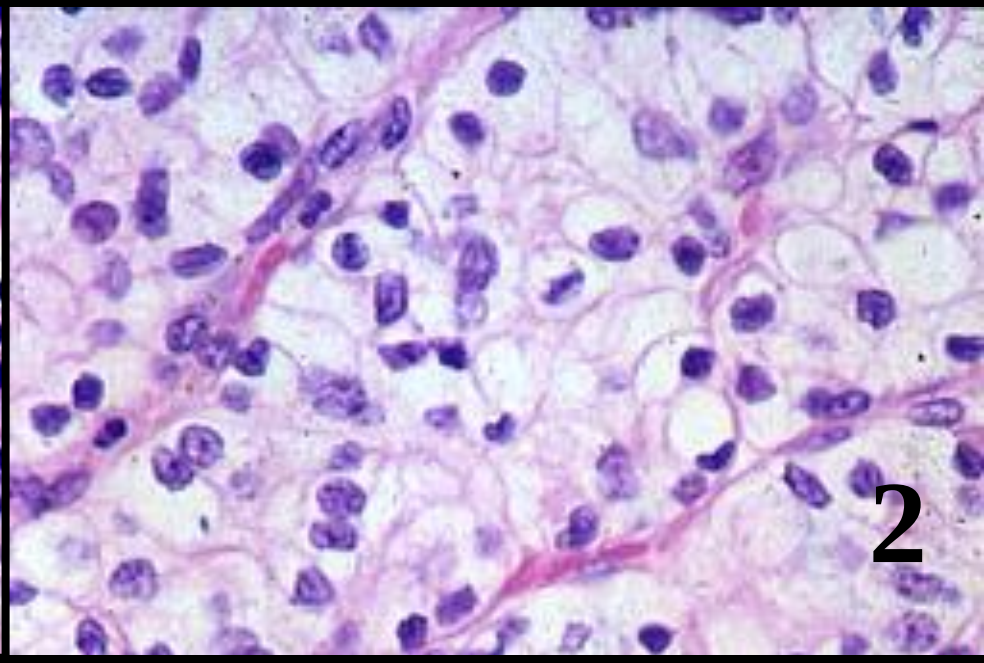
  Grading of renal tumors

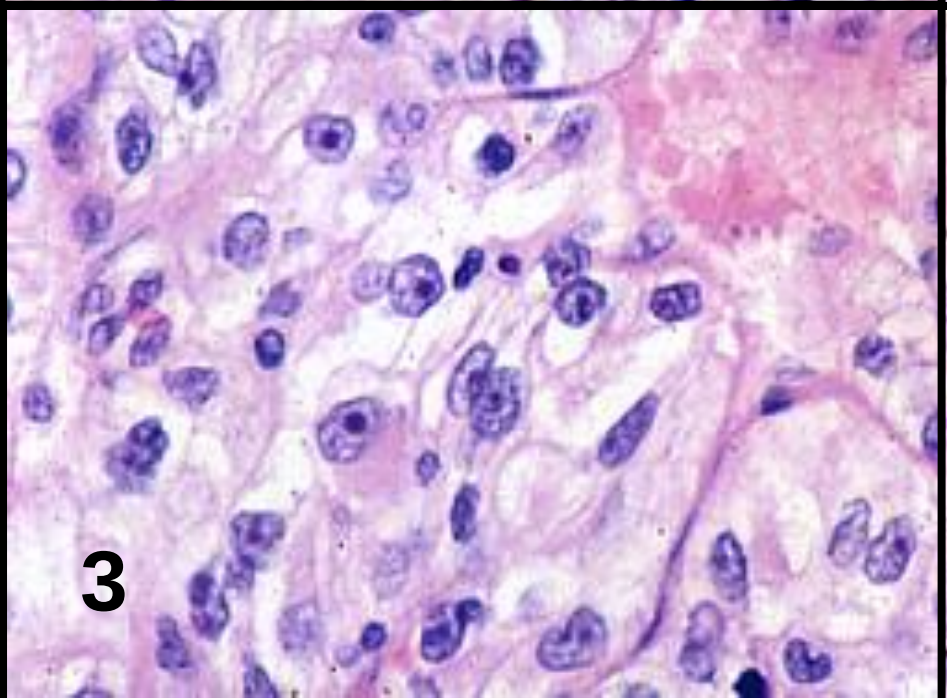
GRADING OF RCC (2016)

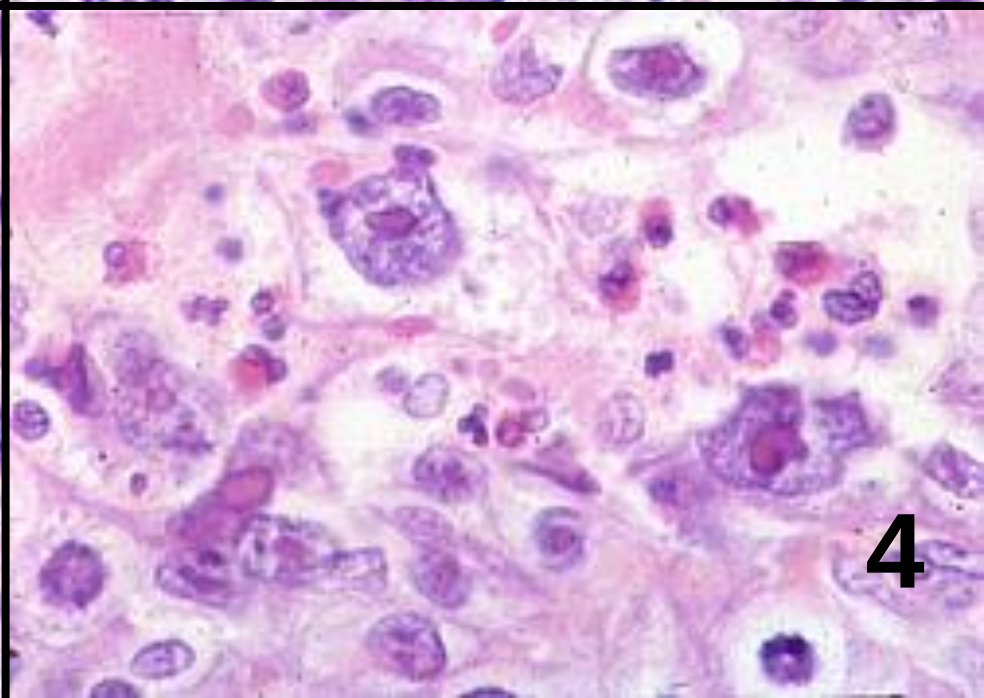
- WHO/ISUP SYSTEM – modified from Fuhrman system
- To factor in necrosis for clear cell RCC
- Recommended to be used in all types of RCC though not validated beyond clear cell RCC

RCC - FUHRMAN GRADING

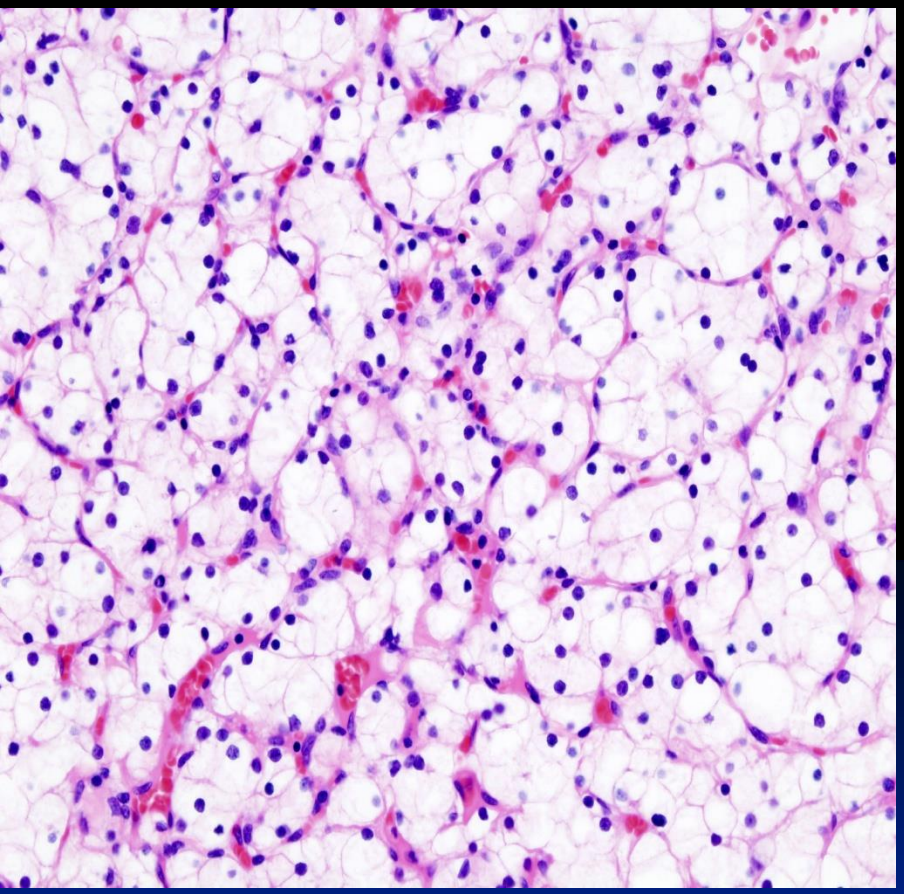


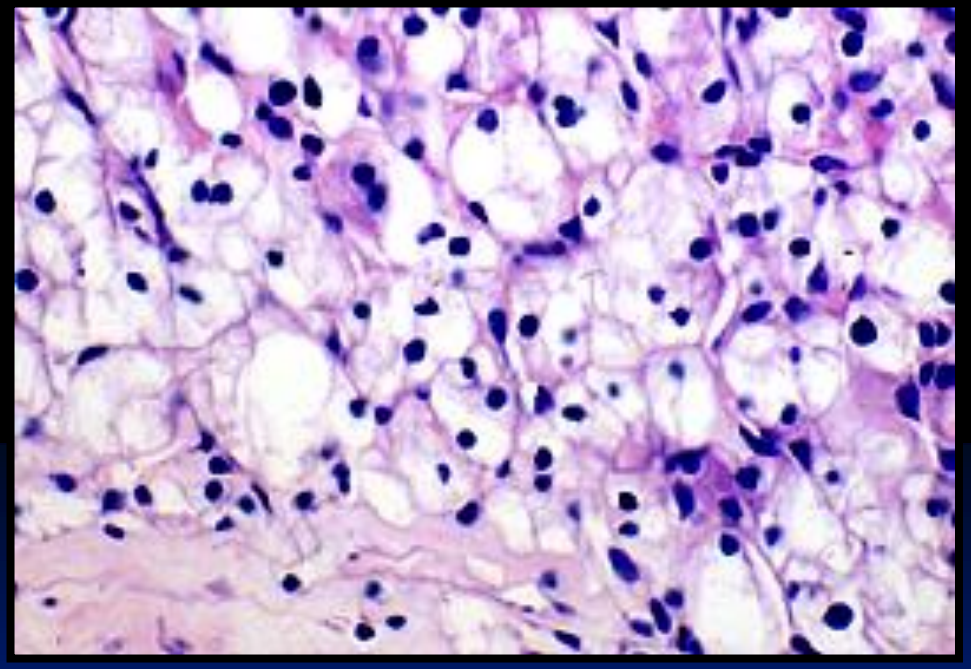






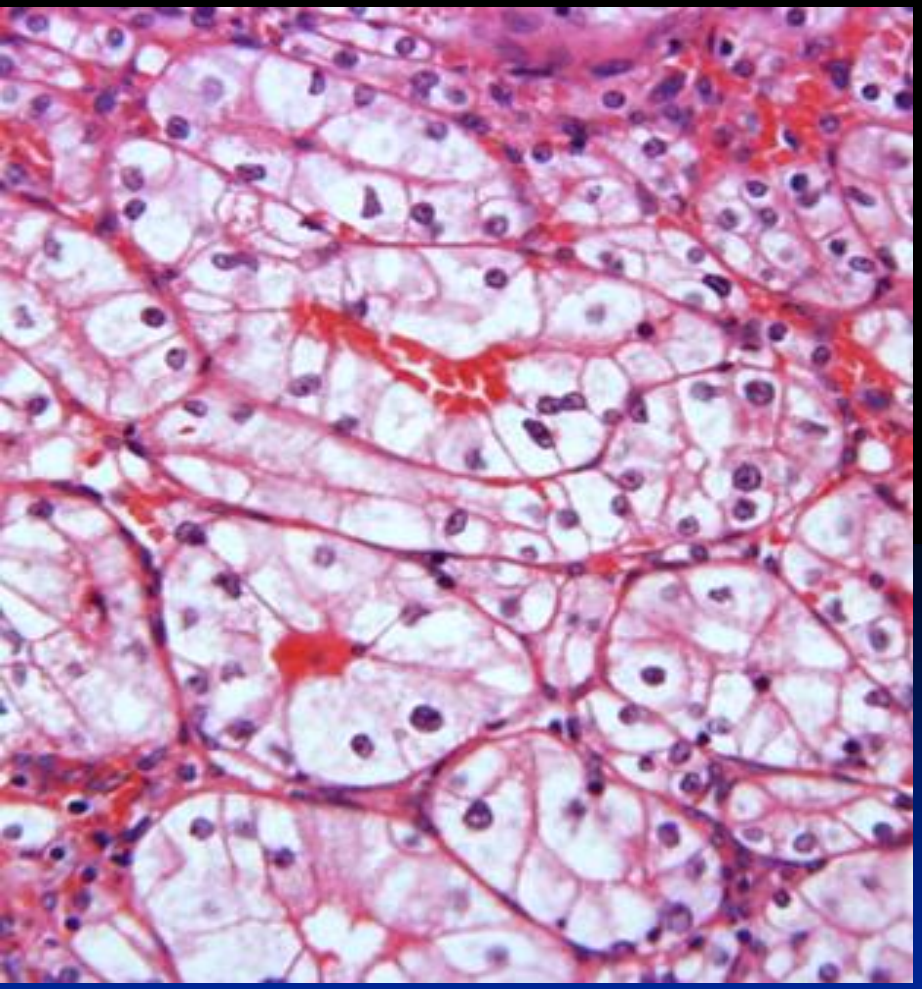
WHO/ISUP grade 1

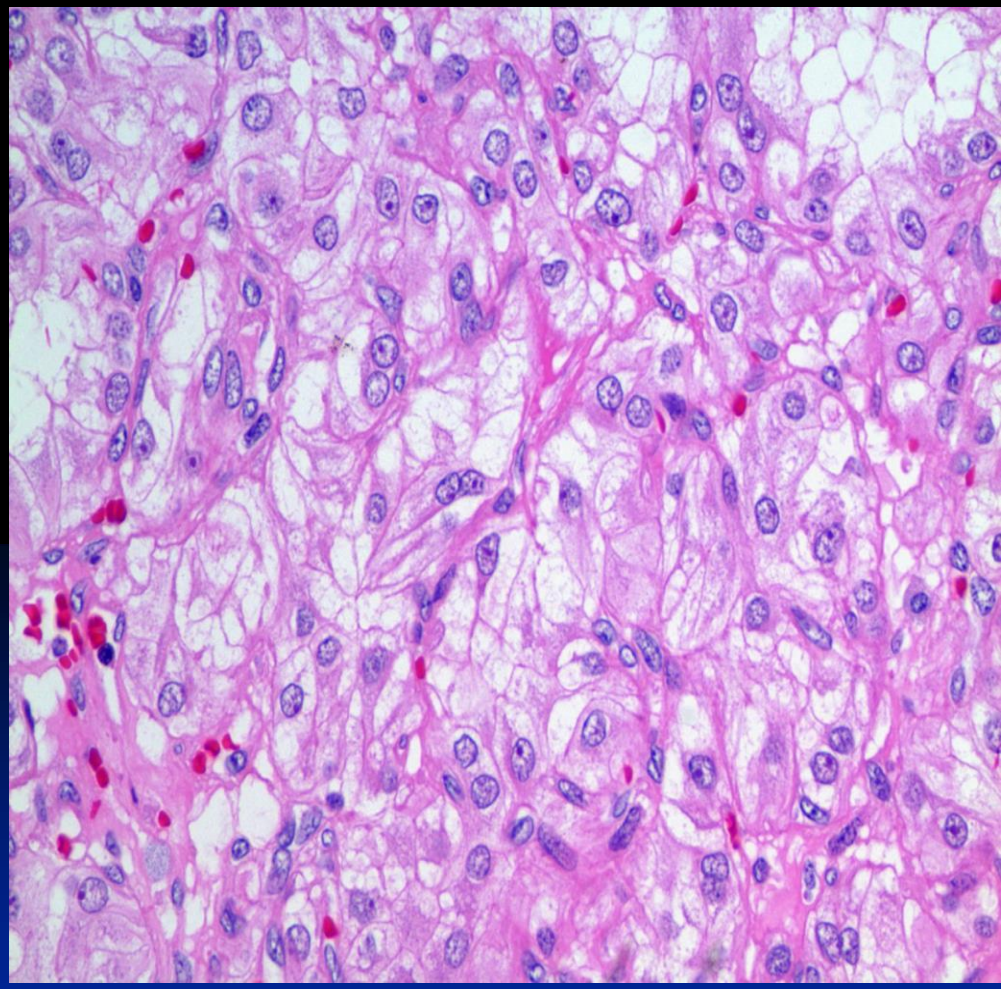




Nucleoli are inconspicuous or absent at low and high power

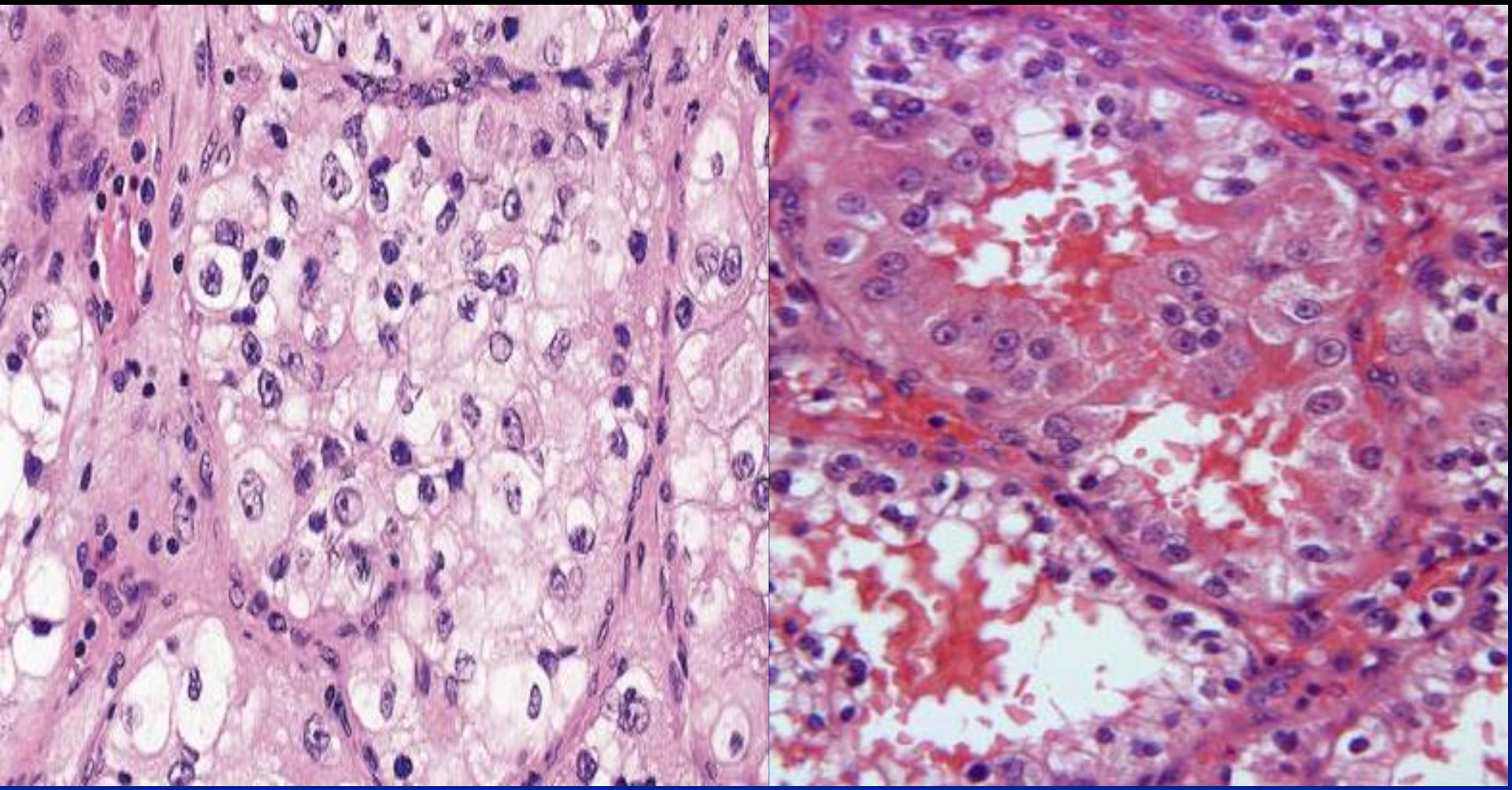
WHO/ISUP grade 2





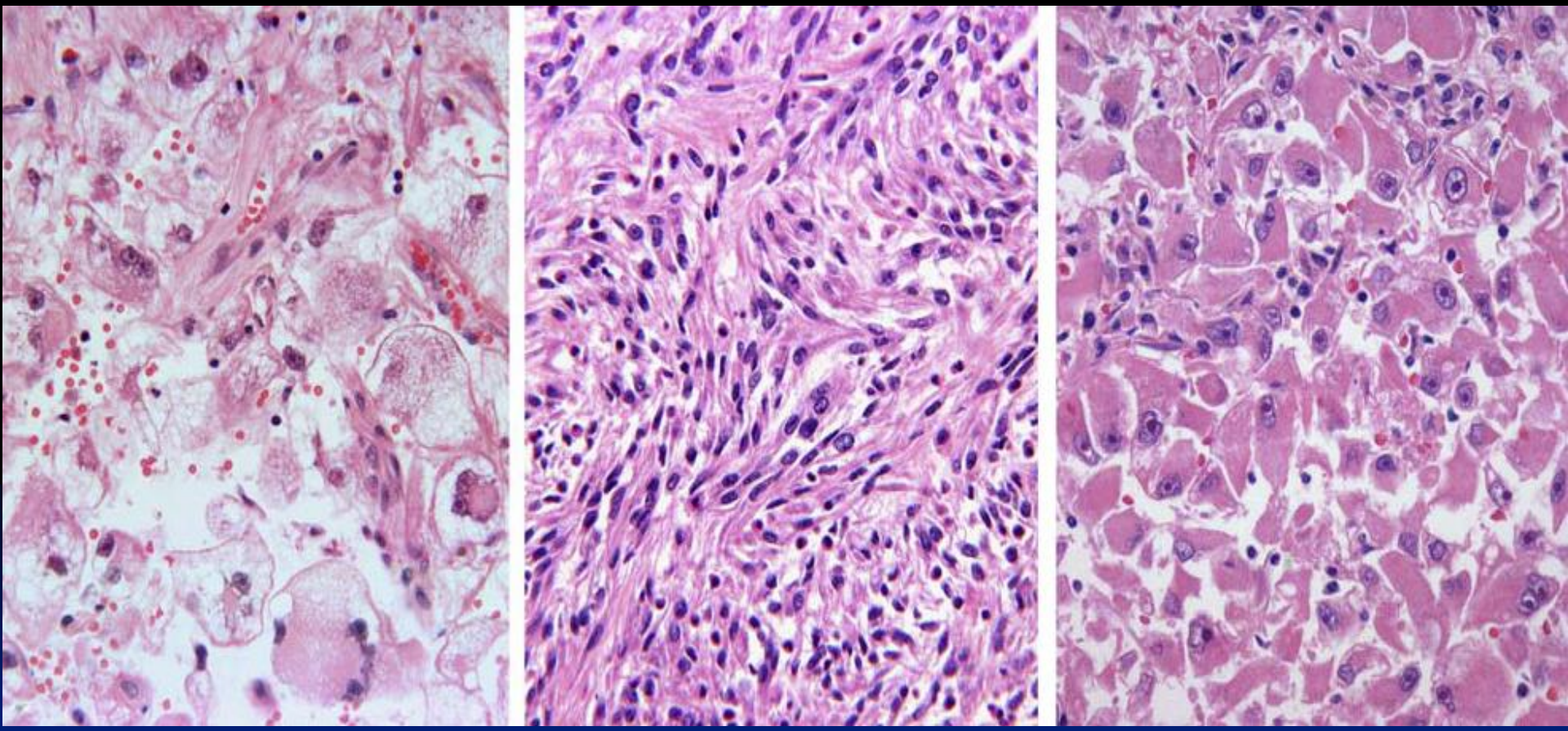
Grade 2: nucleoli are clearly visible at high-power magnification but are not prominent.

WHO/ISUP grade 3



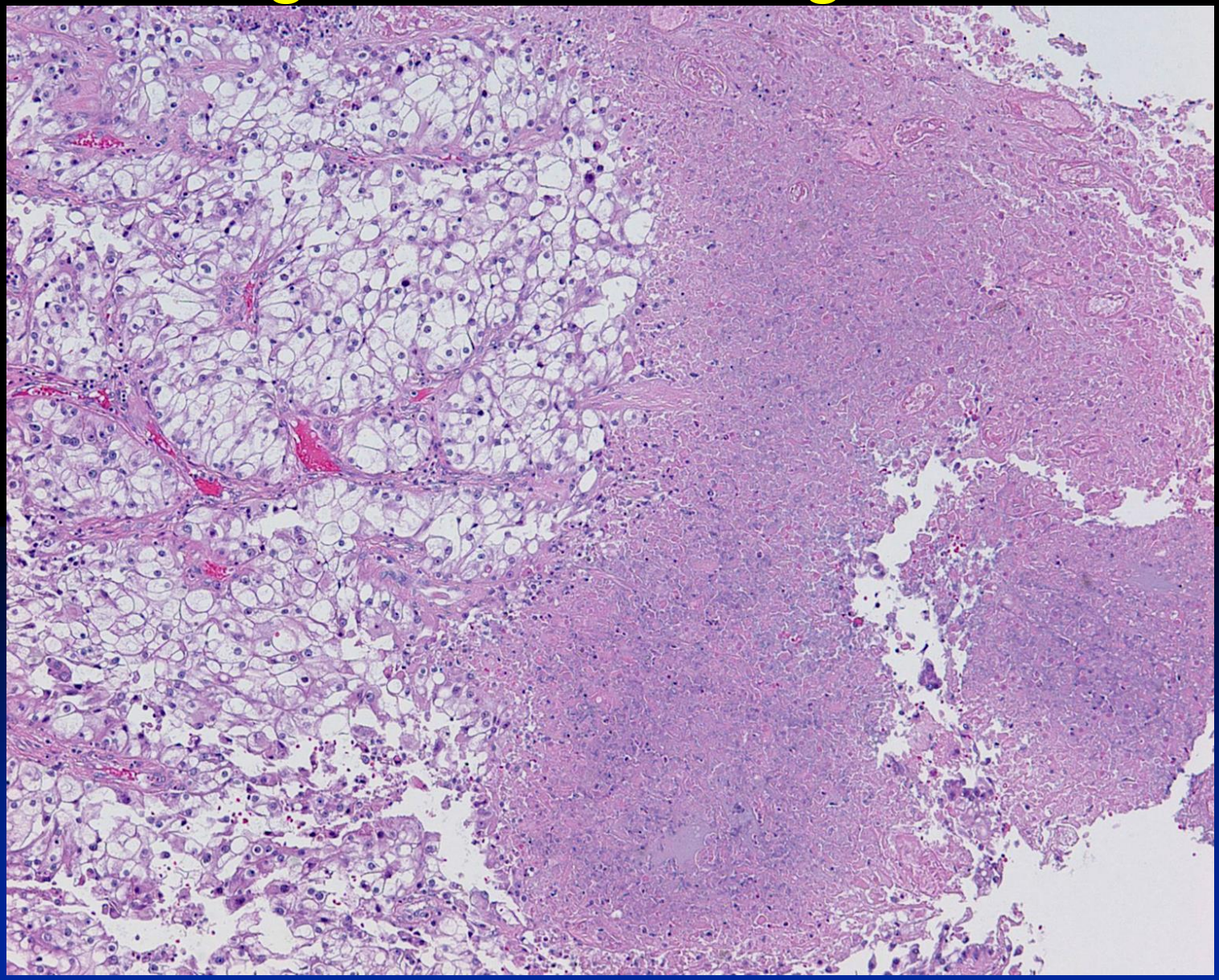
Grade 3: nucleoli are prominent and are easily visualized at low-power magnification

WHO/ISUP grade 4

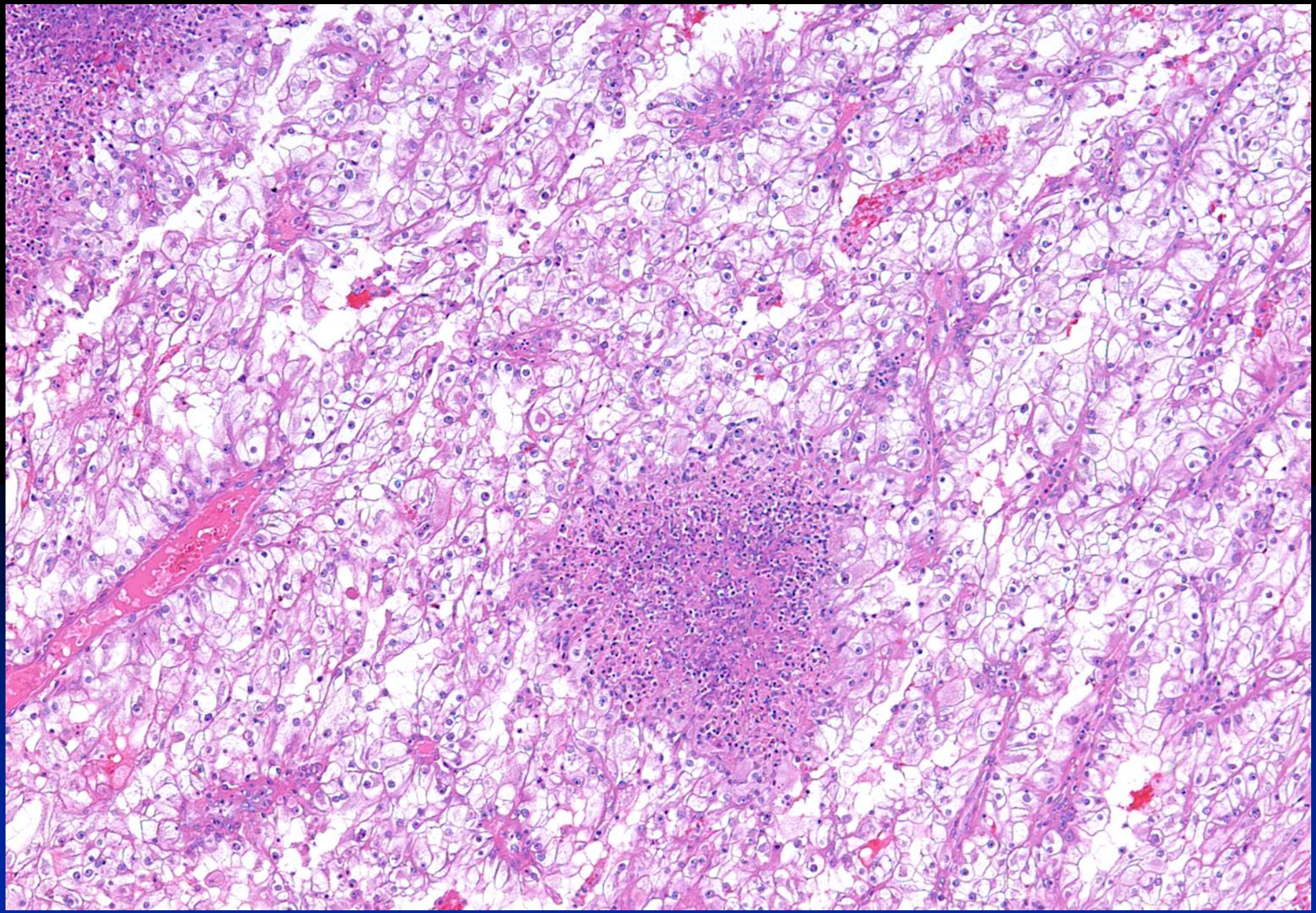


Grade 4: presence of tumor giant cells and/or marked nuclear pleomorphism; sarcomatoid carcinoma; carcinoma showing rhabdoid differentiation

WHO/ISUP grade 3 with coagulative necrosis



ISUP grade 3 with necrosis



NEW IN BLADDER: WHO 2016

VI. Flat lesions –

- Atypia urothelial proliferation of unknown signficance

VII. Classification of variants – large nested, signet ring/plasmacytoid, chordoid

VIII. Urachal carcinoma including low grade cystic tumors

IX. Emerging Molecular subtypes

CLASSIFICATION OF BLADDER EPITHELIAL TUMORS

FLAT LESIONS

PAPILLARY LESIONS

INVERTED LESIONS

INVASIVE LESIONS

THE WHO (2016) / ISUP CLASSIFICATION OF UROTHELIAL (TRANSITIONAL CELL) NEOPLASMS OF THE URINARY BLADDER

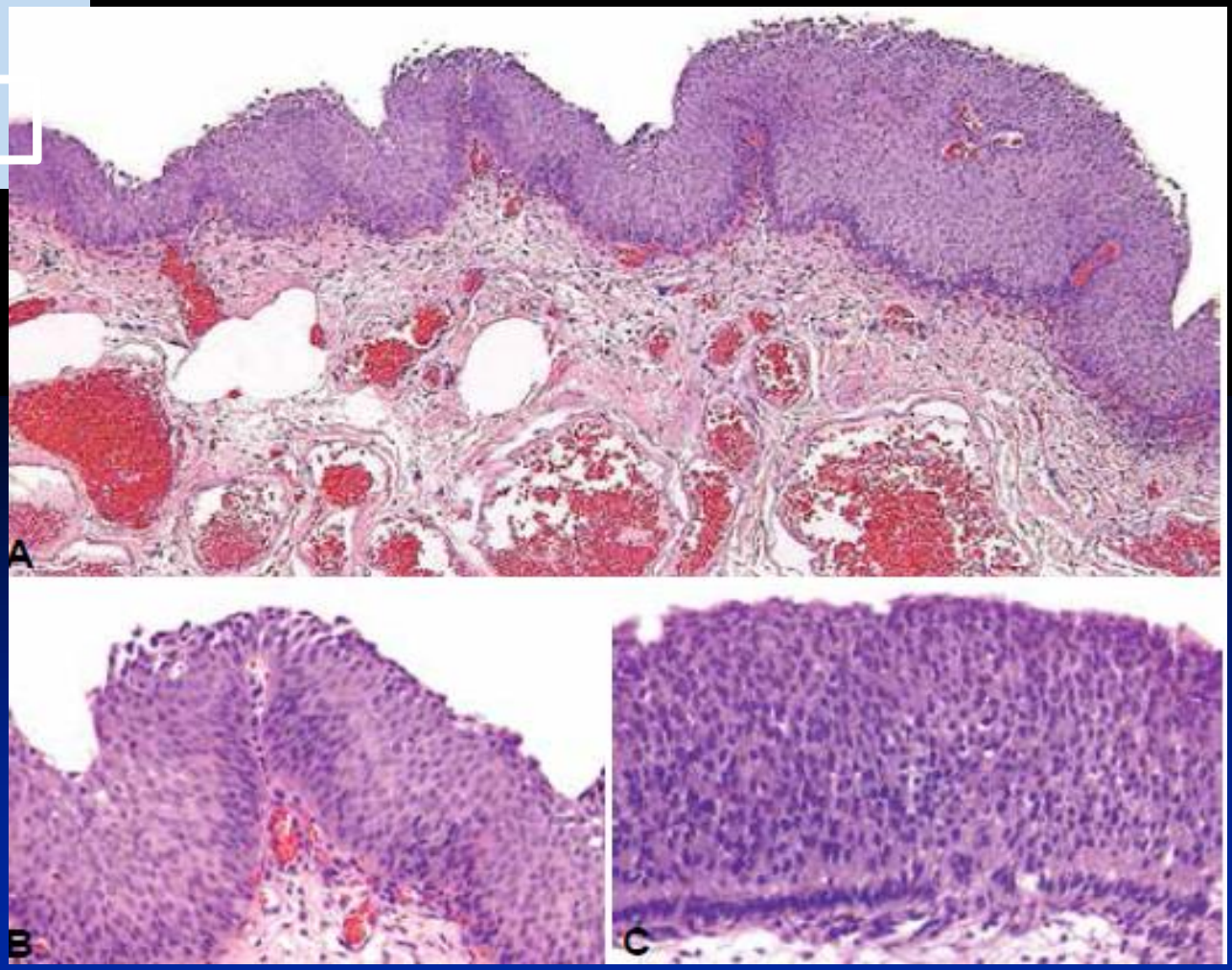
- Normal
- Urothelial proliferation of uncertain malignant potential
- Flat lesions with atypia
  - Dysplasia
  - CIS (high-grade intraurothelial neoplasia)

