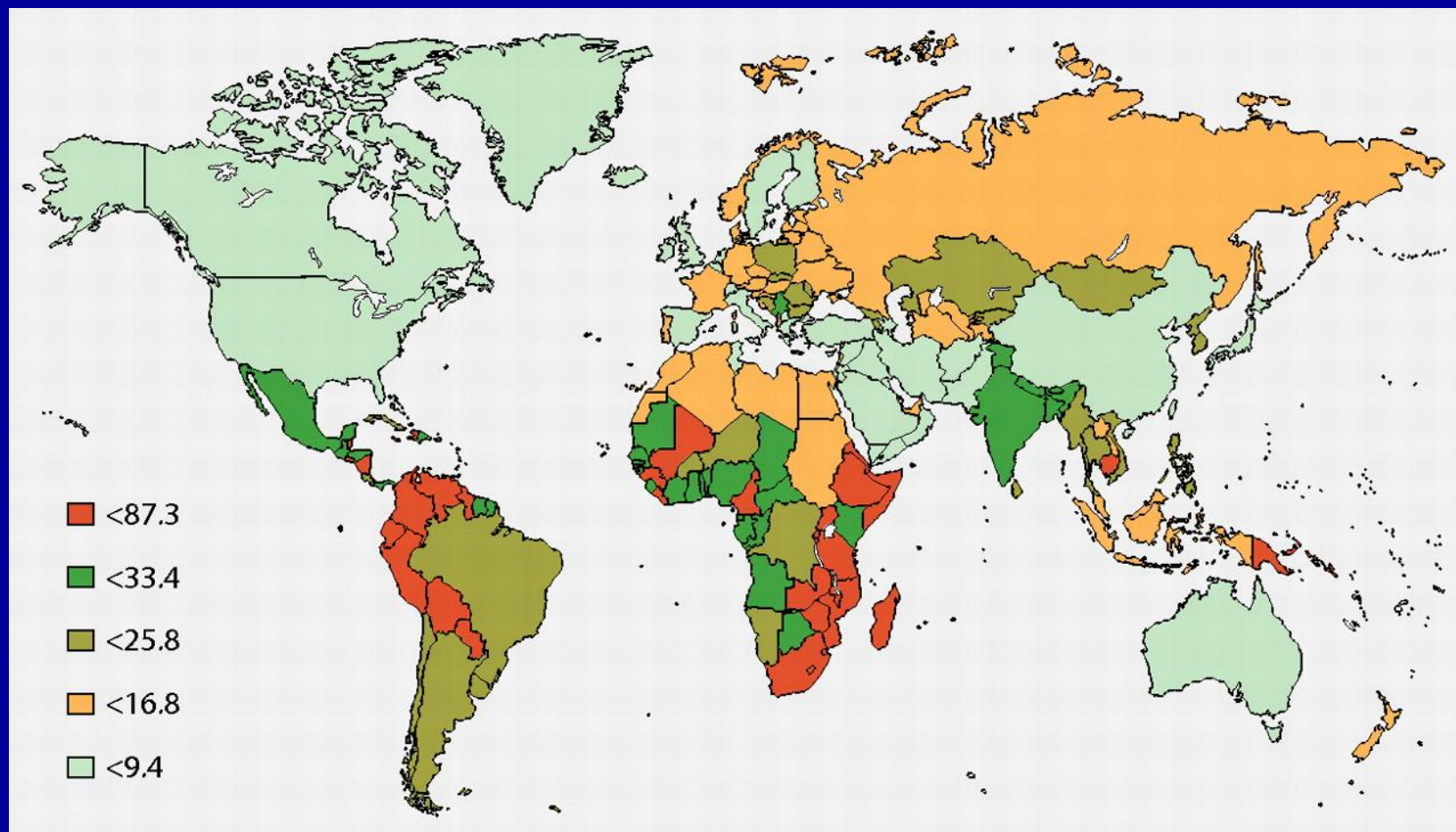


In situ and Invasive Endocervical Carcinoma: Problems and Pitfalls in Diagnosis

Rouba Ali-Fehmi,MD

**The Karmanos Cancer Institute,
*Wayne State University School of Medicine***

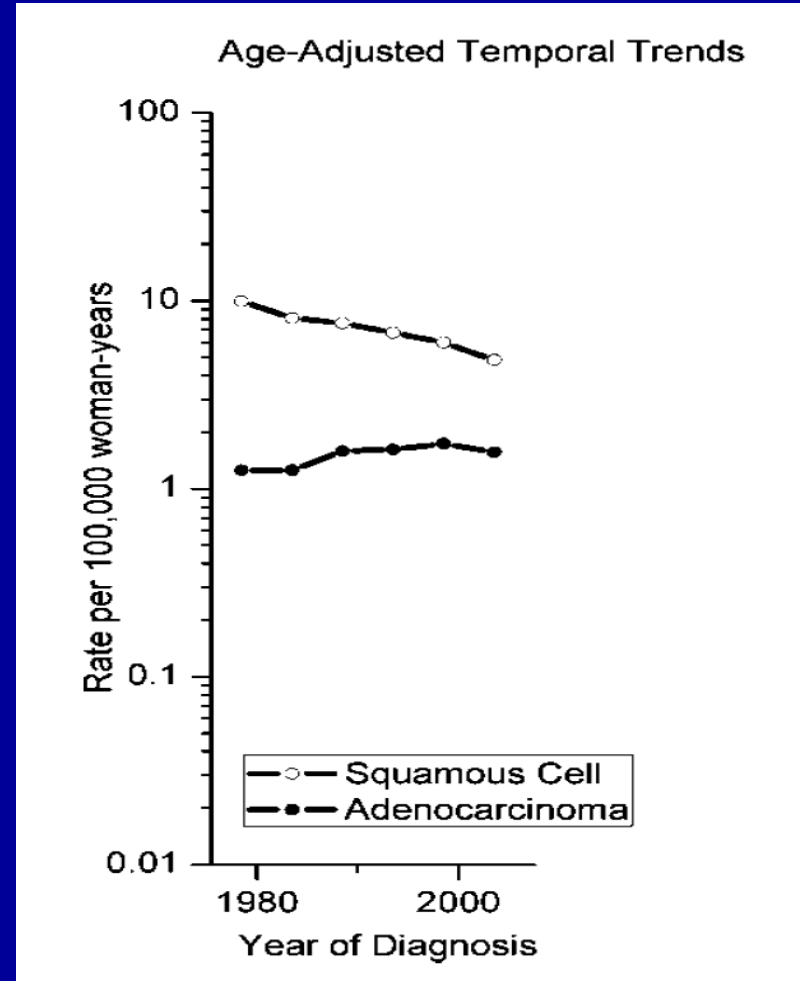




Global incidence of cervical carcinoma

Cervical Carcinoma

- The incidence of SCC of the cervix has greatly decreased during the last 50 years
- The relative and absolute incidence of adenocarcinoma of the cervix has increased during the last 30 years
 - Comprises ~ 25% of cervical carcinoma in the USA

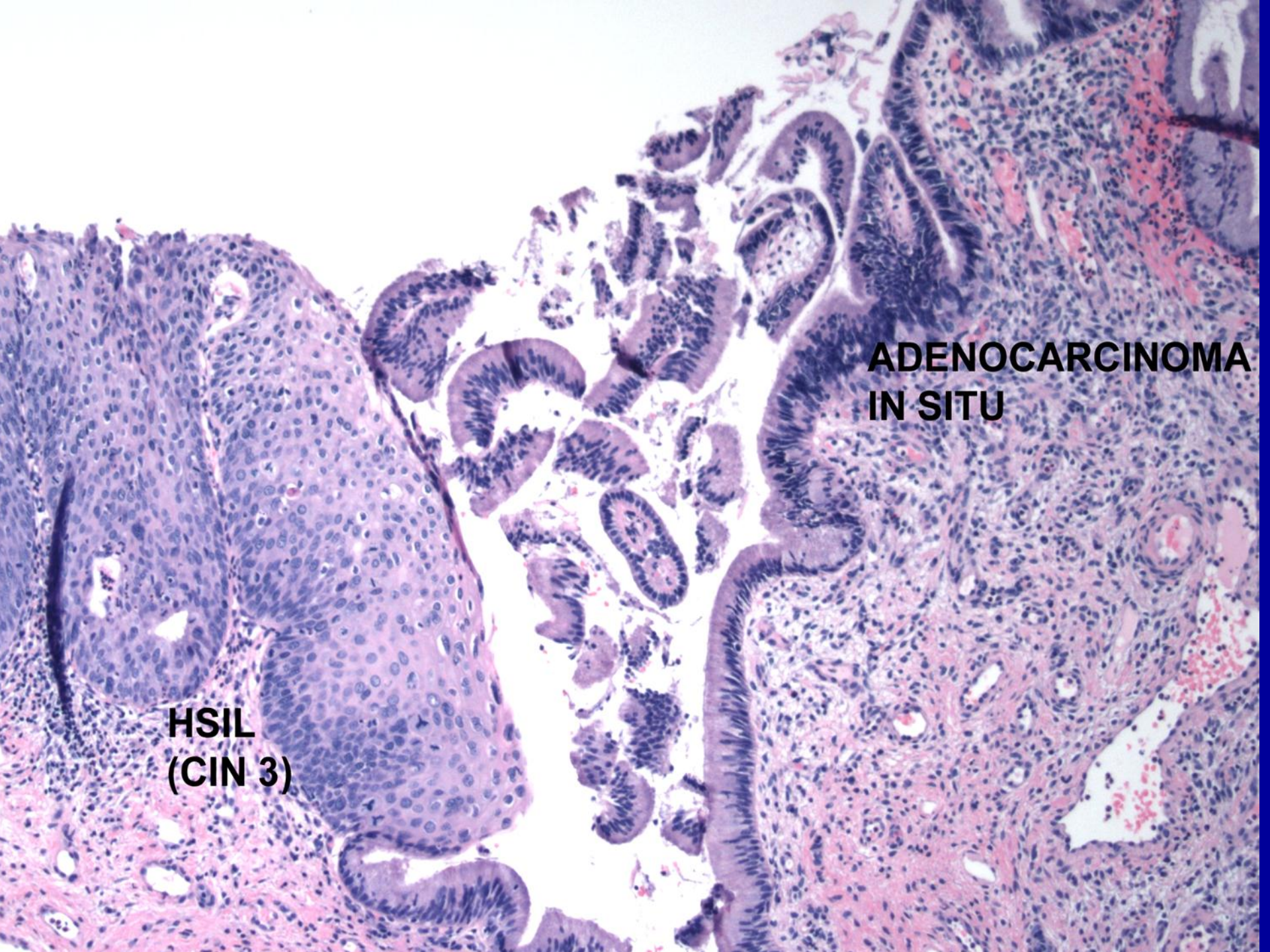


Endocervical Adenocarcinoma

- Endocervical adenocarcinoma in Situ (AIS)
- Dysplasia and pitfalls of AIS
- AIS vs invasive adenocarcinoma
- Early stage and management
- Variants of invasive adenocarcinoma
- Practical problems

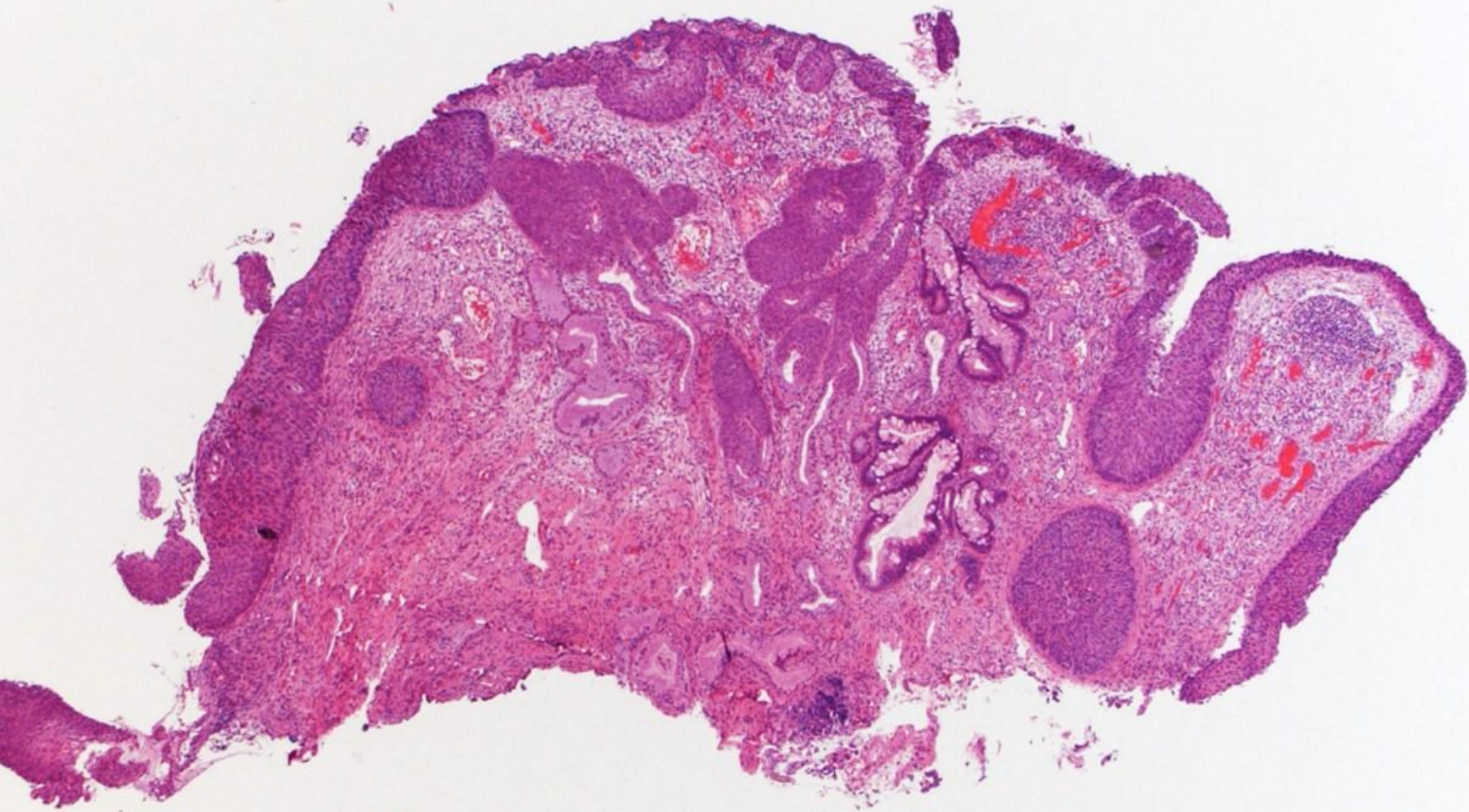
Endocervical Adenocarcinoma in situ (AIS)

