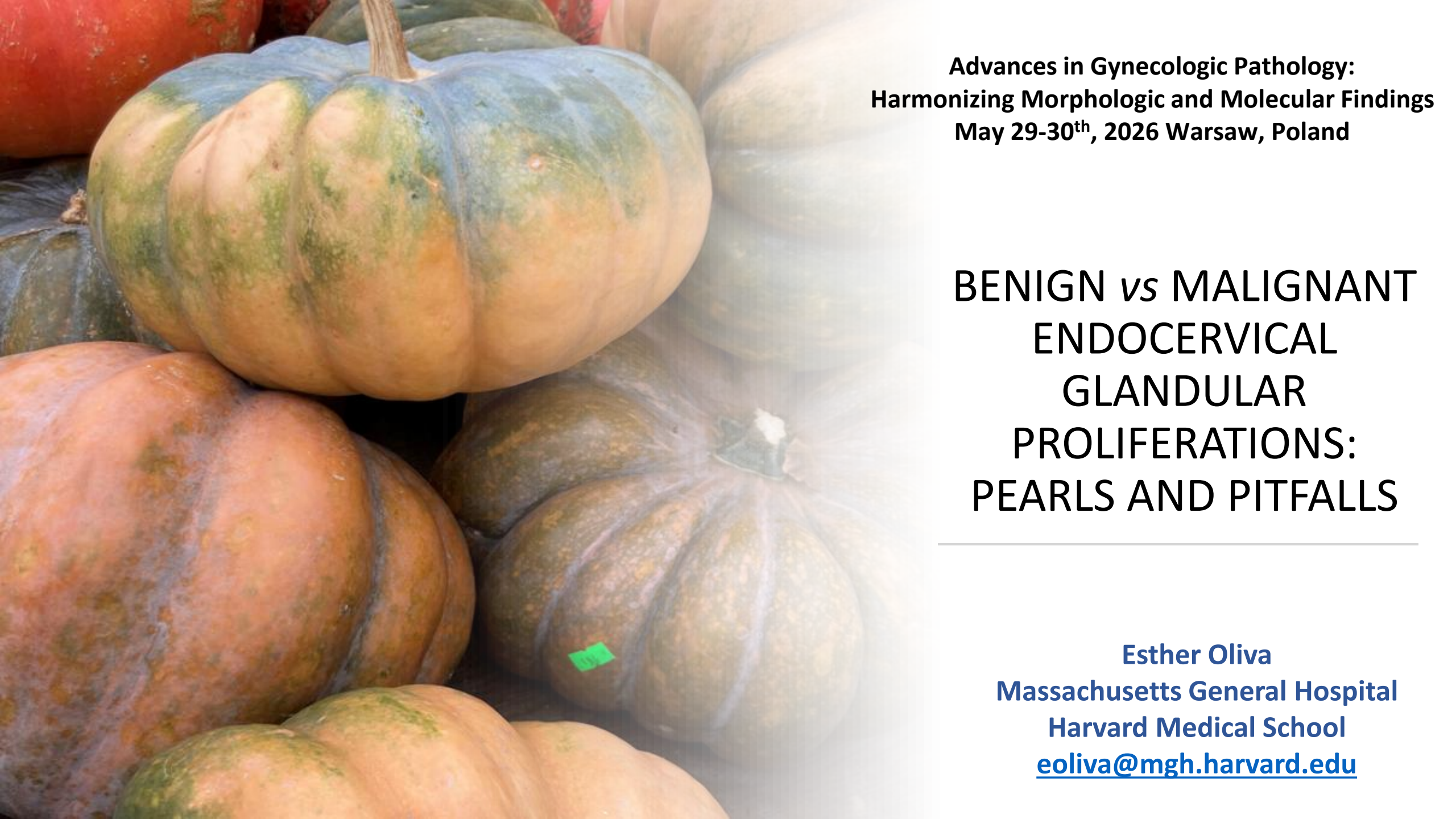




**Advances in Gynecologic Pathology:
Harmonizing Morphologic and Molecular Findings
May 29-30th, 2026 Warsaw, Poland**

**BENIGN vs MALIGNANT
ENDOCERVICAL
GLANDULAR
PROLIFERATIONS:
PEARLS AND PITFALLS**

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CERVICAL GLANDULAR PROLIFERATIONS

BENIGN

- Tunnel Clusters
- Deep Endocervical Glands
- Tubal and Tuboendometrioid Metaplasia
- Endometriosis
- Microglandular Hyperplasia
- Arias-Stella Reaction
- Lobular Endocervical Gland Hyperplasia (LEGH)
- Adenoid Basal Proliferations
- Mesonephric Hyperplasia
- Ectopic Prostatic Glands
- Diffuse Laminar Endocervical Gland Hyperplasia
- Endocervicosis
- Endosalpingiosis

MALIGNANT

- In situ Adenocarcinoma
 - HPV-related (usual, intestinal, SMILE)
 - HPV-independent
 - Gastric/Atypical LEGH
- Invasive Adenocarcinoma
 - HPV-related (usual, mucinous, i-SMILE)
 - HPV-independent
 - Gastric
 - Clear cell
 - Mesonephric
 - Endometrioid

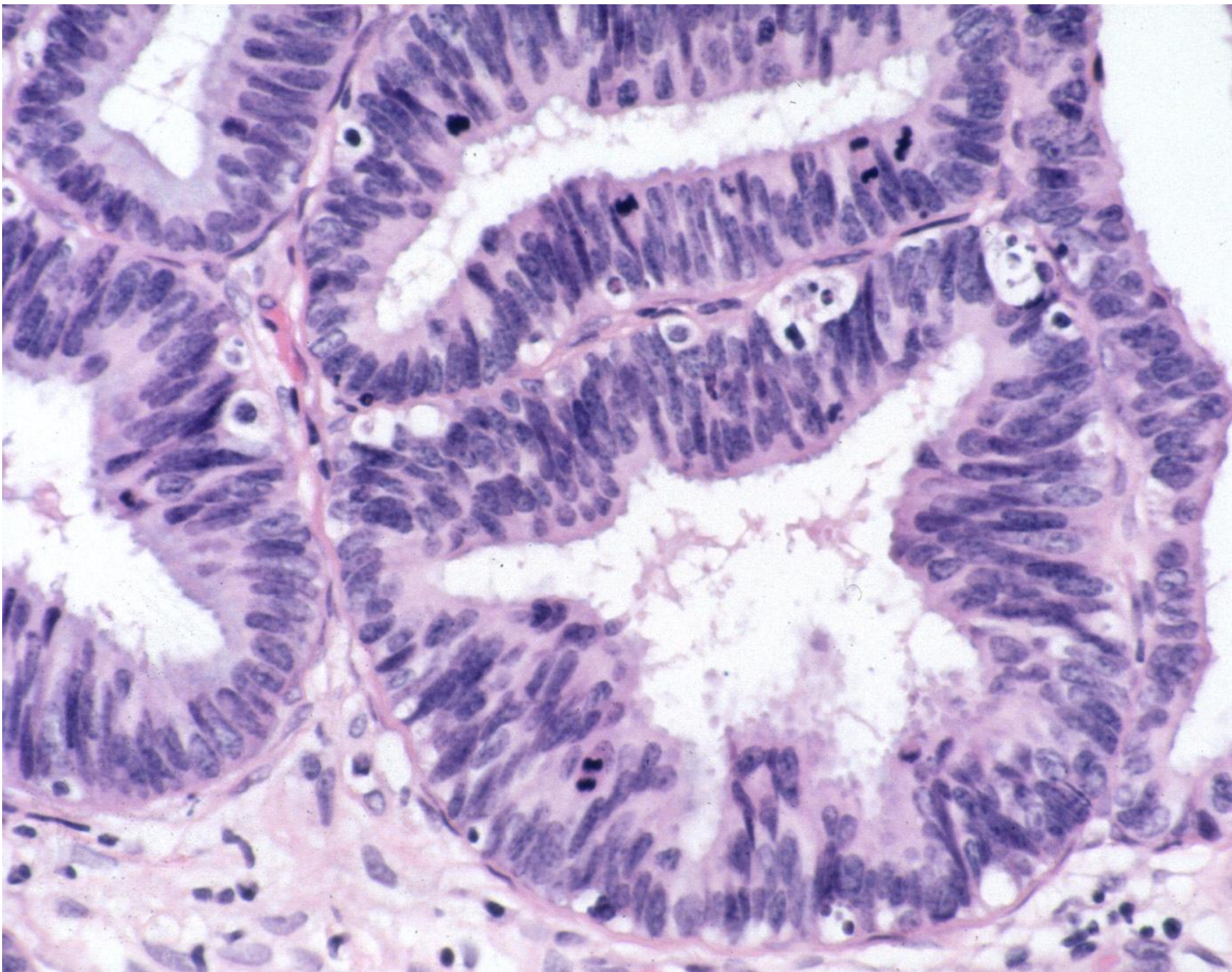
ADENOCARCINOMA IN-SITU

- **HPV-RELATED**

- Typically starts at squamocolumnar junction
- Concomitant high-grade squamous dysplasia in ~ 50%
- High-risk HPVs frequent
- May have skip lesions
- 10 to 20% of all cervical adenocarcinomas

- **HPV-INDEPENDENT**

- Rare, accepted gastric-type and lobular endocervical gland hyperplasia with atypia



HPV-related features:

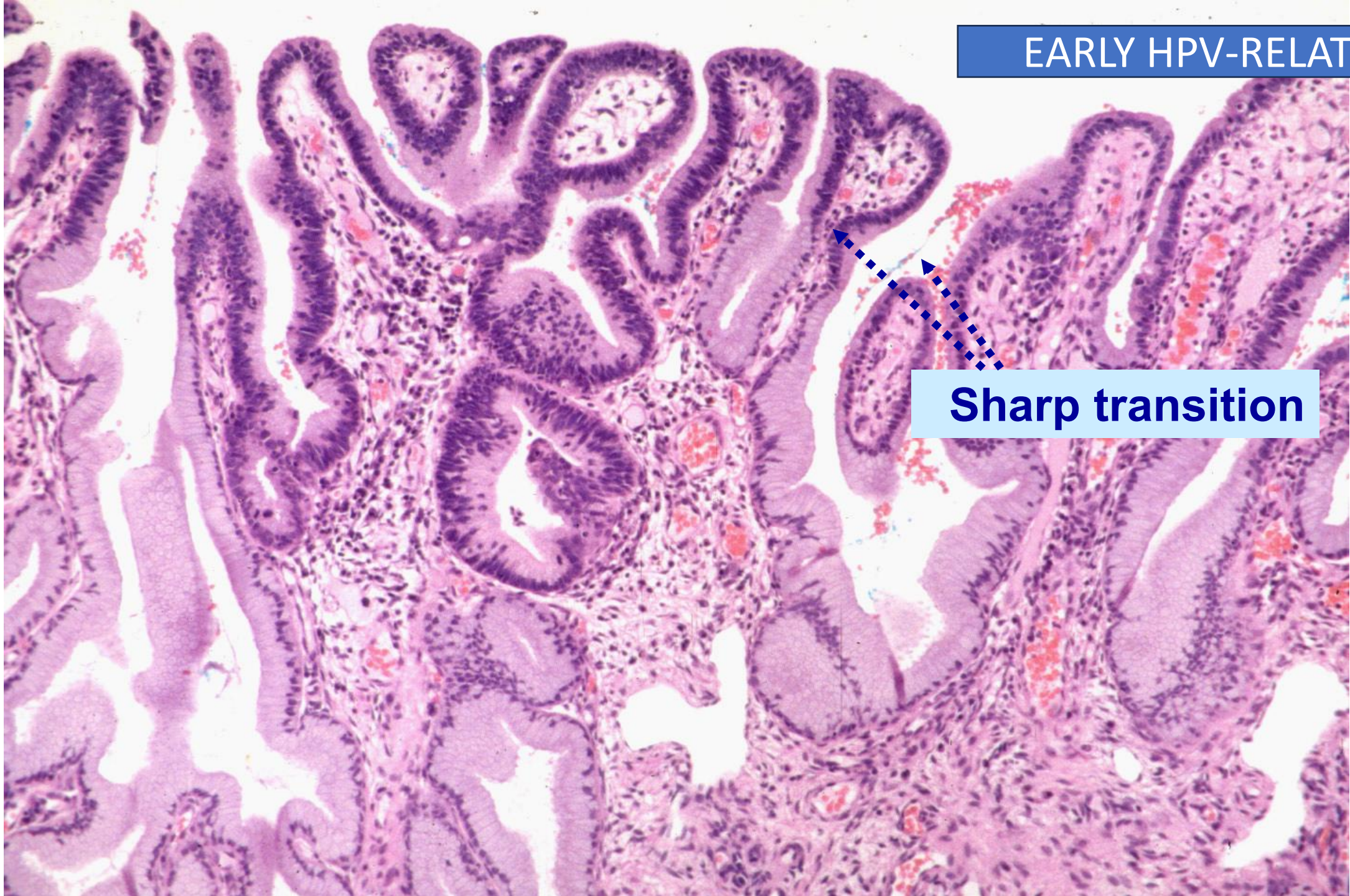
Apical mitoses

Apoptotic bodies

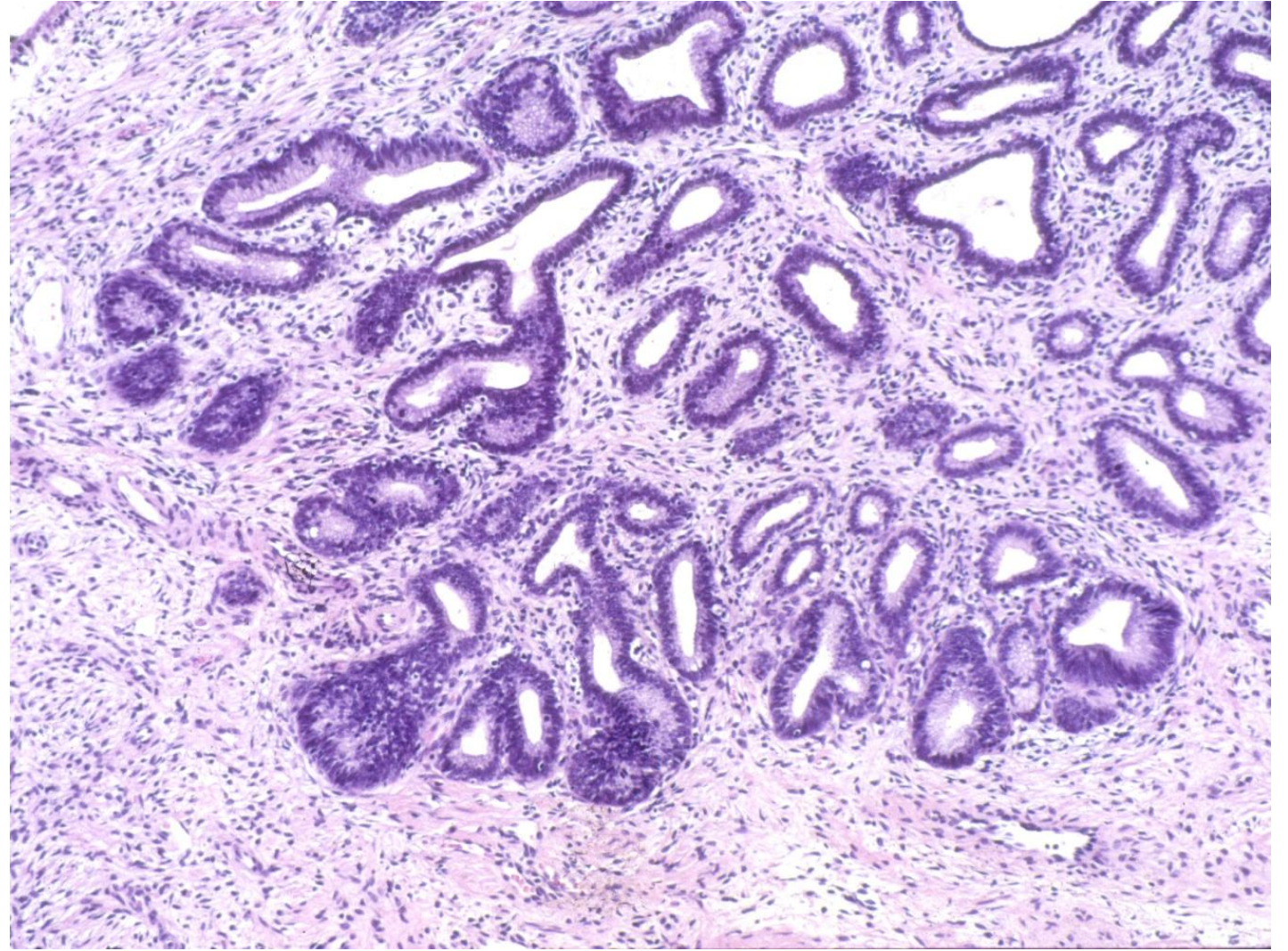
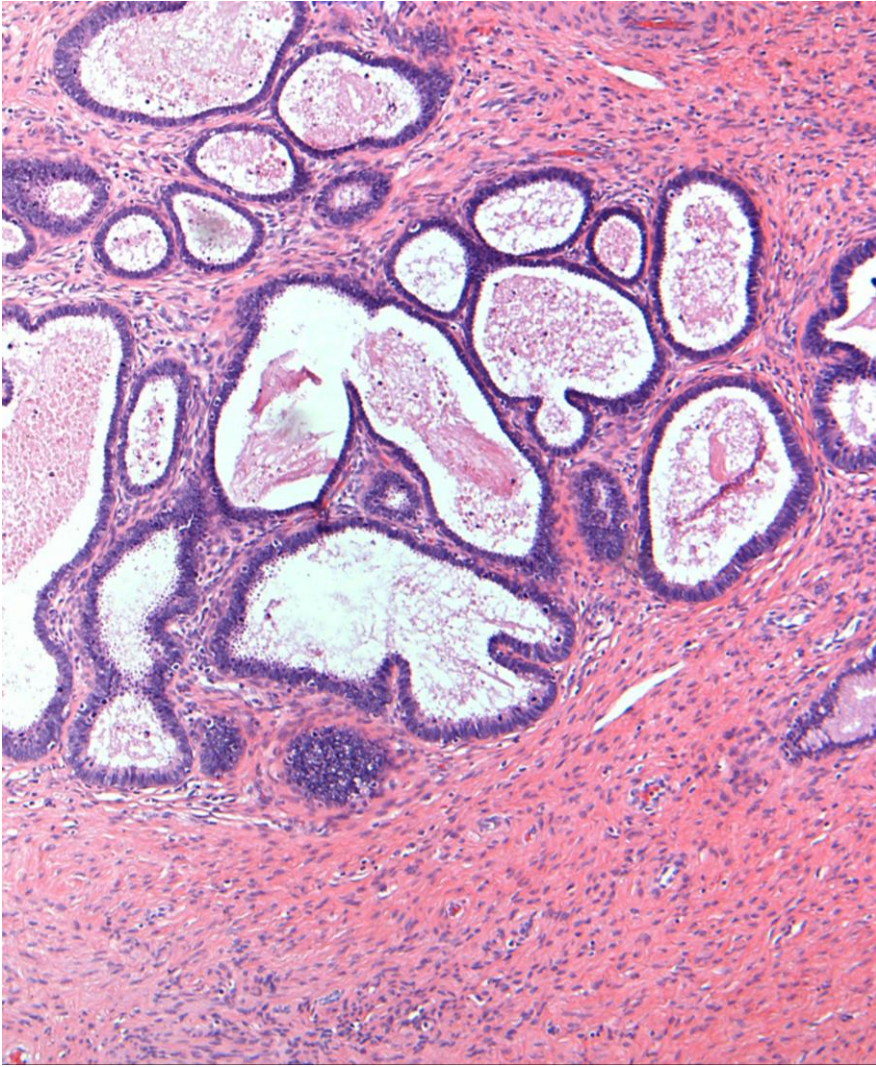
**Most common:
USUAL AIS
(mucin depleted)**

EARLY HPV-RELATED AIS

Sharp transition

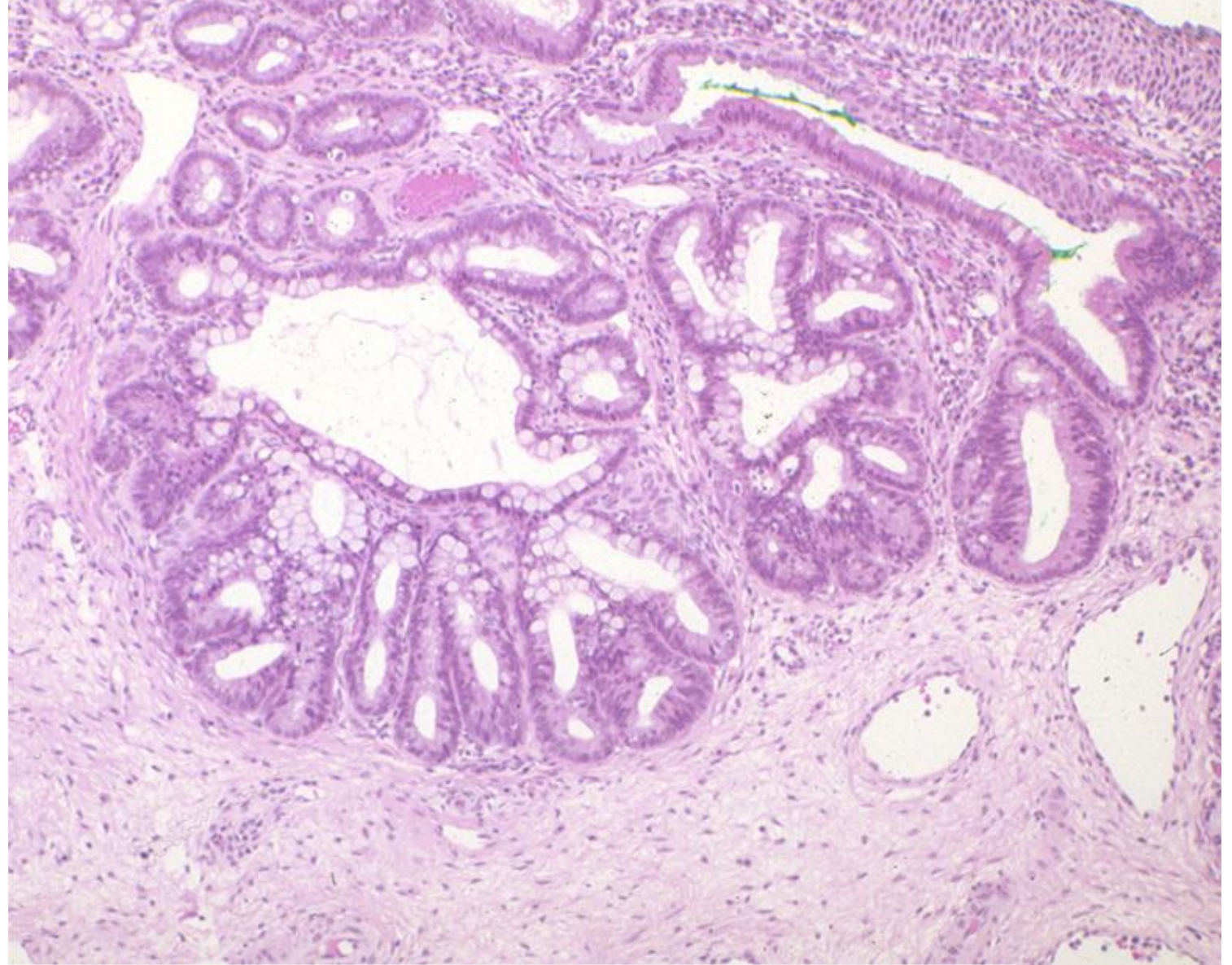
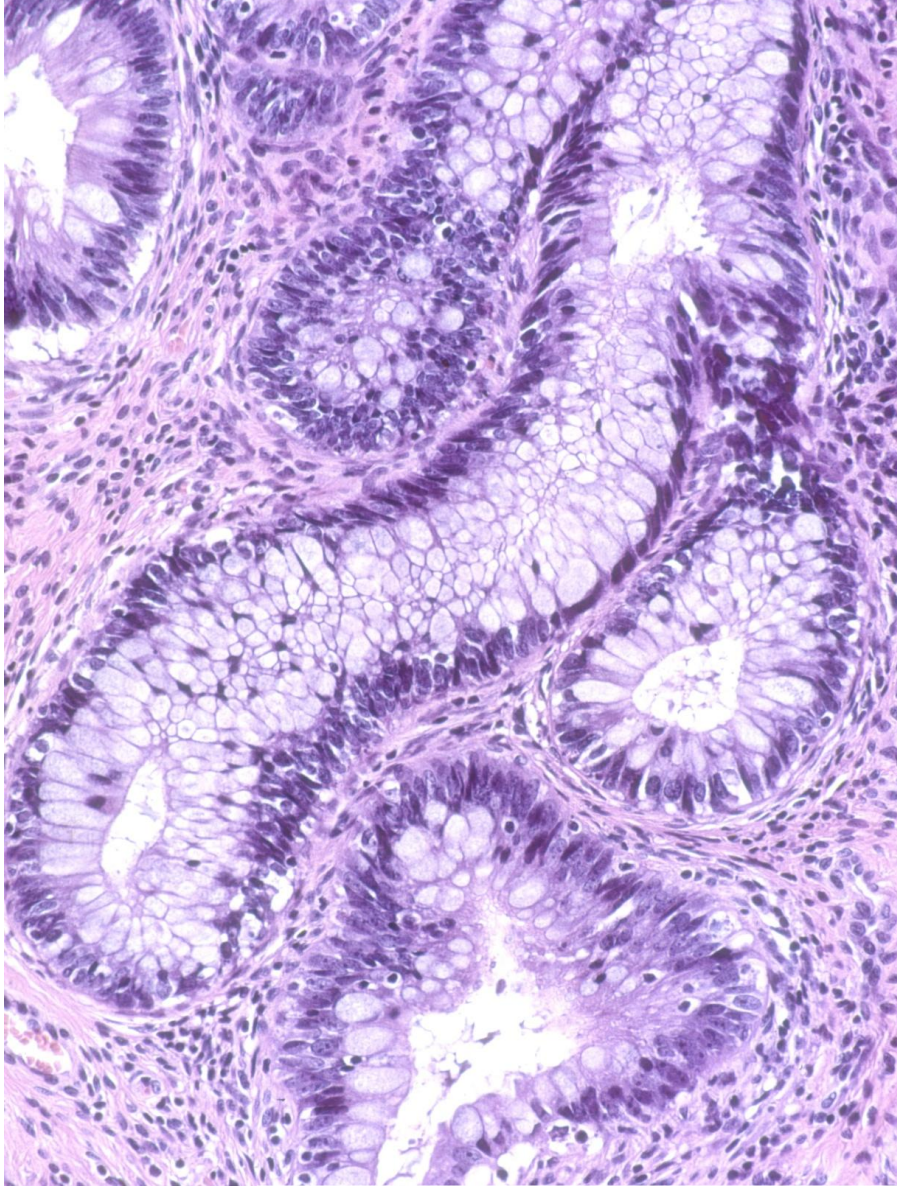


Replacement of pre-existing glands

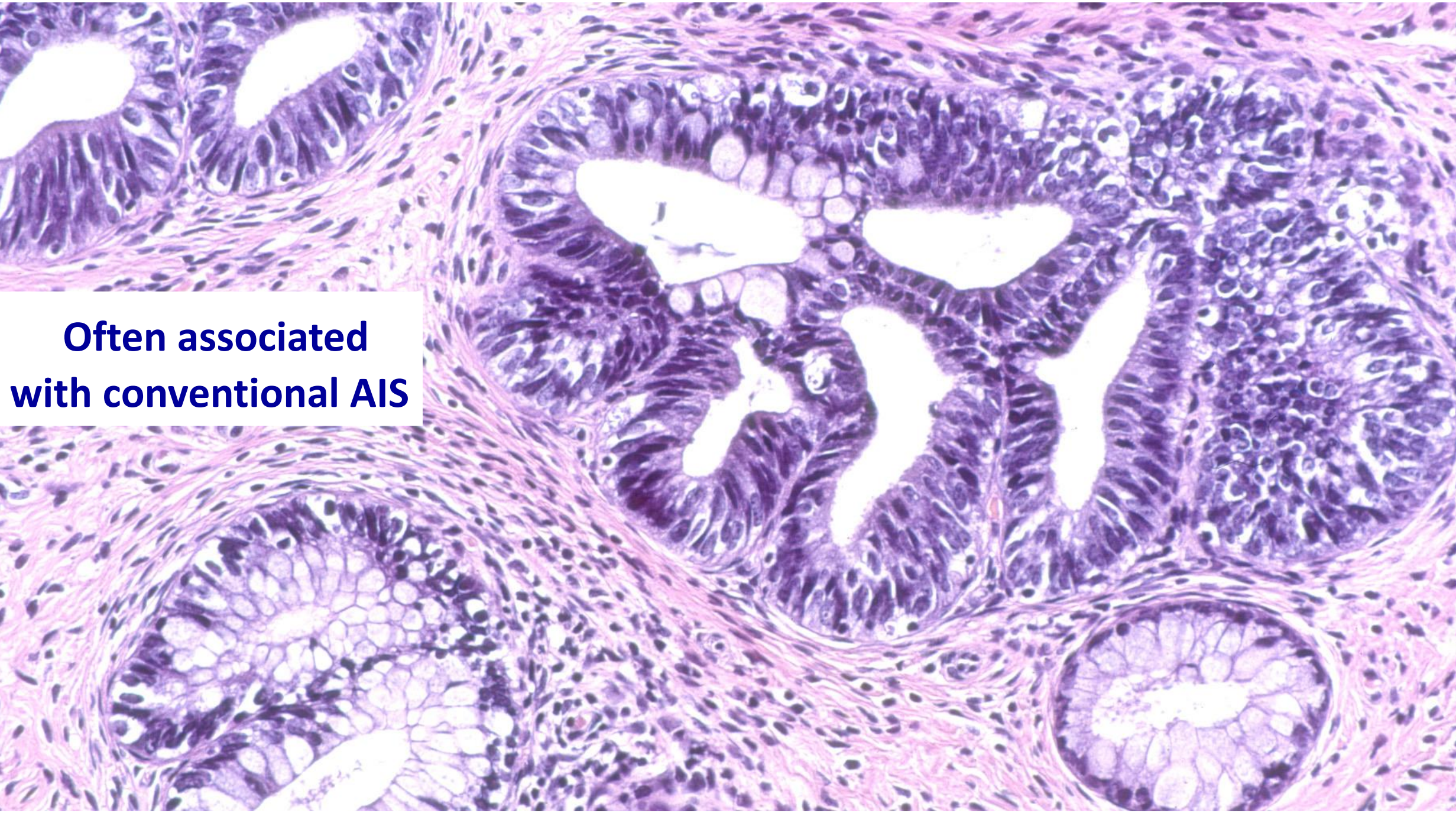


May show lobular configuration as seen in benign proliferations

HPV-RELATED AIS, INTESTINAL TYPE



Less obvious cytologic atypia, mitoses and apoptoses



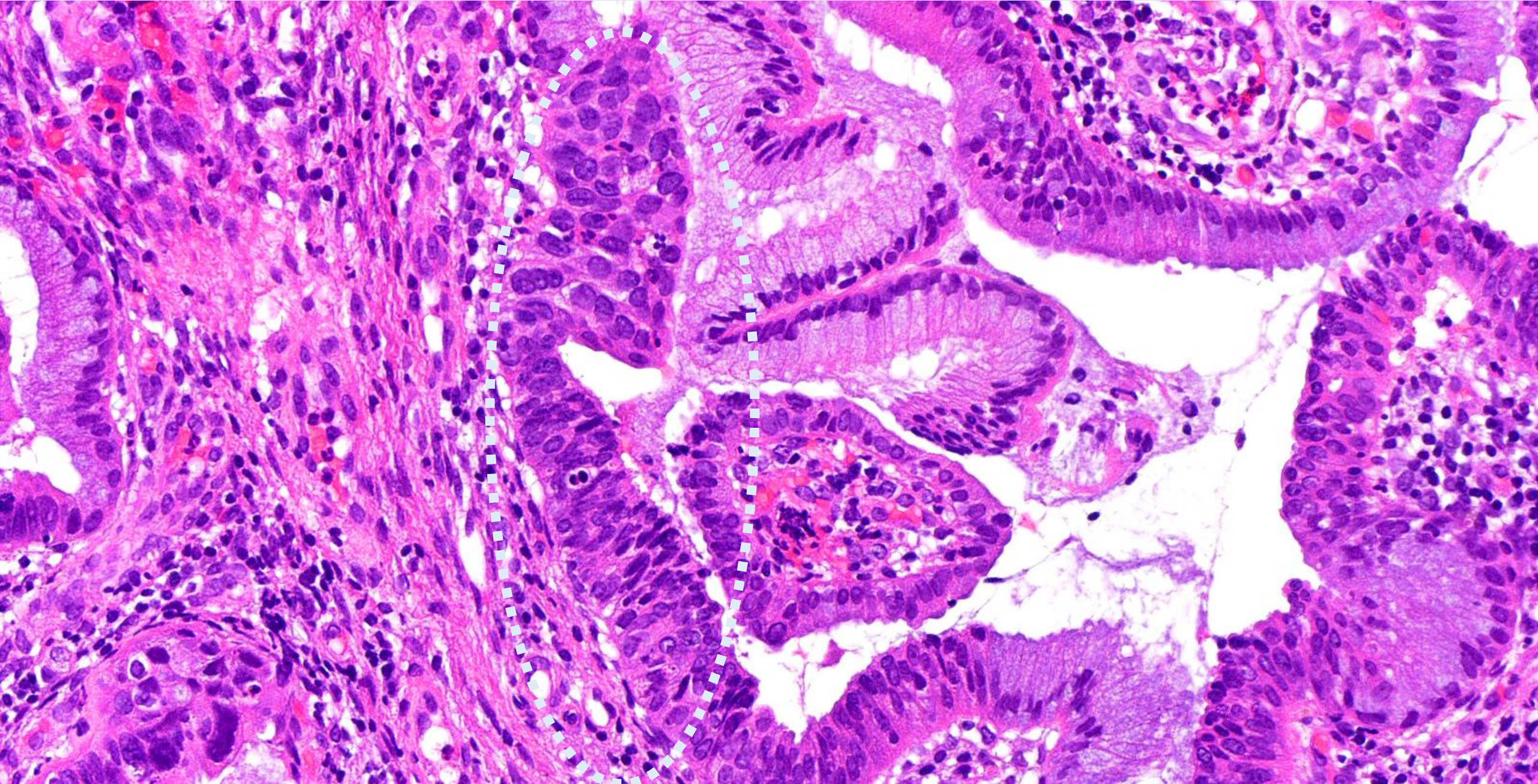
**Often associated
with conventional AIS**

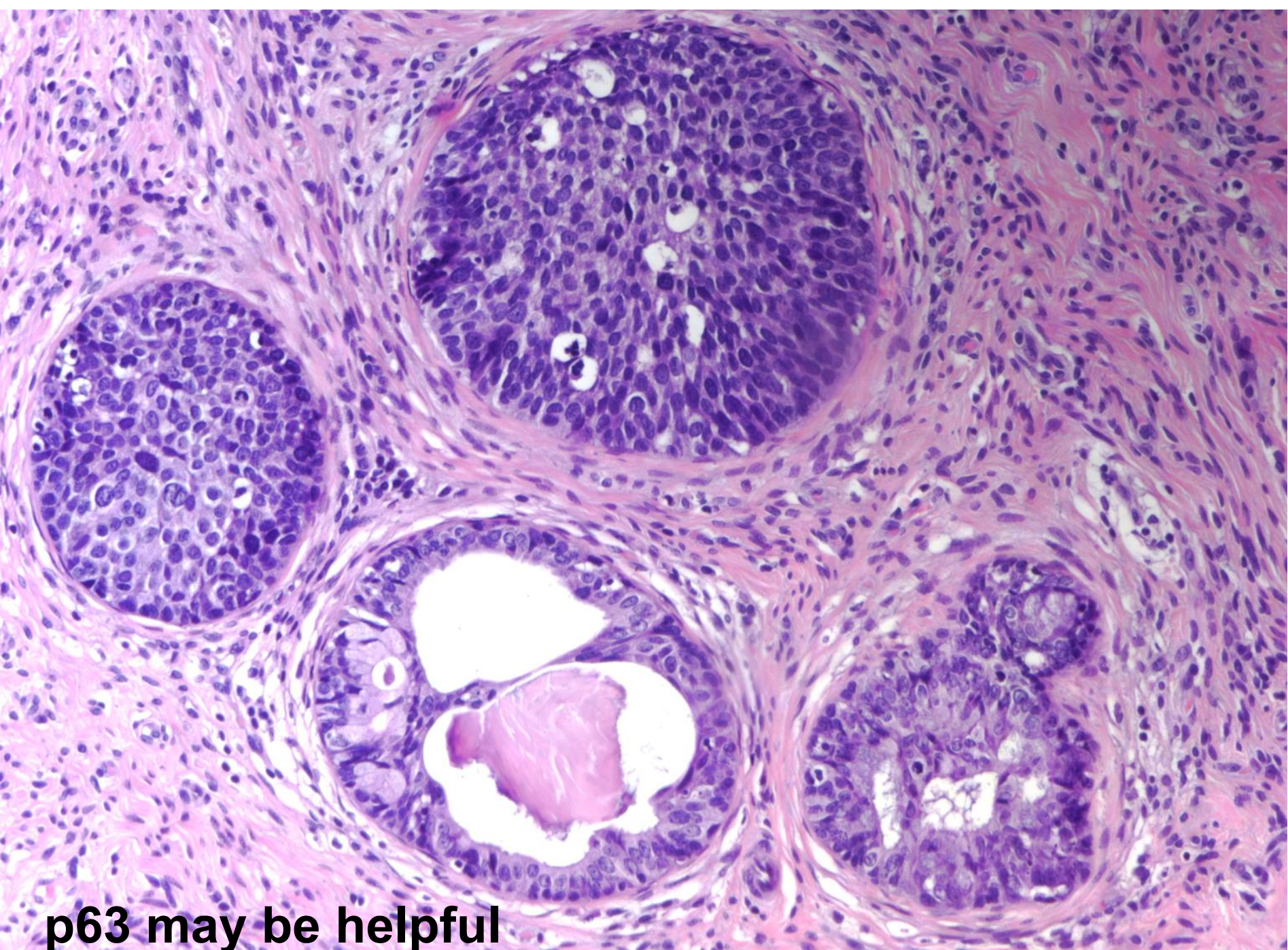
HPV-RELATED AIS, USUAL TYPE

Differential Diagnosis

- High-grade squamous dysplasia within glands
- Reactive glandular atypia
- Endometriosis
- Tubal metaplasia
- Mesonephric hyperplasia
- Radiation induced atypia
- Invasive adenocarcinoma (especially pattern Silva A)

HIGH-GRADE SQUAMOUS DYSPLASIA INVOLVING GLANDS

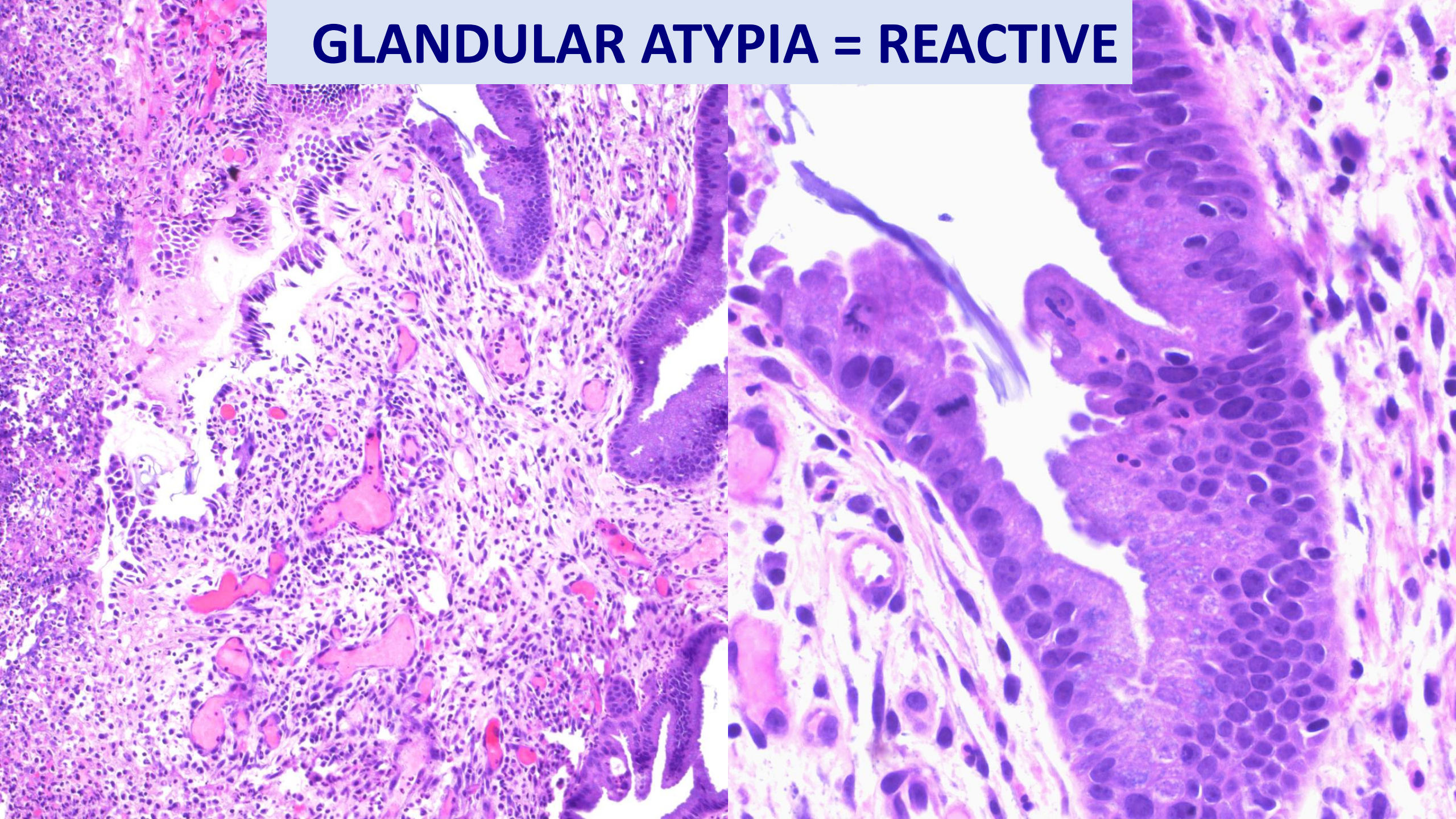




**SCC in situ
mimics AIS**

p63 may be helpful

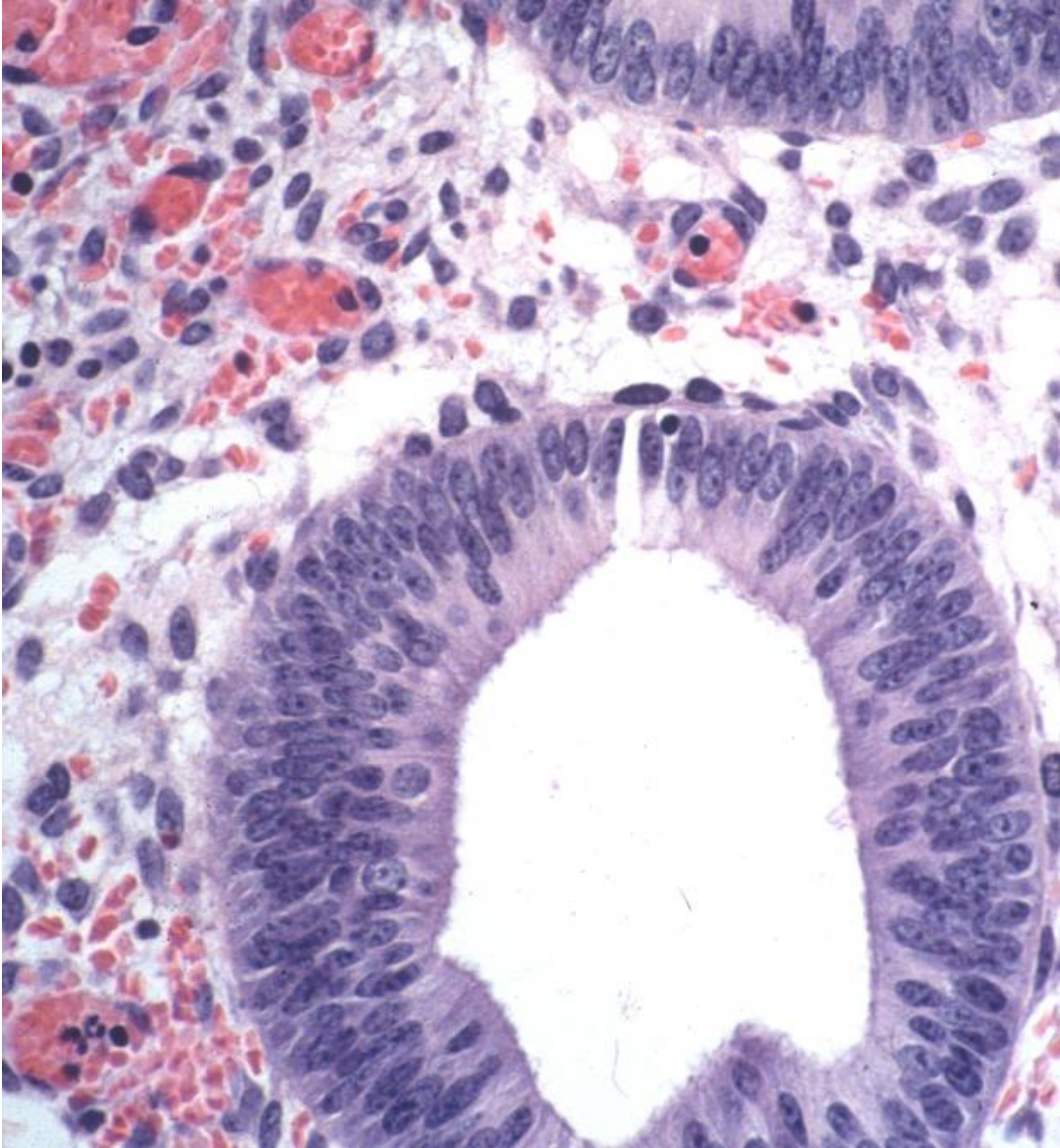
GLANDULAR ATYPIA = REACTIVE



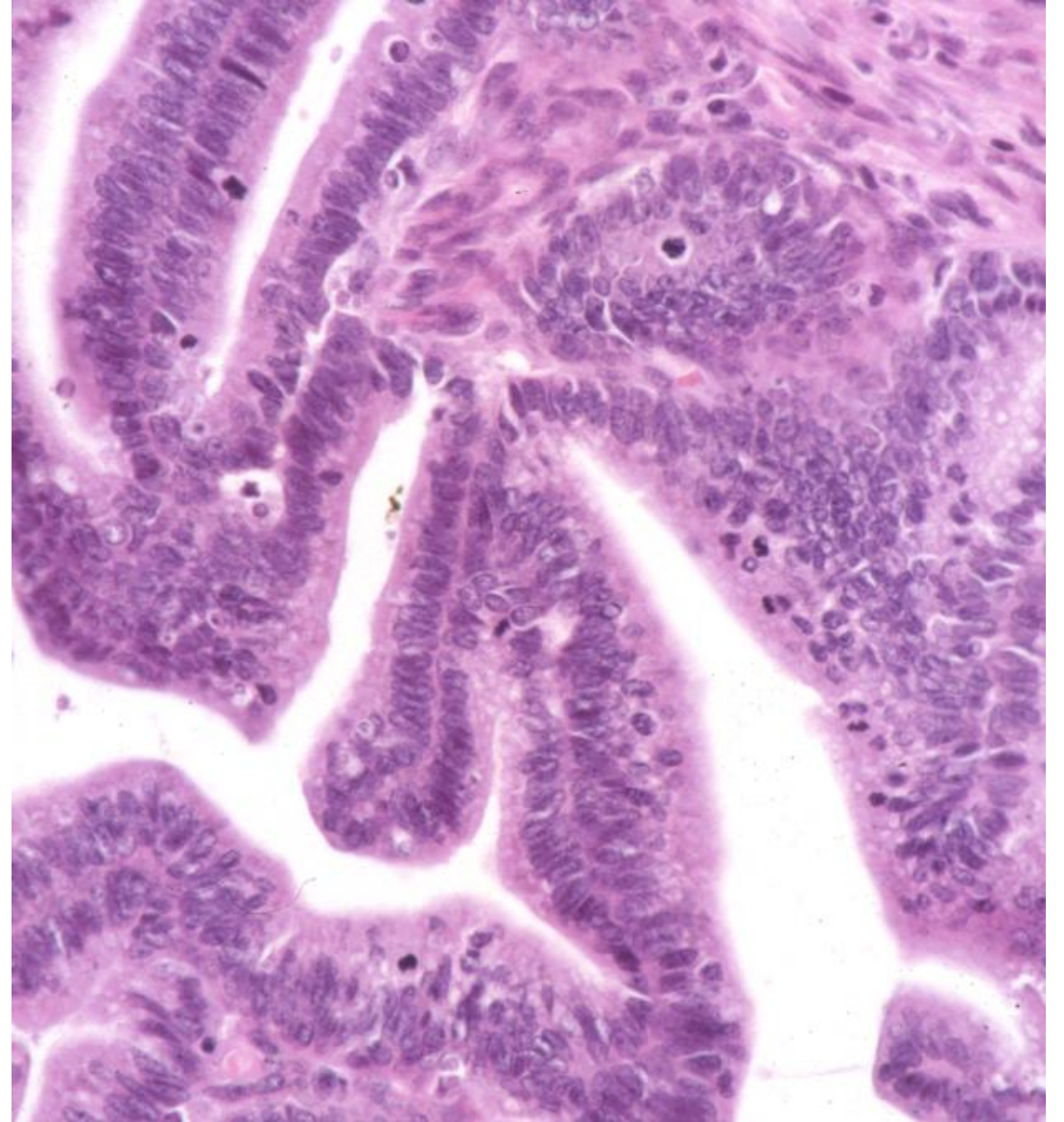
CERVICAL ENDOMETRIOSIS

Two categories:

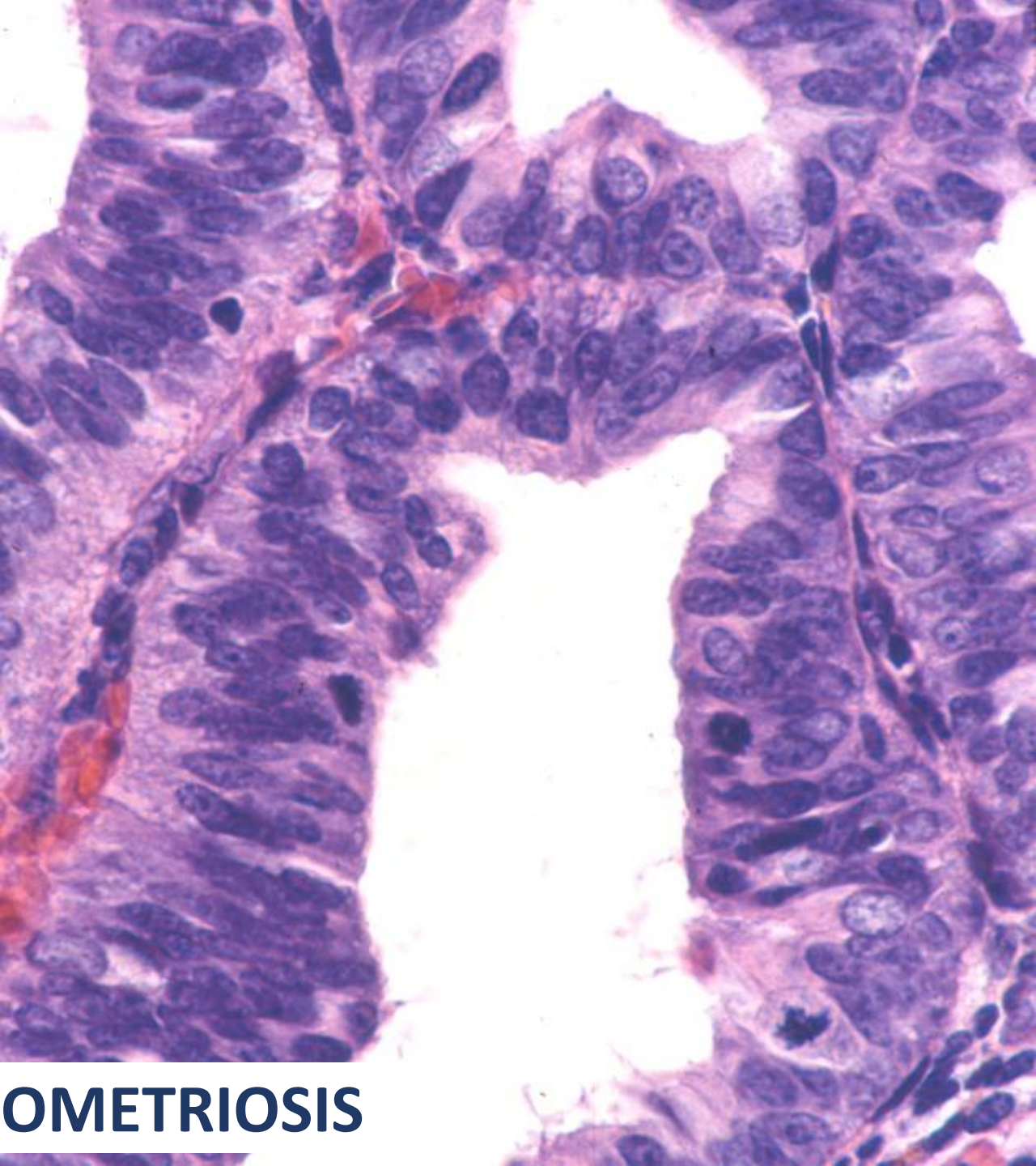
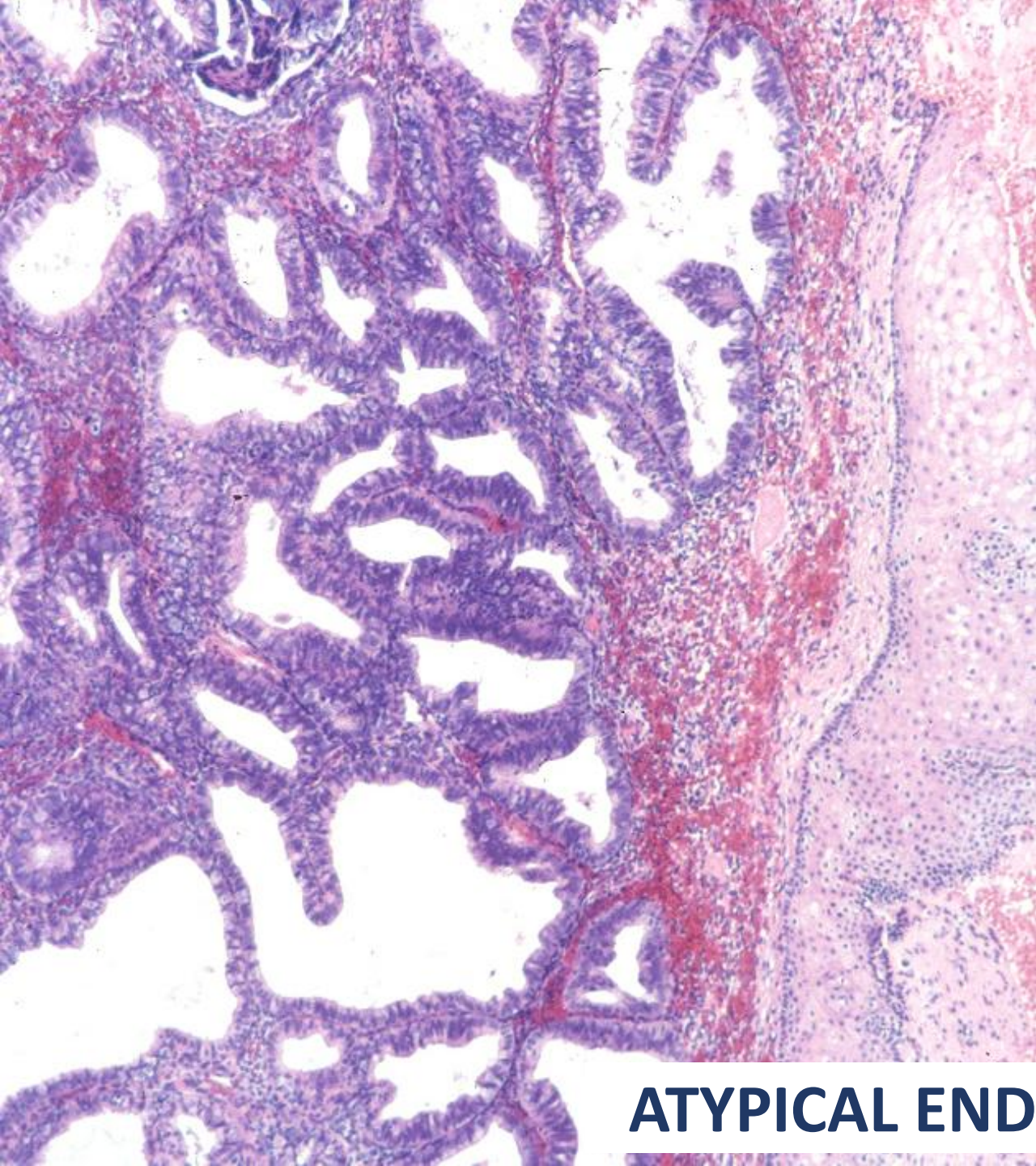
- **Superficial**: Related to previous trauma
No endometriosis elsewhere
- **Deep**: Associated with pelvic endometriosis