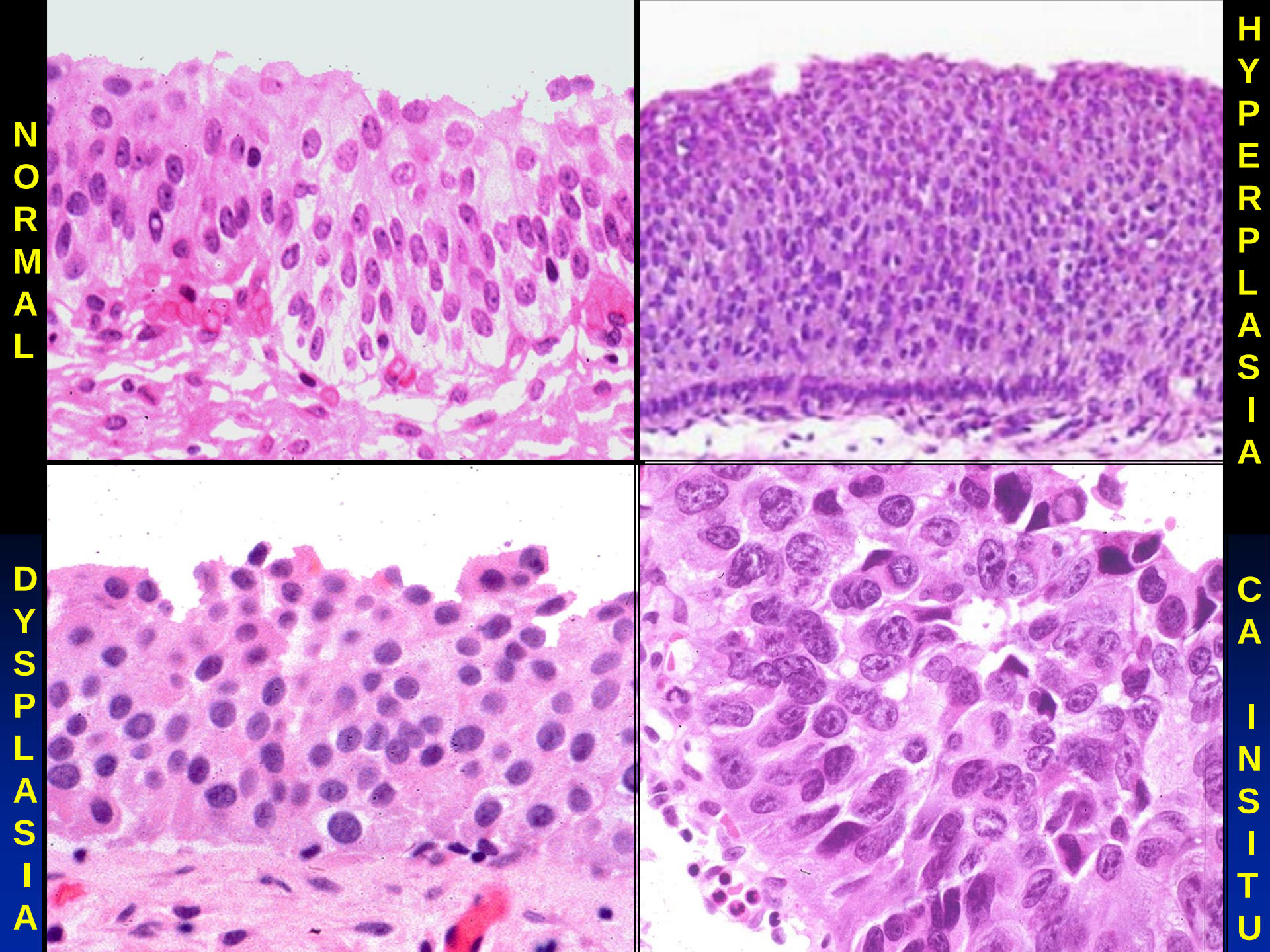
Non-invasive urothelial carcinoma
Urothelial carcinoma in situ
Papillary urothelial carcinoma, low grade
Papillary urothelial carcinoma, high grade
Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma
Inverted urothelial papilloma
Urothelial hyperplasia
Urothelial dysplasia/atypia

Urothelial proliferation of uncertain malignant potential

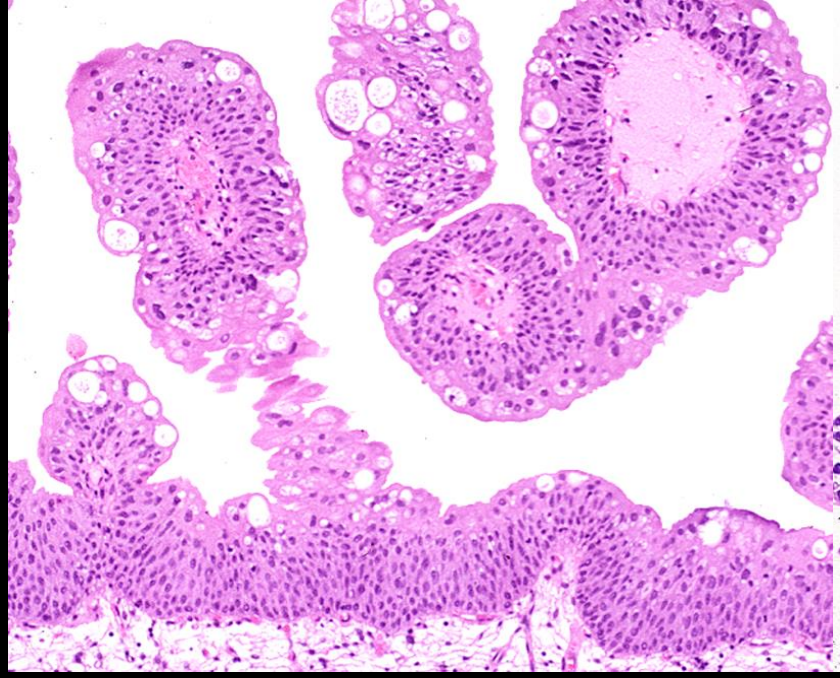
Definition
Urothelial proliferation of uncertain malignant potential is a marked thickening of the urothelium with no or minimal cytological atypia and no true papillary formation.

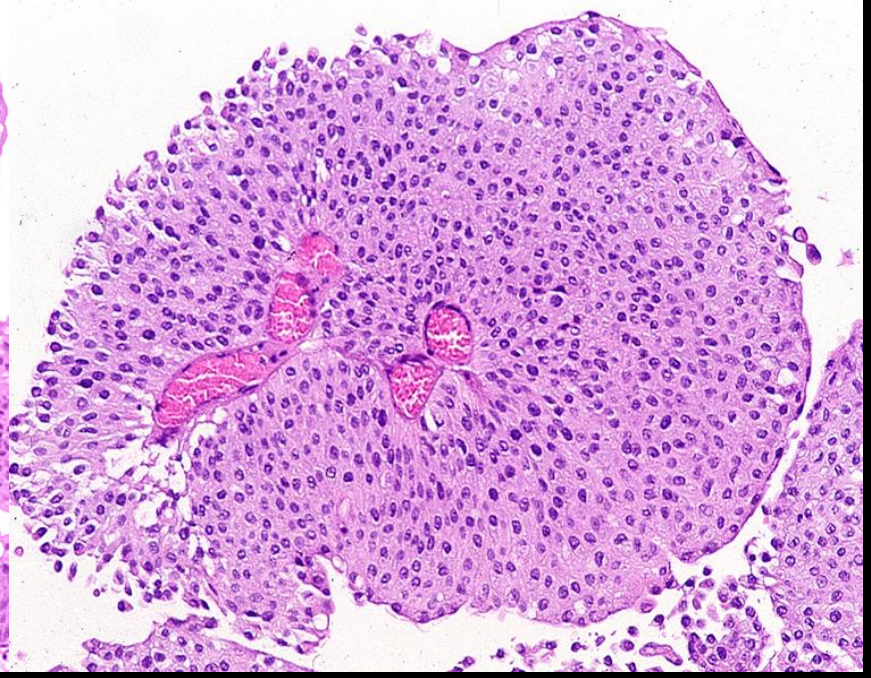
Synonyms
Papillary and flat urothelial hyperplasia (obsolete)




NORMAL
HYPERPLASIA
DYSPLASIA
CA IN SITU

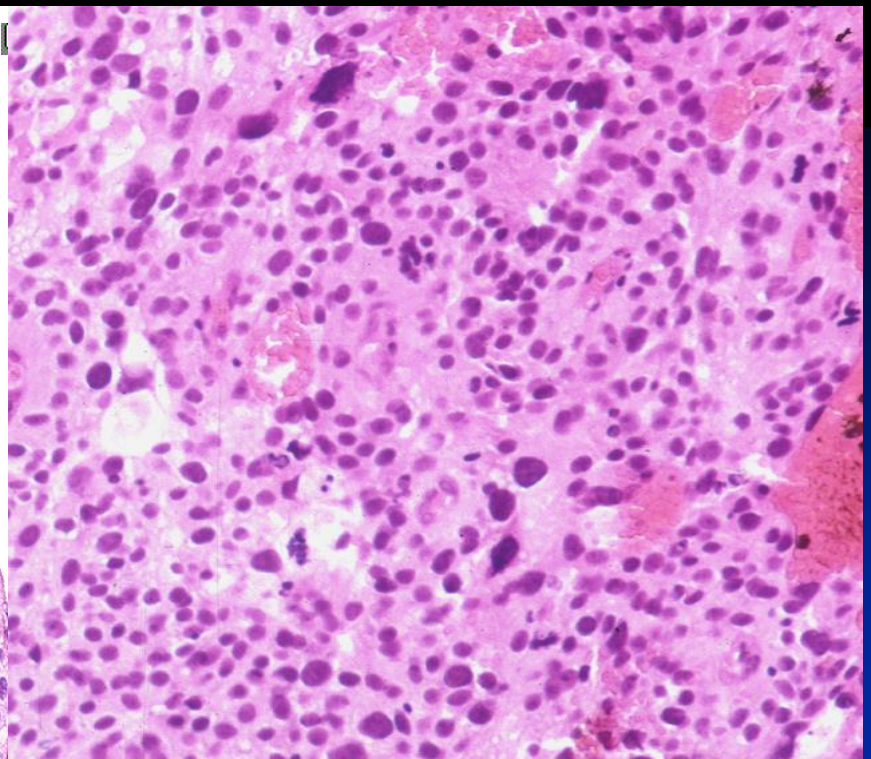
PAPILOMA





LMP

LOW GRADE



HIGH GRADE

Update for the practicing pathologist: The International Consultation On Urologic Disease-European association of urology consultation on bladder cancer

Mahul B Amin[1,27], Steven C Smith[1,27,28], Victor E Reuter[2], Jonathan I Epstein[3], David J Grignon[4], Donna E Hansel[5], Oscar Lin[2], Jesse K McKenney[6], Rodolfo Montironi[7], Gladell P Paner[8], Hikmat A Al-Ahmadie[2], Ferran Algaba[9], Syed Ali[3], Isabel Alvarado-Cabrero[10], Lukas Bubendorf[11], Liang Cheng[4], John C Cheville[12], Glen Kristiansen[13], Richard J Cote[14], Brett Delahunt[15], John N Eble[4], Elizabeth M Genega[16], Christian Gulmann[17], Arndt Hartmann[18], Cord Langner[19], Antonio Lopez-Beltran[20], Cristina Magi-Galluzzi[6], Jorda Merce[14], George J Netto[3], Esther Oliva[21], Priya Rao[22], Jae Y Ro[23], John R Srigley[24], Satish K Tickoo[2], Toyonori Tsuzuki[25], Saleem A Umar[14], Theo Van der Kwast[26], Robert H Young[21] and Mark S Soloway[14]

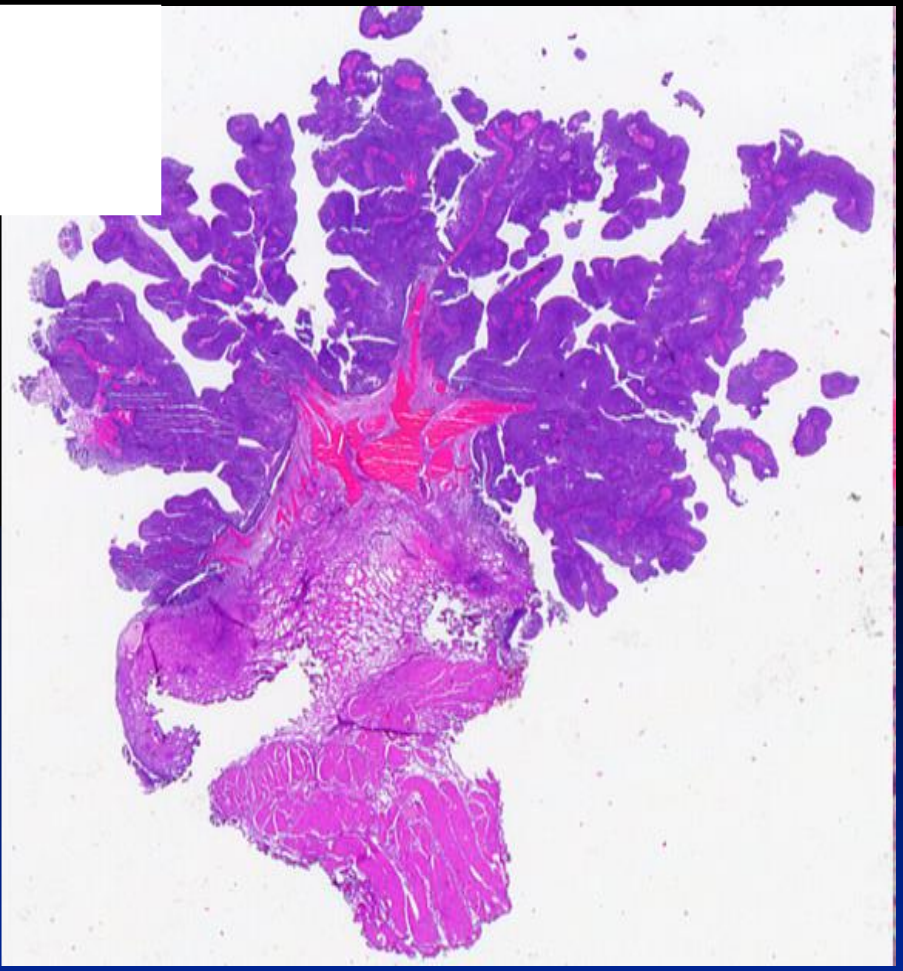
Modern Pathology:2014

Grading of Non-Invasive Urothelial Neoplasms of the Bladder

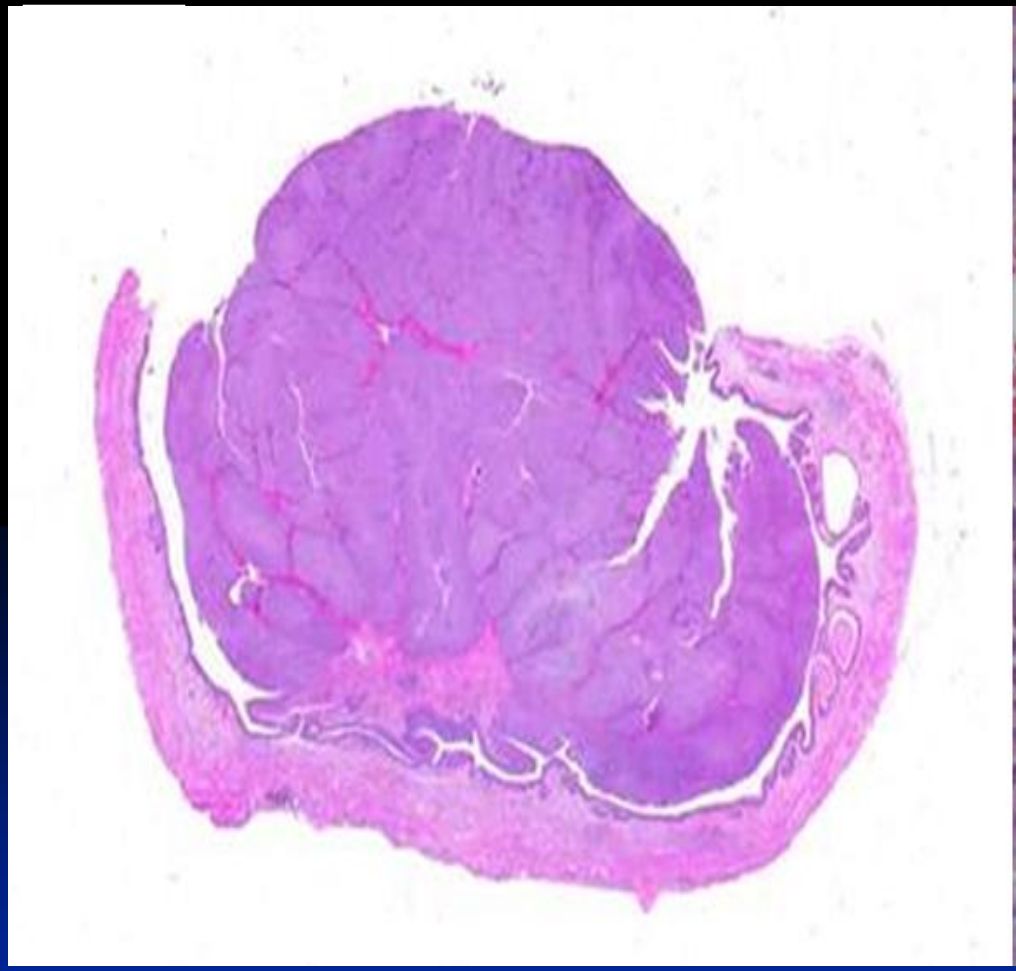
Flat Lesions	Papillary Tumors	Inverted Tumors
Normal	Urothelial Papilloma	Inverted Papilloma
Urothelial Hyperplasia	PUNLMP	Inverted PUNLMP
Urothelial Dysplasia	Papillary UCa, Low Grade	Inverted Papillary UCa, Low grade
Urothelial CIS	Papillary UCa, High Grade	Inverted Papillary UCa, High Grade

- PUNLMP, papillary urothelial neoplasm of low malignant potential

Courtesy R. Montironi, Italy



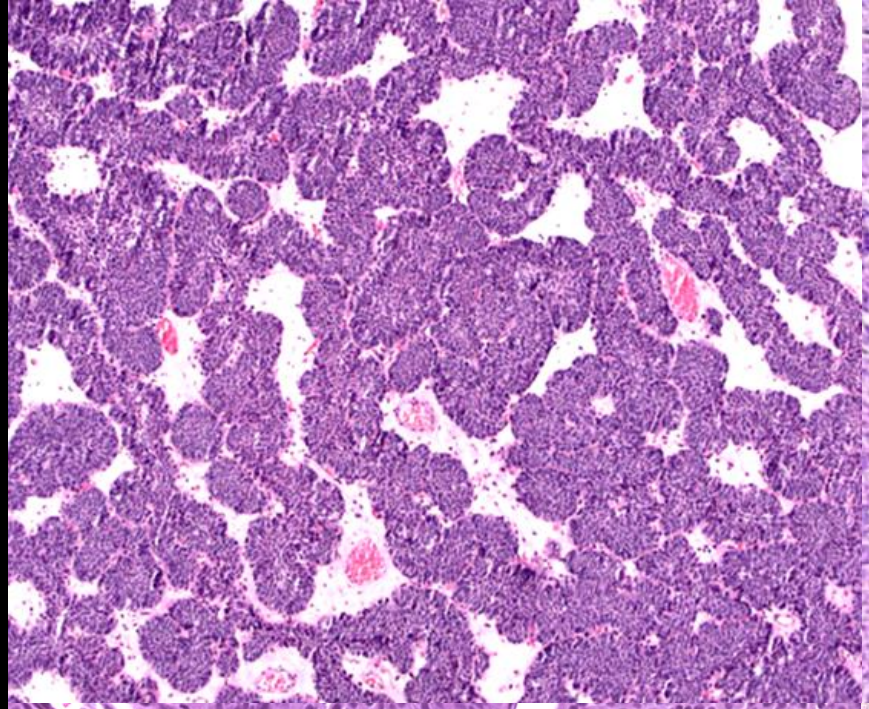
Exophytic tumor



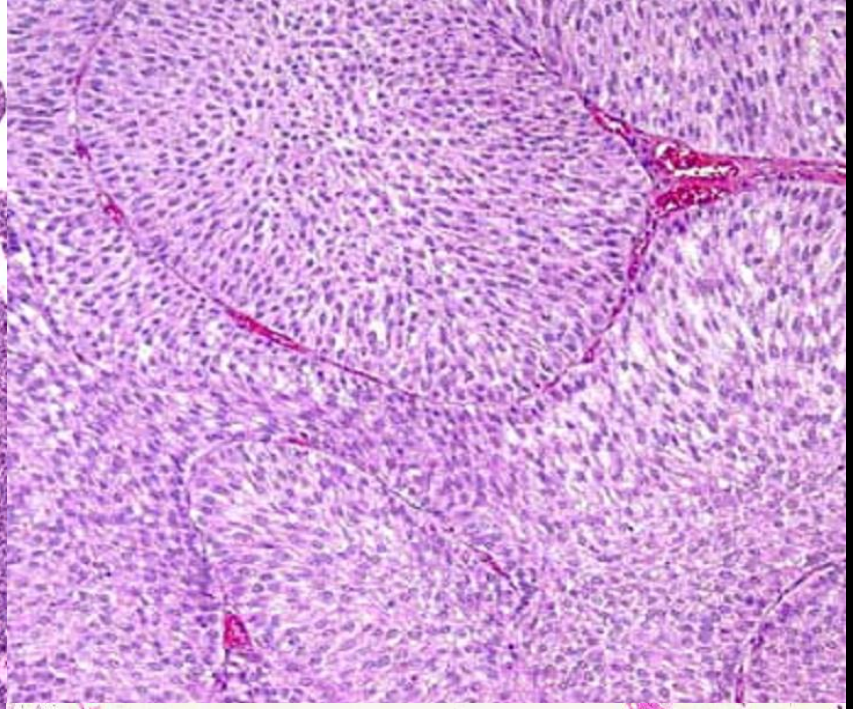
Inverted tumor

CLASSIFICATION OF BLADDER LESIONS WITH INVERTED GROWTH PATTERN

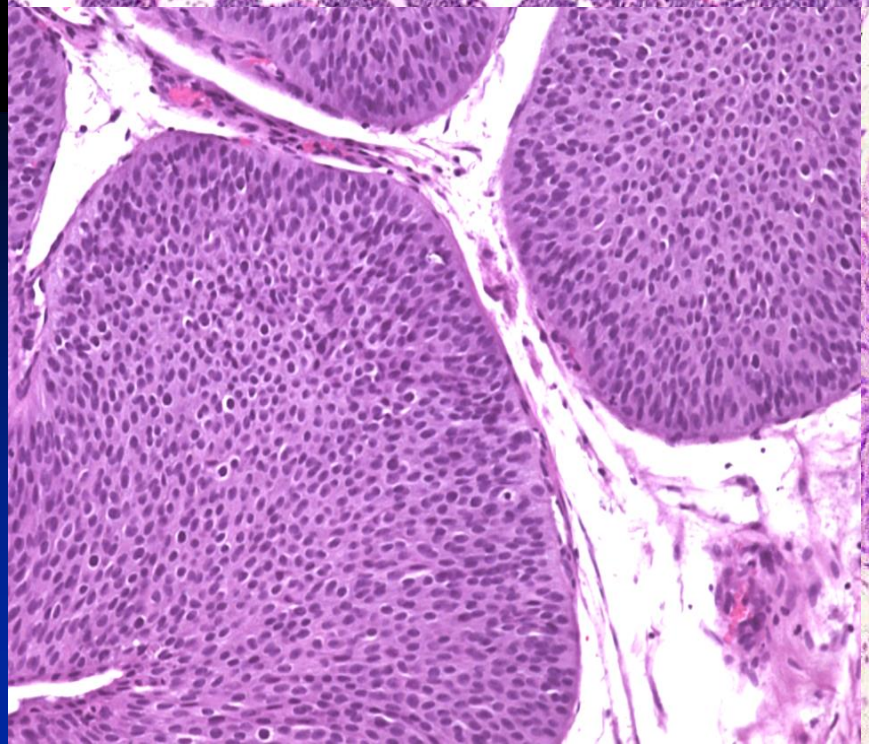
- Inverted papilloma
- Inverted urothelial neoplasm of LMP
- Inverted urothelial carcinoma, low grade, non-invasive
- Inverted urothelial carcinoma, high grade, non-invasive
- Inverted urothelial carcinoma, high grade, invasive



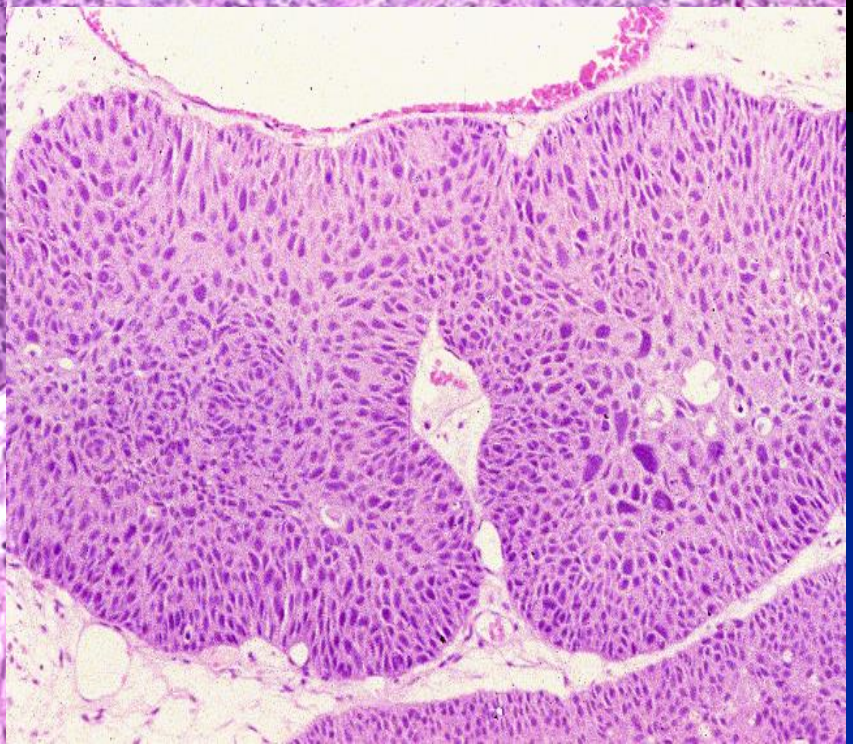
INV PAPILOMA



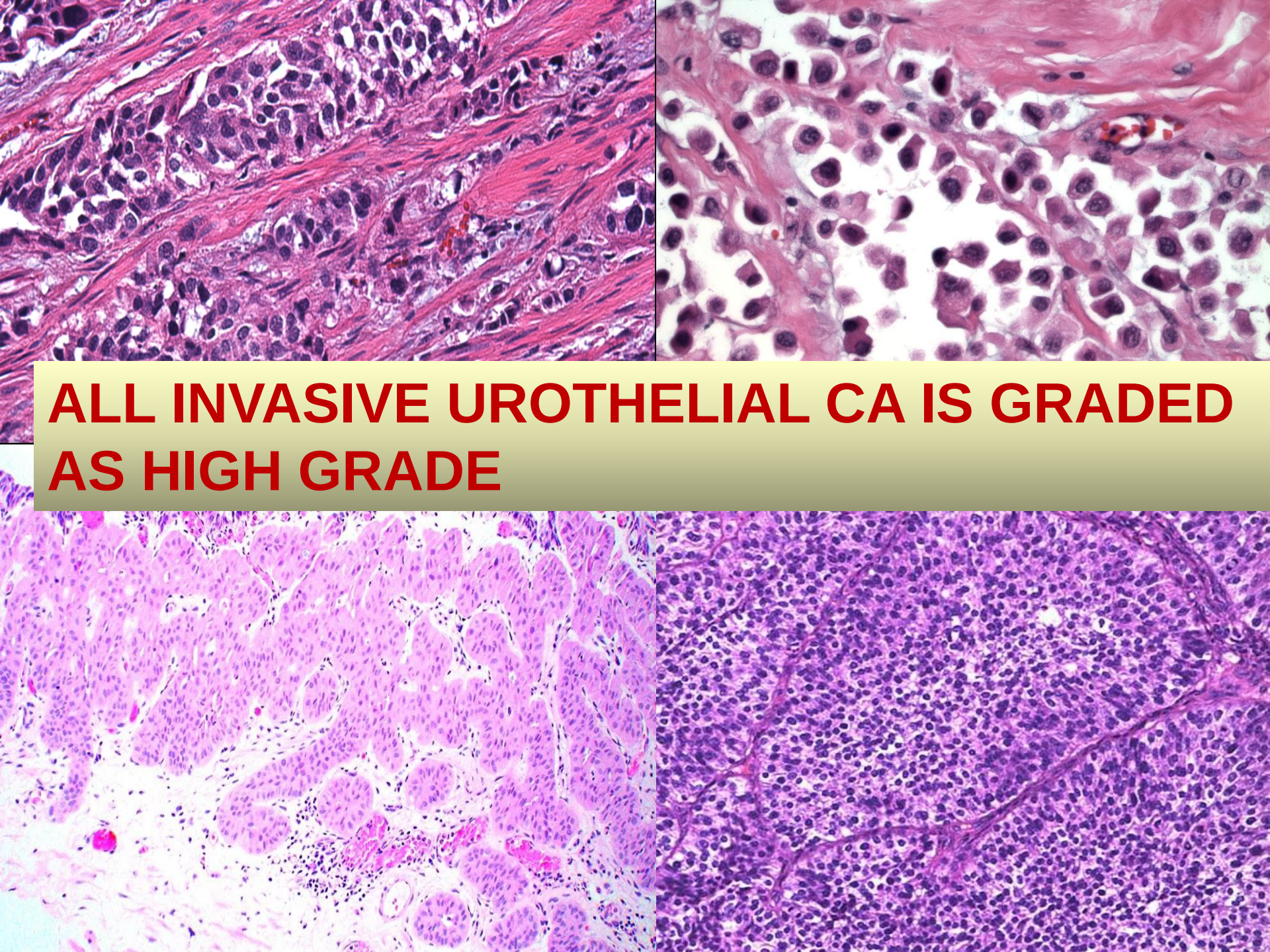
INV LMP



INV LG



INV HG



ALL INVASIVE UROTHELIAL CA IS GRADED AS HIGH GRADE

CLASSIFICATION OF INVASIVE BLADDER CA

- **Urothelial carcinoma**
- **Squamous cell Ca**
  - *conventional*
  - *verrucous*
  - *basaloid*
- **Adenocarcinoma**
  - *mucosal based*
  - *urachal*

Neuroendocrine carcinoma

- Small cell
- Large cell
- Well differentiated tumor
- Paraganglioma

- **Variants of urothelial Ca**
  - *nested (incl. large nested)*
  - *microcystic*
  - *micropapillary*
  - *lymphoepithelioma-like*
  - *sarcomatoid*
  - *diffuse/plasmacytoid signet ring cell*
  - *giant cell*
  - *lipid rich*
  - *clear cell*
  - *undifferentiated*

CLASSIFICATION OF INVASIVE BLADDER CA

Will be covered tomorrow.

PRIMARY ADENOCARCINOMA OF THE BLADDER

Anatomic:

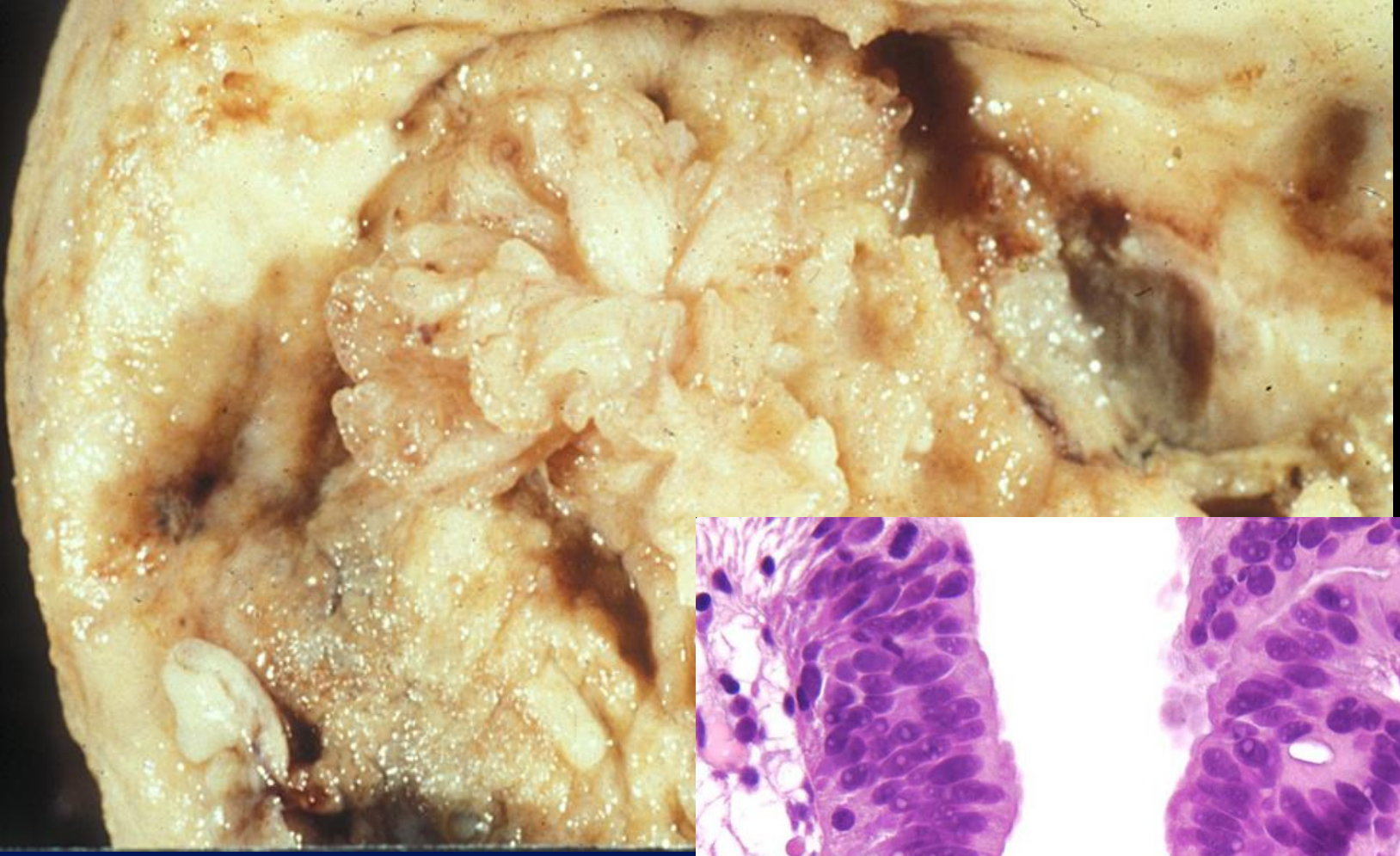
- Urachal
- Bladder mucosa

Histology:

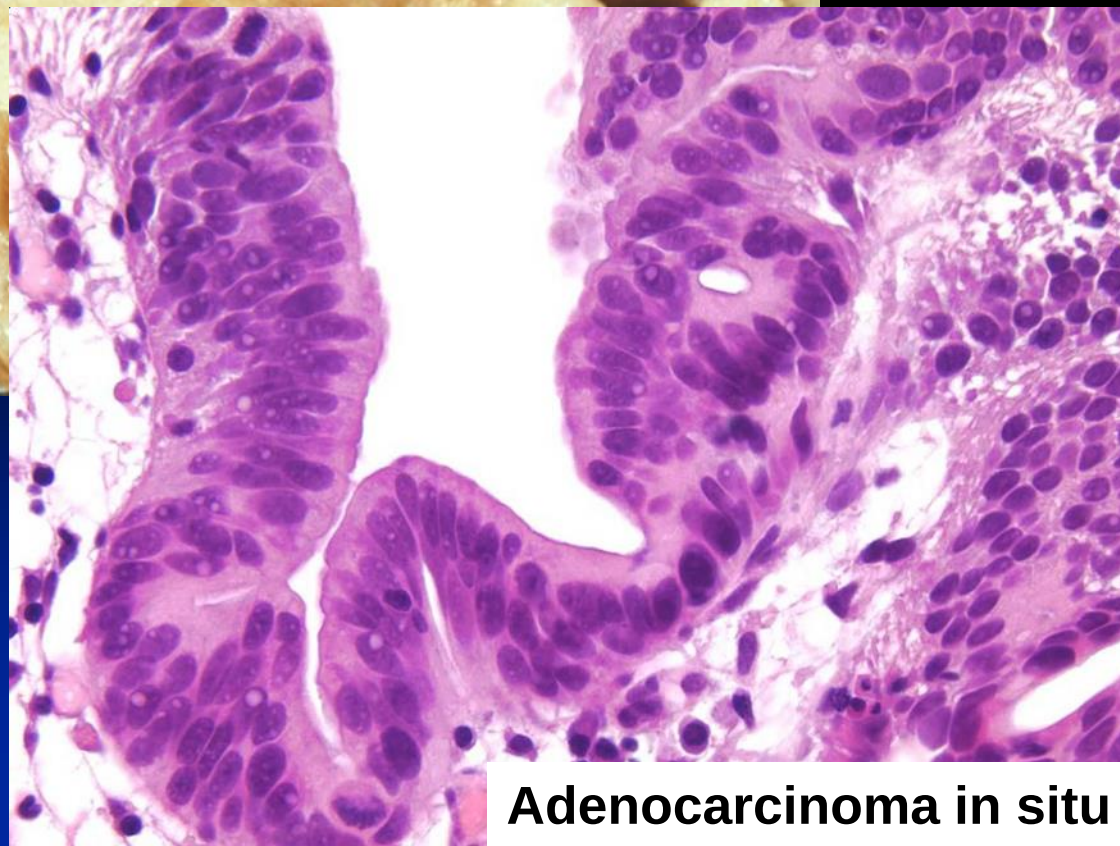
- Adenocarcinoma NOS
- Enteric
- Mucinous
- Signet ring
- Clear cell
- Hepatoid
- Combined (from above)