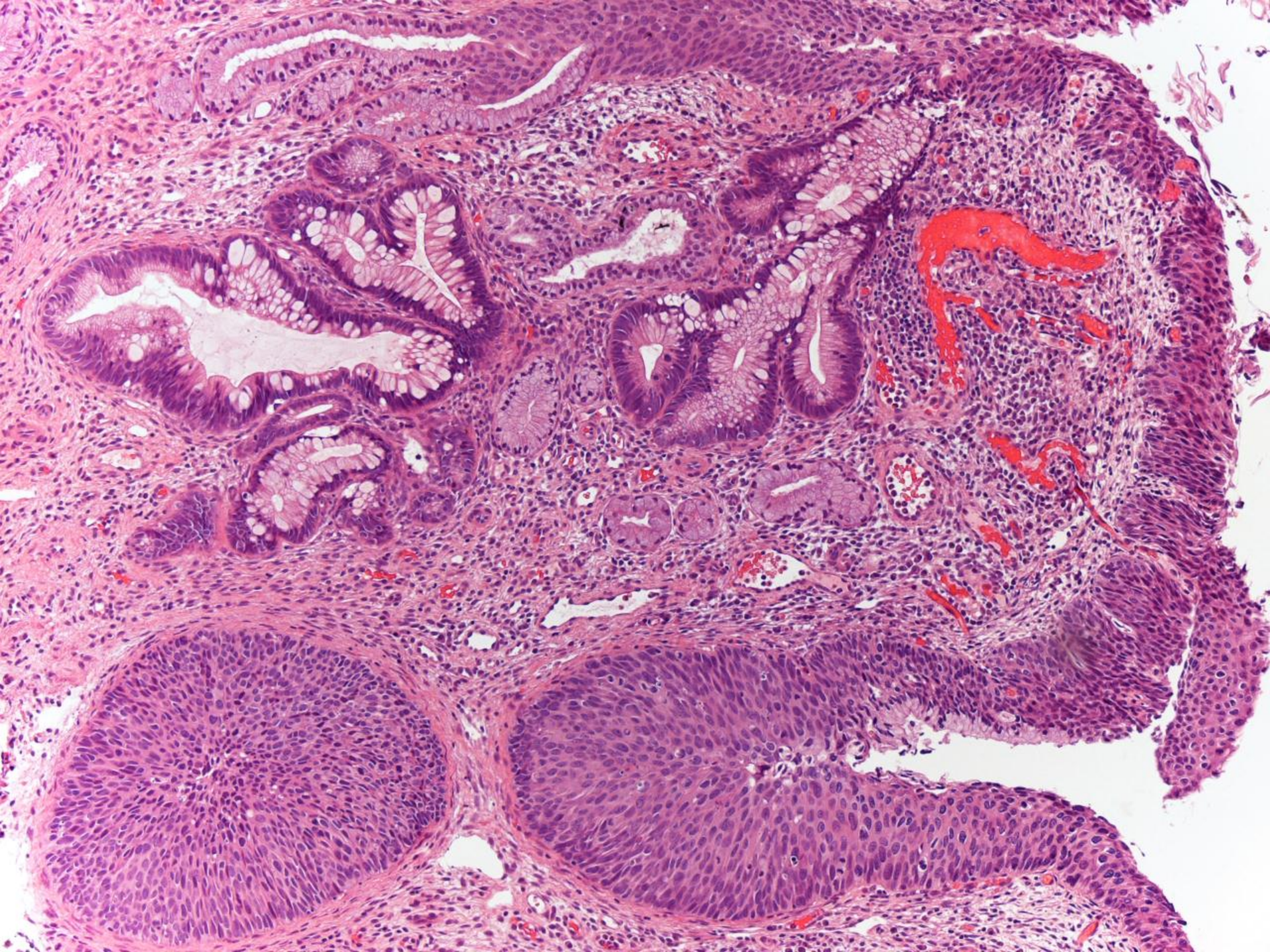
- **Precursor lesion of invasive adenocarcinoma of the cervix**
- **Approximately 50-70% of AIS are associated with high grade squamous intraepithelial lesions**
- **High risk HPV 18 & 16 detected in >95%**



**HSIL
(CIN 3)**

**ADENOCARCINOMA
IN SITU**

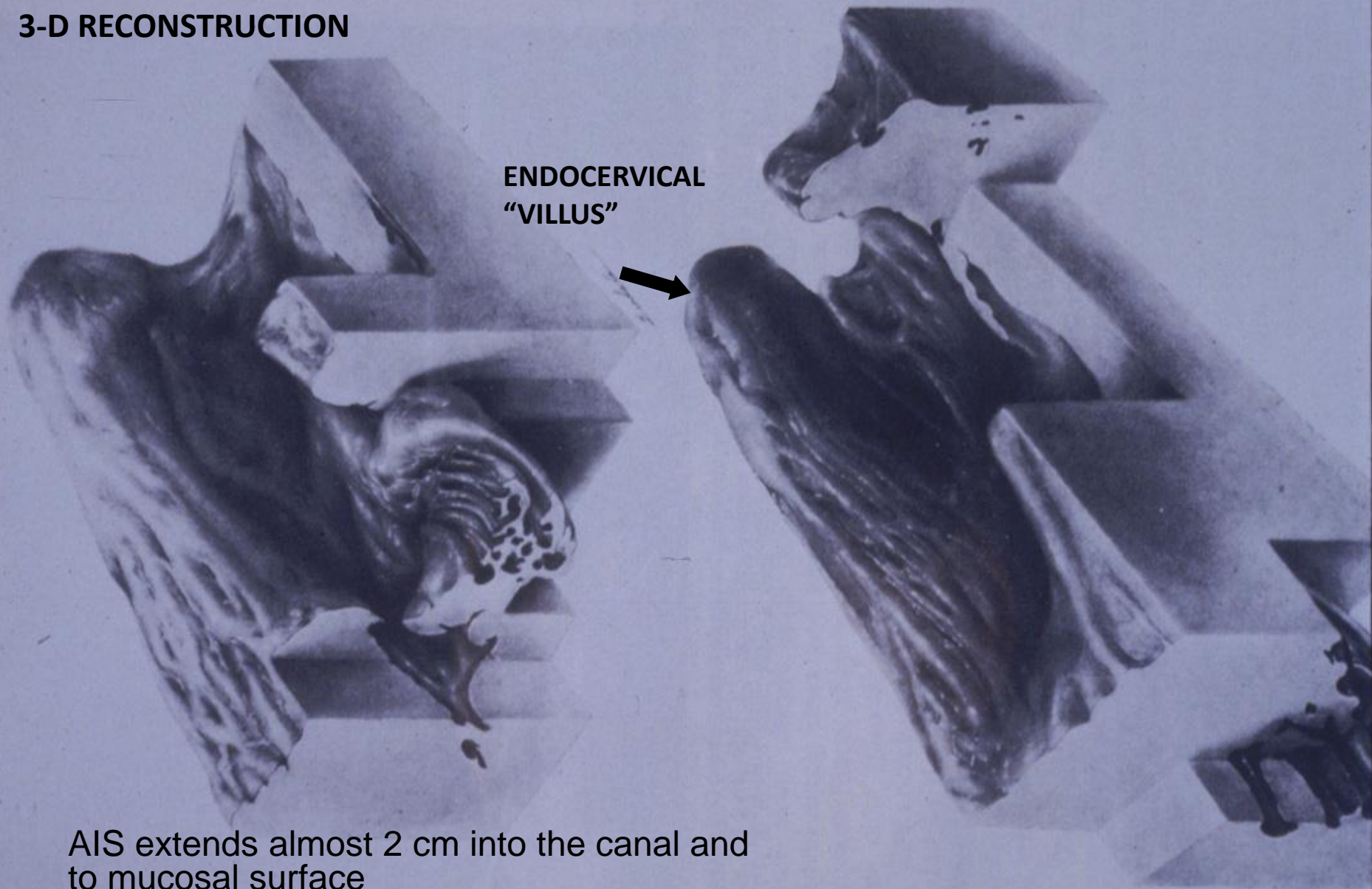




Endocervical Adenocarcinoma in situ

- **Usually begins as a single focus at the transformation zone**
- **Horizontal or lateral spread**
- **Multiple quadrants involved in more than 50% of cases**
- **True skip lesions are rare**