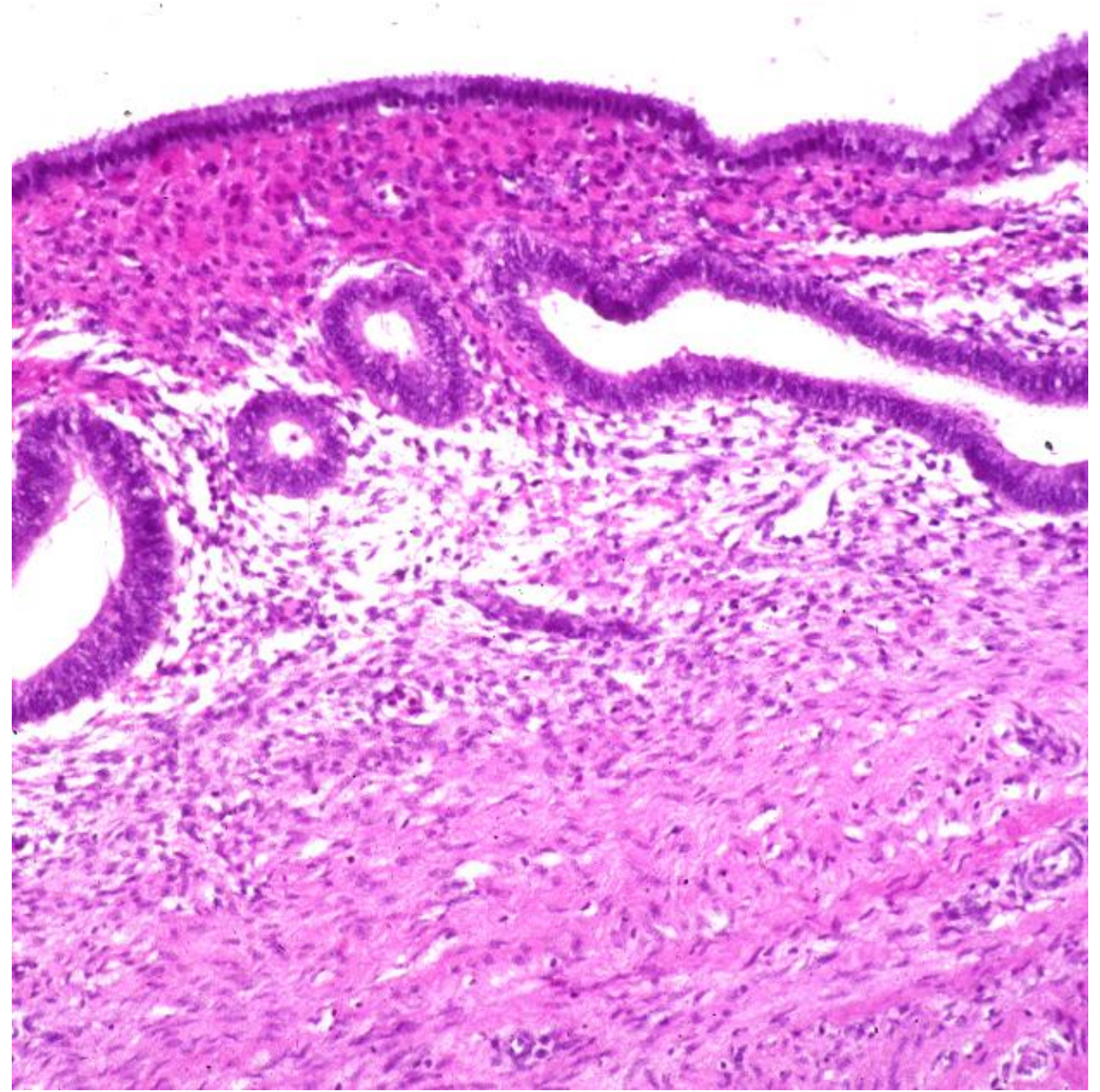
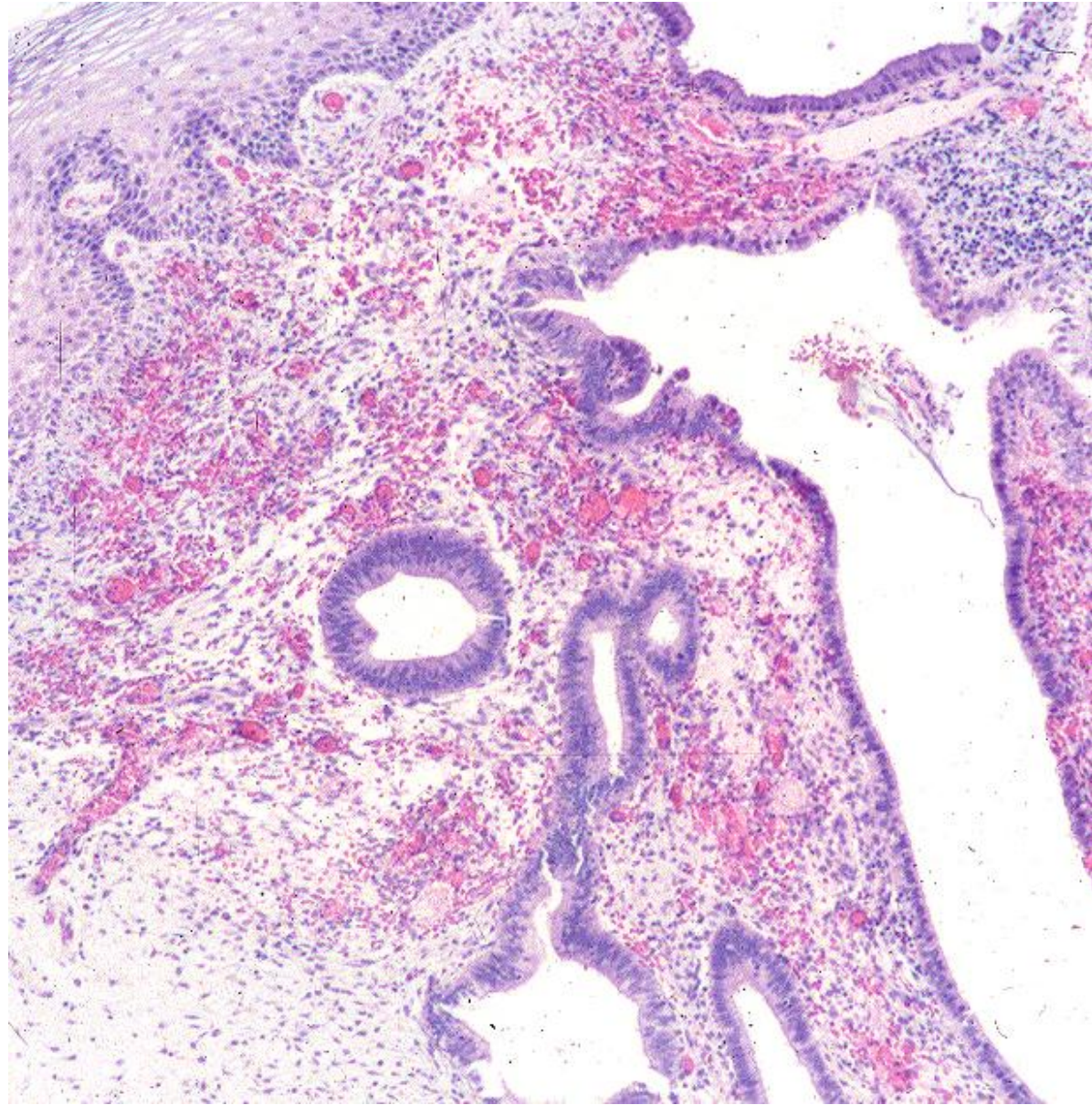
ENDOMETRIOSIS

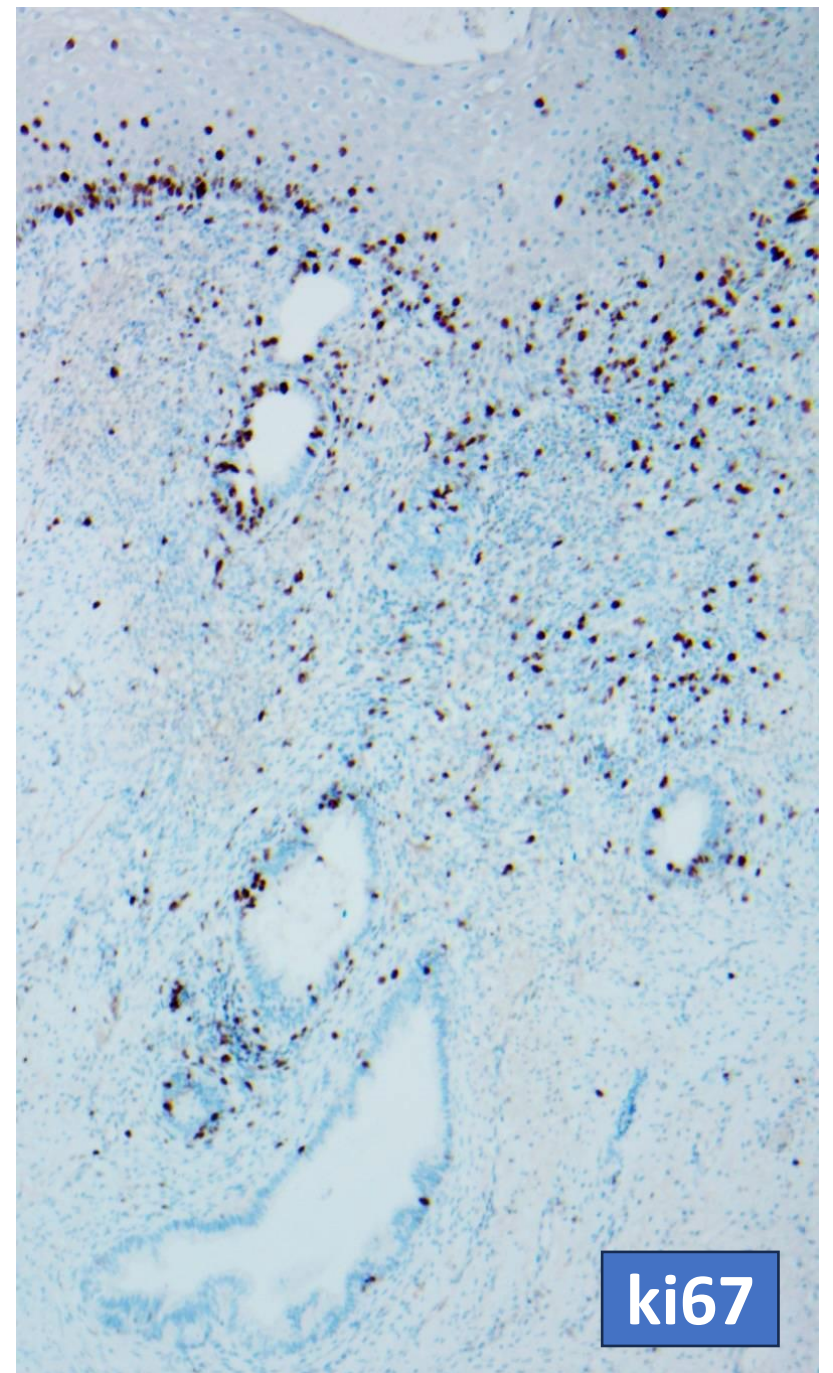
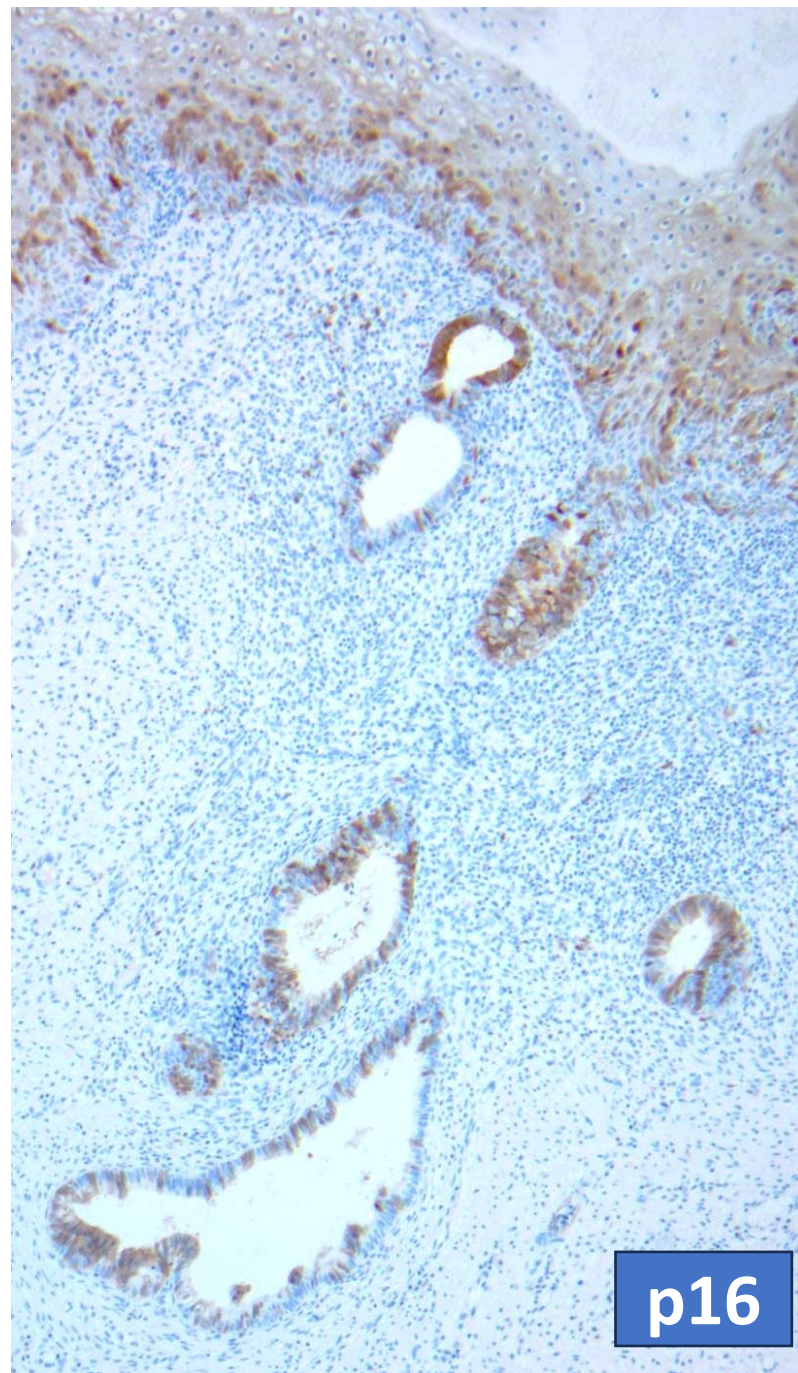
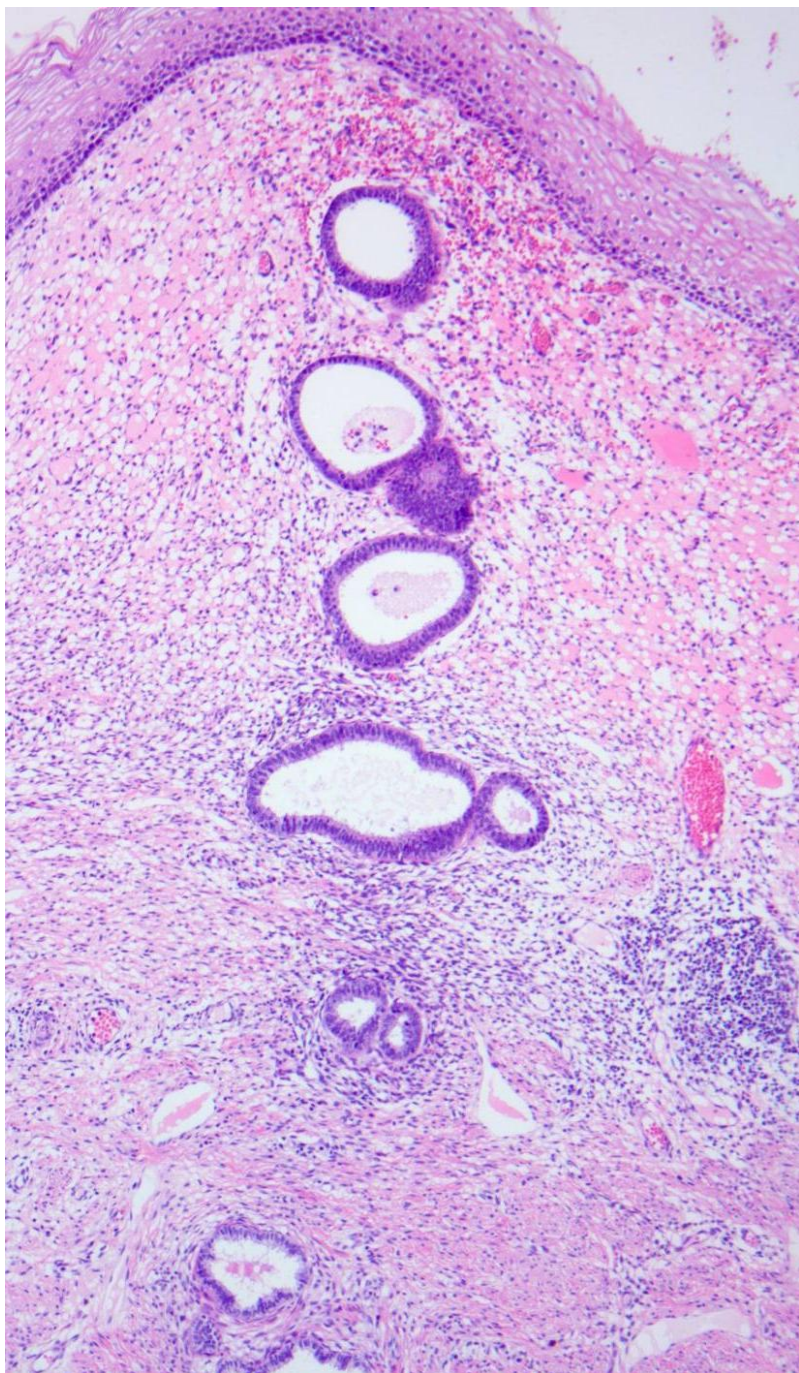


AIS



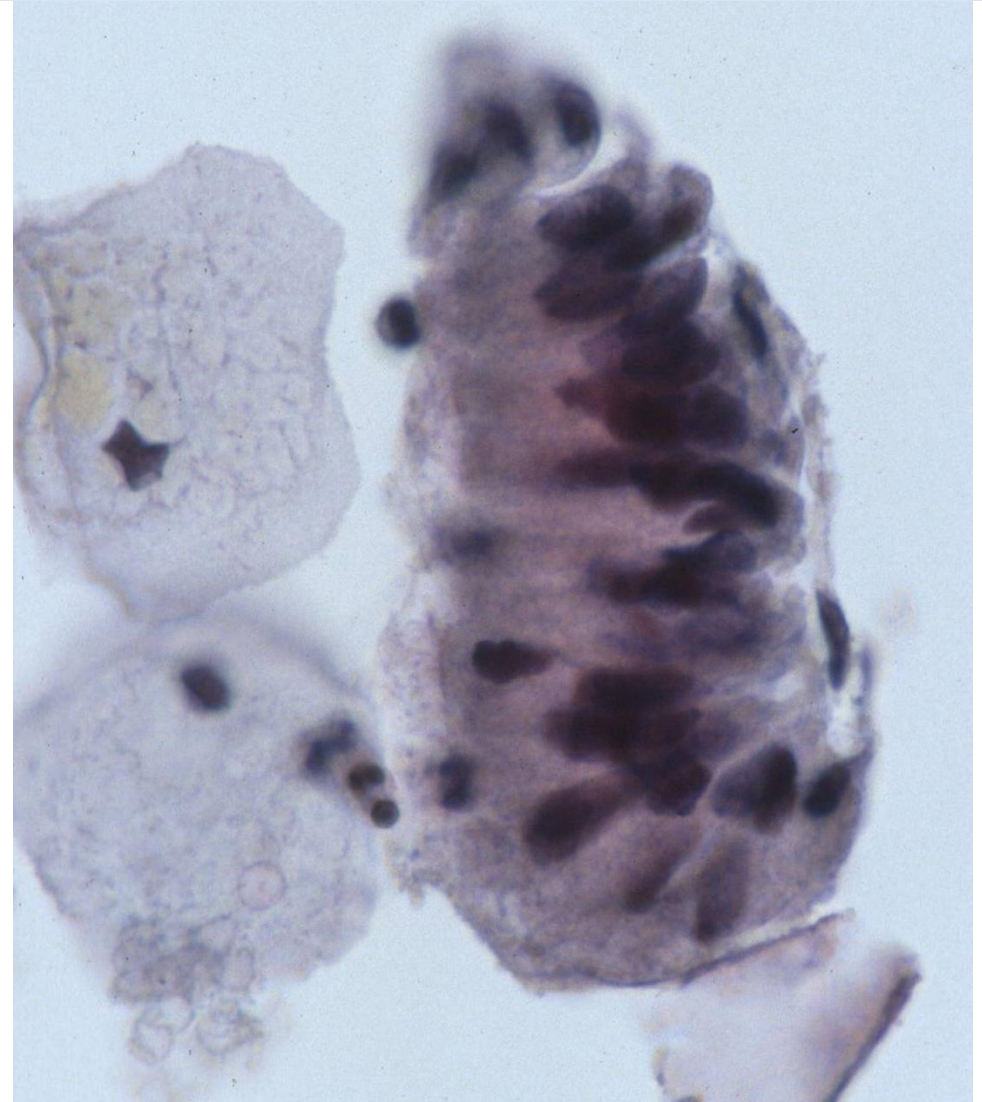
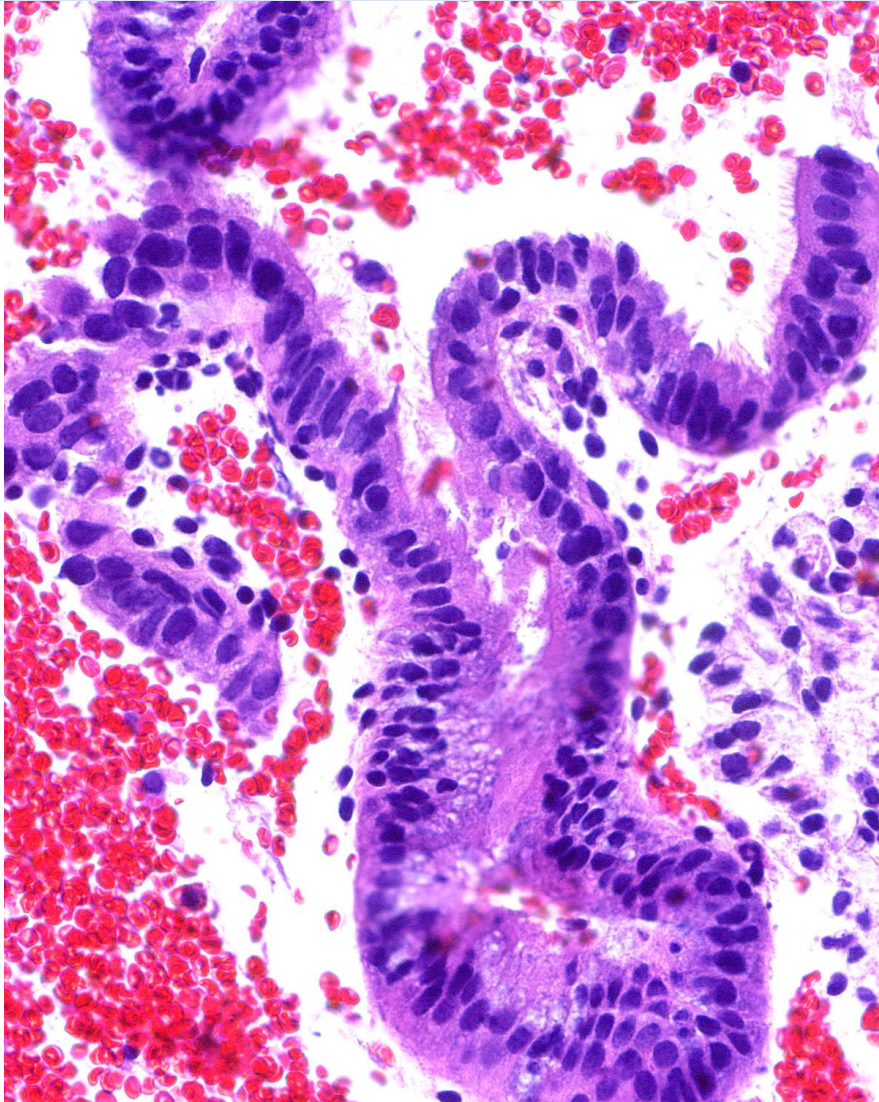
ATYPICAL ENDOMETRIOSIS





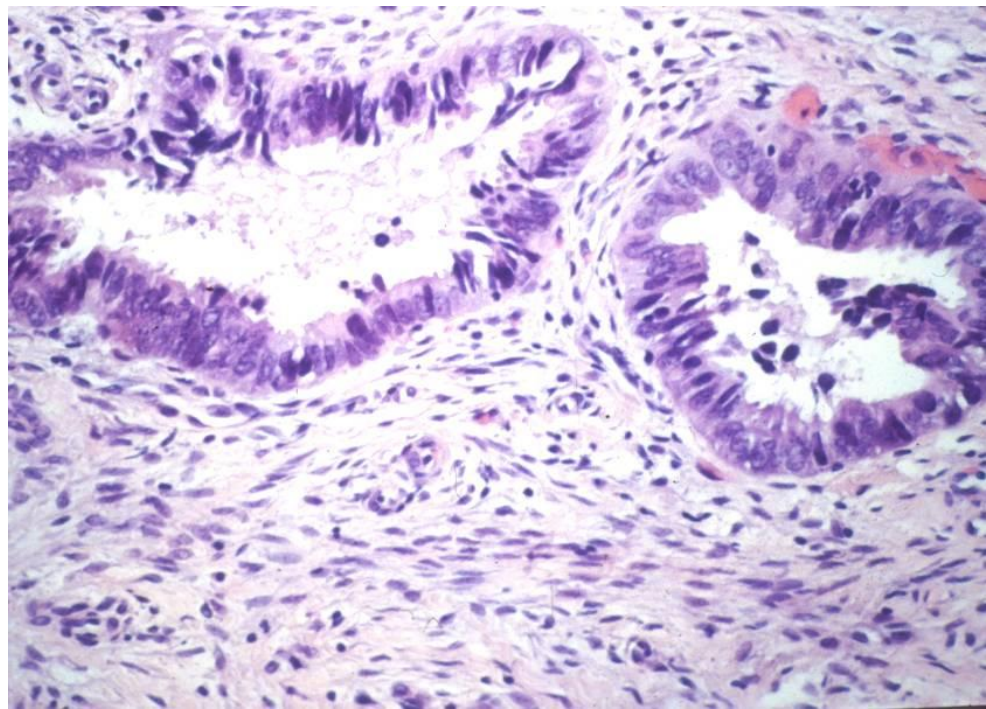
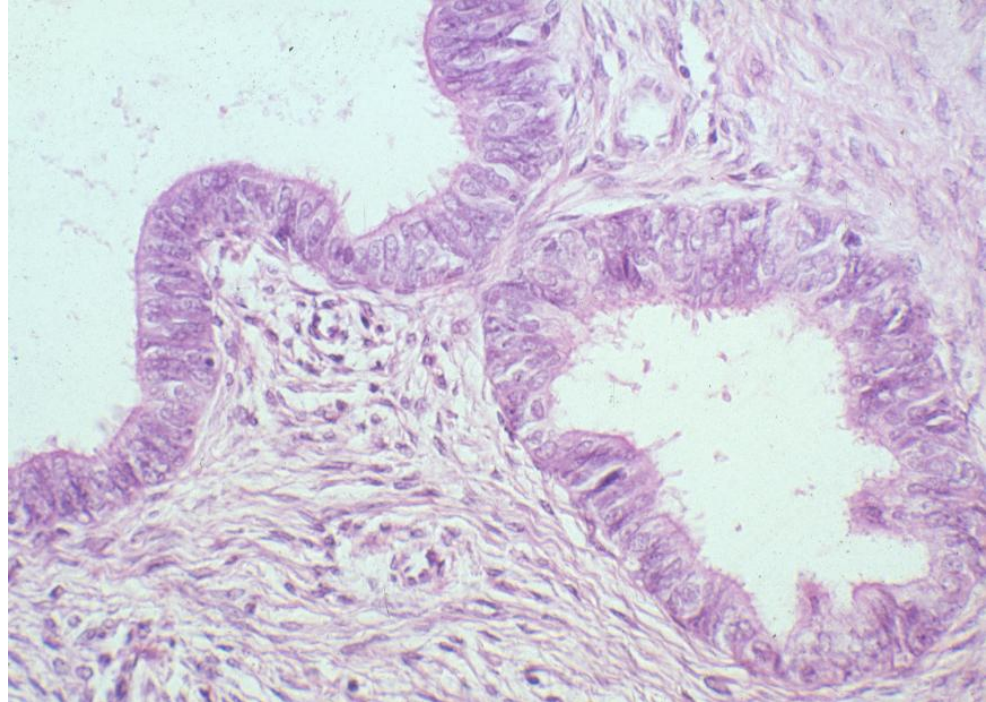
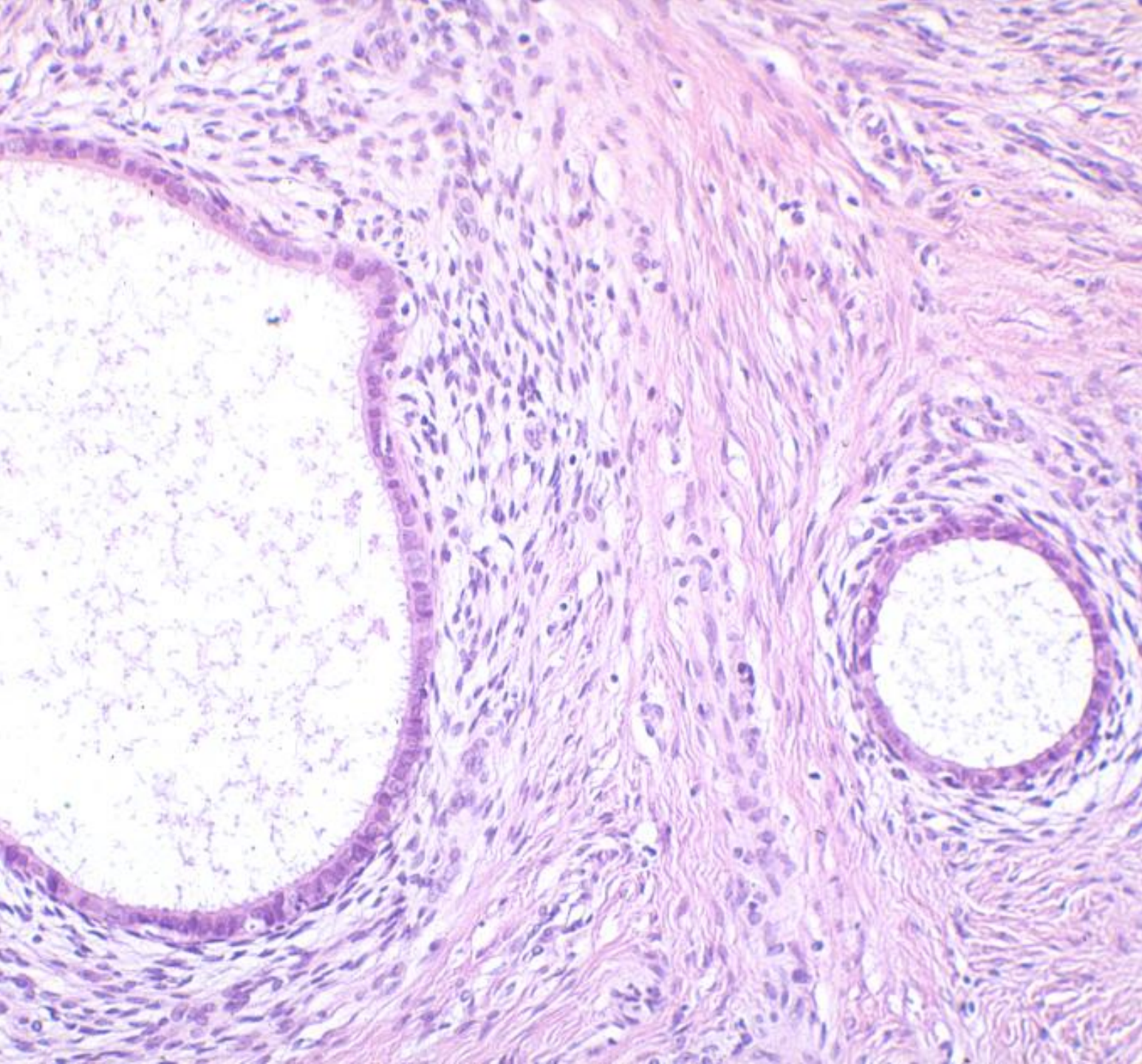
	<u>EMOS</u>	<u>AIS</u>
Abnormal Pap smear	+	+
Endometrial stroma	+	-
Stromal hemorrhage	+	-
Nuclear pseudostratification	+	+
Mitoses	-/+ (+/- stroma)	+
Apoptotic bodies	-/+	+
Squamous dysplasia	-	+
p16 positivity	Focal	Diffuse

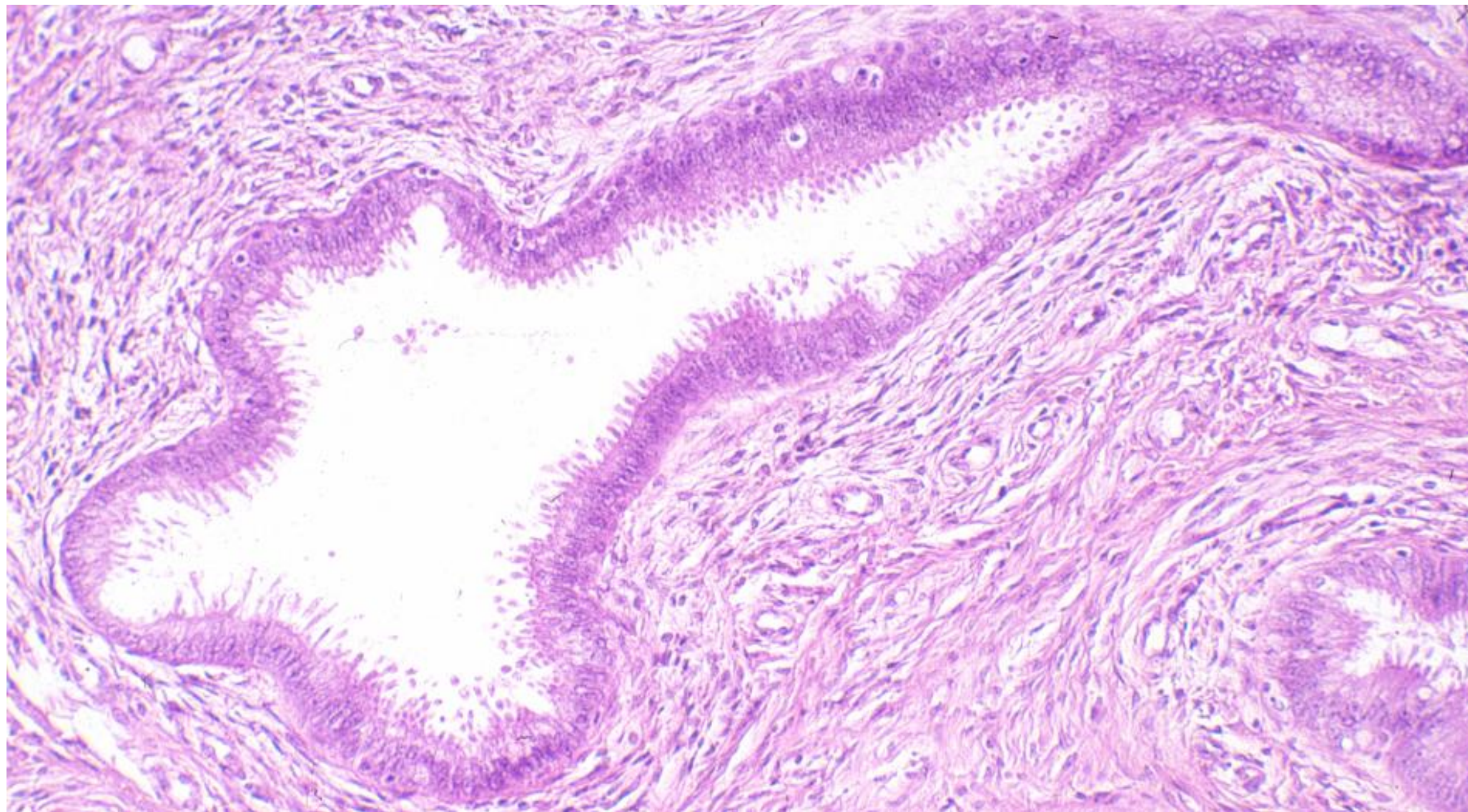
Tubal metaplasia may mimic AIS especially in cytology or curettage/biopsy



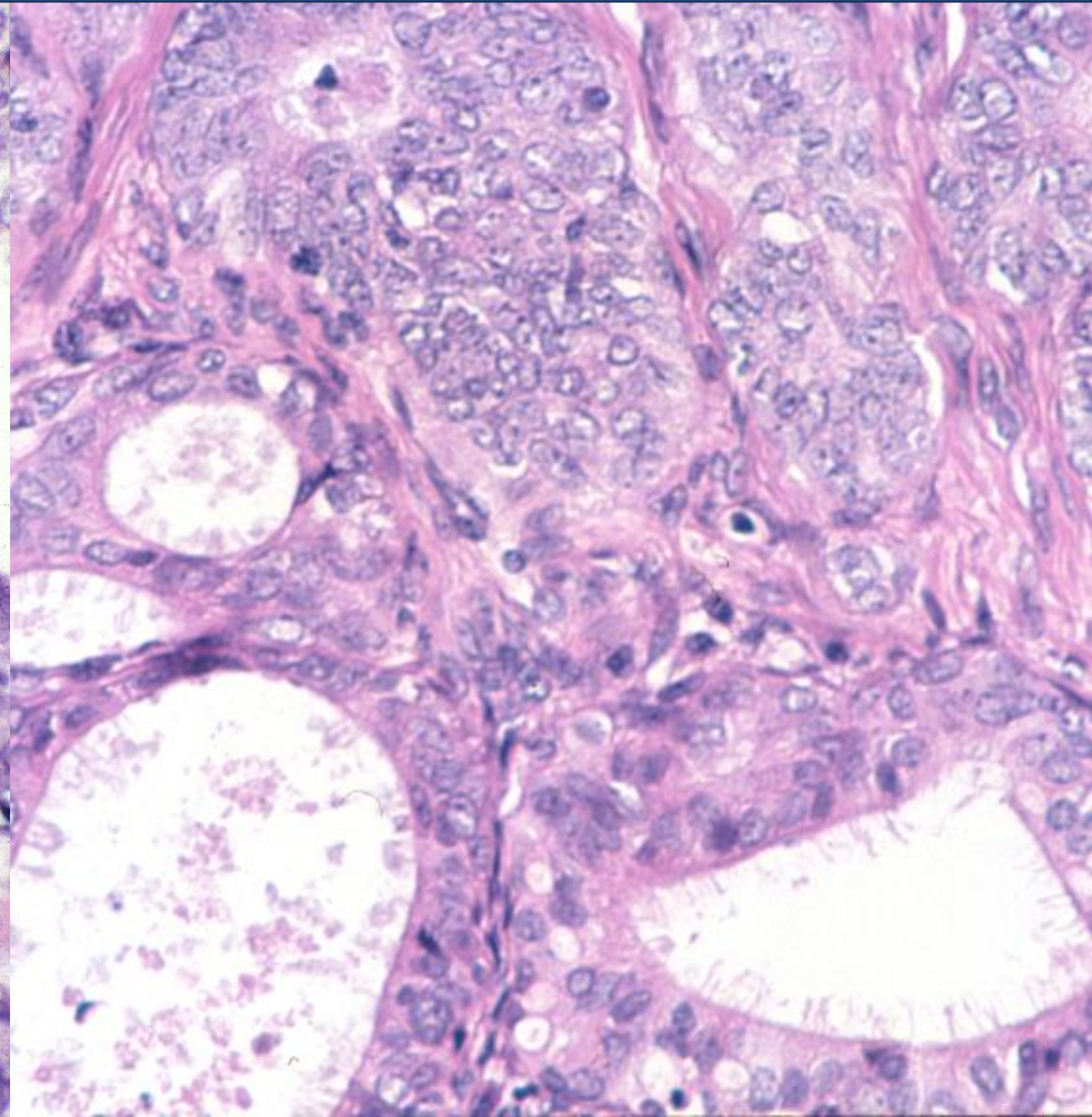
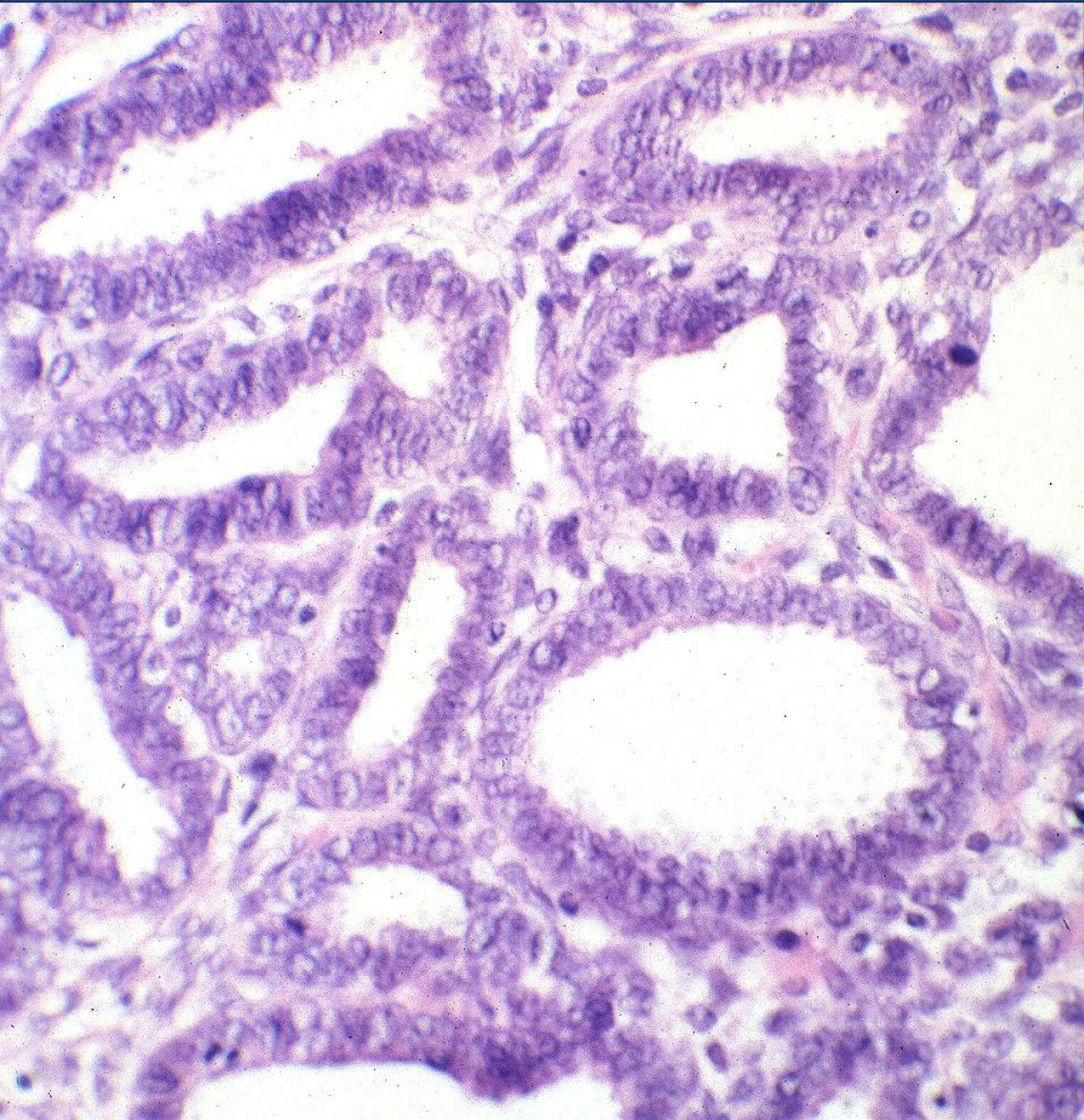
The image is a histological slide showing a comparison between normal fallopian tube tissue and tubal metaplasia. The left half of the image shows normal fallopian tube tissue with large, clear, circular or oval lumens lined by a simple cuboidal epithelium. The right half shows tubal metaplasia, where the normal tubal structure is replaced by a dense proliferation of small, irregular, glandular structures with complex, branching lumens. A central white oval with a black border contains the text 'TUBAL METAPLASIA'.

**TUBAL
METAPLASIA**





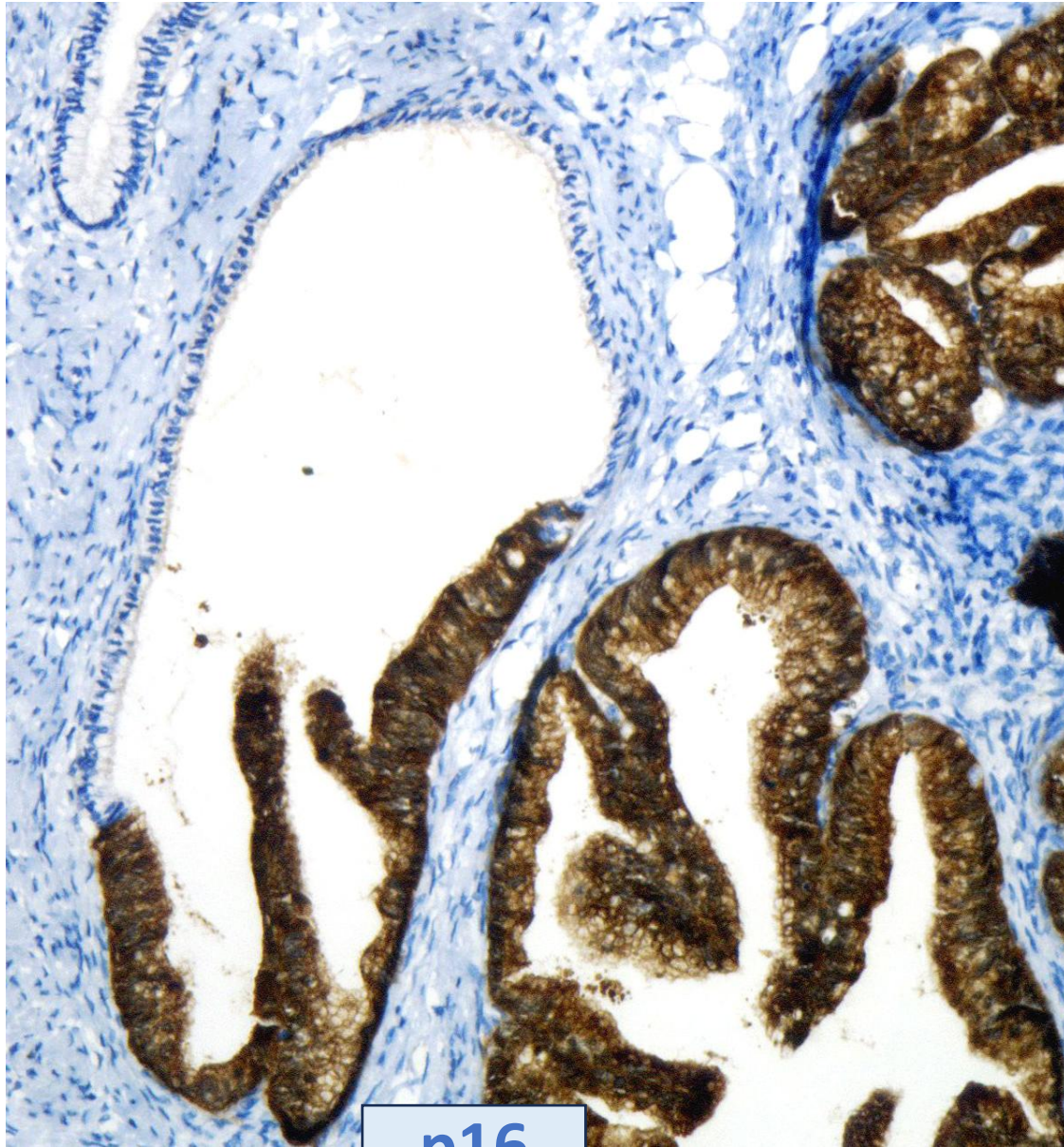
ATYPICAL TUBAL METAPLASIA MAY EVOLVE TO ENDOMETRIOD CARCINOMA



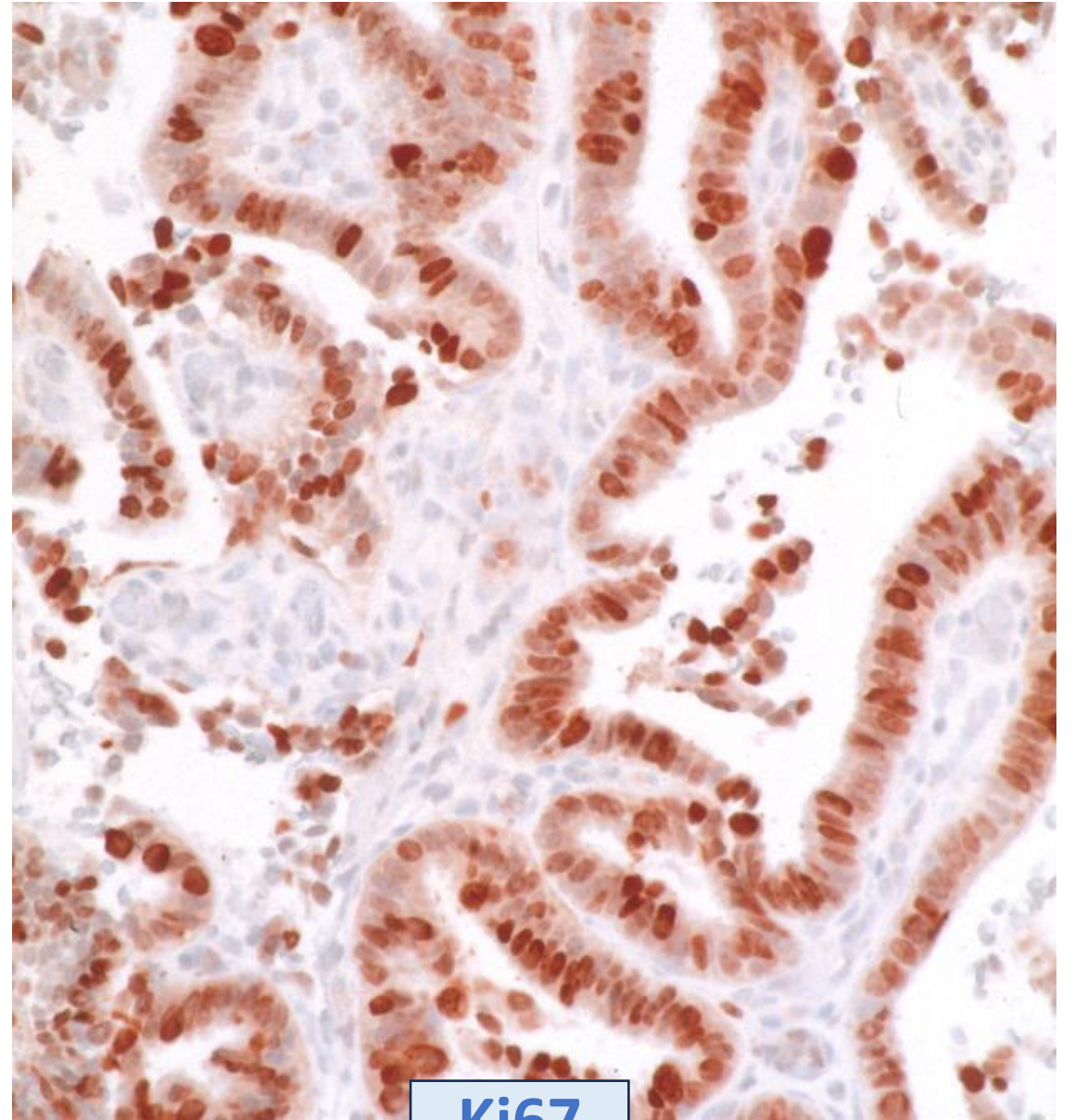
AIS

TEM/EMOS

• MIB 1	> 30%(often D)	< 10%
• ProExC	+ (>50%)	+ (<10%)
• p16	+ (D)	-/+ (F)
• CEA (M)	+ (CP)	-/+ (Luminal)
• Bcl-2	-	+
• Vim	-	+
• ER	-/+ (F)	+ (D)
• PAX2	-	+



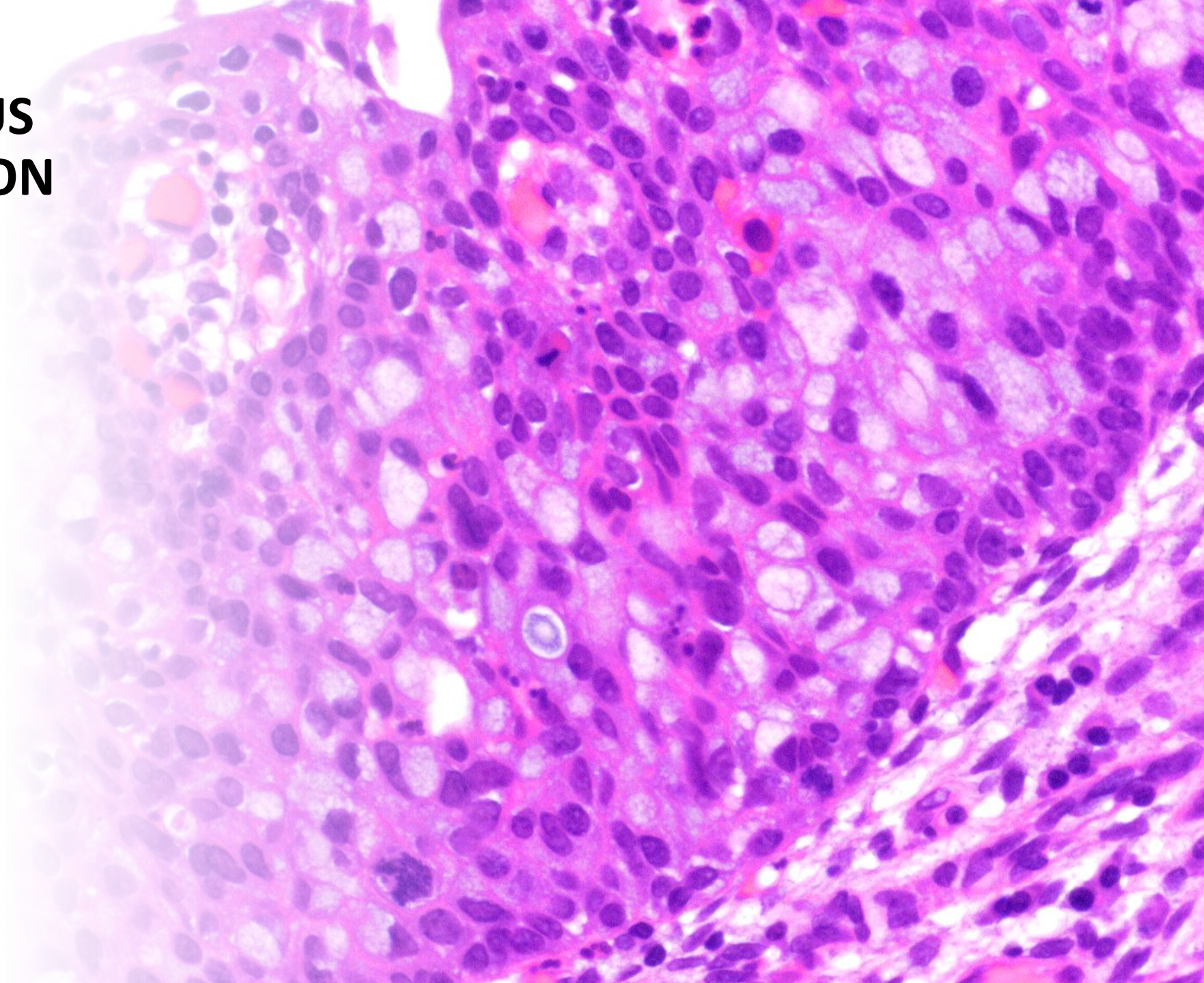
p16

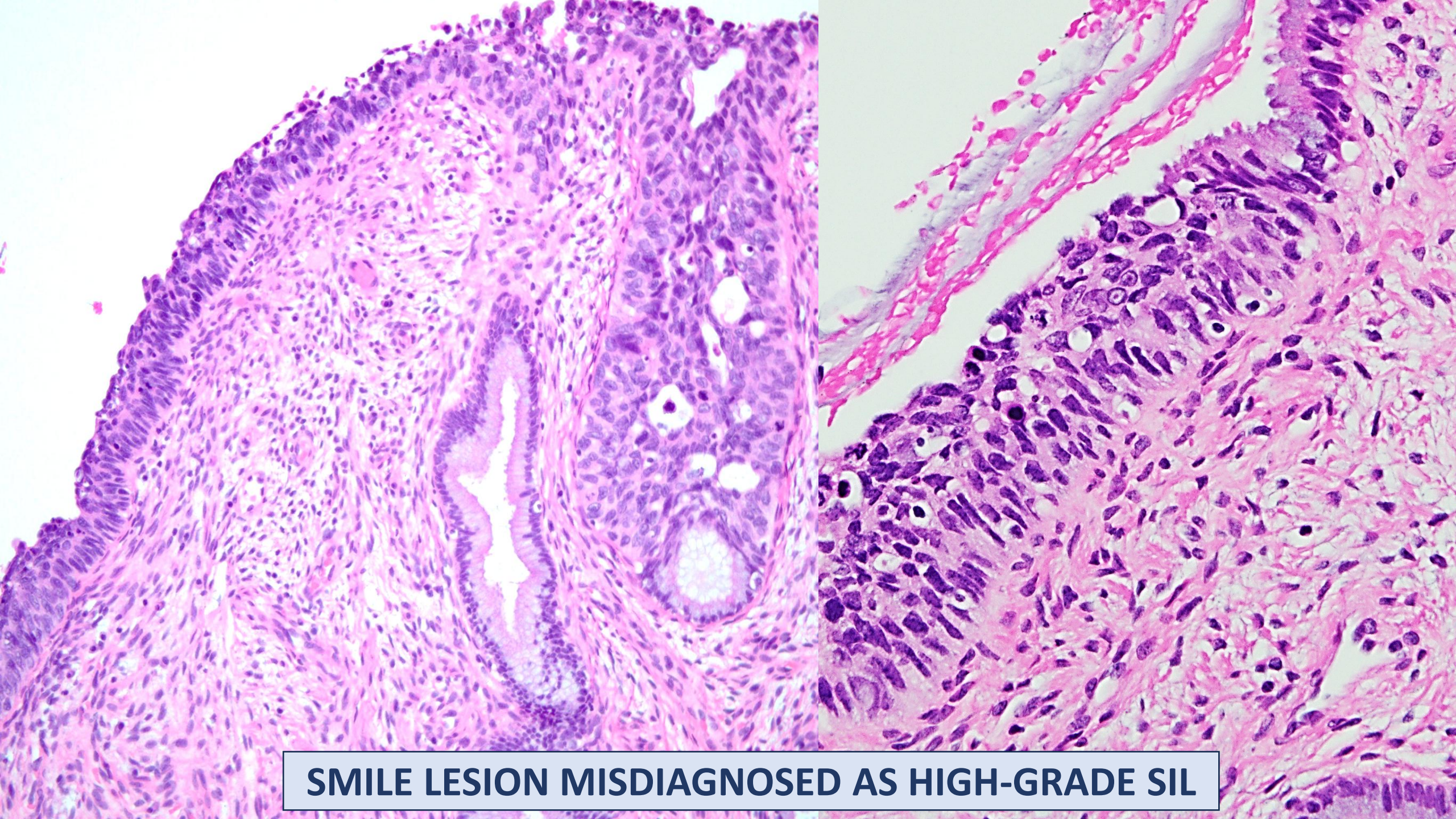


Ki67

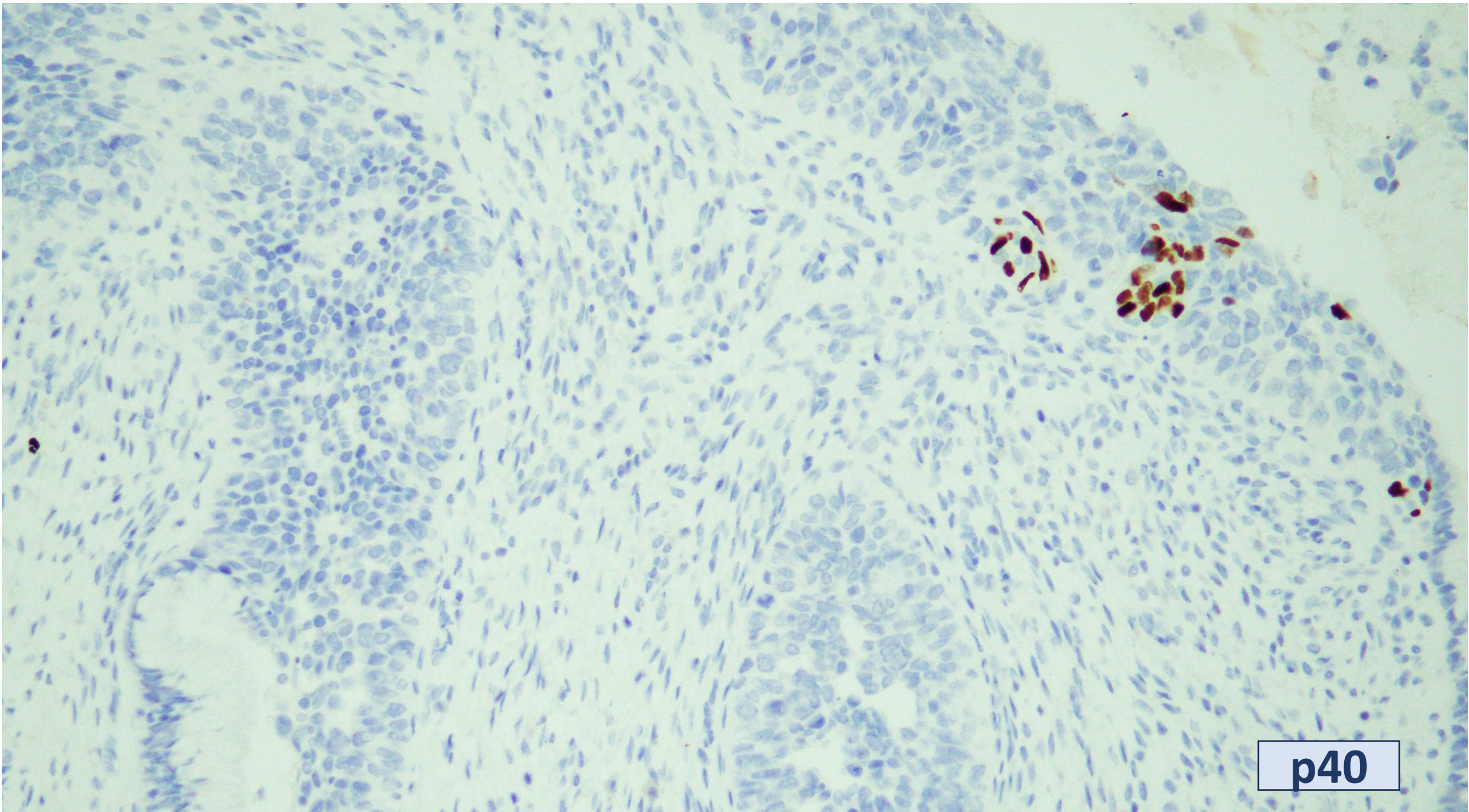
STRATIFIED MUCINOUS INTRAEPITHELIAL LESION (SMILE)