Rule out:

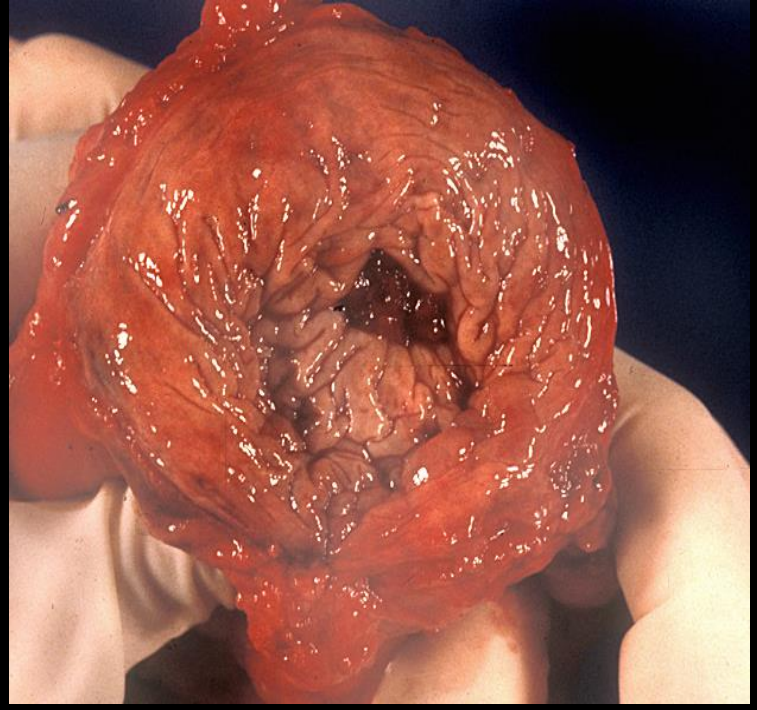
- Urothelial Ca with glandular features
- Metastasis

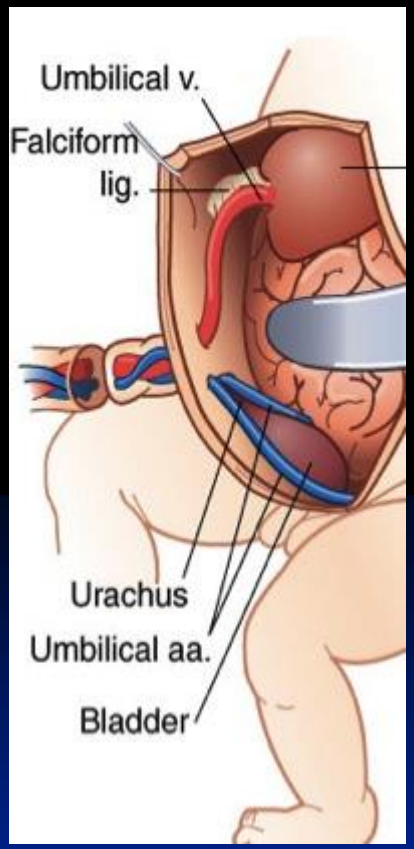


Mucosal based

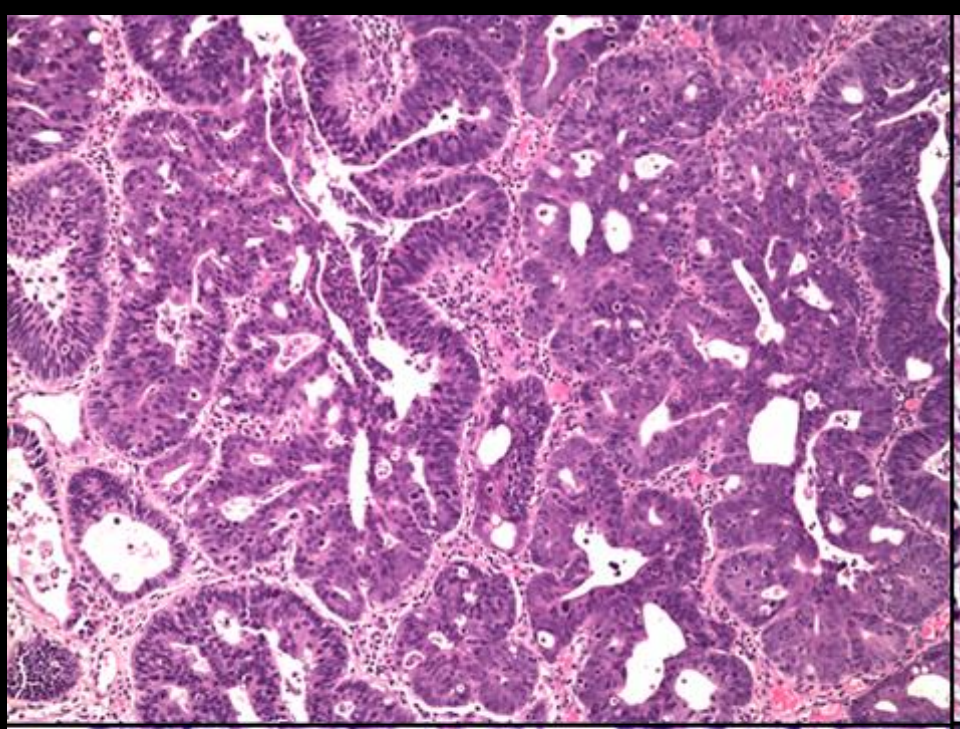
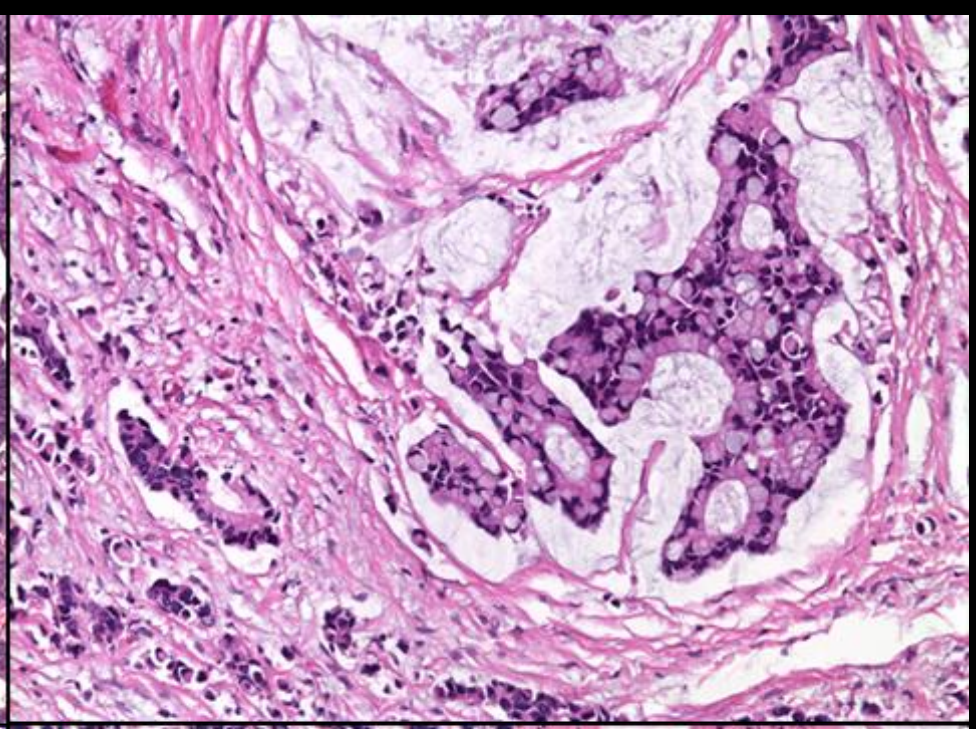
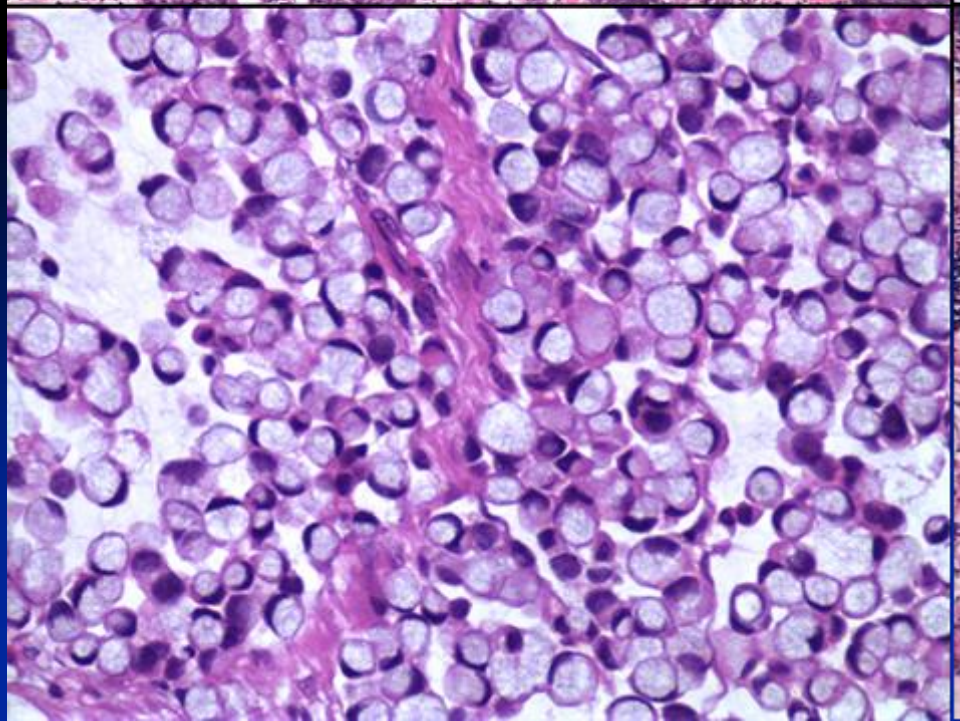
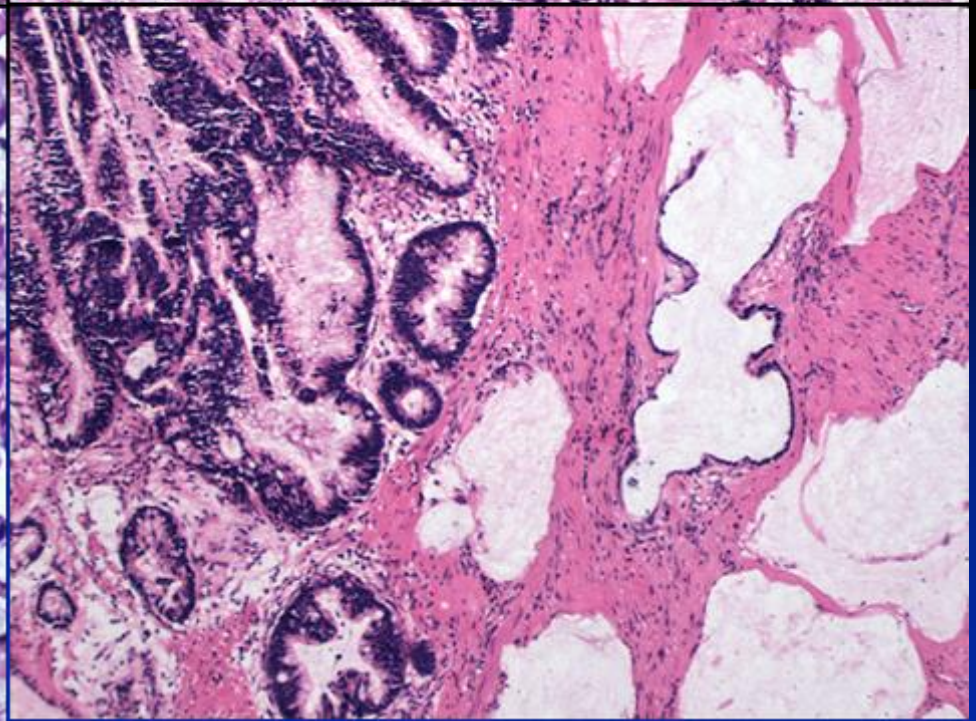


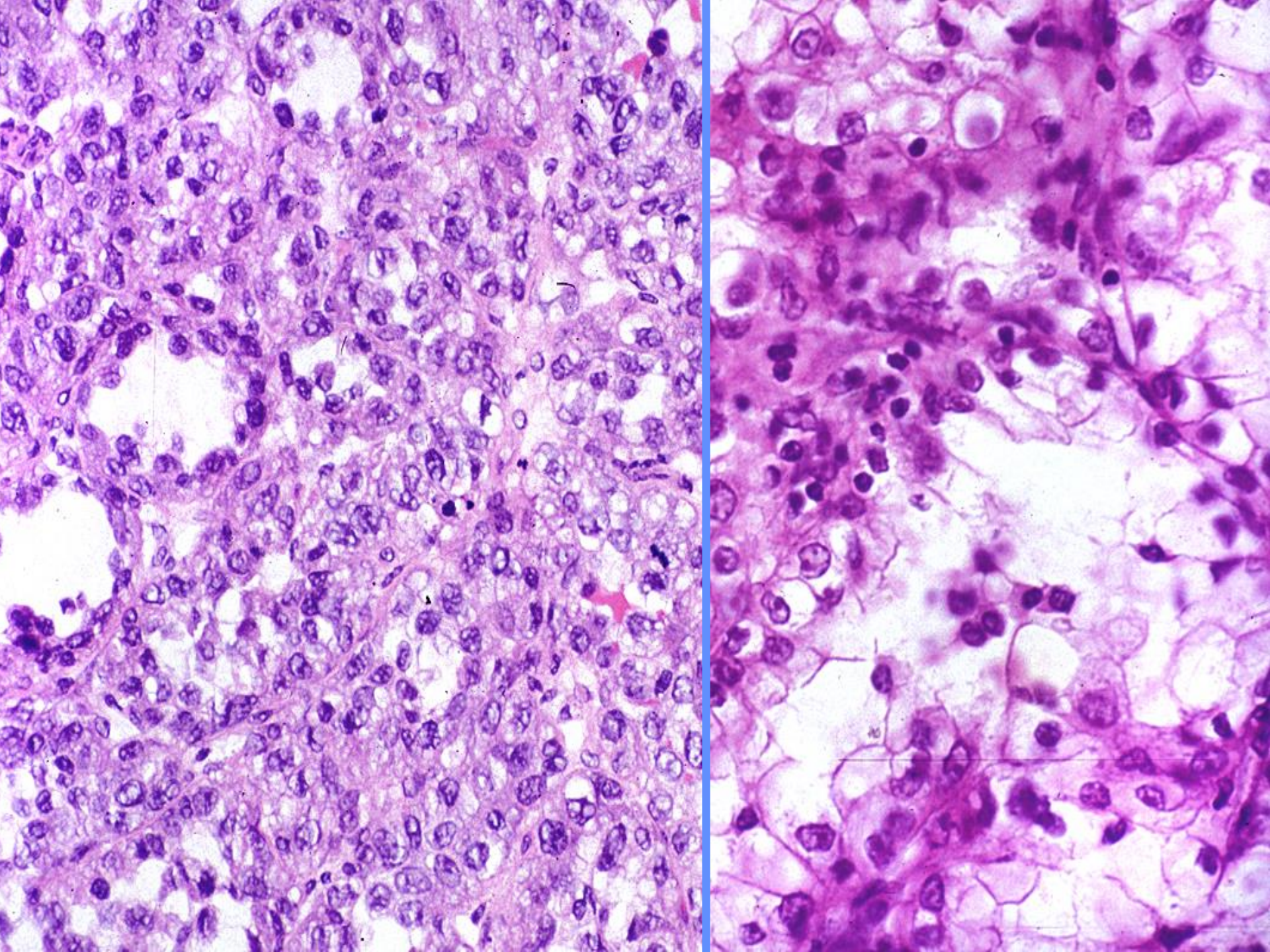
Adenocarcinoma in situ





Urachal

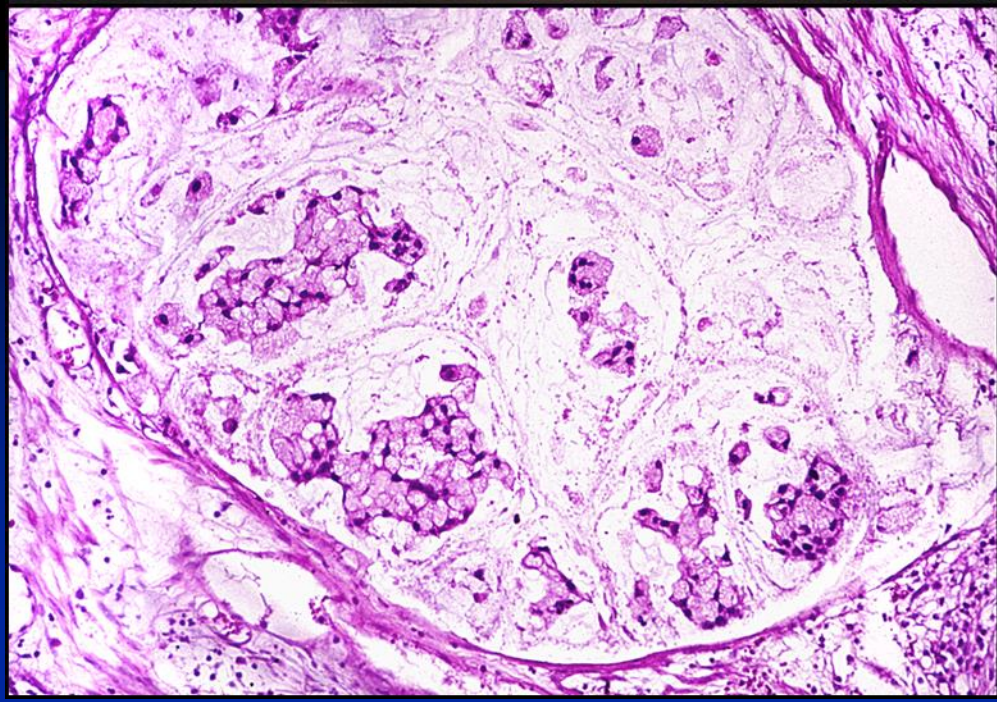







URACHAL CARCINOMA

Clinicopathologic diagnosis

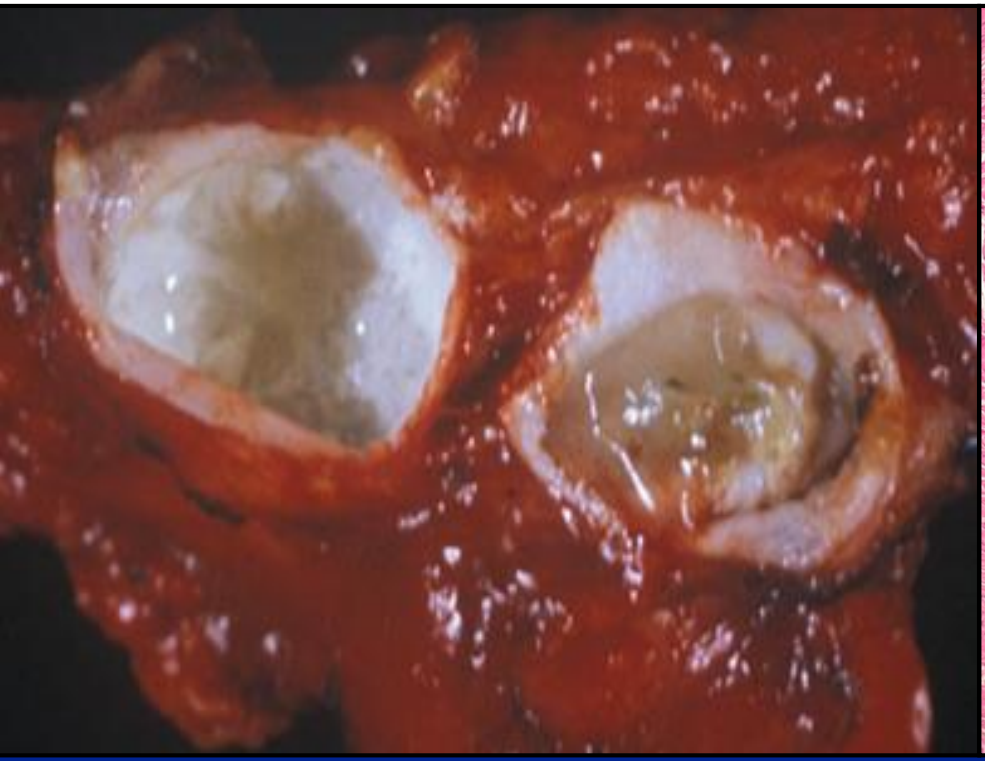
- ***Criteria:***
  - ***Dome or anterior location***
  - ***Absence of cystitis glandularis or intestinal metaplasia***
  - ***Absence of primary elsewhere***
  - ***Epicenter of mass in bladder wall***

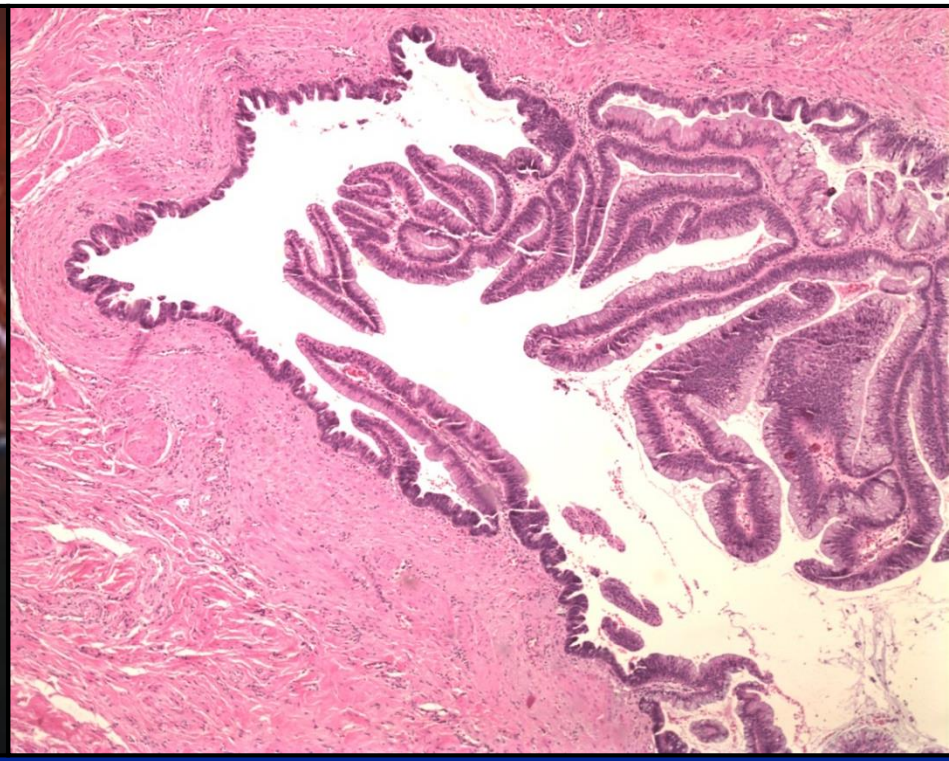


Glandular Neoplasms of the Urachus

A Report of 55 Cases Emphasizing Mucinous Cystic Tumors With Proposed Classification

Mahul B. Amin, MD, Steven C. Smith, MD, PhD,* John N. Eble, MD,† Priya Rao, MD,* William W. L. Choi, MD,‡§ Pheroze Tamboli, MD,‖ and Robert H. Young, MD¶*

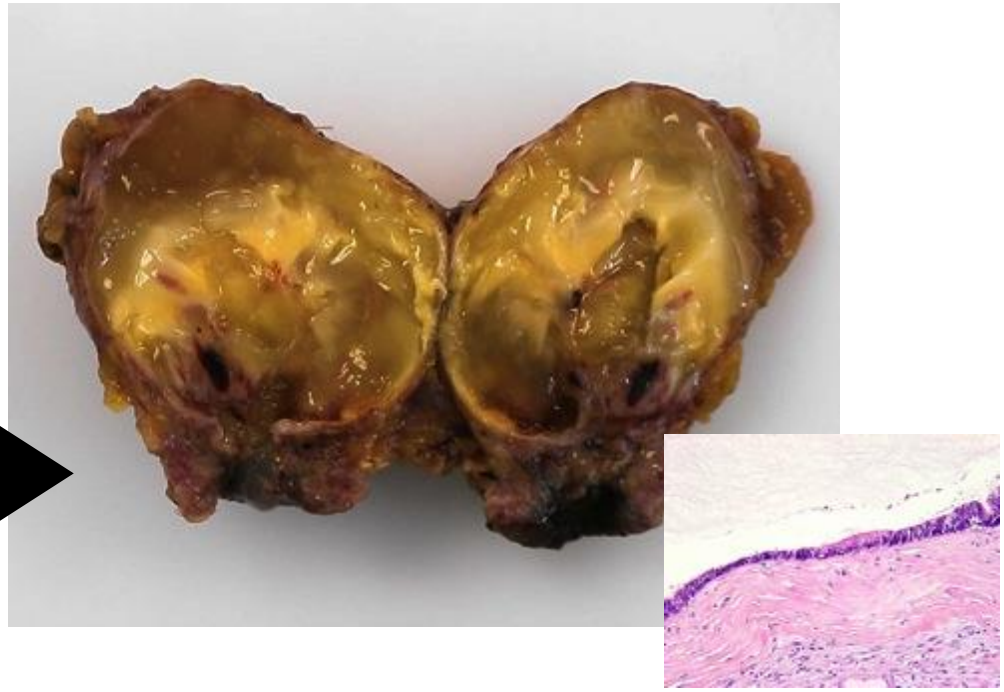




Am J Surg Pathol: 2014

Non-invasive and low grade mucinous cystic tumors of urachus

Cystic urachal tumor



Urachal mucinous cystadenoma

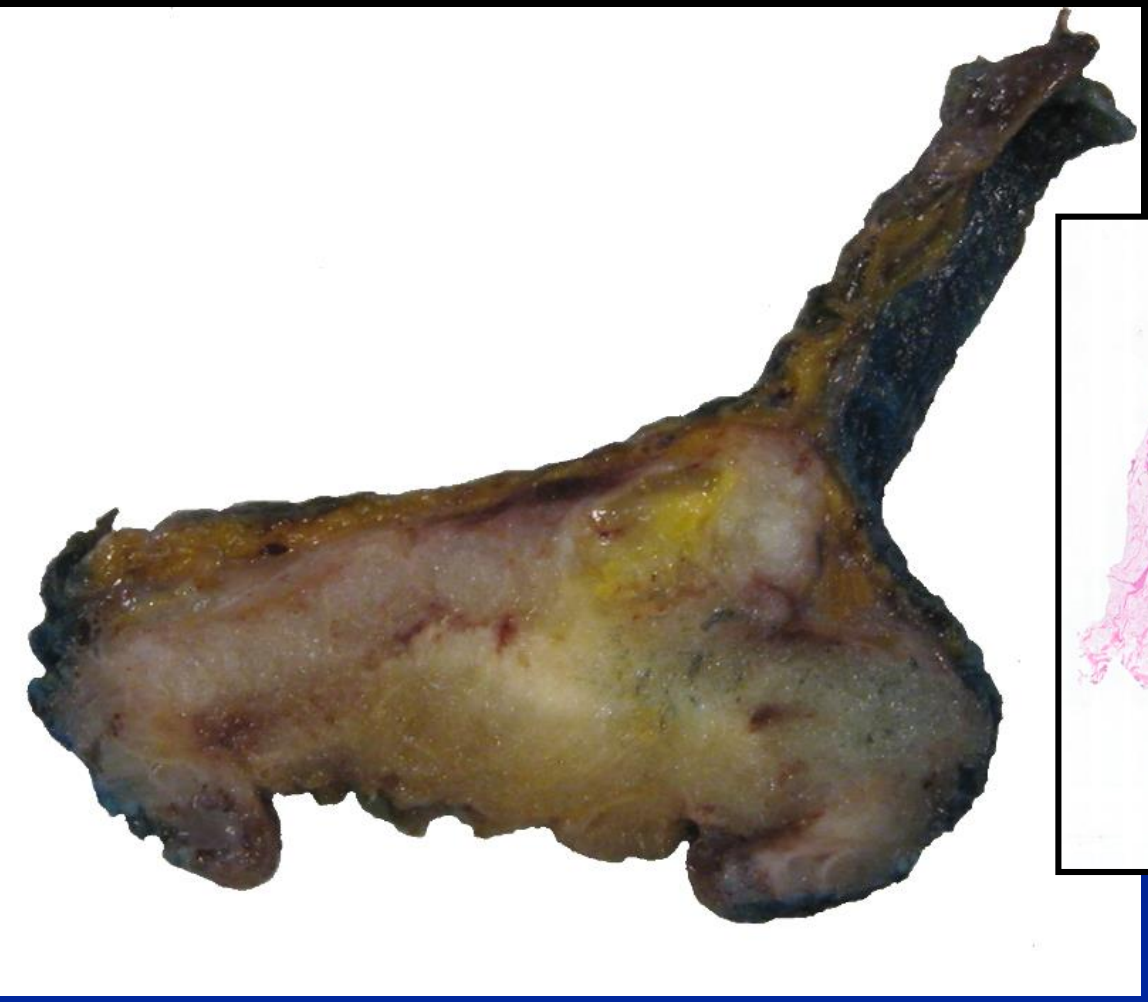
Glandular Neoplasms of the Urachus

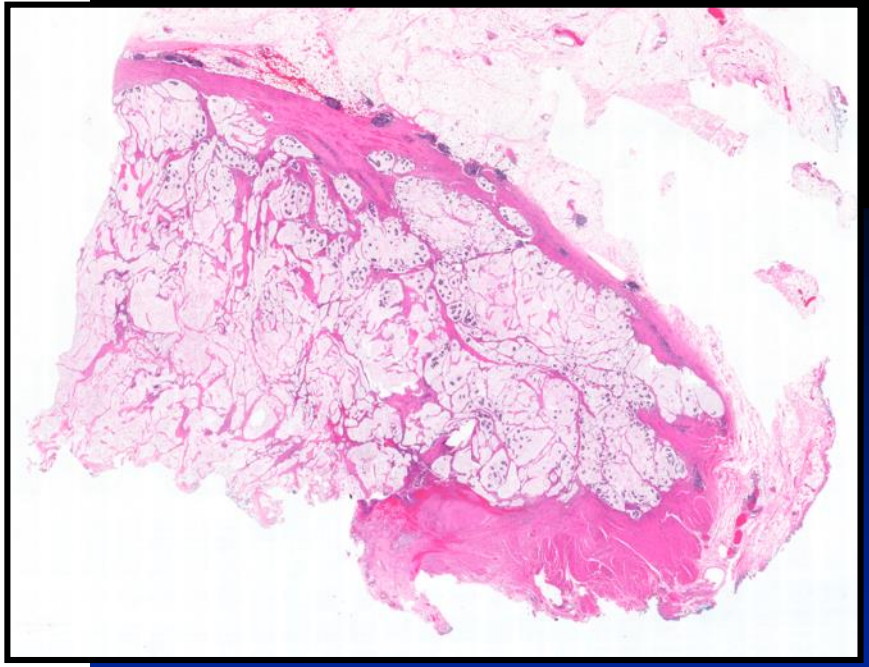
A Report of 55 Cases Emphasizing Mucinous Cystic Tumors With Proposed Classification

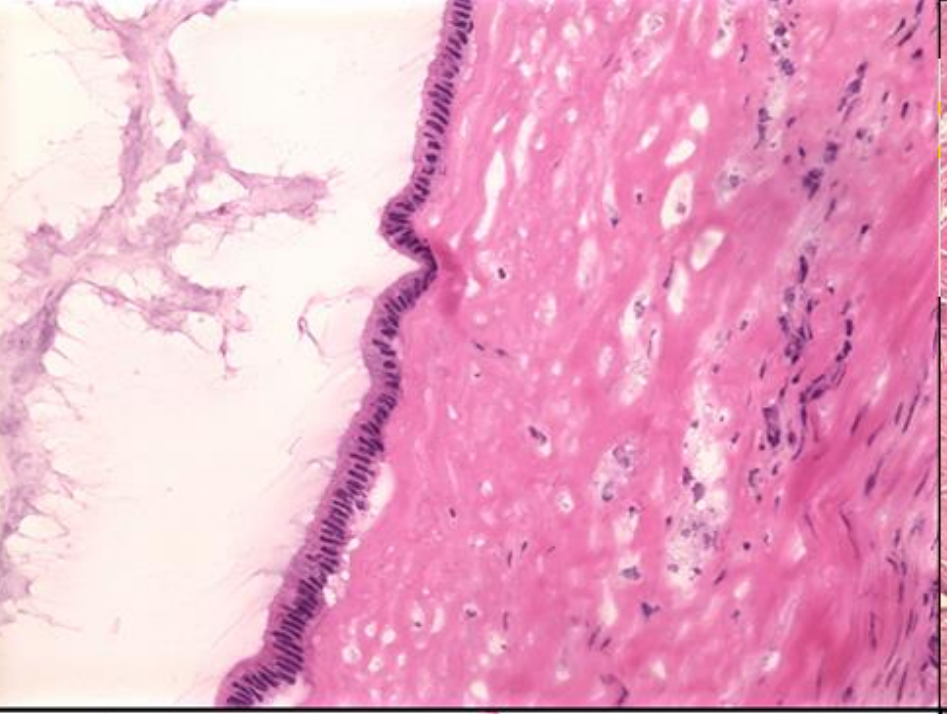
Mahul B. Amin, MD, Steven C. Smith, MD, PhD,* John N. Eble, MD,† Priya Rao, MD,* William W. L. Choi, MD,‡§ Pheroze Tamboli, MD,‖ and Robert H. Young, MD¶*

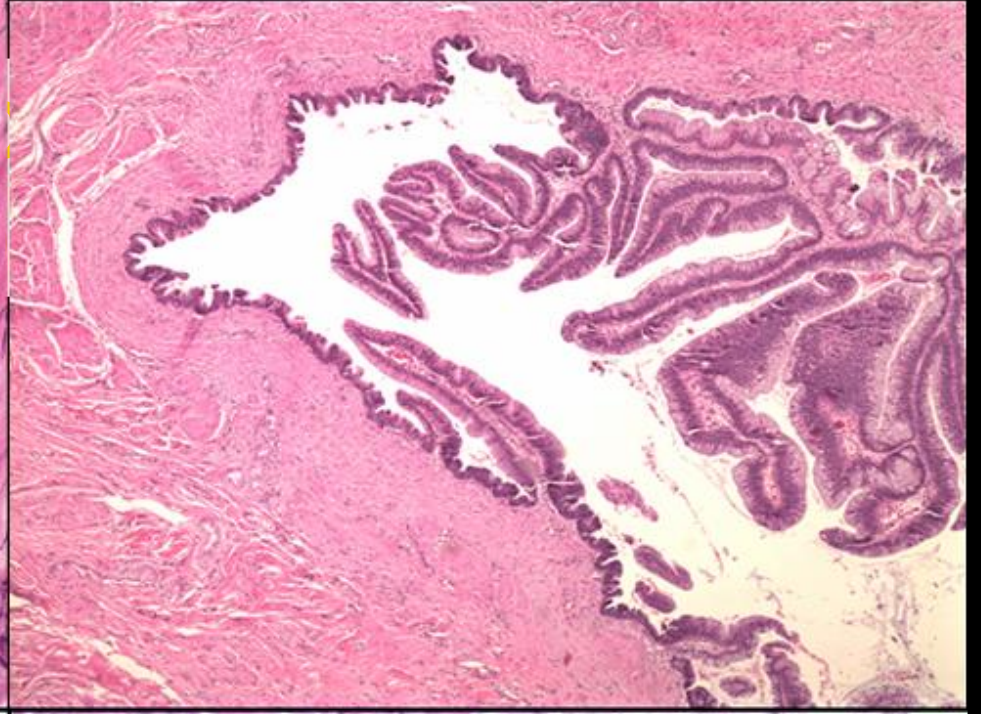
- 31 Mucinous cystic tumors (from 4 institutions & consult cases)
  - 4 cystadenoma
  - 22 low malignant potential (LMP)
    - 2 intraepithelial carcinoma
  - 8 invasive cystadenocarcinoma
    - 4 microinvasive carcinoma
    - 1 frankly invasive carcinoma
- 24 Invasive noncystic adenocarcinomas
  - 8 mucinous (colloid)
  - 6 enteric, 6 mucinous/enteric, 2 NOS