**NORMAL ENDOCERVIX
3-D RECONSTRUCTION**

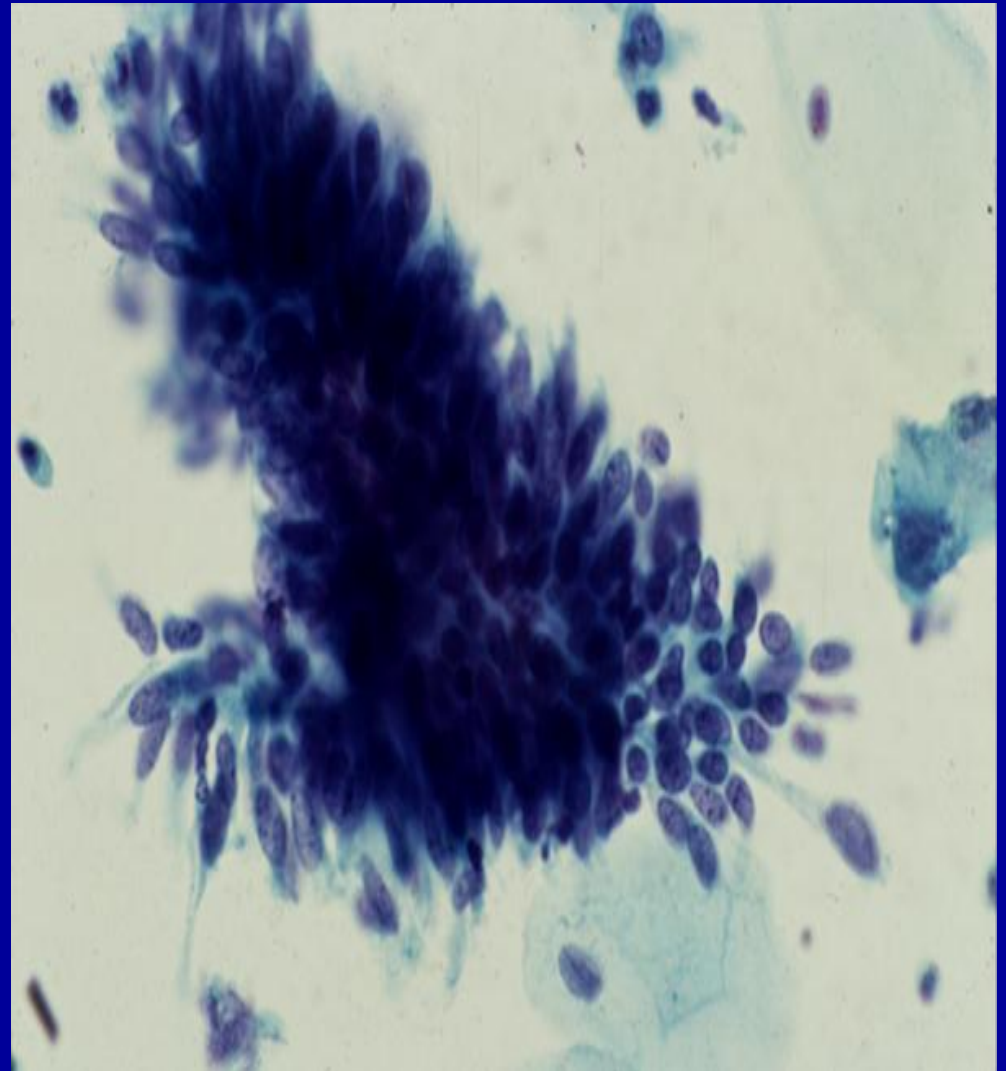


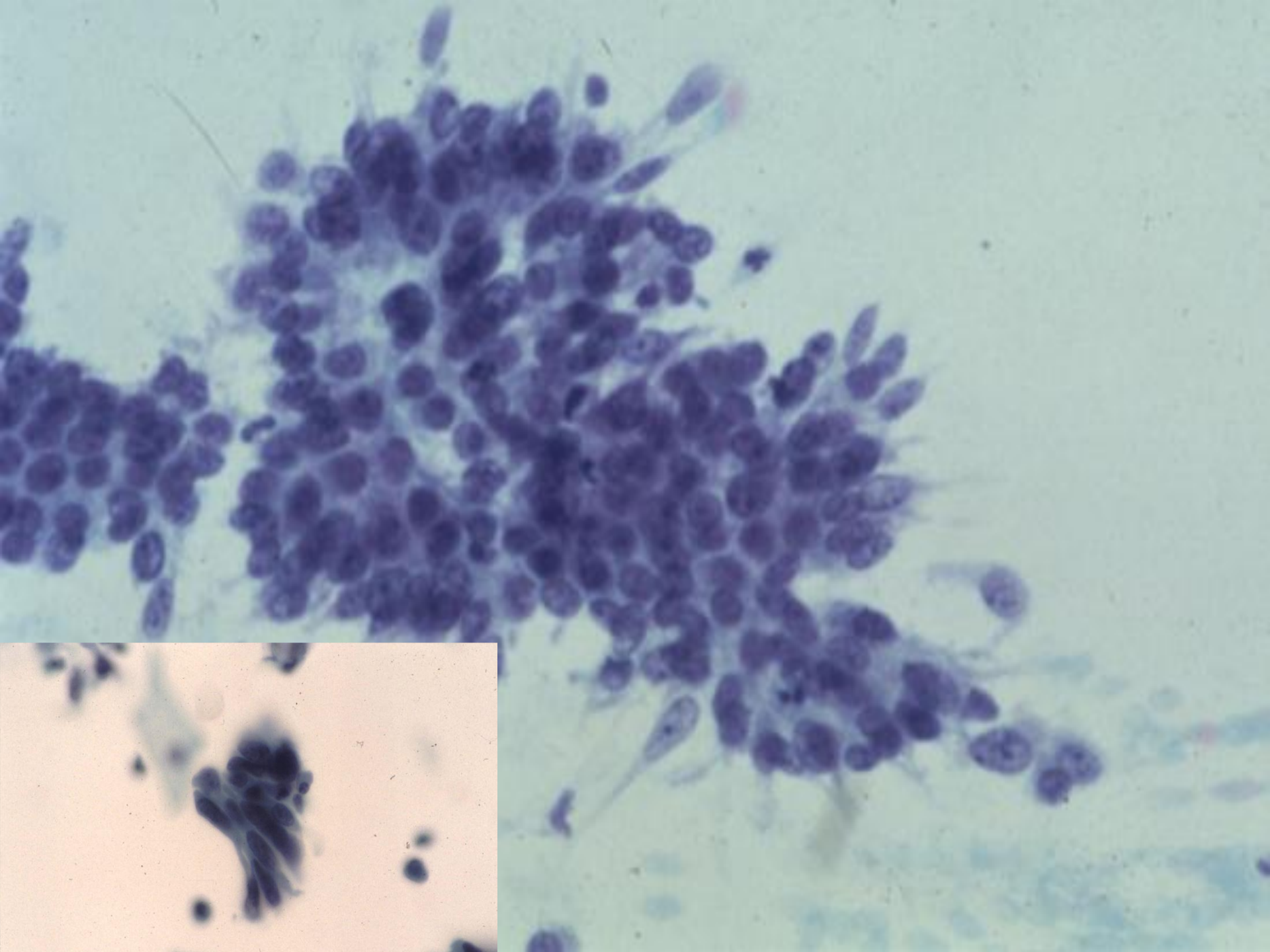
**ENDOCERVICAL
"VILLUS"**

AIS extends almost 2 cm into the canal and
to mucosal surface

Adenocarcinoma In Situ

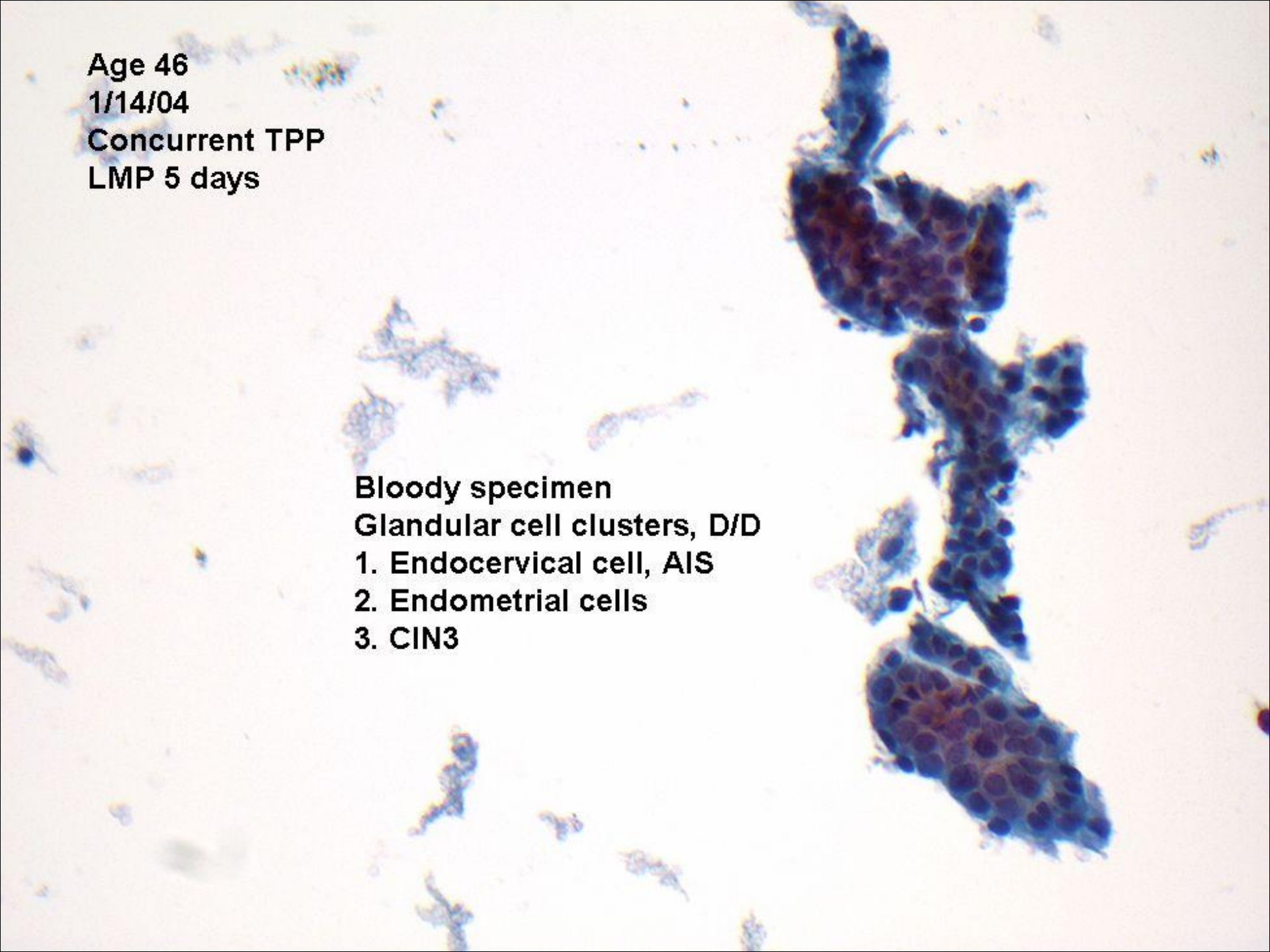
- **Hyperchromatic crowded groups**
- **Increased nucleus to cytoplasmic ratio**
- **Feathering**
- **Strips with pseudostratification**
- **Mitoses and apoptotic bodies**

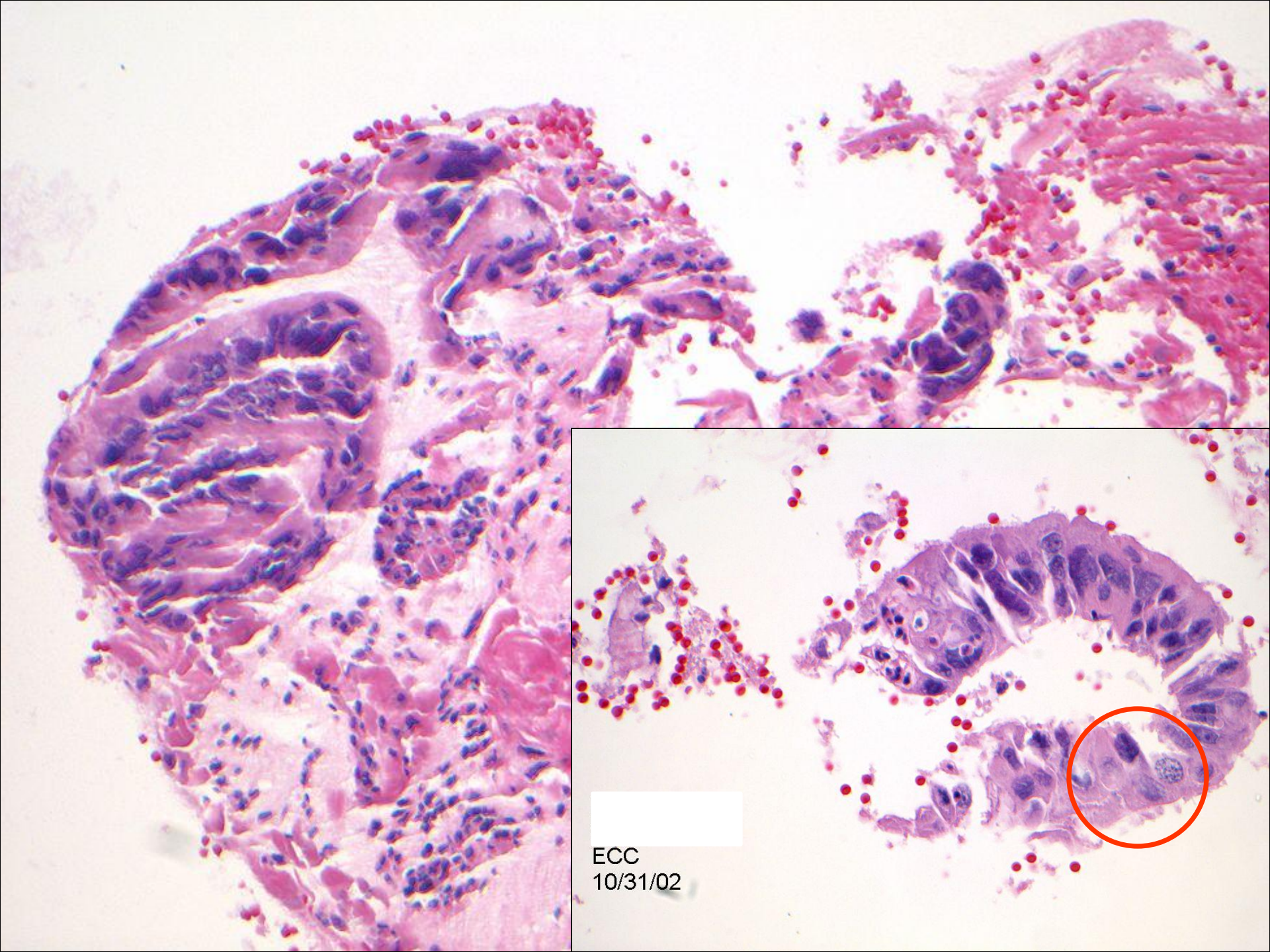




Age 46
1/14/04
Concurrent TPP
LMP 5 days

Bloody specimen
Glandular cell clusters, D/D
1. Endocervical cell, AIS
2. Endometrial cells
3. CIN3

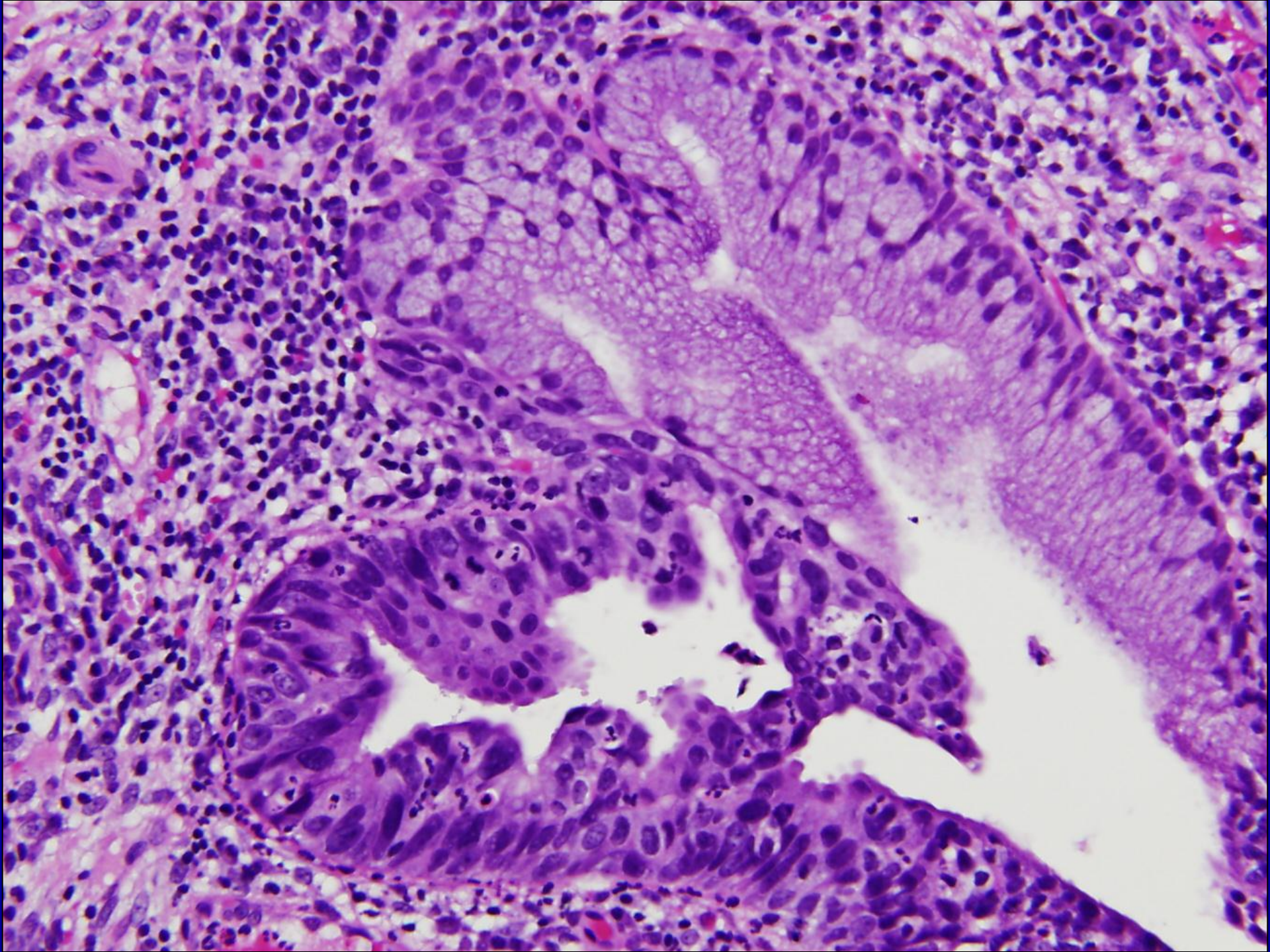
The image shows a microscopic view of a bloody specimen. The background is a light, pale color with scattered small, dark blue-stained cells. On the right side, there is a large, elongated, and somewhat irregular cluster of cells. This cluster is composed of many individual cells, each with a distinct, dark blue nucleus and a lighter, cytoplasmic area. The cells are arranged in a somewhat organized, glandular pattern, with some cells appearing to be in contact with each other. The overall appearance is that of a complex, multi-layered cellular structure. The text on the left side of the image provides clinical context, including the patient's age (46), the date (1/14/04), and the timing of the last menstrual period (LMP 5 days). The text also identifies the specimen as bloody and lists the findings: glandular cell clusters (D/D), endocervical cells (AIS), endometrial cells, and CIN3.