- Minimal p40/p63
(basal)
- IMP3 – (+ in AIS)
- P16 +++++

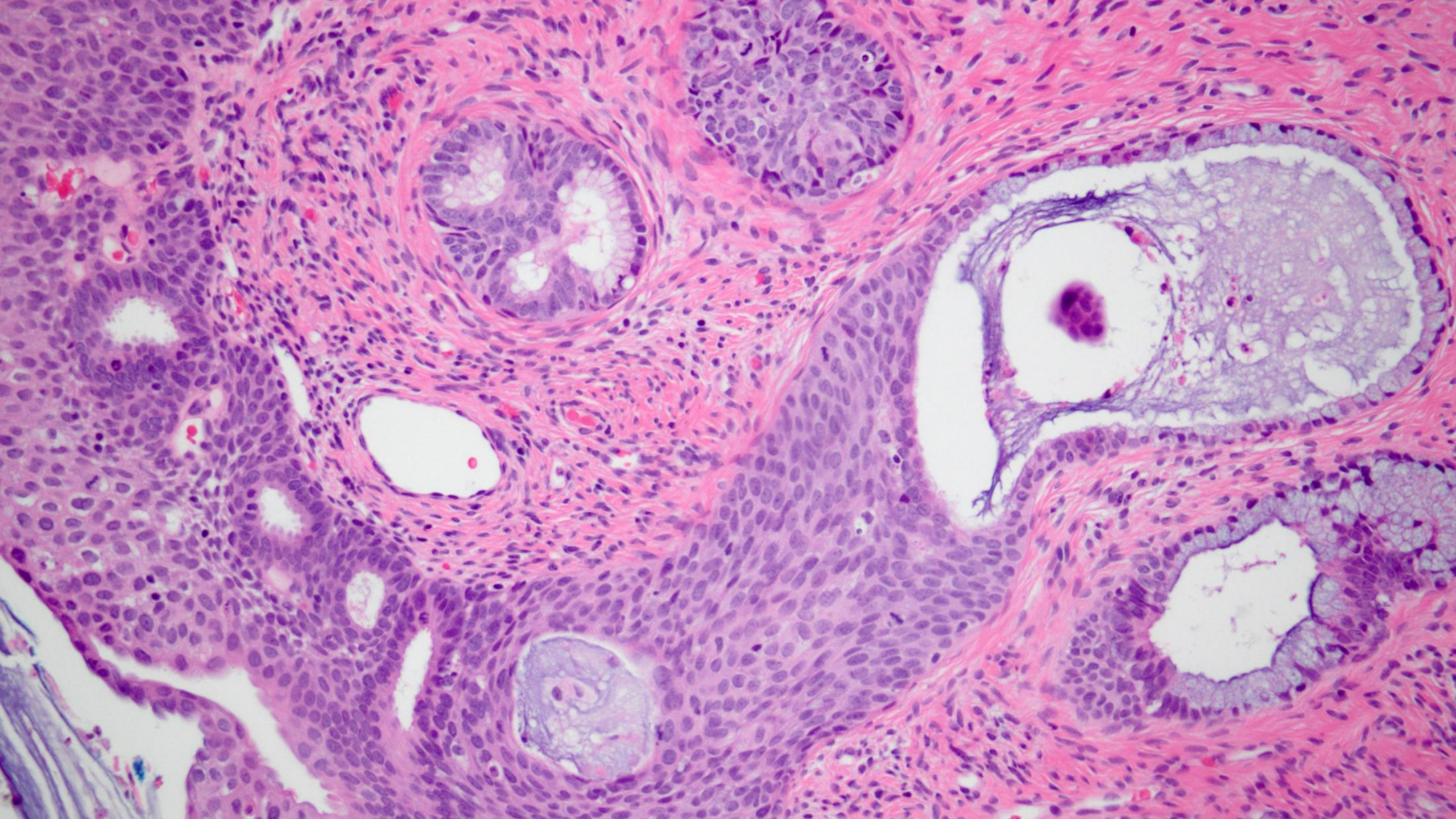




SMILE LESION MISDIAGNOSED AS HIGH-GRADE SIL

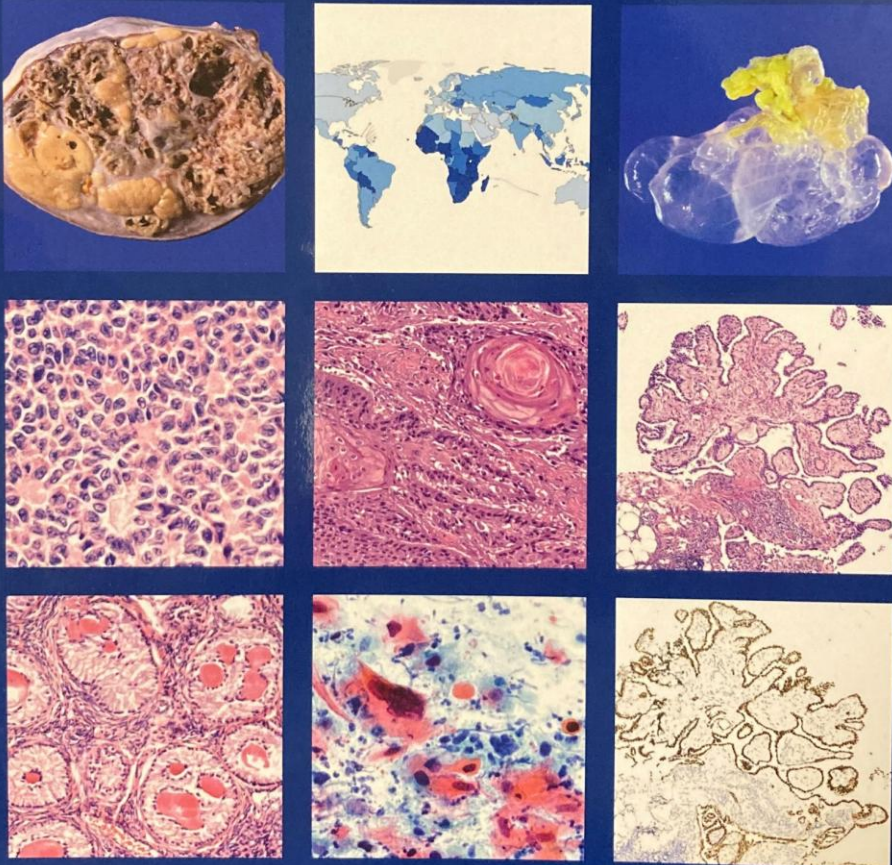


p40



Female Genital Tumours

Edited by the WHO Classification of Tumours Editorial Board



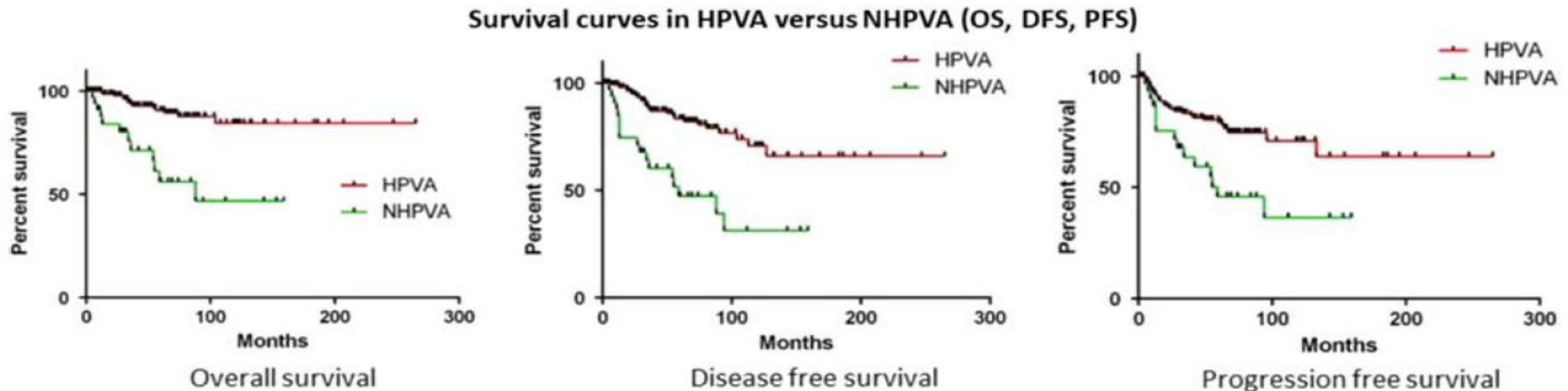
2019 WHO CLASSIFICATION OF CERVICAL ADENOCARCINOMAS

**Integration
of morphologic,
immunohistochemical,
and molecular findings**

**Based on morphologic features
linked to etiology (ie, human
papillomavirus infection)**

HPV-RELATED vs HPV INDEPENDENT ADENOCARCINOMAS

- If HPV-related:
 - Younger age at presentation (42 vs 55 years)
 - More commonly precursor lesions
- If HPV independent:
 - Larger size (3.8 vs 2.1 cm)
 - Greater frequency of advanced stage



ENDOCERVICAL ADENOCARCINOMA CLASSIFICATION

HPV- ASSOCIATED

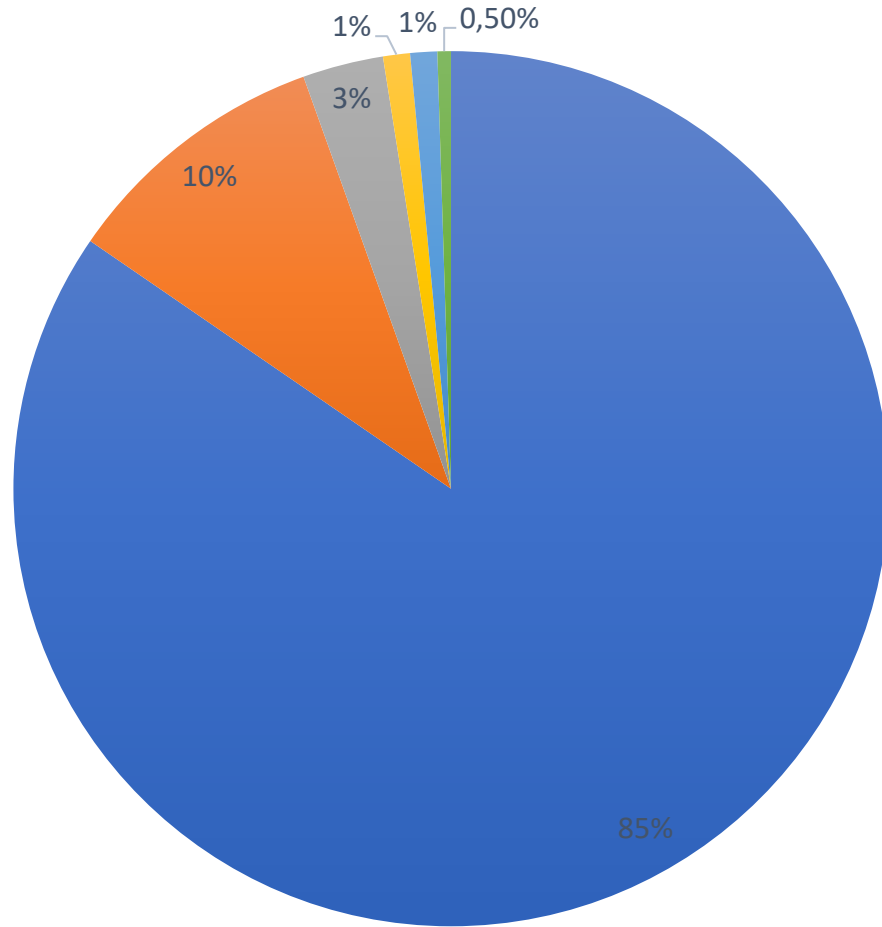
- Usual
- Mucinous

HPV-INDEPENDENT

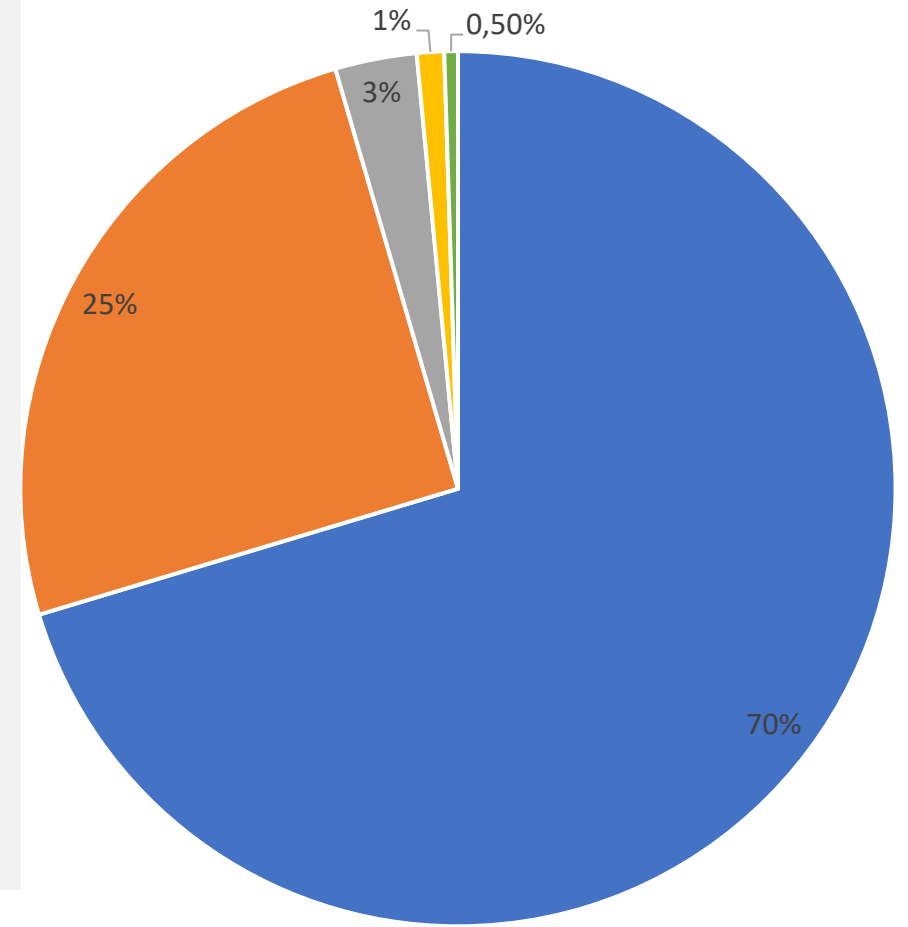
- Gastric
- Clear cell
- Mesonephric
- Endometrioid

NOS

Endocervical Adenocarcinoma Subtypes



Variable HPV prevalence in contrast to cervical SCC with almost 100% HPV association



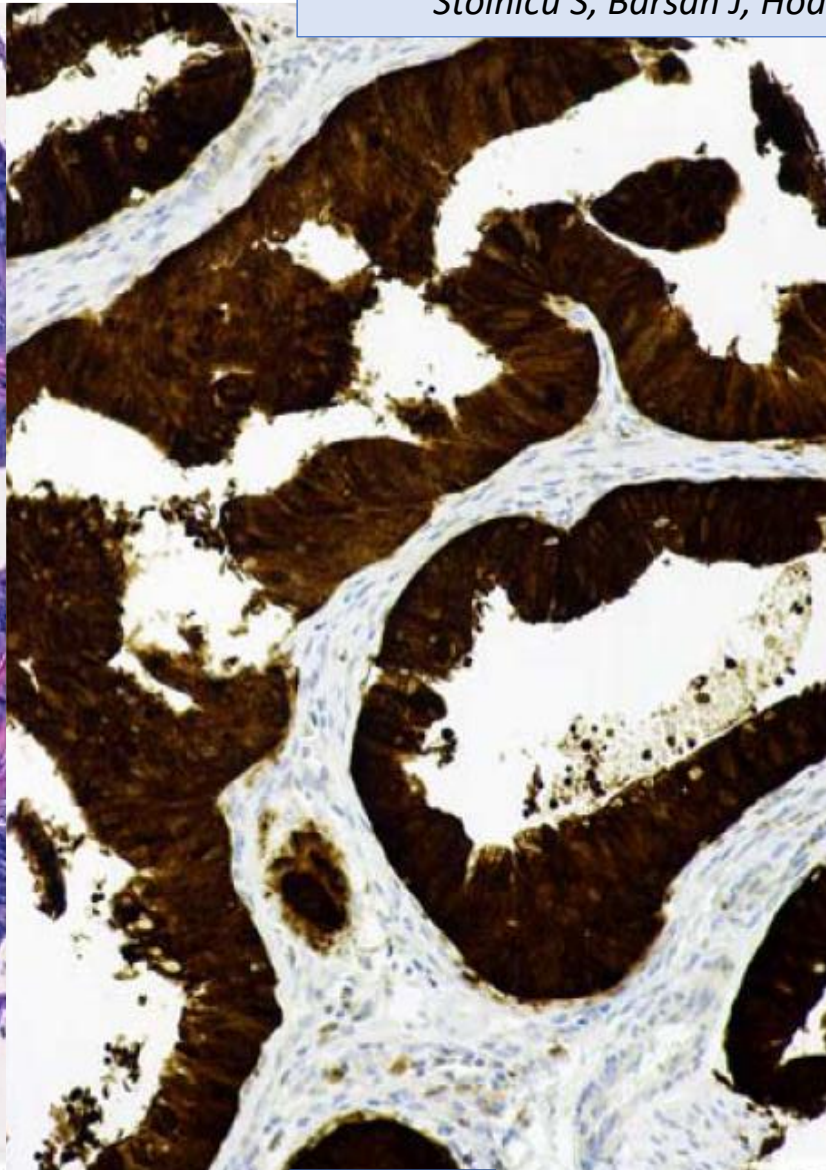
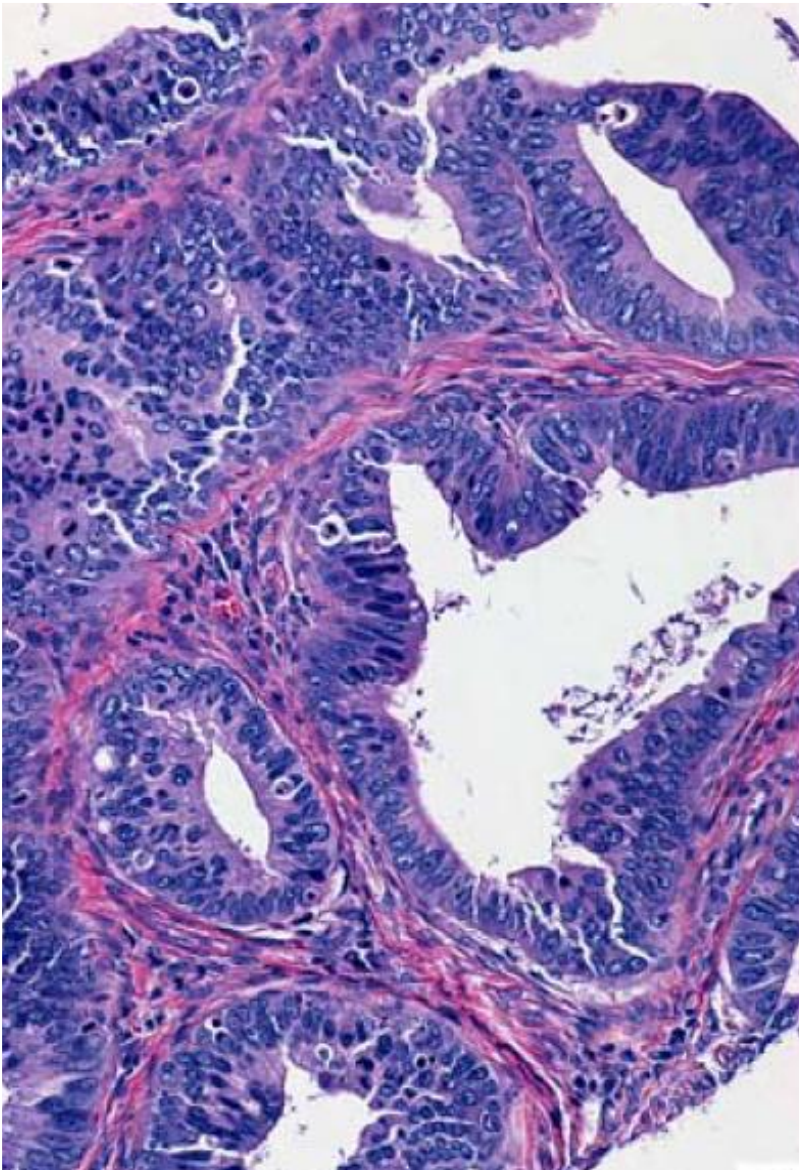
■ HPV related ■ Gastric ■ Clear cell ■ Mesonephric ■ Endometrioid ■ Other

■ HPV related ■ Gastric ■ Clear cell ■ Mesonephric 1% ■ Endometrioid 1% ■ Other

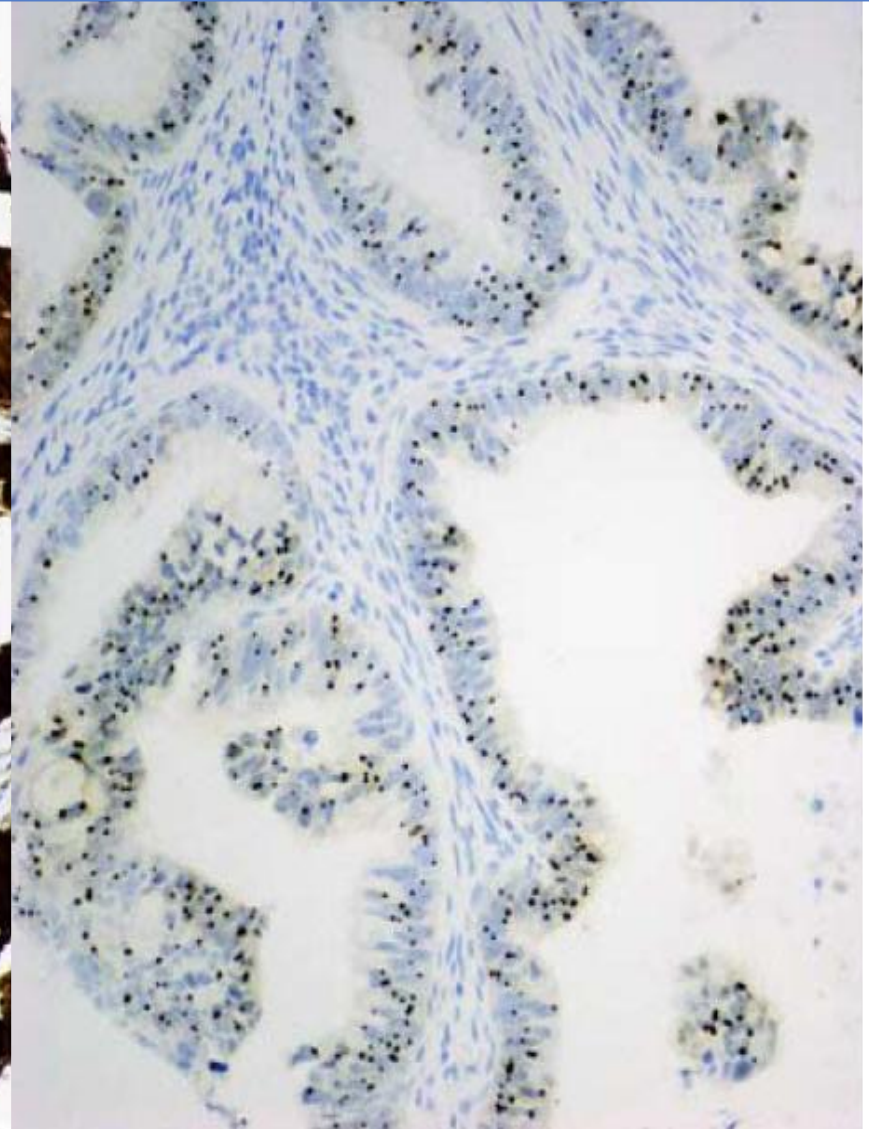
Much higher frequency of gastric-type adenocarcinoma in Japan

HPV-HR ISH superior sensitivity, specificity, and (-) predictive values than p16

Stolnicu S, Barsan J, Hoang L, et al. Am J Surg Pathol 2018;42:989-1000



p16

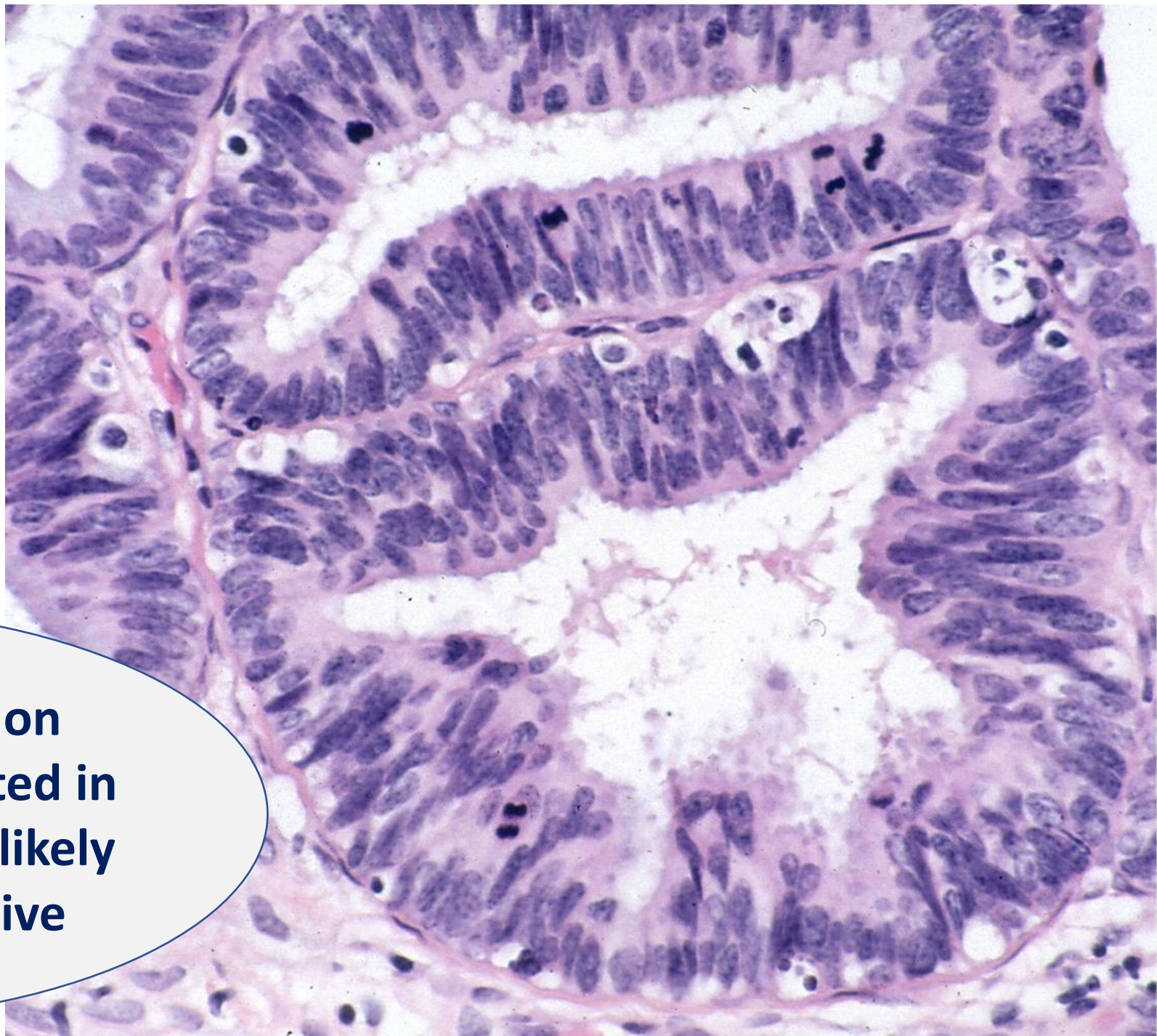


HPV

Distinction of HPV from non-HPV related adenocarcinomas based on:

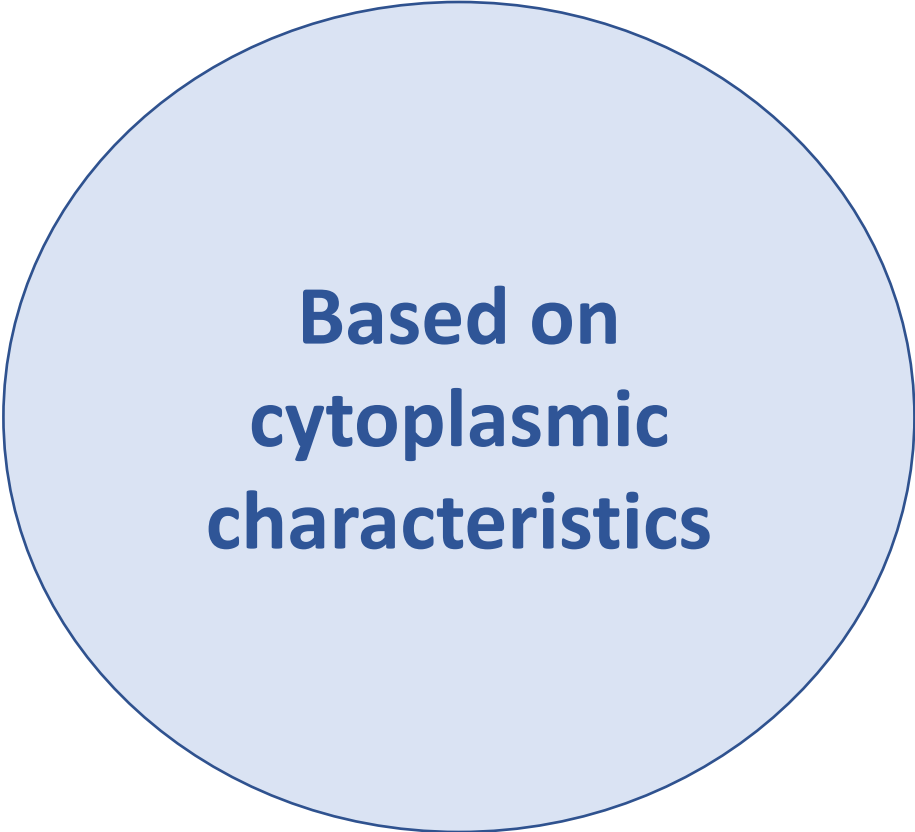
Presence of luminal
mitoses and apoptoses at
scanning magnification

**Classification based on
pathogenesis as reported in
vulva and oropharynx likely
to be more informative**

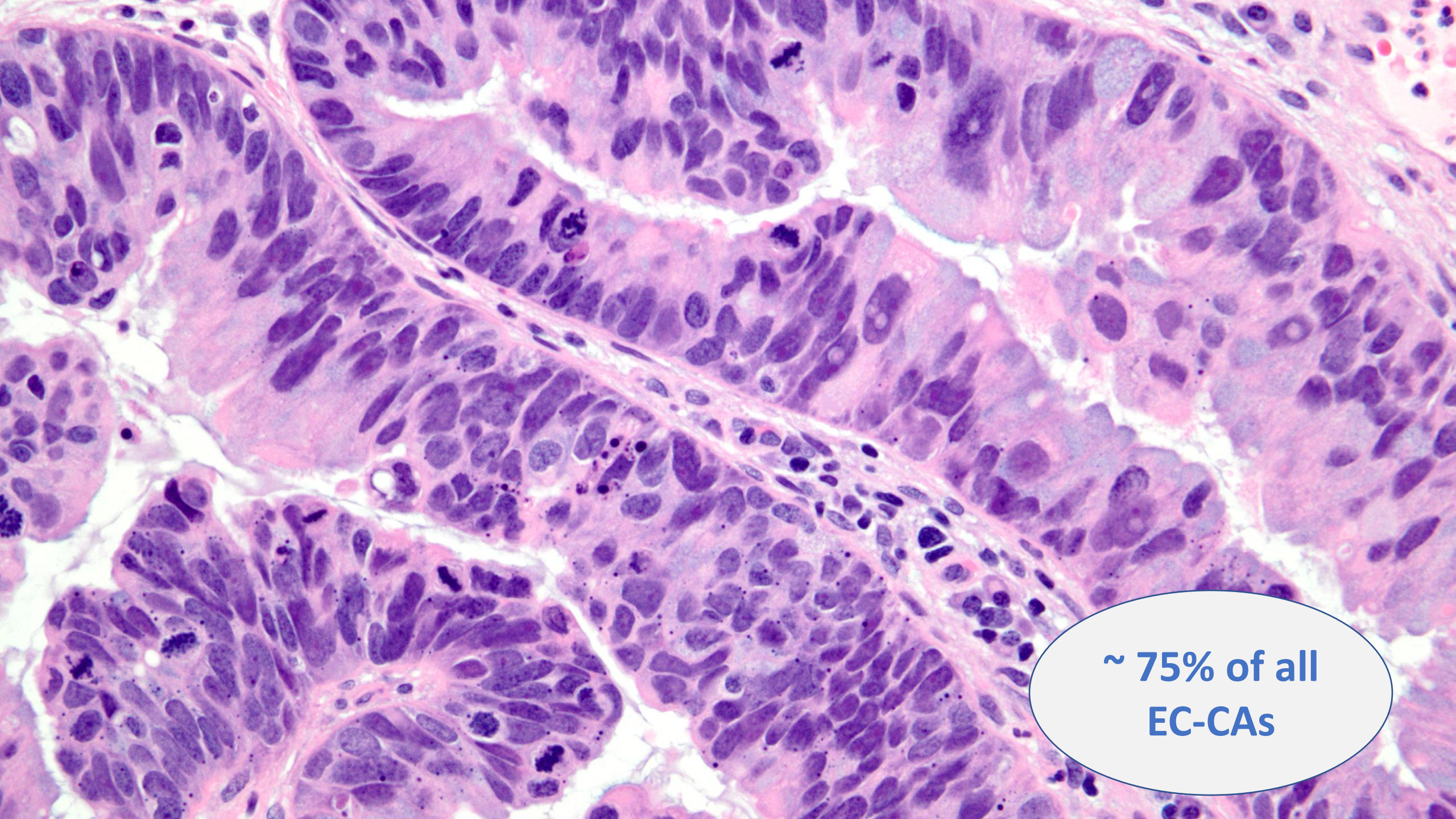


HPV-RELATED ENDOCERVICAL ADENOCARCINOMA: WHO 2019

- Usual type
 - Villoglandular variant
- Mucinous type (>50% of cells with intracytoplasmic mucin)
 - Mucinous, NOS
 - Intestinal (>50% of goblet cells)
 - Signet-ring cell (>50%)
 - Stratified mucin producing



**Based on
cytoplasmic
characteristics**



~ 75% of all
EC-CAs

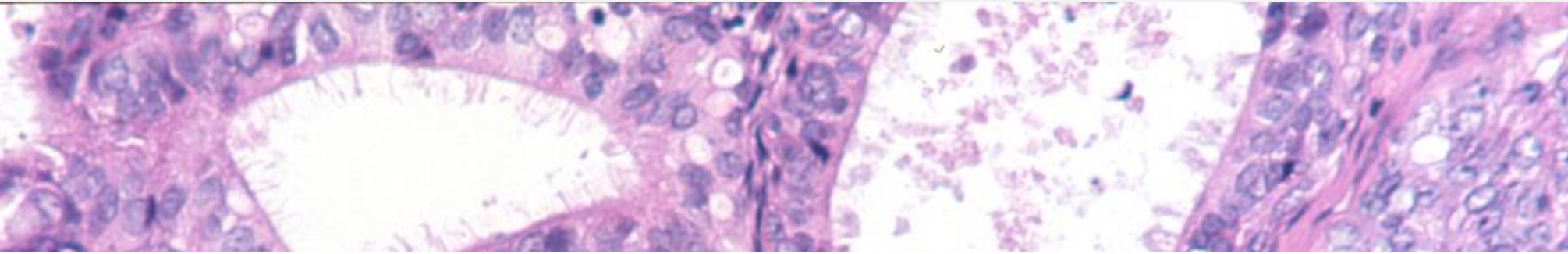
ENDOMETRIOID vs ENDOCERVICAL ADENOCARCINOMA

A significant minority of HPV-associated endocervical adenocarcinomas express Vimentin (~13%), ER (~5%) and PR (~20%) (limited utility)

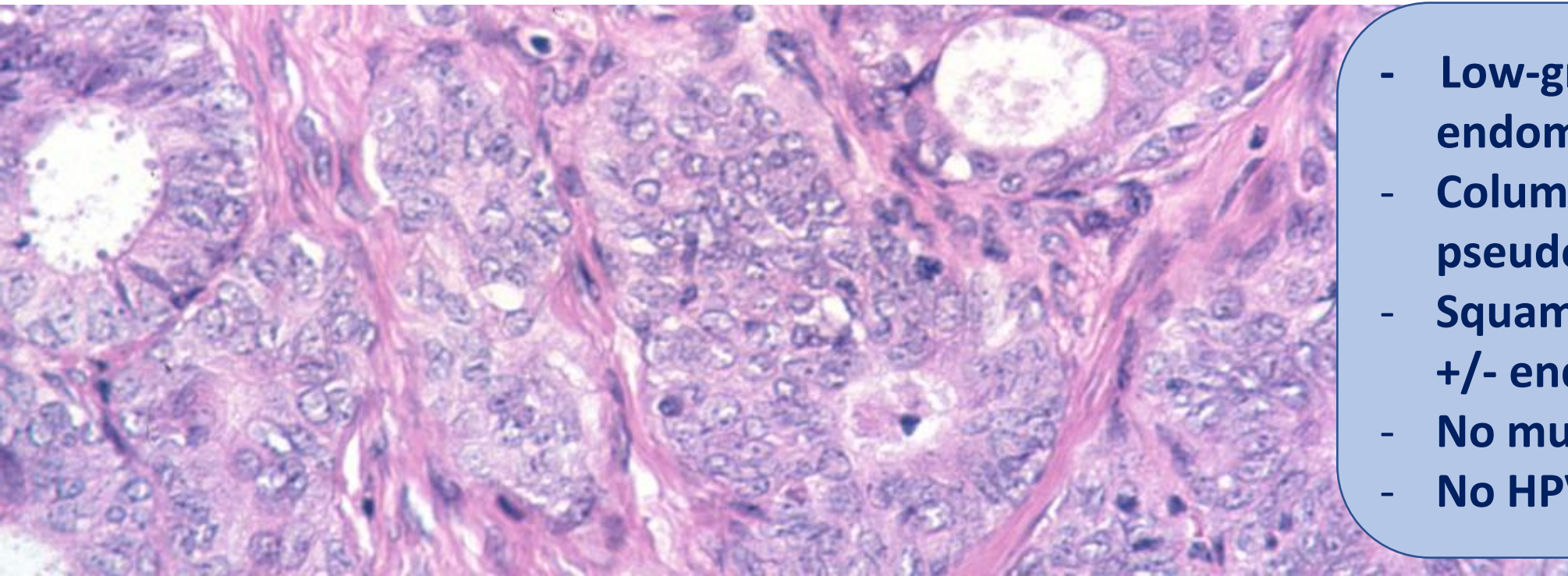
p16 can be extensively positive in squamous metaplasia within endometrioid carcinoma but typically only patchy in glandular component especially if low-grade

Combination of ER and p16 (HR-HPV ISH) most helpful in distinction

CERVICAL ENDOMETRIOID CARCINOMA



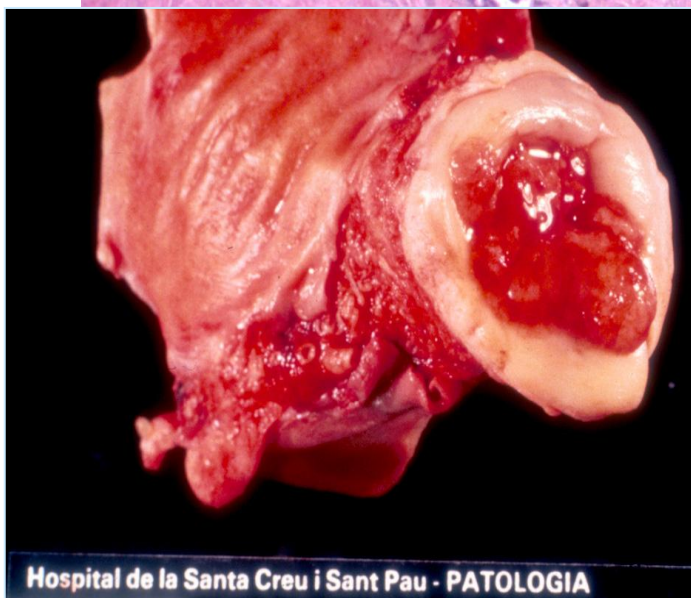
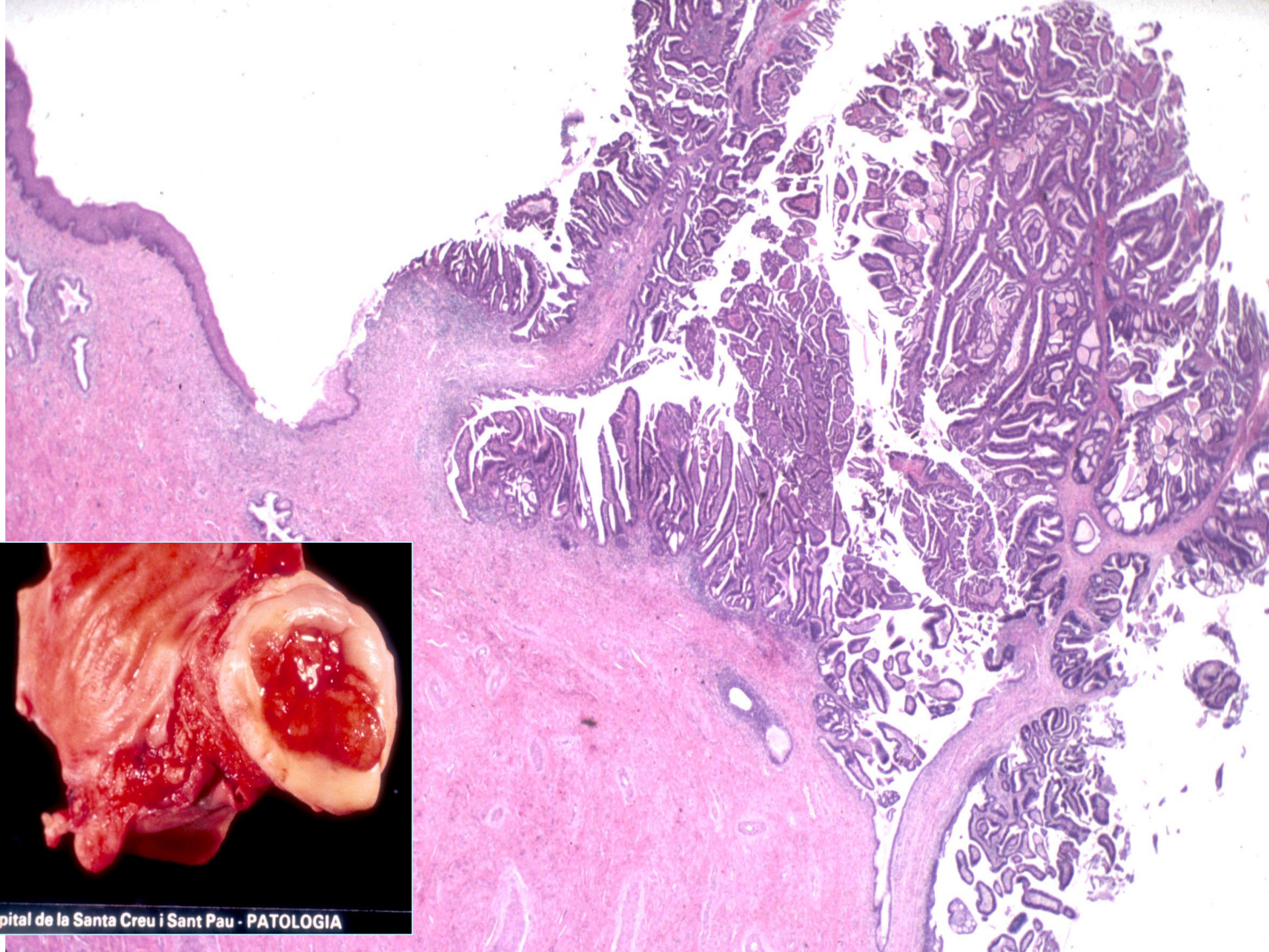
Most adenocarcinomas originally diagnosed as endometrioid reclassified as usual-type, with similar rates of p16 overexpression and HPV positivity to usual-type HPV-related adenocarcinoma (78 vs 83% and 82 vs 87%)

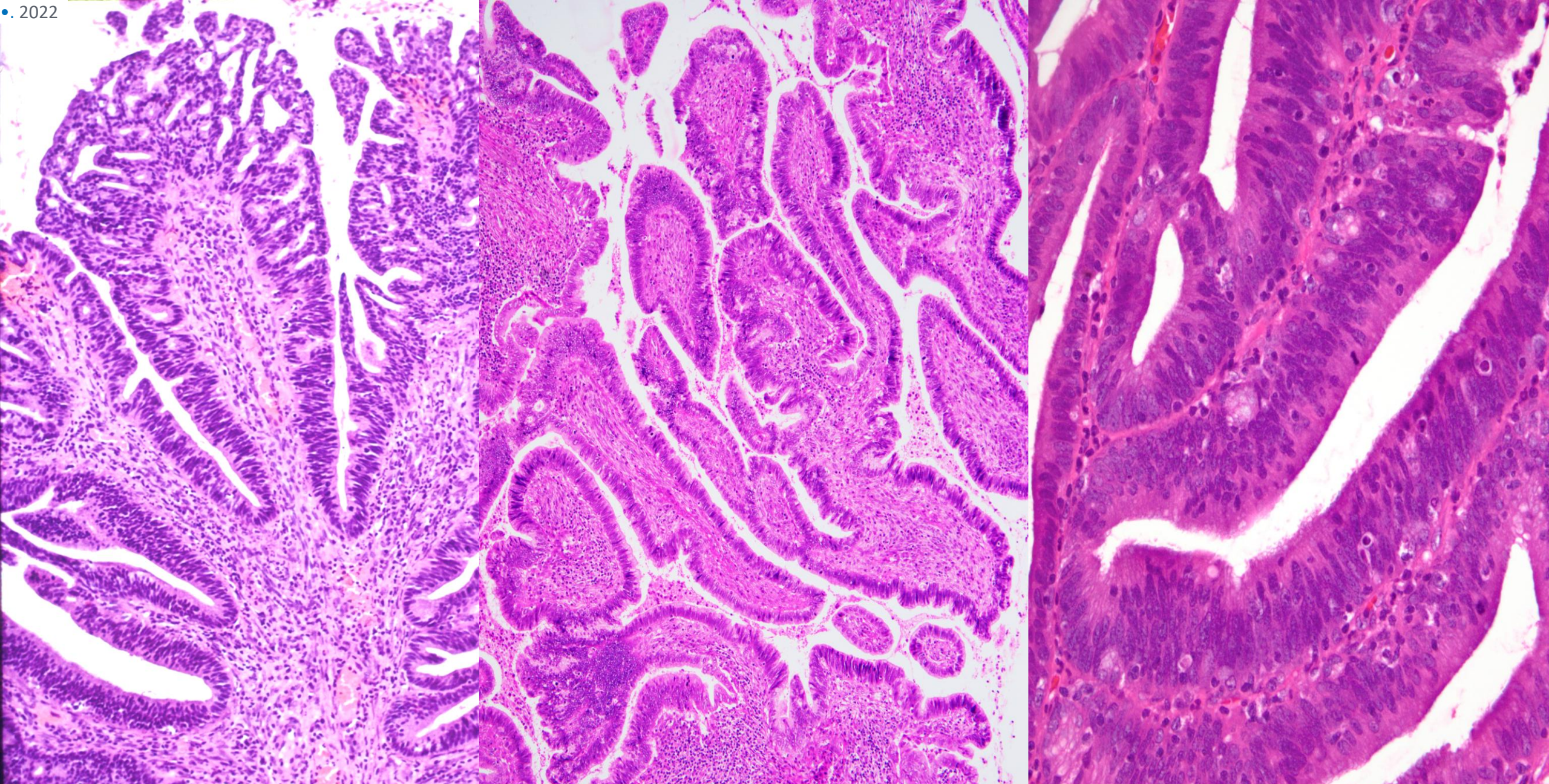


- Low-grade endometrioid glands
- Columnar cells and pseudostratified nuclei
- Squamous, ciliated diff, +/- endometriosis
- No mucin
- No HPV features

VILLOGLANDULAR

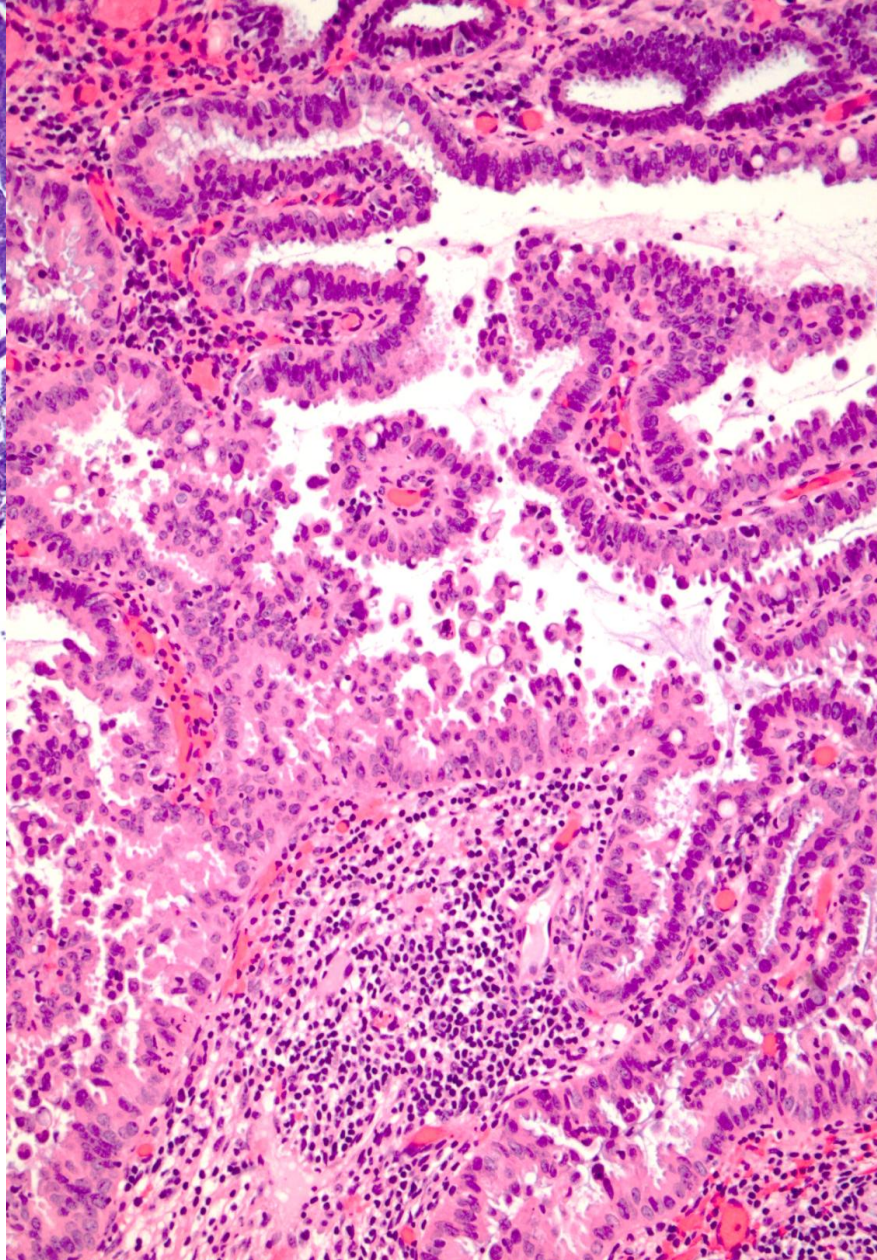
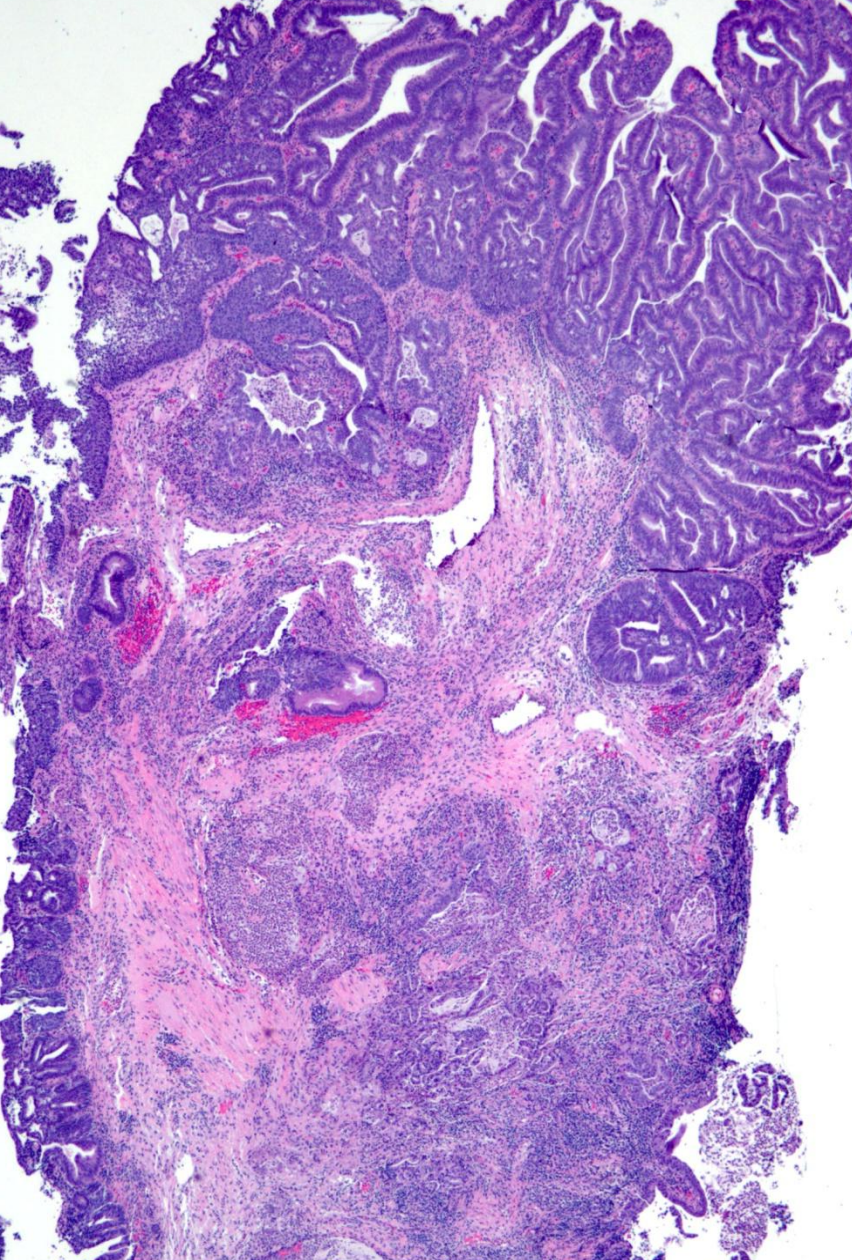
ADCA