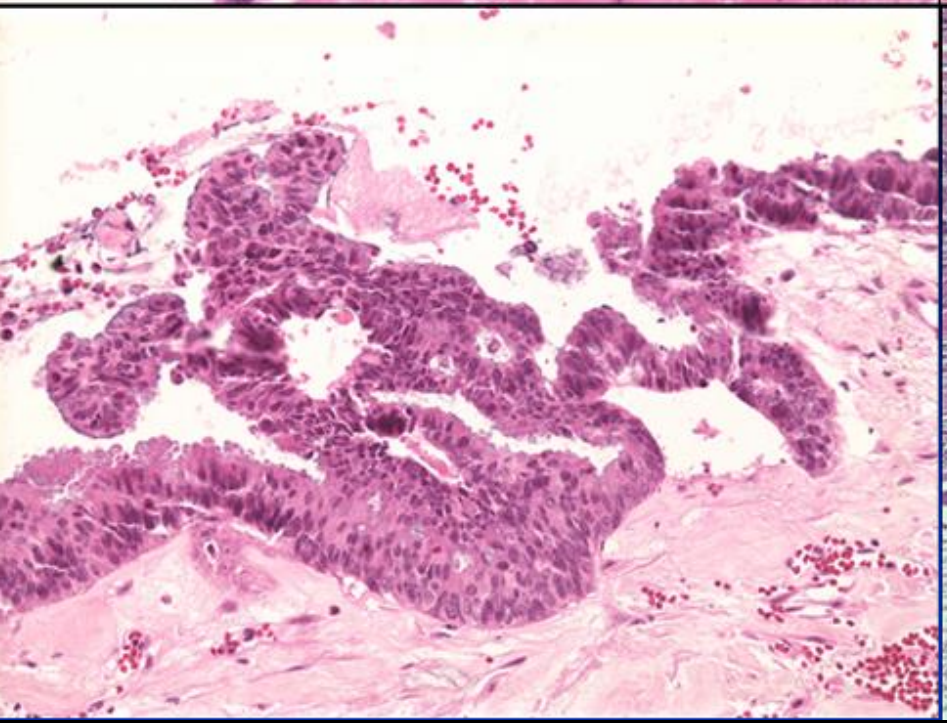
- Am J Surg Pathol 2014;38:1033

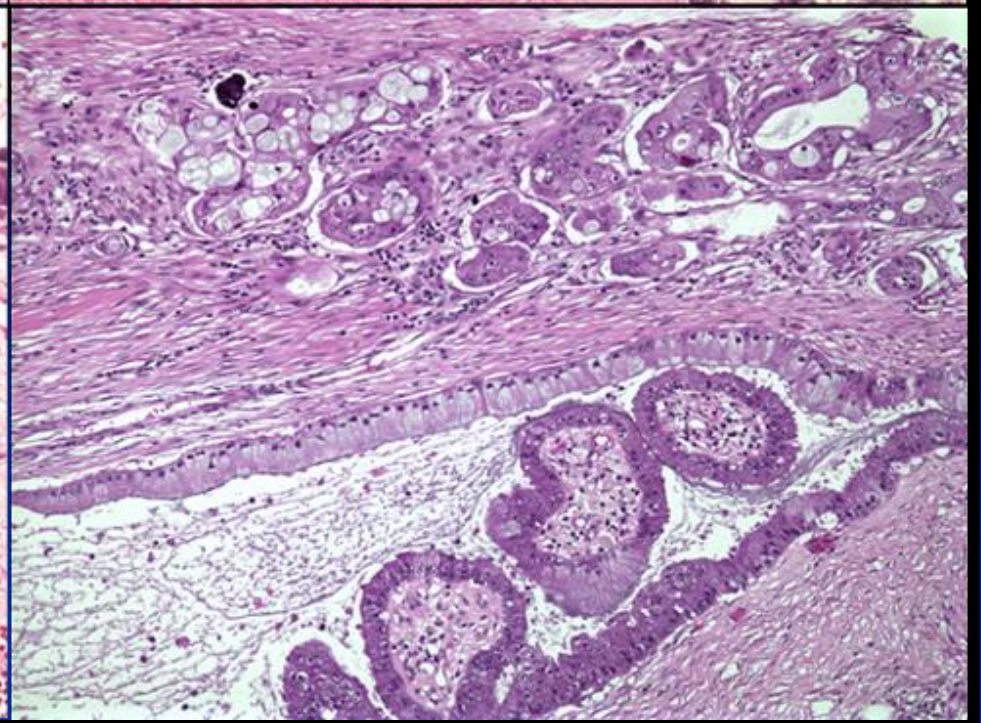




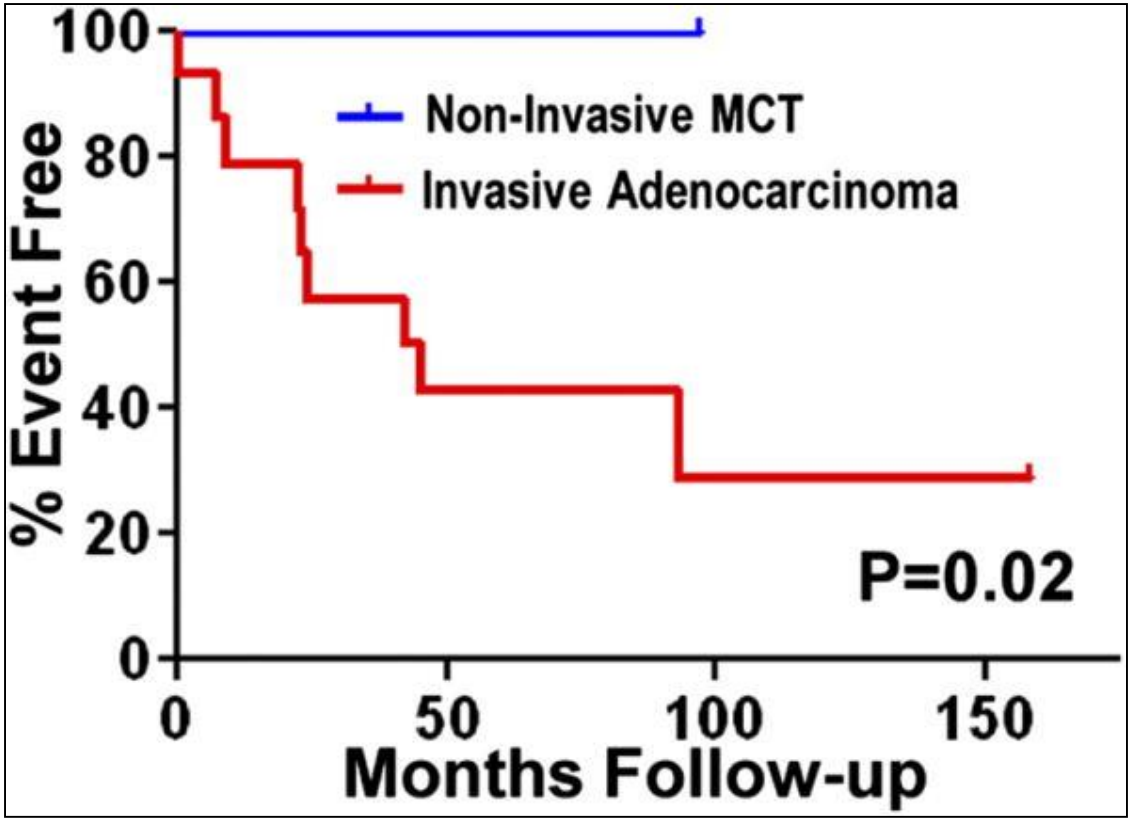




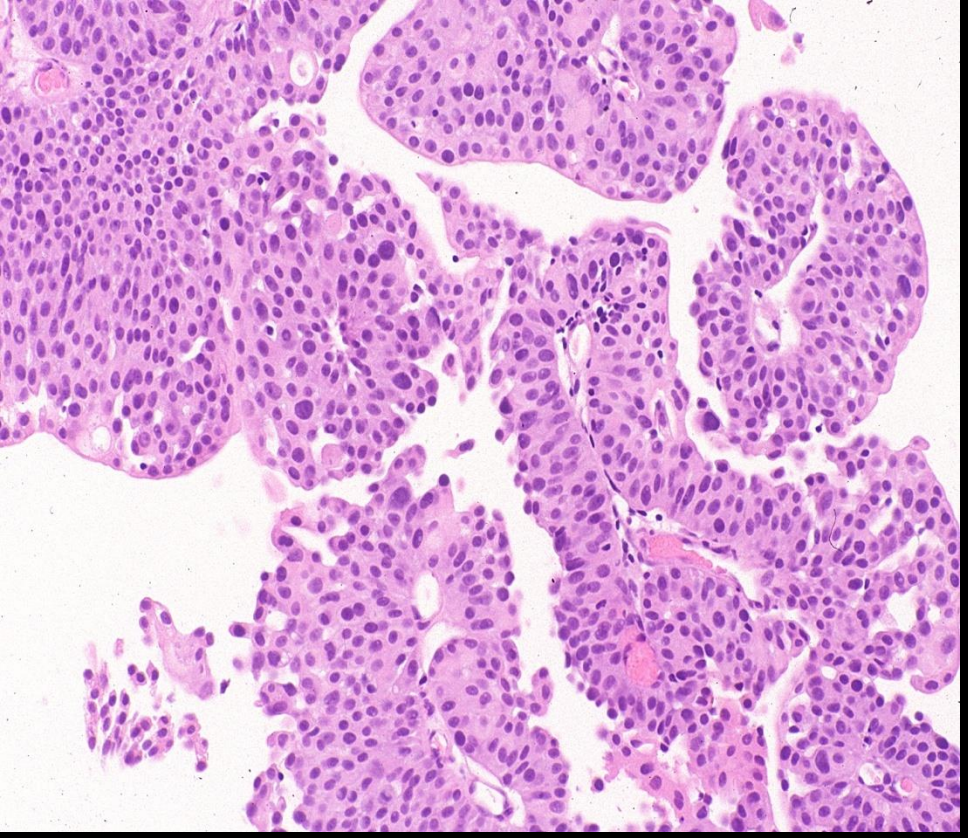


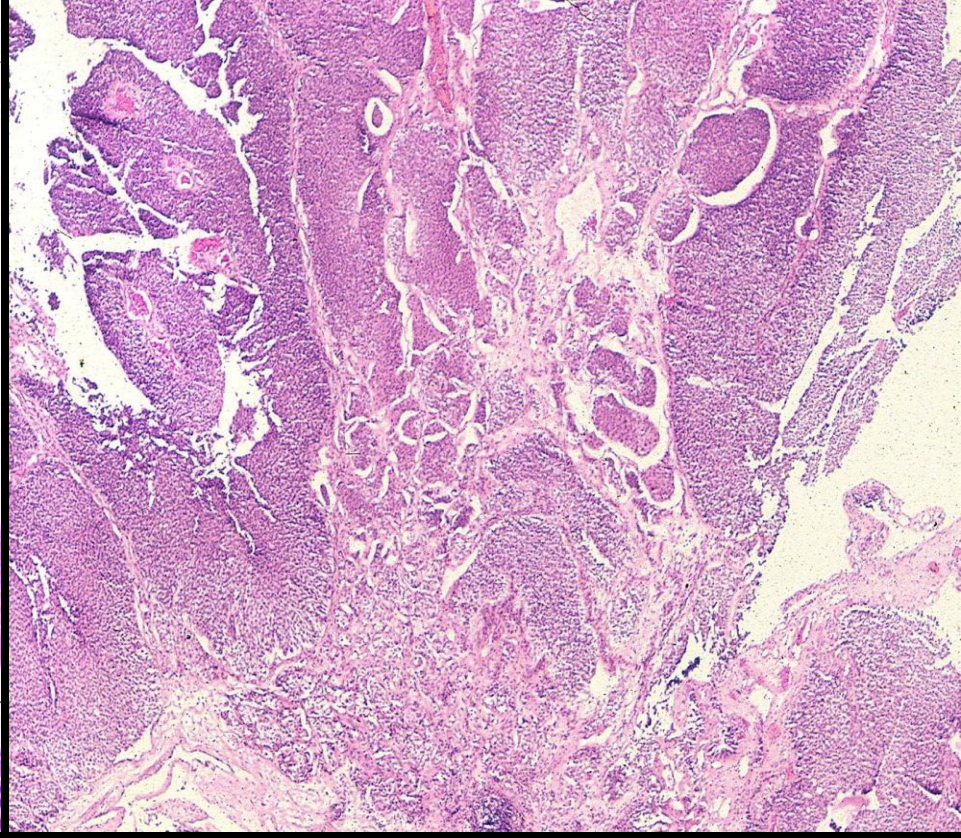


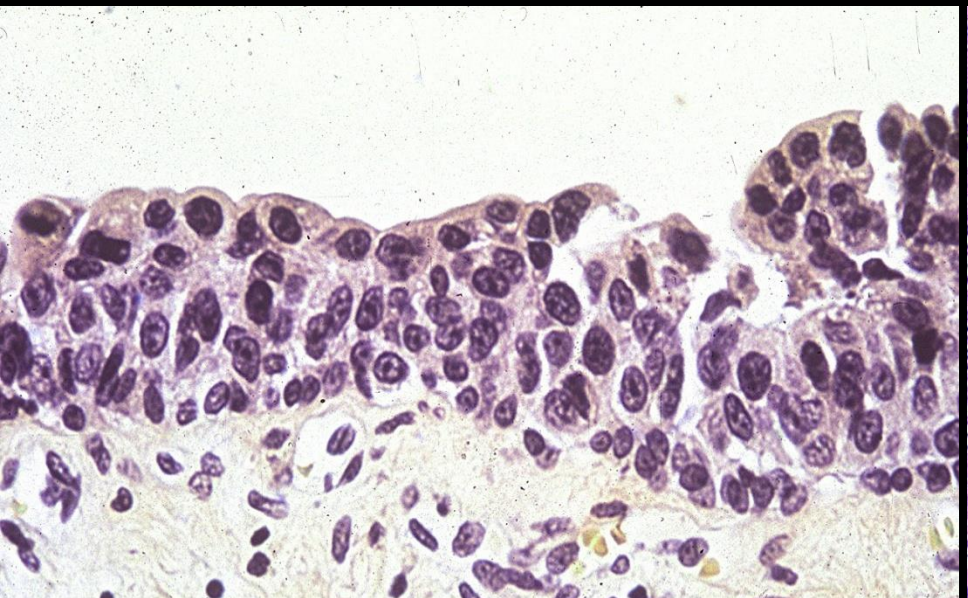
Survival of noninvasive mucinous cystic tumors of urachus

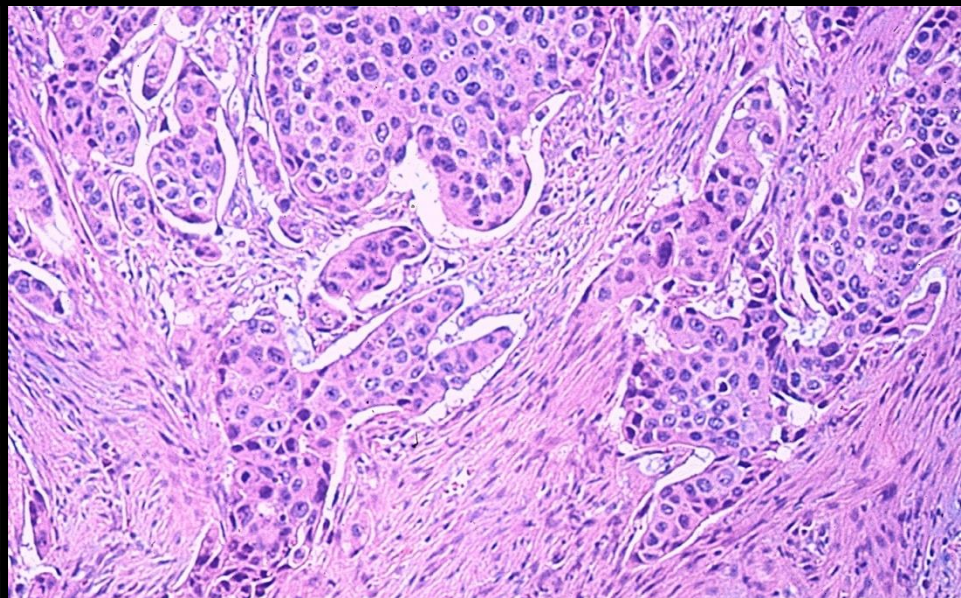


- Amin et al, Am J Surg Pathol 2014

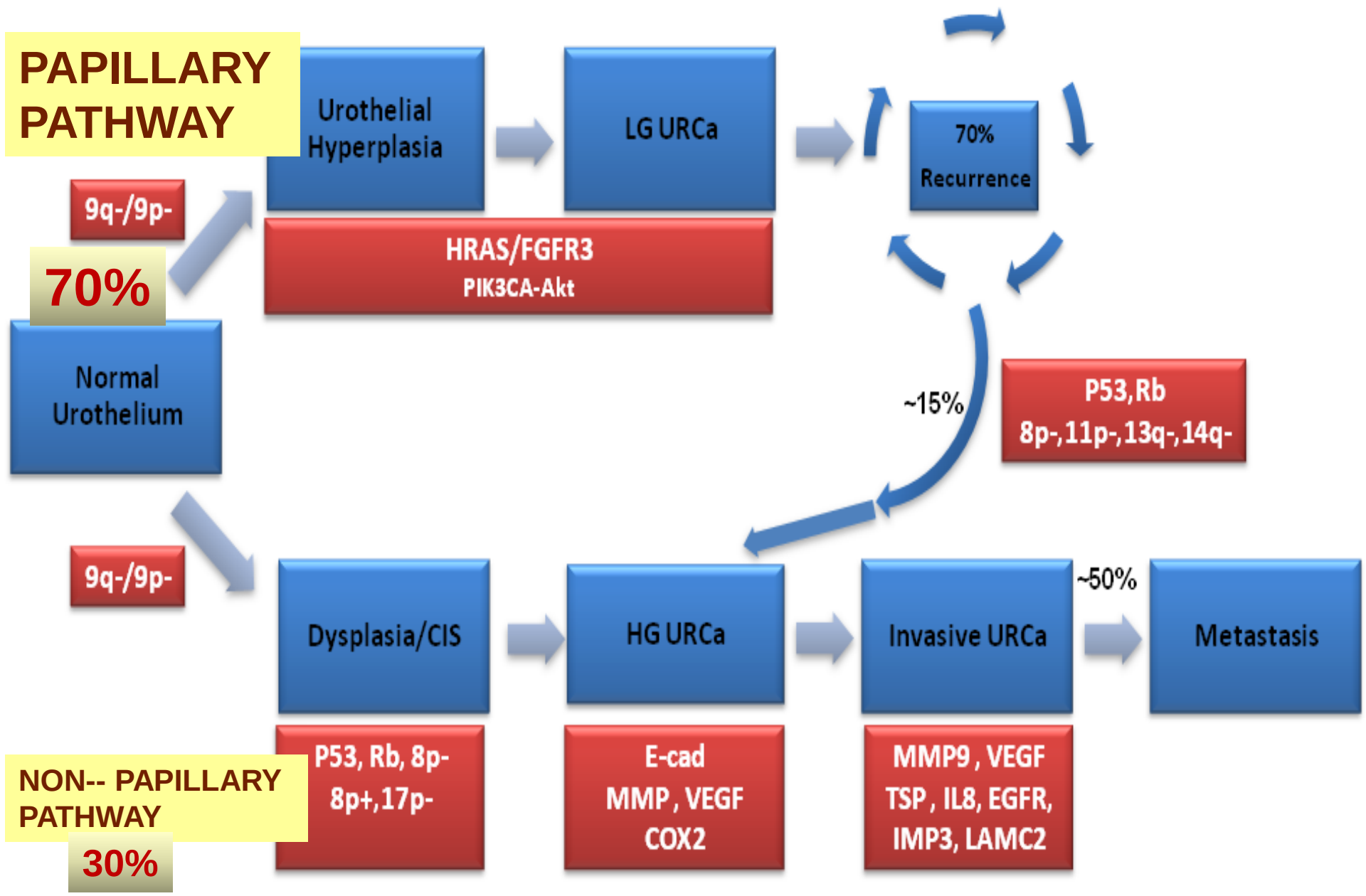




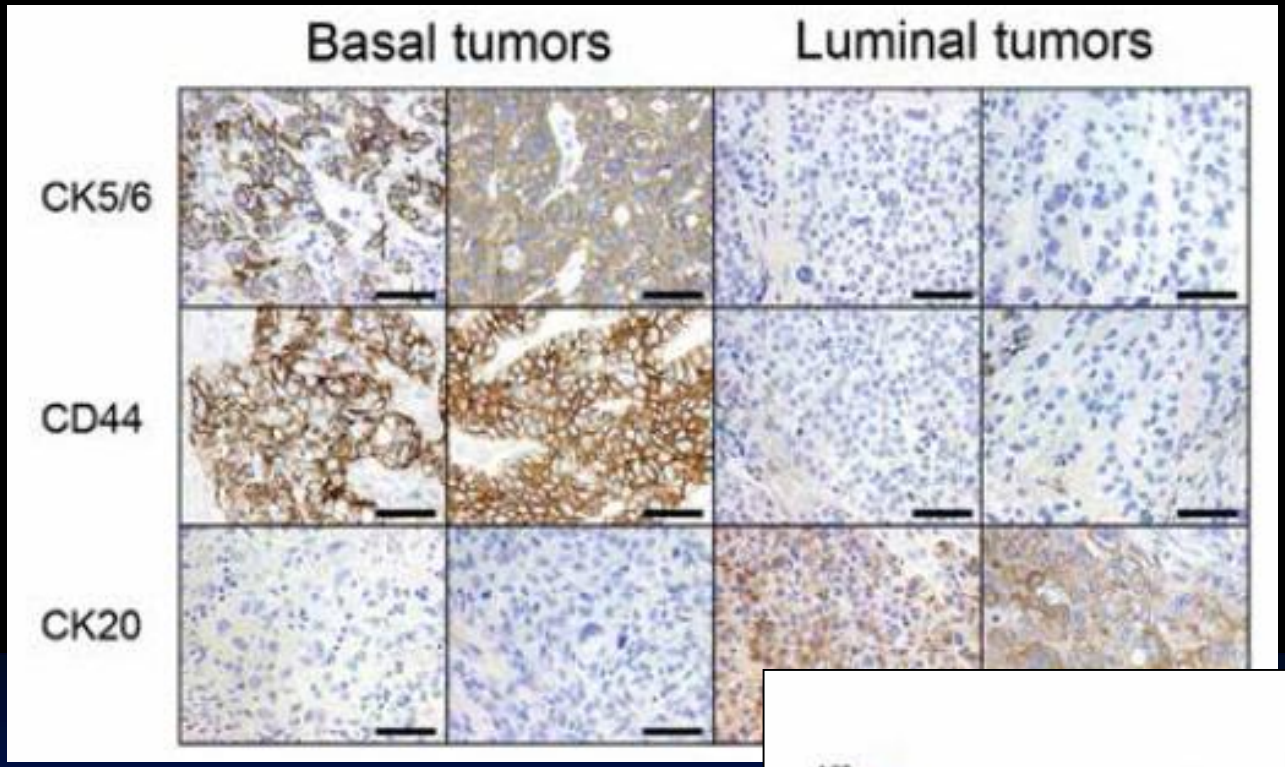


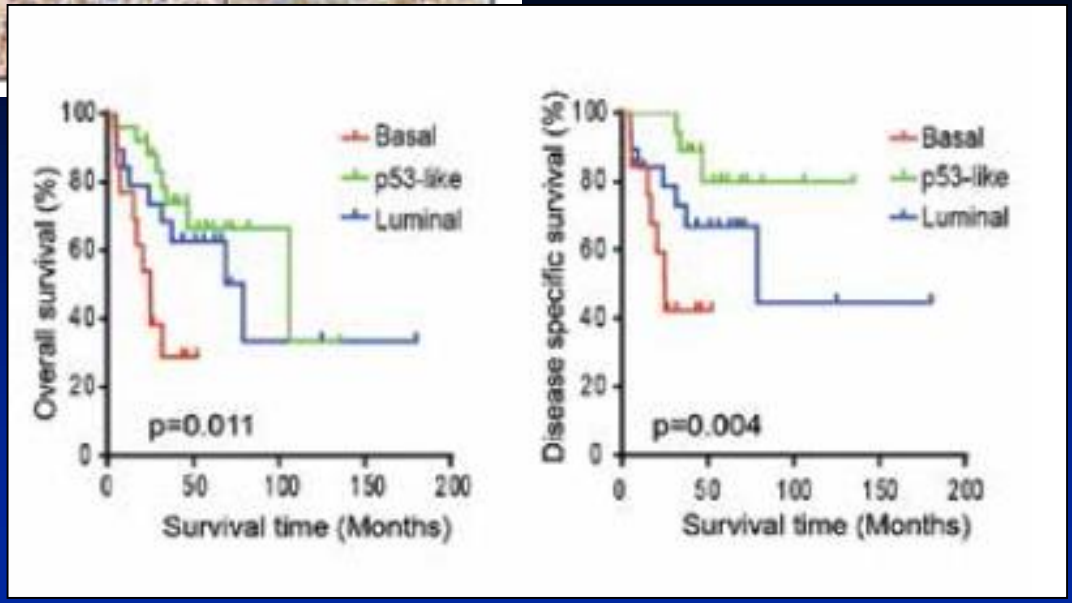


Molecular Pathways for Bladder Cancer Oncogenesis



Molecular Subtypes of UBCA





TESTIS CANCER

What is new in the WHO 2016:

- **Topic 10: Precursor lesion nomenclature for germ cell tumor of the testis**
- **Topic 11: Revised Classification for germ cell tumors**

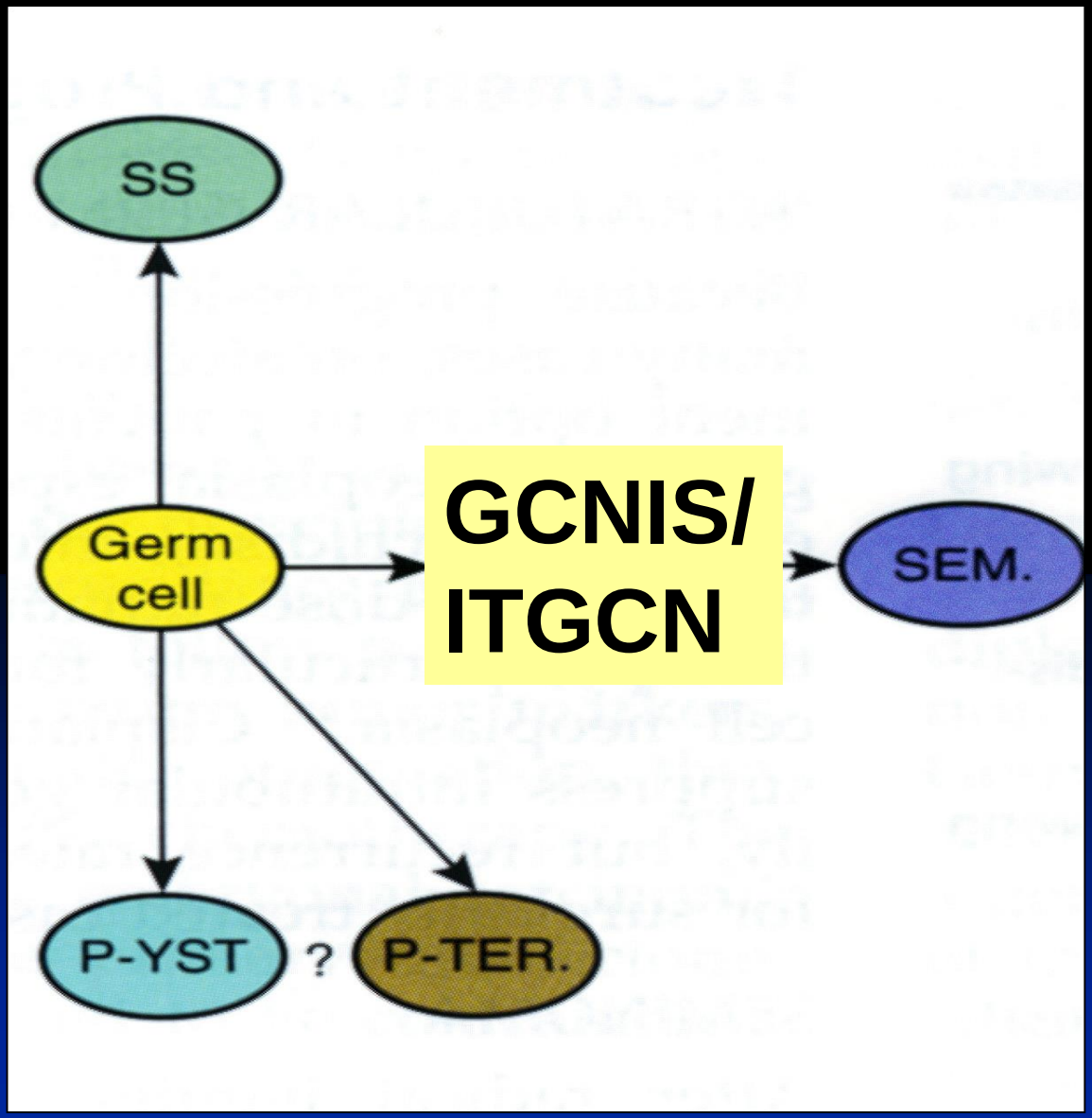
GERM CELL TUMORS

ITGCN = GCNIS (Germ Cell Neoplasia in Situ)

- **ASSOCIATED WITH GCNIS**
- **NOT ASSOCIATED WITH GCNIS**

- **ASSOCIATED WITH GCNIS**
  - Similar epidemiologic associations
  - Arise from maturation delayed germ cells arising in a damaged testicular milieu: *impaired spermatogenesis, tubular shrinkage, peritubular sclerosis, immature Sertoli cells, interstitial widening, hyalinized tubules, and microlithiasis*
  - *Isochromosome 12 p*

HISTOGENESIS



GCNIS/ ITGCN

programmed EC CELL

Non seminomatous GCTs

WHO 2015 CLASSIFICATION OF GERM CELL TUMORS OF TESTIS

- **ASSOCIATED WITH GCNIS**
  - **Classic seminoma**
  - **Pure or Mixed (non-seminomatous) tumor**
    - ***Embryonal carcinoma***
    - ***Yolk sac tumor***
    - ***Choriocarcinoma & other trophoblastic tumors***
    - ***Teratoma, post-pubertal type***
    - ***Mixed – combinations of above incl. Seminoma***

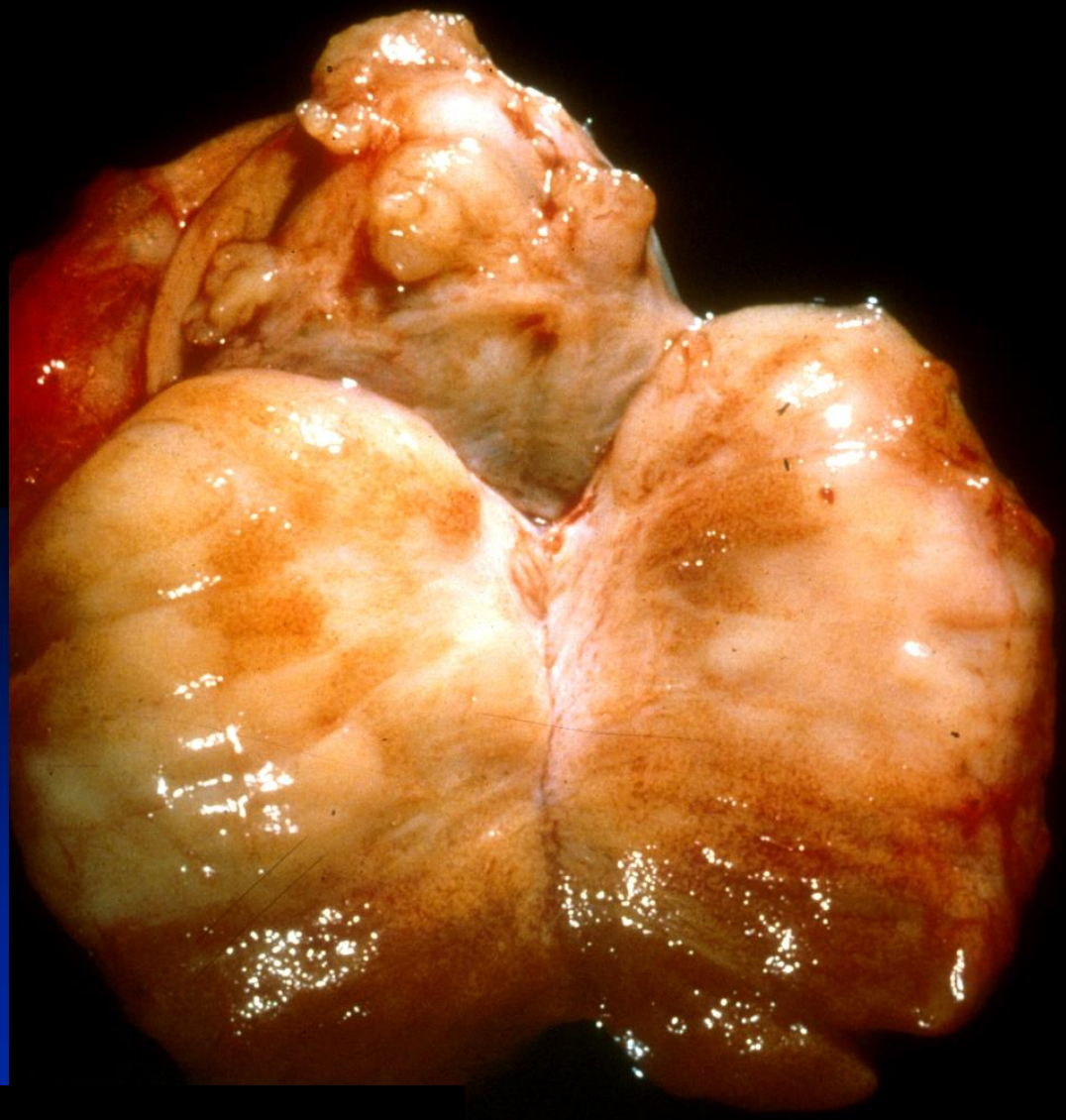
REGRESSED GERM CELL TUMOR
(Germ cell tumor of unknown type)