ECC
10/31/02

Diagnosing AIS: Morphology

- Blue lesion (loss of mucin); tubular adenoma-like
- Lobular architecture
- Enlarged, elongate, darkly stained nuclei
- **Evident mitotic activity (apical)**
- **Apoptotic bodies**
- Superficial lesion



Diagnosing AIS: Morphology

Apoptotic Body and Mitotic Figure Count

Lesion	n	AB (mean \pm SEM)	MF (mean \pm SEM)
NG	32	1.3 \pm 0.4	0.1 \pm 0.1
EGA	35	5.9 \pm 0.7	0.9 \pm 0.2
EGD	30	27.5 \pm 2.6	10.7 \pm 1.7
AIS	34	42.4 \pm 4.2	18.7 \pm 2.3
IA	30	34.9 \pm 3.6	21.5 \pm 2.3
		$p < 0.001$	$p < 0.001$

Diagnosing AIS: Morphology

	0	1	2	3
Stratification	None	Mild	Moderate	Severe
Nuclear atypia	None	Mild	Up to x3 nl	>x3 nl
Mitosis/ Apoptosis*	None	<0.5	0.6-3.0	>3.0

Total score 0-3 = benign

Total score 4-5 = “endocervical glandular dysplasia”

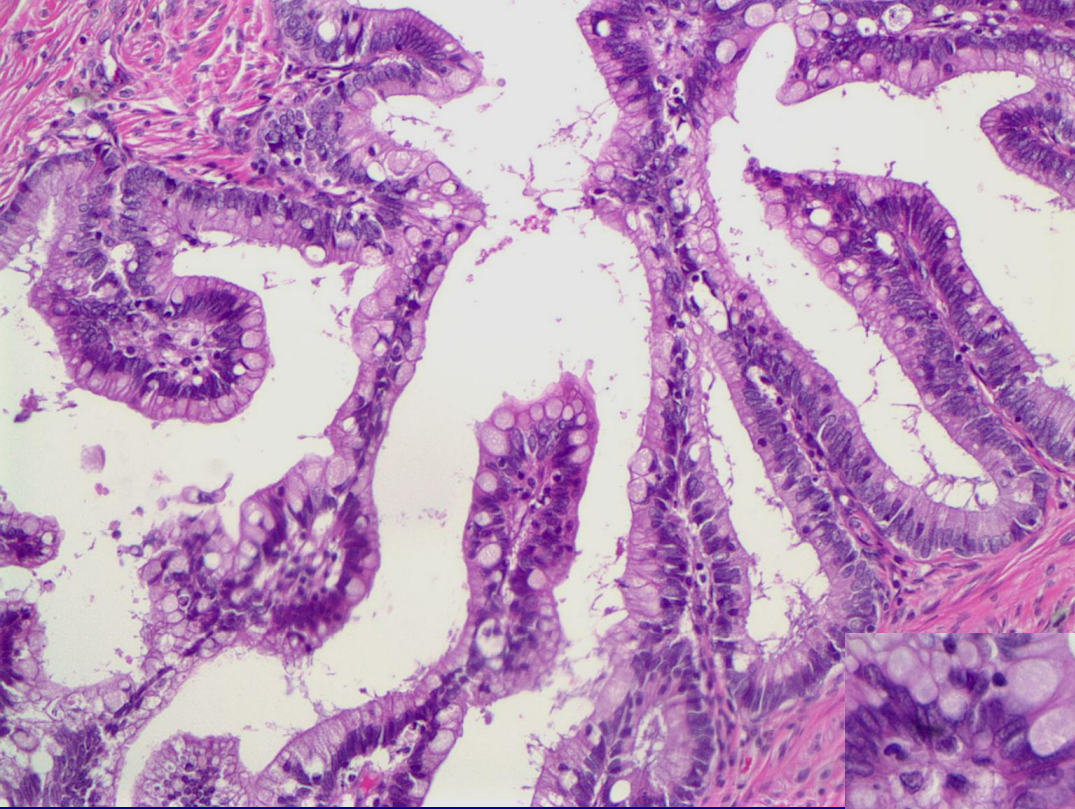
Total score 6-9 = adenocarcinoma in situ (AIS)

Endocervical- AIS variants **no biologic significance!**

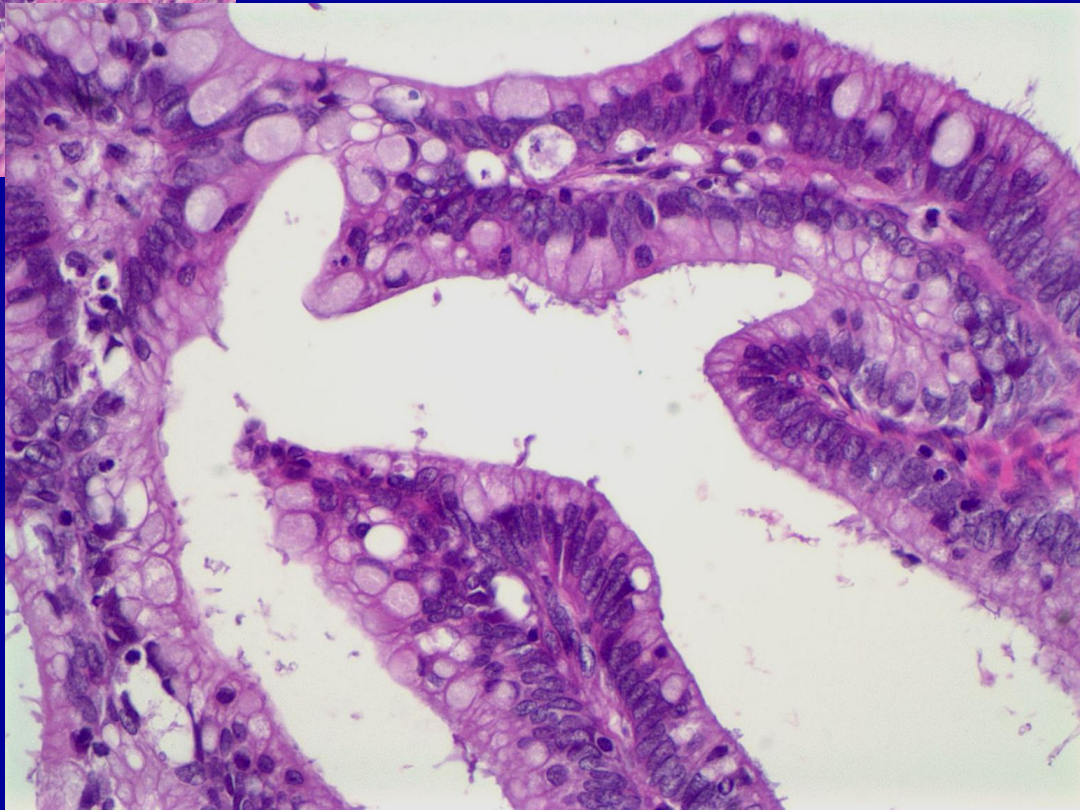
- **Intestinal**
- **Stratified mucin producing intraepithelial lesion (SMILE)**
- **Mucin-poor (“endometrioid”)**
- **Superficial/early**

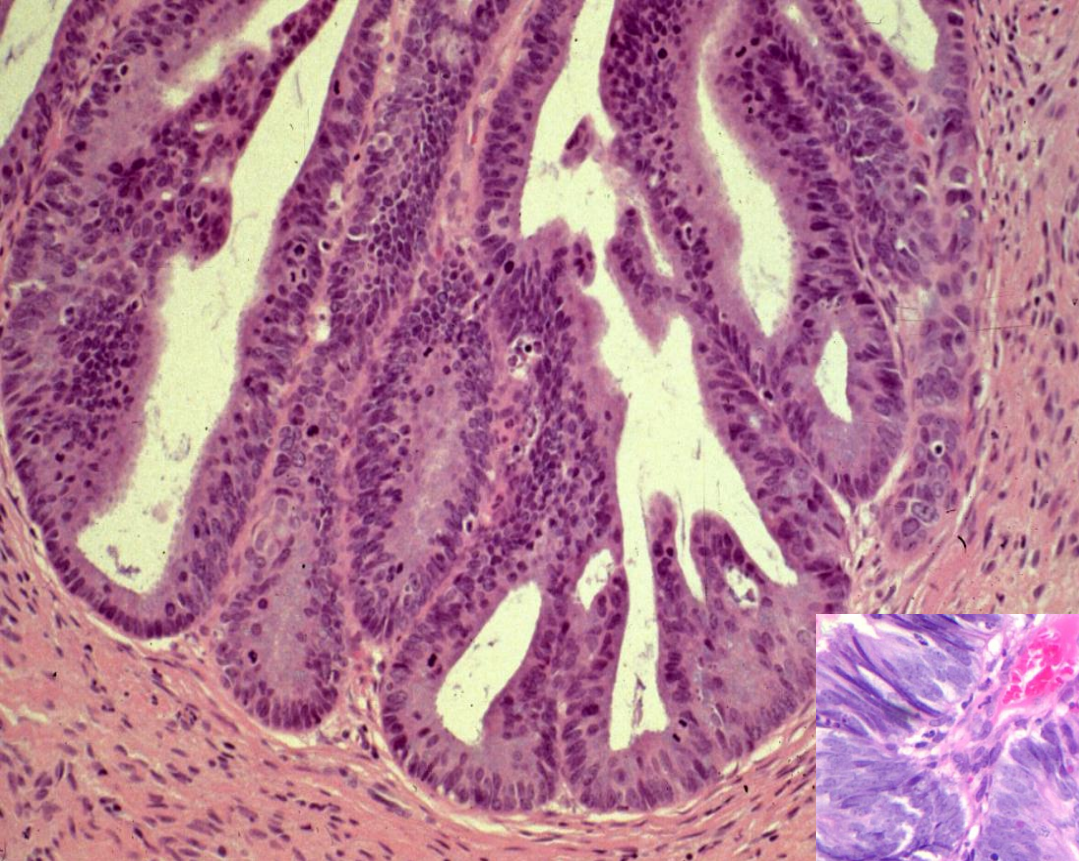


Endocervical Type

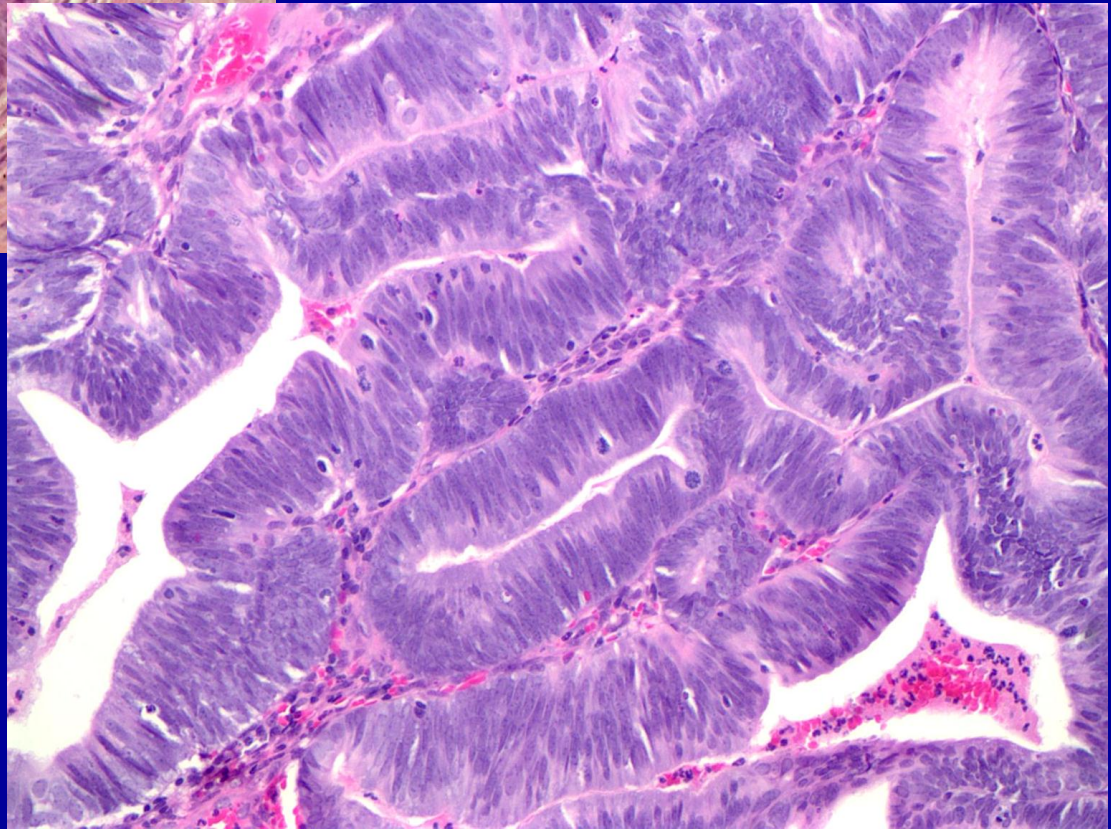


Intestinal Type

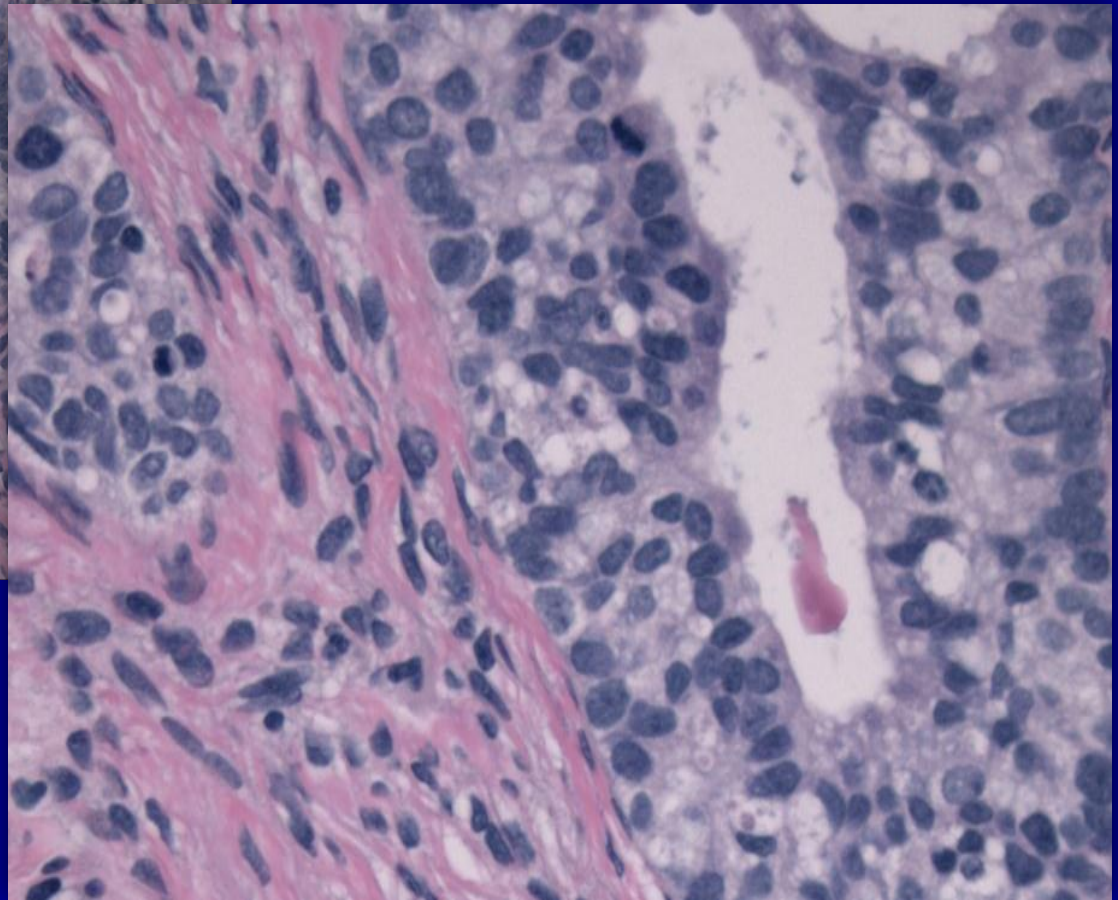
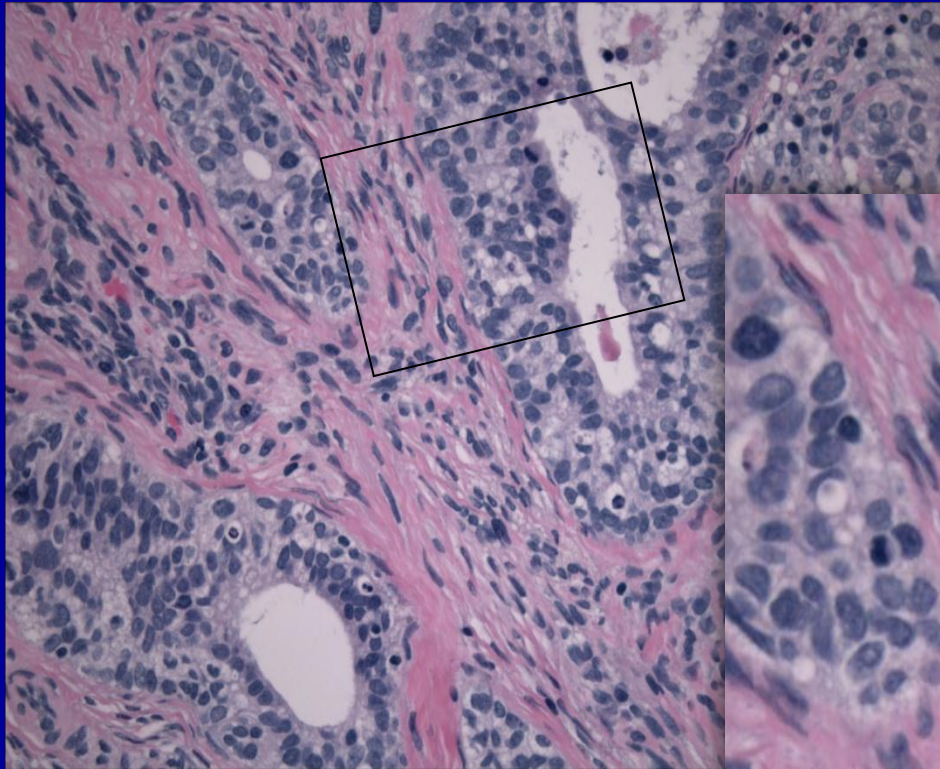