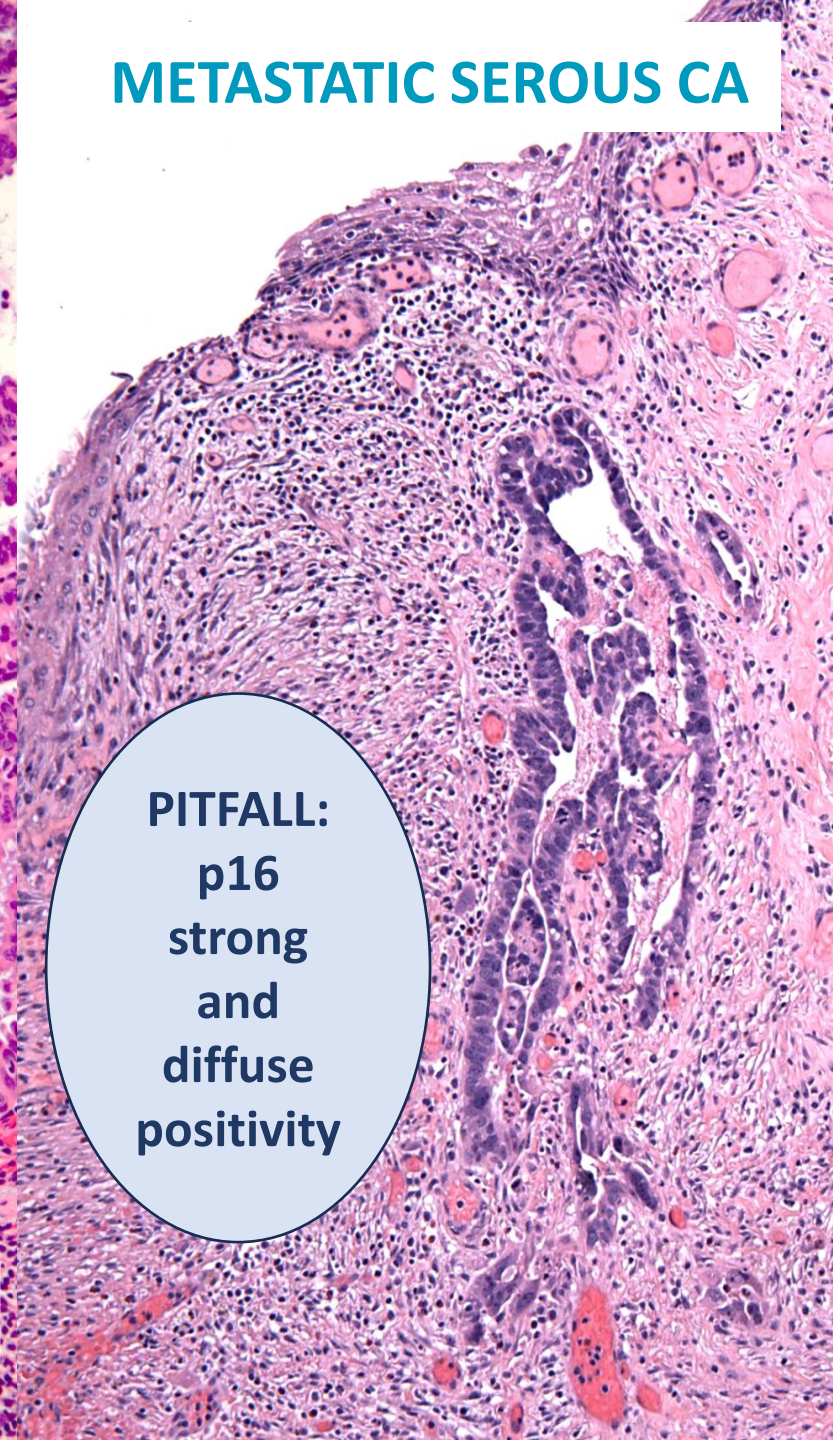


VILLOGLANDULAR ADENOCARCINOMA (31 tumors-EXCELLENT OUTCOME)

Stolnicu S, Brito MJ, Karpathiou G, et al, Int J Gynecol Pathol. 2023;42:270-277



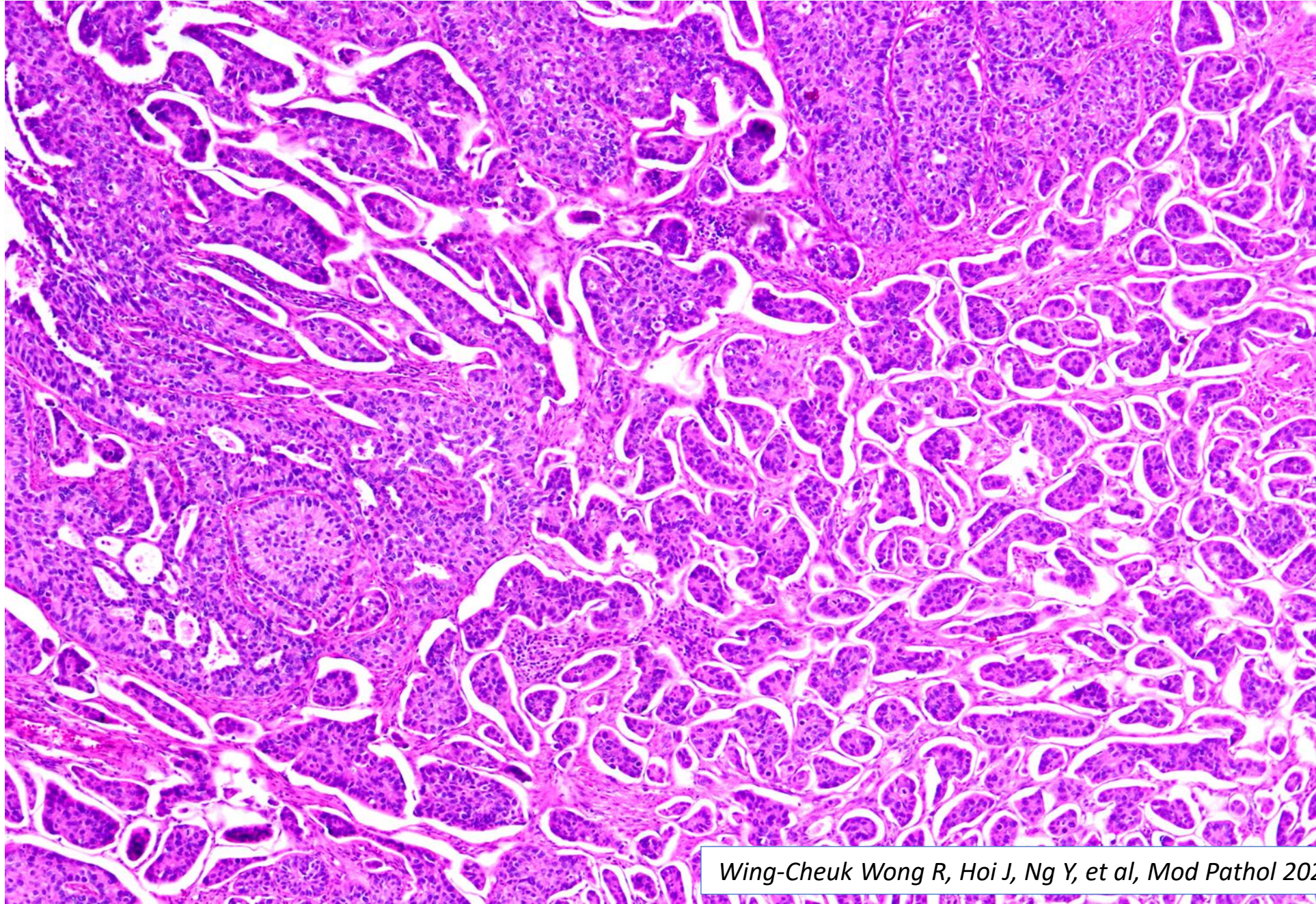
METASTATIC SEROUS CA



**PITFALL:
p16
strong
and
diffuse
positivity**

ADENOCARCINOMA, USUAL TYPE, with PAPILLAE

CERVICAL MICROPAPILLARY ADENOCARCINOMA

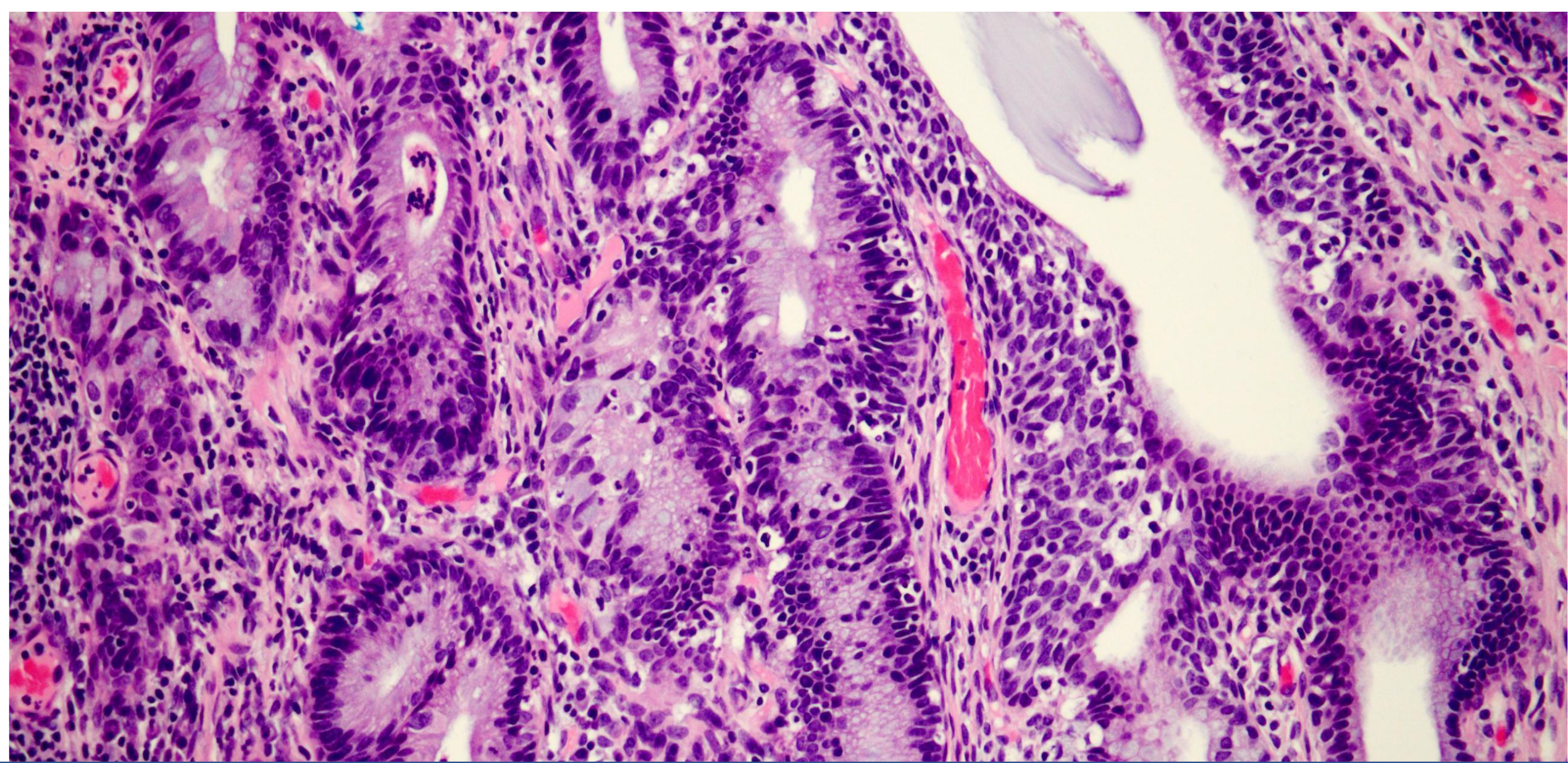


	No. Cases	Micropapillary Component	
		10% ≤ 50%	> 50%
Usual-type	37	3	34
Endometrioid	2	2	0
Mucinous, NOS	2	2	0
Gastric-type	2	2	0
Adenosquamous	1	1	0

ALL USUAL AND MUCINOUS
p16 en block +/- wild-type p53

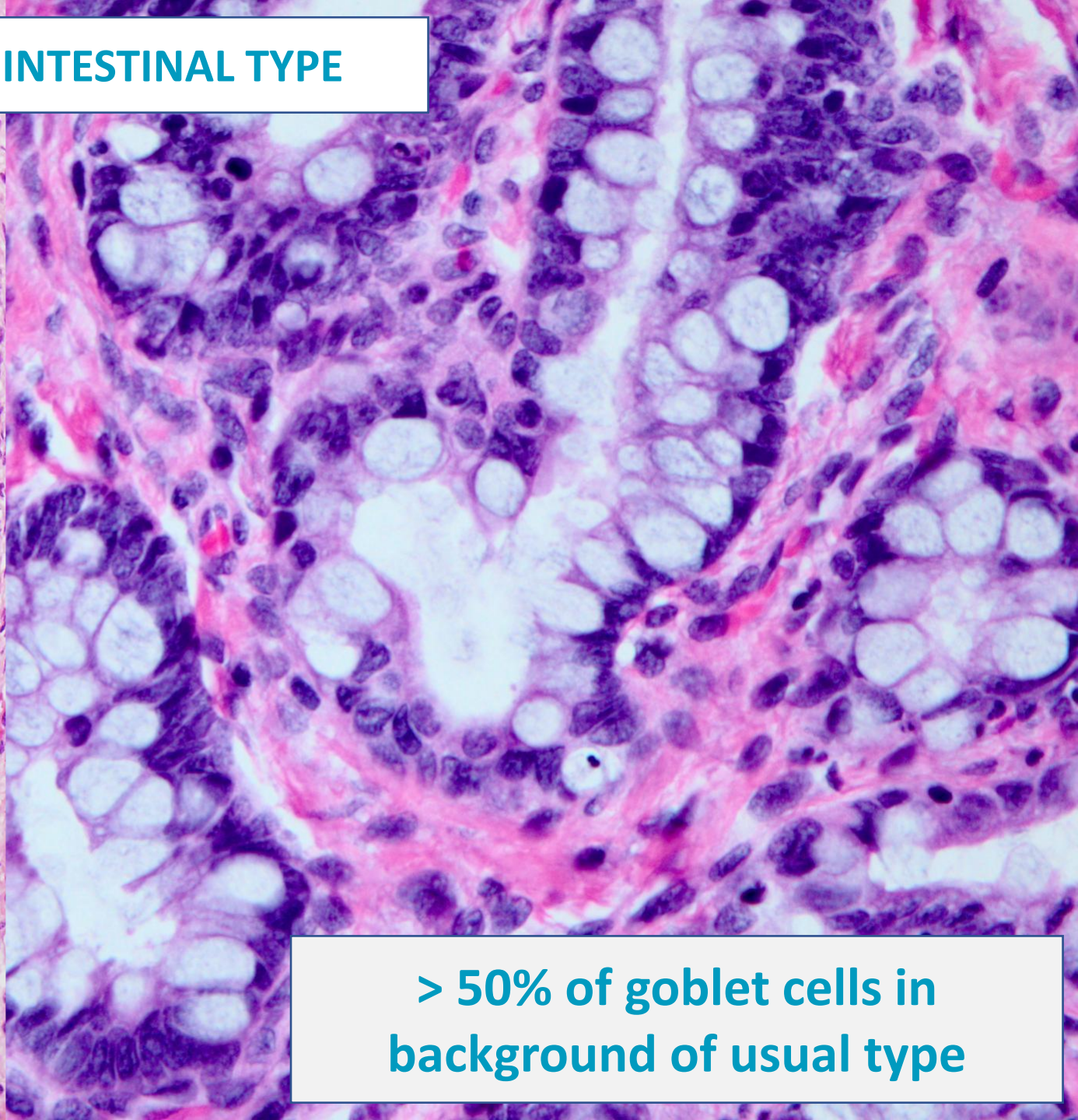
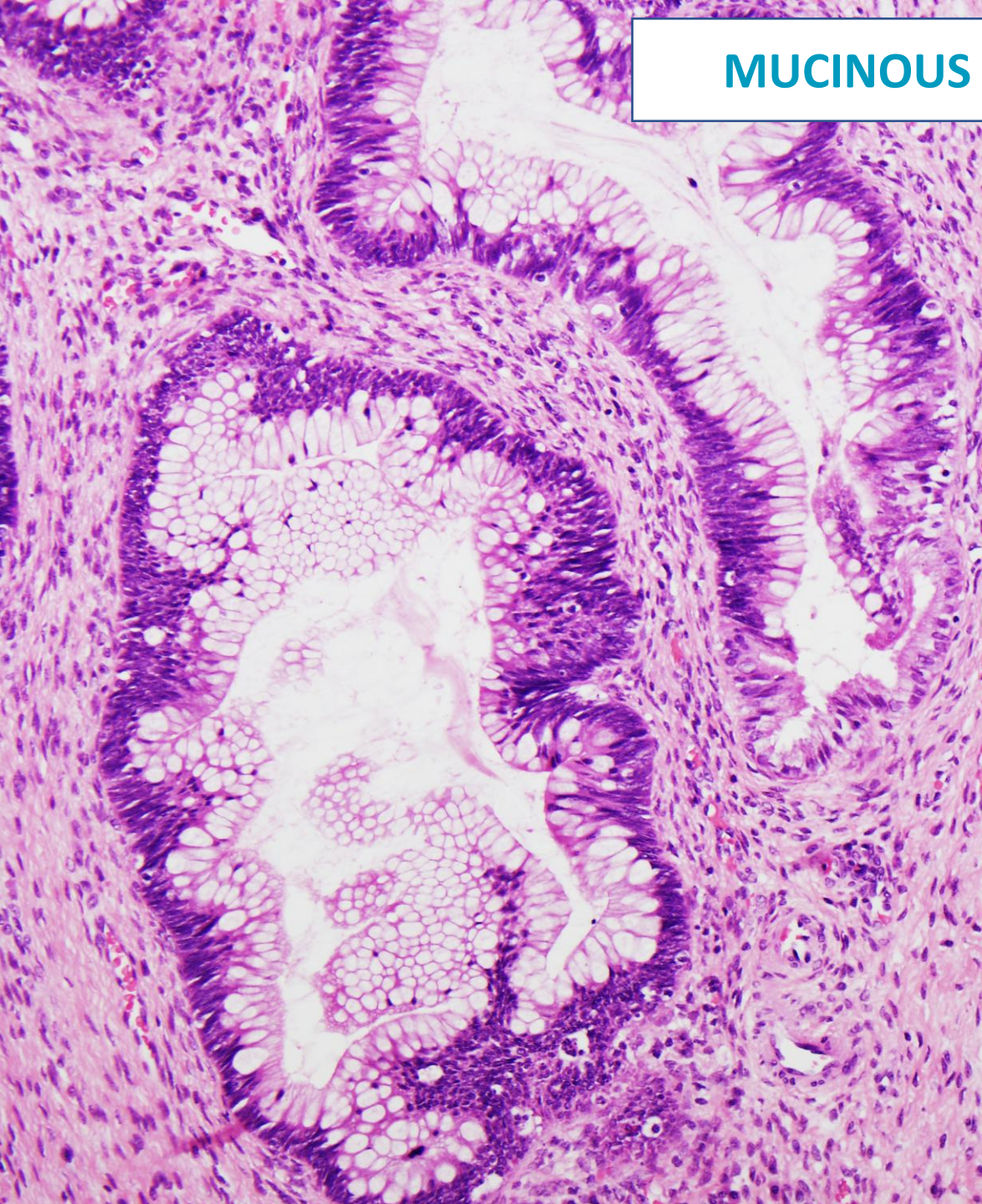
GASTRIC TYPE
OFTEN p53 mutant with variable p16 +

Aggressive behavior comparable to similar tumors at other locations

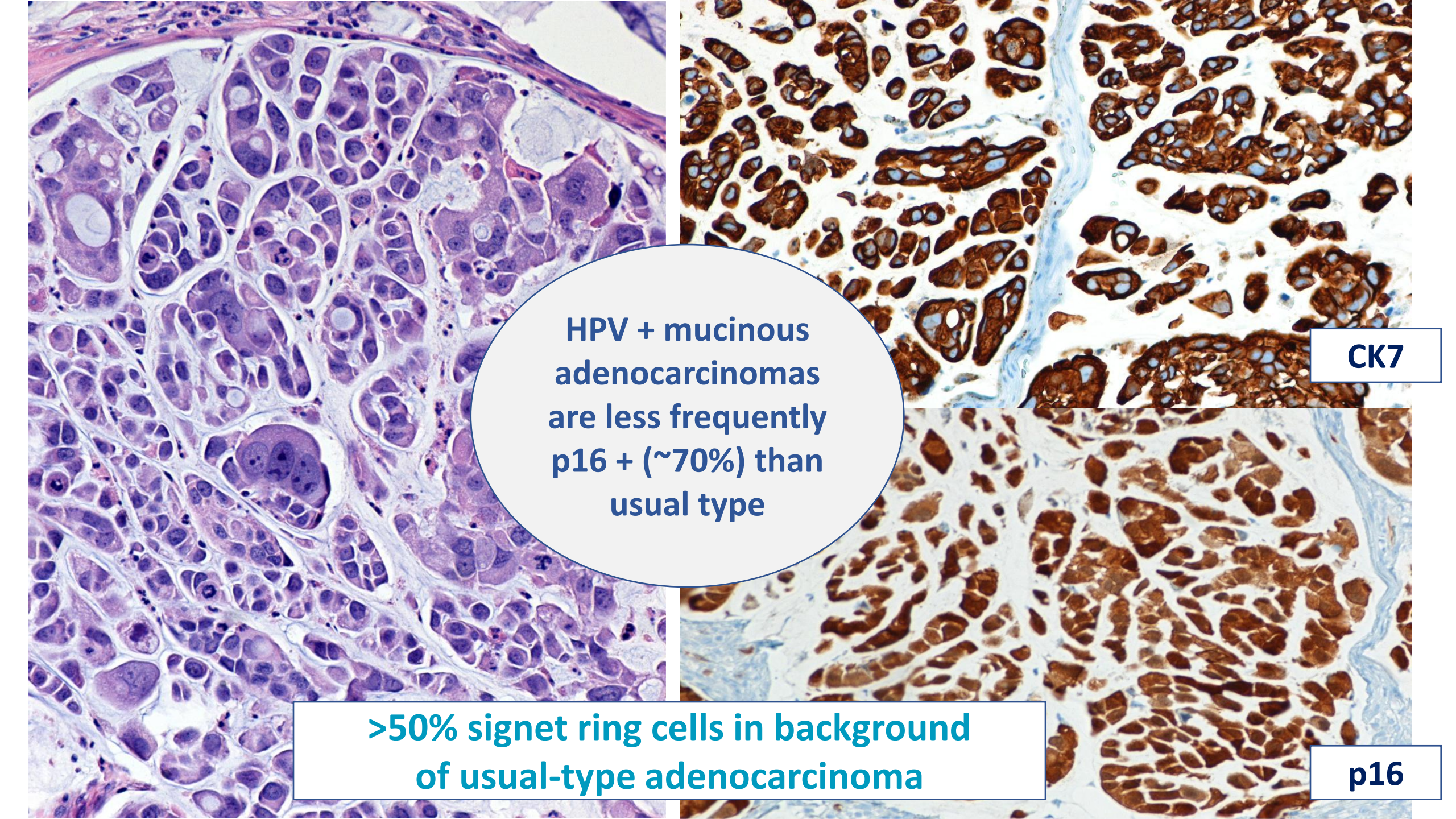


MUCINOUS, NOT OTHERWISE SPECIFIED
>50% with intracytoplasmic mucin in background of usual adenoca

MUCINOUS INTestinal TYPE



**> 50% of goblet cells in
background of usual type**

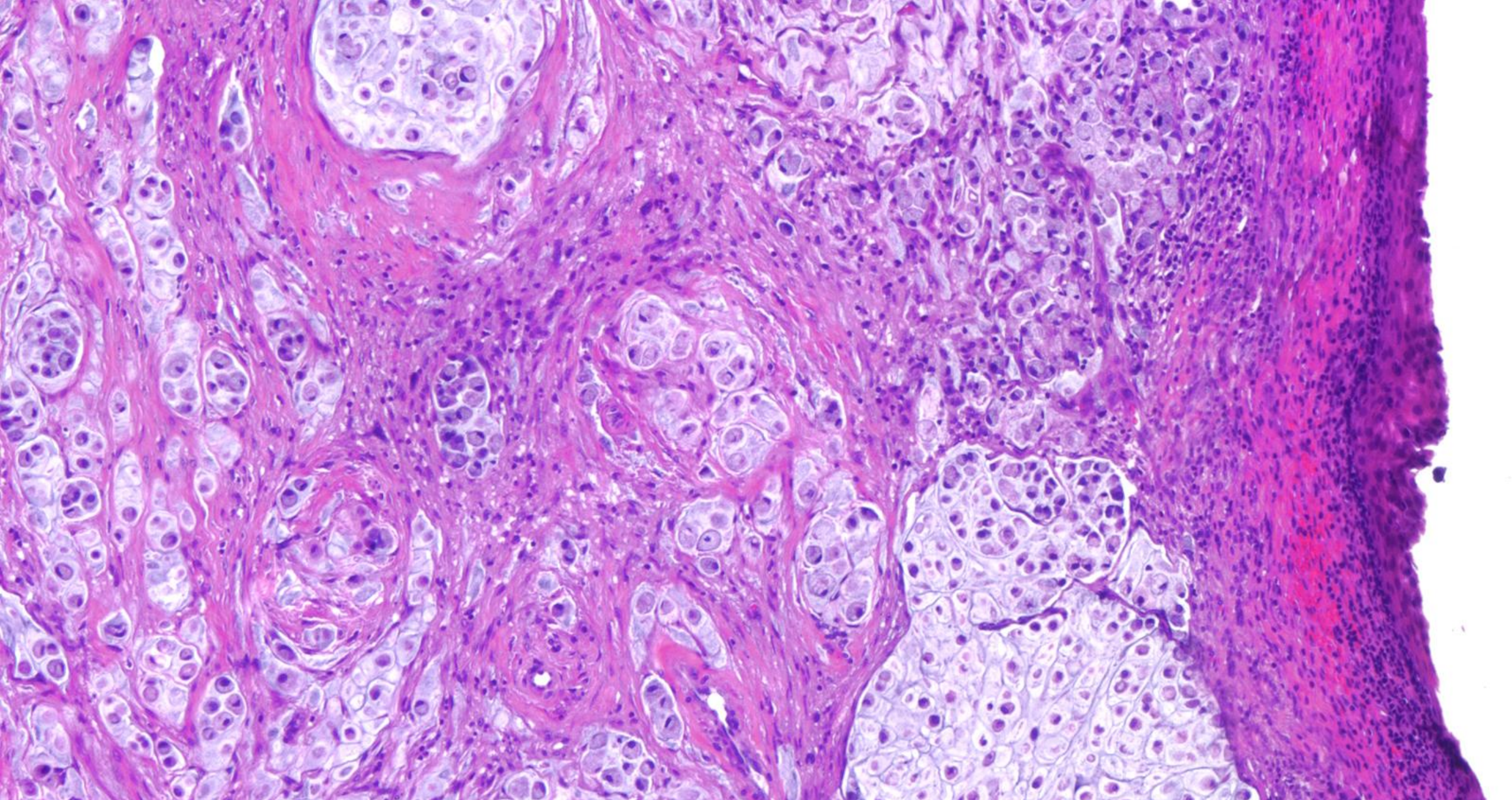


HPV + mucinous
adenocarcinomas
are less frequently
p16 + (~70%) than
usual type

CK7

>50% signet ring cells in background
of usual-type adenocarcinoma

p16

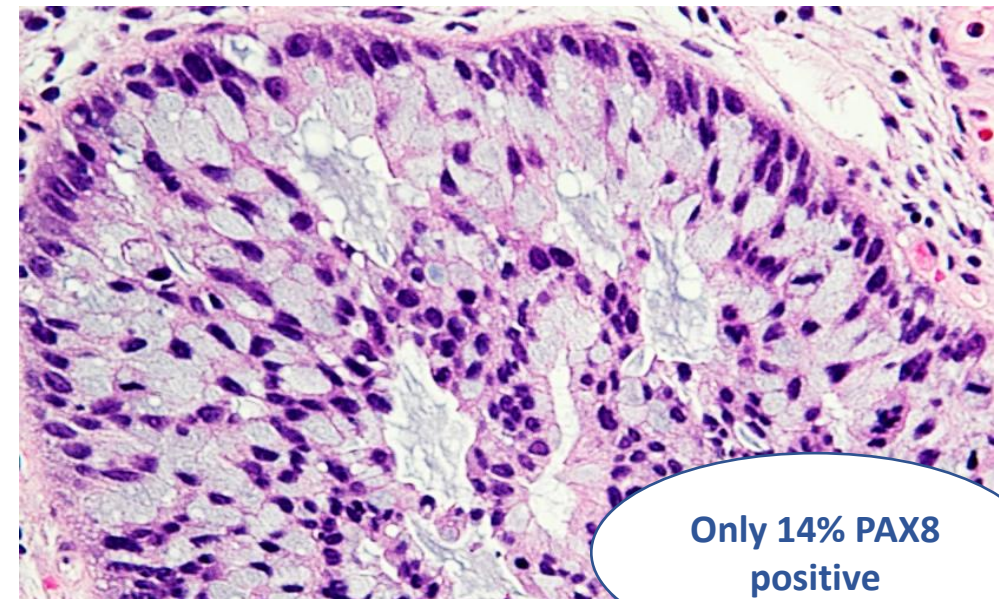
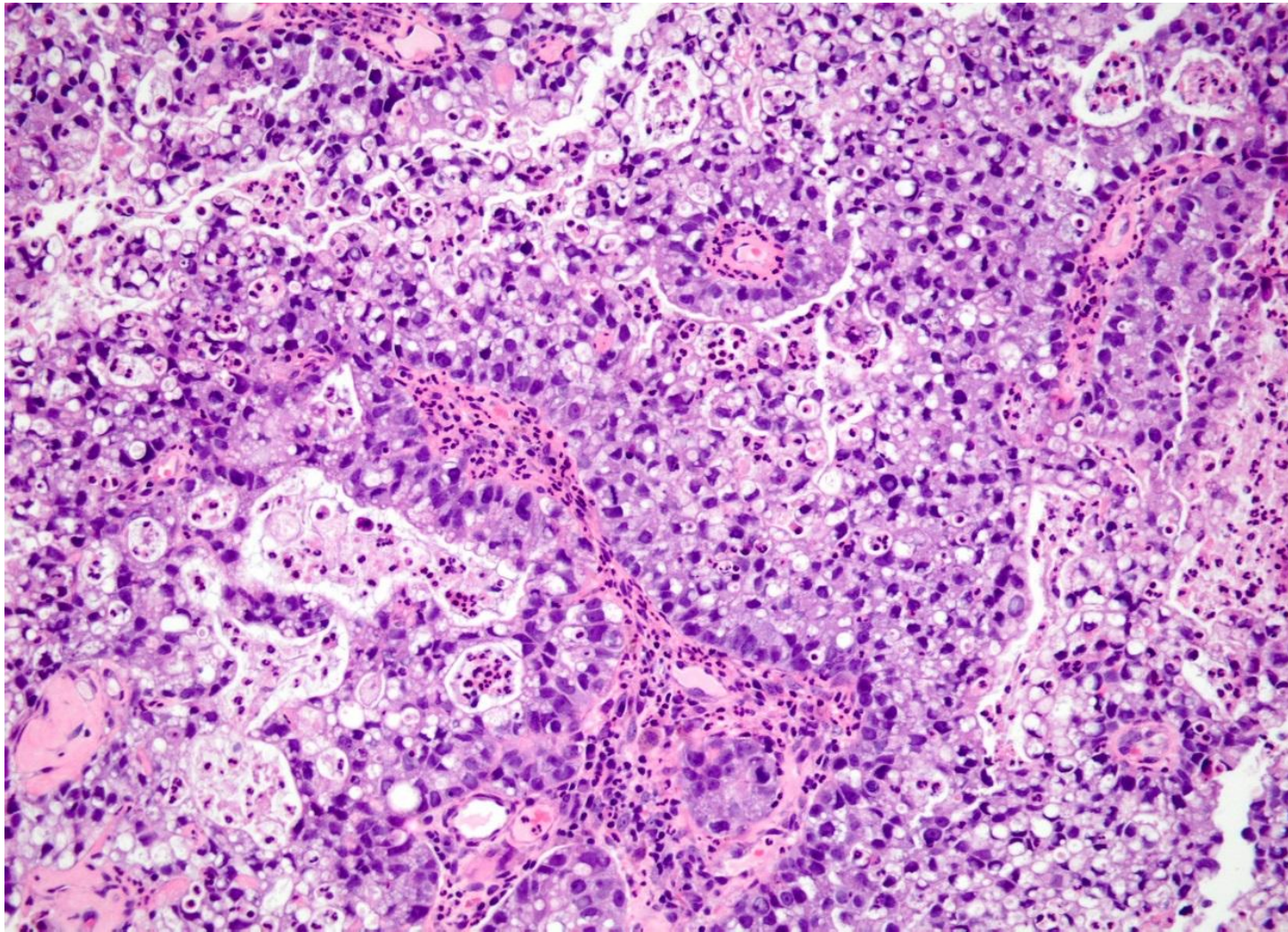


ALWAYS EXCLUDE METASTATIC SIGNET RING CELL CARCINOMA (BREAST, GASTROINTESTINAL, OTHER)

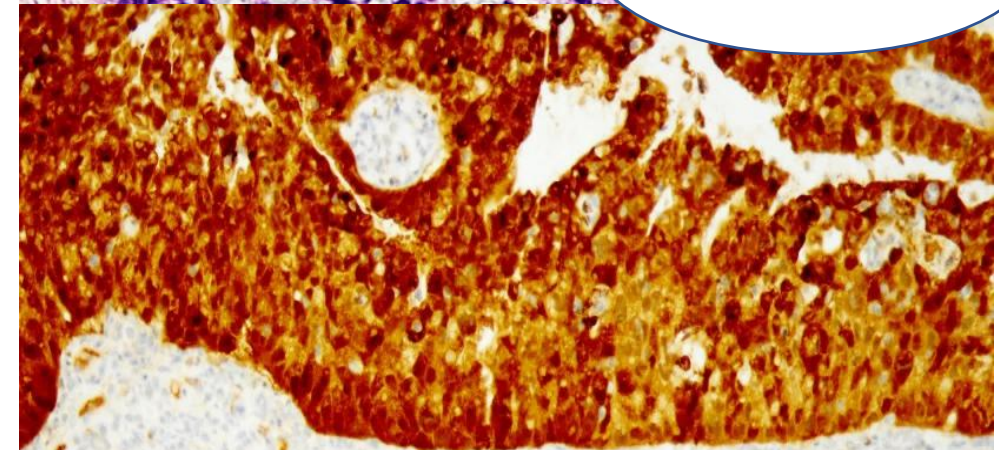
Invasive Stratified Mucin-producing Carcinoma and Stratified Mucin-producing Intraepithelial Lesion (SMILE)

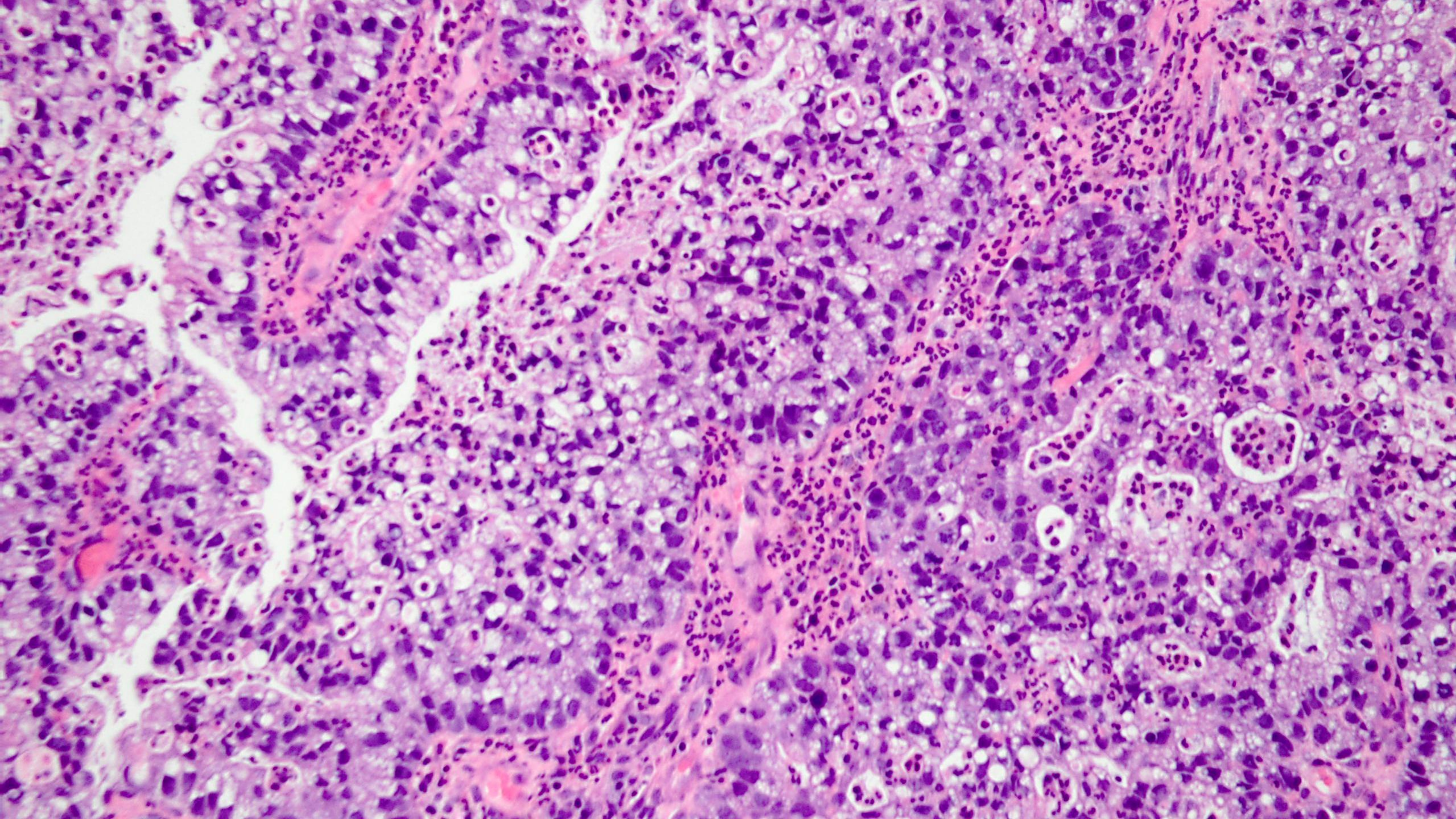
15 Cases Presenting a Spectrum of Cervical Neoplasia With Description of a Distinctive Variant of Invasive Adenocarcinoma

Lastra RR, Park KJ, Schoolmeester JK, Am J Surg Pathol 2016; 40:262-9

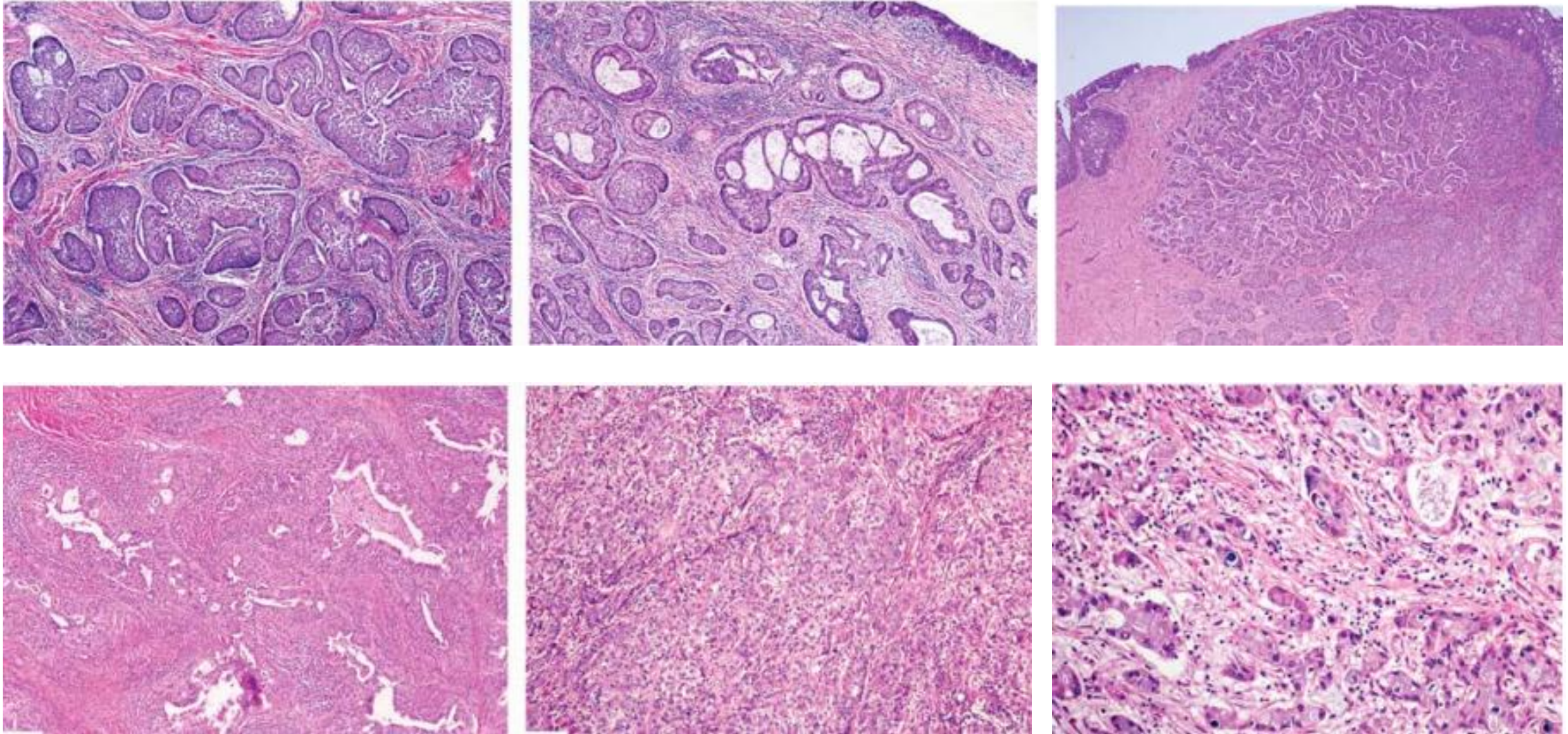


Only 14% PAX8 positive





Invasive Stratified Mucin-producing Carcinoma (ISMC) of the Cervix: A Study on Morphologic Diversity



iSMILE is an AGGRESSIVE FORM OF HPV-ASSOCIATED ADENOCARCINOMA

TABLE 3. Comparison of Clinicopathologic Features in iSMC Versus Usual-type HPVA

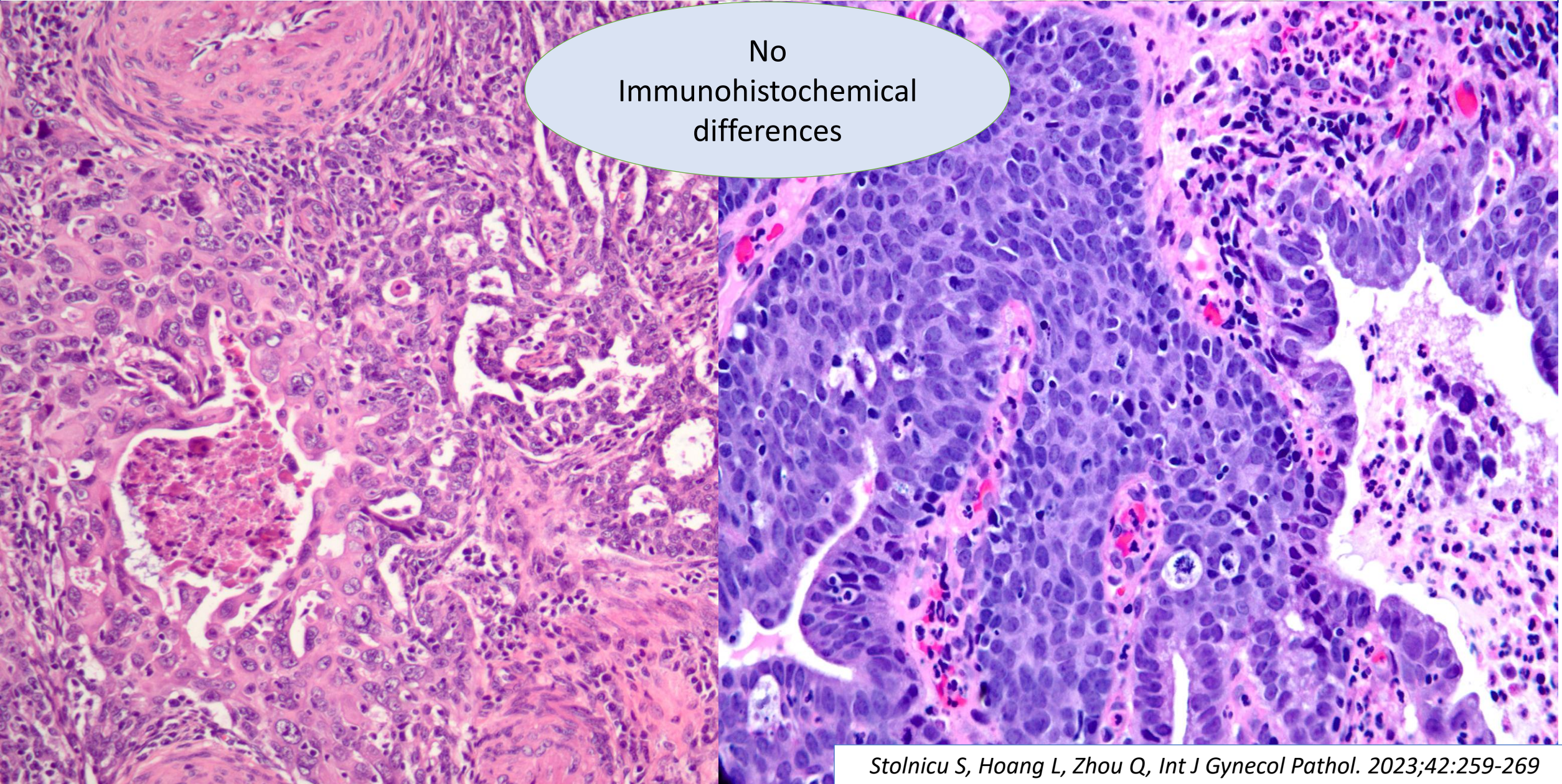
	iSMC (N = 52 Cases)	Usual-type HPVA (N = 262 Cases) ⁹
Mean age (y)	41.8	42
Tumor size (median) (mm)	21	23
LVI (% of cases)	42.3	49.8
LNM (% of cases)	33	12.2
Local recurrence (% of cases)	25	8.8
Distant recurrence (% of cases)	7.6	5.4
FIGO stage II or higher (% of cases)	30	14
Silva C pattern (% of cases)	92	76
Died of disease (% of cases)	13.4	7.2



Tumors should
be treated with
radical surgery

DDX: ADENOSQUAMOUS CARCINOMA

No
Immunohistochemical
differences



NEW PATTERN-BASED CLASSIFICATION WITH IMPORTANT CLINICAL IMPLICATIONS

Diaz de Vivar A, Roma AA, Park KJ, et al. ,Int J Gynecol Pathol 2013;32:592-601
Roma AA, Diaz De Vivar A, Park KJ, et al. Am J Surg Pathol. 2015;39:667-72
Roma AA, Mistretta T, Diaz De Vivar A, et al, Gynecol Oncol 2016;141:36-42

Three patterns (352):

- Pattern A: ALL stage I (73; 21%)
No LVI or LN metastases
- Pattern B: ALL stage I (90; 26%)
LVI: 24; LN metastases: 4
- Pattern C: Stage I:157;83% (T:189; 54%)
Stage II-IV:32;17%
LVI:117; LN metastases:45



**ONLY IF
HPV-
RELATED**

PATTERN A

Well-demarcated glands with rounded contours, usually in groups

No destructive stromal invasion

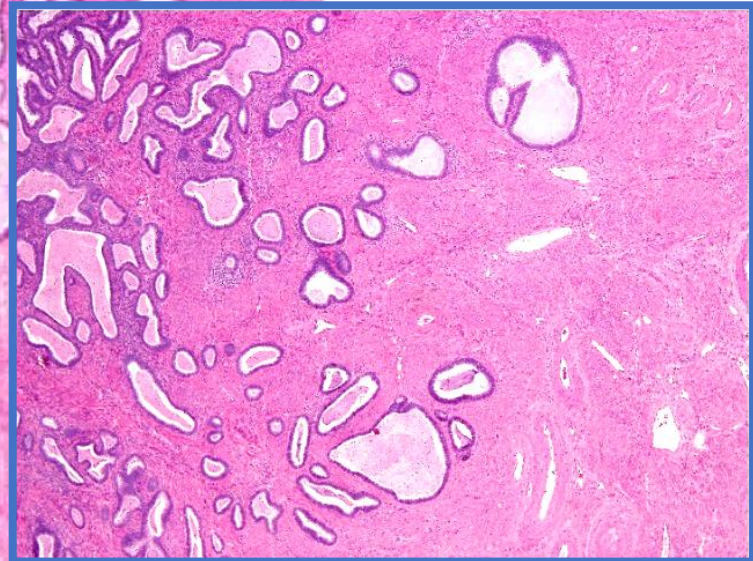
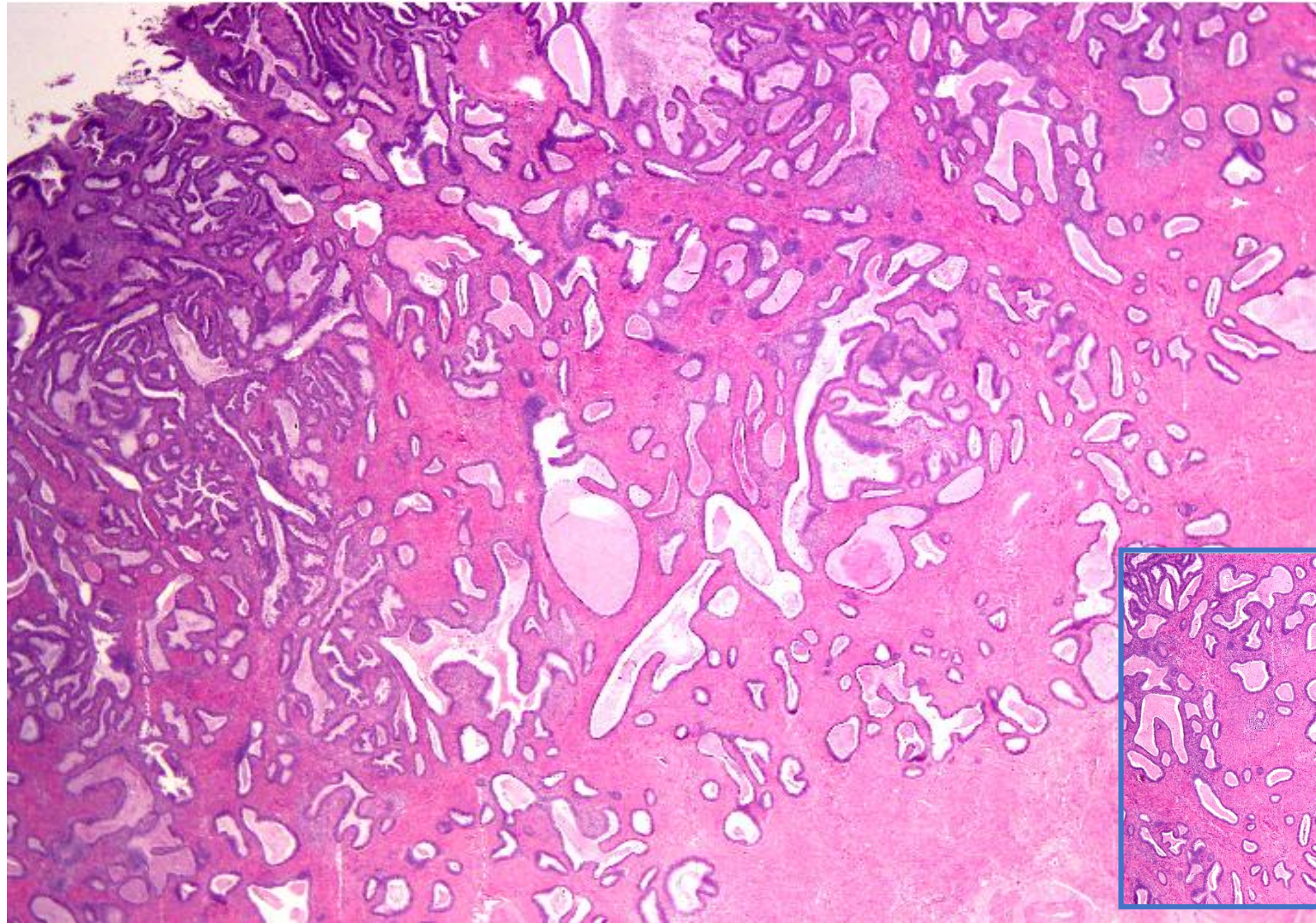
No single cells or cell detachment

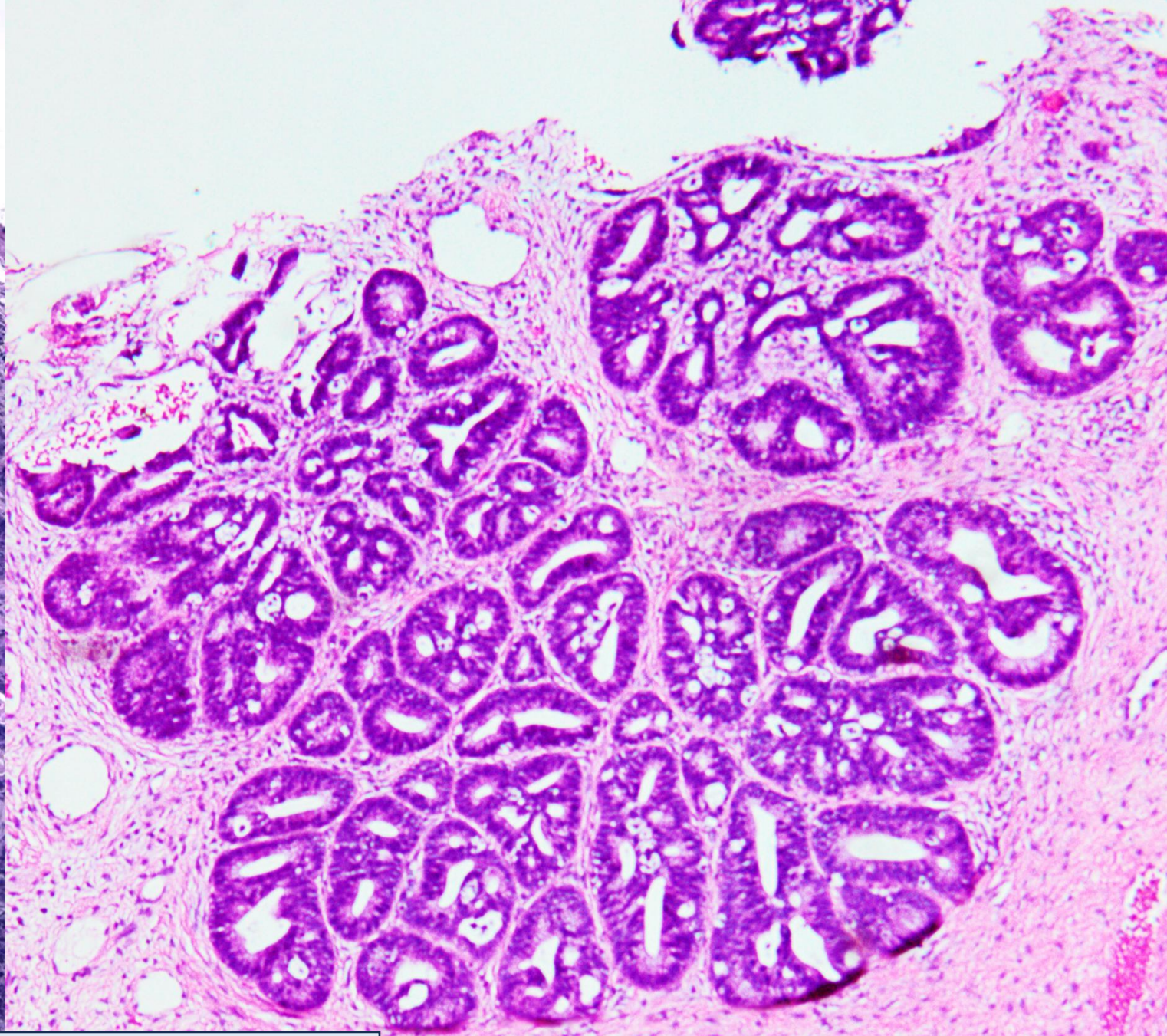
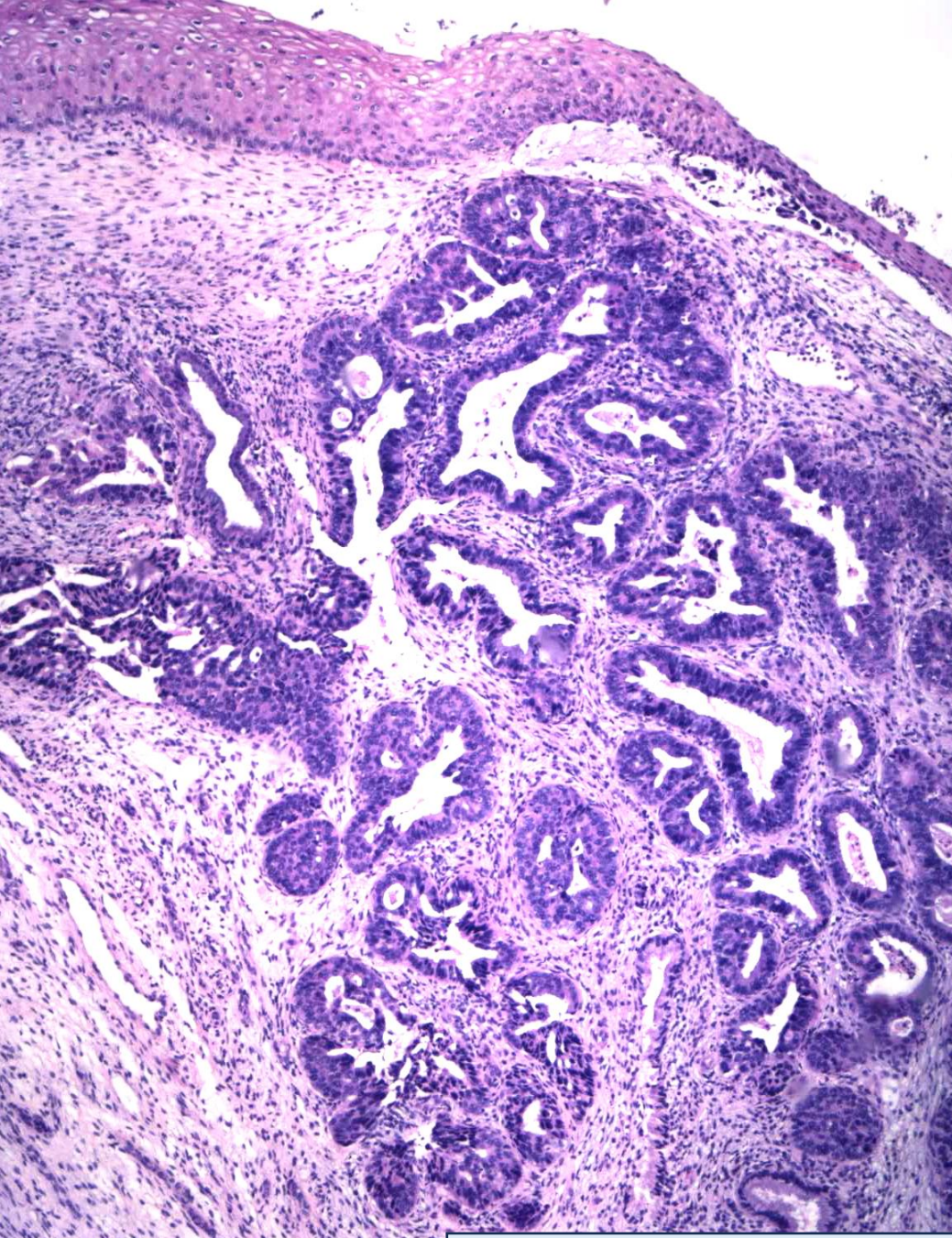
Complex intraglandular growth acceptable (cribriform or papillae) (no more than one 4X)