- **Spontaneous regression first presents with metastasis**

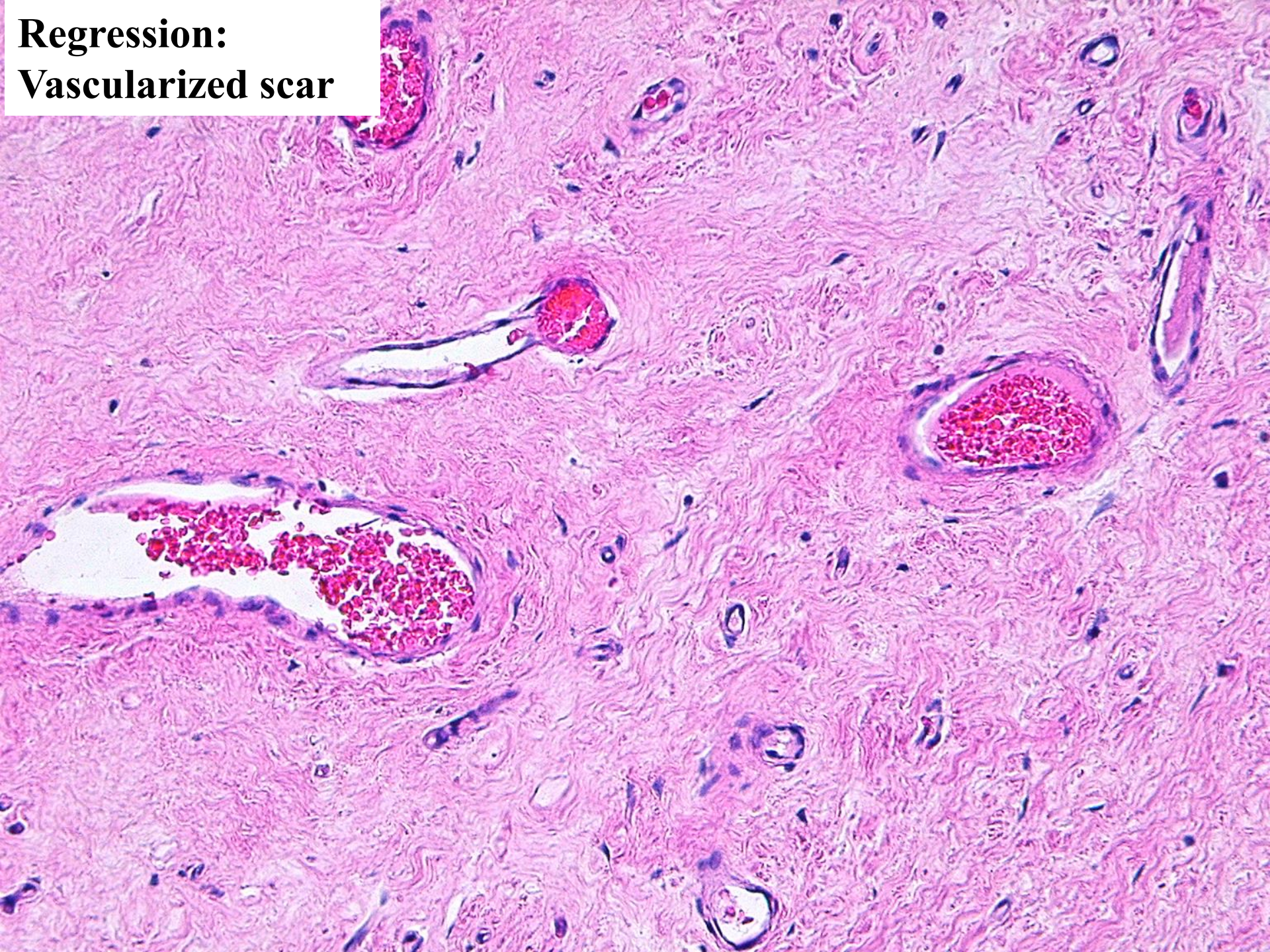
- Scar – band like or stellate

- Cysts

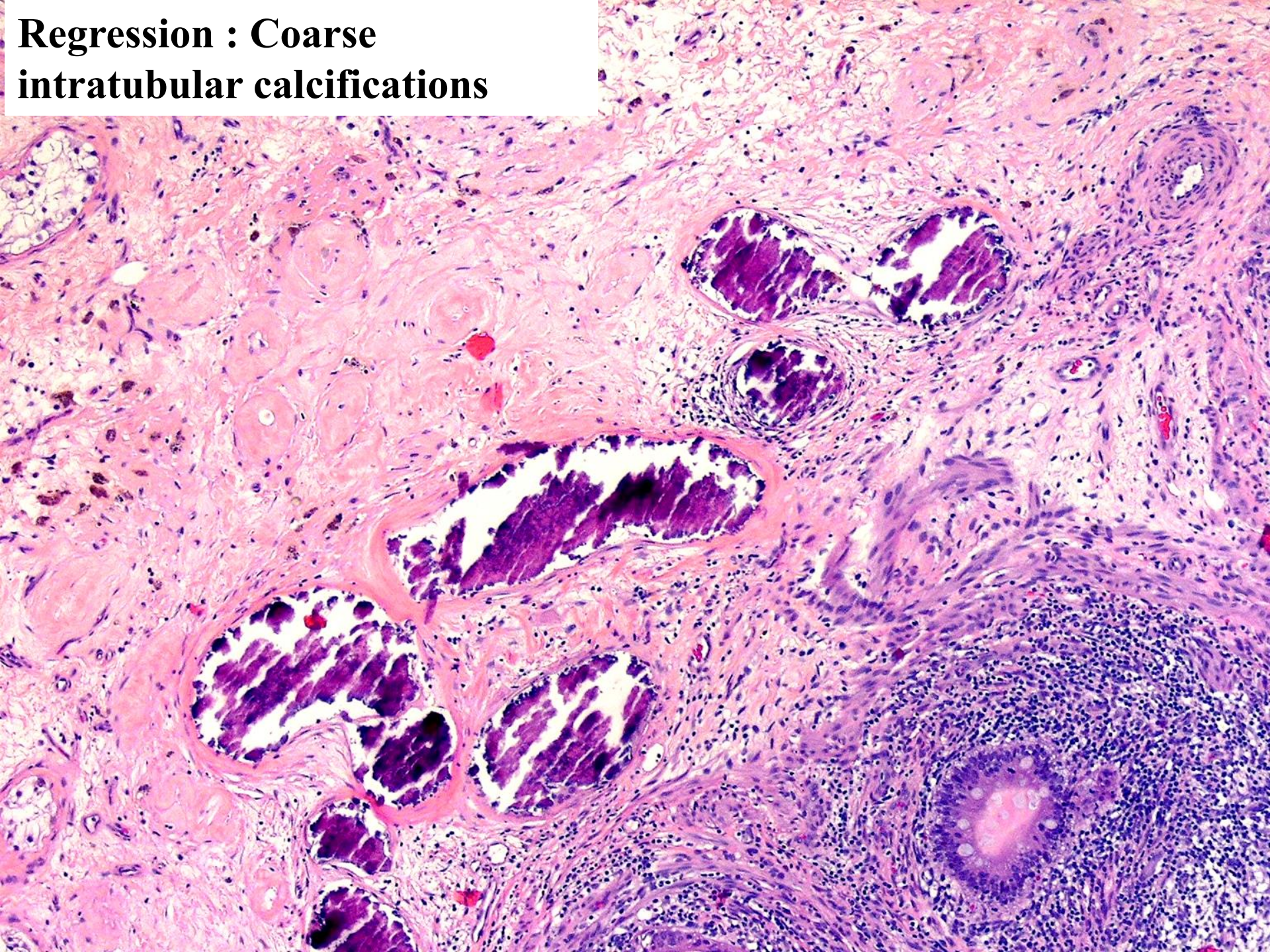
- Calcification



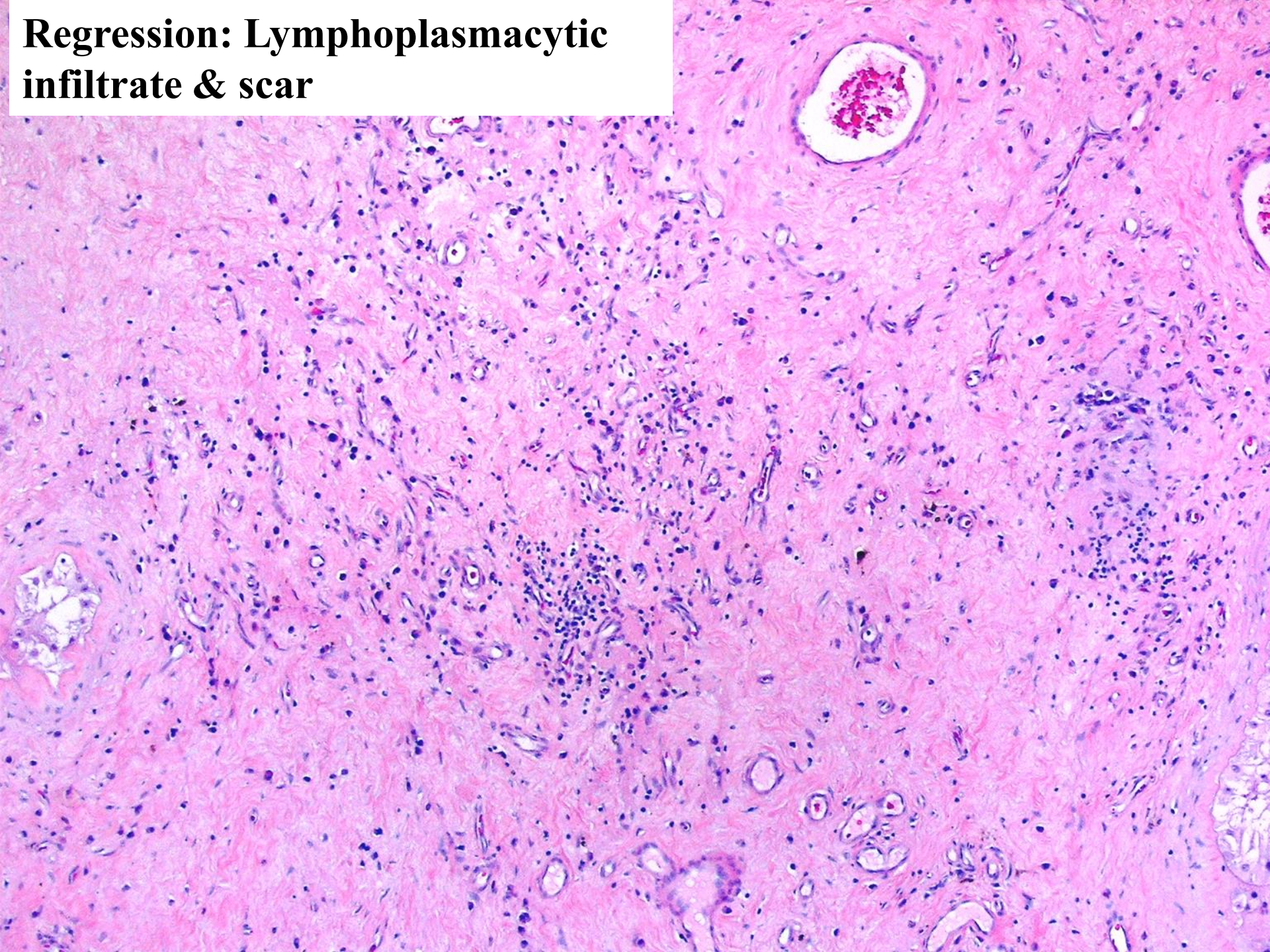
Regression:
Vascularized scar

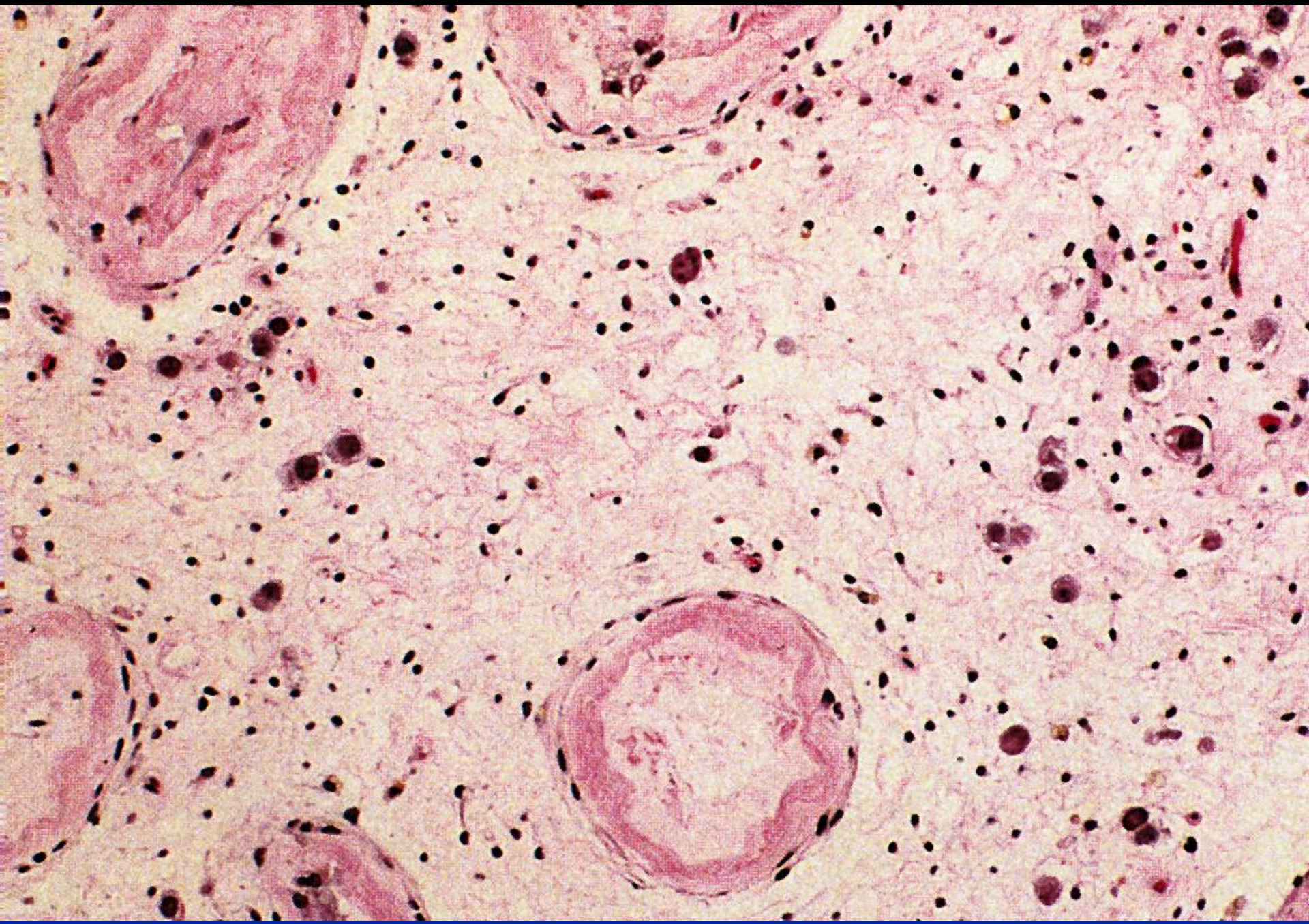


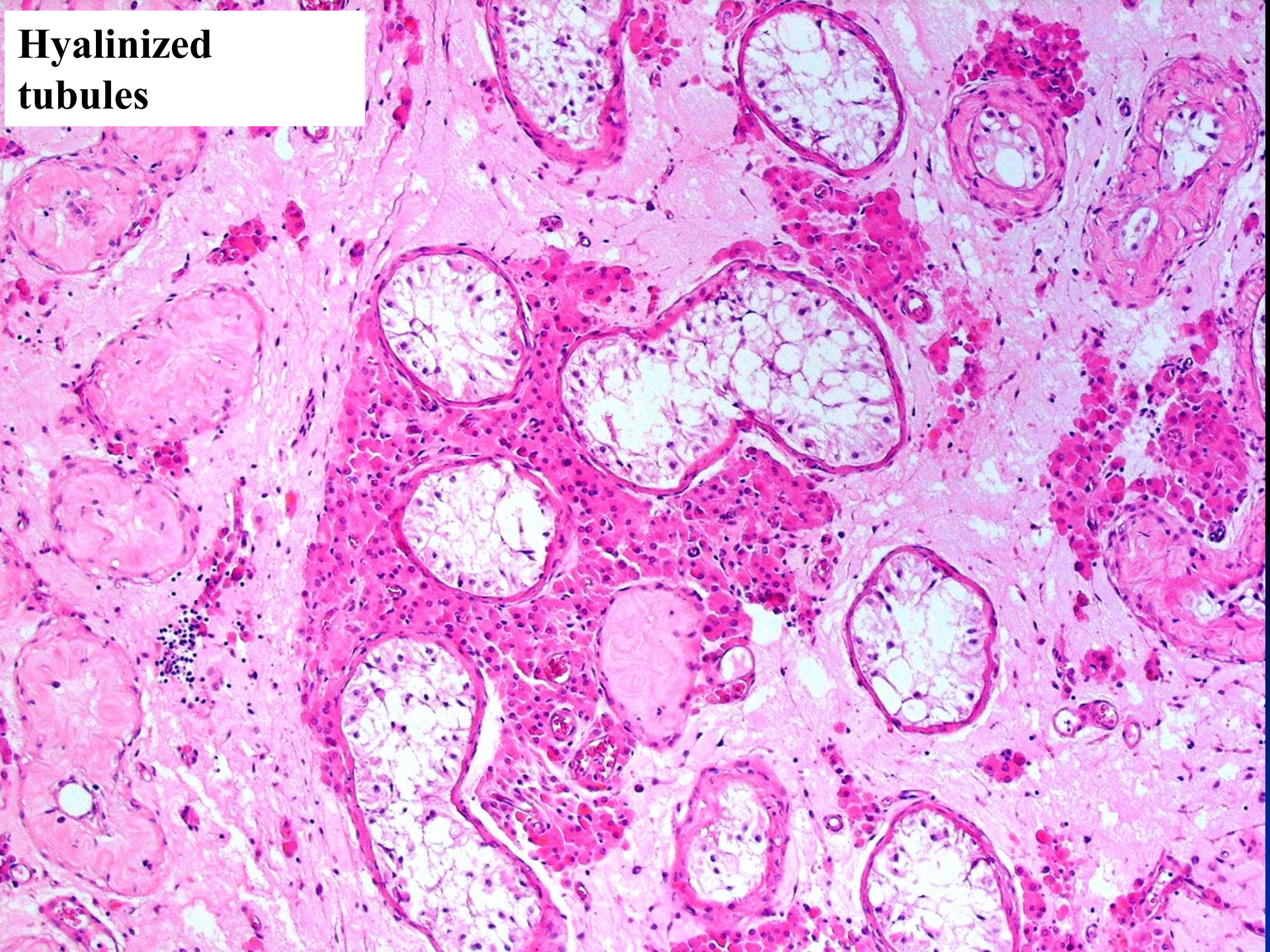
Regression : Coarse intratubular calcifications



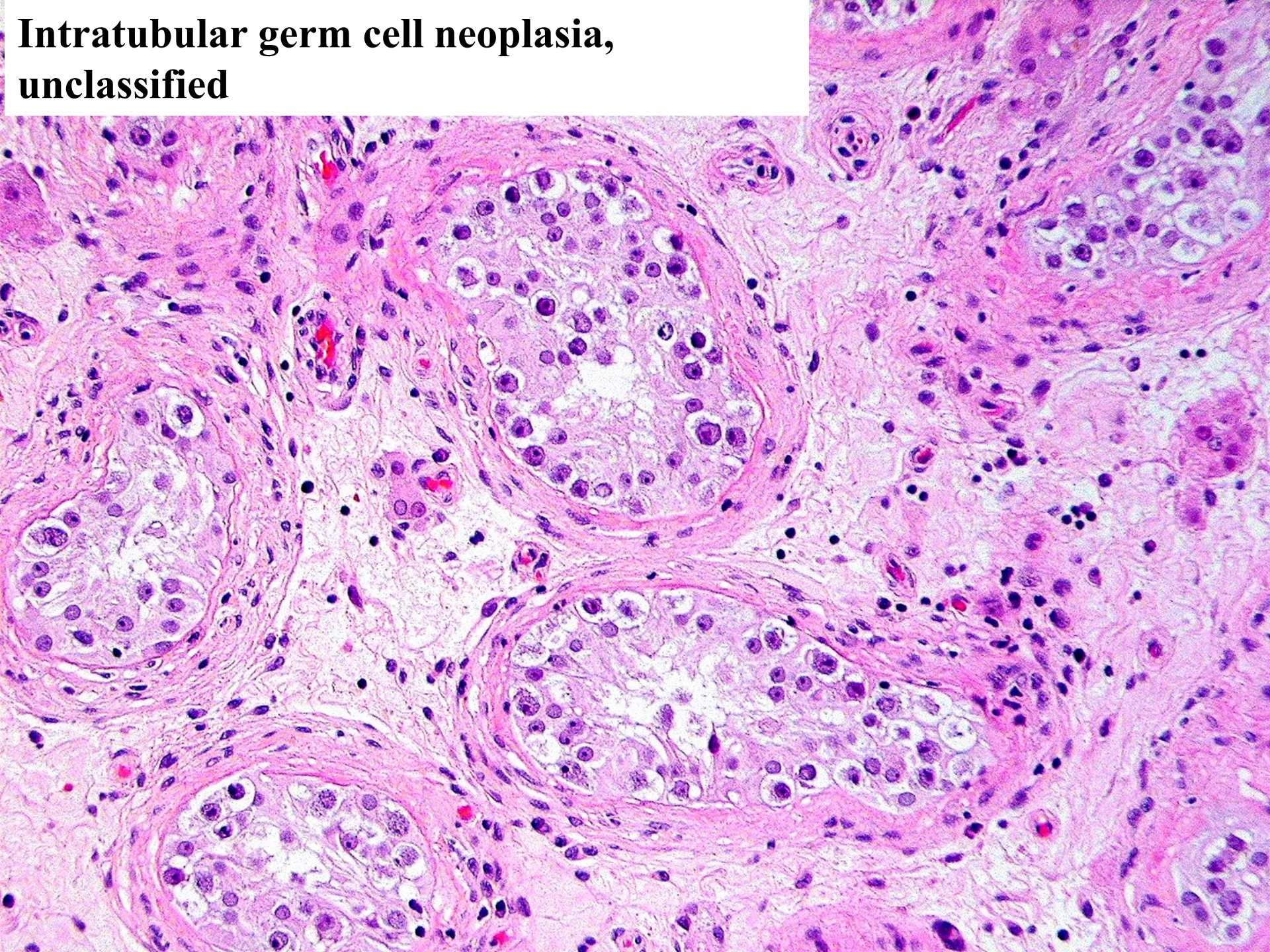
Regression: Lymphoplasmacytic infiltrate & scar






Hyalinized
tubules

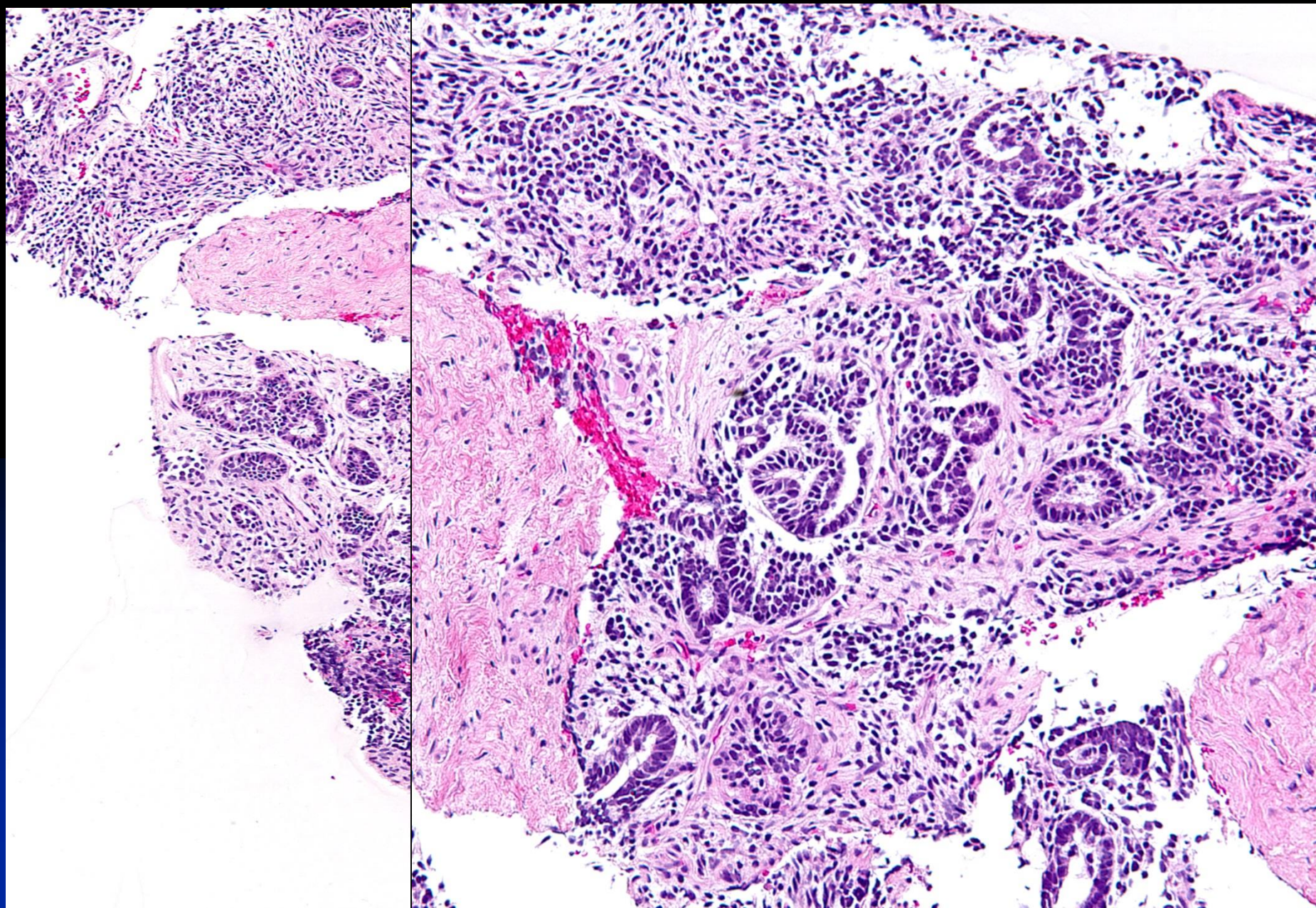
Intratubular germ cell neoplasia, unclassified



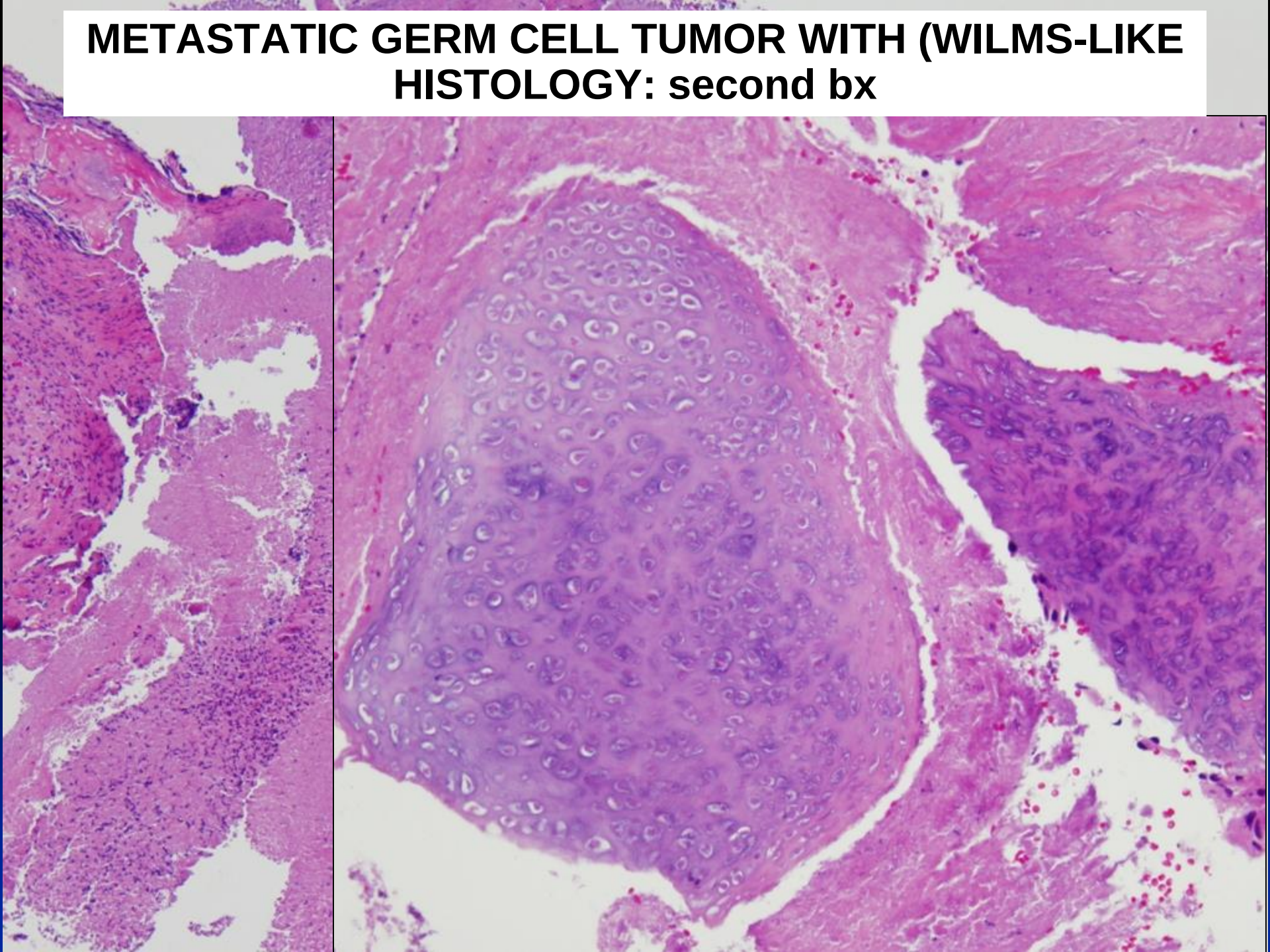
LESSONS FROM REGRESSION : when to look for signs of regression

- Patient presents with widespread metastatic choriocarcioma
- Patient presents with retroperitoneal GCT
- Patient with unusual tumor in retroperitoneum – Wilms', PNET
- Orchiectomy in a young patient for pain or non specific symptoms and scar in first few sections
- Patient with germ cell tumor in spermatic cord but none in testis
- Histology of the primary and mets does not match

METASTATIC GERM CELL TUMOR WITH NEPHROBLASTOMA (WILMS-LIKE TUMOR)



METASTATIC GERM CELL TUMOR WITH (WILMS-LIKE HISTOLOGY: second bx



TROPHOBLASTIC TUMORS OF TESTIS

- **Choriocarcinoma (including monophasic CC)**
- ***Placental site trophoblastic tumor (HPL+. p63 -)***
- ***Epithelioid trophoblastic tumor (HPL -. p63 +)****
- ***Cystic trophoblastic tumor****

*** Frequently at metastatic sites***

WHO 2016 CLASSIFICATION OF GERM CELL TUMORS OF TESTIS

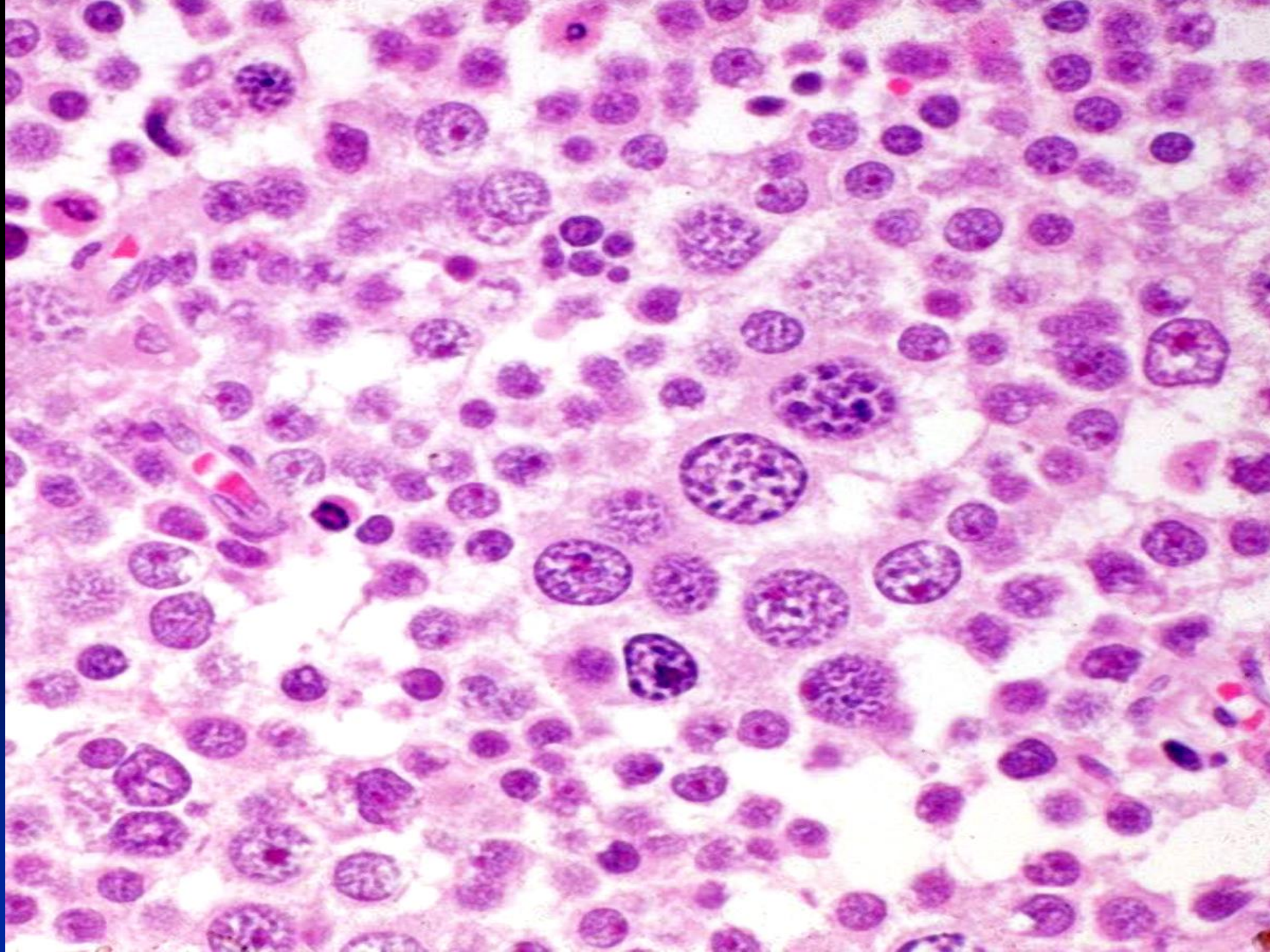
- **NOT ASSOCIATED WITH GCNIS**
  - *-Spermatocytic tumor*
  - *- Yolk sac tumor, prepubertal type*
  - *- Teratoma, prepubertal type (all age groups)*
    - *- Epidermoid and Dermoid cyst*
    - *- Well differentiated neuroendocrine tumor (monodermal teratoma)*
  - *- Mixed teratoma and Yolk sac tumor, prepubertal type*

SPERMATOCYTIC TUMOR (2016 WHO NOMENCLATURE)

Unique

- Older age group (average age 52 yrs; 19-92 range)
- Not associated with GCNIS/ITGCN
- Not associated with cryptorchidism
- Not associated with 12p abnormalities – gains of Chr 9 and1:*FGFR3* & *HRAS* mutations or gene amplifications
- Not associated with other germ cell components
- No ovarian counterpart or extragonadal location
- Clinically benign, rare metastasis. Death if associated with sarcomatous transformation

SPERMATOCYTIC TUMOR



PEDIATRIC YST

- **Unlike Adult YST**

- No racial or geographic predilection

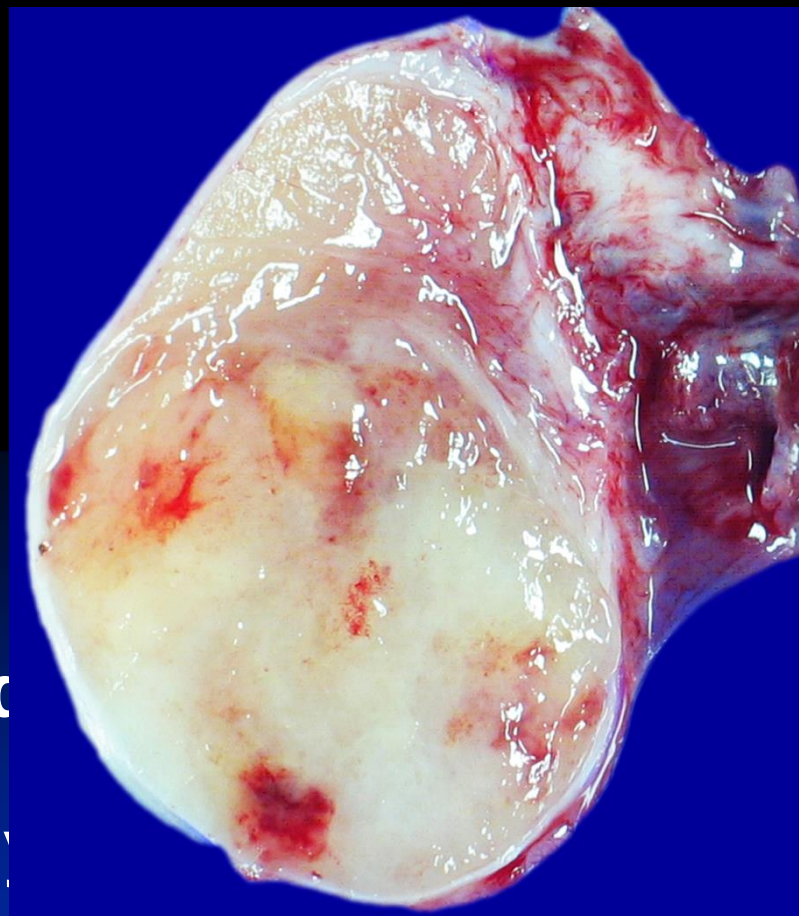
- Stable incidence

- not associated with GCNIS/ITGCN

- Always pure

- 16-20 months age

- **Low incidence of advanced and metastasis**
- **Responds to chemotherapy**
- **Survival approaches 100%**



TERATOMA

“Prepubertal”

- ***Teratoma in prepubertal age***
  Teratoma without ITGCN/GCNIS
- **Teratoma in postpubertal age**
  Teratoma without ITGCN/GCNIS

“Postpubertal”

- **Teratoma in postpubertal age**
  with ITGCN/GCNIS

PEDIATRIC TERATOMA

- No association with GCINIS, dysgenetic gonadal changes, scarring or i12p
- Tumors with this histology occur in post-pubertal age – “benign prepubertal teratoma”- designation encompasses all ages

Distinct differences from adult teratoma:

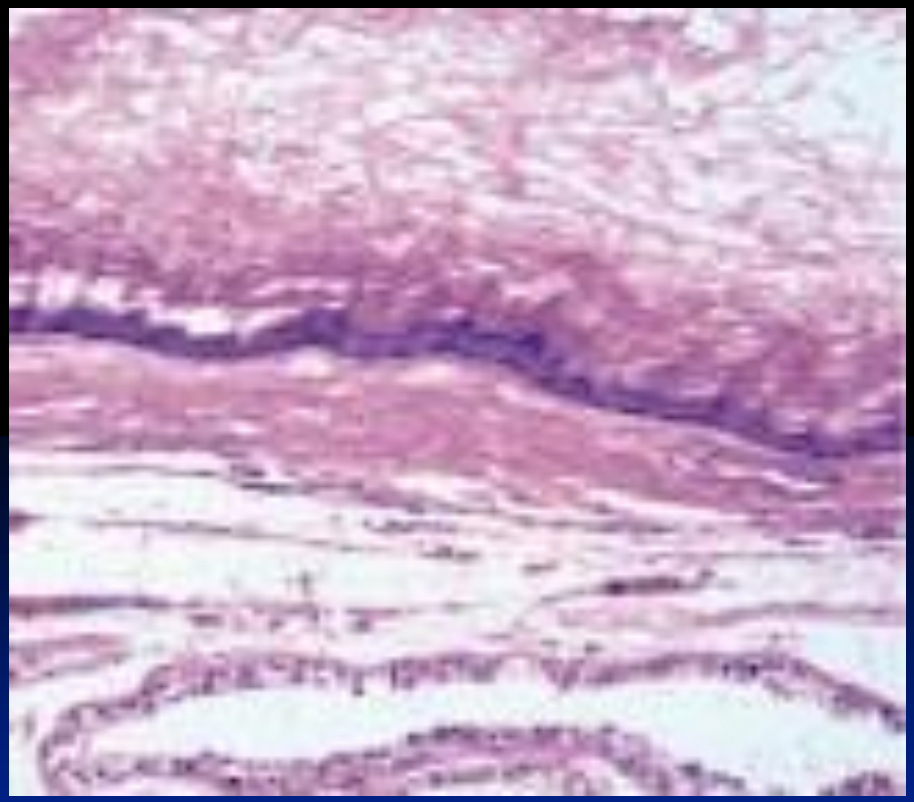
Calcification, hair follicles frequest; may have other endodermal, mesenchymal or ectodermal components