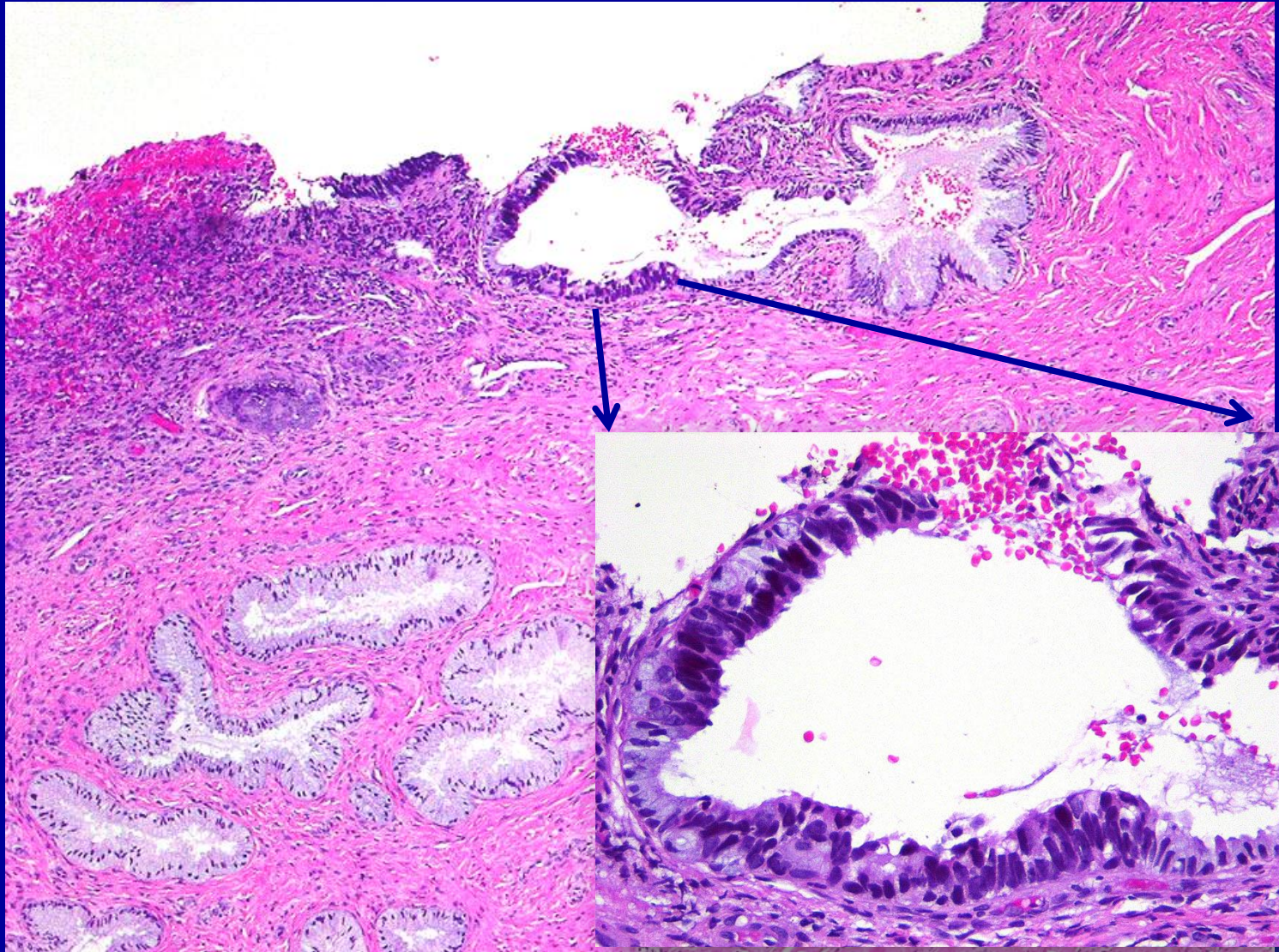
Endometrioid Type

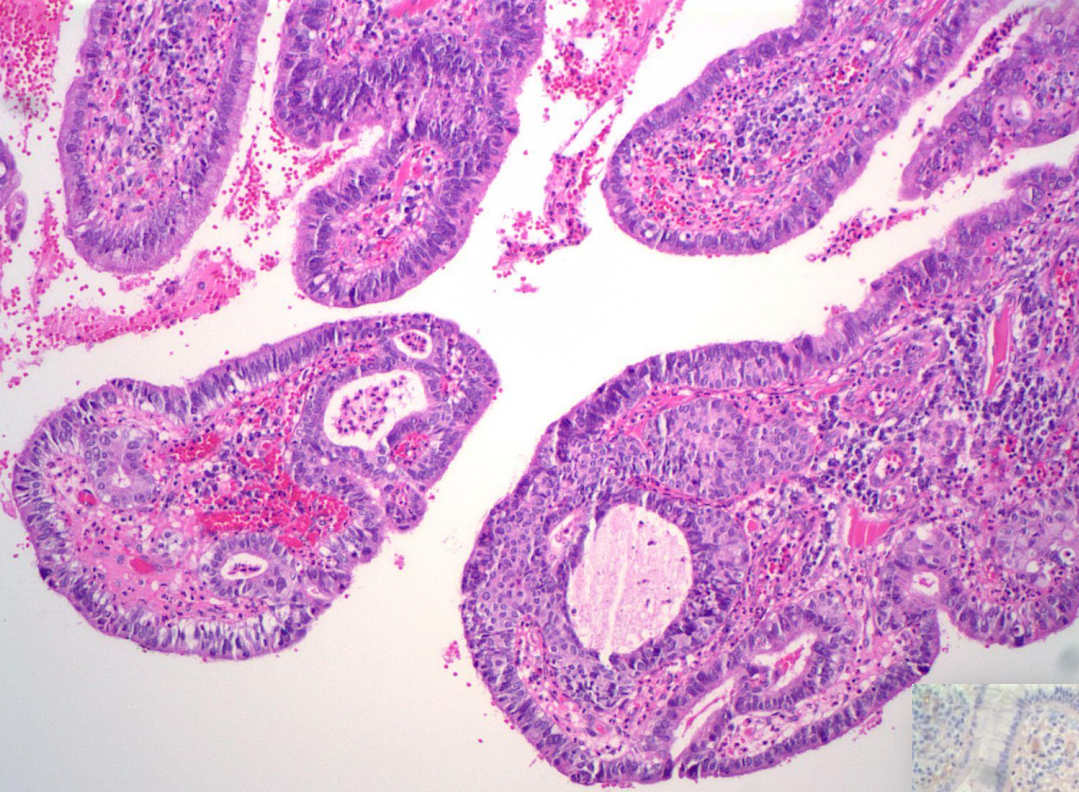


Adenosquamous Carcinoma *In Situ* (Stratified Mucin Producing Intraepithelial Lesion=smile)