No solid growth or high-grade atypia

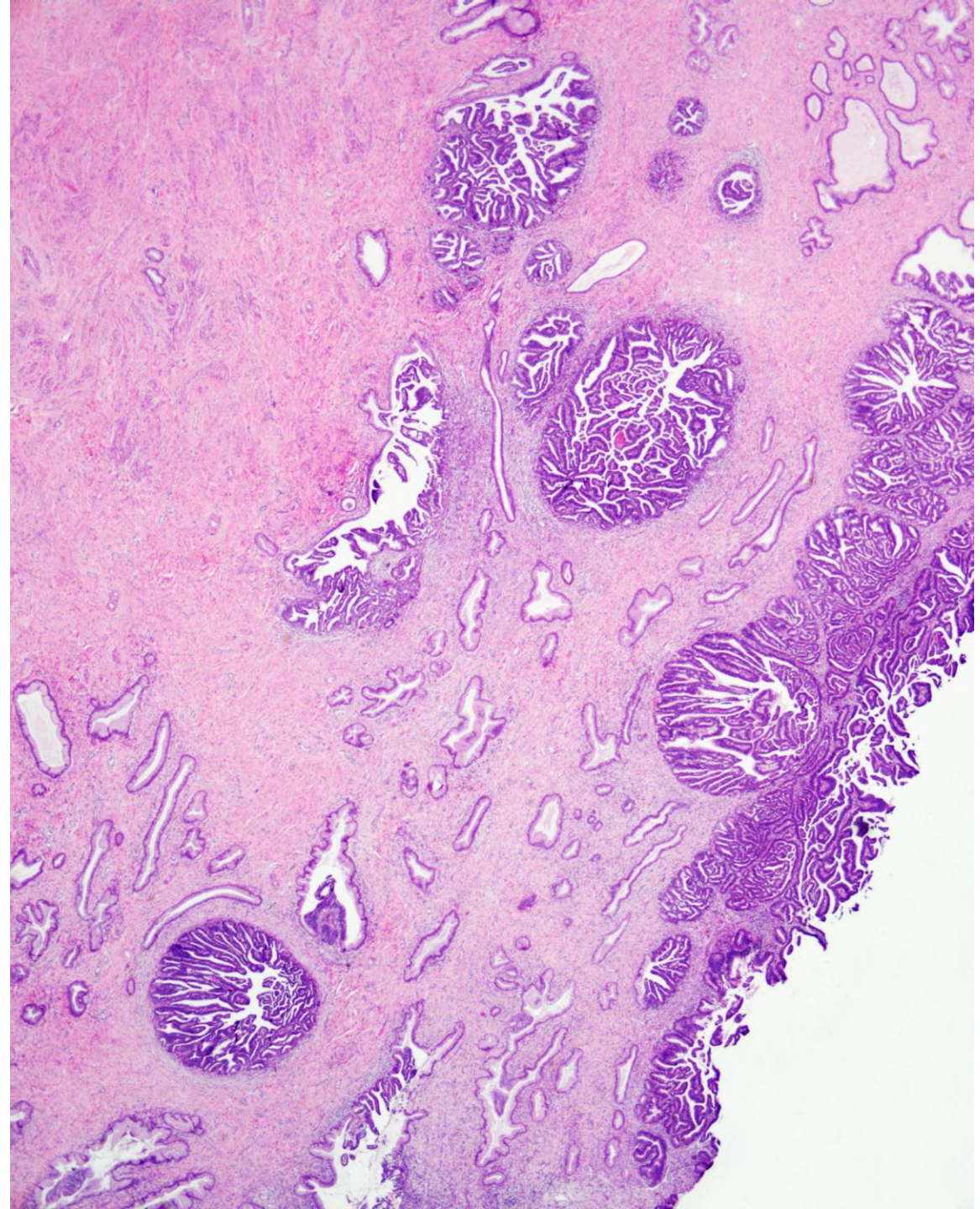
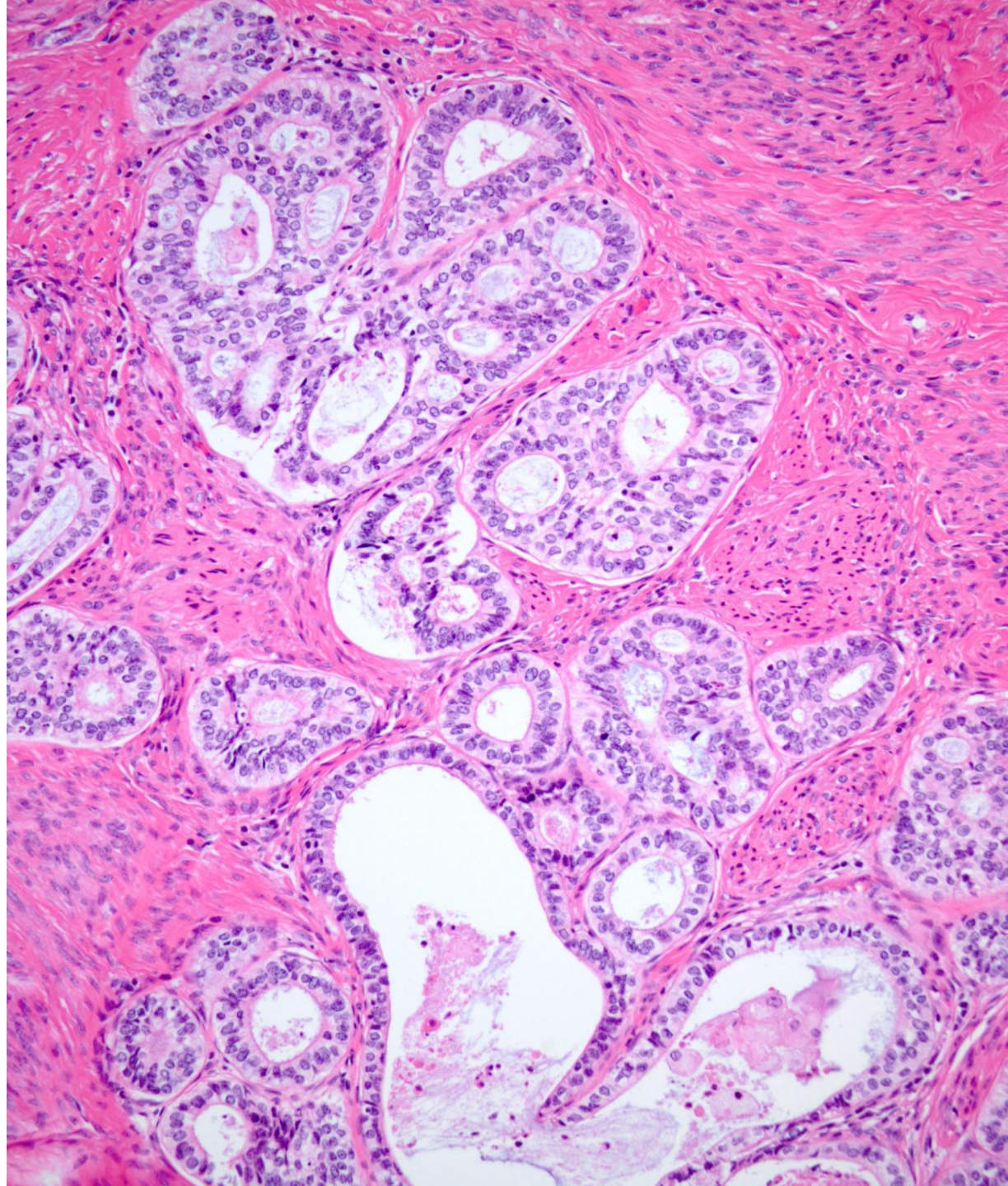
Irrelevant depth or relation to large cervical vessels

No lymphovascular invasion





EARLY INVASIVE ADENOCARCINOMA



PATTERN B

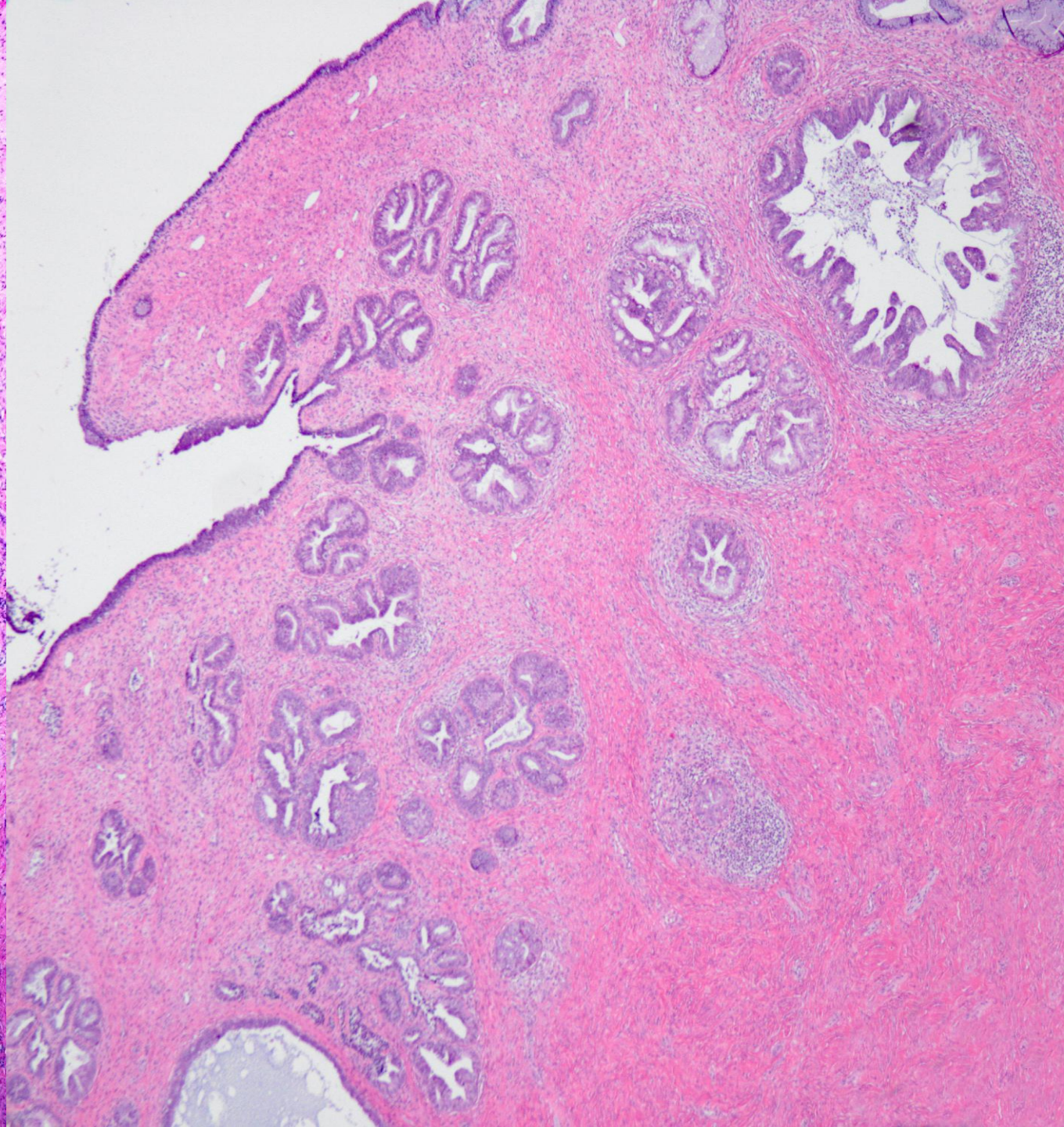
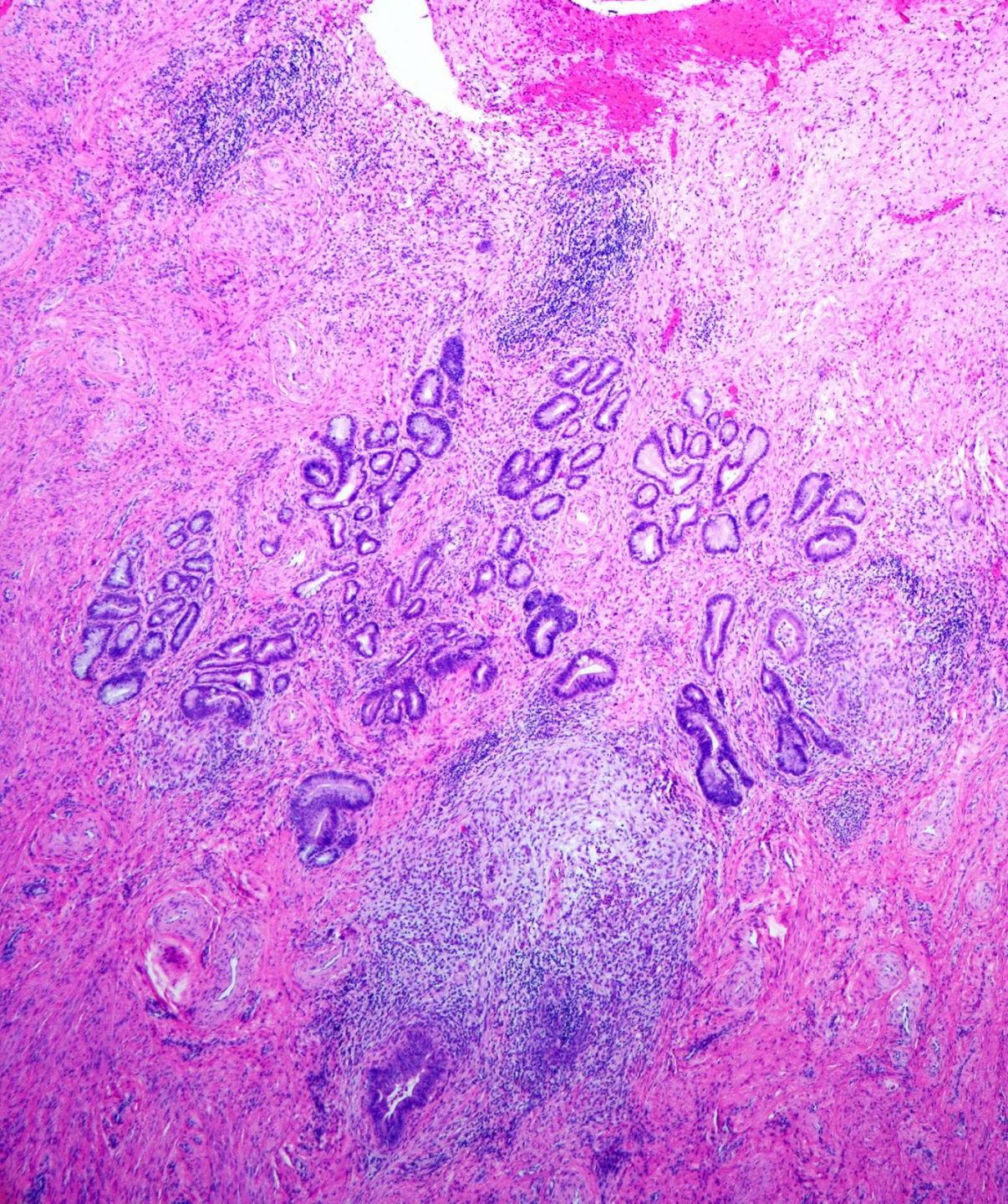
Localized (limited, early) destructive stromal invasion arising from pattern A glands

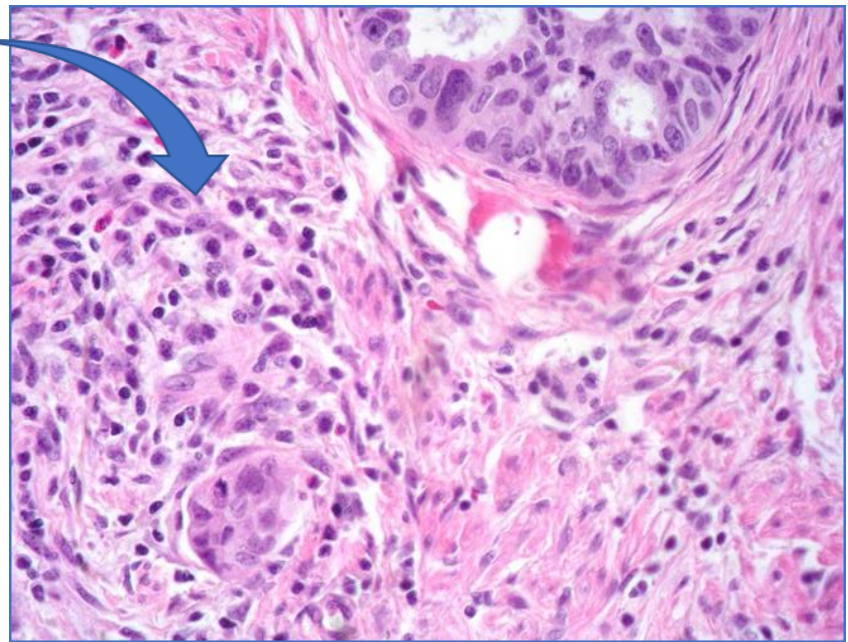
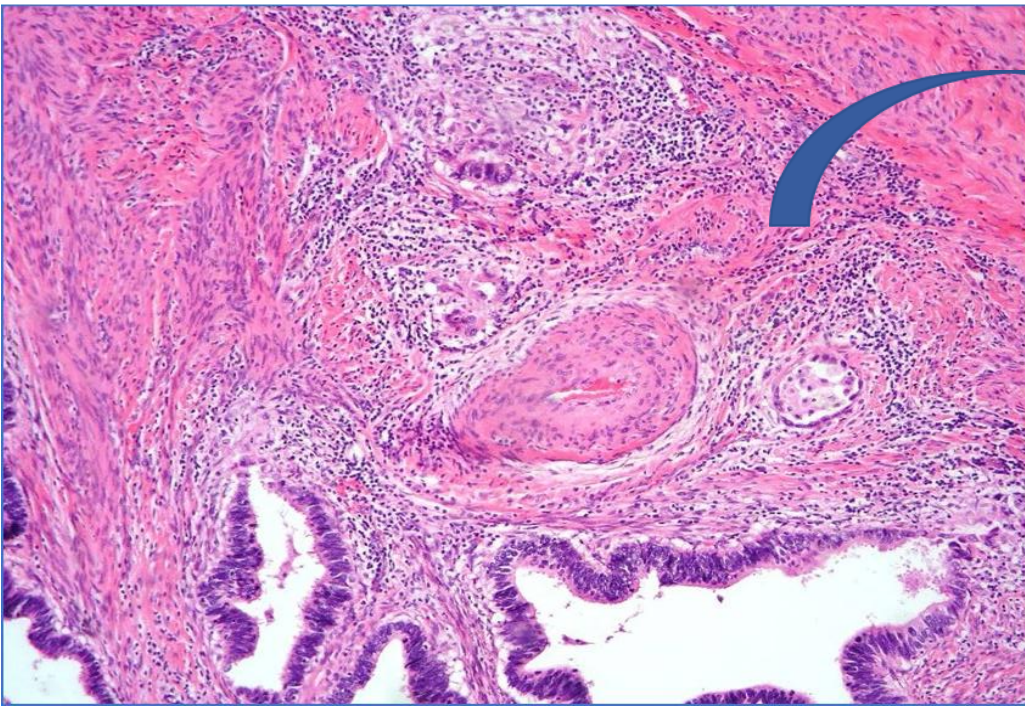
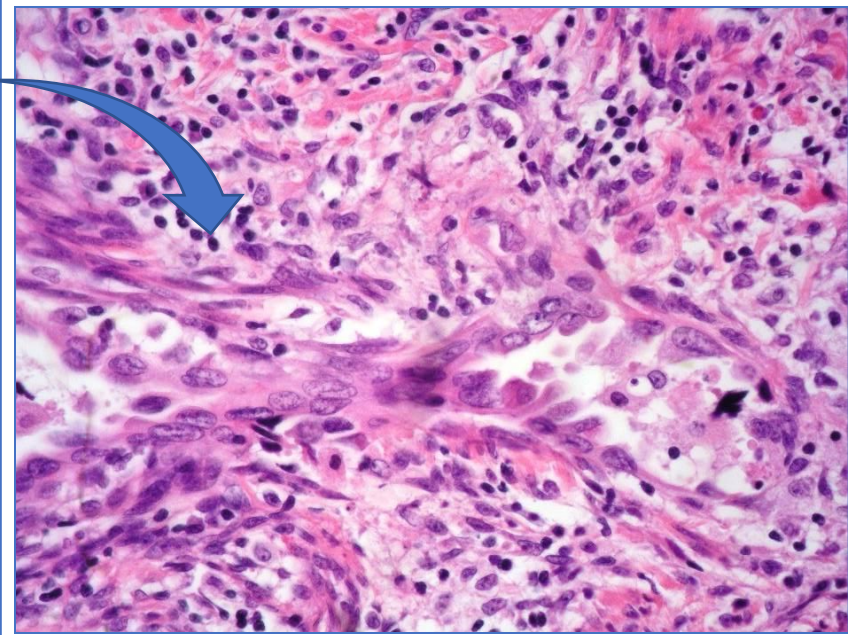
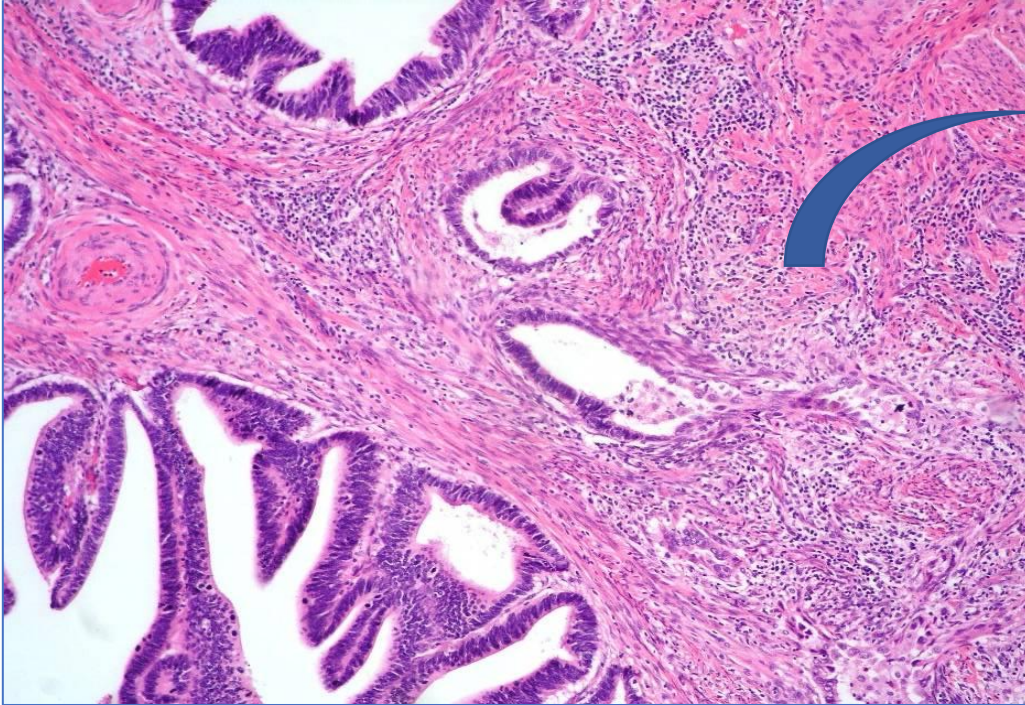
Individual or small groups of tumor cells, separated from pattern A, frequently in desmoplastic stroma

Single, multiple, or linear foci at base of tumor (no more than 5mm, 4x field)

Lymphovascular invasion (present or absent)

Lack of solid growth





PATTERN C

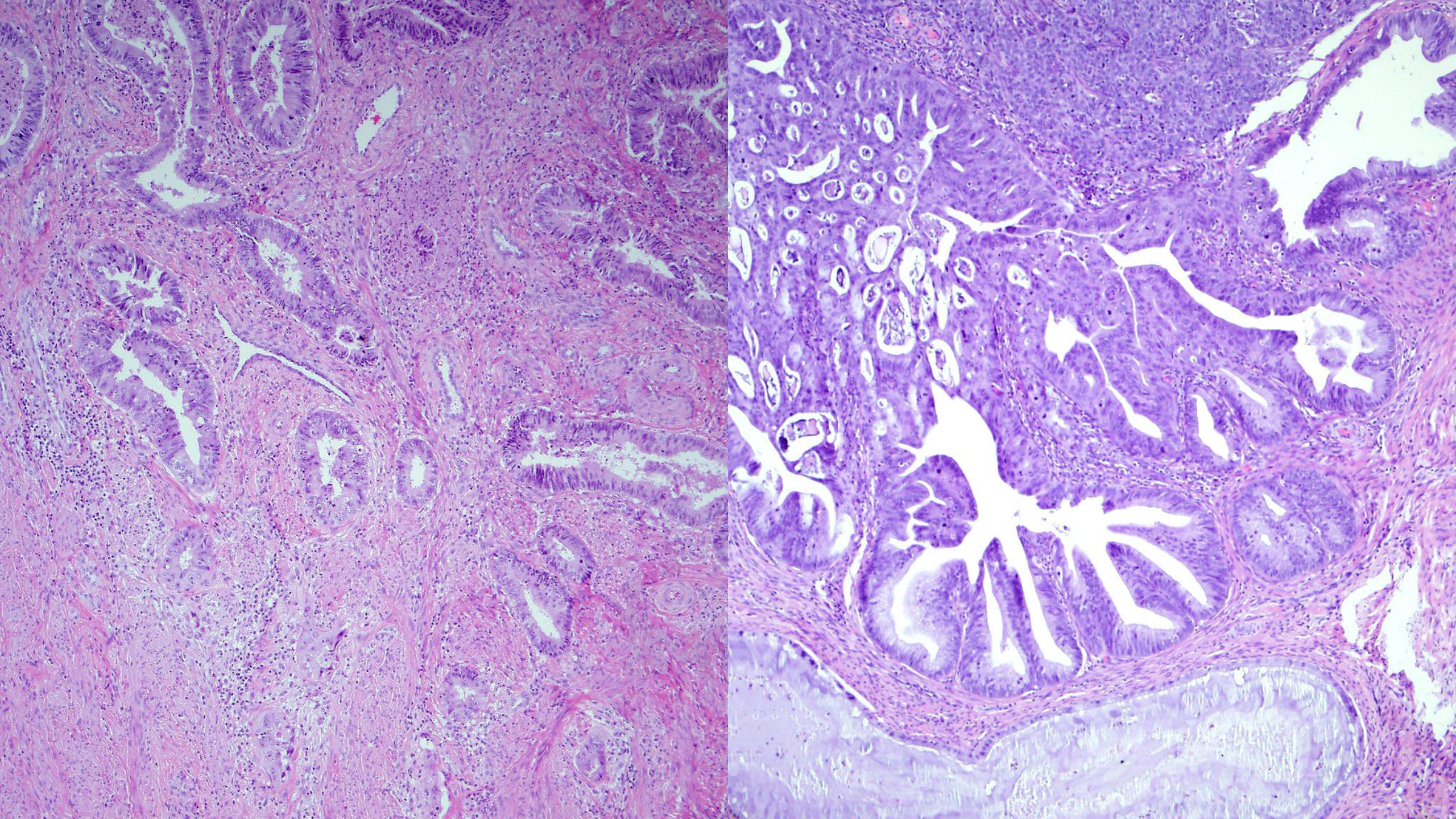
Diffuse destructive stromal invasion with:

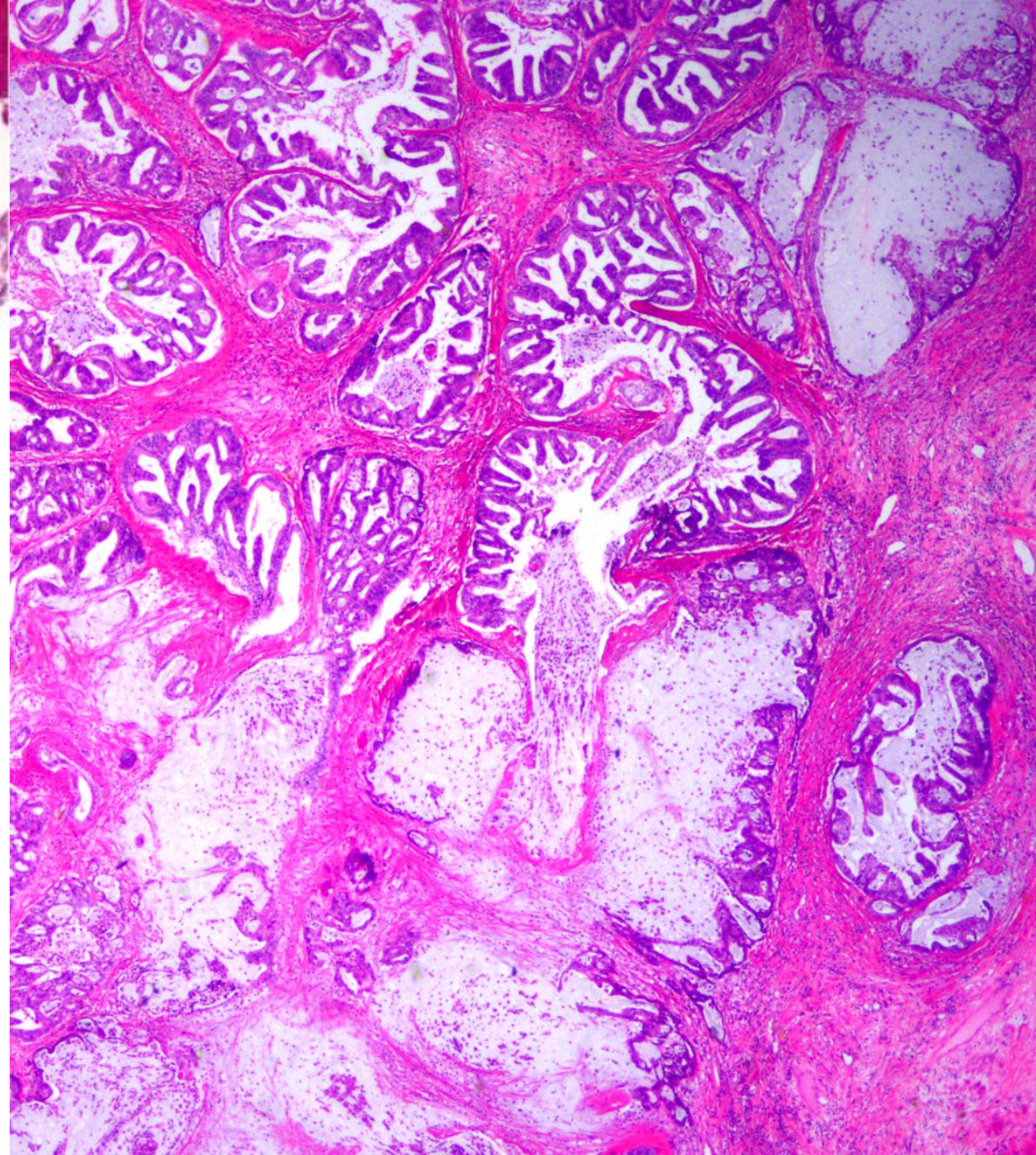
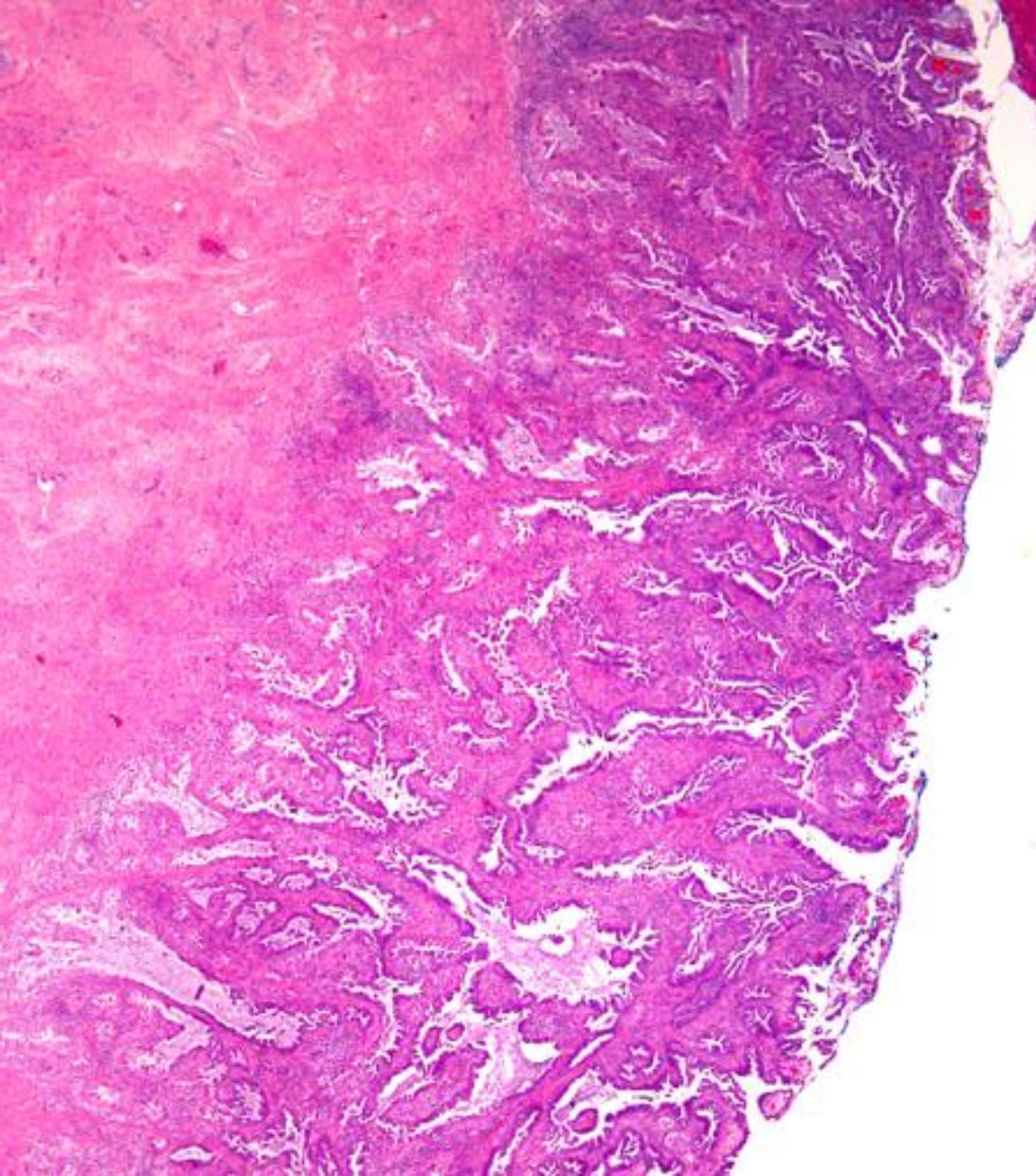
Diffusely infiltrative glands with associated extensive desmoplastic response and often angulated glands or canalicular pattern with interspersed open glands

Confluent growth filling 4 field (5 mm); Glands, papillae(stroma with only papillae) or mucin lakes

Solid, poorly differentiated component (not based on nuclear grade)

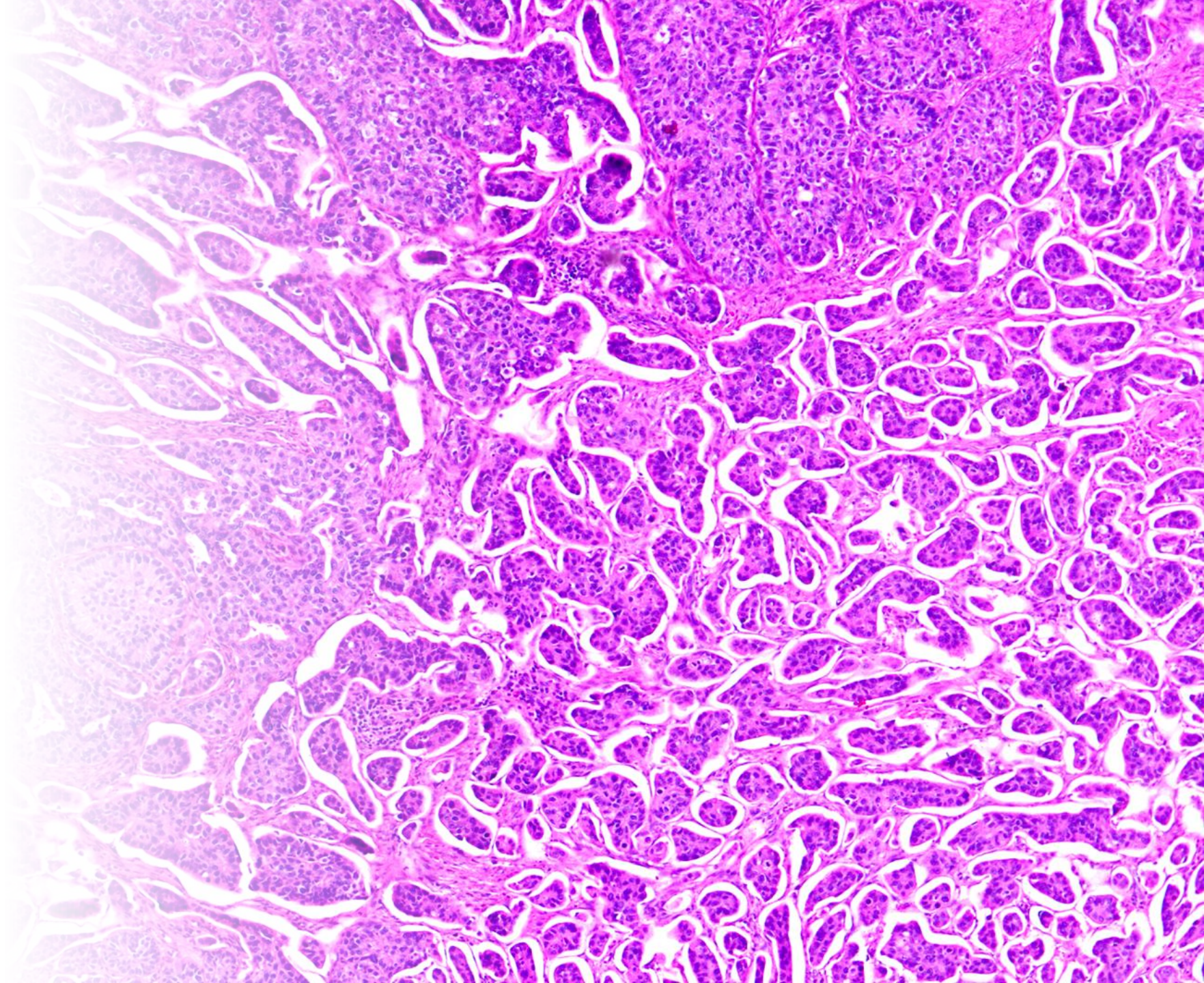
Lymphovascular invasion present or absent





MICROPAPILLARY:

Small clusters of tumor cells, polygonal in shape, with abundant eosinophilic cytoplasm



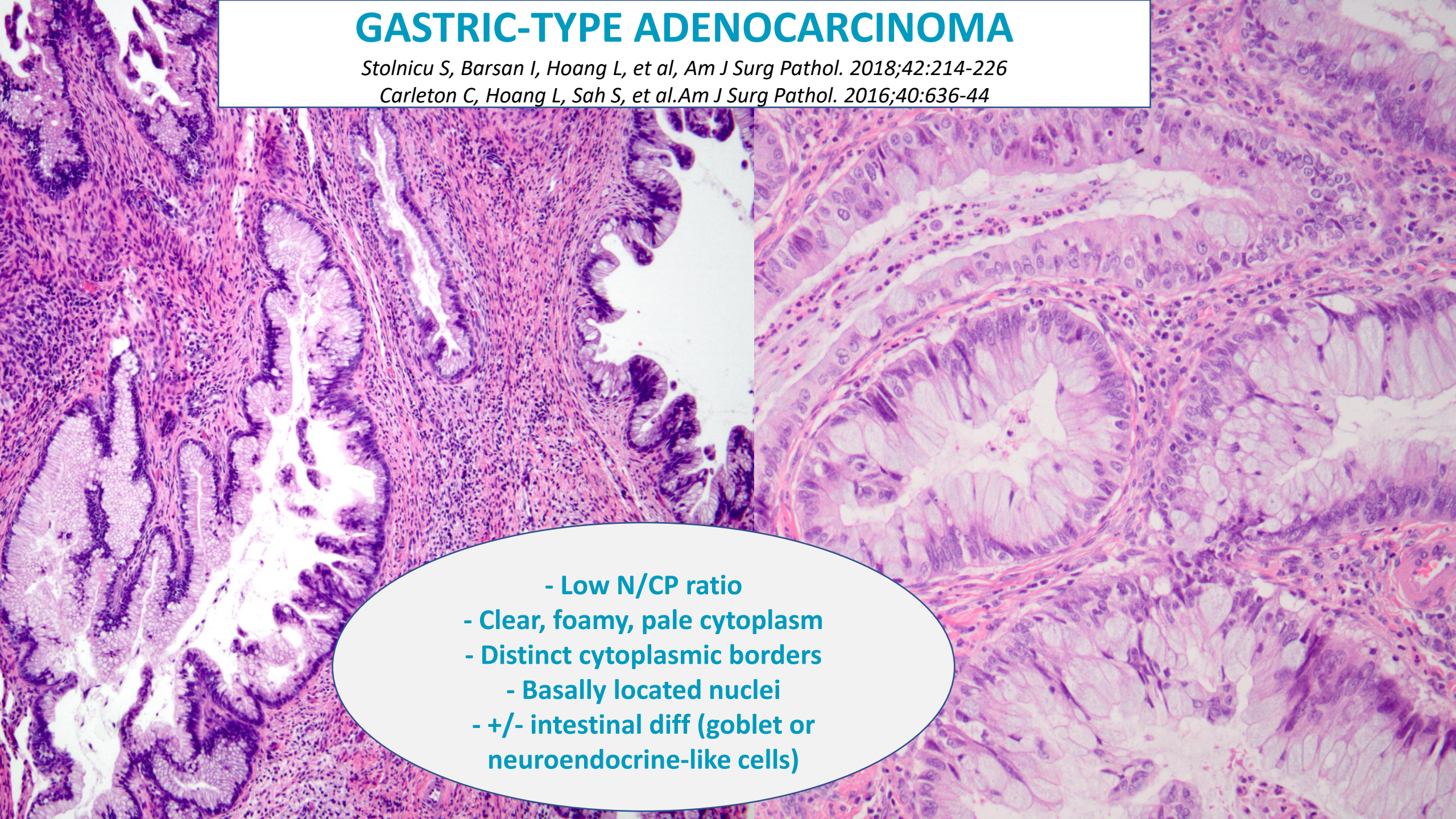
HPV-INDEPENDENT ADENOCARCINOMAS

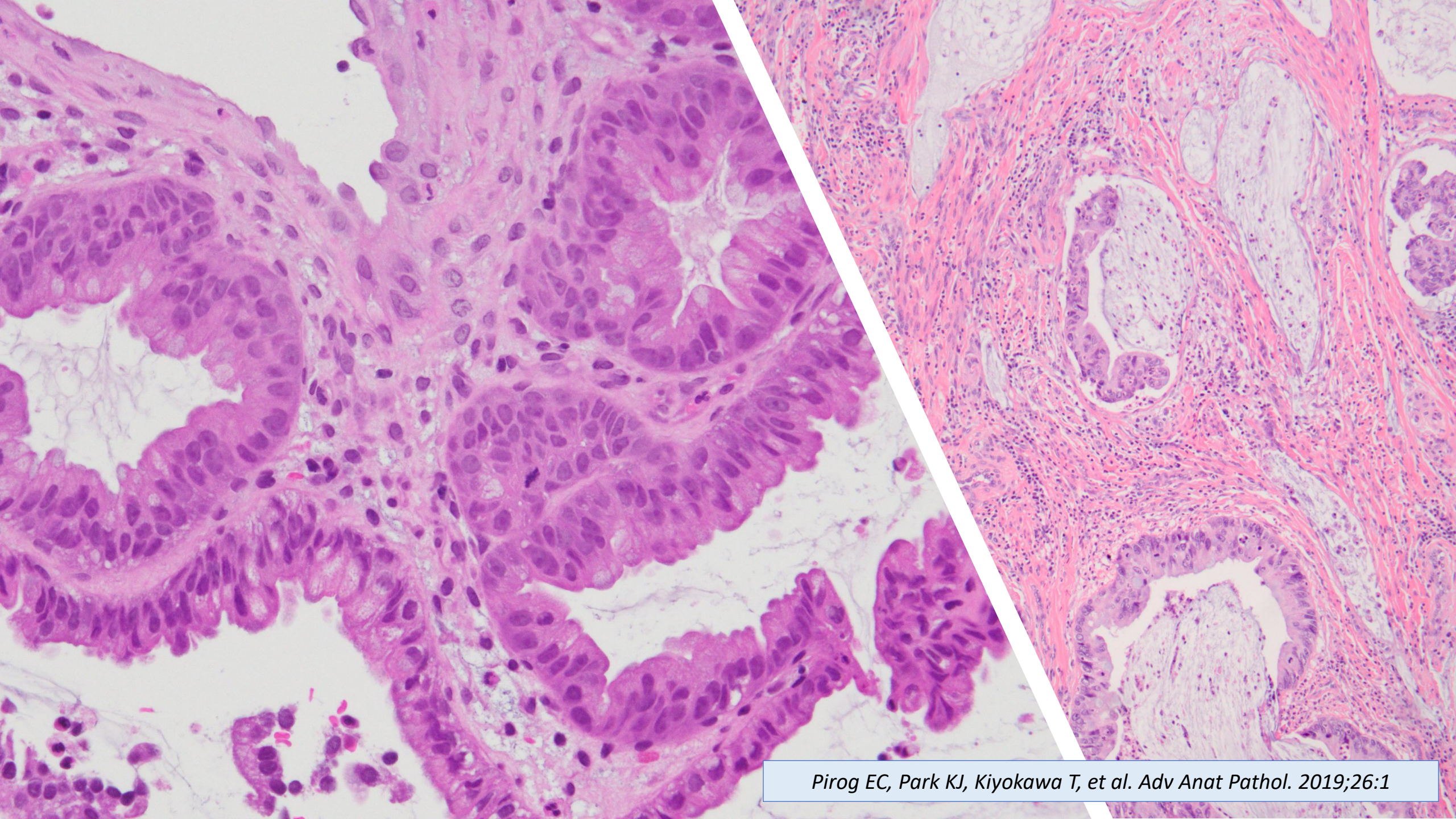
- **Gastric**
- **Clear cell**
- **Mesonephric**
- **Endometrioid**

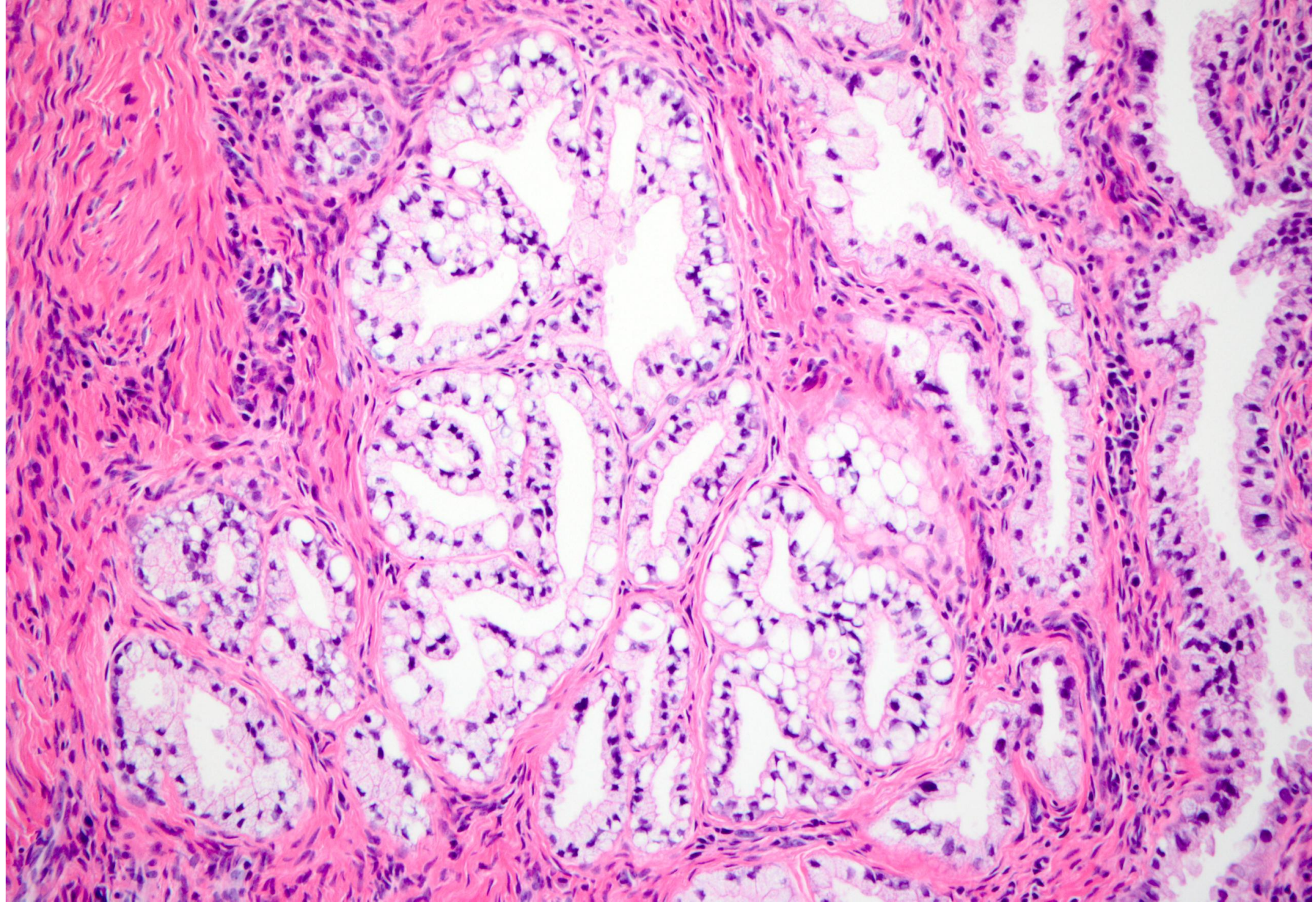
GASTRIC-TYPE ADENOCARCINOMA

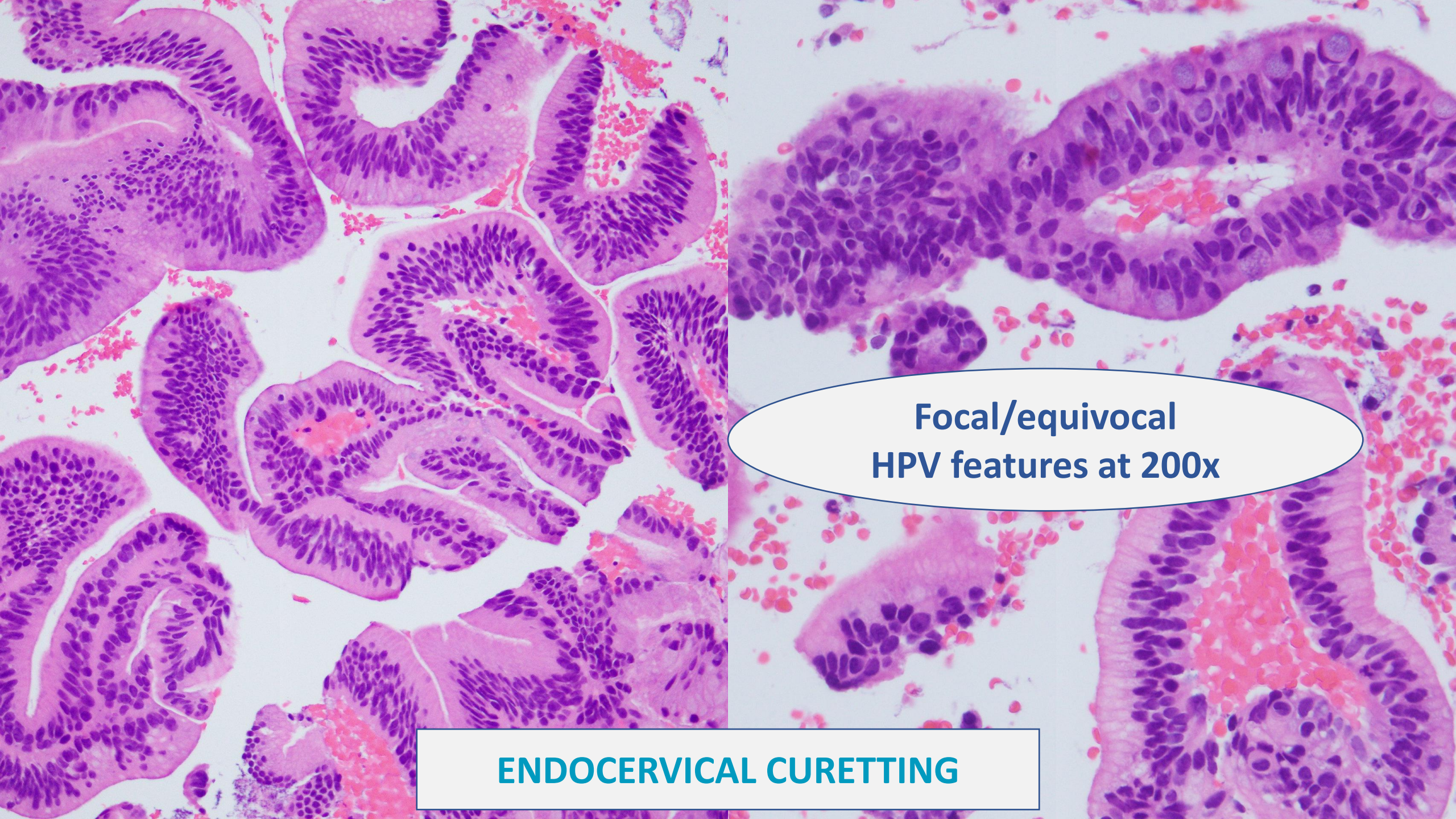
Stolnicu S, Barsan I, Hoang L, et al, Am J Surg Pathol. 2018;42:214-226

Carleton C, Hoang L, Sah S, et al. Am J Surg Pathol. 2016;40:636-44

- 
- The background of the slide features two histological images of gastric-type adenocarcinoma. The left image is a low-magnification view showing irregular glandular structures with varying degrees of architectural complexity. The right image is a high-magnification view focusing on individual glandular units, highlighting the cellular morphology and the pale, foamy cytoplasm characteristic of this cancer type.
- Low N/CP ratio
 - Clear, foamy, pale cytoplasm
 - Distinct cytoplasmic borders
 - Basally located nuclei
 - +/- intestinal diff (goblet or neuroendocrine-like cells)