Smooth muscle tends to envelop epithelium

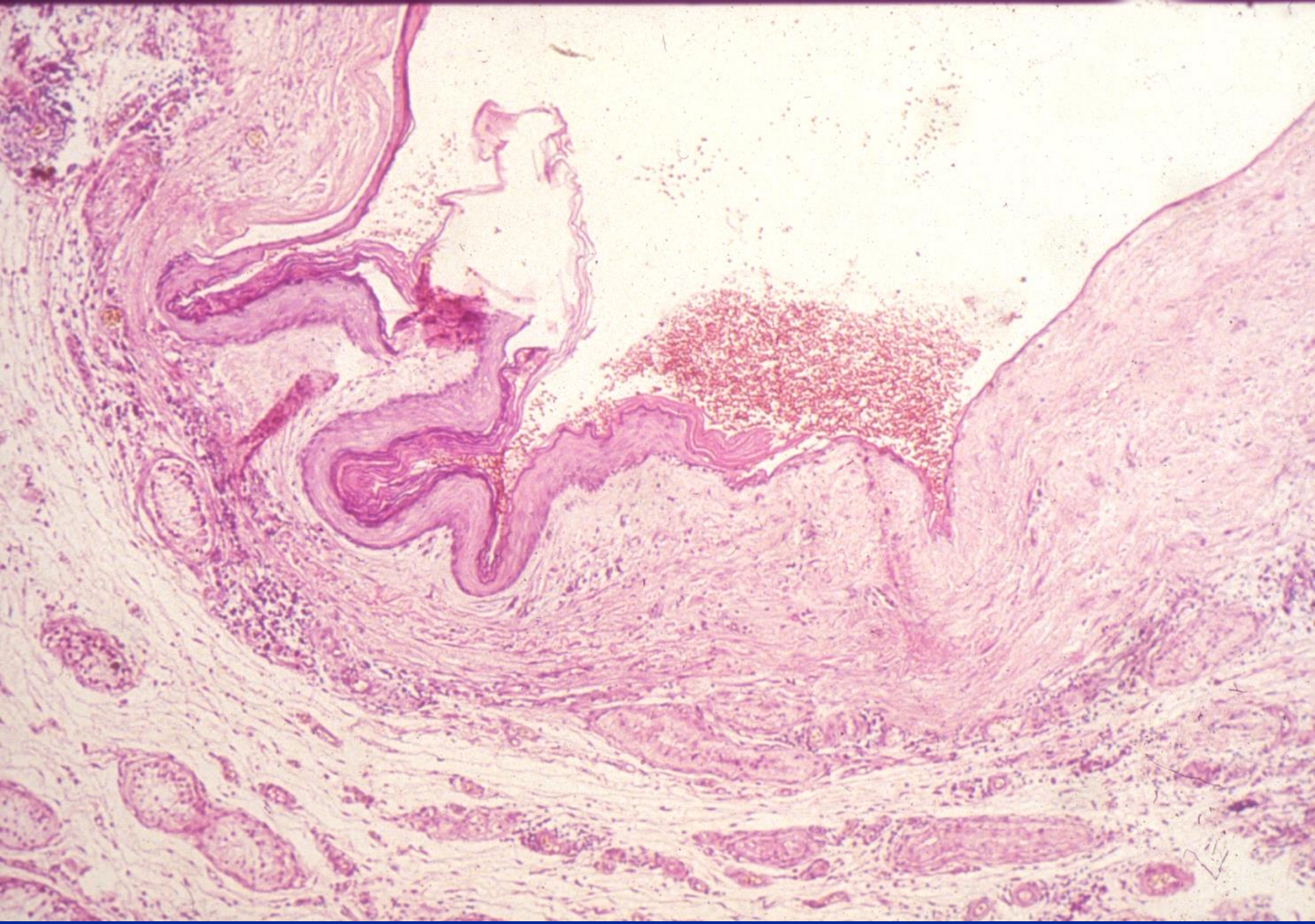
Salivary gland, pancreas etc

In postpubertal setting: Lack scar, tubular atrophy, necrosis, microlithiasis – consider 12p study

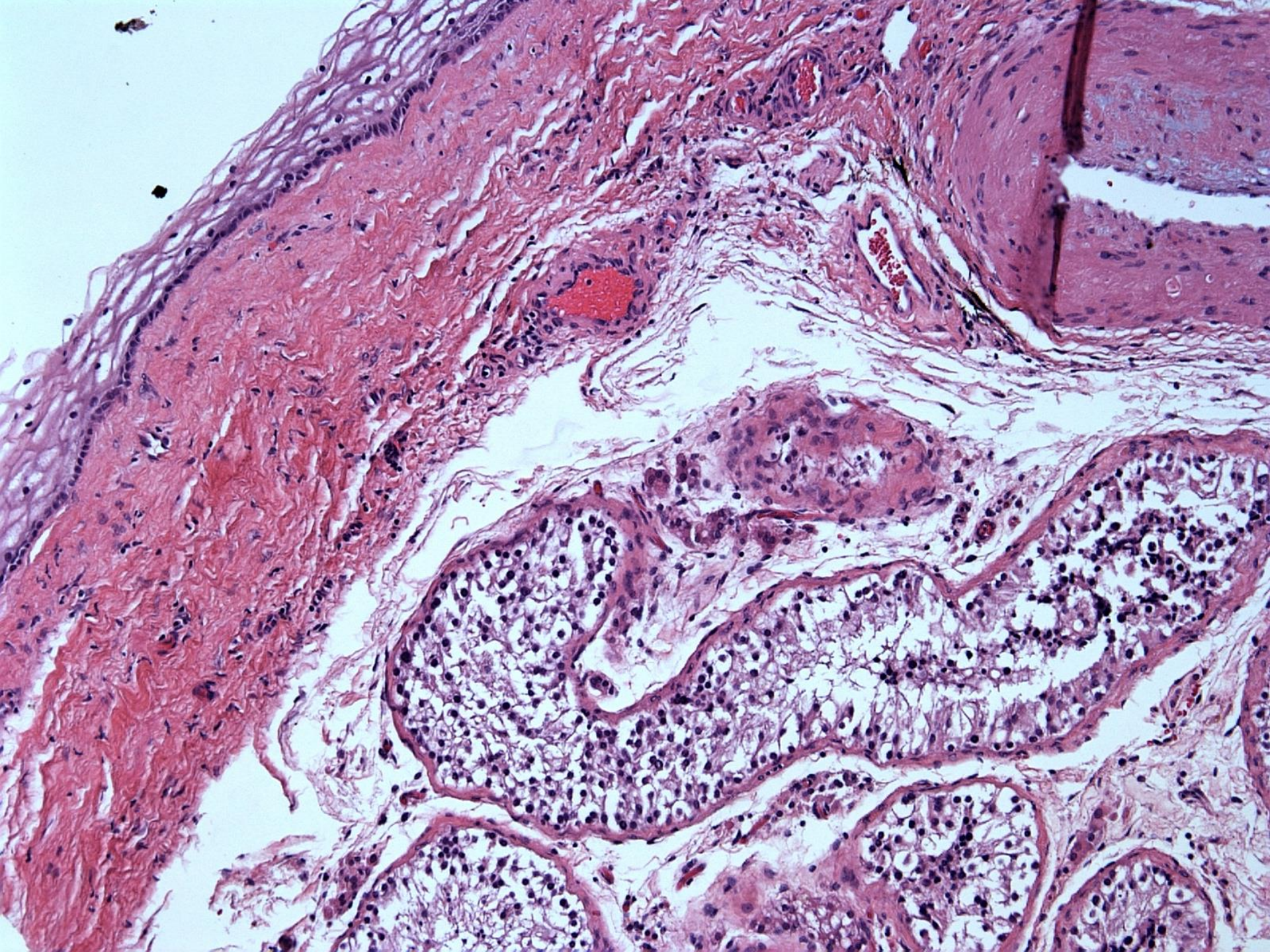
TERATOMA, “prepubertal type” - EPIDERMOID CYST - BENIGN



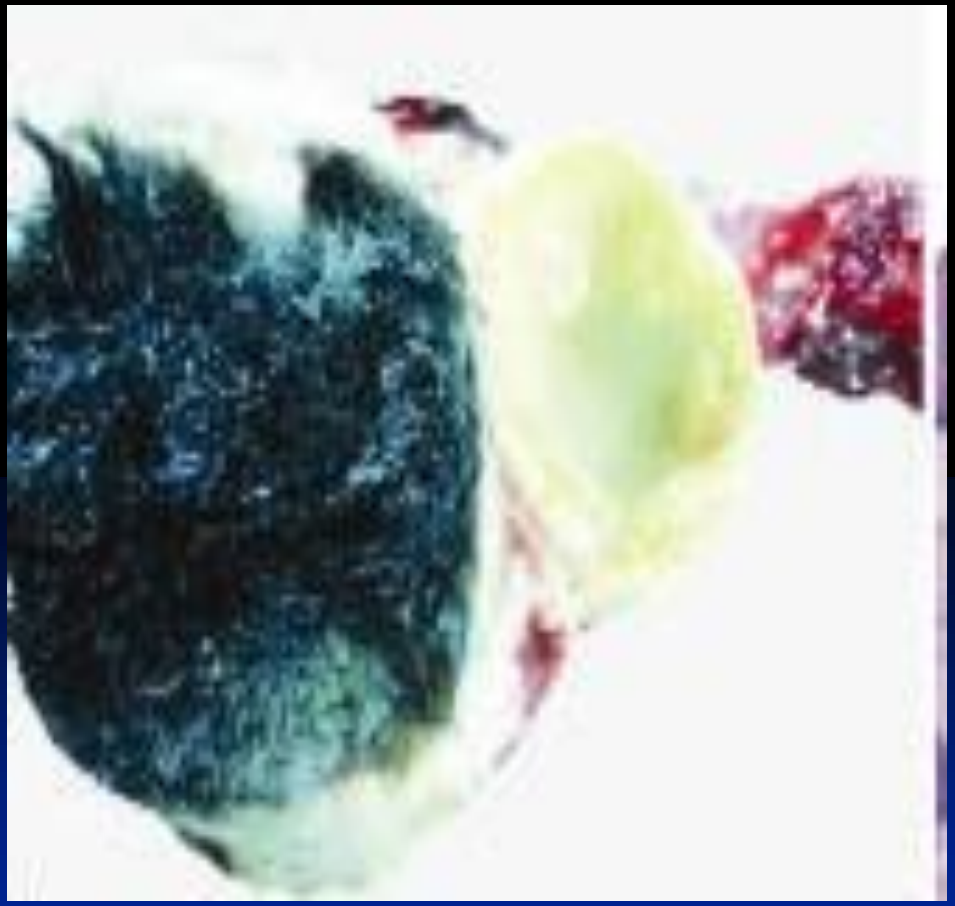
Lacks
ITGCN

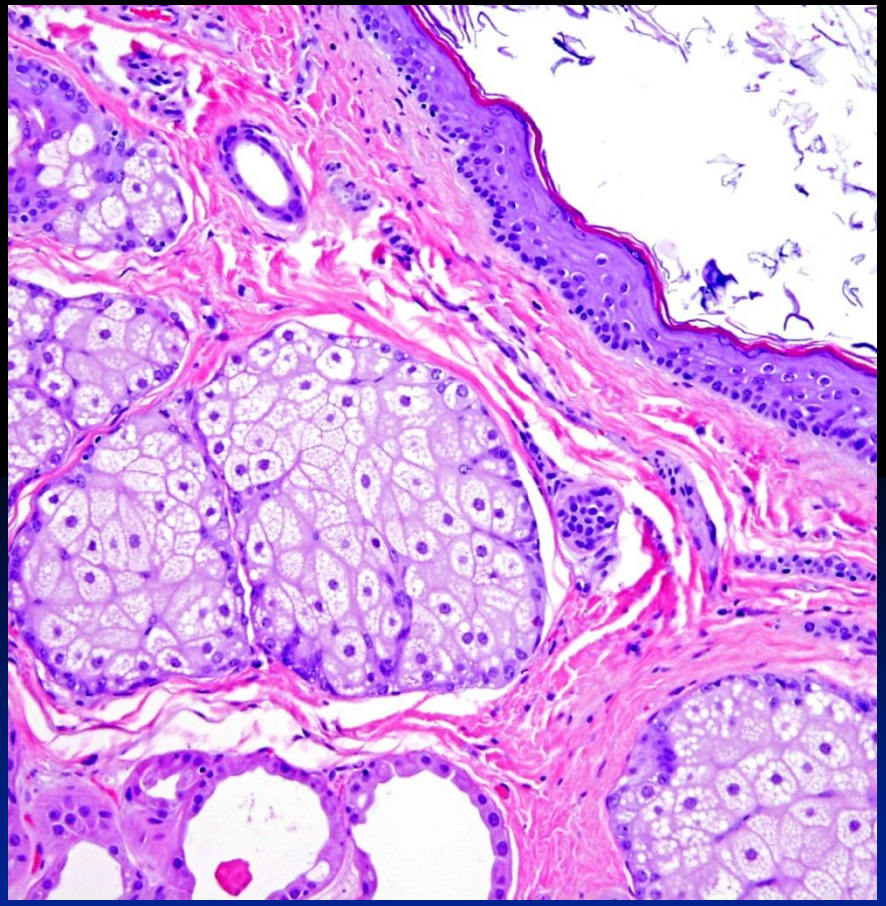


Look for GCNIS



TERATOMA “prepubertal type”, - DERMOID CYST





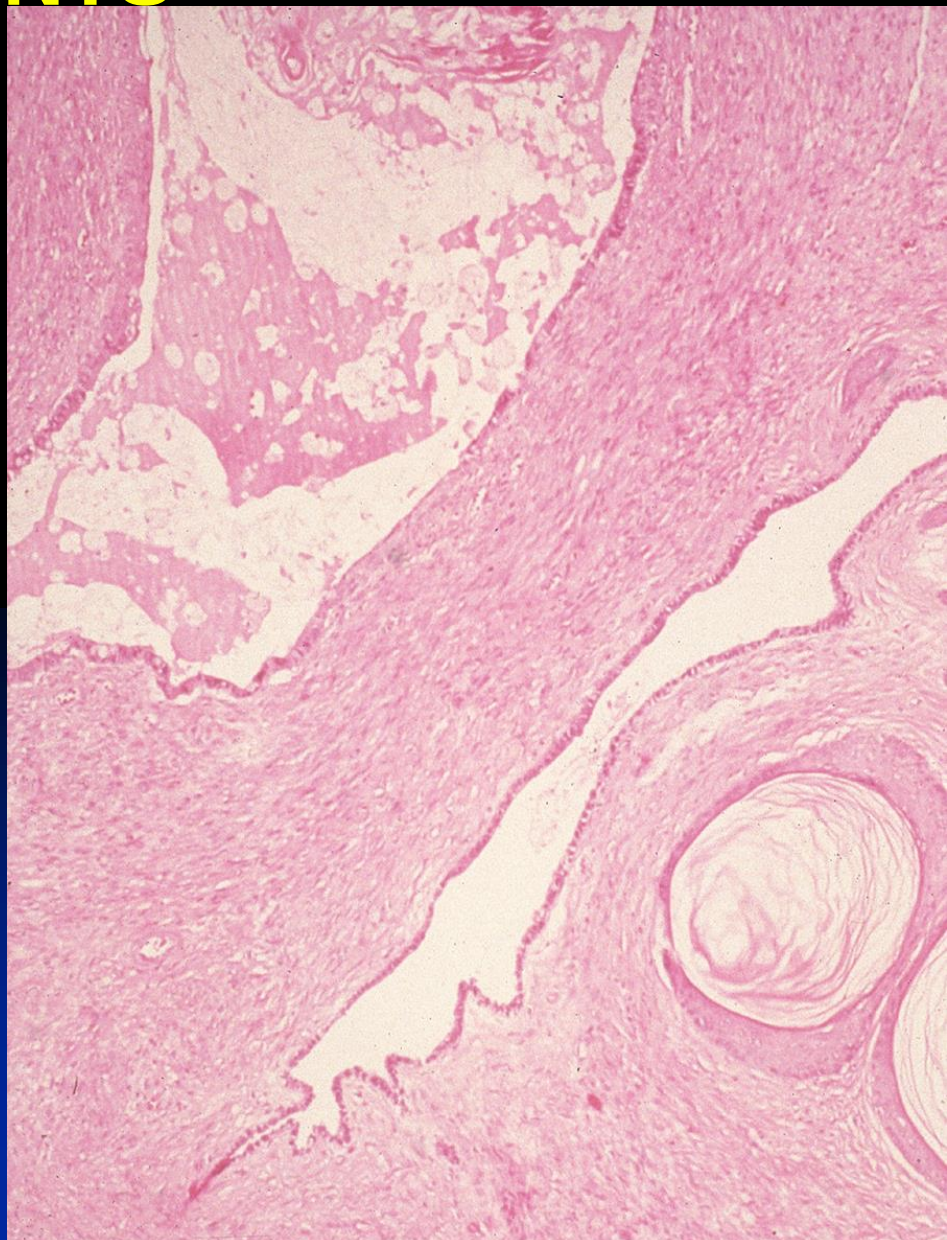
Lacks GCNIS

TERATOMA –POST PUBERTAL TYPE

- Young adults
- 3-7% pure
- Almost 50% of mixed GCT contain teratoma
- Immaturity in epithelial or mesenchymal elements no impact on prognosis – *atypia is not graded*
- Cytologic atypia with architectural overgrowth – X4 –low power field - *“ malignant transformation in teratoma”*

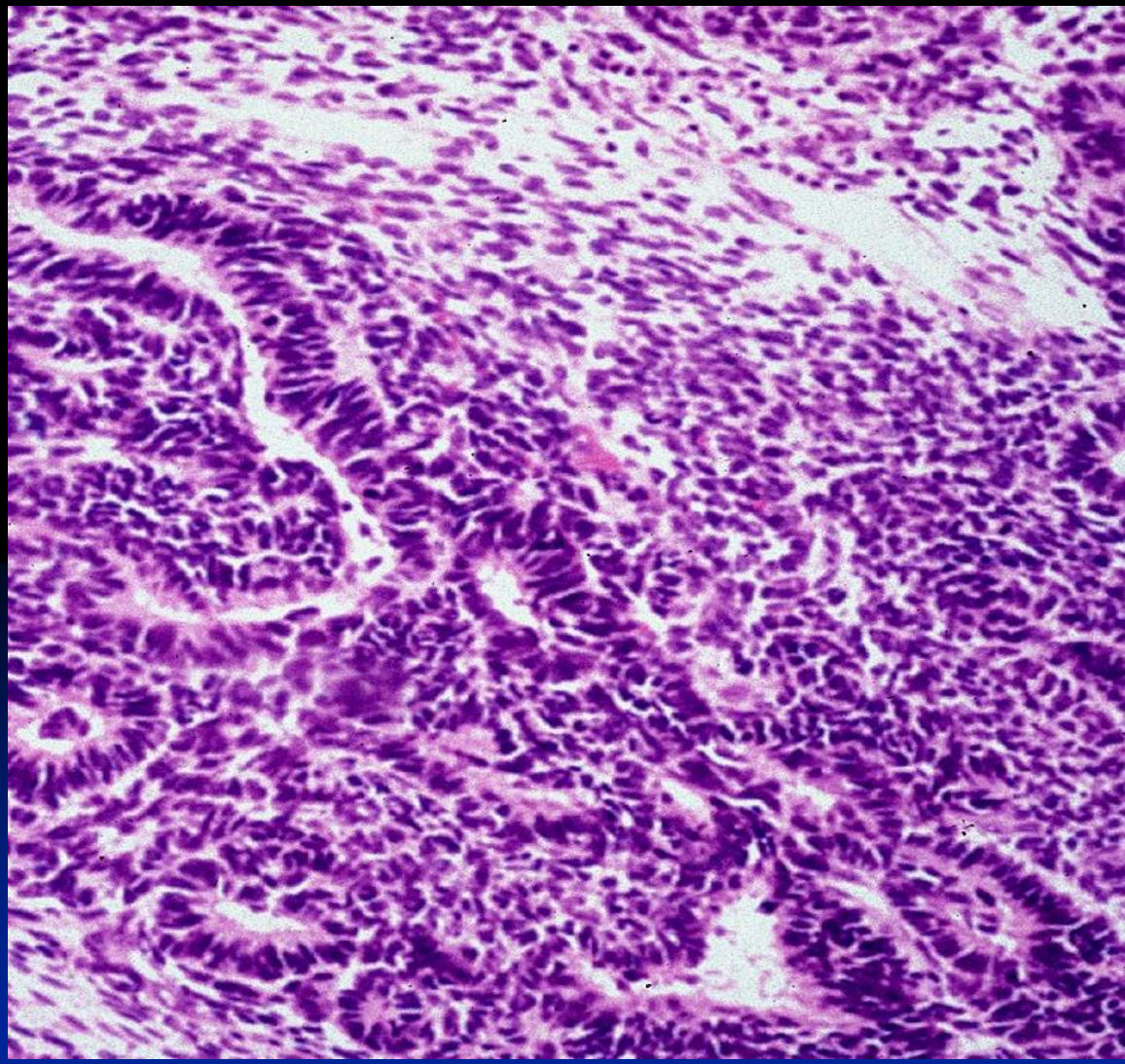
POST PUBERTAL, MATURE TERATOMA ELEMENTS

- Adult type tissue
- Organoid
- Histologically recognizable as adult tissue
- Ectoderm – Epidermis, neuronal tissue
- Endoderm – GI, respiratory muscosa, mucous glands, etc.
- Mesoderm – Bone, cartilage, muscle, fat, etc.



IMMATURE TERATOMA ELEMENTS

- Fetal type
- Embryonic tissue
- Immature mesenchyme – cellular spindled
- Immature skeletal muscle – rhabdomyoblasts
- Immature neuroepithelial structures



PENILE CANCER

What is new in the WHO 2016:

- Topic 11: Classification of Intraepithelial lesions

CLASSIFICATION OF PENILE SCC

Non HPV-related	HPV-related
INTRAEPITHELIAL LESIONS	INTRAEPITHELIAL LESIONS
INVASIVE LESIONS	INVASIVE LESIONS

Penile intraepithelial neoplasia (PeIN)
Historical nomenclature

- Erythroplasia of Queyrat (glans)
- Bowen's disease (shaft)
- Bowenoid papulosis
- Dysplasia (Mild, moderate, and severe)
- Carcinoma in situ
- Squamous intraepithelial lesion (SIL); low and high grade
- Penile intraepithelial neoplasia (PeIN 1, 2, 3)

Penile intraepithelial neoplasia (PeIN)

HPV-UNRELATED

DIFFERENTIATED (Simplex) PeIN

HPV-RELATED

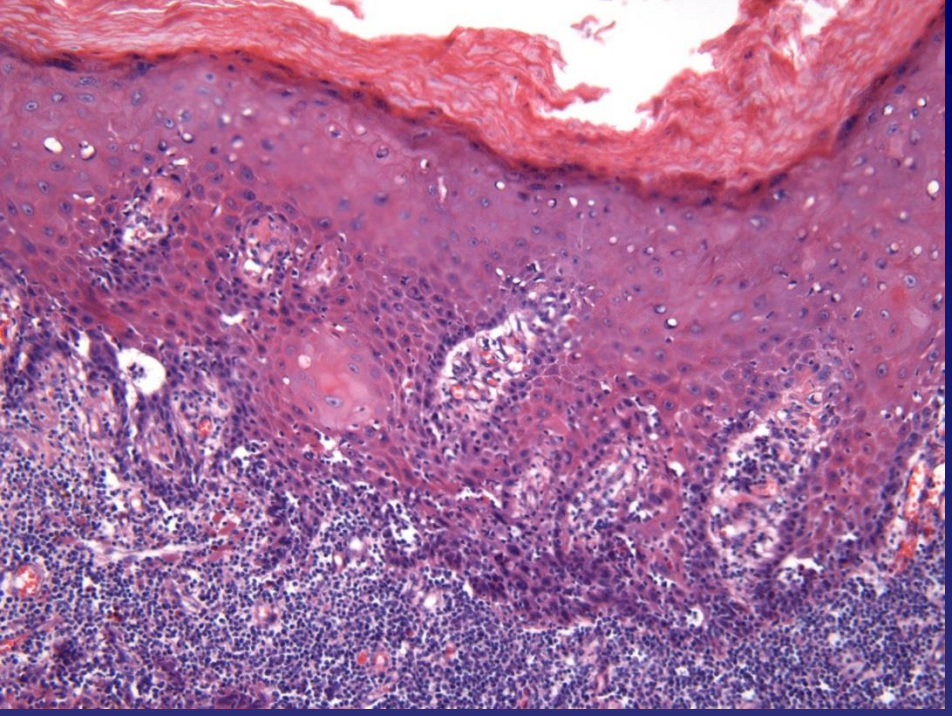
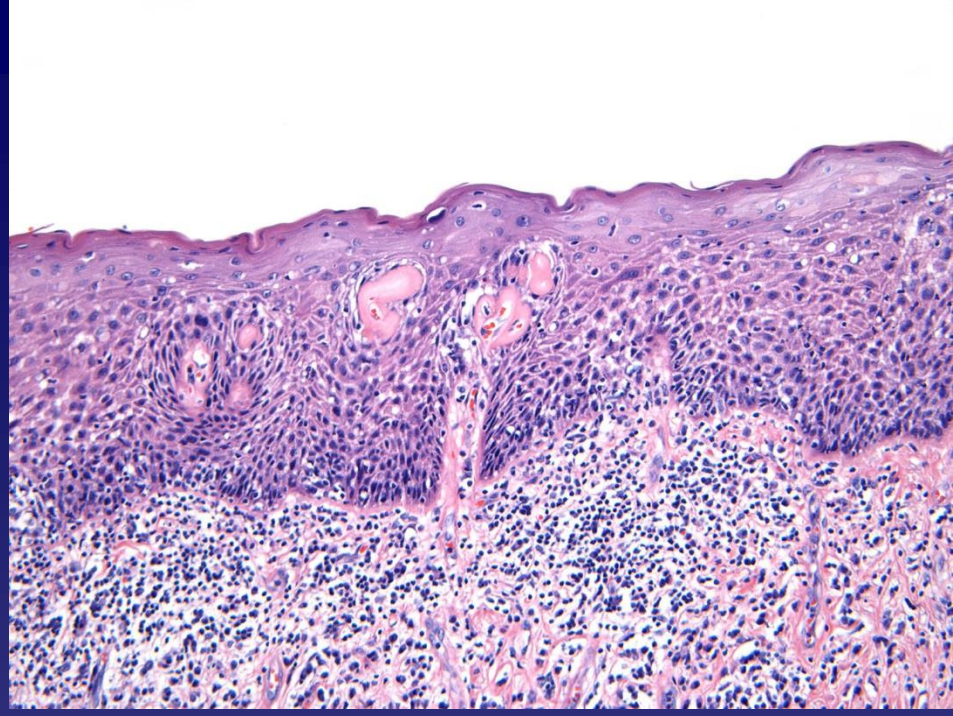
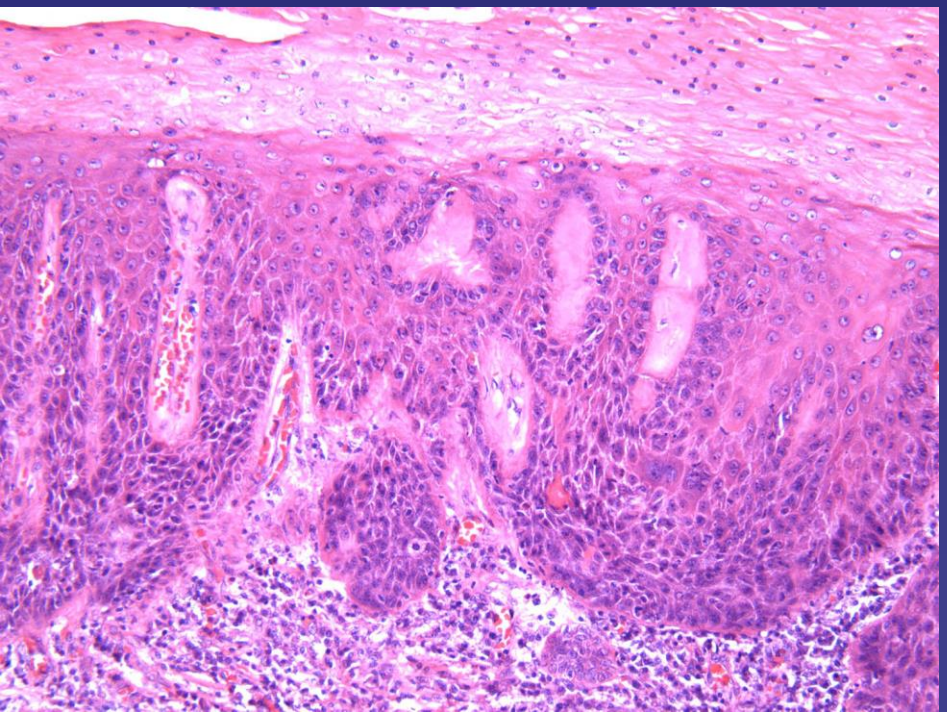
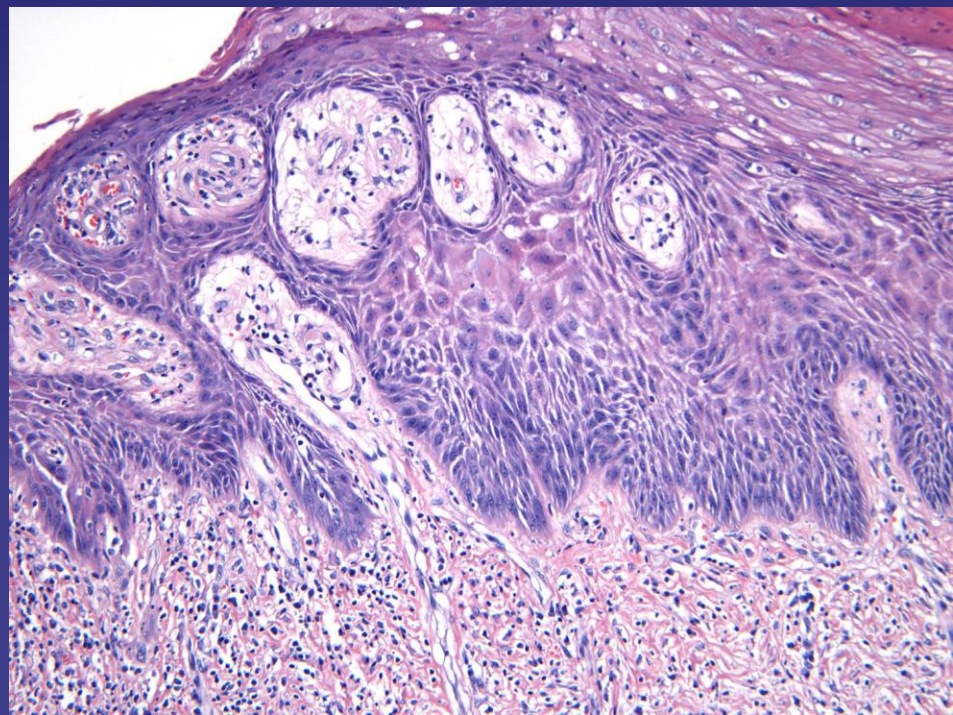
UNDIFFERENTIATED PeIN

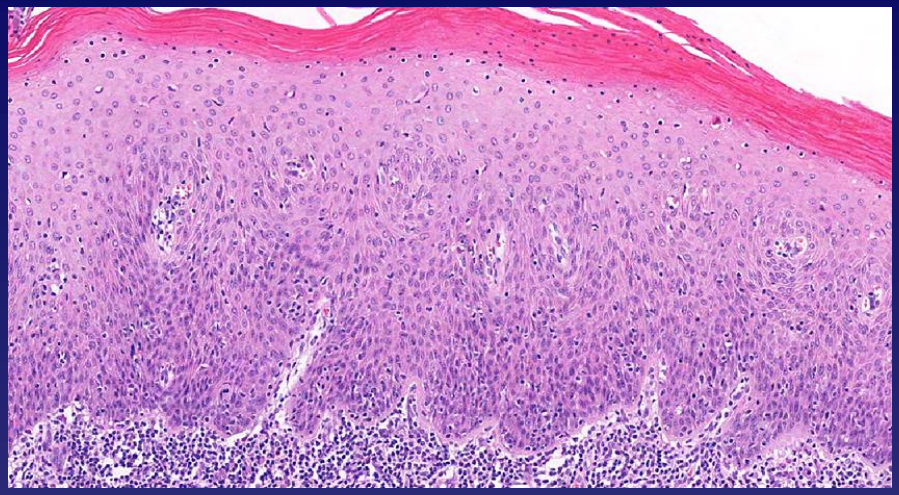
Basaloid

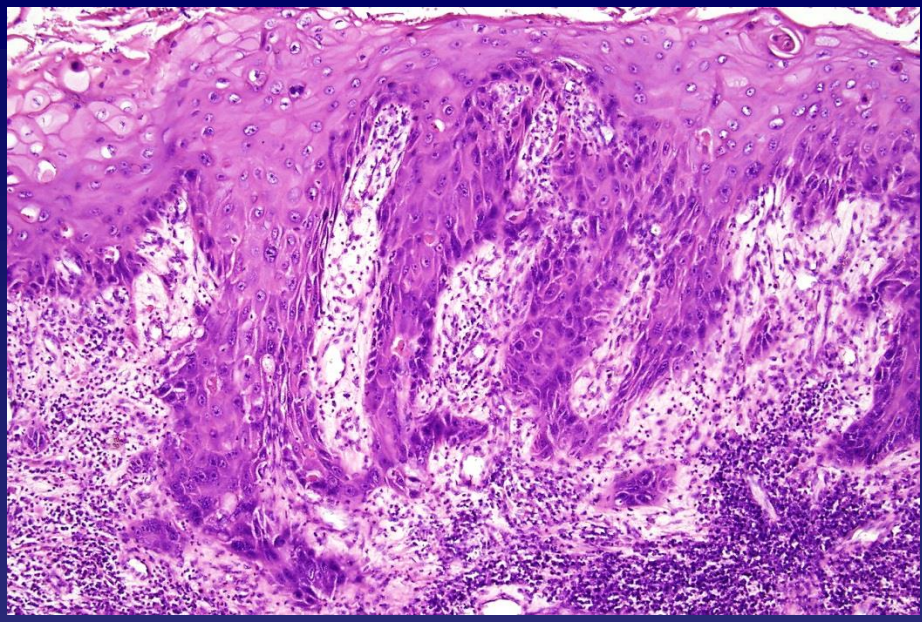
Warty

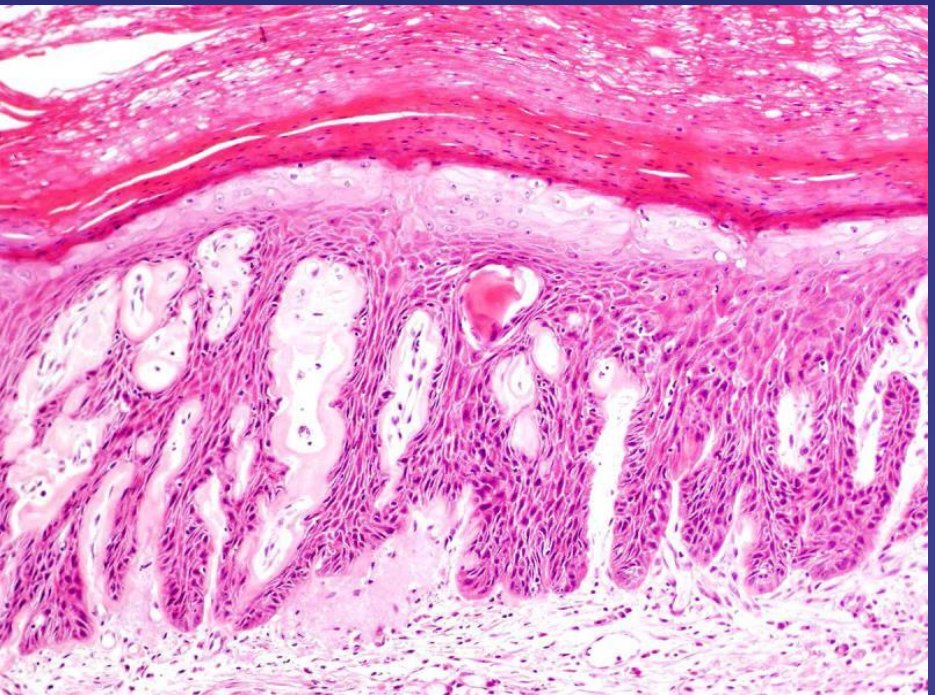
Warty/basaloid

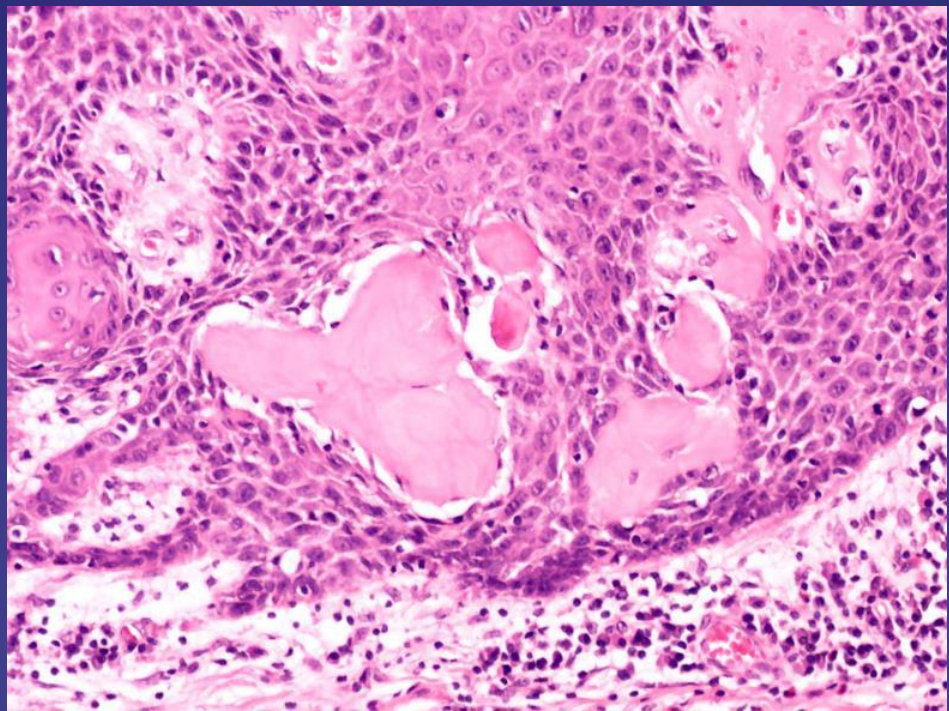
	Differentiated PeIN	Undifferentiated PeIN
Age (years)	>60	40-50
Location	Foreskin	Glans
Color	White/gray	Red
Multifocal	Sometimes	Often
HPV-related	No	Yes
p16	Negative	Positive
LS	Yes	No
Associated SCC	Usual Verrucous Sarcomatoid	Warty Basaloid Warty-Basaloid