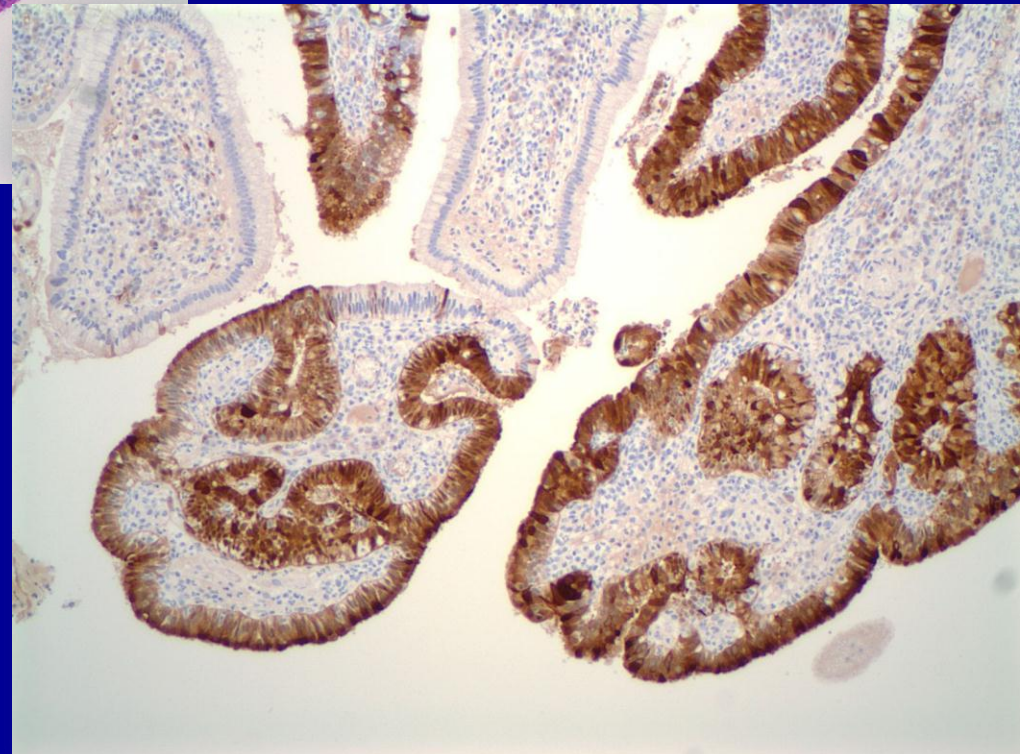
Superficial/Early AIS

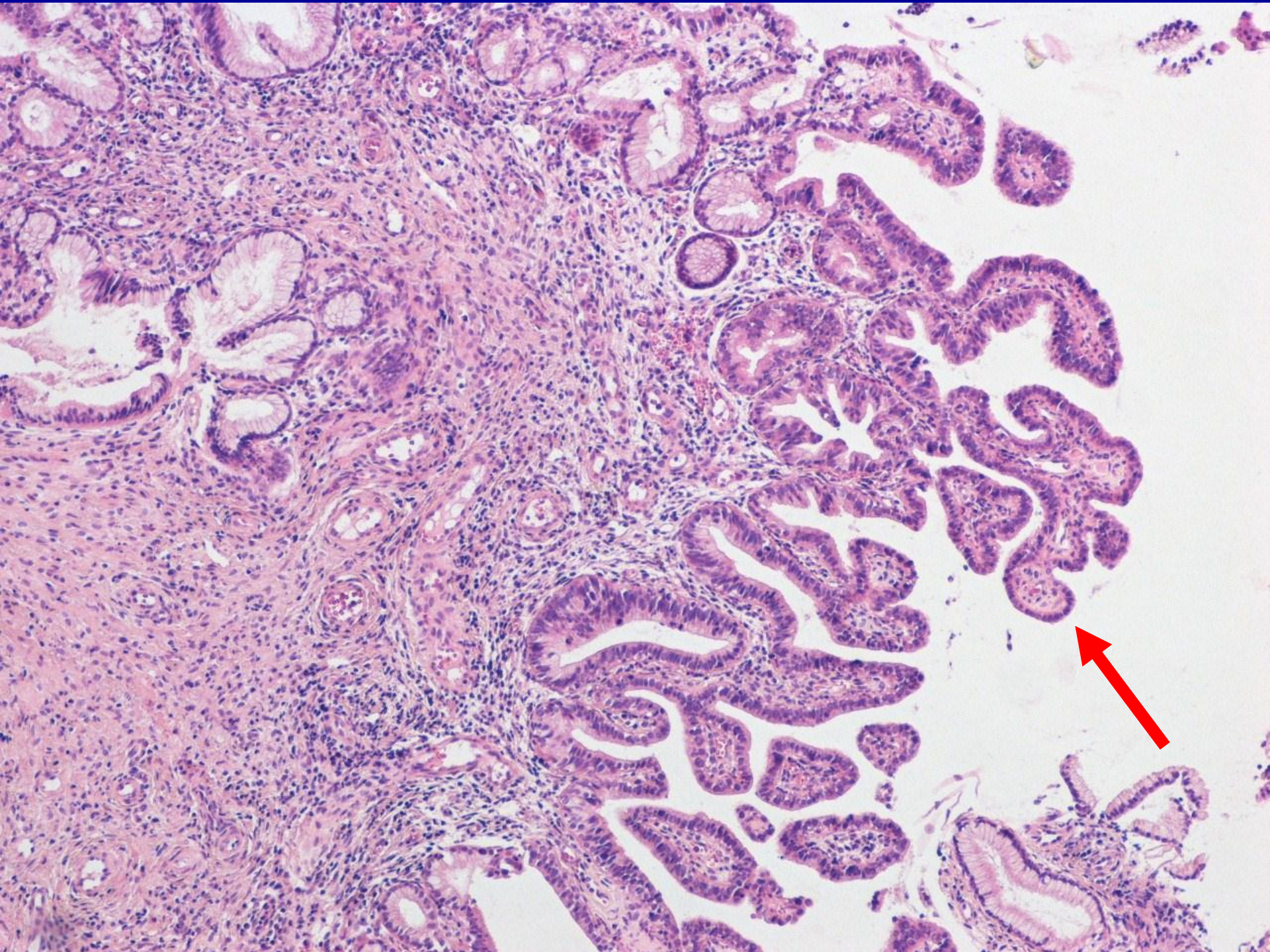




P16

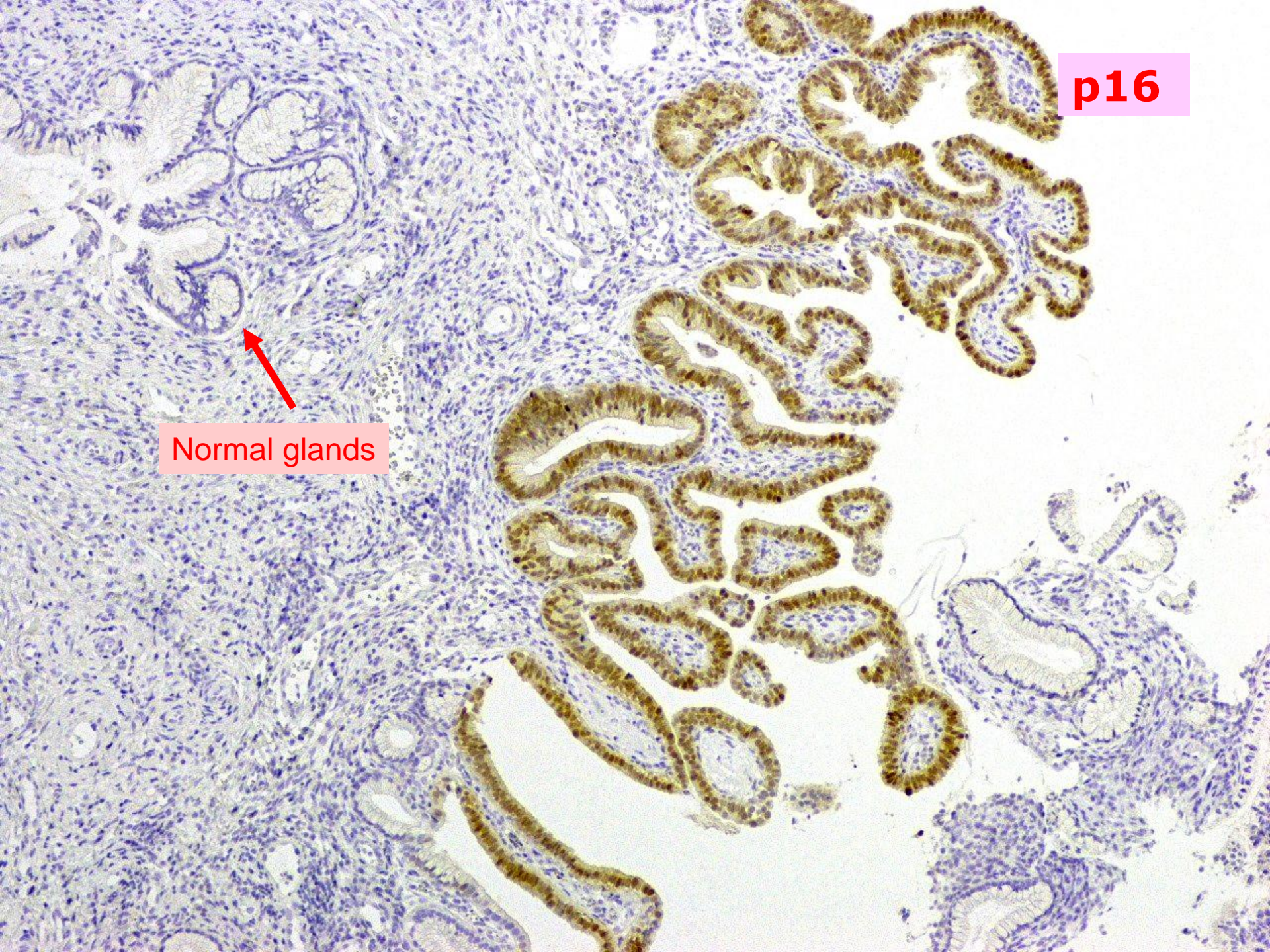
Superficial AIS

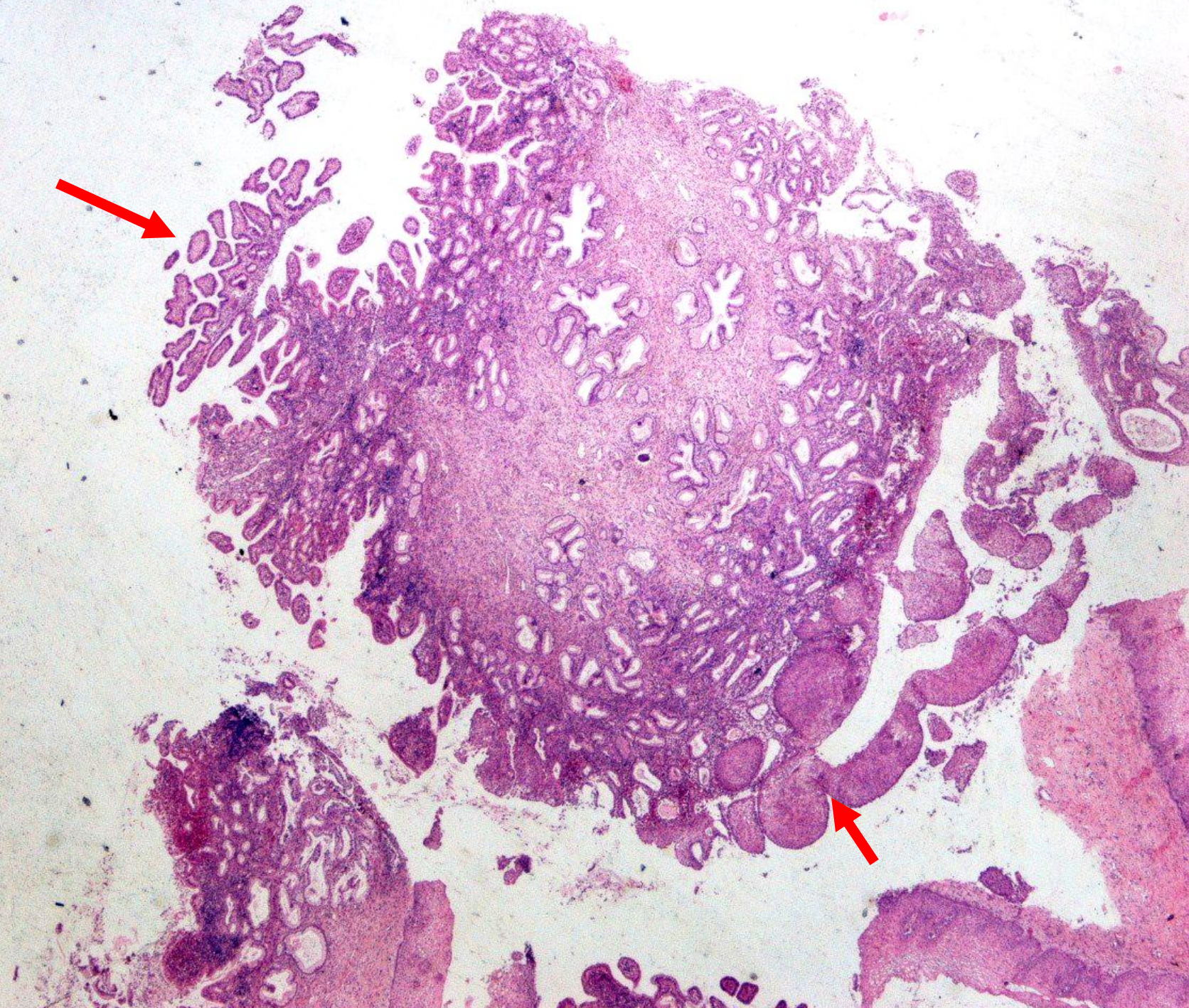


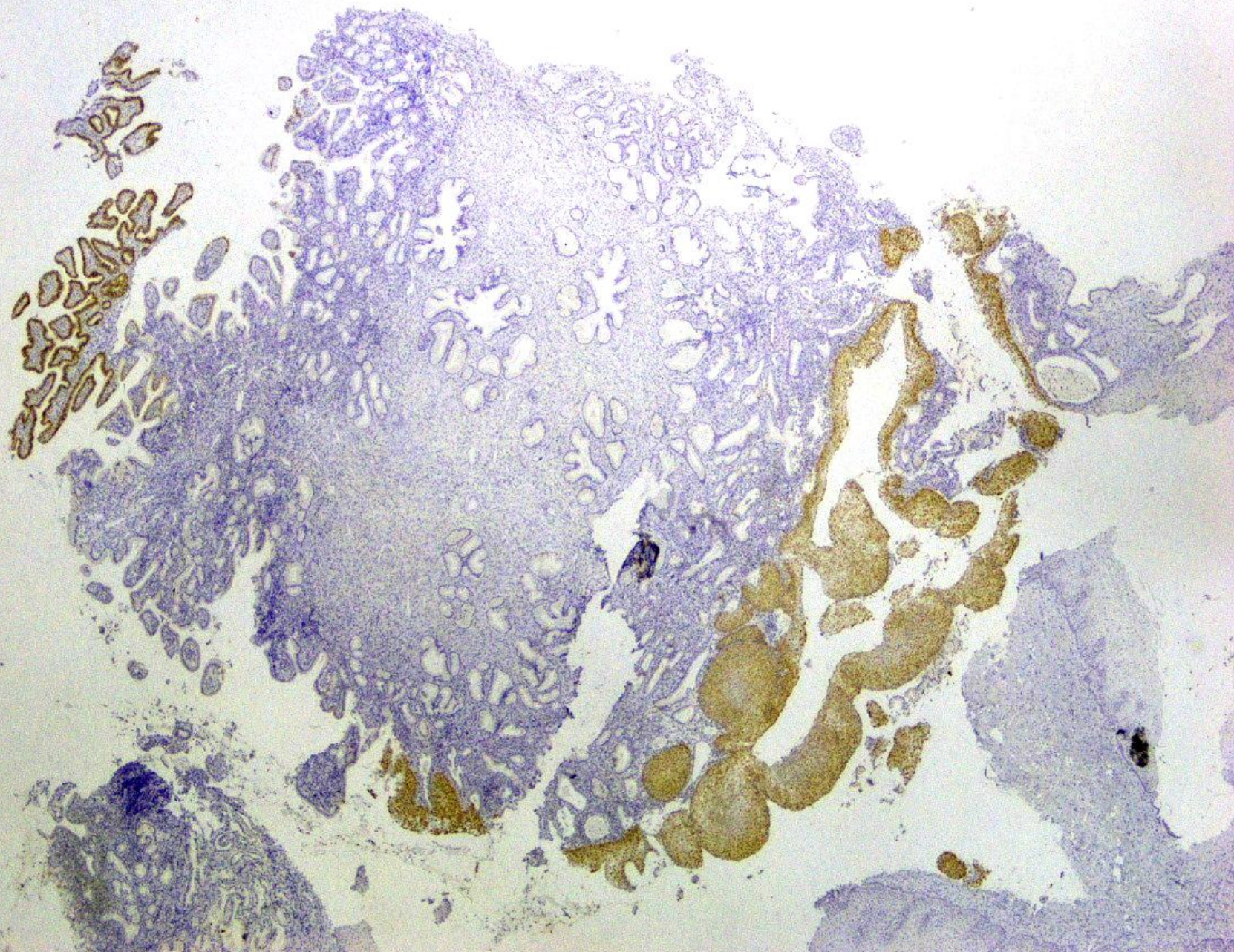


p16

Normal glands







p16

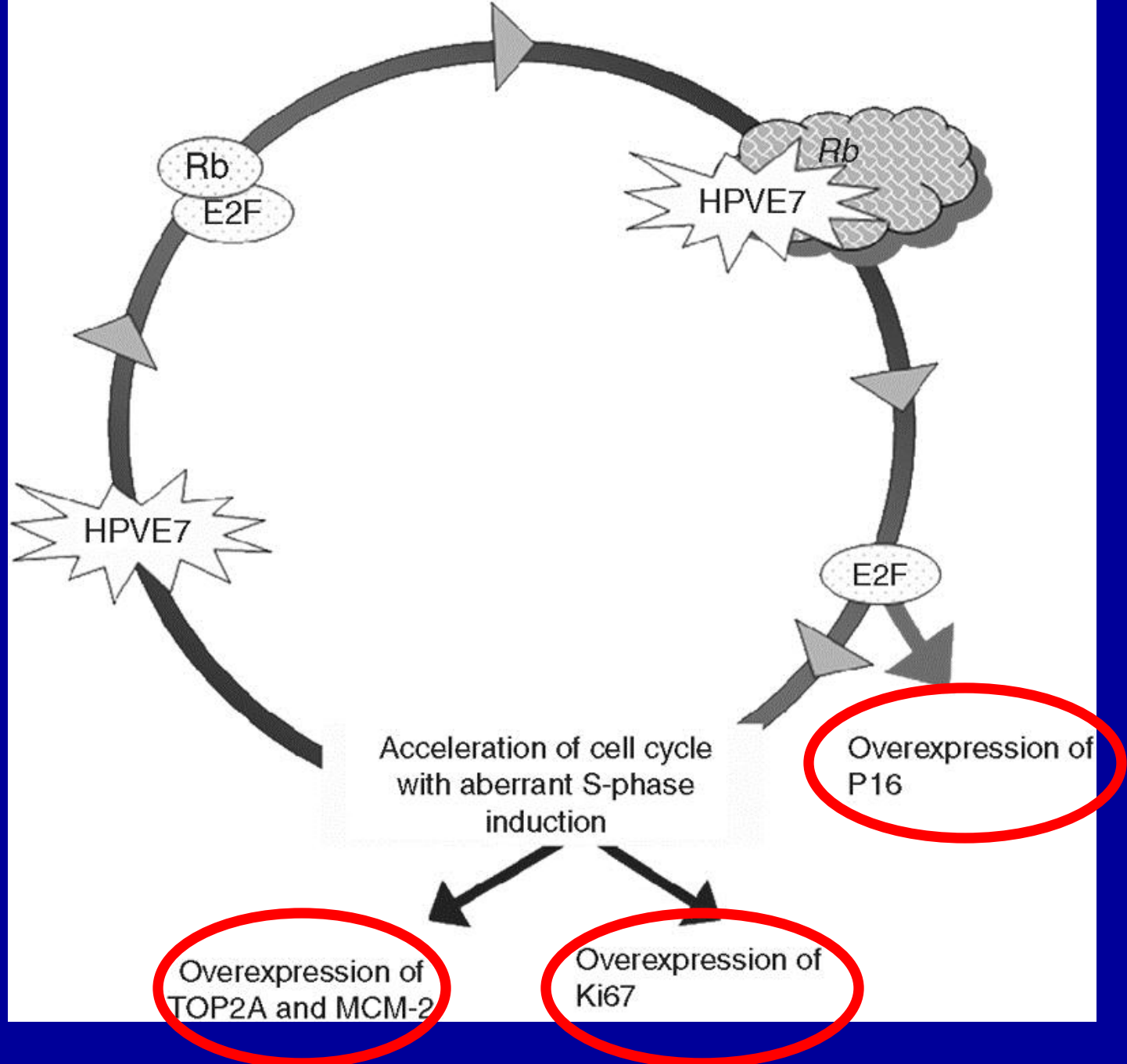
Immunohistochemistry and ancillary tests