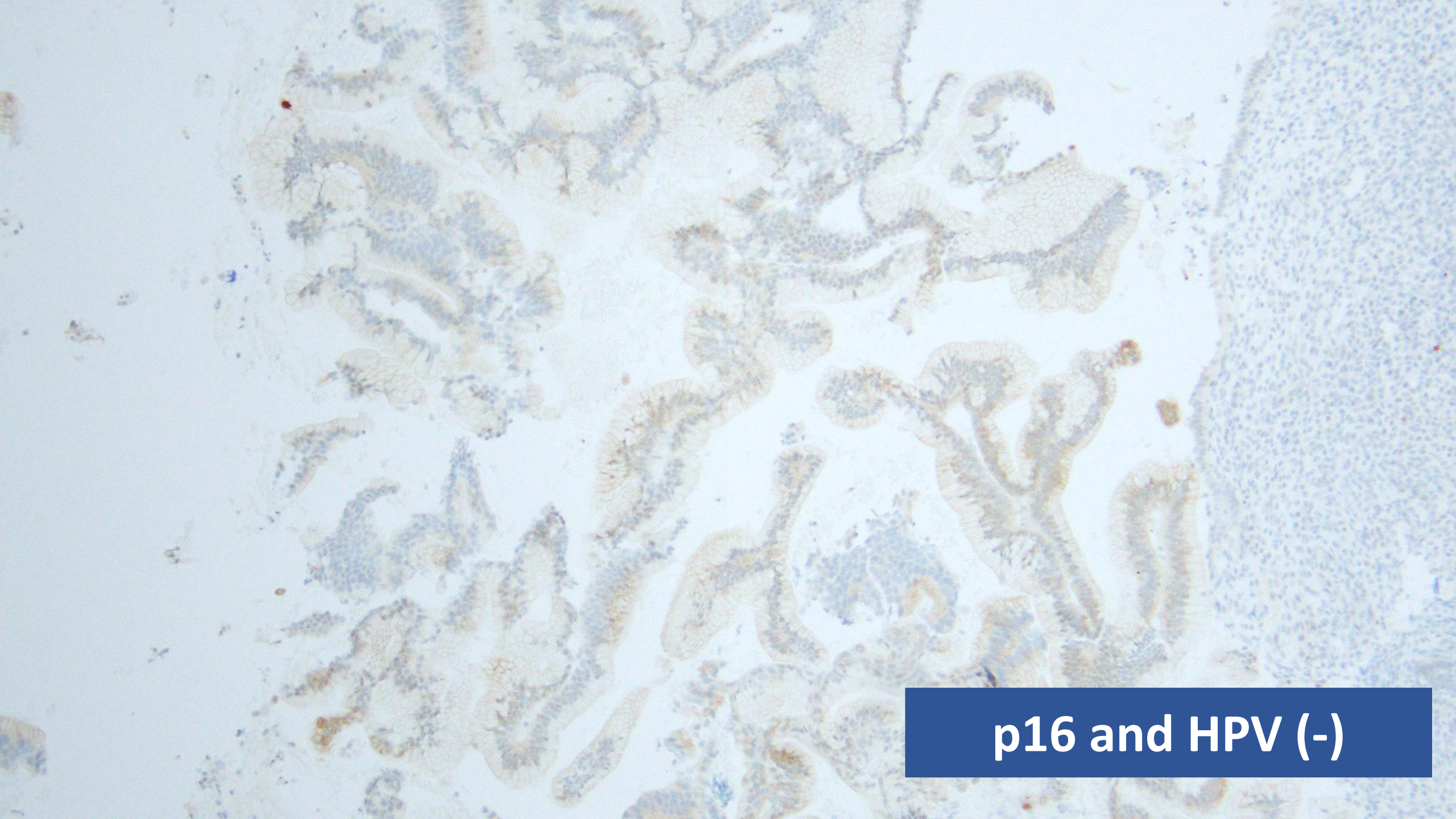




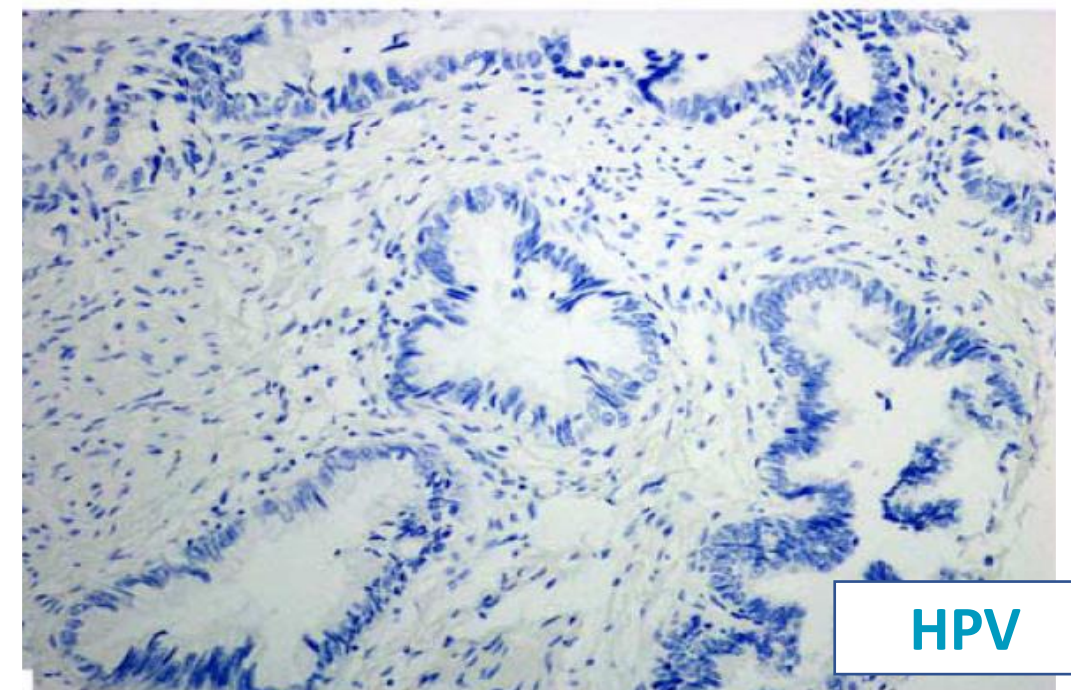
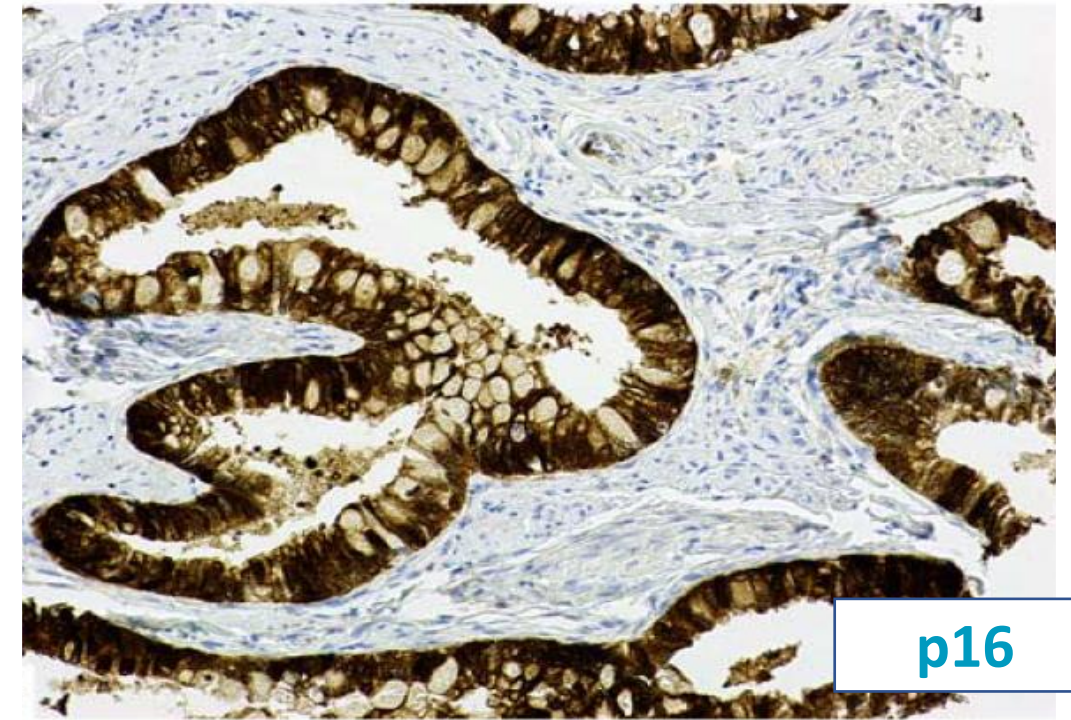
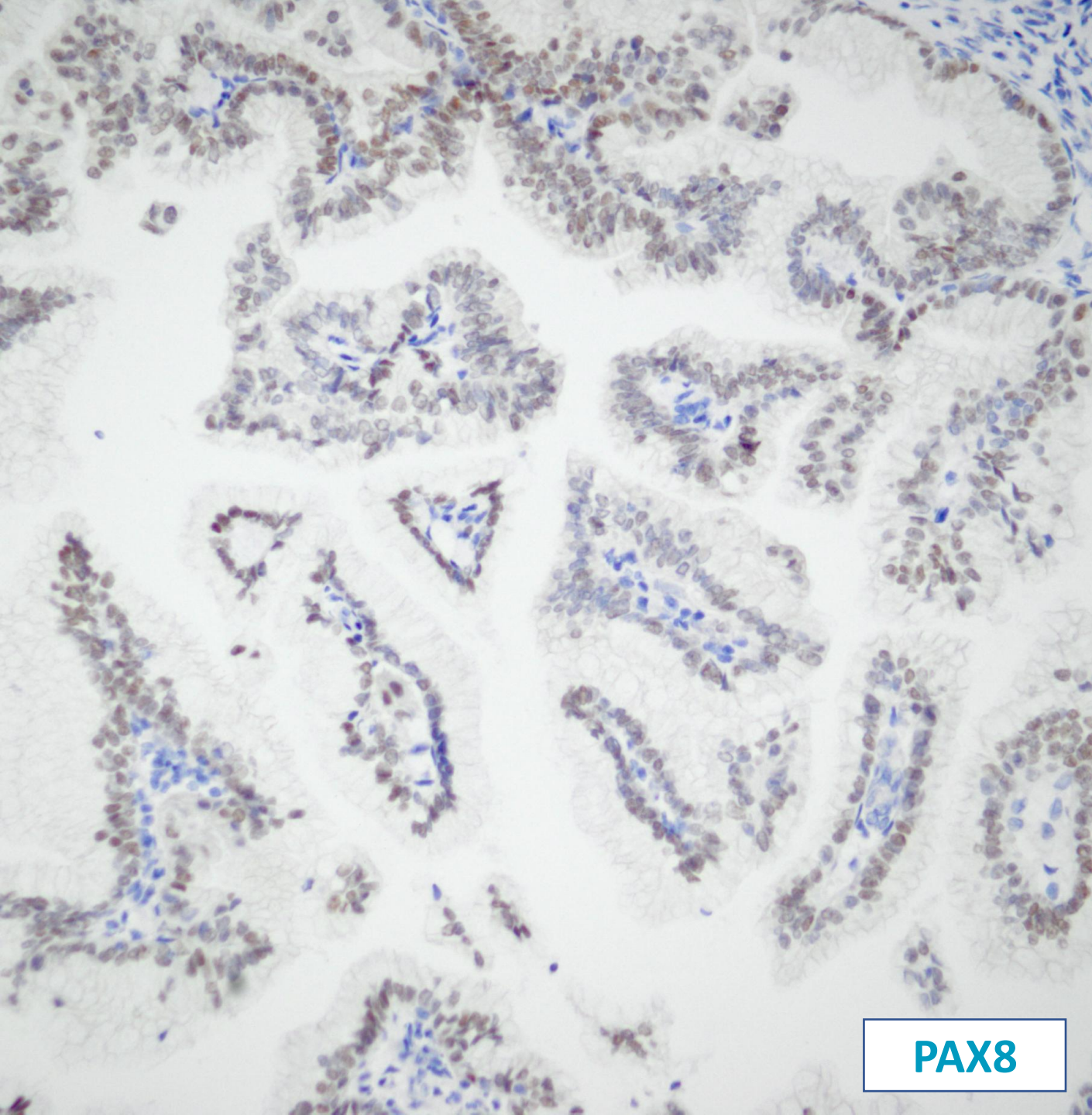


**Focal/equivocal
HPV features at 200x**

ENDOCERVICAL CURETTING



p16 and HPV (-)



ADENOMA MALIGNUM

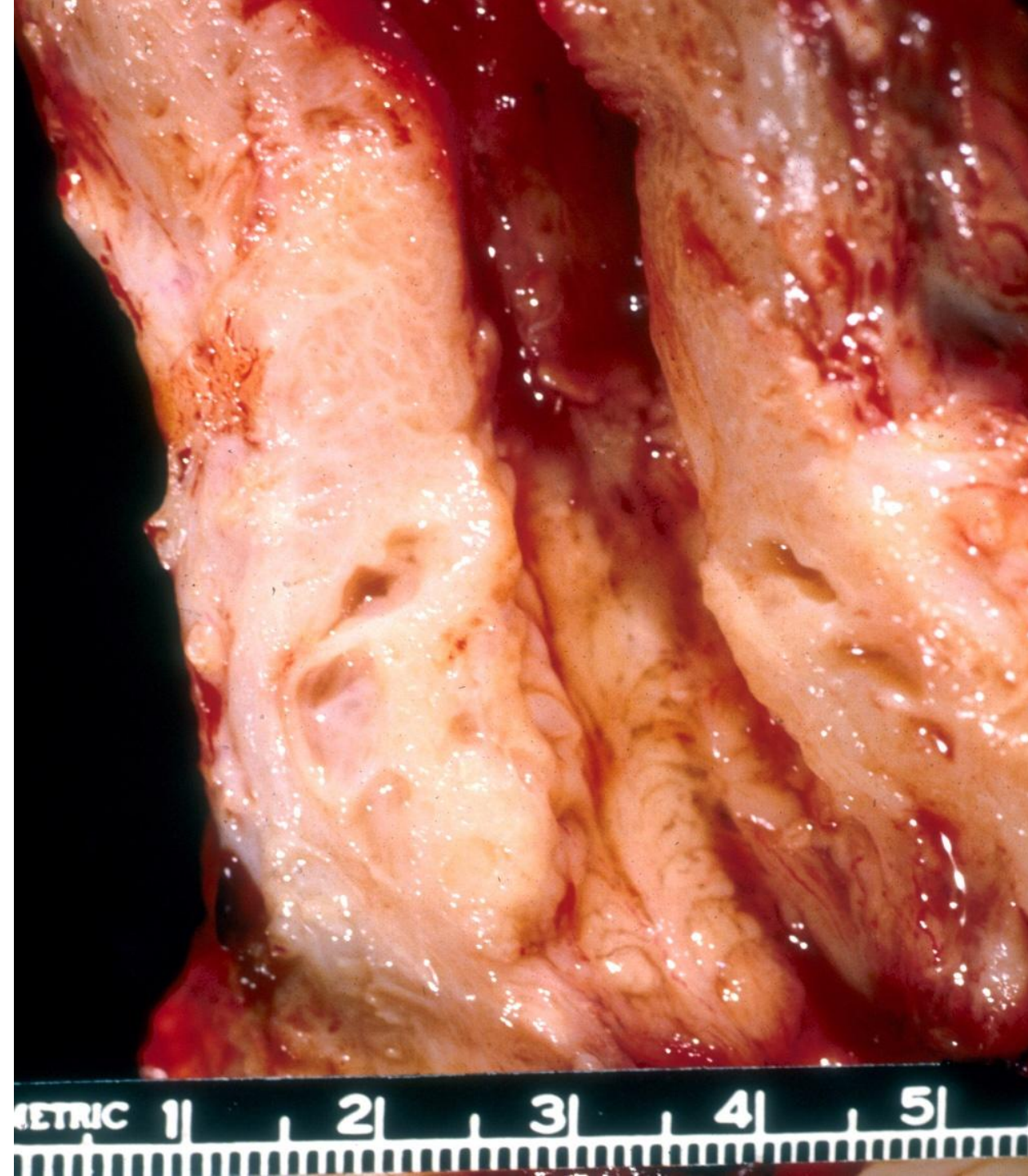
(Minimal deviation
gastric-type
adenocarcinoma)

TERM NOT RECOMMENDED

***Peutz-Jeghers syndrome with
"adenoma malignum" of the cervix.
A report of two cases***

McGowan L, Young RH, Scully RE

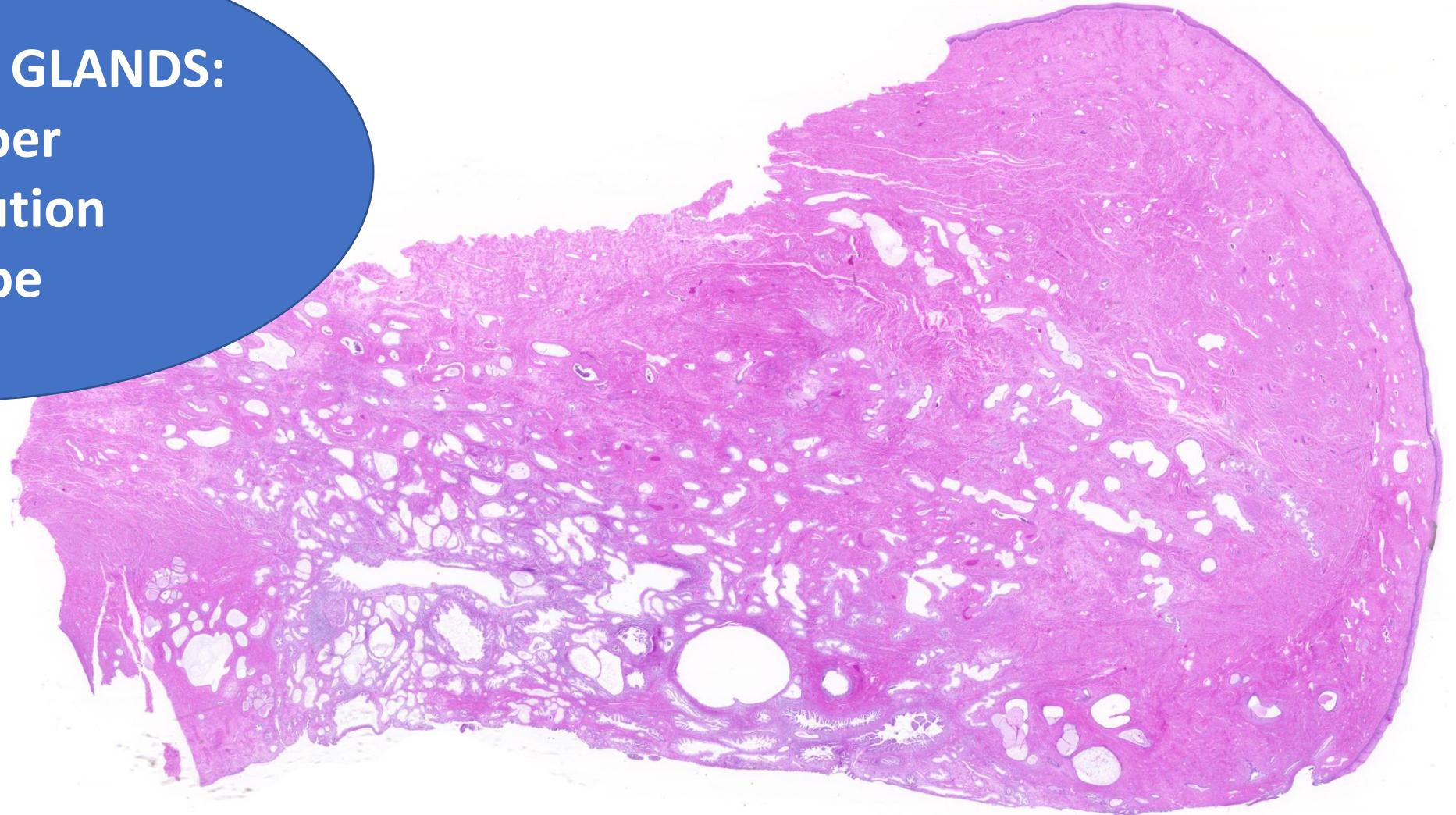
Gynecol Oncol. 1980;10:125-33



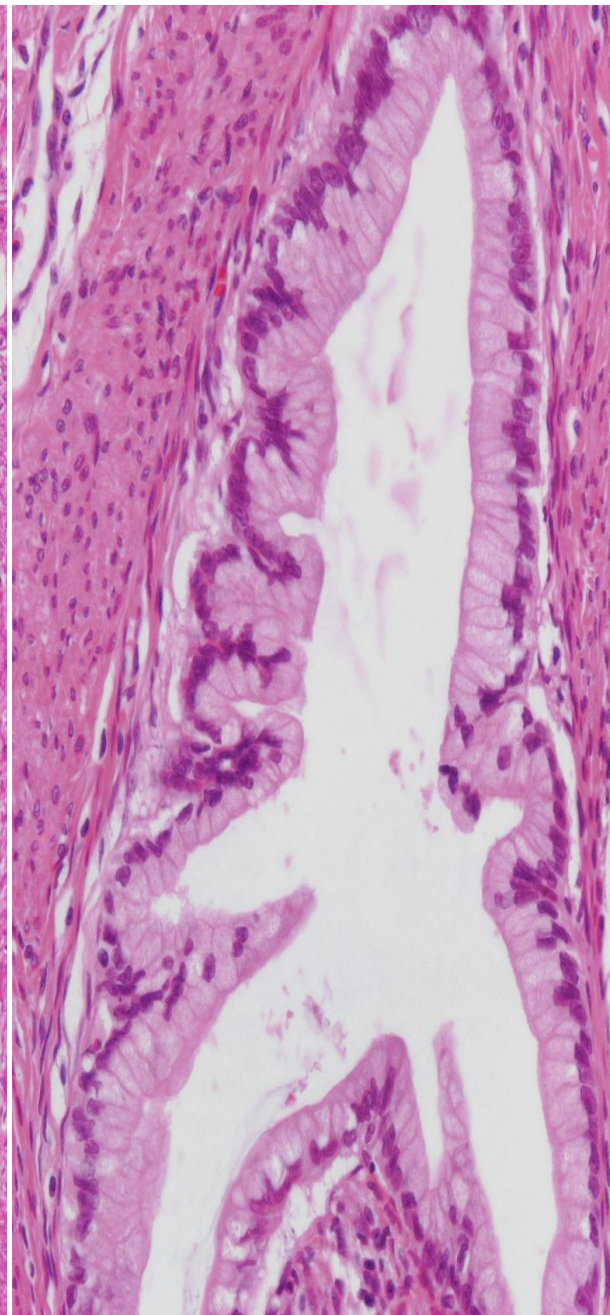
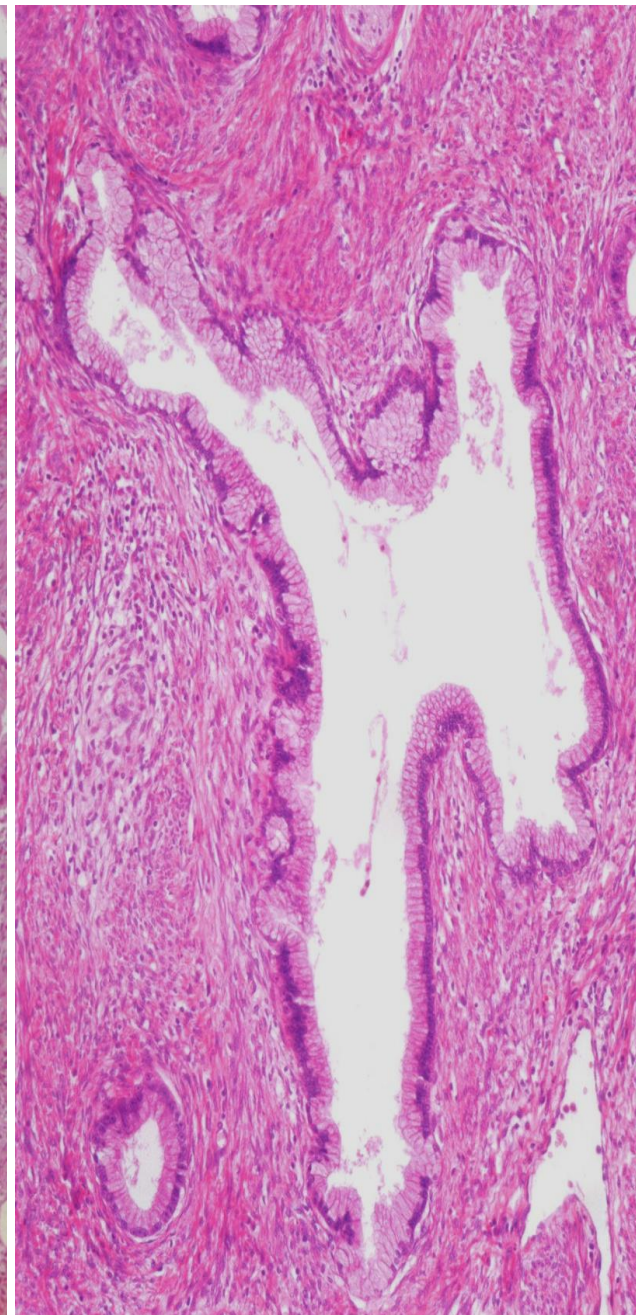
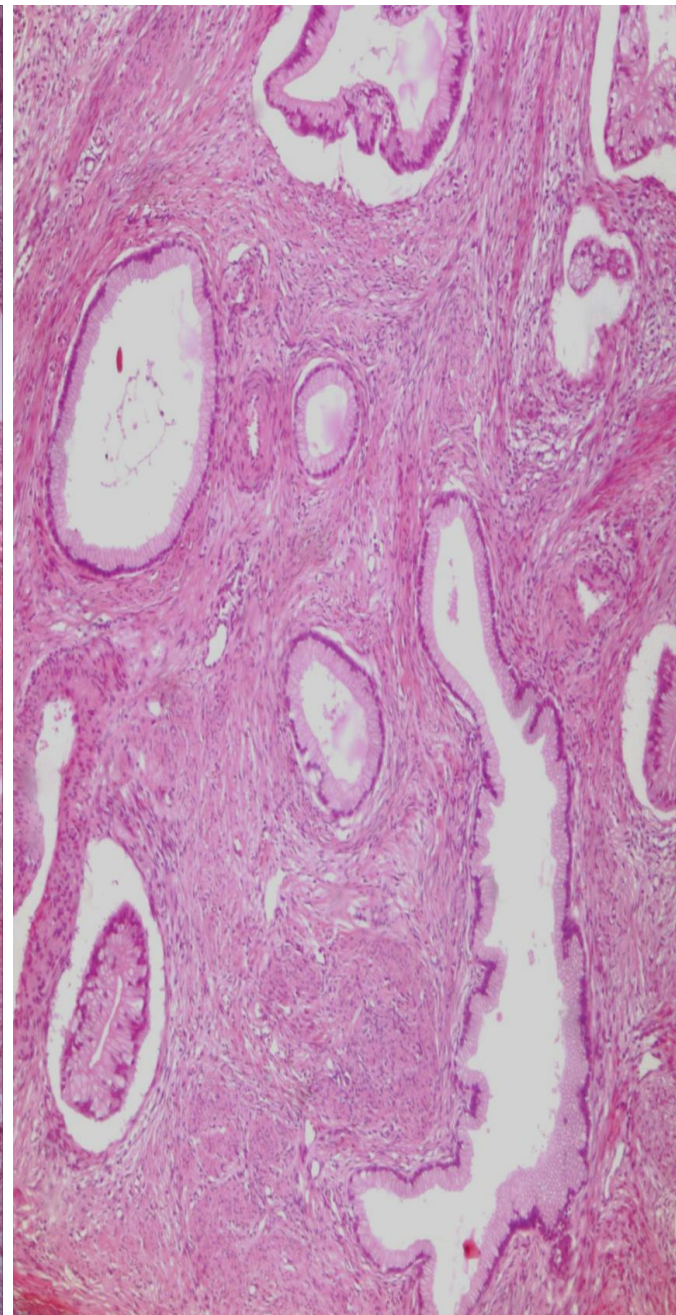
GASTRIC-TYPE ADENOCARCINOMA ("ADENOMA MALIGNUM")

ABNORMAL GLANDS:

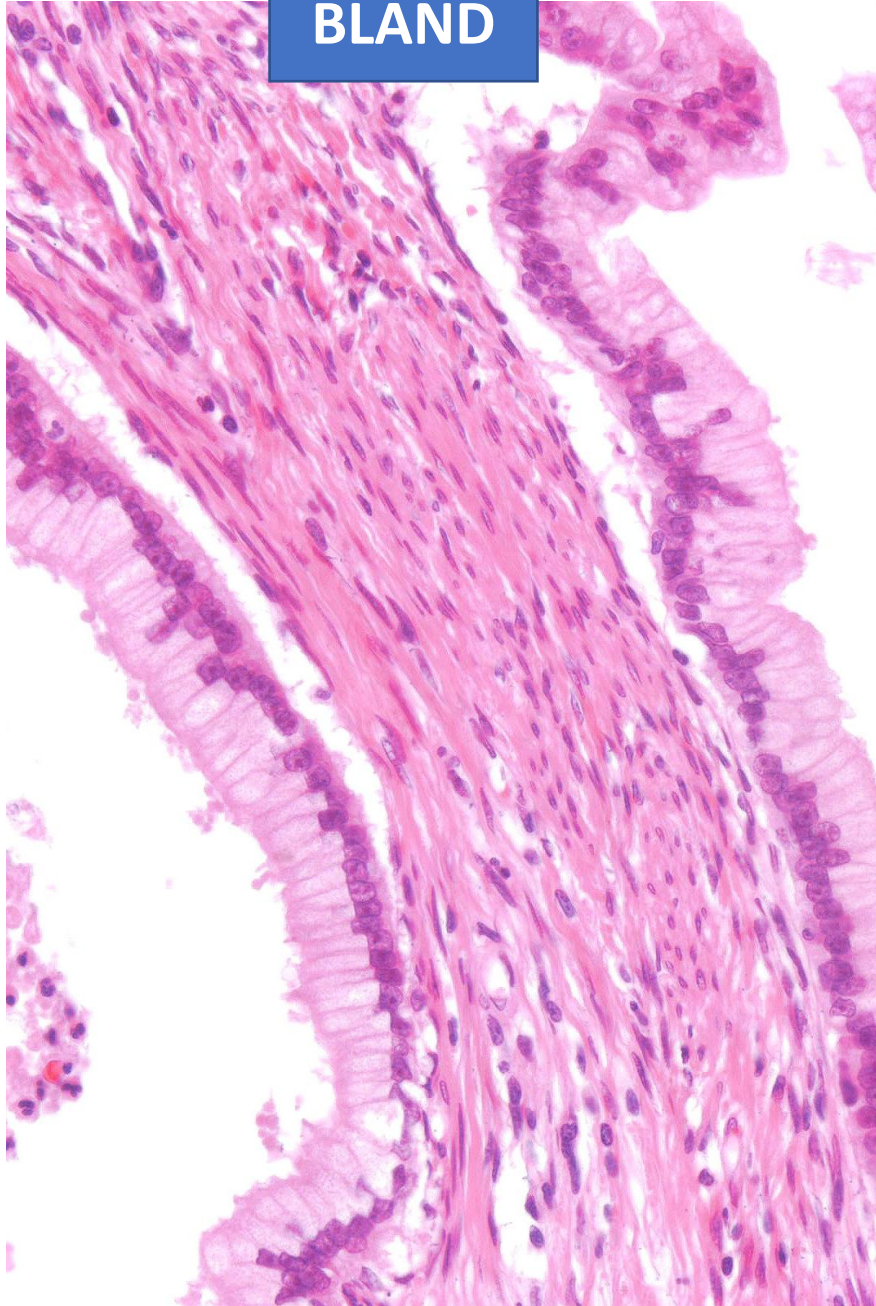
- Number
- Distribution
- Shape



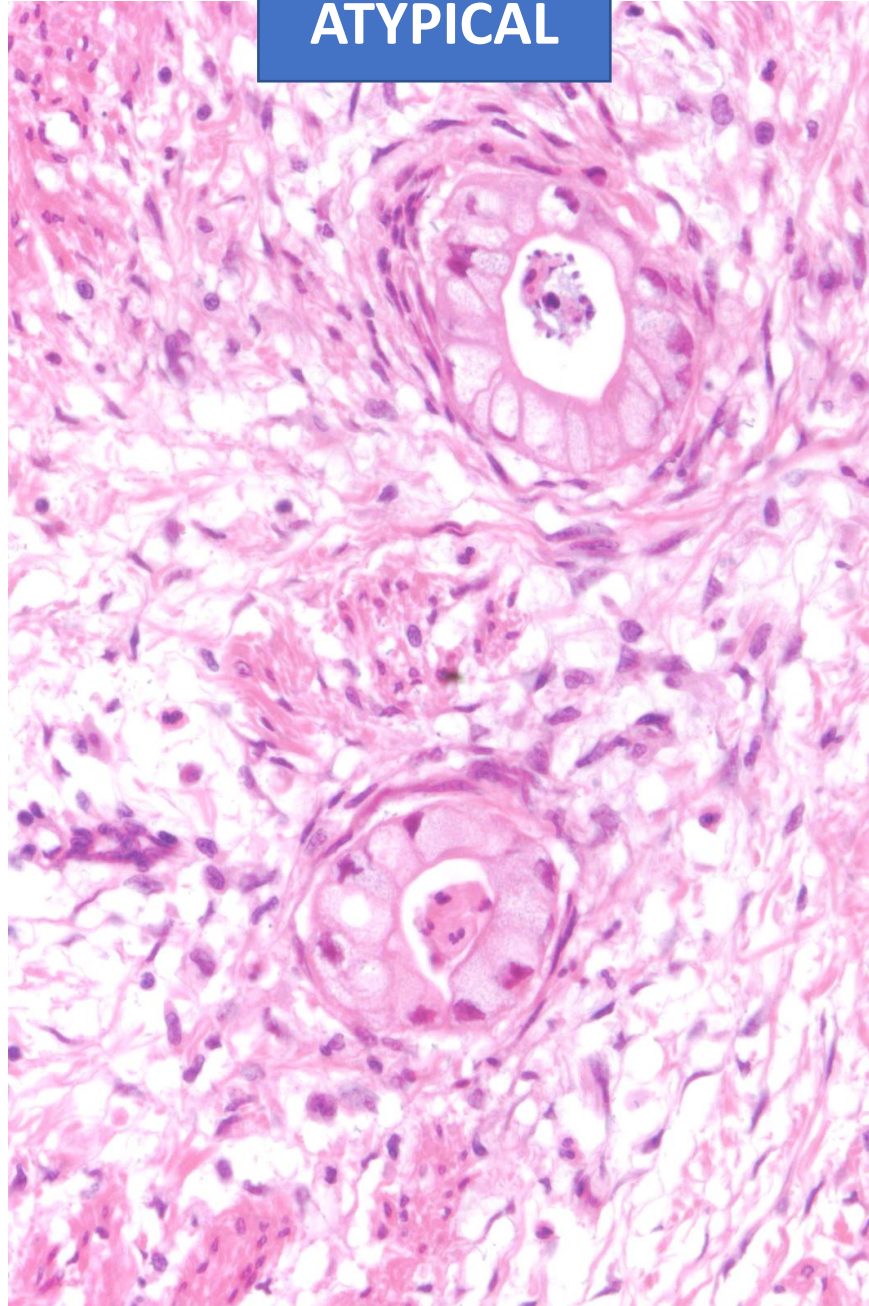
ENDOCERVICAL CANAL



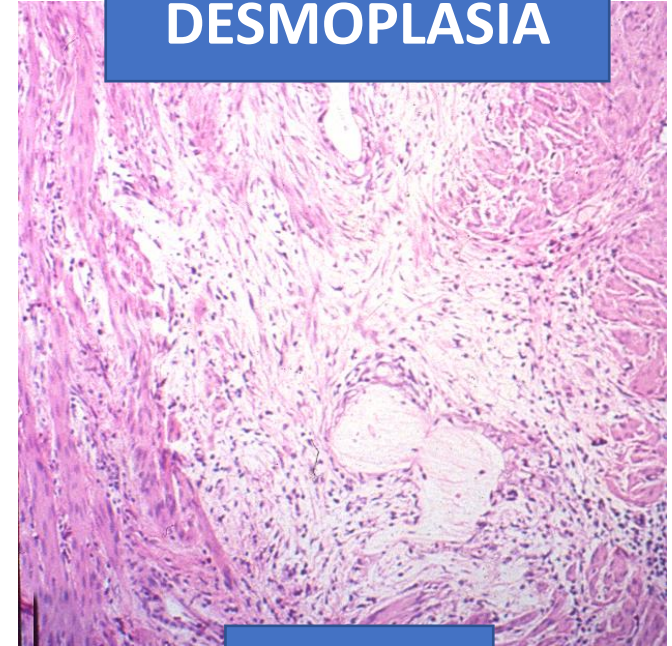
BLAND



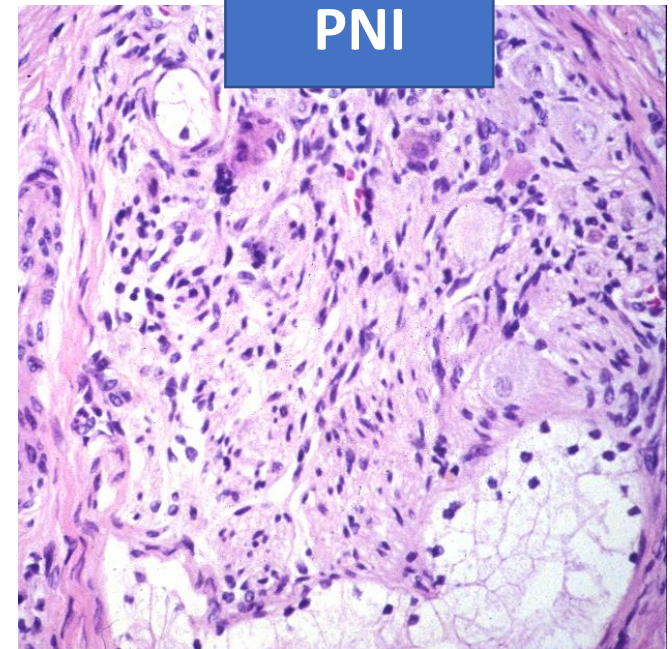
ATYPICAL



DESMOPLASIA



PNI



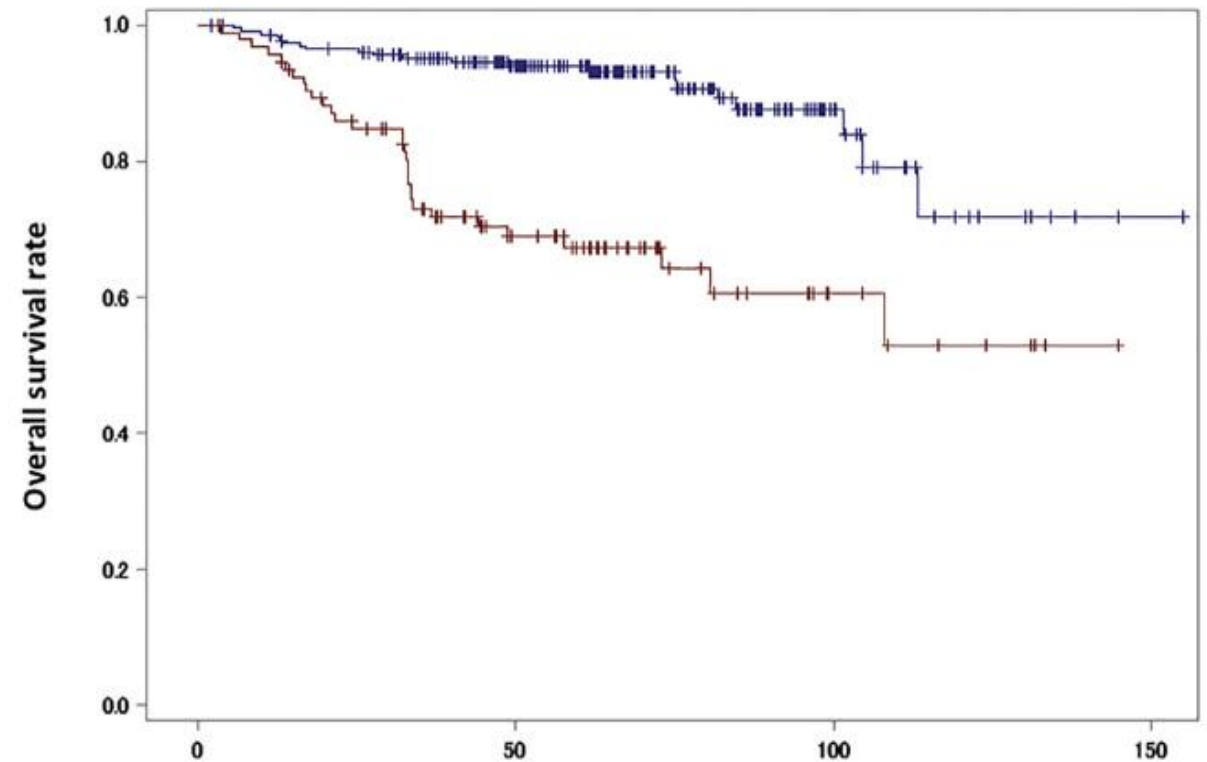
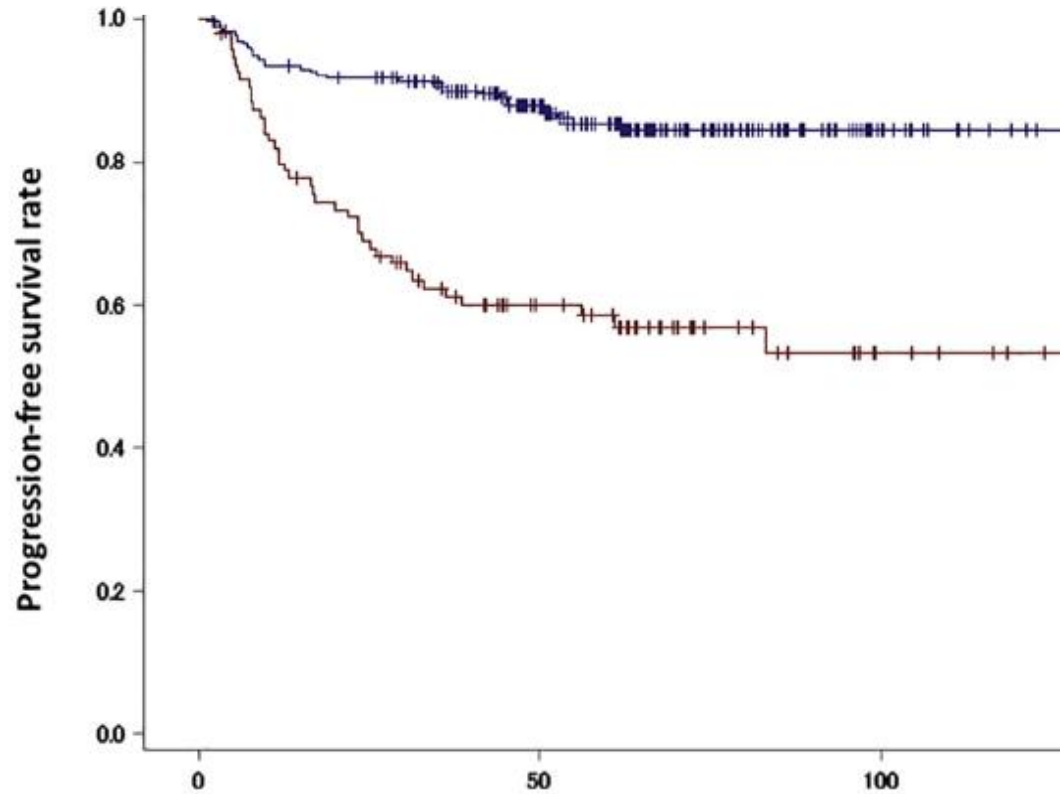
A Detailed Immunohistochemical Analysis of a Large Series of Cervical and Vaginal Gastric-type Adenocarcinomas

Carleton C et al, Am J Surg Pathol 2016;40:636-44

		Positive	Diffuse	Most common somatic mutations:
CK7		47/47	45	
MUC6	NON-SPECIFIC!..HJK1083 or TTF2	17/21	6	p53 CDKN2A KRAS STK11 SMAD4 . . ERBB3/2 and BRAF
CEA		25/31	2	
CA125		36/45	5	
PAX8		32/47	20	
CK20		23/47	6	
CDX2		24/47	4	
p16		18/47	4 (ALL HPV NEGATIVE)	
p53		19/46	19	
HNF-1b		13/14	6	
ER, PR, PAX2, HER2		Mostly negative		



Analysis of gastric-type mucinous carcinoma of the uterine cervix – An aggressive tumor with a poor prognosis: A multi-institutional study☆

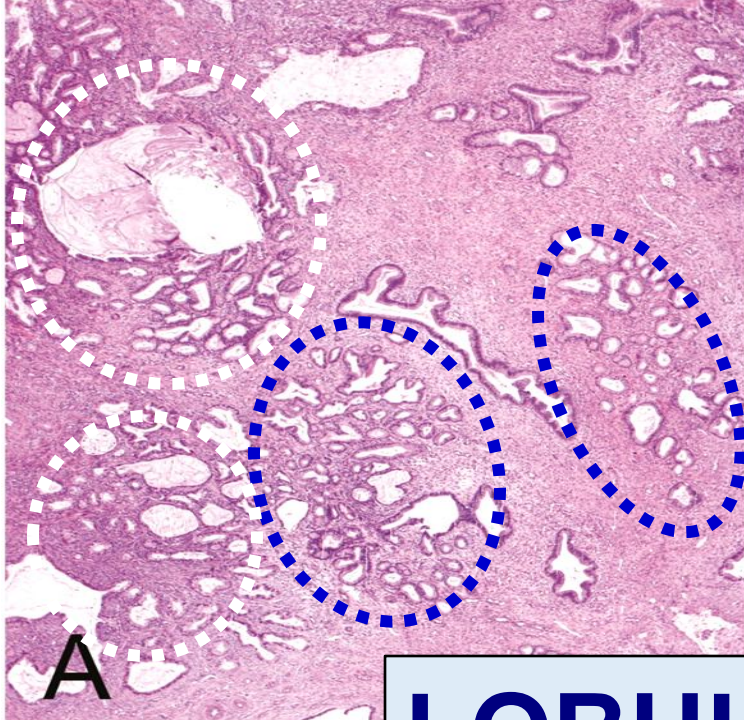


**Overall, poorer survival when compared to HPV-associated adenocarcinomas
(~ 40% versus 90%; 62% vs 96% if stage I tumors; chemoresistant)**
**Metastases to adnexa, omentum, liver, brain and bone in contrast to HPV-associated
adenocarcinomas (typically pelvis)**

ADENOMA MALIGNUM (GASTRIC-TYPE CARCINOMA (Minimal Deviation Adenocarcinoma)

Differential Diagnosis

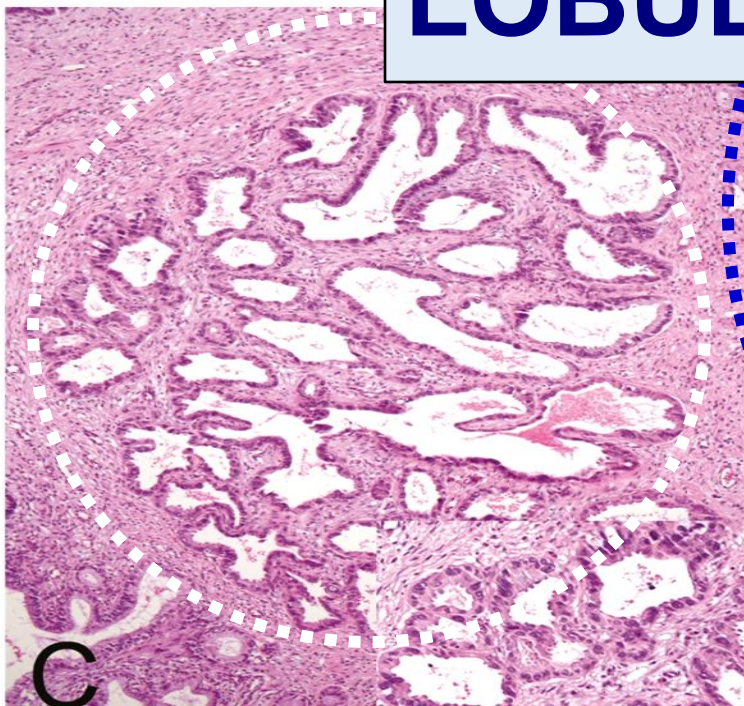
- Deep endocervical glands and Nabothian cysts
- Tunnel clusters
- Endocervical hyperplasia, NOS
- Lobular endocervical gland hyperplasia or pyloric gland metaplasia
- Cervical adenomyoma
- Endocervicosis



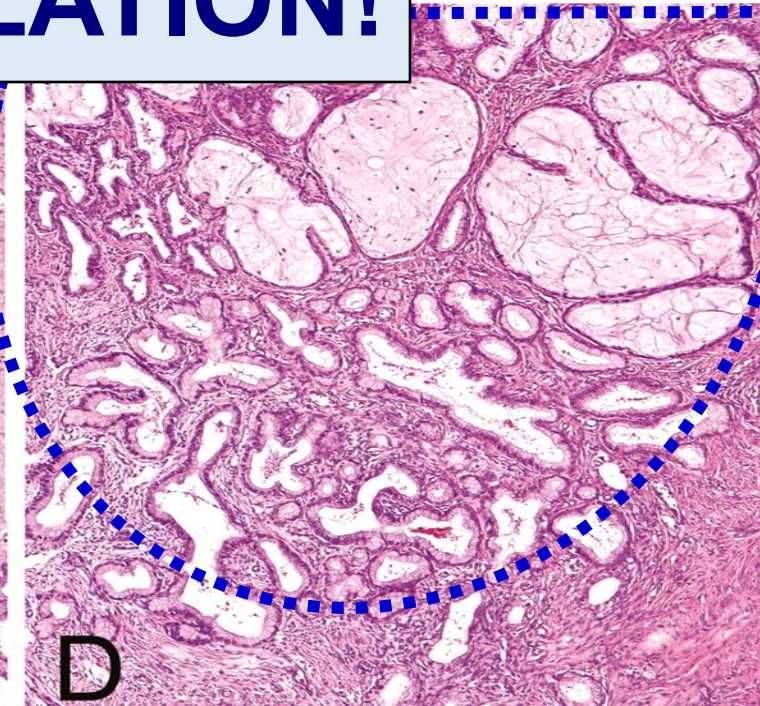
A



B



C



D

LOBULATION!