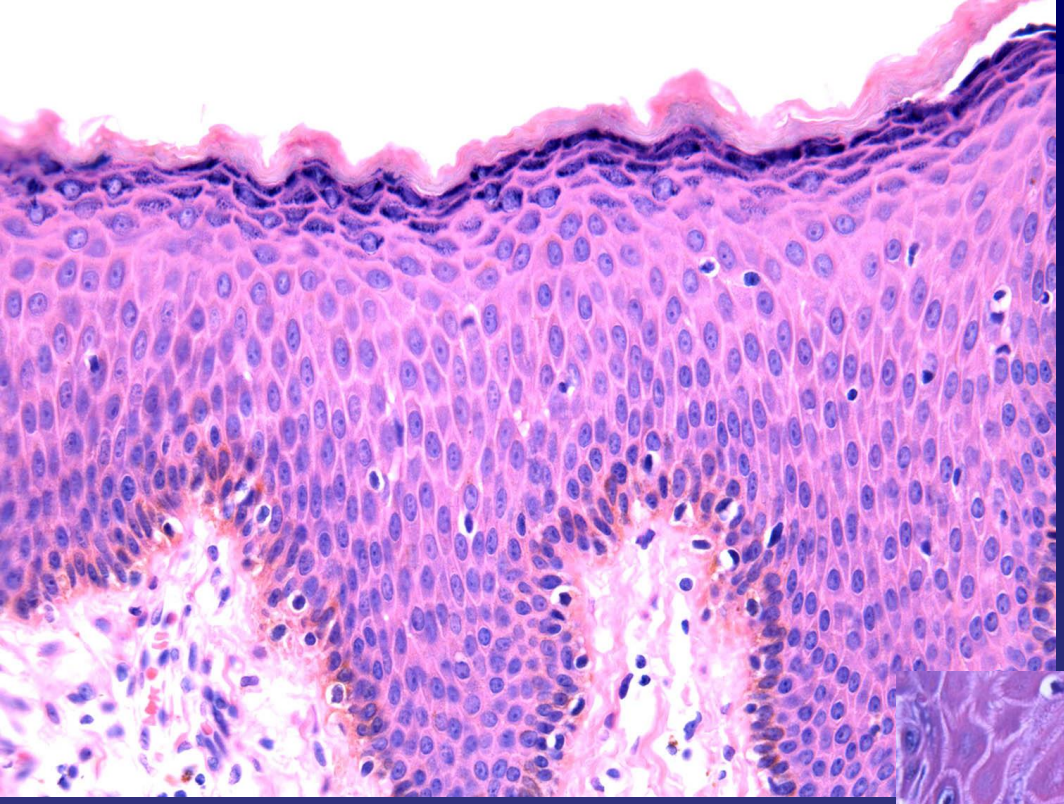









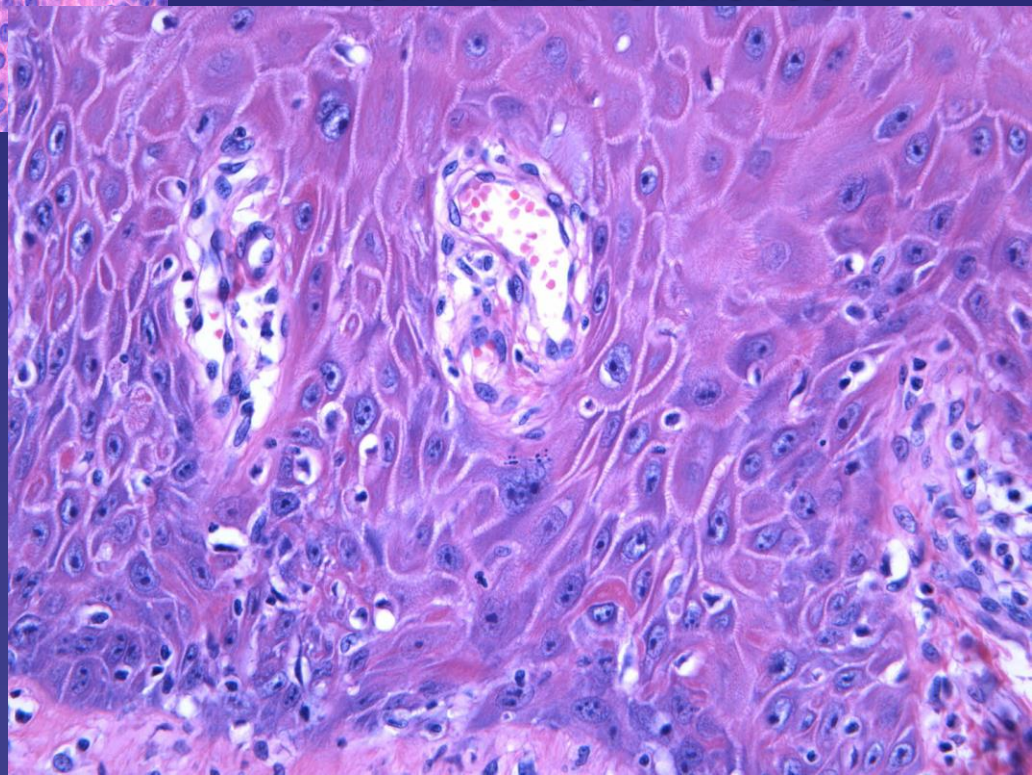


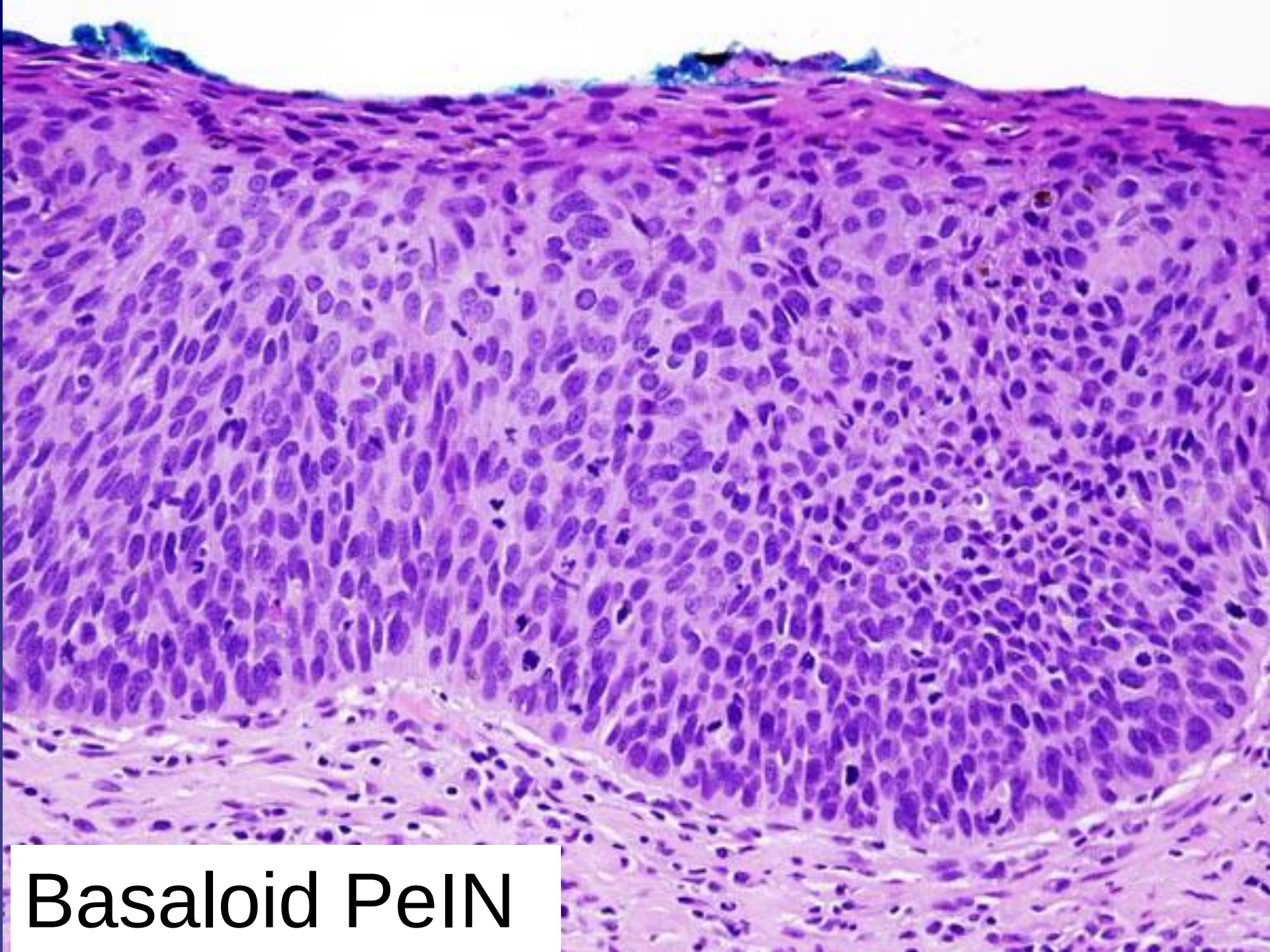




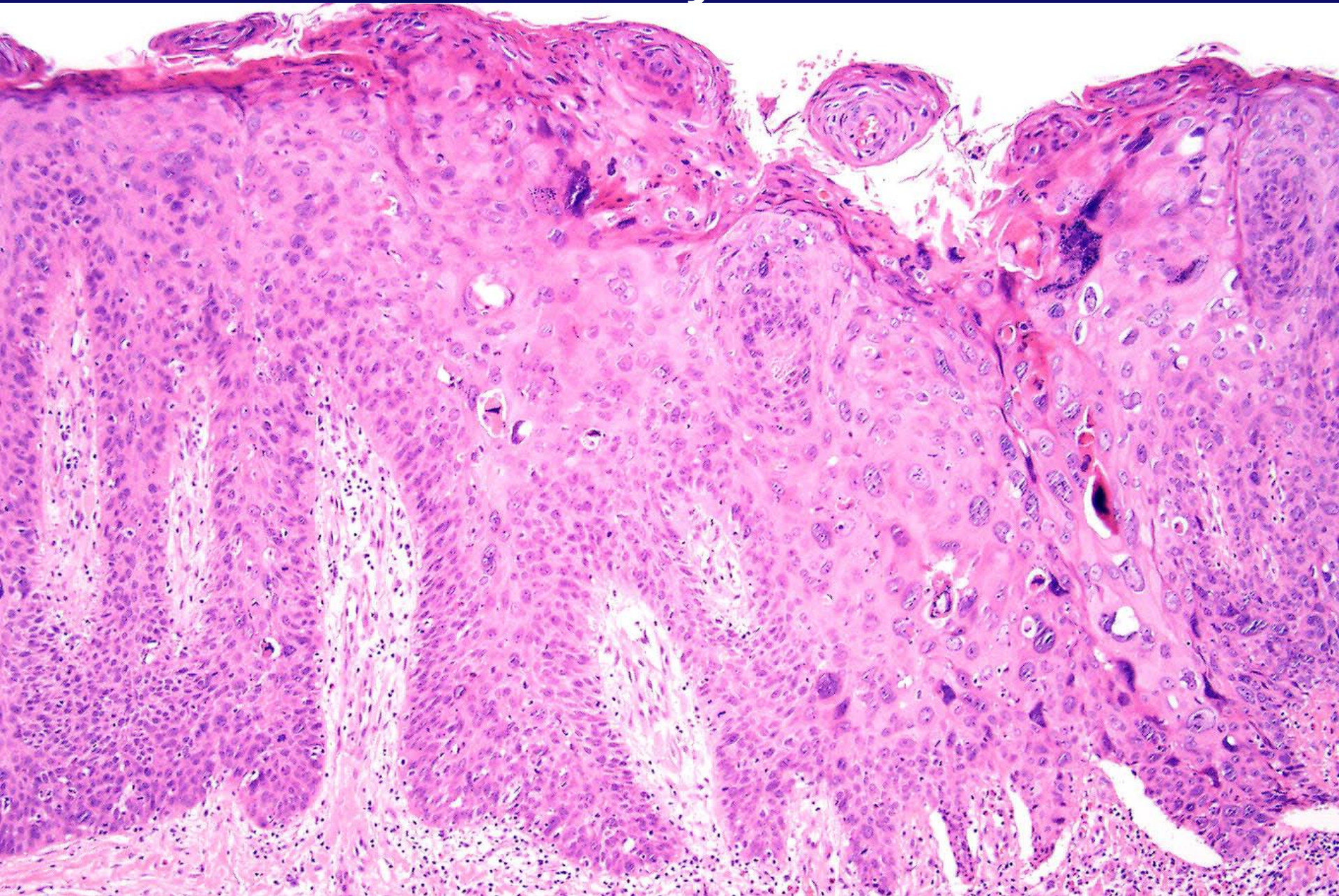
Normal epithelium

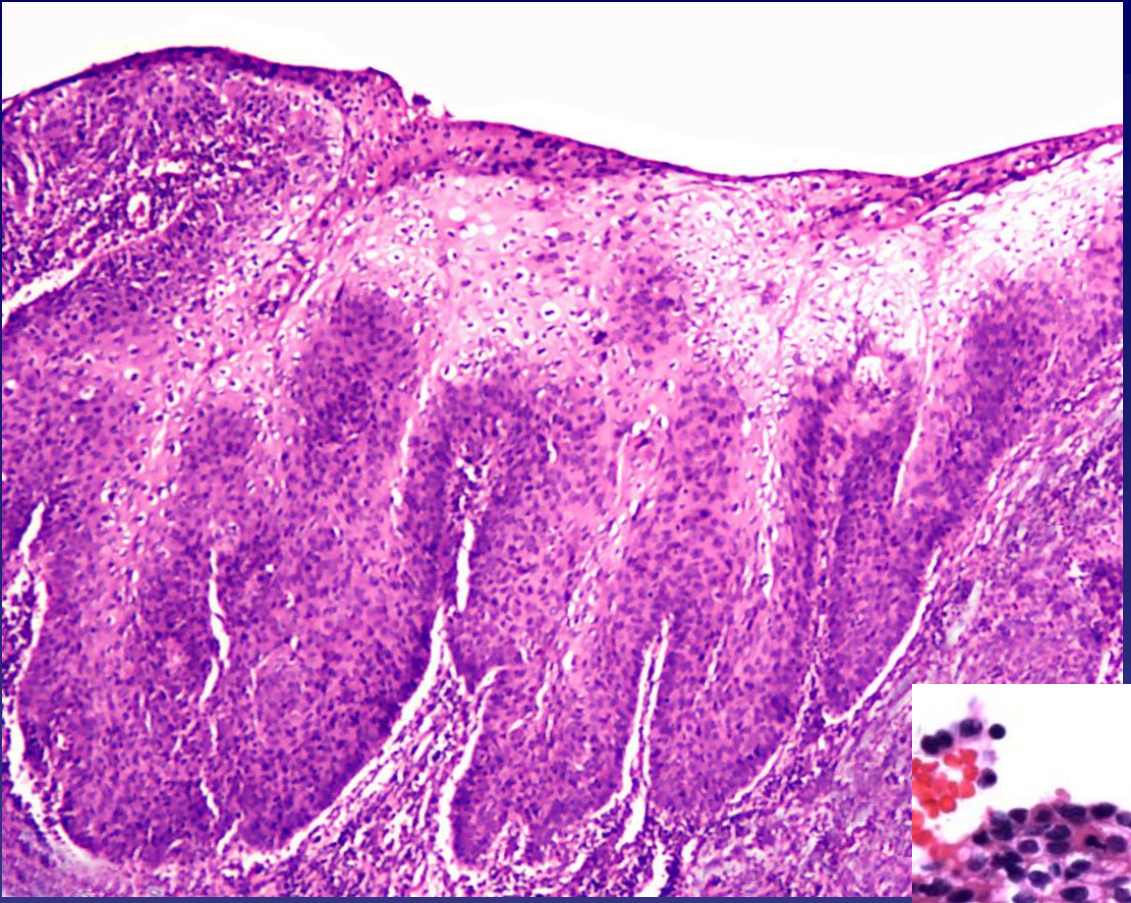
PeIN differentiated

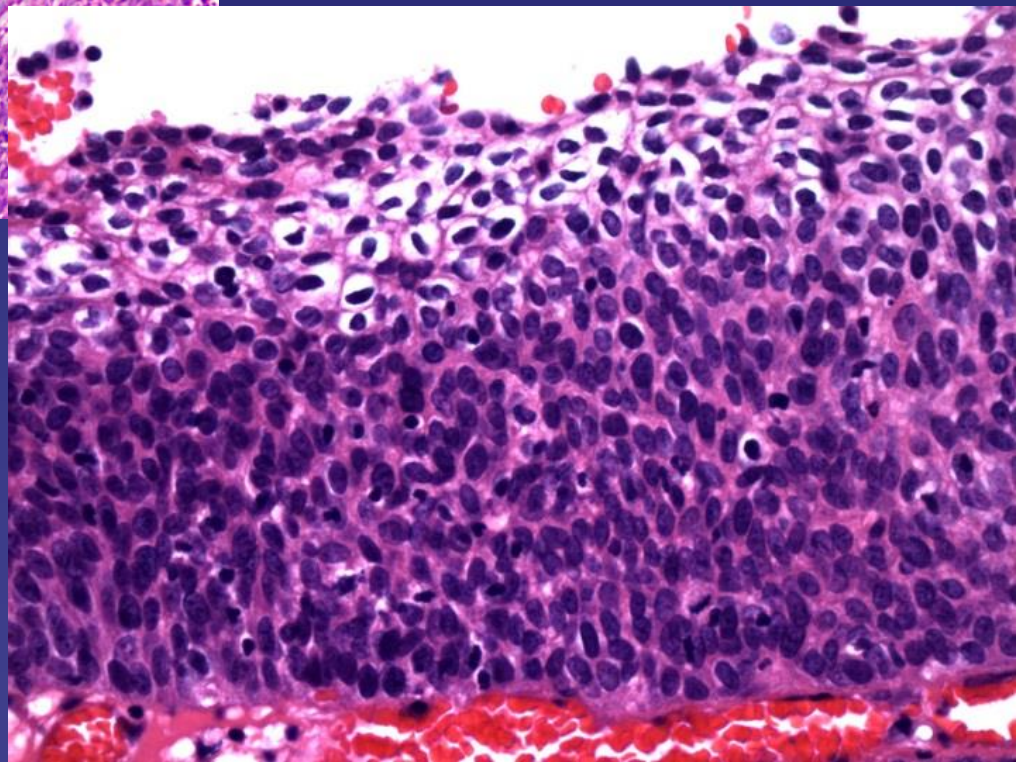



Basaloid PeIN

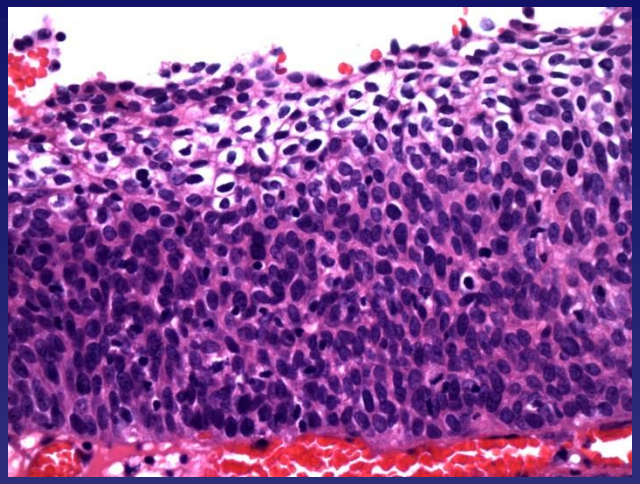
Warty PeIN







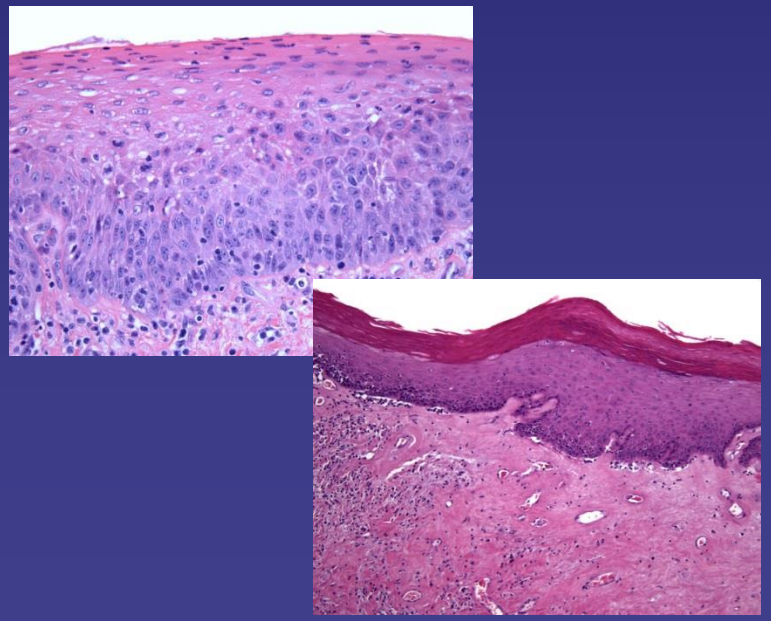
Penile SCC
Bimodal pathway of ca progression



40%

HPV-related

- Warty Ca (100%)
- Basaloid Ca (>80%)



60%

HPV-unrelated

- Keratinizing SCC (>65%)
- Verrucous Ca (>65%)
- Pseudohyperplastic Ca (100%)

What is new in the WHO 2016:

- **Topic 12: Classification & Grading of Squamous cell carcinoma**

WHO CLASSIFICATION OF PENILE SQUAMOUS CELL CA

Non HPV related:

SCC:

- -usual
- -pseudoglandular
- -Psudohyperplastic

Verrucous:

- - pure
- - cuniculatum

Papillary NOS

Adenosquamous

Sarcomatoid

Mixed

HPV related

Basaloid

- -classical
- -papillary variant

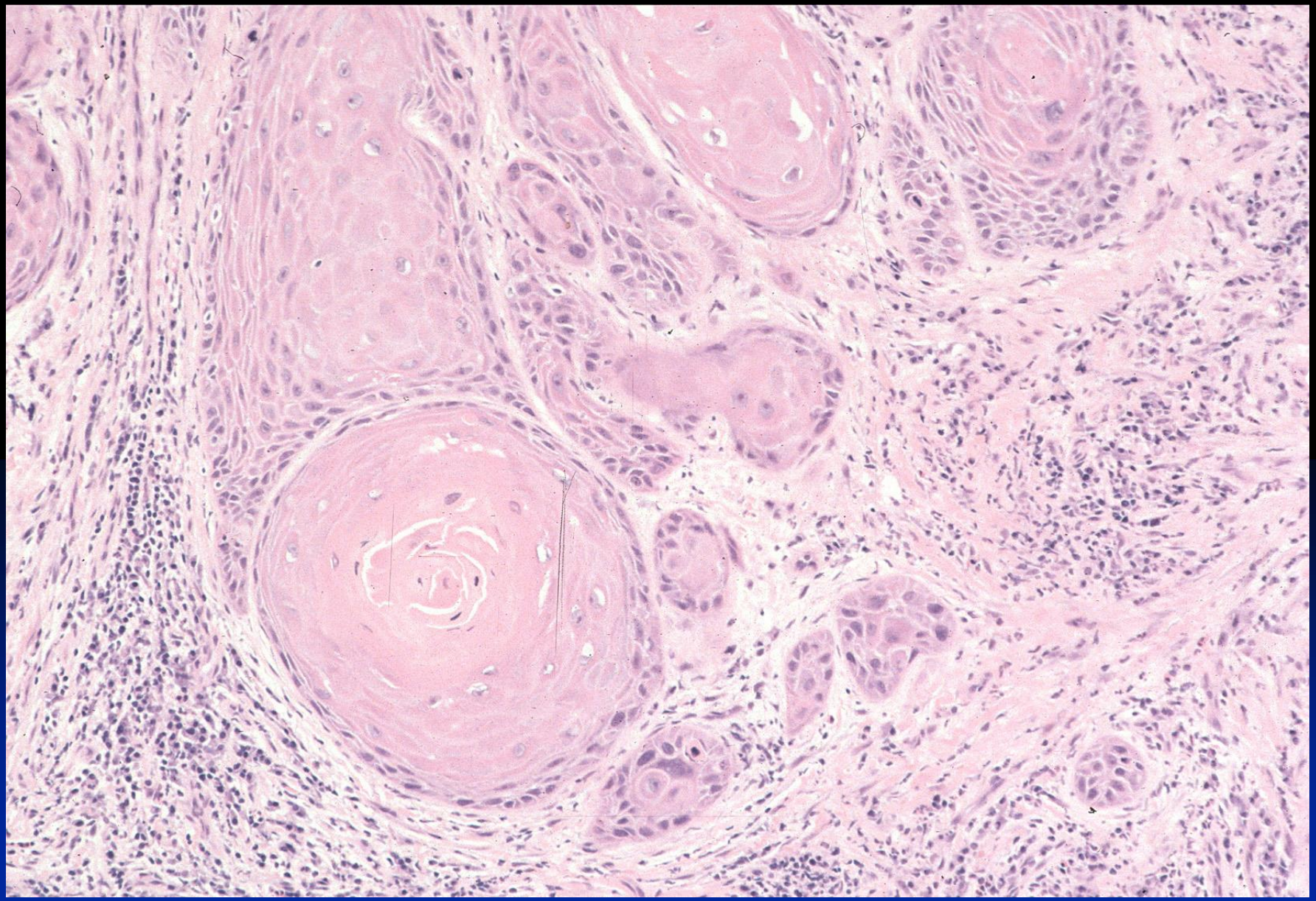
Warty

- - classical
- - warty-basaloid
- - clear cell

Lymphoepithelioma like

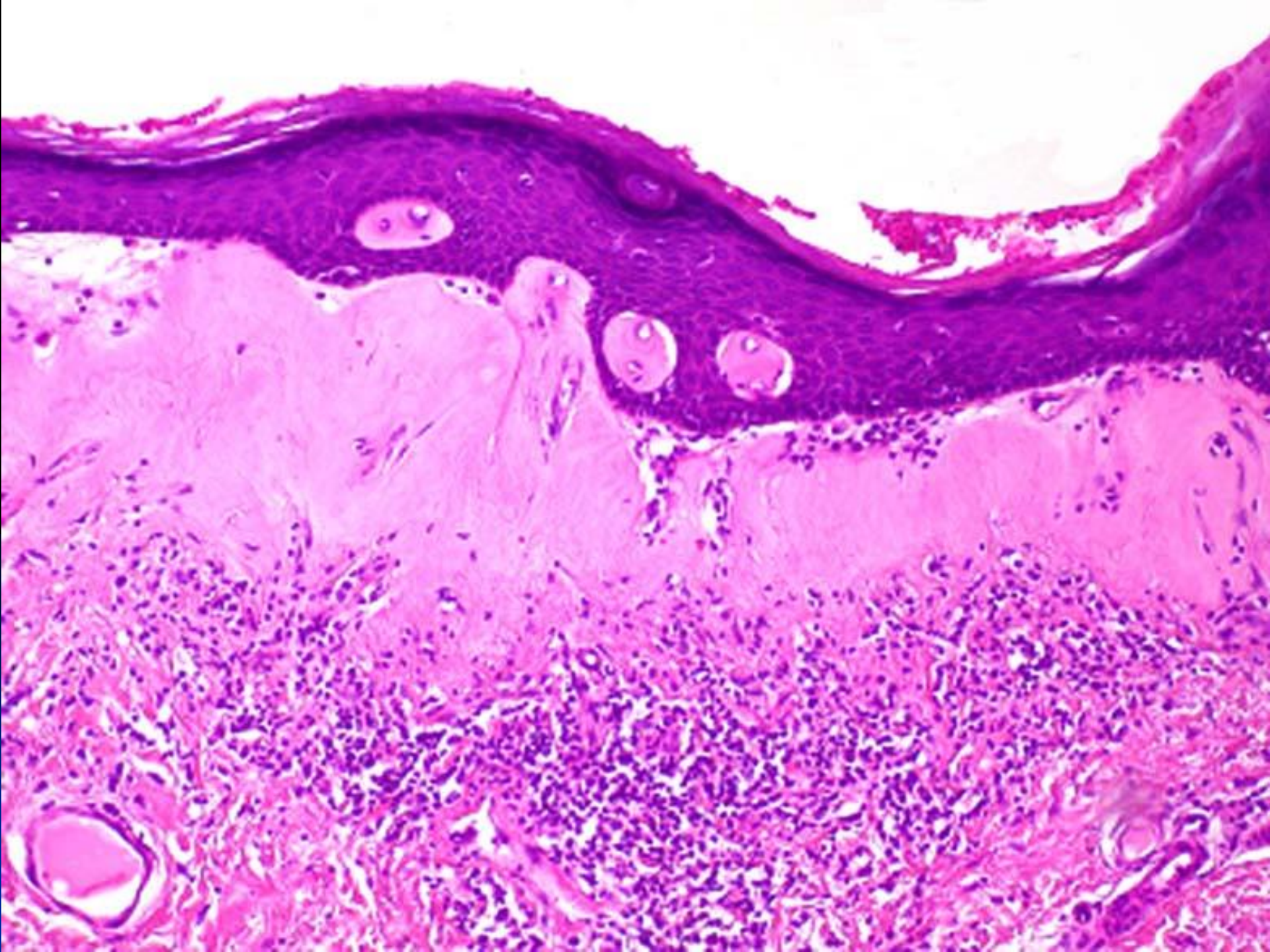
Other rare

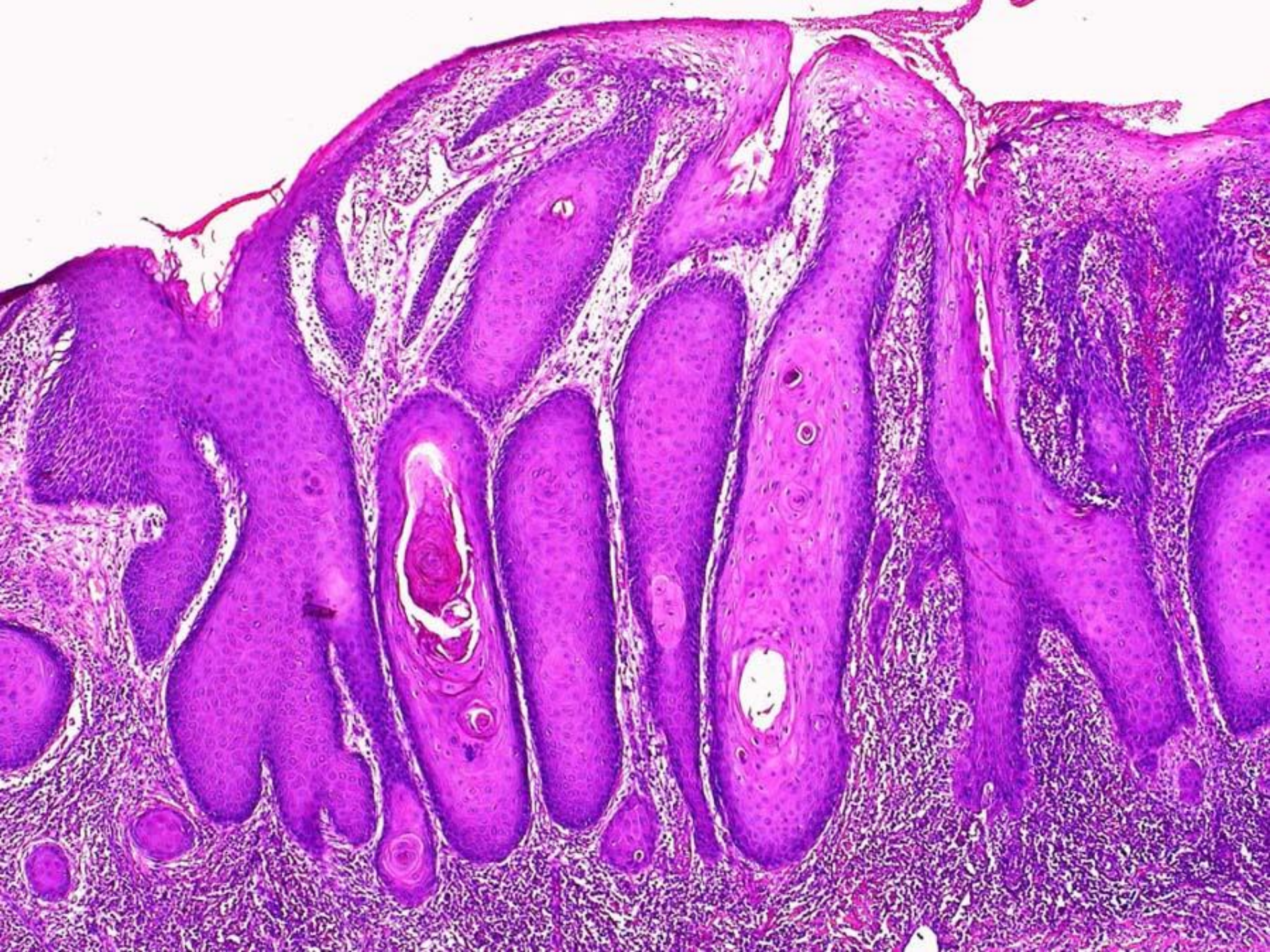
SQUAMOUS CELL CARCINOMA



PSEUDOHYPERPLASTIC SQUAMOUS CELL CARCINOMA ASSOCIATED WITH BXO

- Foreskin mucosal lesions, frequently multicentric
- Background of balanitis xerotica obliterans
- Very well-differentiated squamous cell carcinoma with features resembling pseudoepitheliomatous hyperplasia
- Carcinoma – pushing invasion beyond lamina propria into dartos or corpus spongiosum
  - *Marked asymmetry of pushing edges of neoplasm*
  - *Nests may show keratinization at base*
  - *Destructive invasion lacking*