- Mib-1 (Ki-67)
- P16*
- Pro Ex C

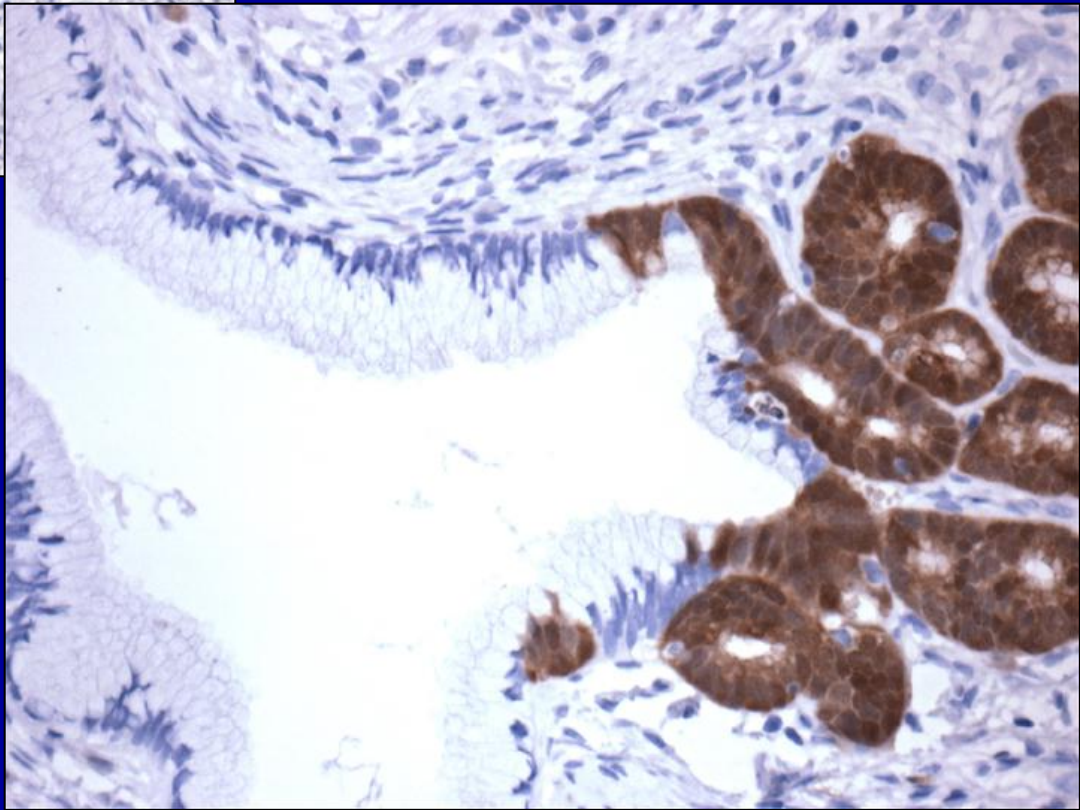
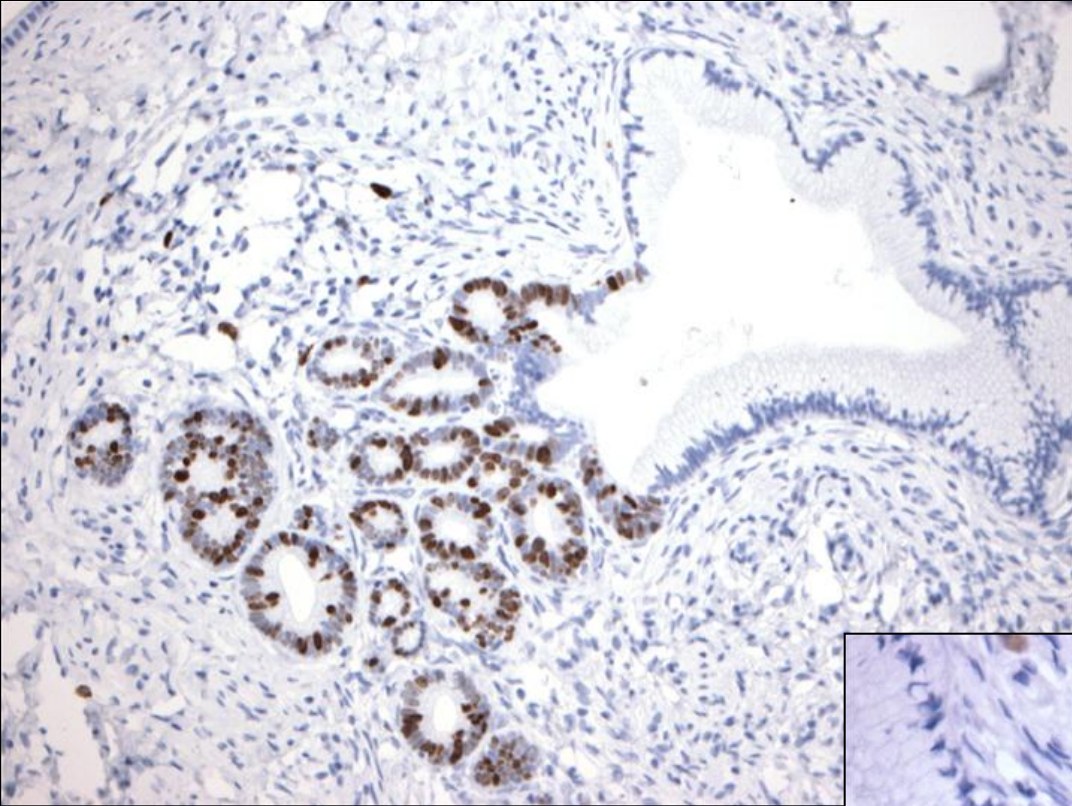
- HR-HPV in situ hybridization (ISH)

- HPV polymerase chain reaction (PCR)

*Ordi J, et al. *Int J Gynecol Pathol* 2009;28:90-7



AIS – Ki67



AIS – P16

AIS Immunohistochemistry

AIS



>95% HR-HPV+
p16+/Ki-67 elevated
ProEx C +

Reactive/metaplastic

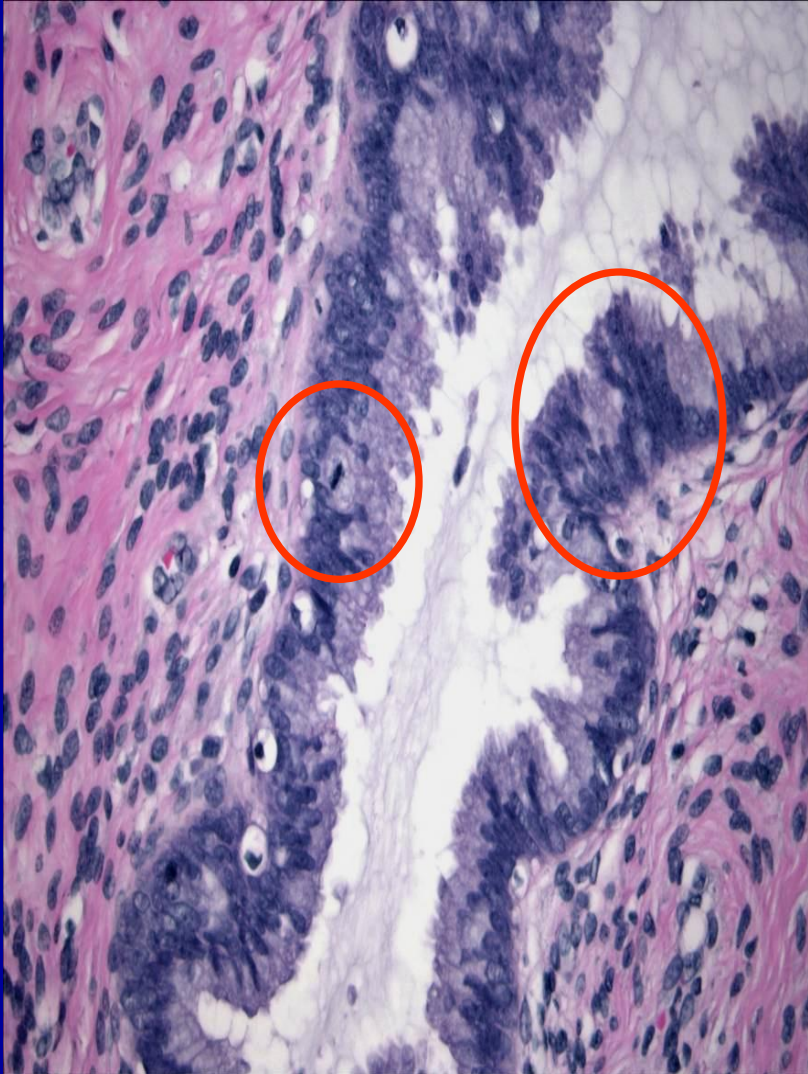
Rarely HR-HPV+

(neg or patchy p16/Ki-67 elevated)

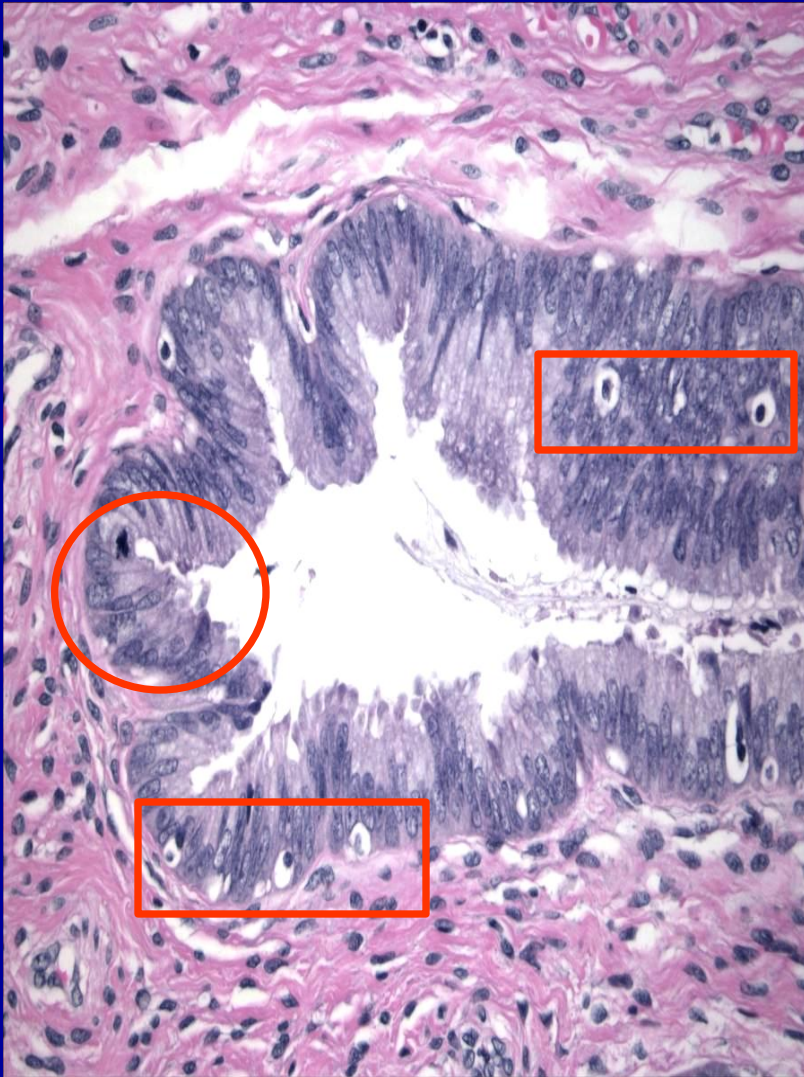
ProEx C

- Similarities with p16:
 - Highly sensitive for HR-HPV associated glandular cervical lesions
 - “False positive” staining of endometriosis and repair
- Possible advantage over p16:
 - Nuclear stain
 - Negative in tubal metaplasia

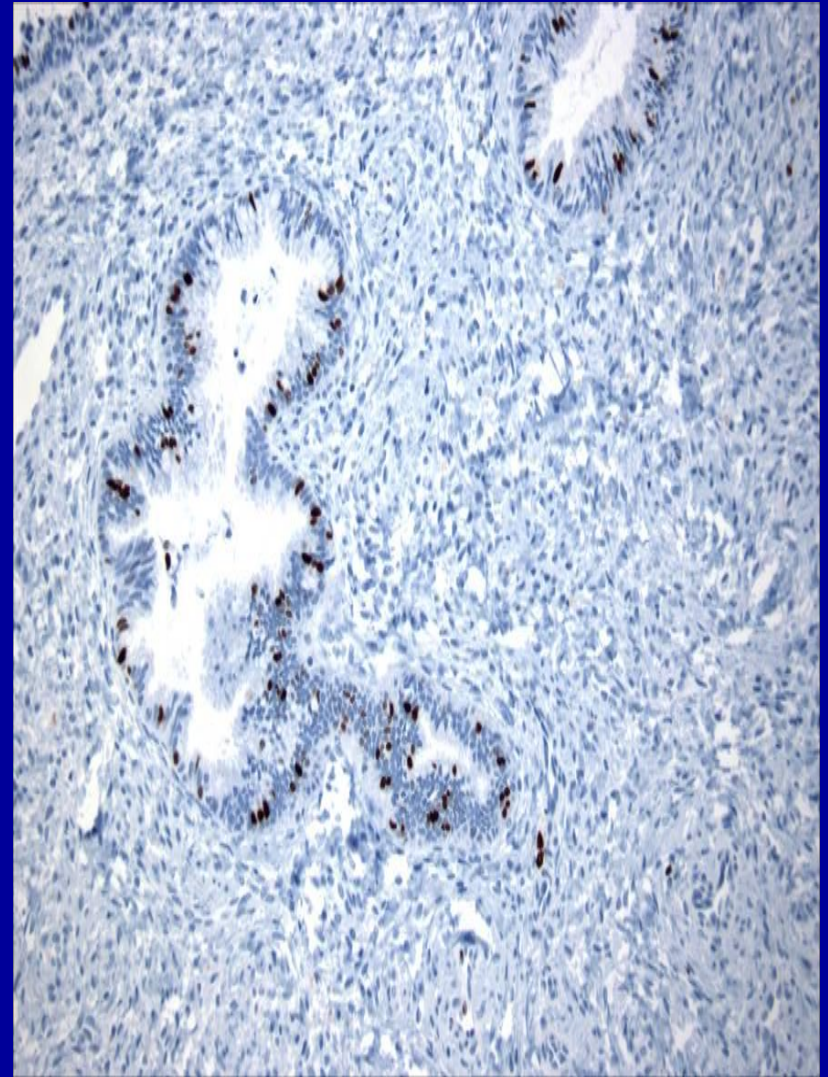
Endocervical Glandular Lesion ?



Endocervical Glandular Dysplasia?