**T
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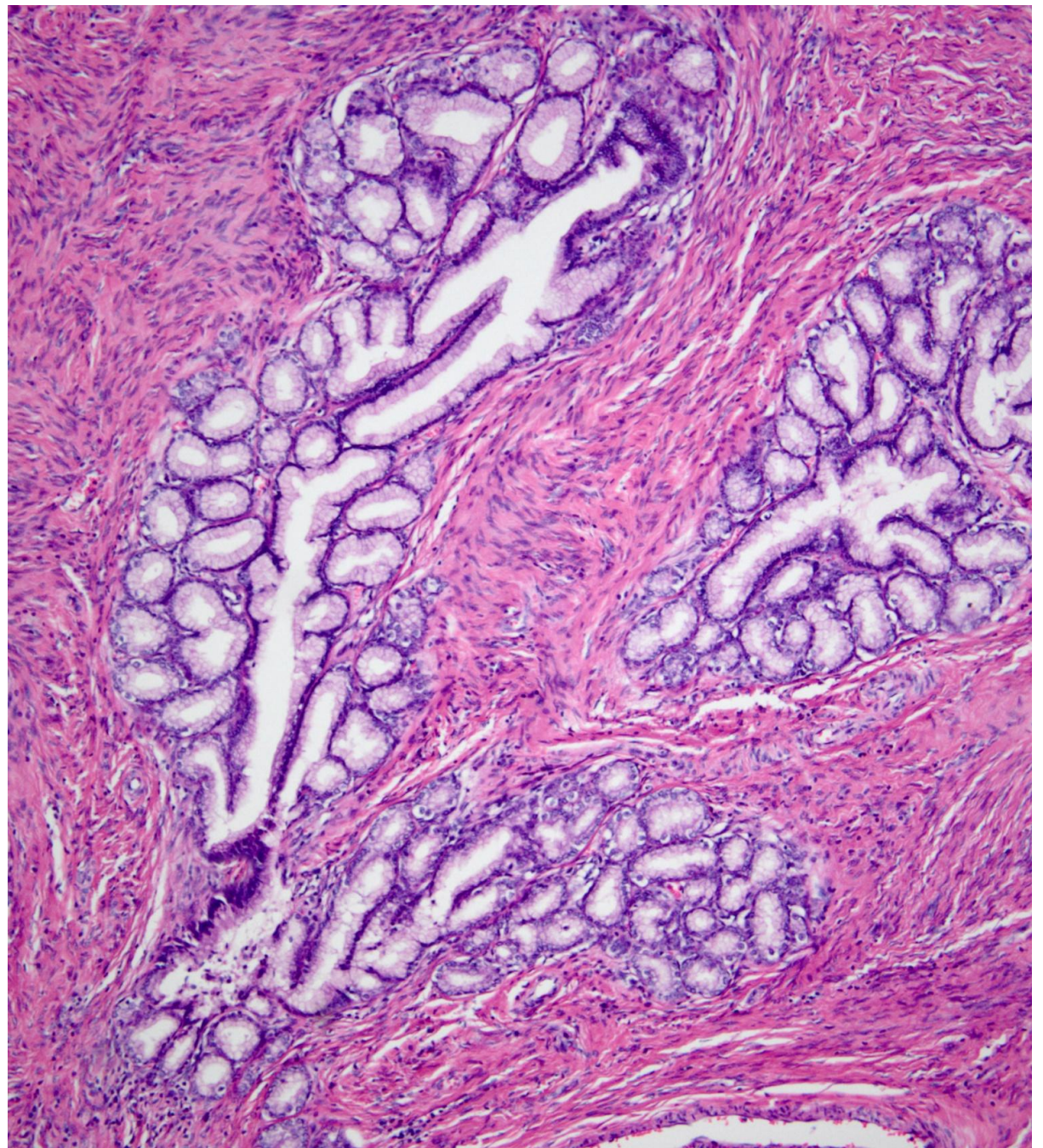
C
L
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S
T
E
R
S**

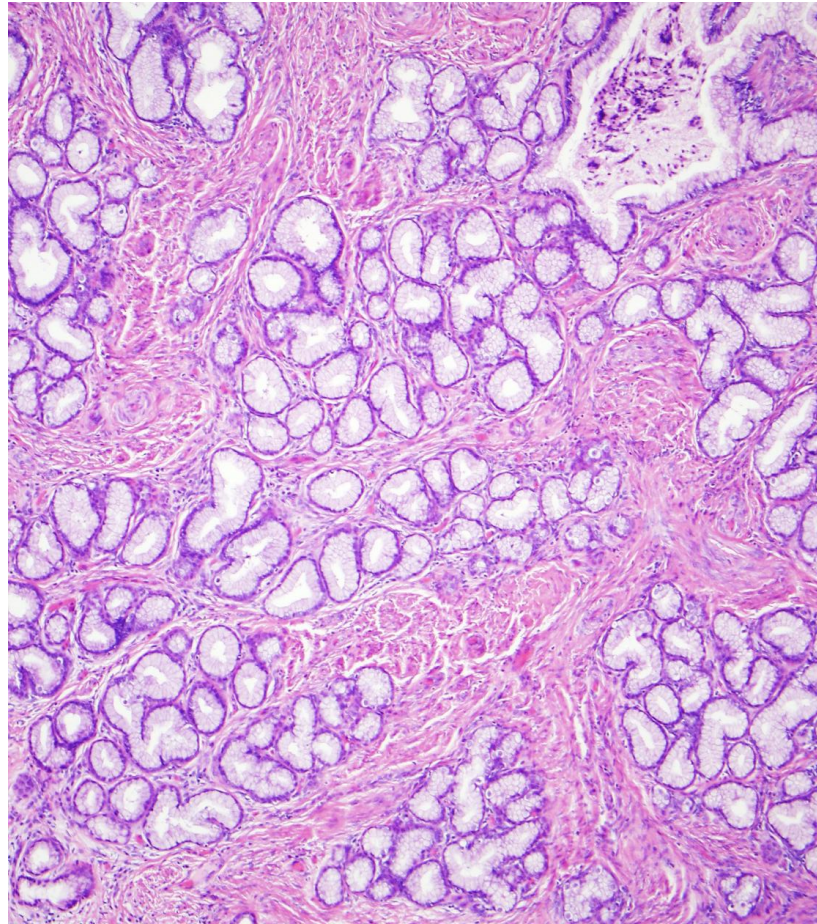
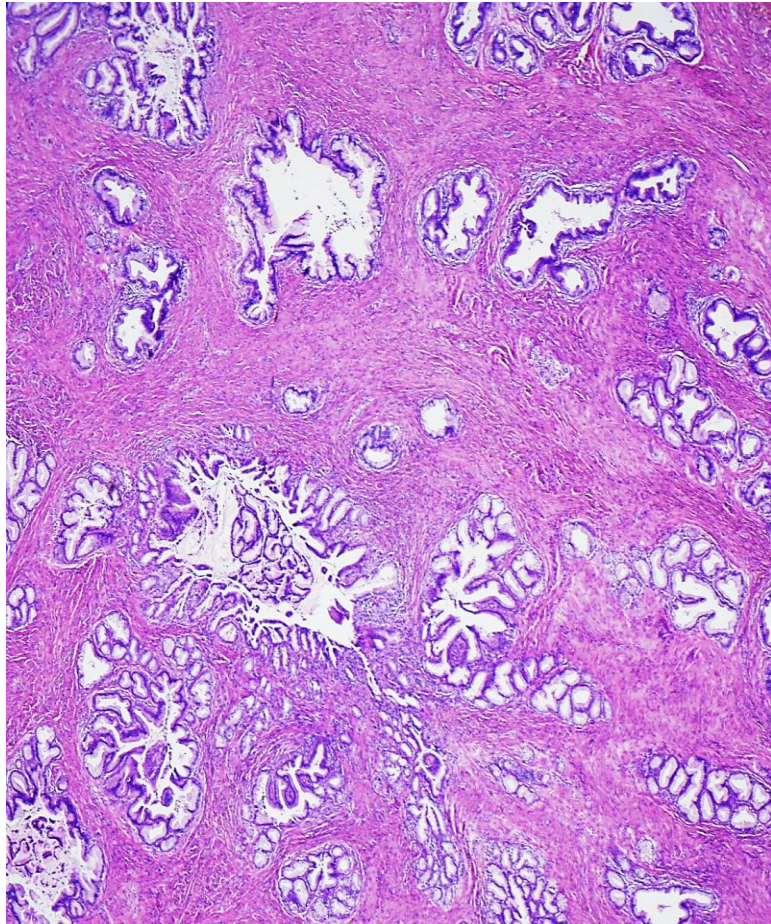
HISTOLOGIC FEATURES FAVORING BENIGN GLANDULAR PROLIFERATIONS OVER ADENOCARCINOMA

- Lobulated architecture
- Lack of deep, widely infiltrative glands
- Absence of stromal reaction
- Absence of overt malignant cytologic features

DEEP GLANDS, TUNNEL CLUSTERS, AND ENDOCERVICAL GLAND HYPERPLASIA, NOS, TYPICALLY ARE INCIDENTAL FINDINGS

LOBULAR ENDOCERVICAL GLAND HYPERPLASIA

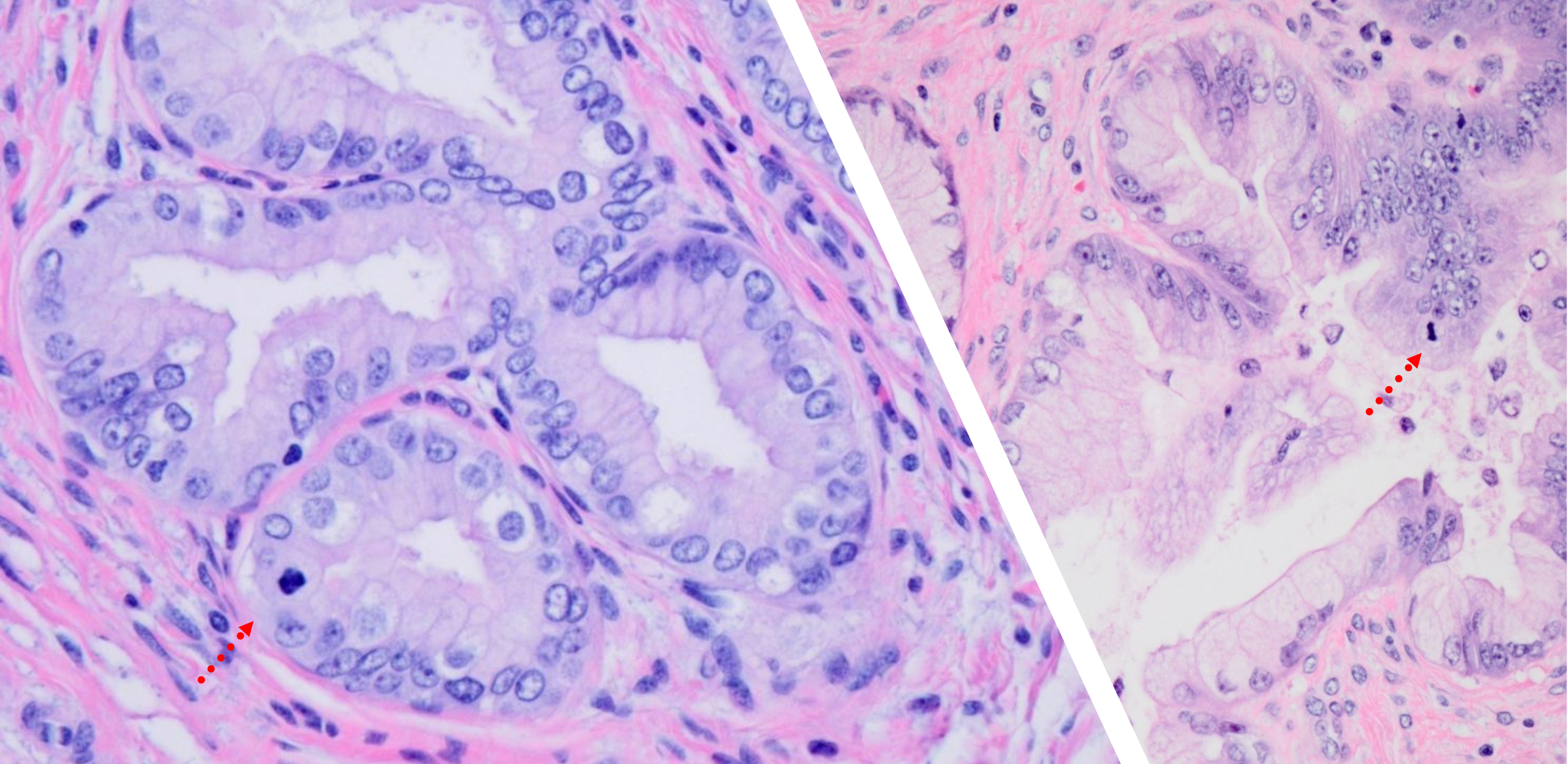




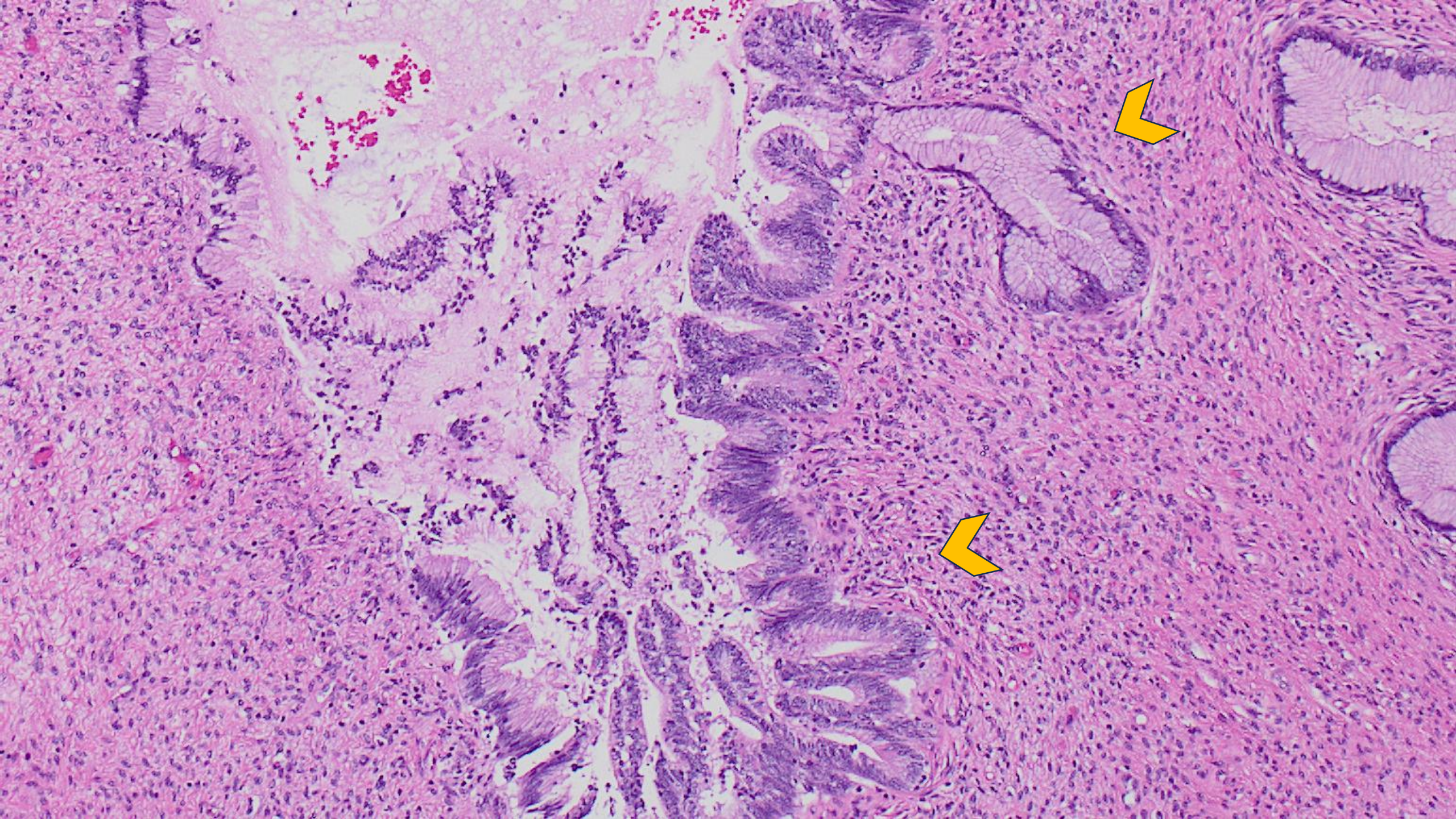
Nucci MR, Clement PB, Young RH. Am J Surg Pathol. 1999;23:886-91

GASTRIC-TYPE ADCA “ADENOMA MALIGNUM” vs LEGH

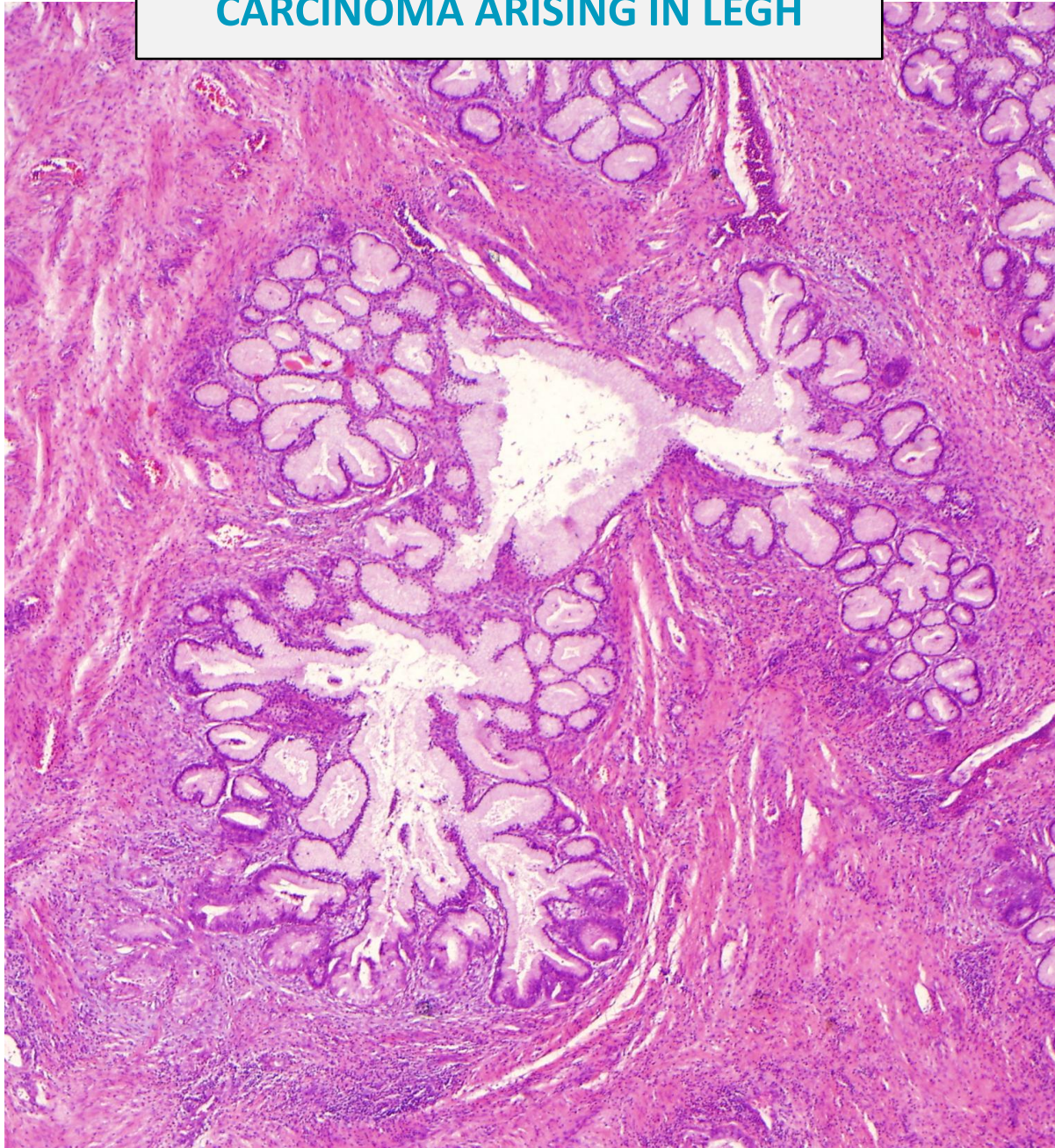
	LEGH	AM
Mucous discharge	+/-	+/-
Mass	Rarely	Typically
Depth of involvement	<50%	Often >>50%
Demarcation	Present	Absent
Lobulation	+	-
Cytologic atypia	Minimal	Prominent (at least focally)
Stromal response	-	+



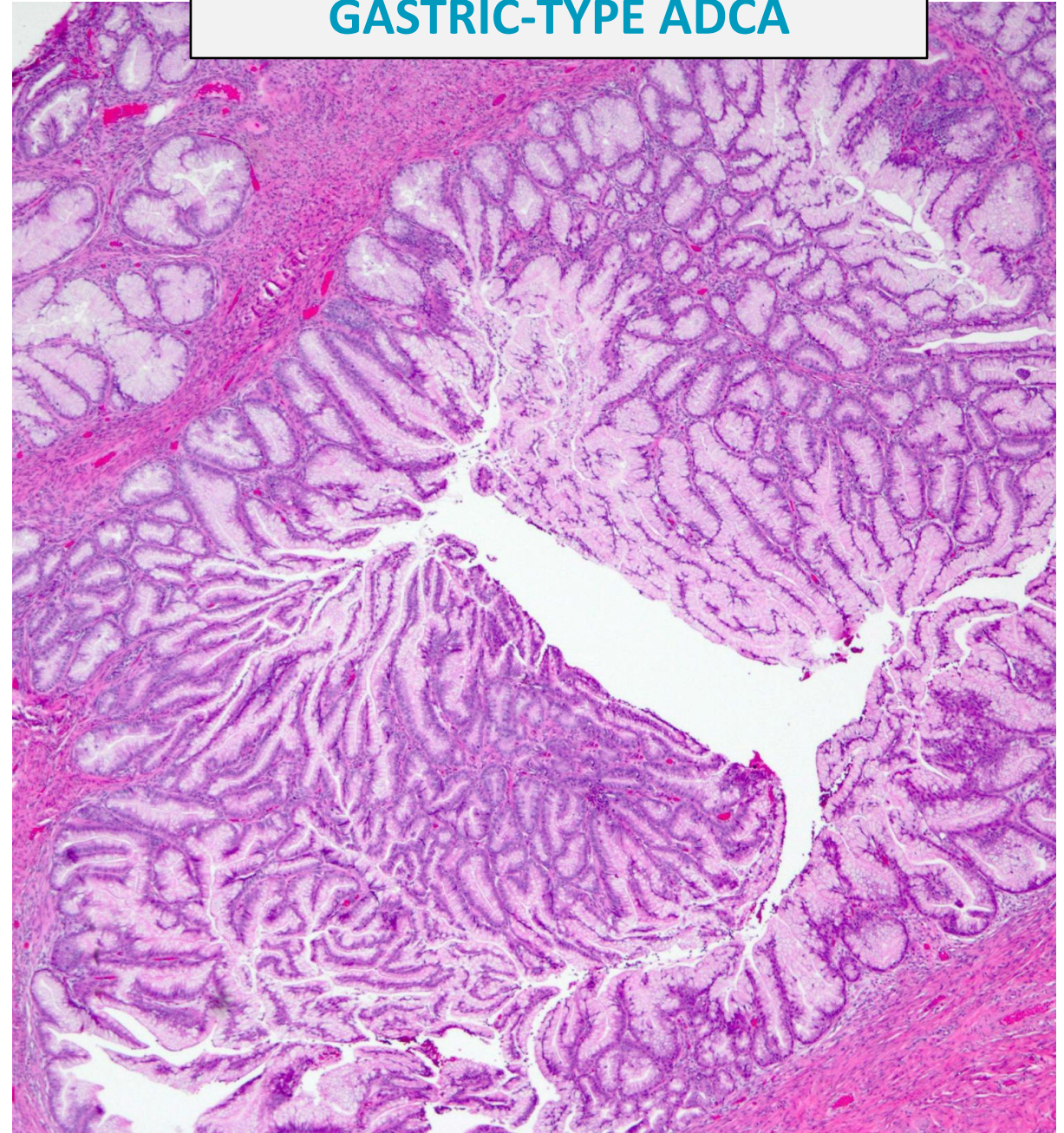
LOBULAR ENDOCERVICAL GLAND HYPERPLASIA
with SEVERE CYTOLOGIC ATYPIA



CARCINOMA ARISING IN LEIGH



GASTRIC-TYPE ADCA

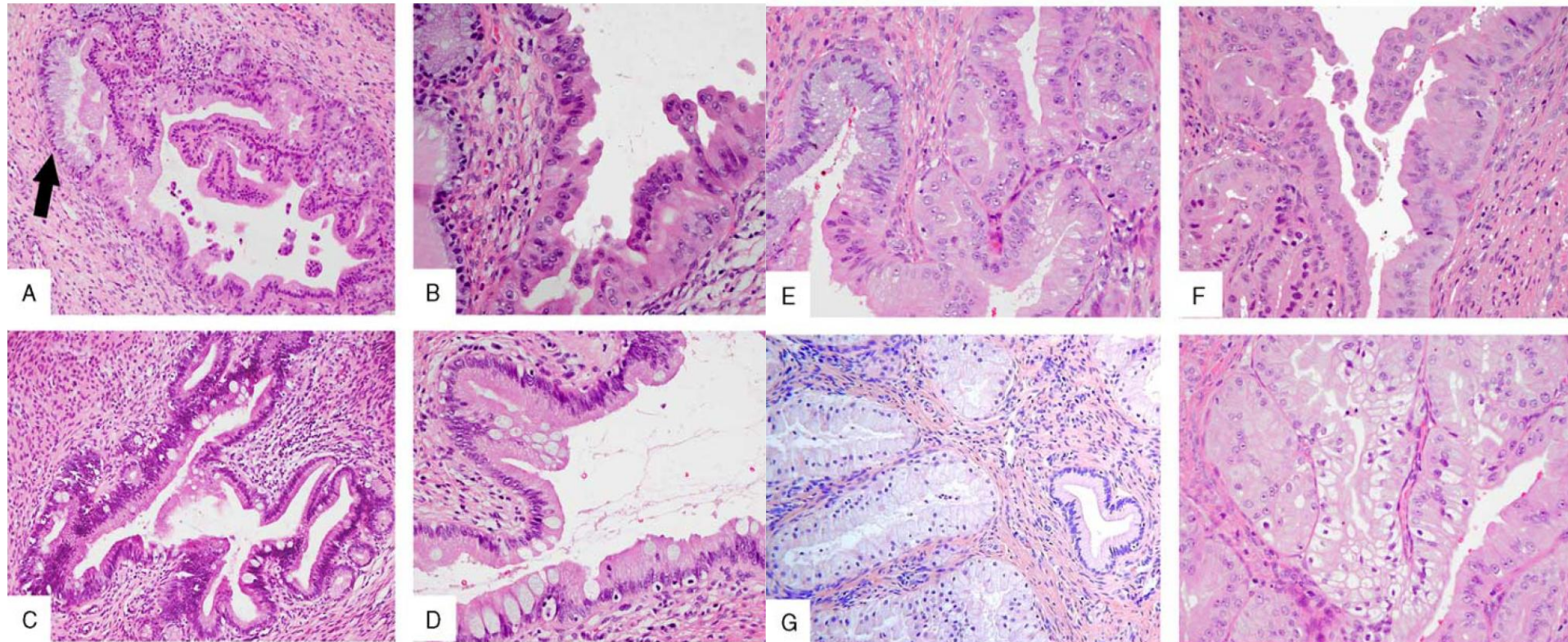


HPV-negative Gastric Type Adenocarcinoma In Situ of the Cervix

A Spectrum of Rare Lesions Exhibiting Gastric and Intestinal Differentiation

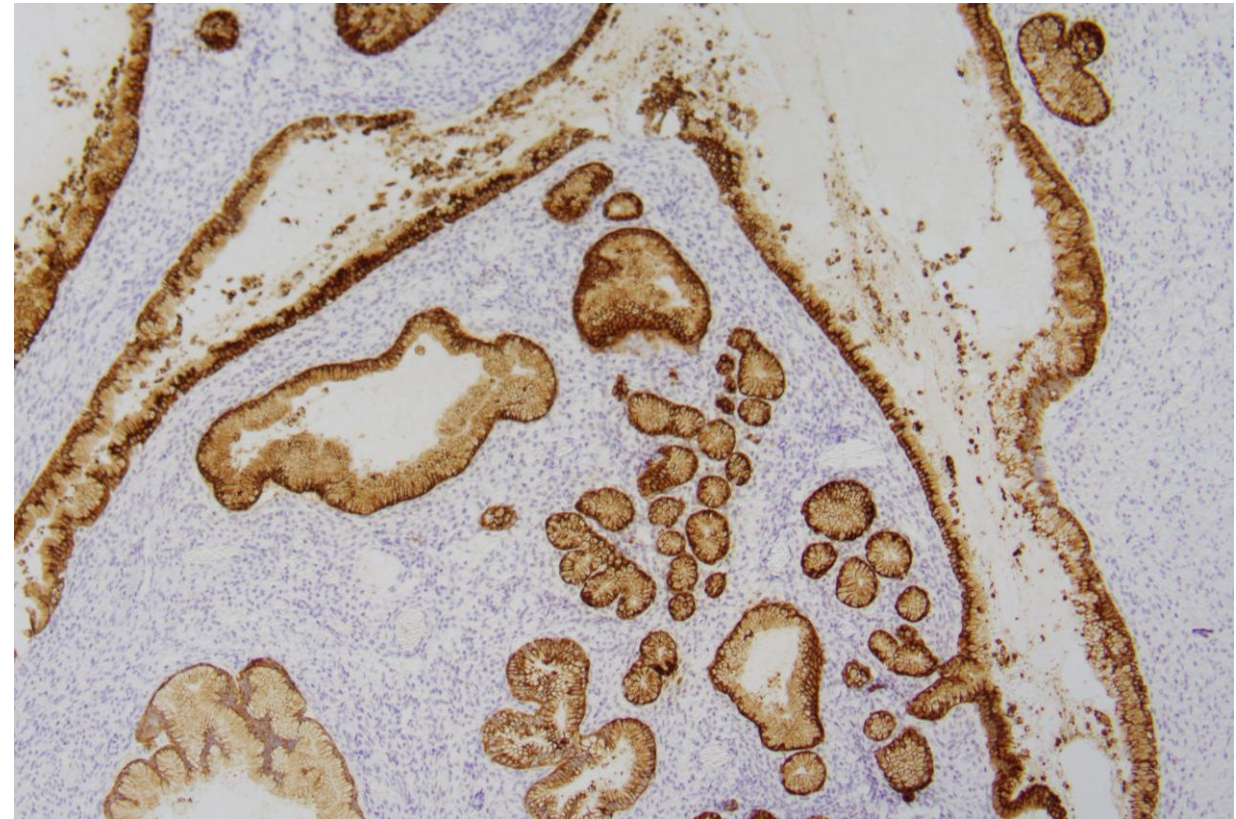
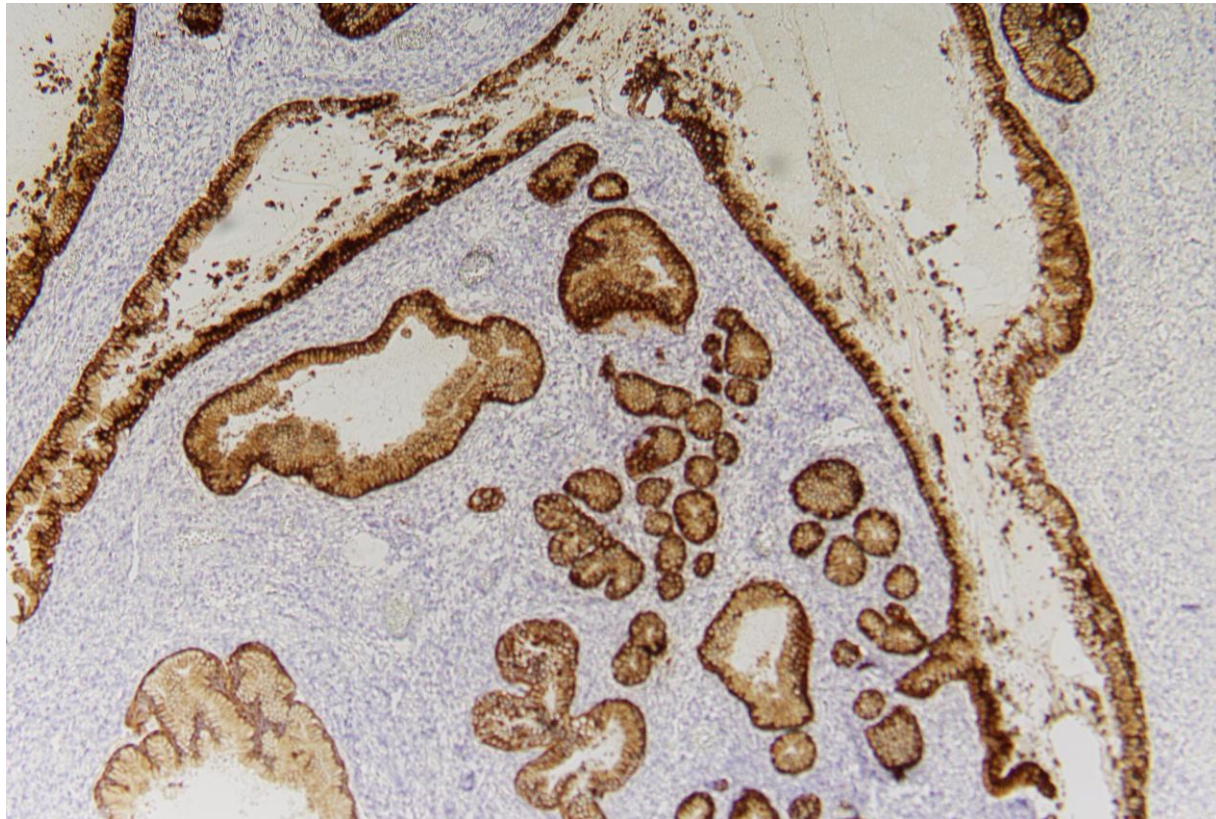
Karen L. Talia, FRCPA, Colin J.R. Stewart, FRCPA,† Brooke E. Howitt, MD,‡
Marisa R. Nucci, MD,‡ and W. Glenn McCluggage, FRCPath§*

Am J Surg Pathol 2017;41:123-1033



CLAUDIN18 POSITIVE (100% benign, 78% GAS, most often well to moderately differentiated)
NEGATIVE in all benign Mullerian endocervical specimens
in HPV-associated neoplasia (18%, always focal)

Zolbetuximab Anti-CLDN18.2 monoclonal AB approved for gastric and gastroesophageal CA
Companion diagnostic IHC: Positive: 2+/3+ in $\geq 75\%$ of tumor



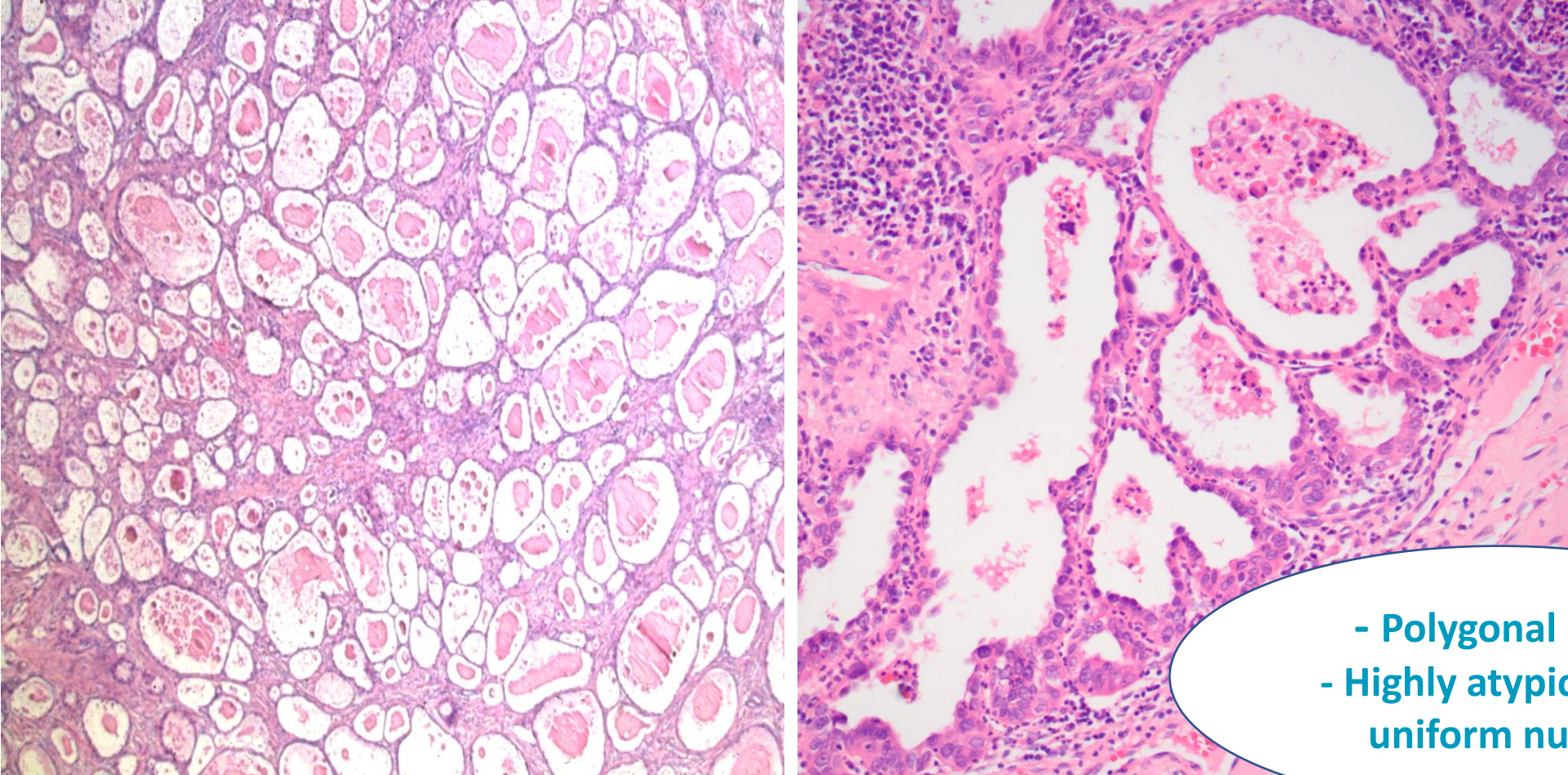


CLEAR CELL CARCINOMA

- Biphasic age distribution (<5%)
- 1/3 associated with in utero exposure to DES and non-steroidal estrogen before 18th gestation week (more commonly exocervix)
- Frequent coexistence with vaginal adenosis > transverse vaginal or cervical ridges 2/3
- Abnormalities in Hippo signaling pathway in 50%, including recurrent WWTR1 S89W somatic mutations in 40% harboring mutations in this pathway
- Poor prognosis as other non-HPV related adenocarcinomas

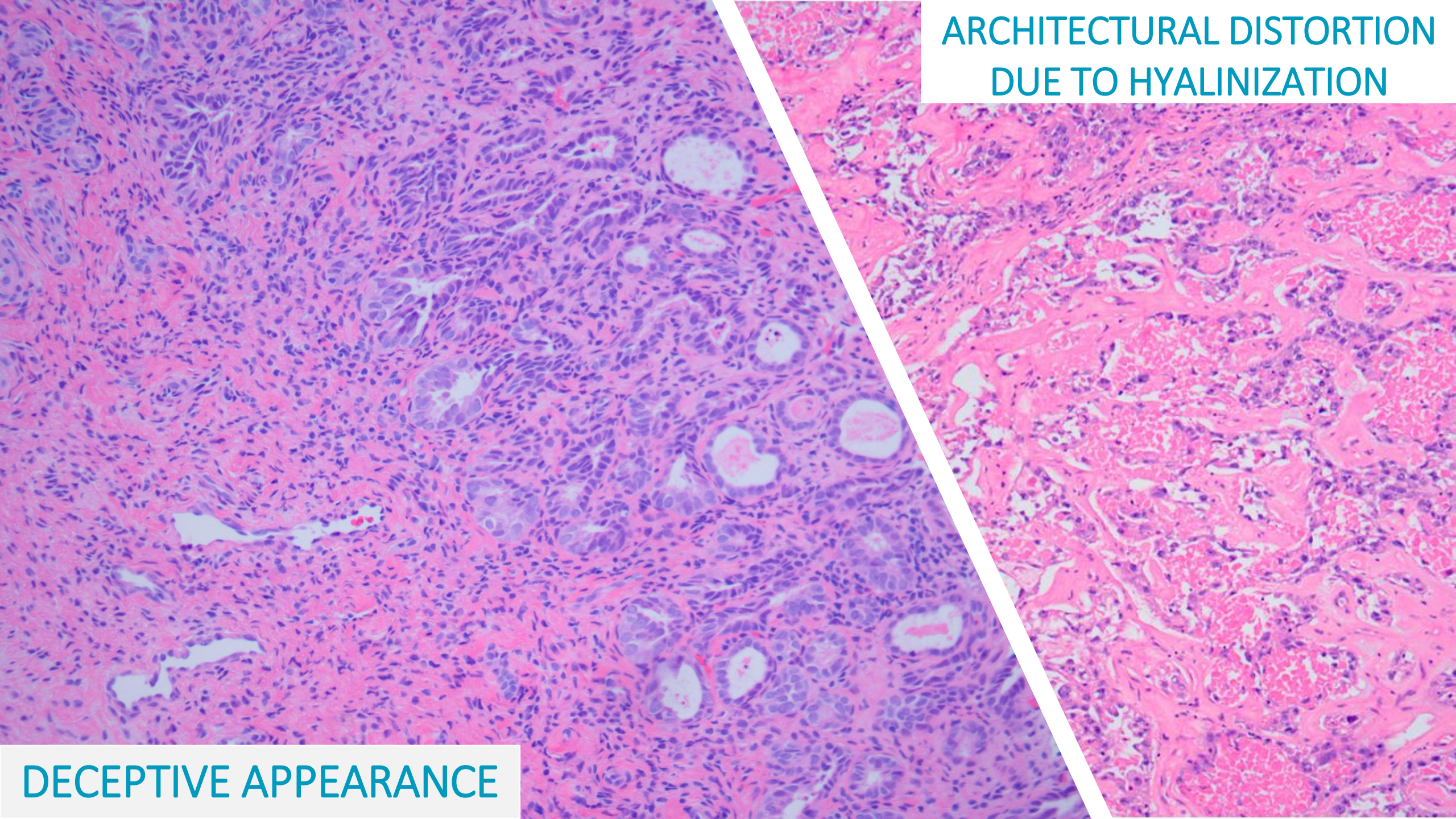
CLEAR CELL CARCINOMA: TUBULOCYSTIC PATTERN

Stolnicu S, Karpathiou G, Guerra E, Am J Surg Pathol. 2022;46:765-773
Herbst AL, Cole P, Norusis MJ, et al. Am J Obstet Gynecol. 1979;135:876-86



- Polygonal cells
- Highly atypical but uniform nuclei

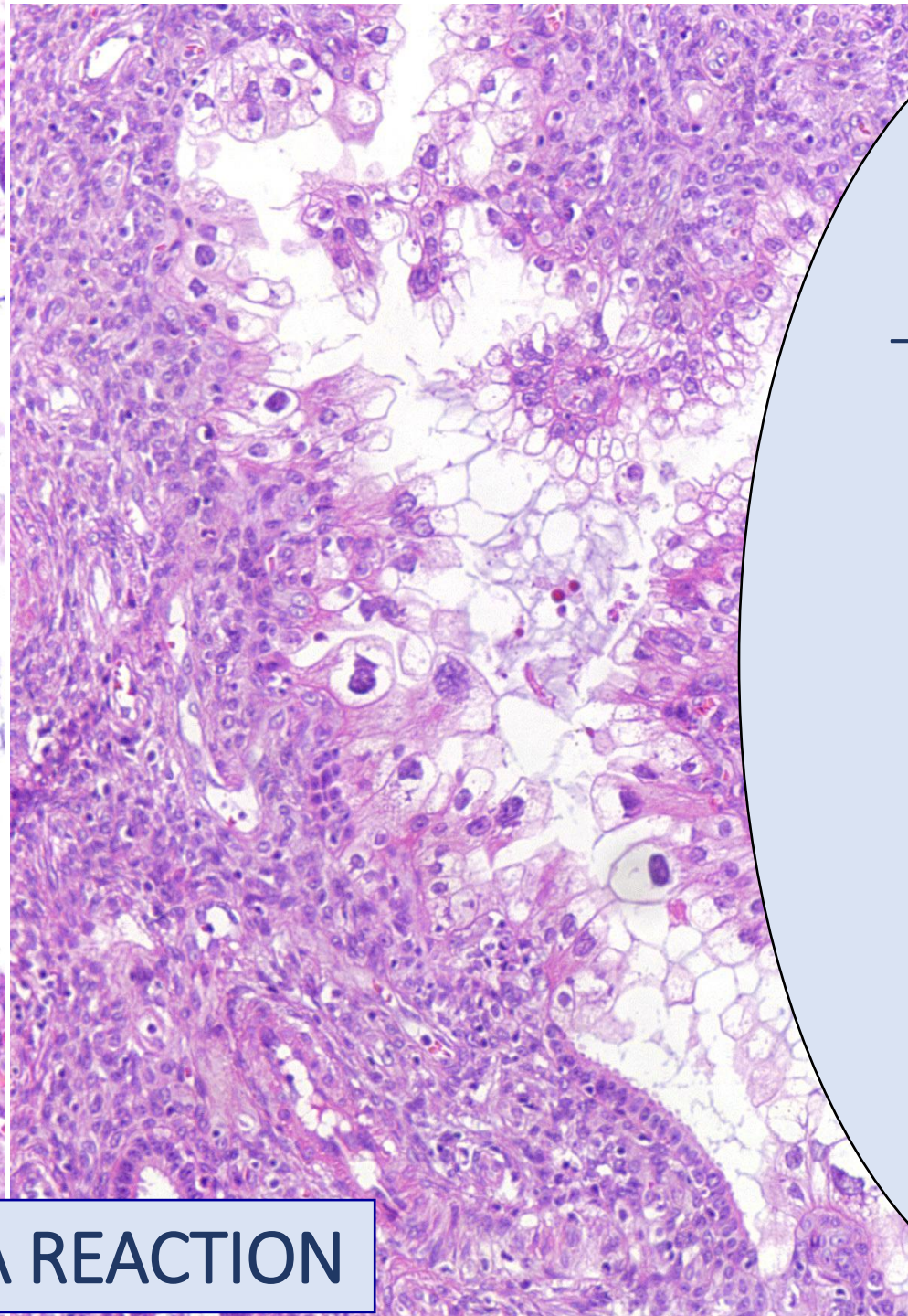
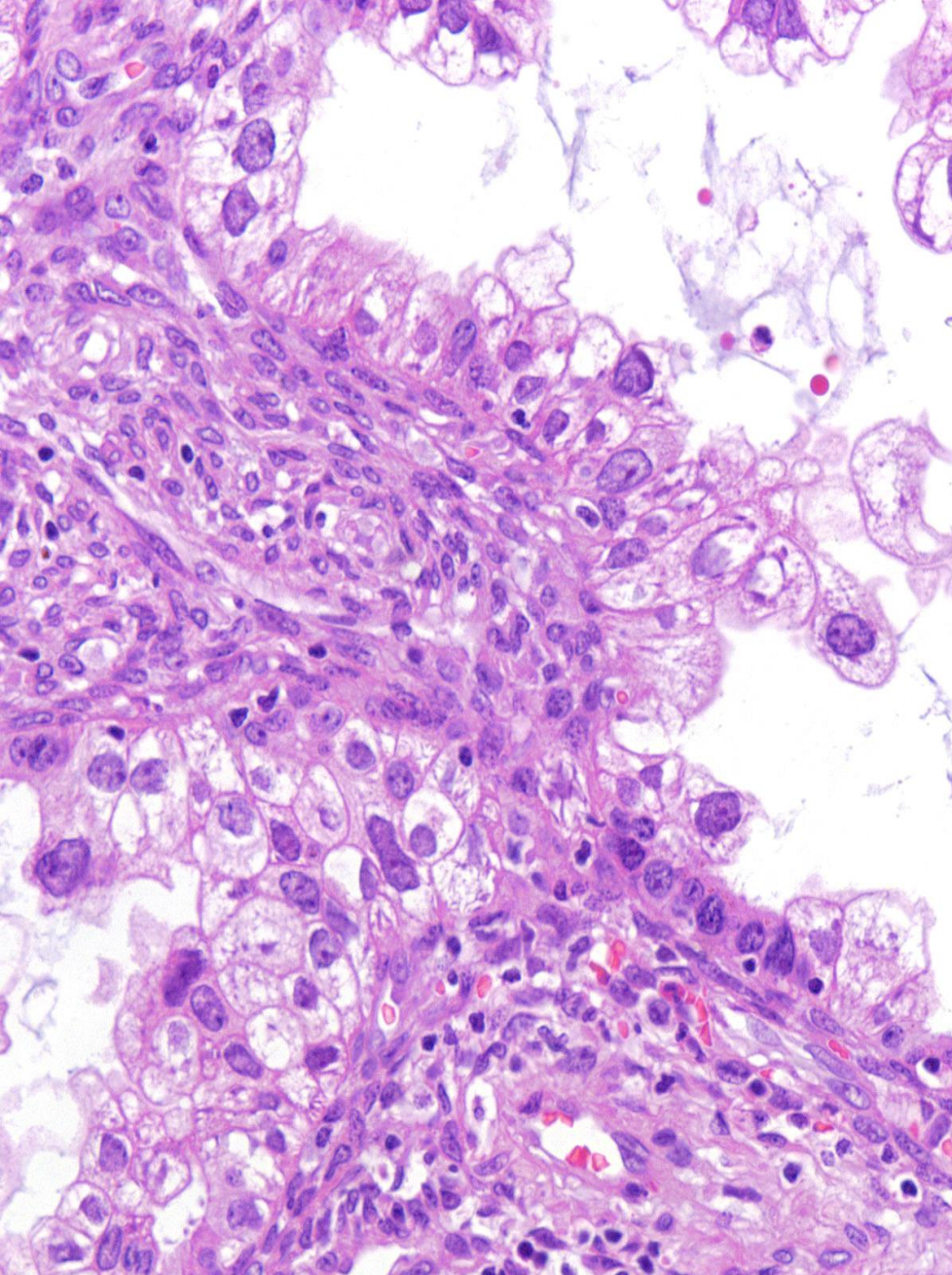
Great variability in number and distribution



ARCHITECTURAL DISTORTION
DUE TO HYALINIZATION

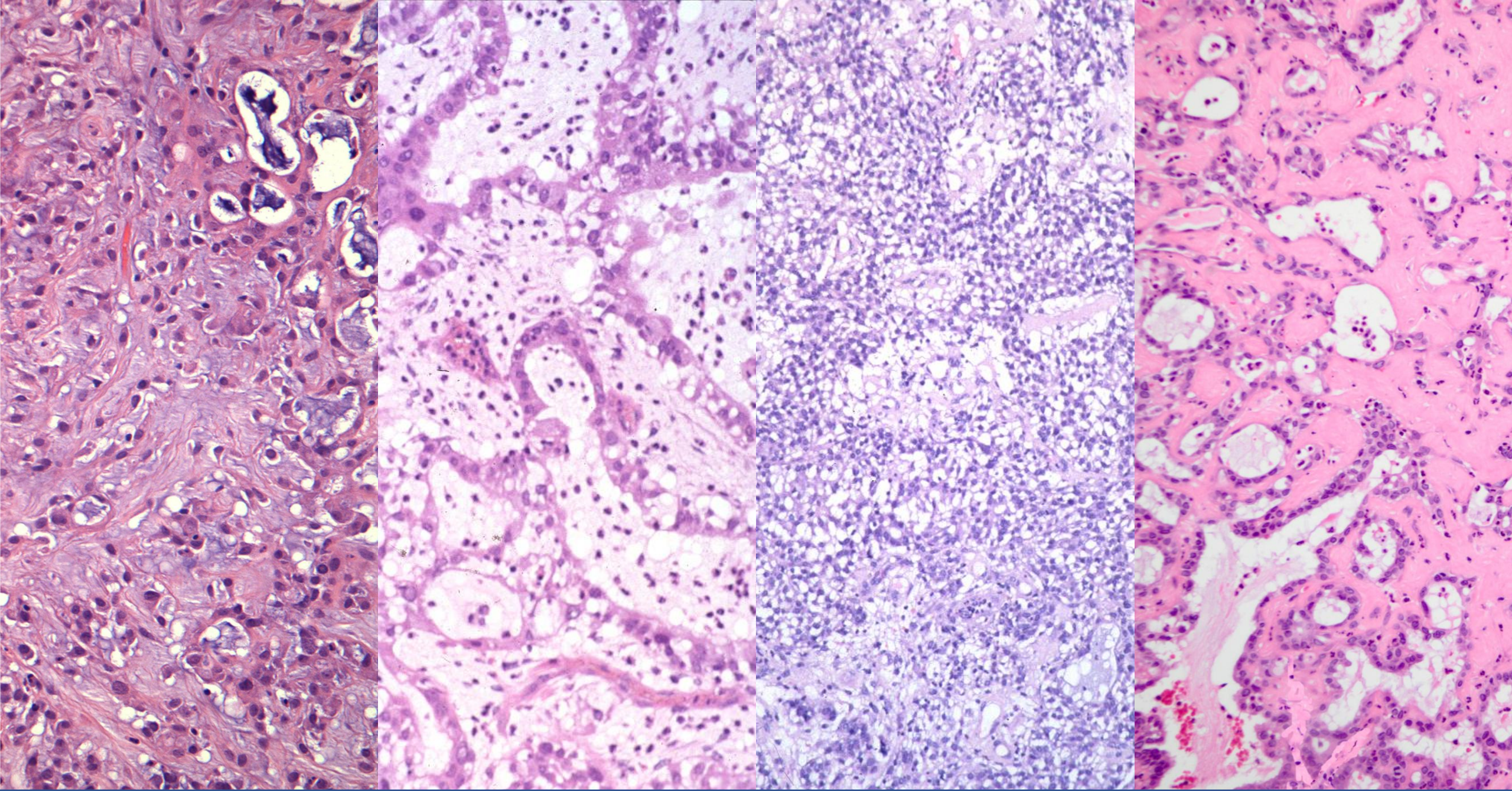
This histological image is split vertically by a white diagonal line. The left side shows normal glandular architecture with well-defined, rounded acini and clear lumens. The right side shows architectural distortion due to hyalinization, where the glandular structures are irregular, fragmented, and surrounded by a dense, pink-stained fibrous stroma. The overall appearance on the right is more disorganized and less cellular than the left side.

DECEPTIVE APPEARANCE

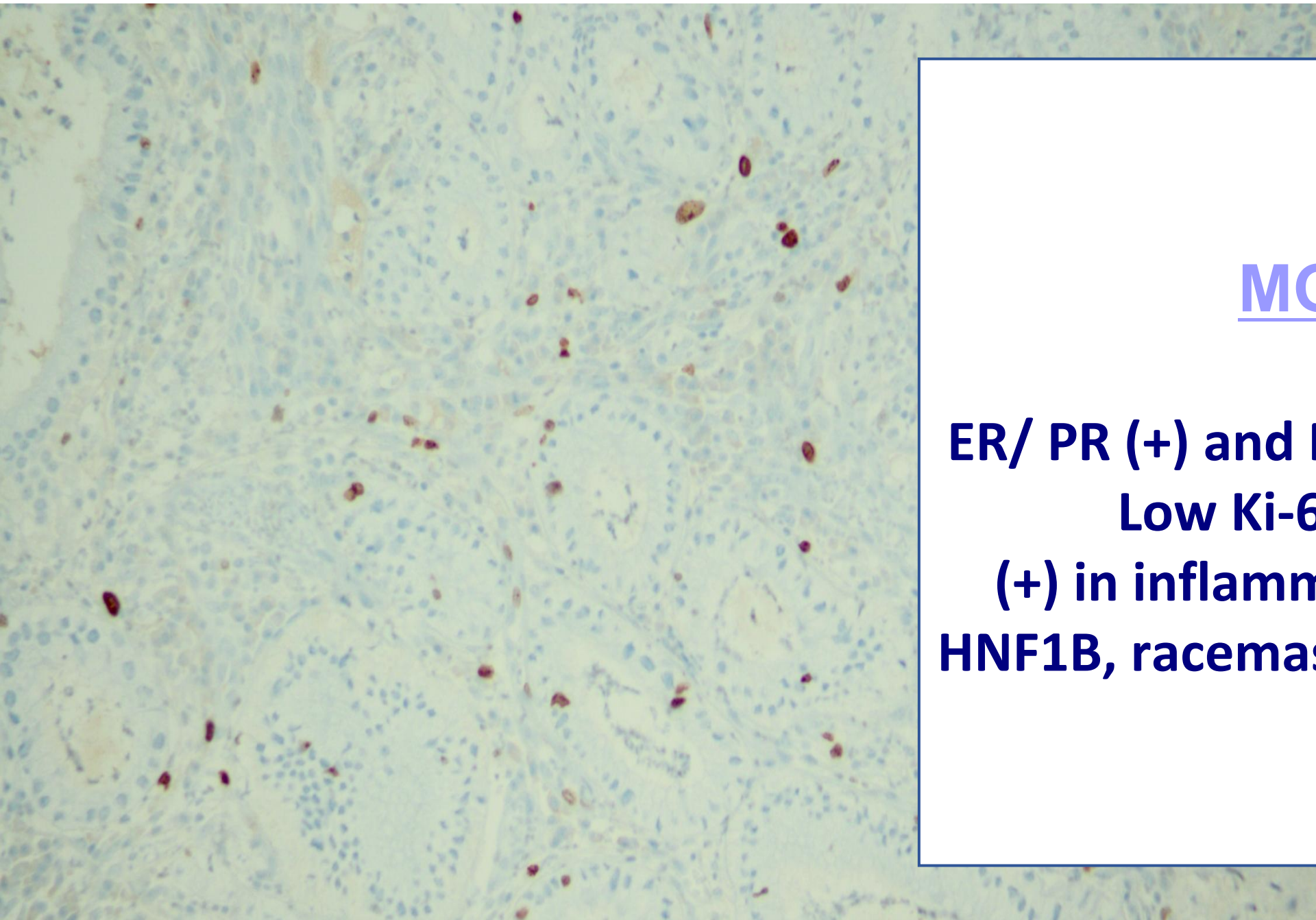


- May occur in post-menopausal women
- History of hormone intake does not always exist

ARIAS STELLA REACTION



UNUSUAL APPEARANCES IN MICROGLANDULAR HYPERPLASIA



MGH

**ER/ PR (+) and PAX2 weakly (+)
Low Ki-67 index;
(+) in inflammatory cells!!!
HNF1B, racemase, and napsin ?**

The diagnosis of microglandular hyperplasia should be made with caution in a postmenopausal woman, particularly if there is cytologic atypia > than usual and morphologic appearance is not typical of this lesion

HNF-1B and Napsin A variably expressed in clear cell carcinoma

Overall, HNF-1b less specific than Napsin A:

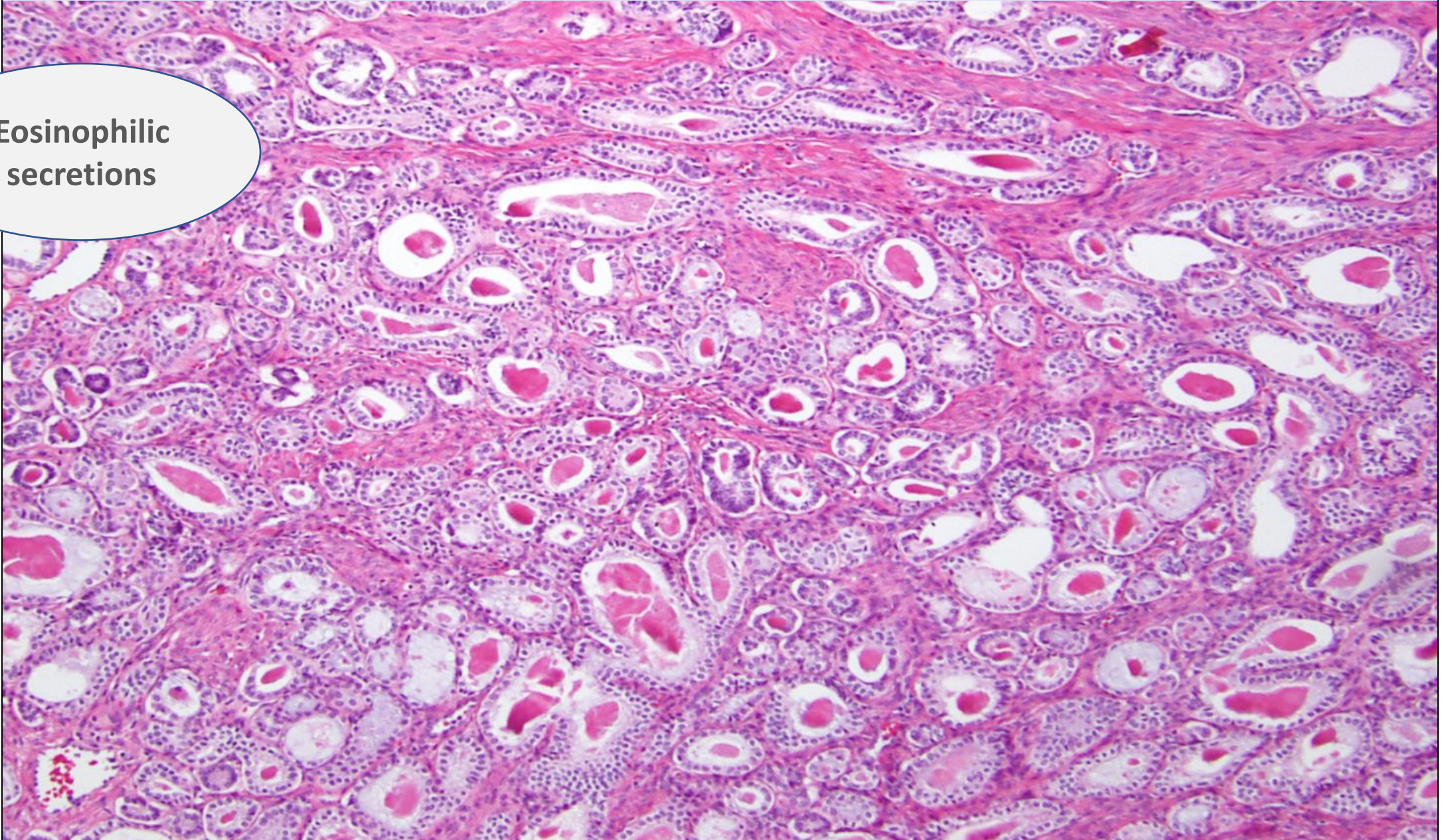
- **HNF-1b ubiquitously expressed in gastric-type and most HPV-adenocarcinomas**
- **Napsin A expressed in 1/4 of gastric-type adenocarcinomas and all intestinal-type HPV adenocarcinomas**
- **p16 may be positive and p53 may be mutant**
- **CEA and CA-IX negative (in contrast to gastric-type adenocarcinoma)**

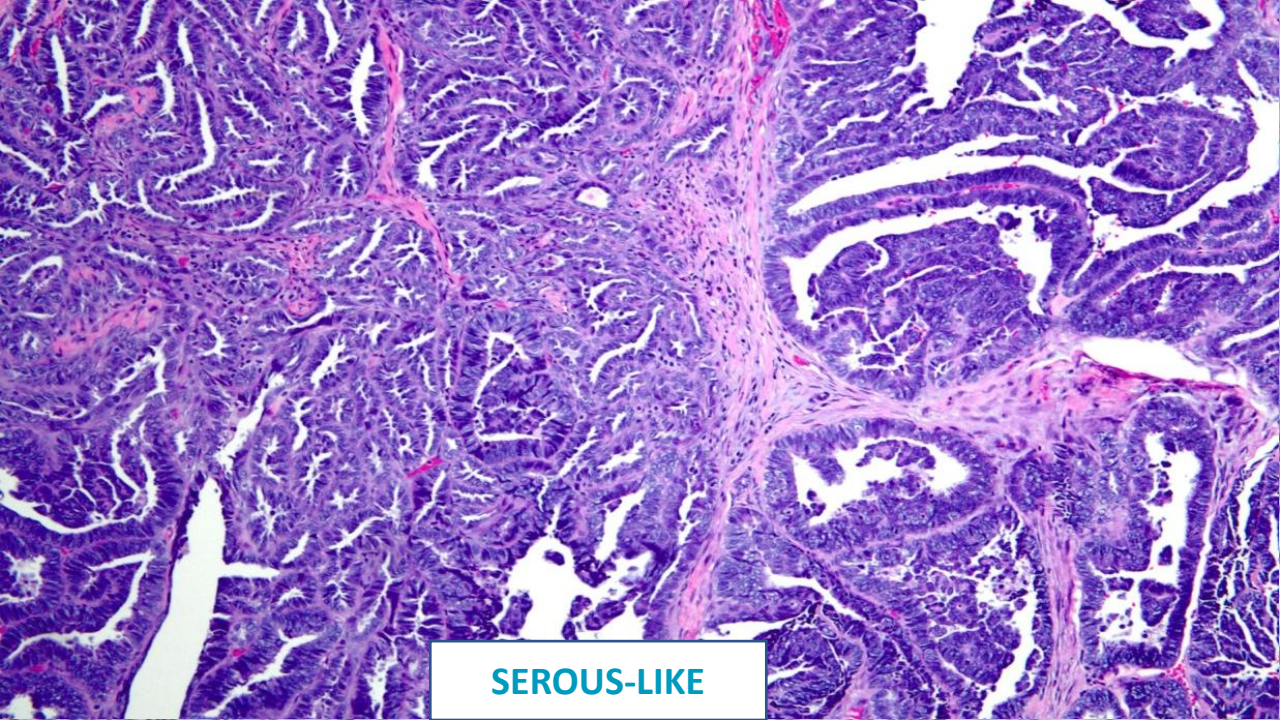
MESONEPHRIC CARCINOMA
<1% of adenocarcinomas
Aggressive behavior

**Pseudoendometrioid/ductal appearance most common;
scant cytoplasm, no intracytoplasmic mucin or squamous differentiation**