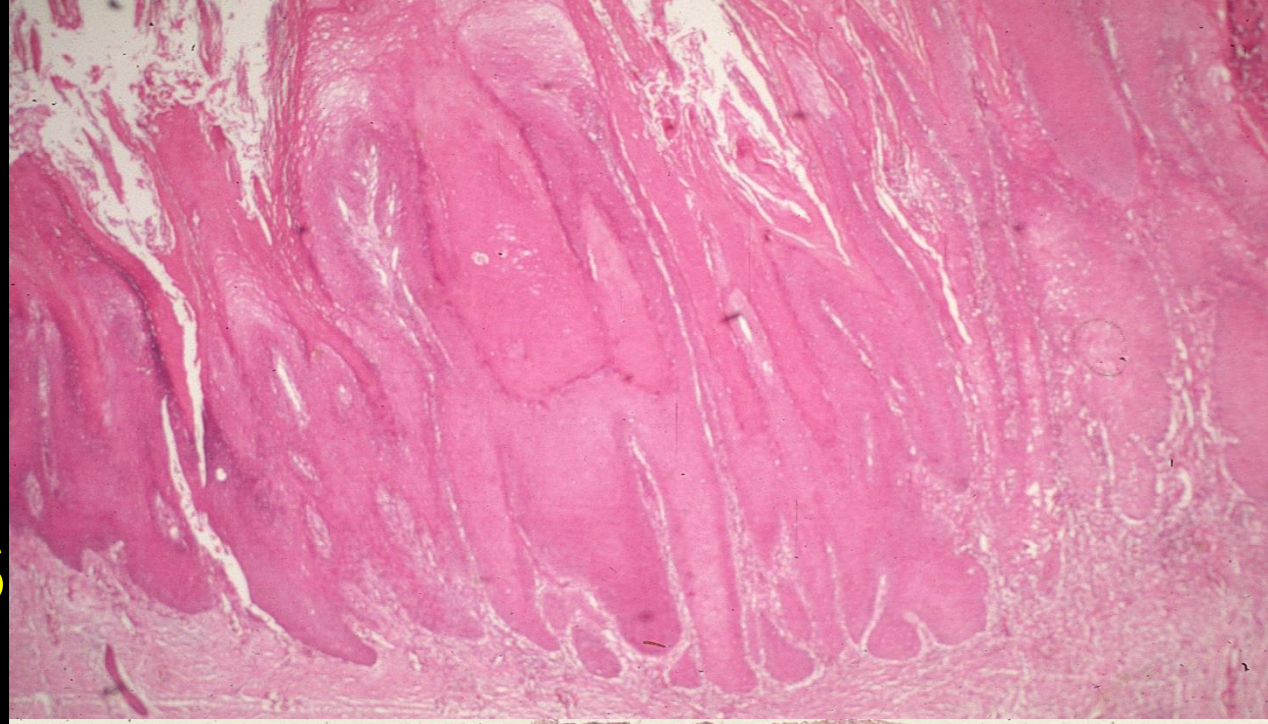


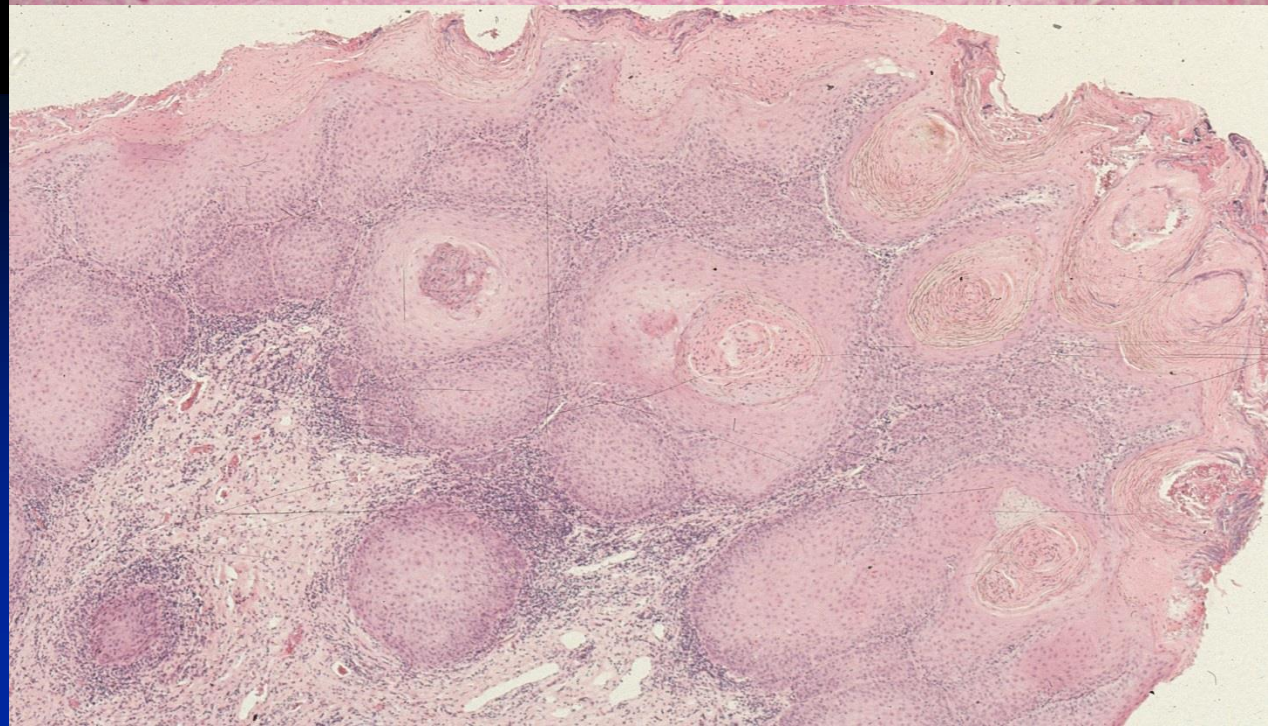


exophytic component

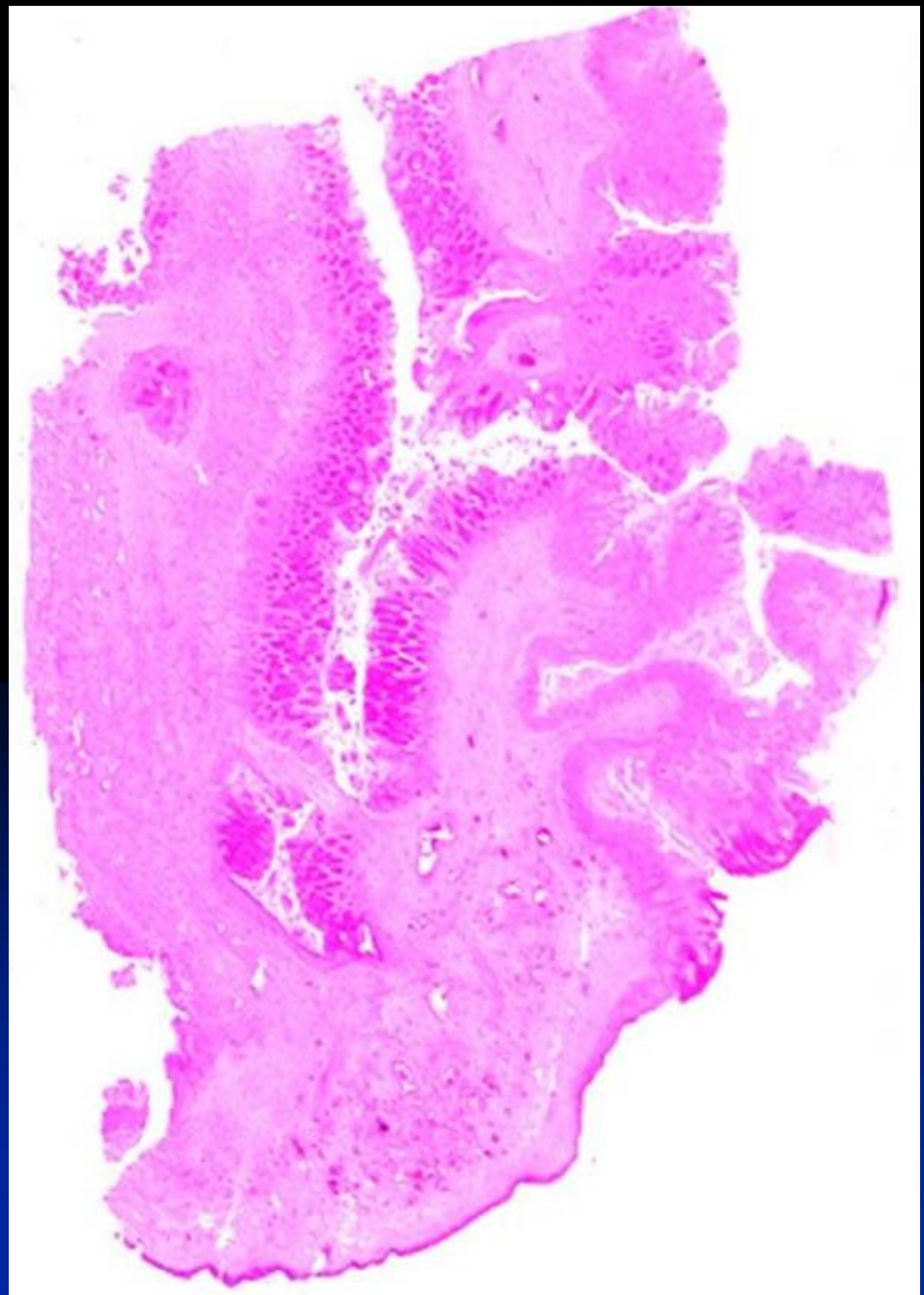
VERRUCOUS CARCINOMA OF PENIS

endophytic component

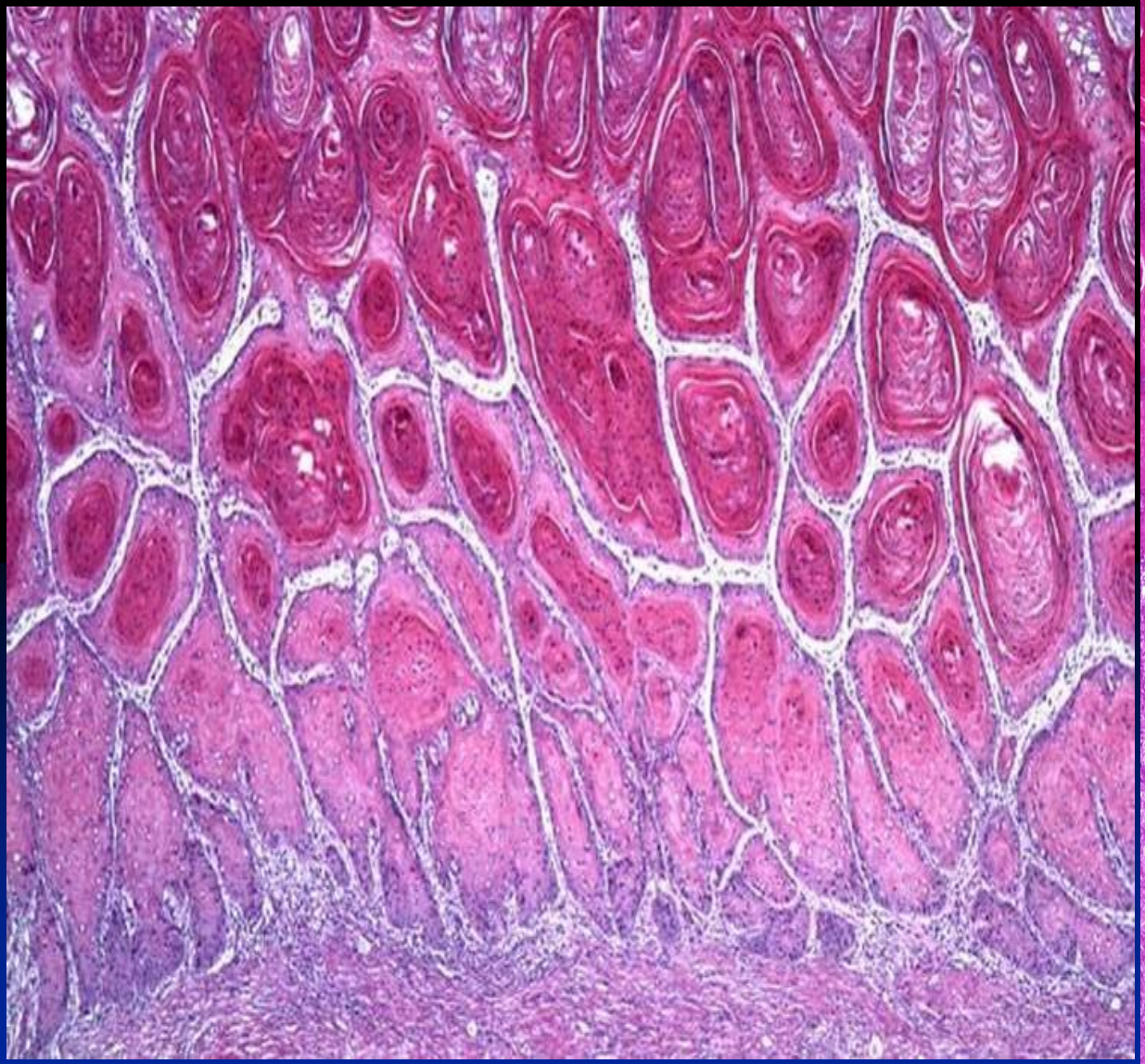


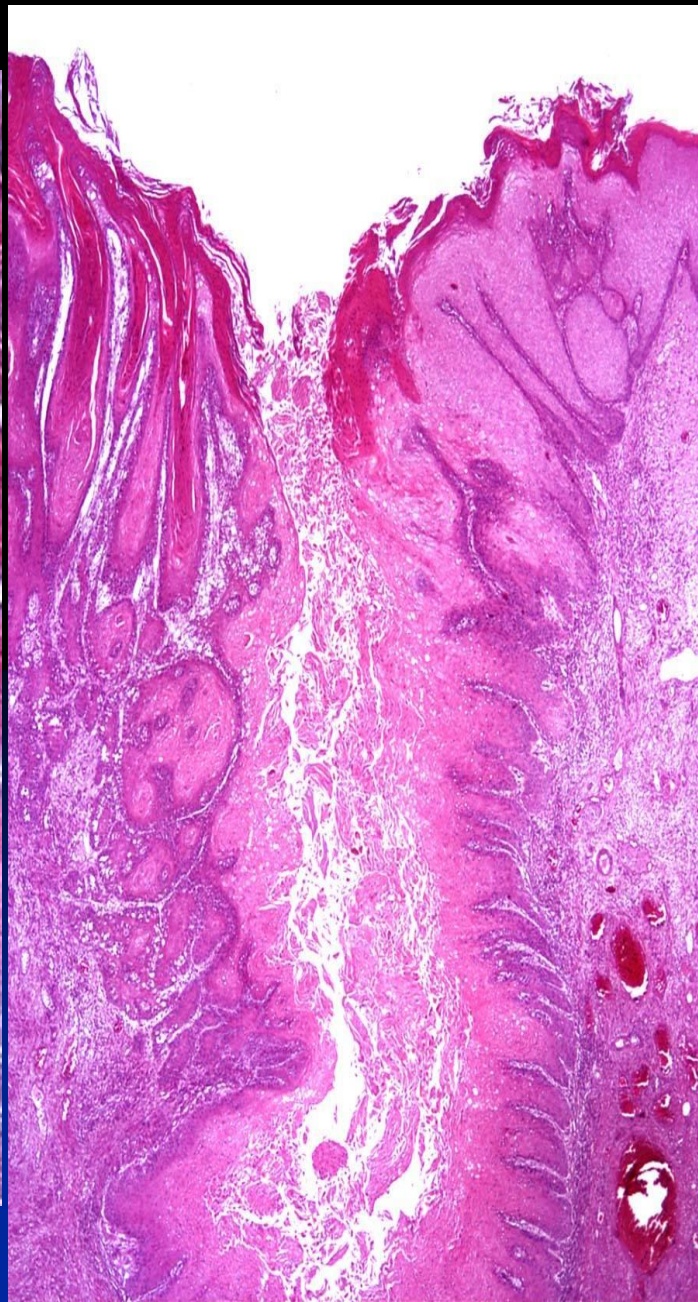


Carcinoma Cuniculatum of Penis



Carcinoma Cuniculatum of Penis

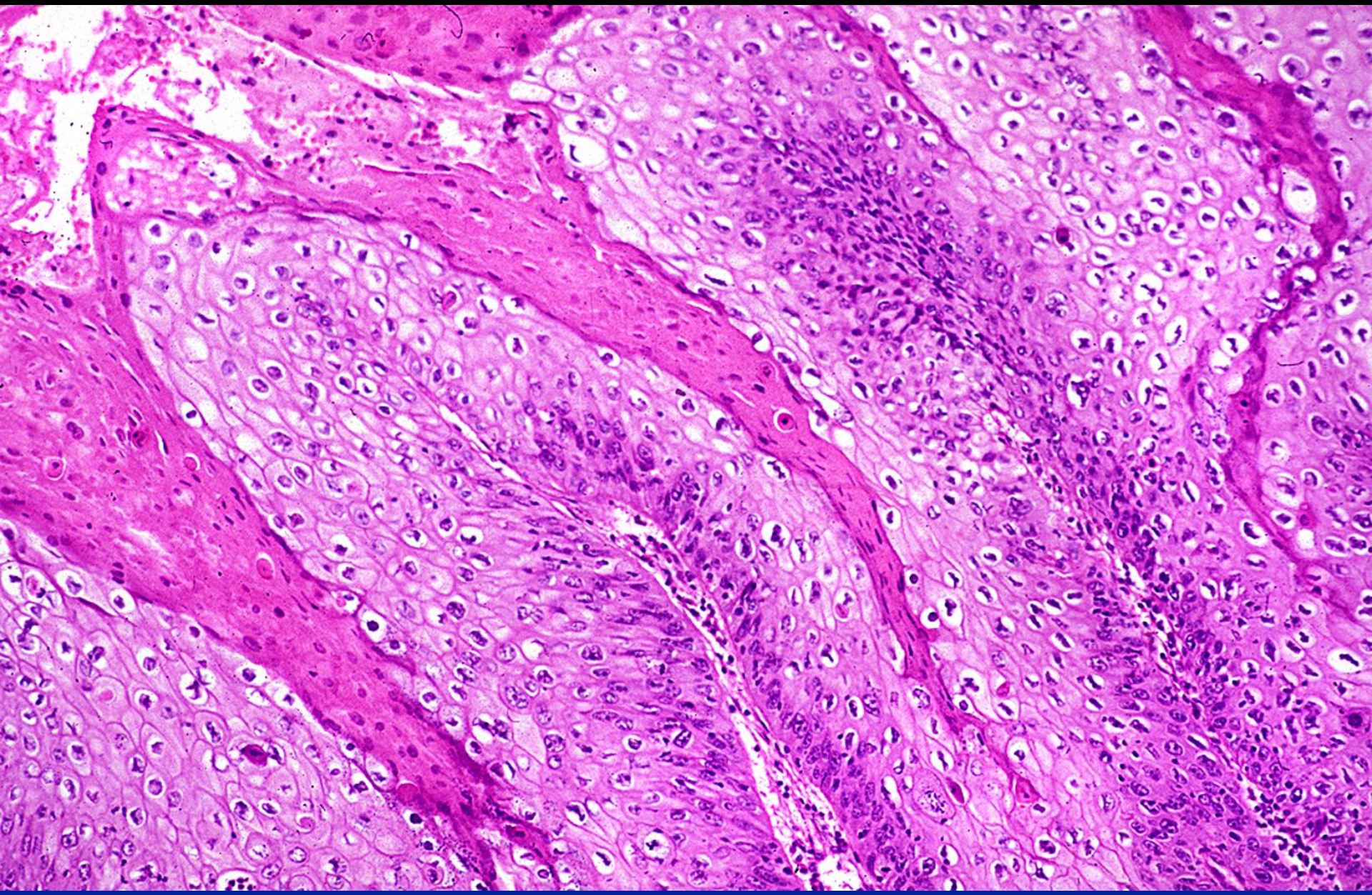


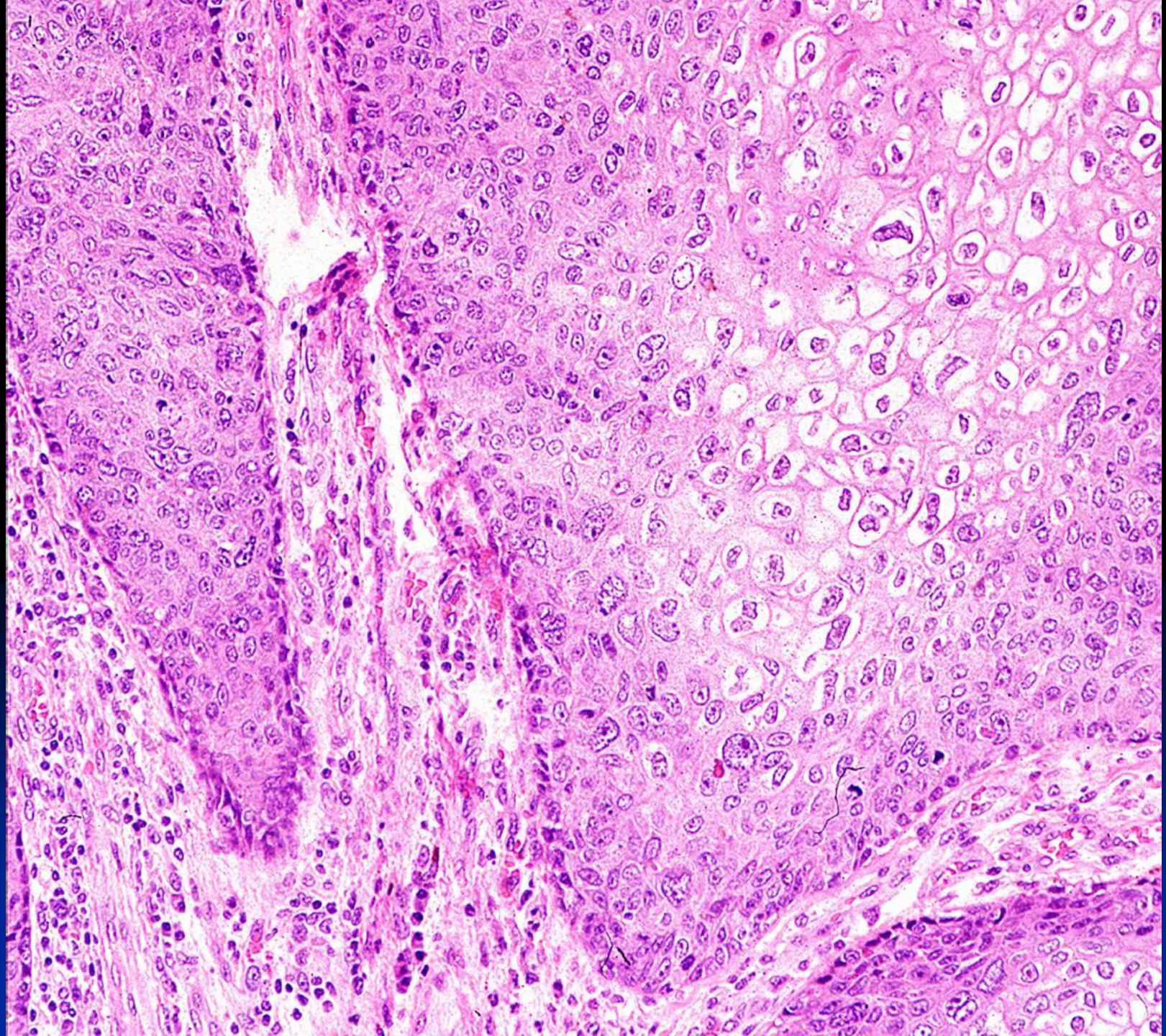


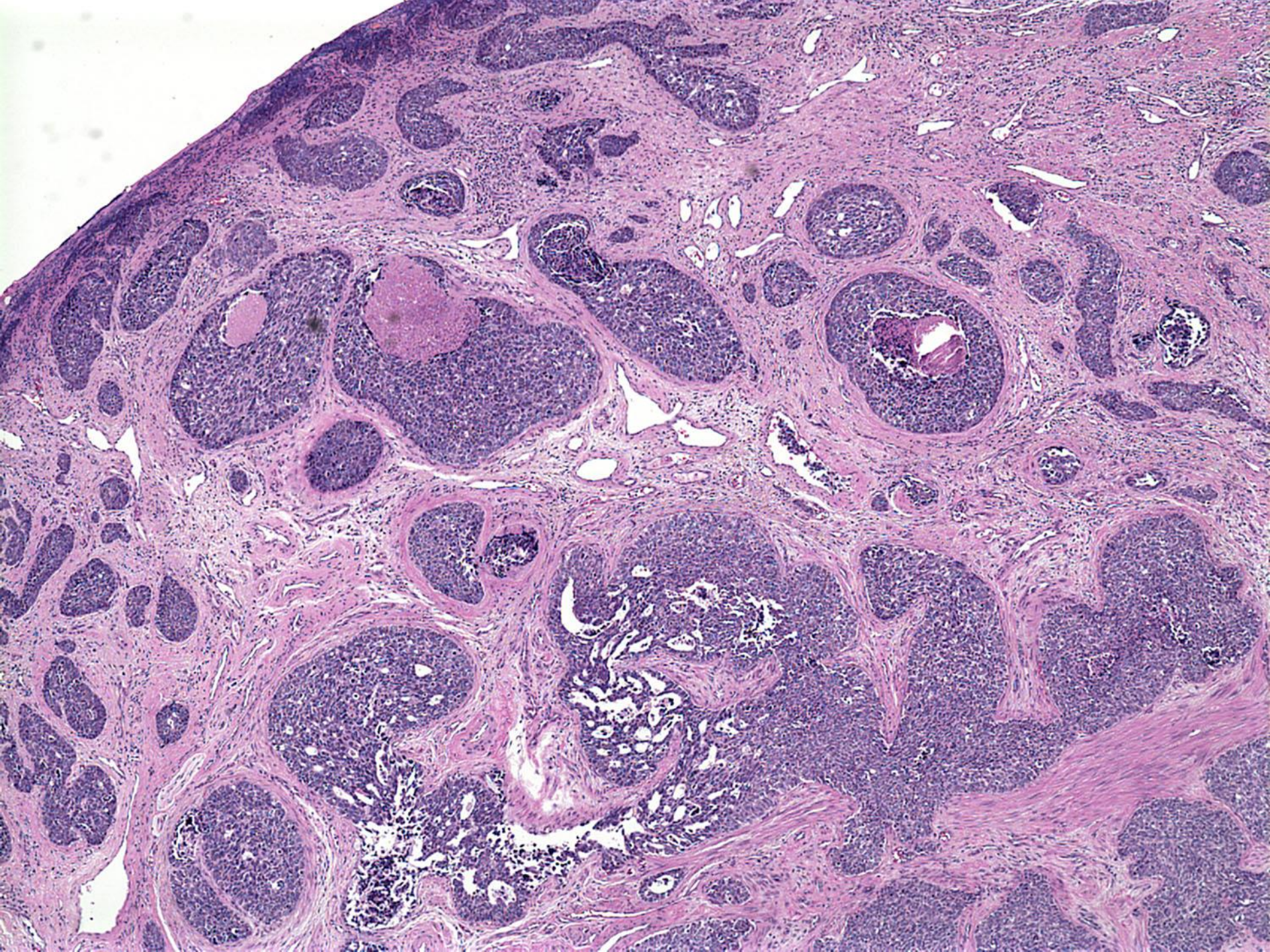
Courtesy Dr Velasquez

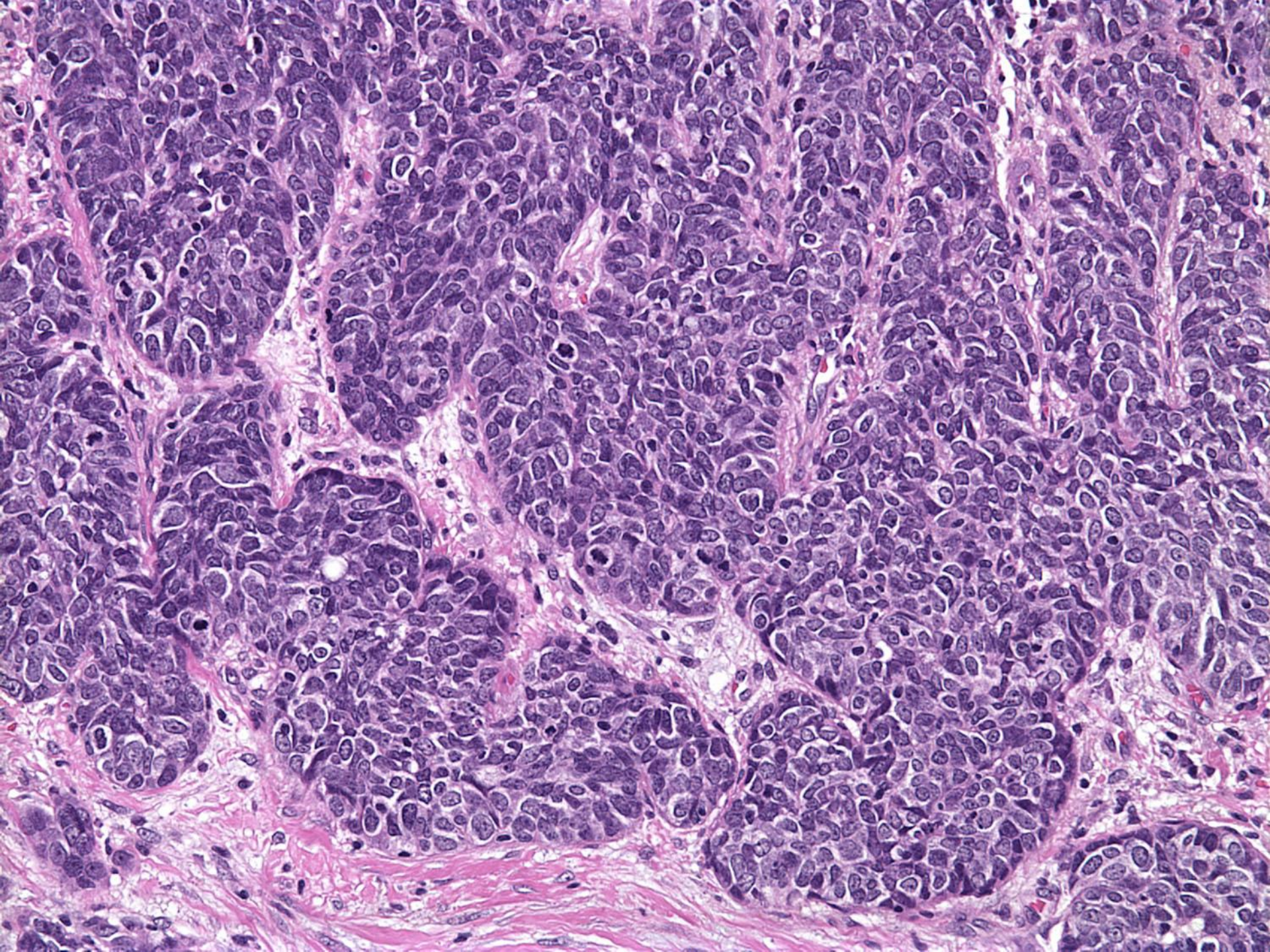
WARTY (CONDYLOMATOUS) CARCINOMA

- Complex undulating appearance
- Long papillae - fibrovascular cores
- Deeper - burrowing into lamina propria and corpus spongiosum
- Hyperkeratosis, parakeratosis, HPV changes
- Obvious cytologic atypia (well to moderately differentiated)



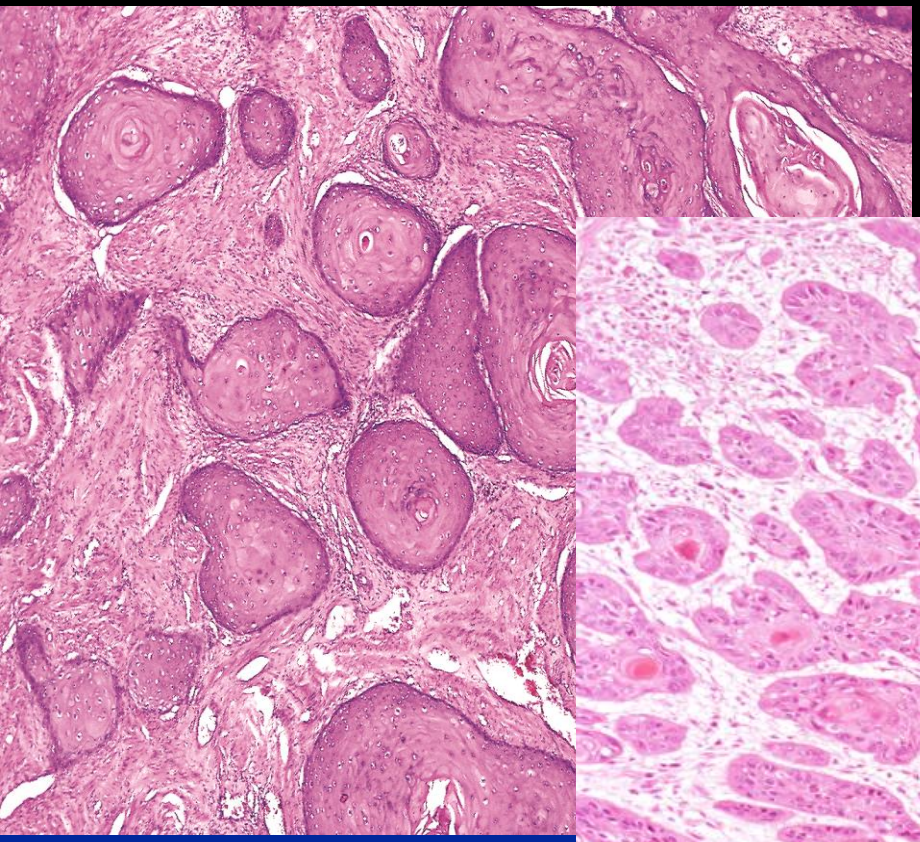




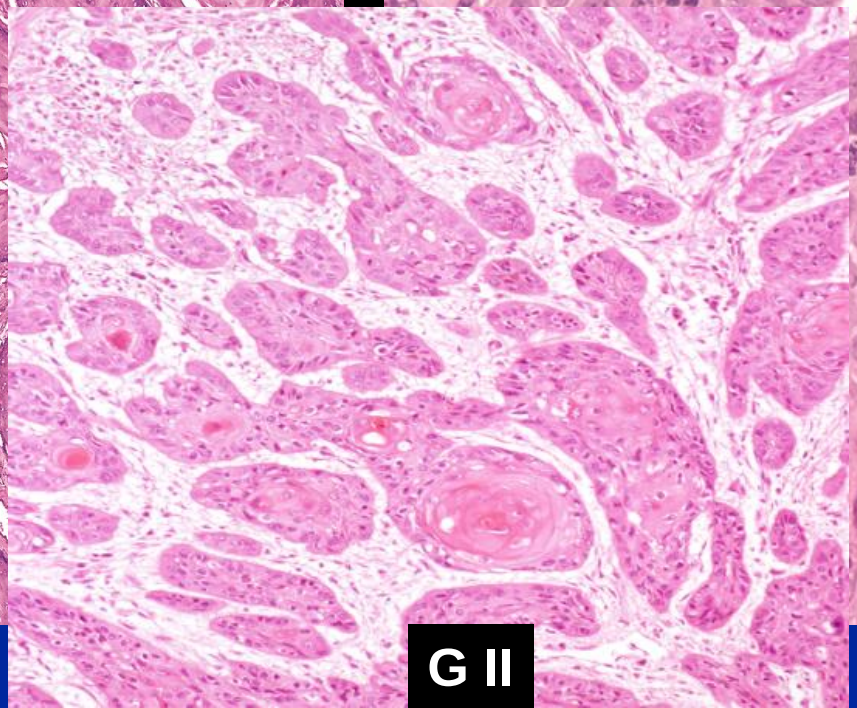


WHO/ISUP Grading in penile SCC.

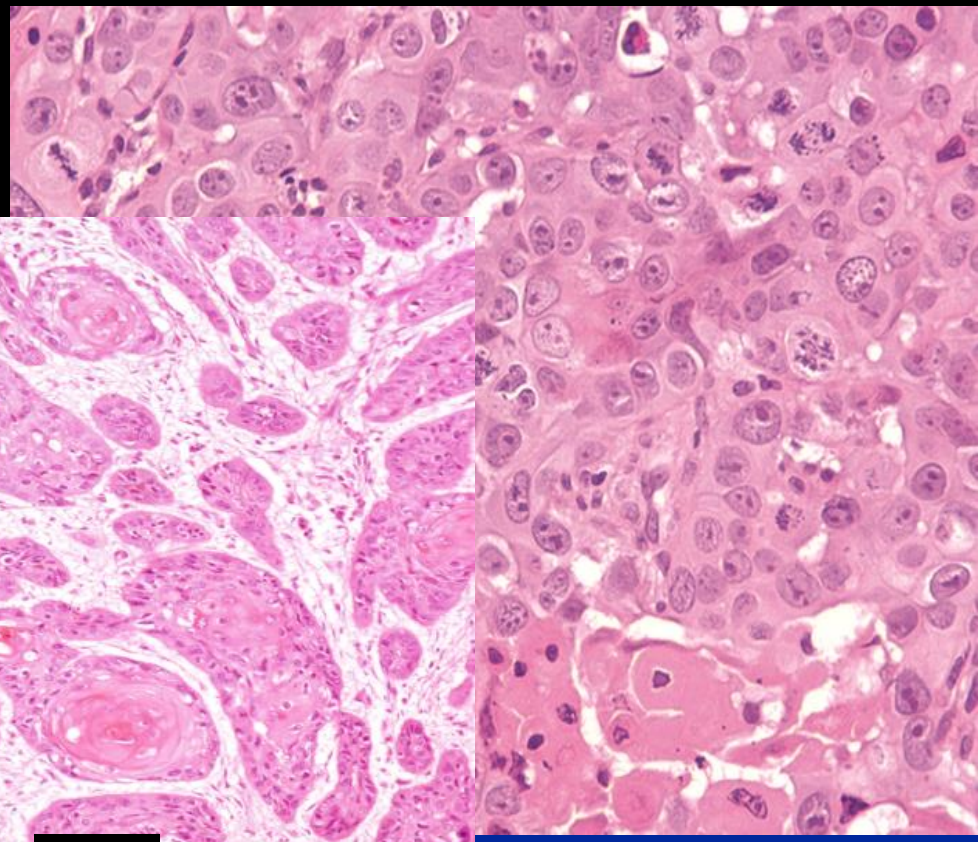
- Gr I, well differentiated
- Gr II, moderately differentiated
- Gr III, poorly differentiated



Gr I



G II



G III


THANK YOU