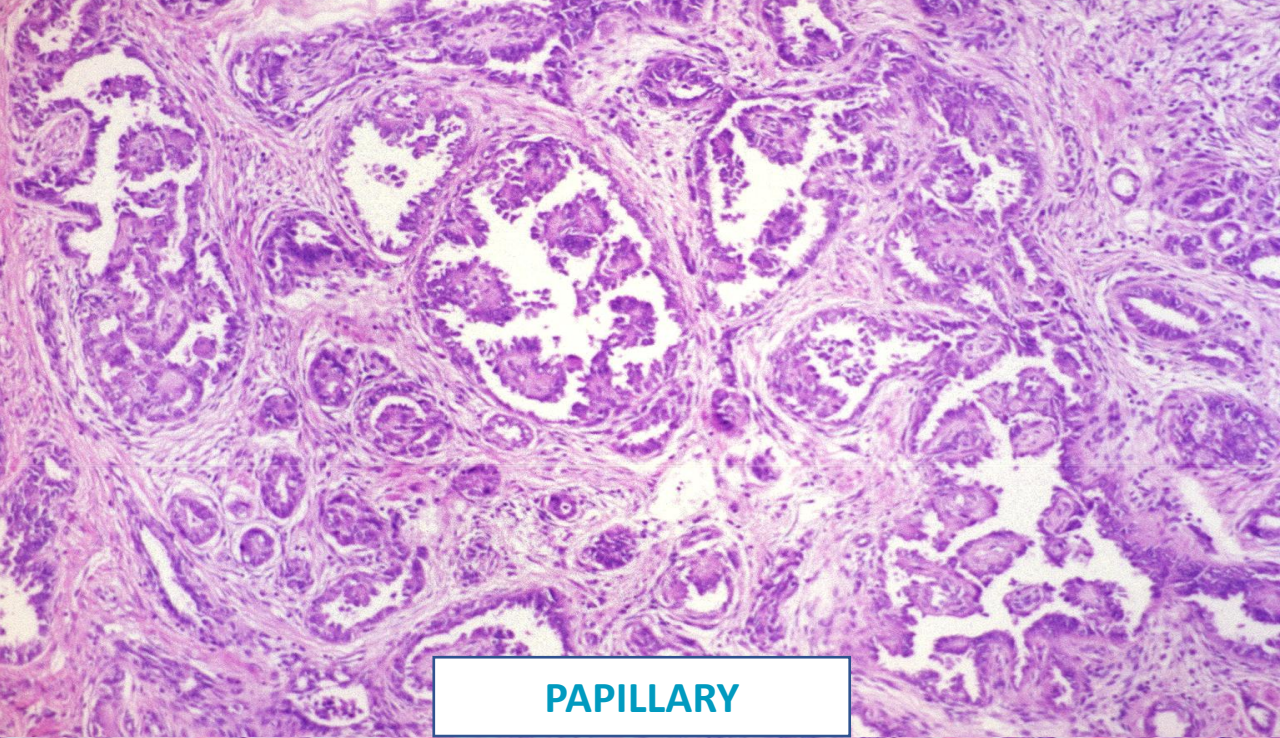
MESONEPHRIC CARCINOMA: Tubular growth

Eosinophilic
secretions

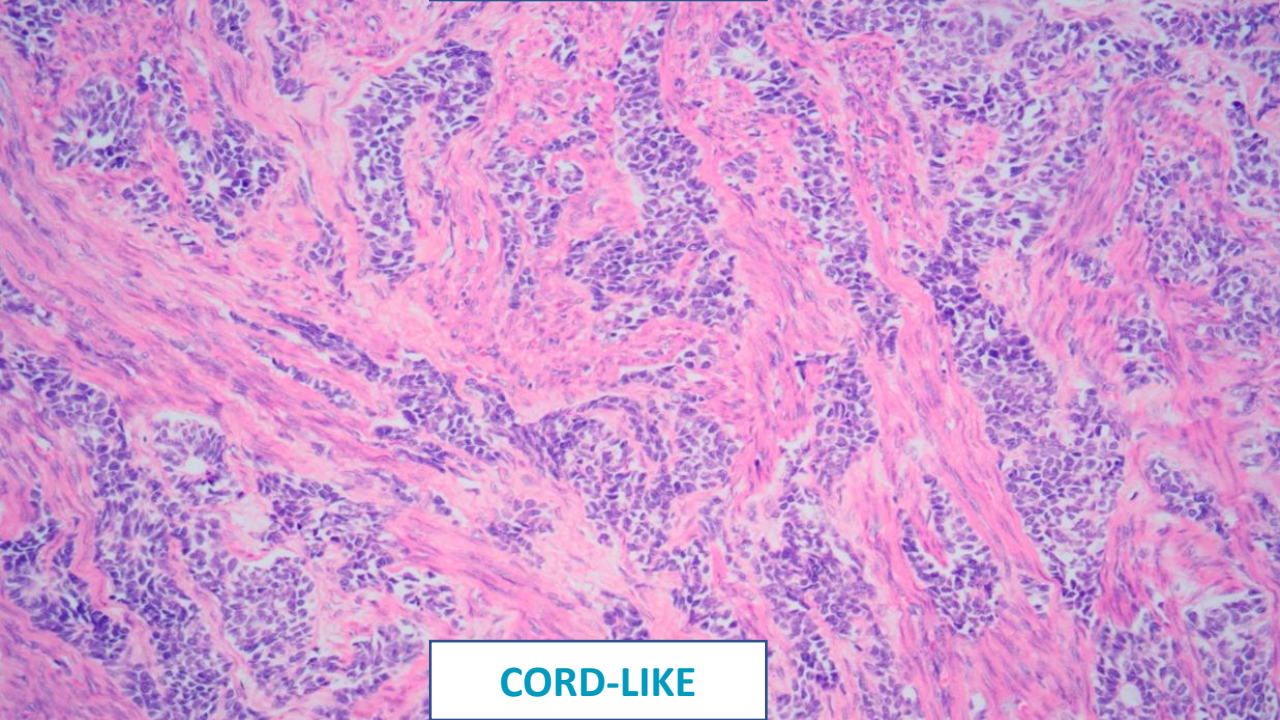




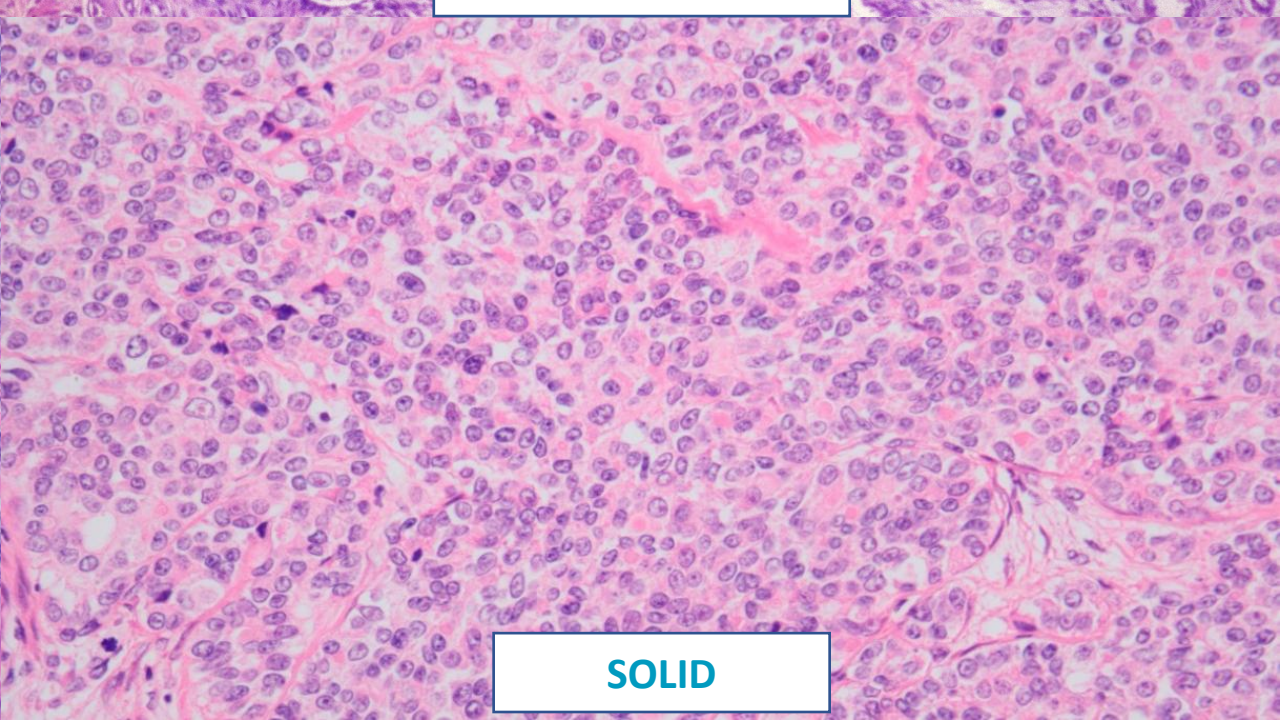
SEROUS-LIKE



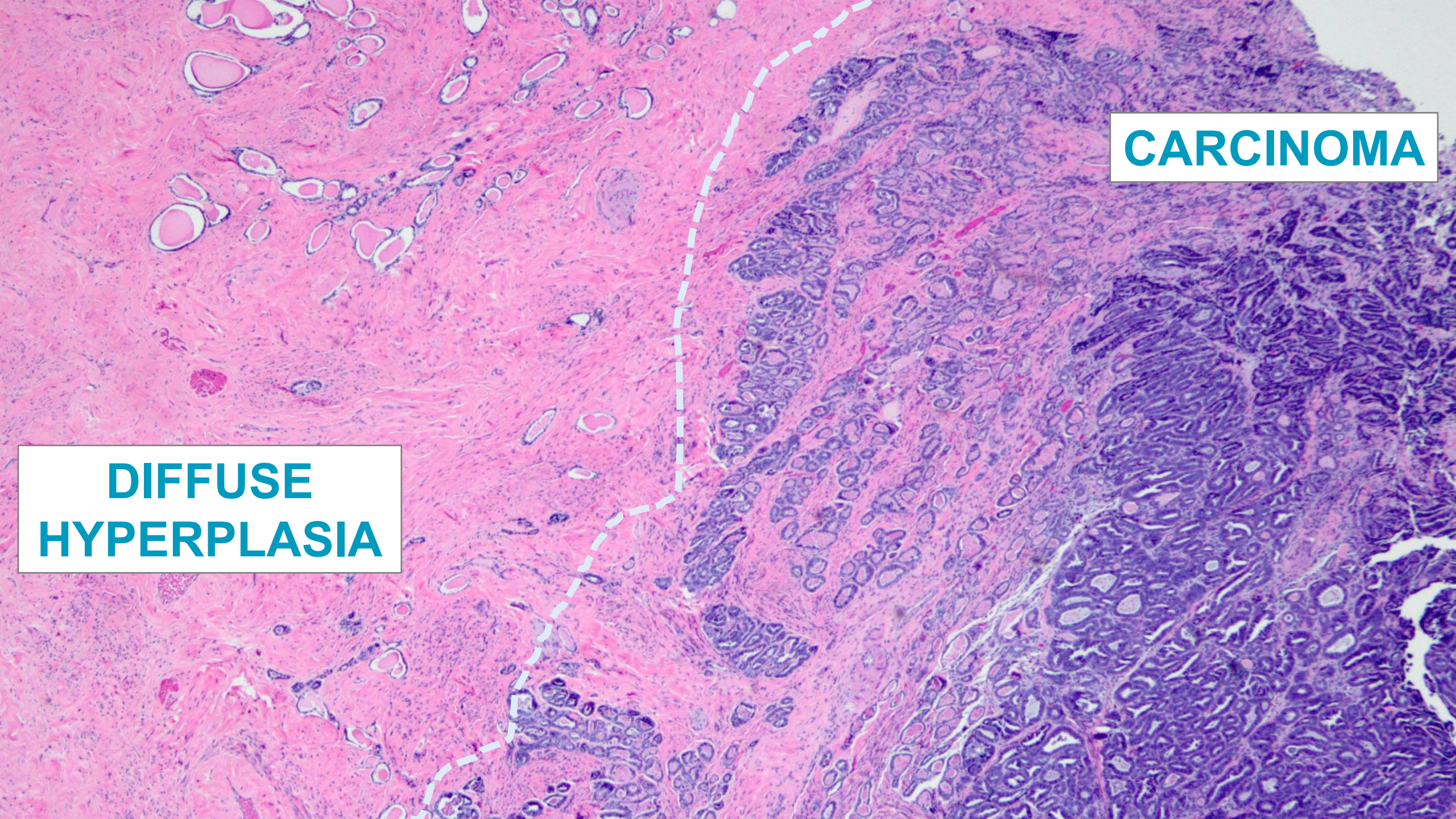
PAPILLARY



CORD-LIKE



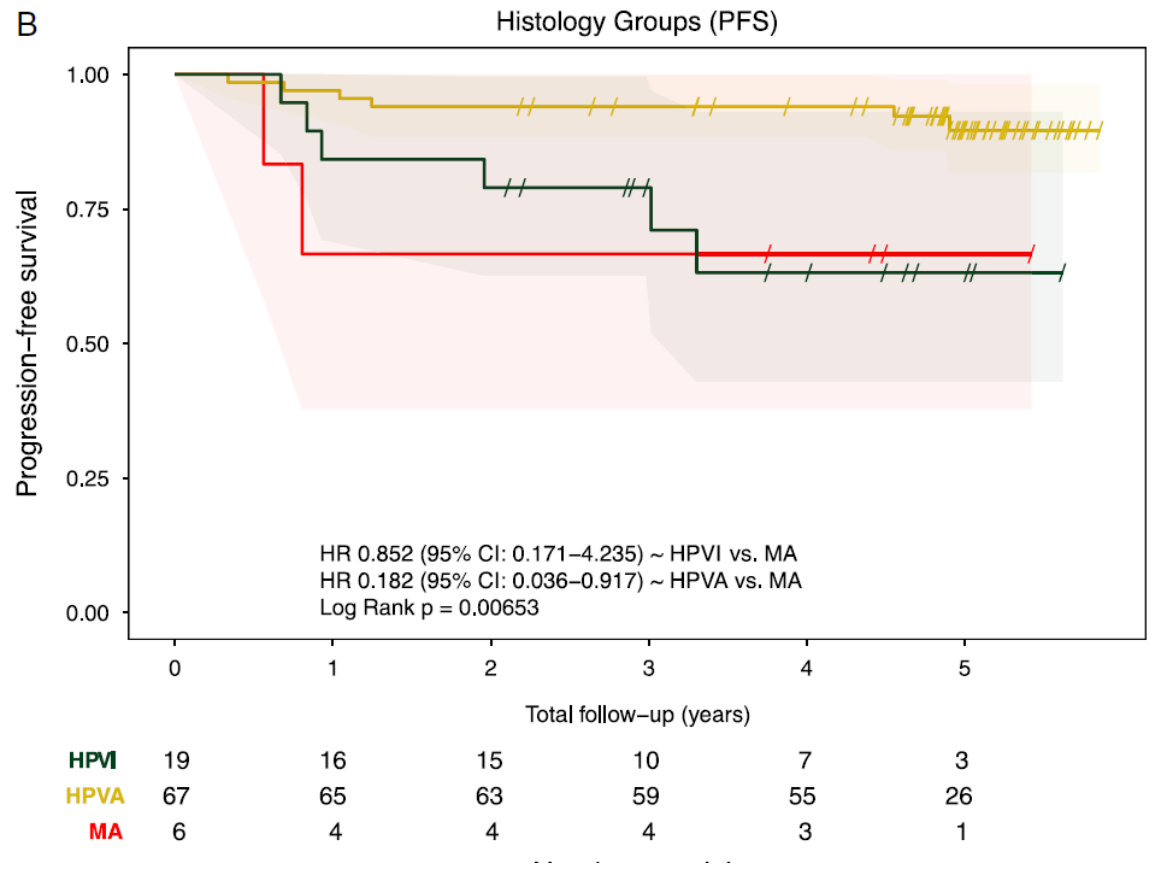
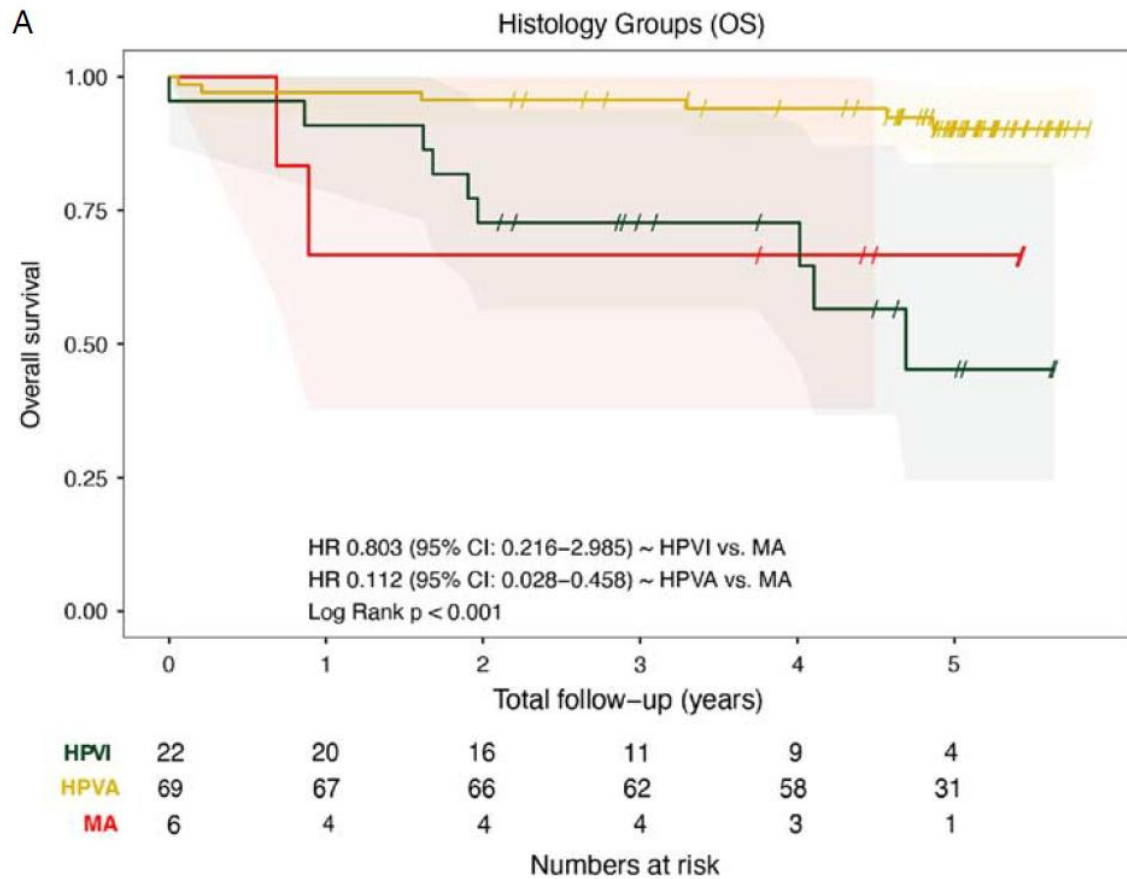
SOLID



A histological slide stained with H&E, showing a transition from diffuse hyperplasia to carcinoma. A dashed white line separates the two regions. The left side shows diffuse hyperplasia with small, uniform glands in a pinkish stroma. The right side shows carcinoma with larger, more complex, and crowded glands in a darker, more cellular stroma.

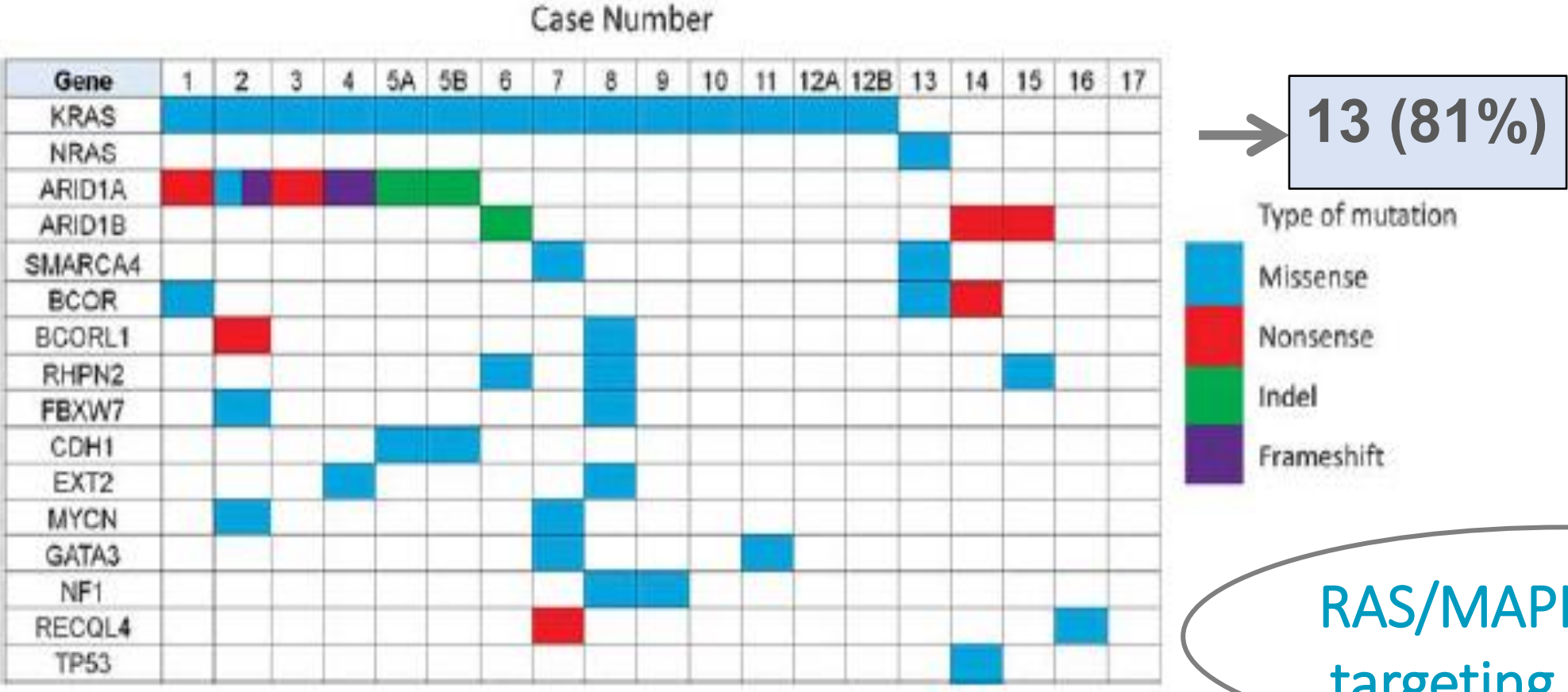
CARCINOMA

**DIFFUSE
HYPERPLASIA**



- Mesonephric carcinomas are associated with outcomes similar to other HPV-independent carcinomas; typically worse than HPV-related adenocarcinomas
- ~50% of patients have recurrences, lung being most common site; other: vagina, abdomen, liver, bowel, omentum

MOLECULAR ALTERATIONS IN MESONEPHRIC TUMORS



No PTEN or PIK3CA mutations

RAS/MAPK pathway
targeting inhibitors

Mirkovic J, Sholl LM, Garcia E, et al. Mod Pathol. 2015;28:1504-14.
da Silva EM, Fix DJ, Sebastiao APM et al. Mod Pathol. 2021 ;34:1570-158

MESONEPHRIC CARCINOMA

Differential Diagnosis

- Mesonephric hyperplasia
- Clear cell carcinoma
- Endometrioid endometrial carcinoma extending to cervix
- Endometrioid adenocarcinoma
- Serous carcinoma
- Uterine tumor resembling ovarian sex-cord tumor

	EEC	Mesonephric Ca
CD10	+	+
AR	+/-	+/-
Calretinin	-/+	+/-
Vimentin	+	+/-
ER	+	-
PR	+	-
p16	-/+	-/+
PAX2	Loss	+
PAX8	+	+
GATA3	- (rarely positive)	+ (may be focal)
TTF1	-/ rare +	-/ rare +

TAKE HOME MESSAGES

- Benign glandular proliferations may mimic either AIS or invasive adenocarcinoma: they show demarcation/lobulation, lack of atypia and desmoplastic reaction
- HPV vs non-HPV classification (apical mitoses and apoptotic bodies with cytoplasmic characteristics as secondary feature) appears more reproducible and prognostically helpful than the old WHO classification
- Primary cervical endometrioid carcinoma rare; most reclassified as HPV usual type
- Before making a diagnosis of endocervical signet-ring cell carcinoma, rule out metastases
- Stratified mucin producing adenocarcinoma often confused with adenosquamous carcinoma
- Gastric adenocarcinoma has a wide array of morphologies and can be p16 positive; do not use the term “adenoma malignum”
- Mesonephric carcinoma can mimic any other adenocarcinoma subtype
- Serous carcinoma of cervix does not exist. Cervical adenocarcinomas may be papillary. If truly serous, origin should be sought from upper gynecologic tract

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MASSACHUSETTS GENERAL HOSPITAL



THANK YOU!



THANK YOU!

Remember...

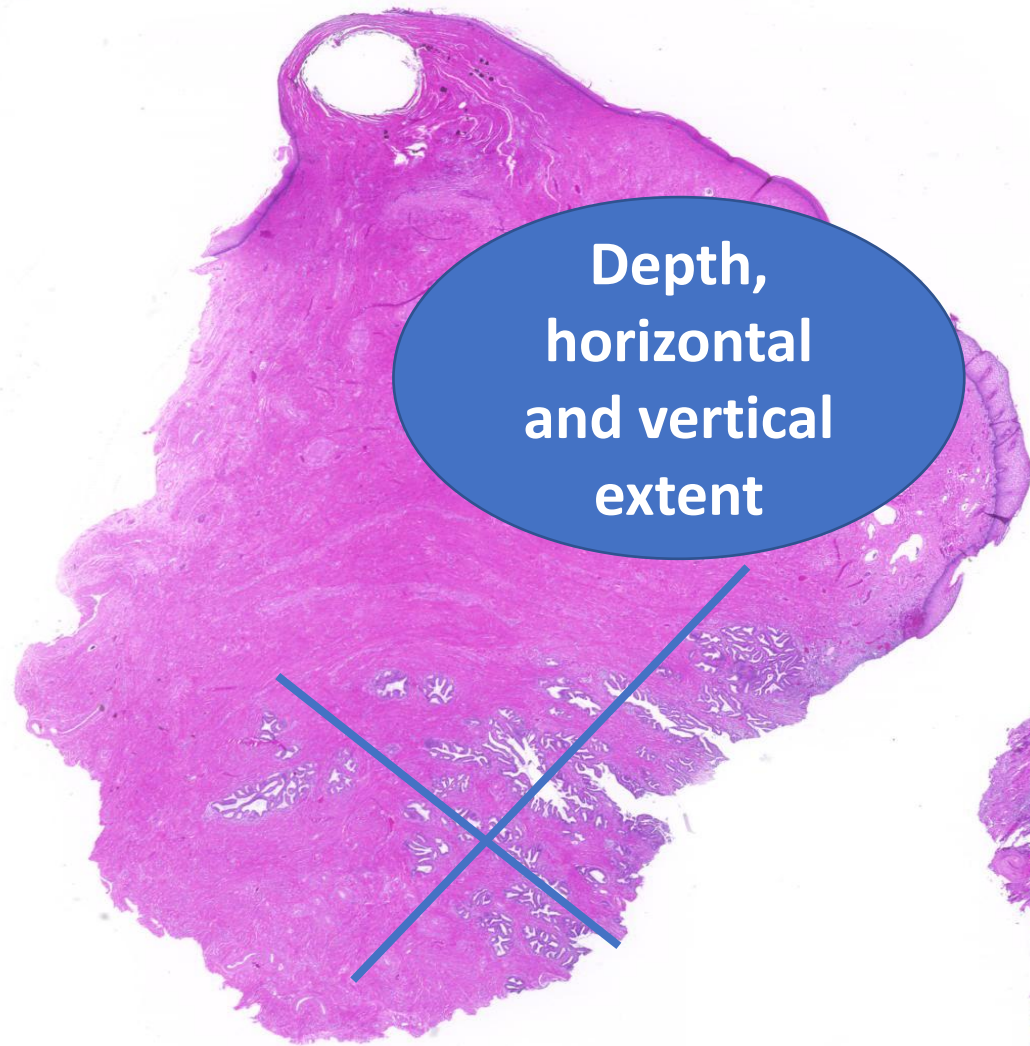
- **PAX8, CD10, p16, calretinin- not helpful to separate mesonephric lesions from EEC extending to cervix**
- **Vimentin and HNF1B may be + in mesonephric lesions**
- **GATA3 only rarely positive in EEC but in ~10% of usual type endocervical adenocarcinoma**

CERVICAL CARCINOMA

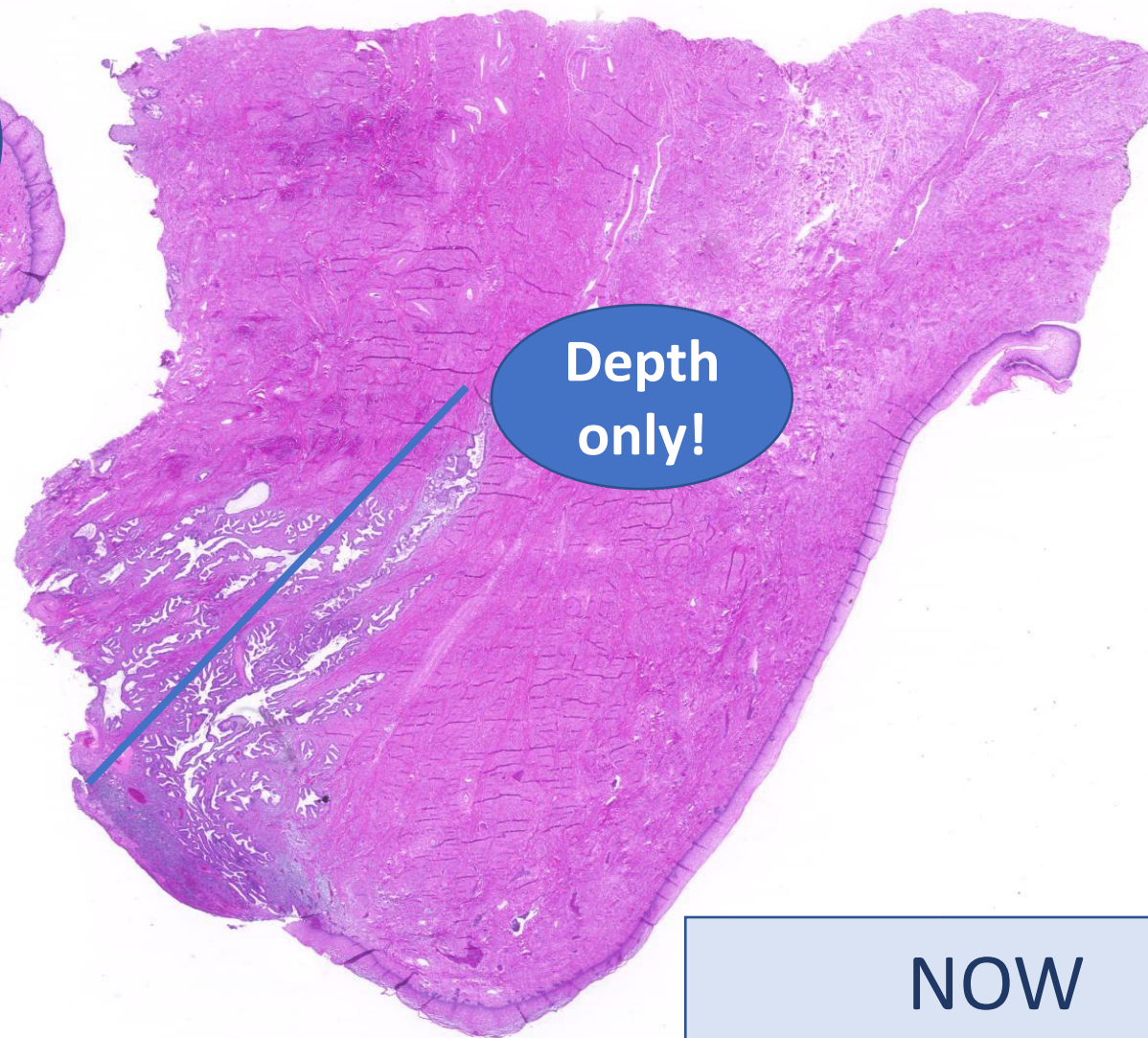
2018 FIGO STAGING SYSTEM CHANGES

STAGE IA- MAJOR CHANGES

- Horizontal/vertical dimensions no longer used in defining Stage IA carcinoma, only depth of invasion ($<3\text{mm} = \text{IA1}$; $\geq 3\text{mm}$ and up to $<5\text{ mm} = \text{IA2}$)
- Stage IA1 and IA2 carcinomas diagnosed on microscopic examination of surgical specimen, which should include entire tumor. Margins of an excision specimen should be reported as negative for invasive carcinoma
- If positive margins in cone biopsy, patient should be re-evaluated before a stage is given



BEFORE



NOW

CERVICAL CARCINOMA: 2018 FIGO STAGING SYSTEM CHANGES

STAGE IB – NEW CATEGORY

- Sub-divided into IB1, IB2 and IB3 based on maximum tumour size

IB1: Invasive carcinoma $\geq$ 5mm depth of invasion and size < 2 cm

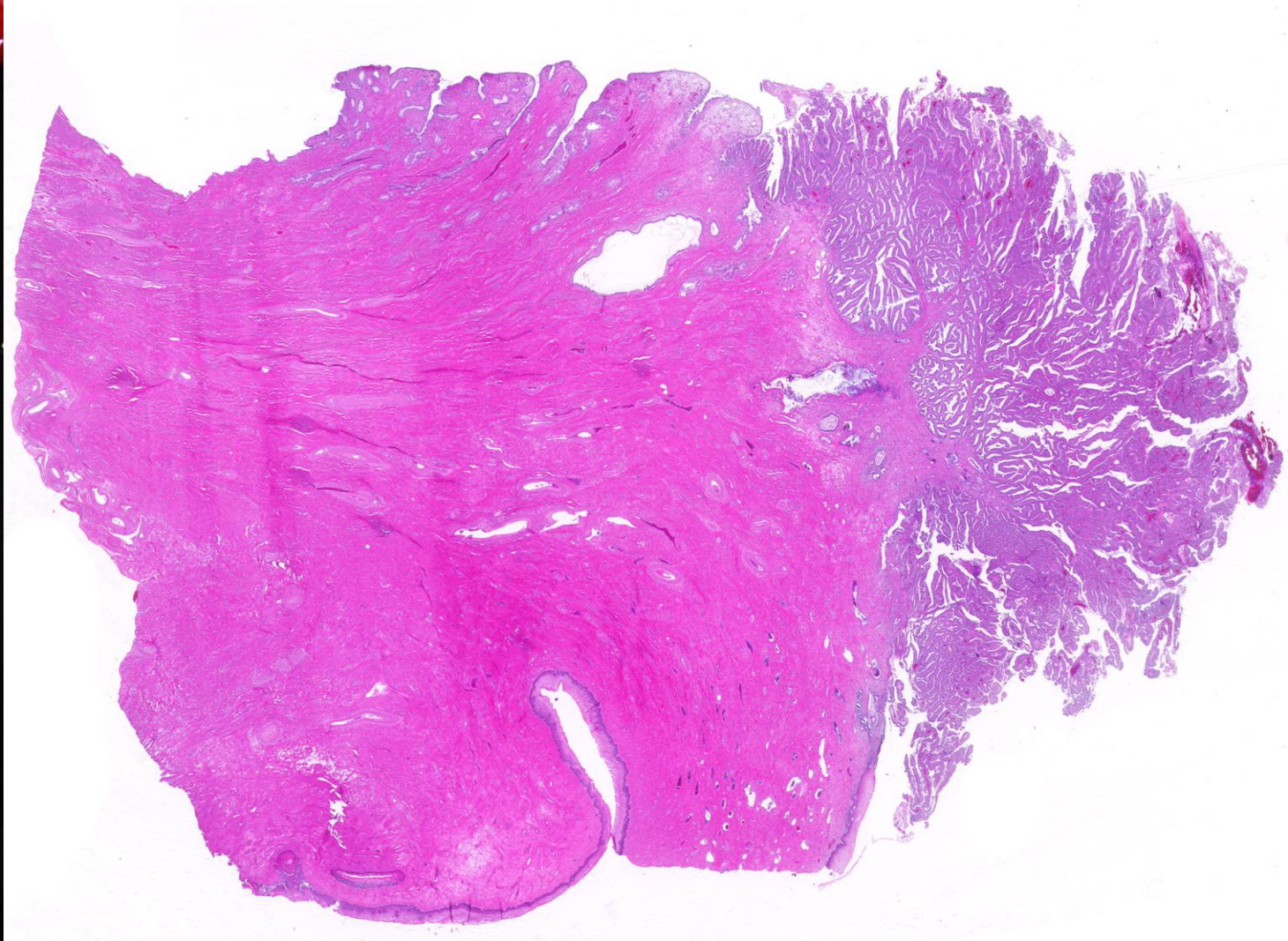
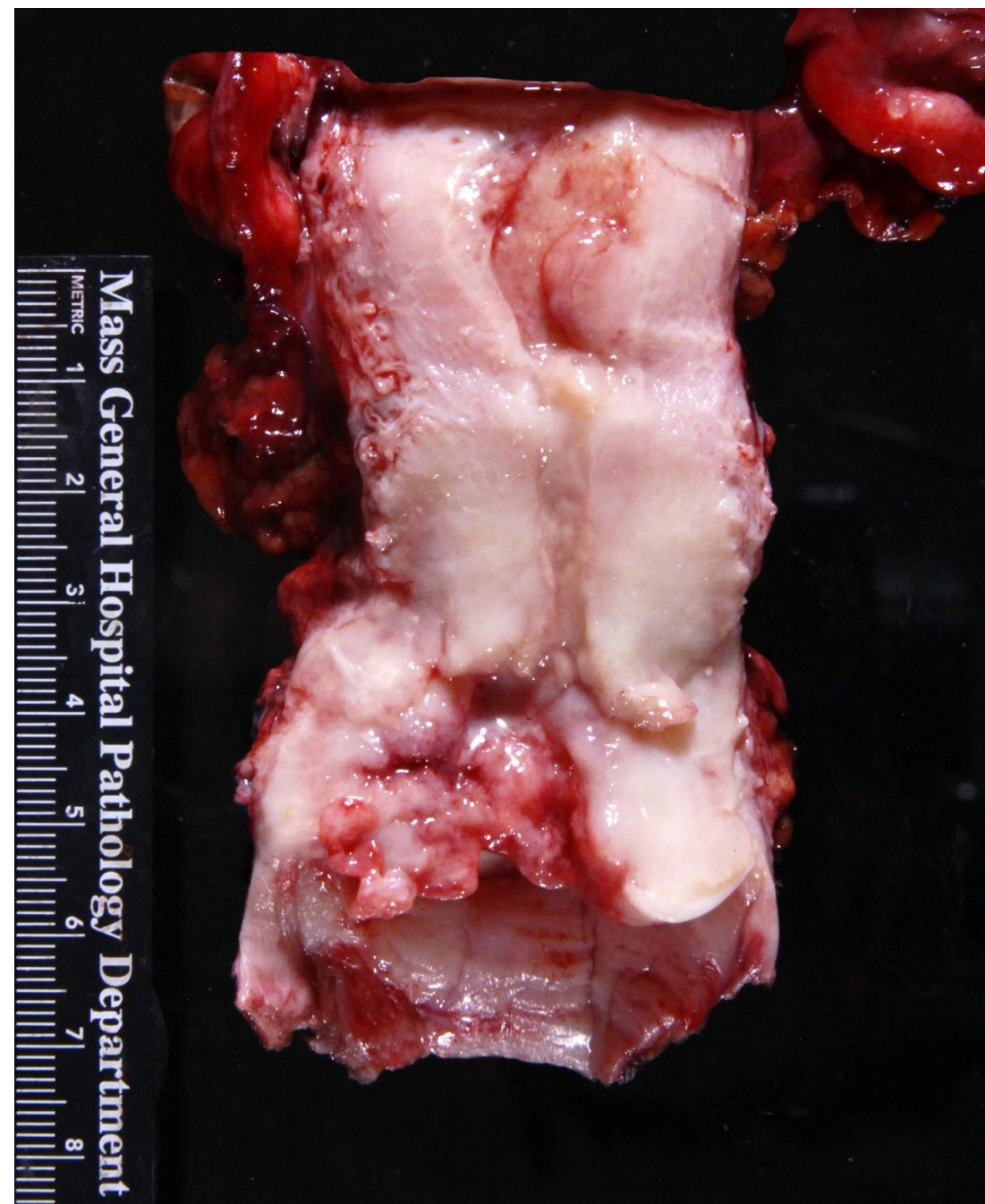
IB2: Invasive carcinoma ≥ 2 cm and < 4 cm

IB3: Invasive carcinoma ≥ 4 cm

Clinical correlation of lymphovascular invasion and Silva pattern of invasion in early-stage endocervical adenocarcinoma: proposed binary Silva classification system

Stolnicu S, et al, Pathology 2022;54:548-54

- Silva pattern and lymphovascular invasion important prognostic factors in stage IA1–IB1 endocervical adenocarcinomas and can supplement 2019 International Federation of Gynecology and Obstetrics staging system
- A binary Silva classification system subdivides patients into two categories:
 - low risk (patterns A and B without lymphovascular invasion)
 - high risk (pattern B with lymphovascular invasion and pattern C)
- Lymphovascular invasion only variable with statistically significant association with stage IA2 versus IA1



**Polypoid tumor >20mm and or < or equal 40 mm-
STAGE IB2 regardless of thickness or depth of invasion**

CERVICAL CARCINOMA: 2018 FIGO STAGING SYSTEM CHANGES

STAGE IIA

Involvement limited to vaginal upper two thirds without parametrial involvement

IIA1: Invasive carcinoma < 4cm

IIA2: Invasive carcinoma ≥ 4 cm

STAGE IIB: No changes

STAGE IIIA and IIIB: No changes

STAGE IIIC - NEW CATEGORY

Nodal involvement in any size tumour upstaging it to IIIC

IIIC1 – pelvic positive nodes

IIIC2 - para-aortic positive nodes

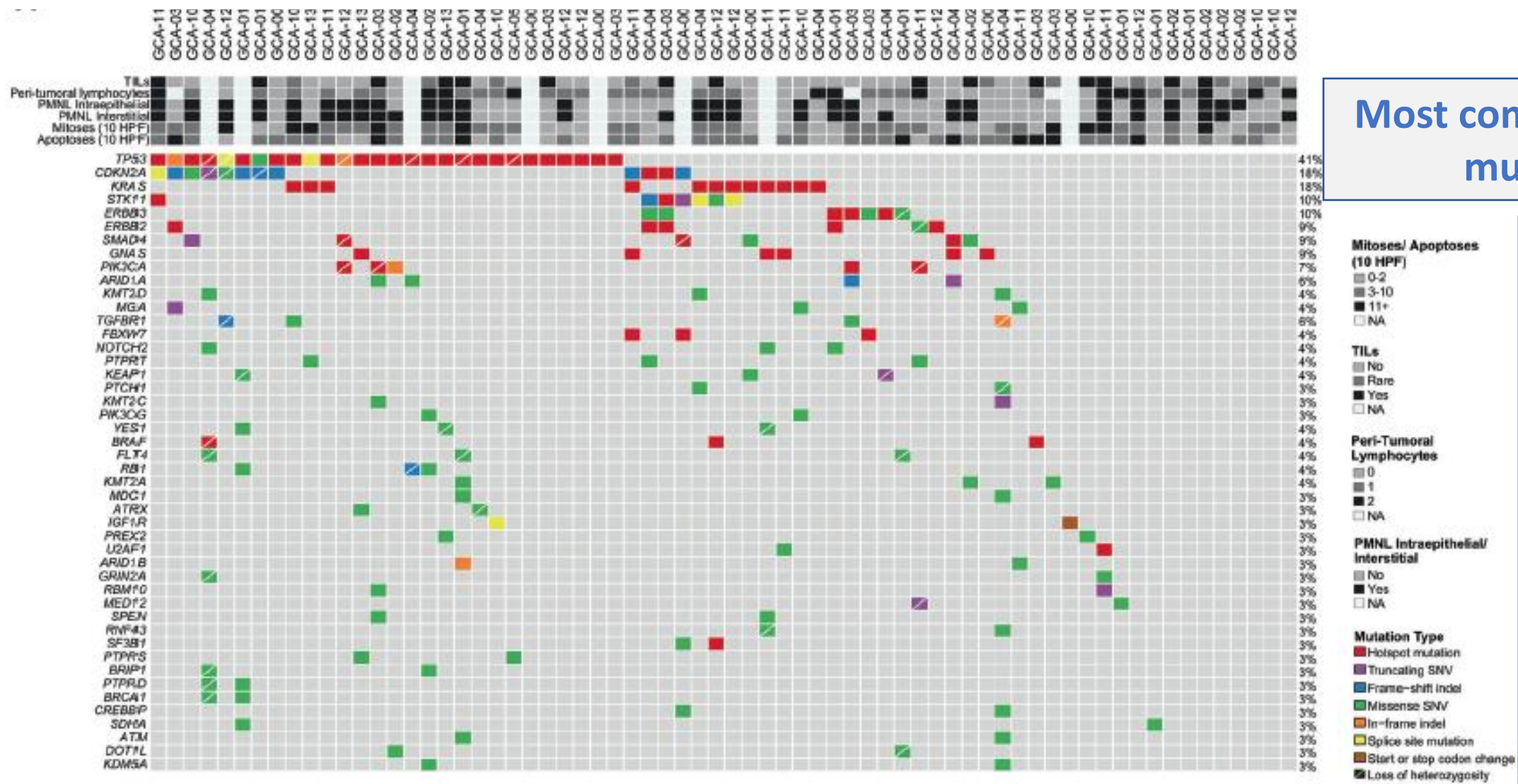
STAGE IV: No changes

CERVICAL CARCINOMA: 2018 FIGO STAGING SYSTEM CHANGES

- Do not use term “microinvasive” adenocarcinoma
- Lymphovascular invasion must be reported even though does not affect FIGO stage; although quantification has not been evaluated, it may be helpful
- Revised FIGO classification more closely aligned with TNM classification system

Massively parallel sequencing analysis of 68 gastric-type cervical adenocarcinomas reveals mutations in cell cycle-related genes and potentially targetable mutations

Selenica P, Alemar B, Matrai C, et al. Mod Pathol. 2021; 34:1213-1225



Most common somatic mutations:

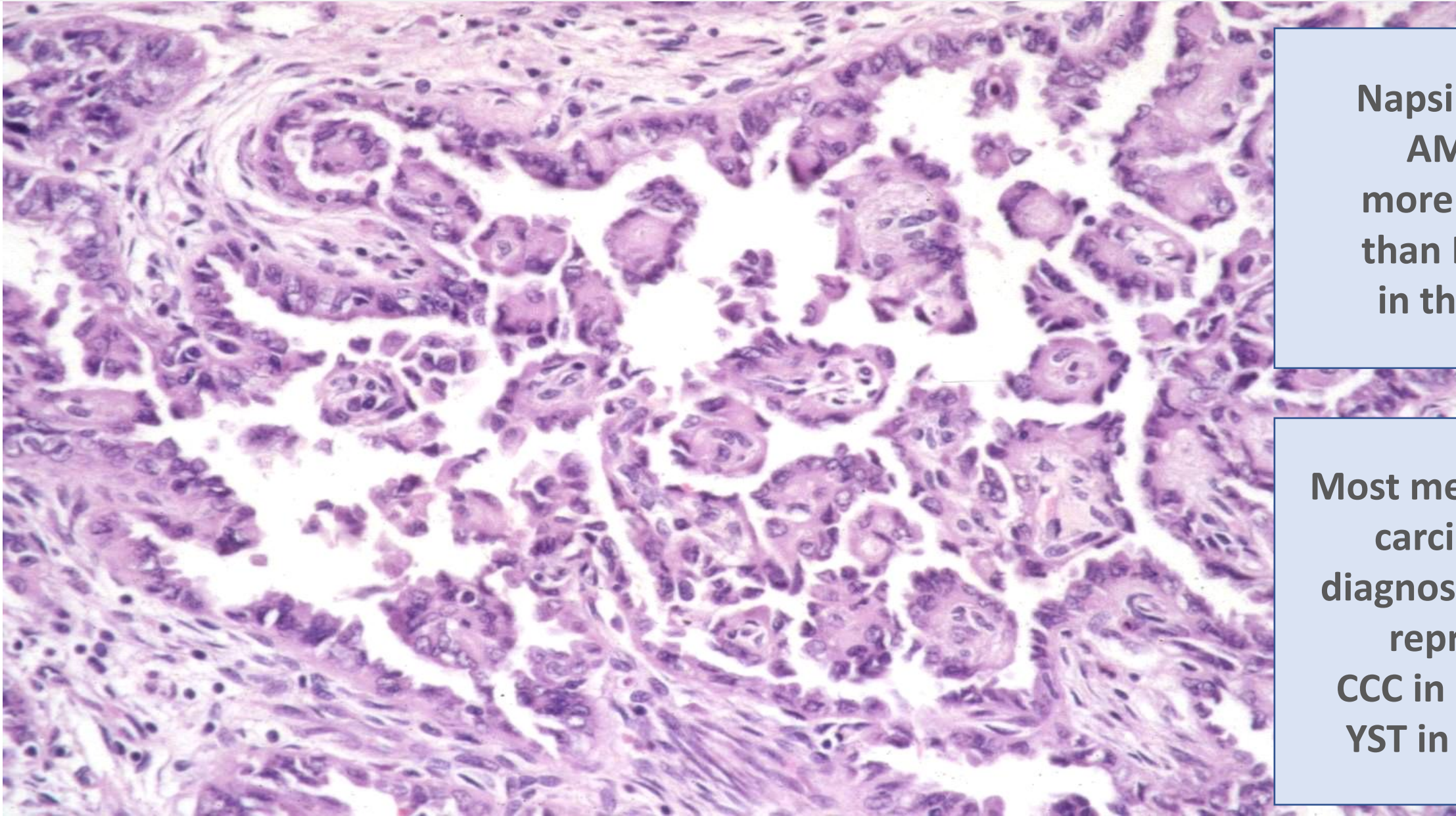
p53
CDKN2A
KRAS
STK11
.
.
ERBB3/2
and BRAF

MESONEPHRIC HYPERPLASIA *vs* CARCINOMA

- No clinical manifestations
- Predominance of small tubules
- +/- lobular arrangement
- Absent malignant nuclear features
- Lack of stromal response

MESONEPHRIC CARCINOMA:

Papillary growth/hobnail cells may mimic CCC

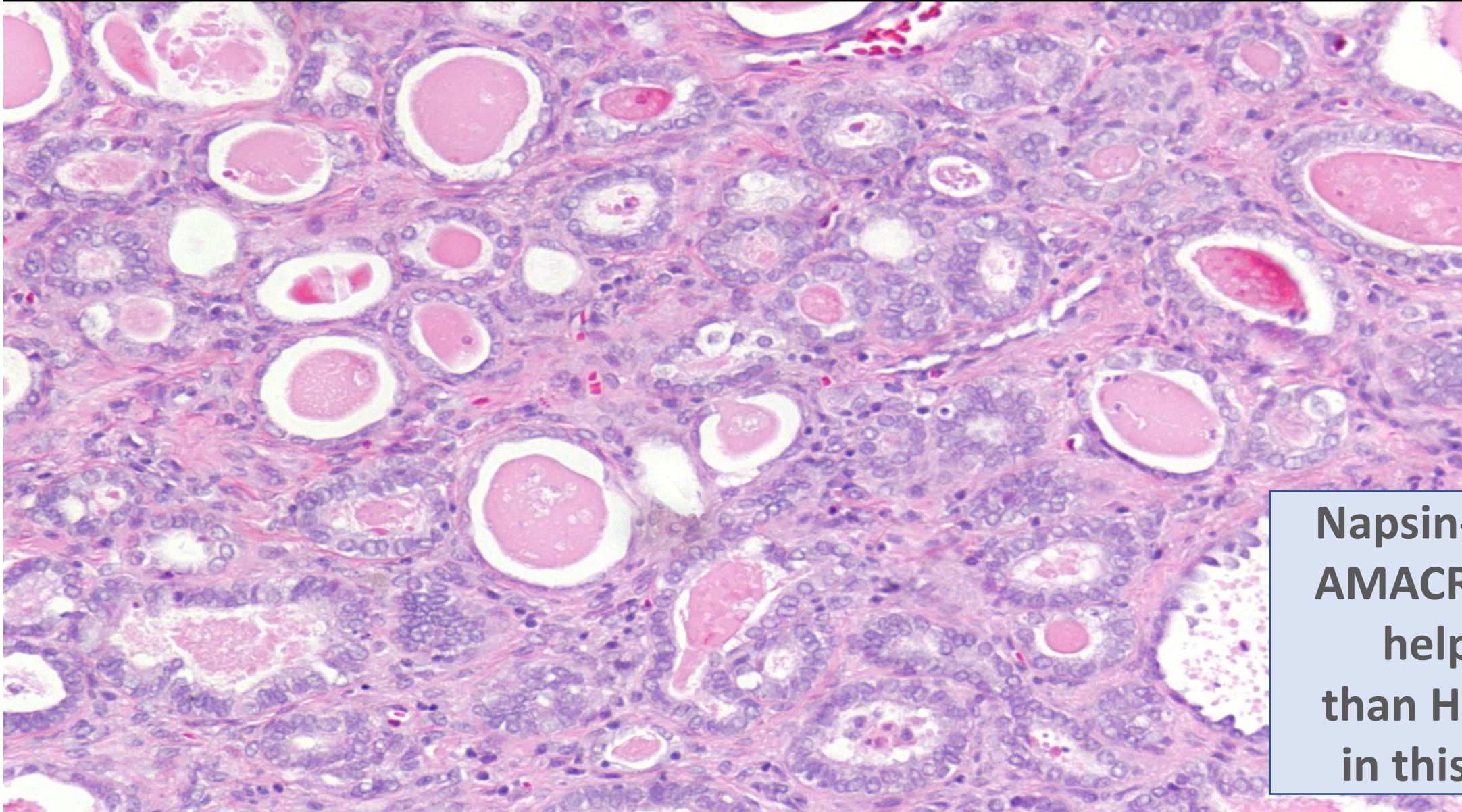


Napsin-A and
AMACR
more helpful
than HNF-1 β
in this DDX

Most mesonephric
carcinomas
diagnosed in past
represent
CCC in adults or
YST in children

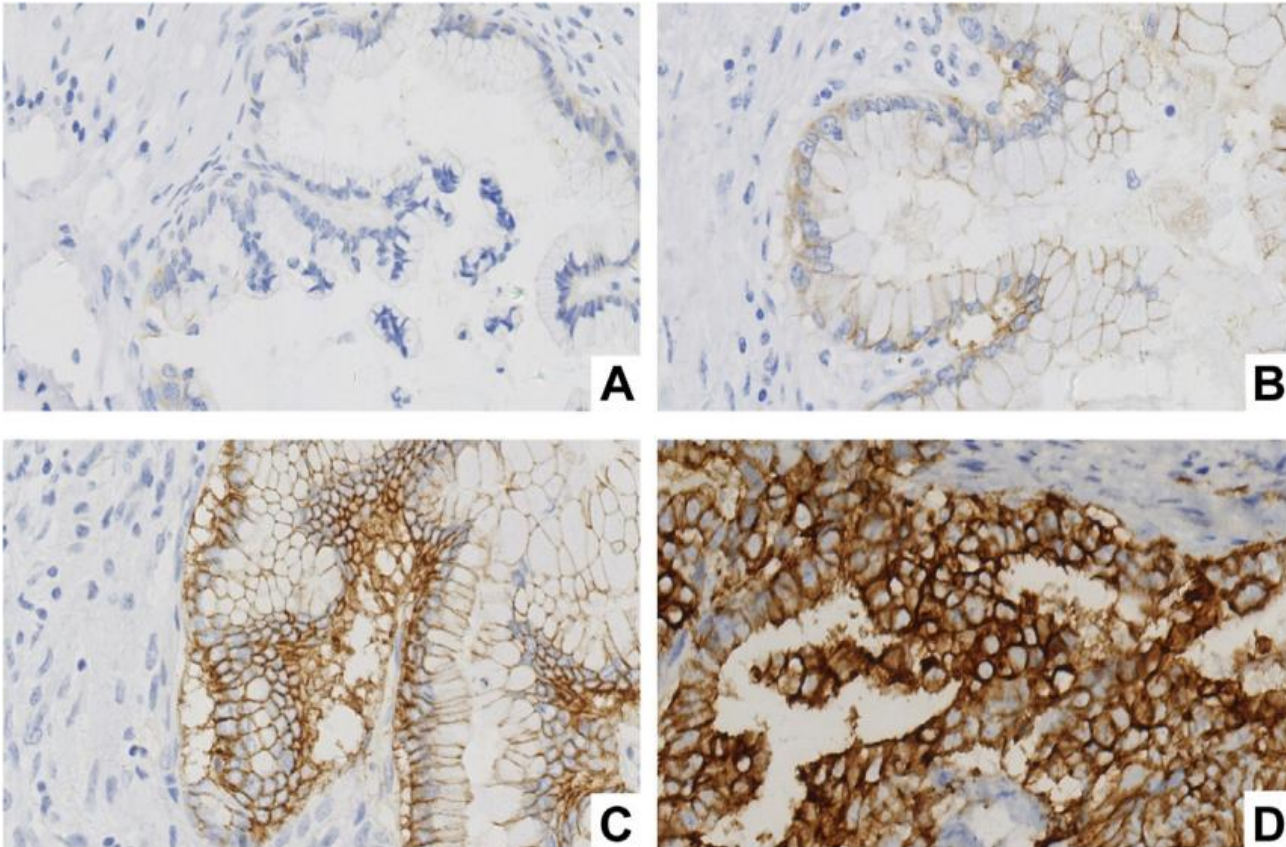
MESONEPHRIC CARCINOMA:

Tubulocystic growth may mimic Clear Cell Carcinoma



Napsin-A and
AMACR more
helpful
than HNF-1 β
in this DDX

CLDN18.2 as predictive biomarker



Zolbetuximab

- Anti-CLDN18.2 monoclonal antibody approved for gastric and gastroesophageal adenocarcinoma
- Companion diagnostic IHC: Positive: 2+/3+ in $\geq 75\%$ of tumor
- Studies with non-companion diagnostic monoclonal anti-CLDN18.2 in GAS:
 - Xi et al: 44.3%
 - Yang et al: 48.4%
 - Zhong et al: $\sim 22.2\%$ (score >6)

Zhong F et al. Hum Pathol. 2025;160:105837

Yang J et al. Mod Pathol. 2024;37:100569

Xi Y et al. Ther Adv Med Oncol. 2025 PMID: 40755833