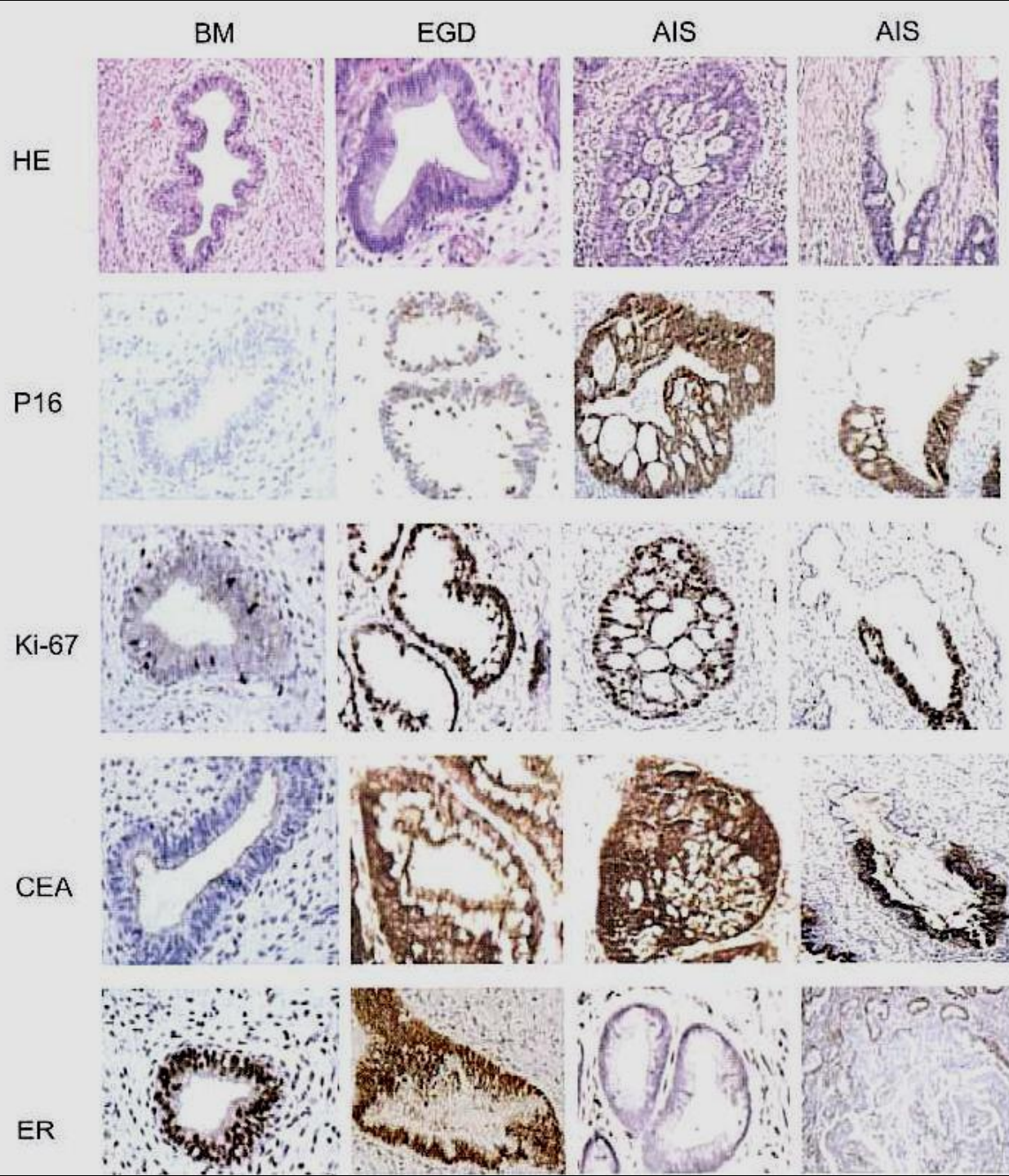
Mitotic Activity & ? Apoptosis

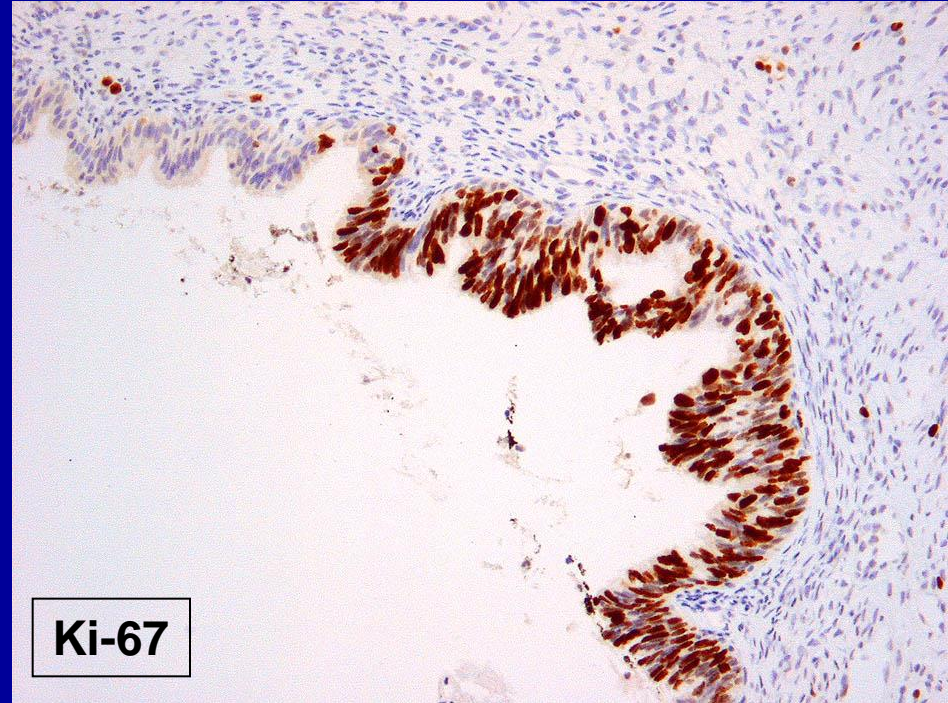
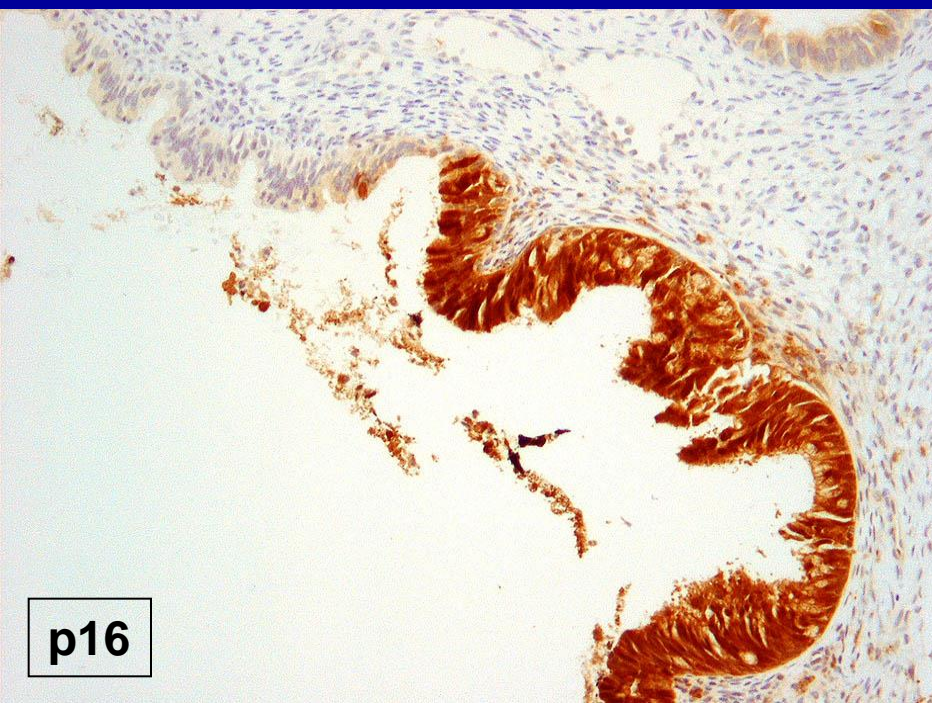
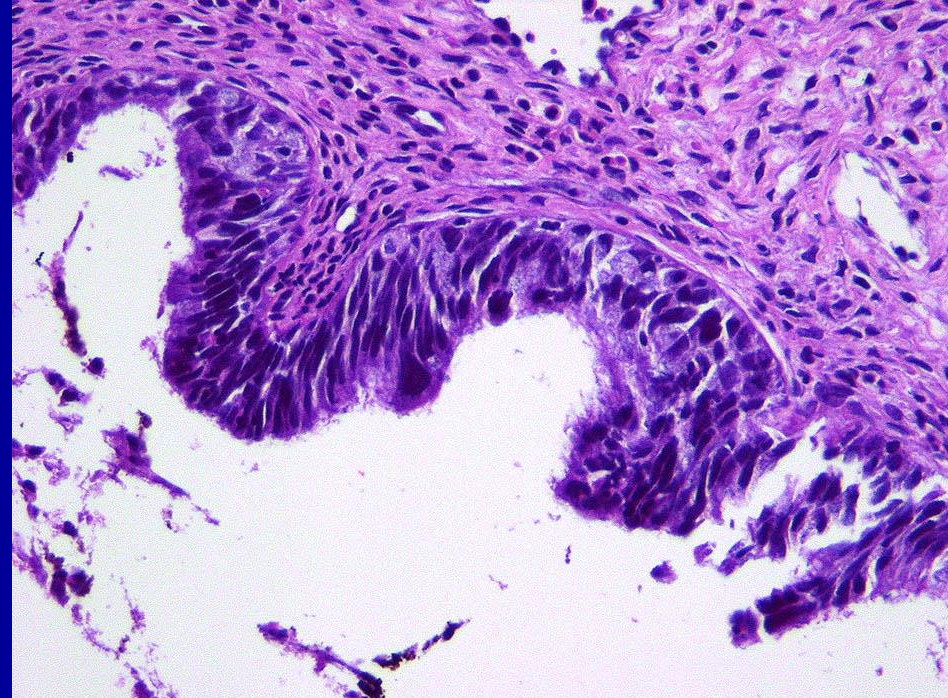
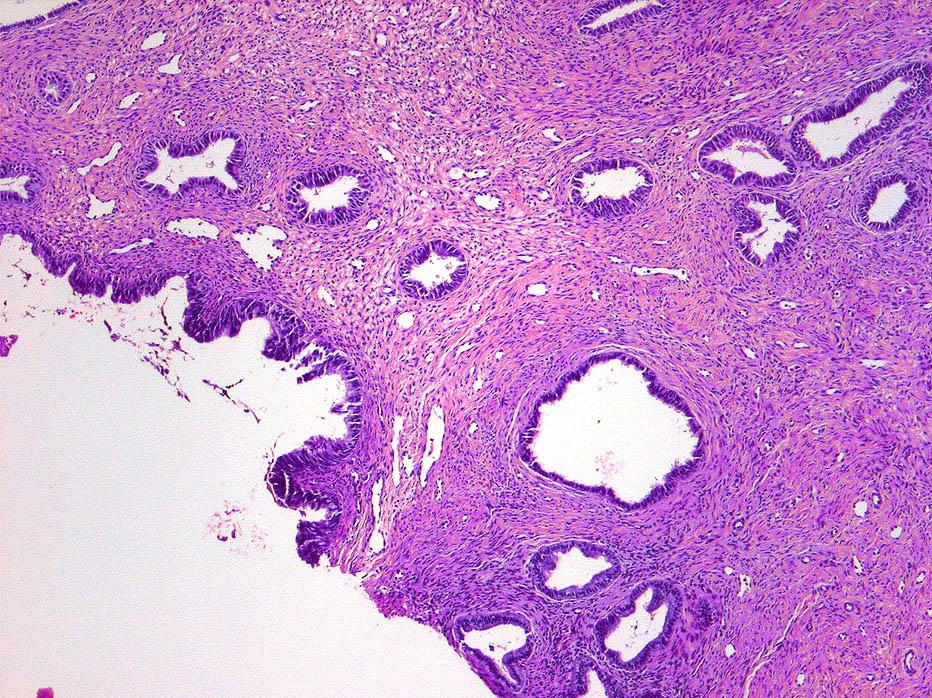


Ki67 Proliferation Marker

Endocervical glandular dysplasia: A Real Entity?

- Clinical implication and progression rate: **unclear**
- HPV association: **unclear**
- Diagnostic reproducibility: **less than AIS**
- Unsure about the diagnosis?
 - Cut deeper, request an additional biopsy
 - **P16, Ki-67, HPV-ISH**





- **Glandular dysplasia may exist!**
- **Don't mention in main diagnosis, add a comment**
- **No standard management**
 - **May manage like atypical squamous metaplasia?**

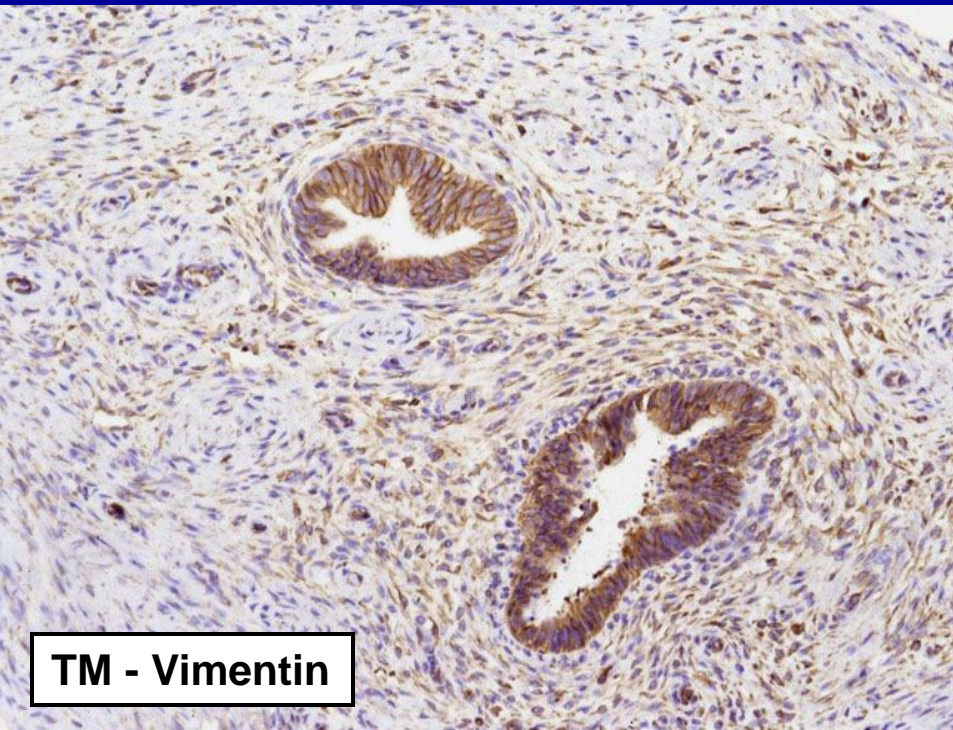
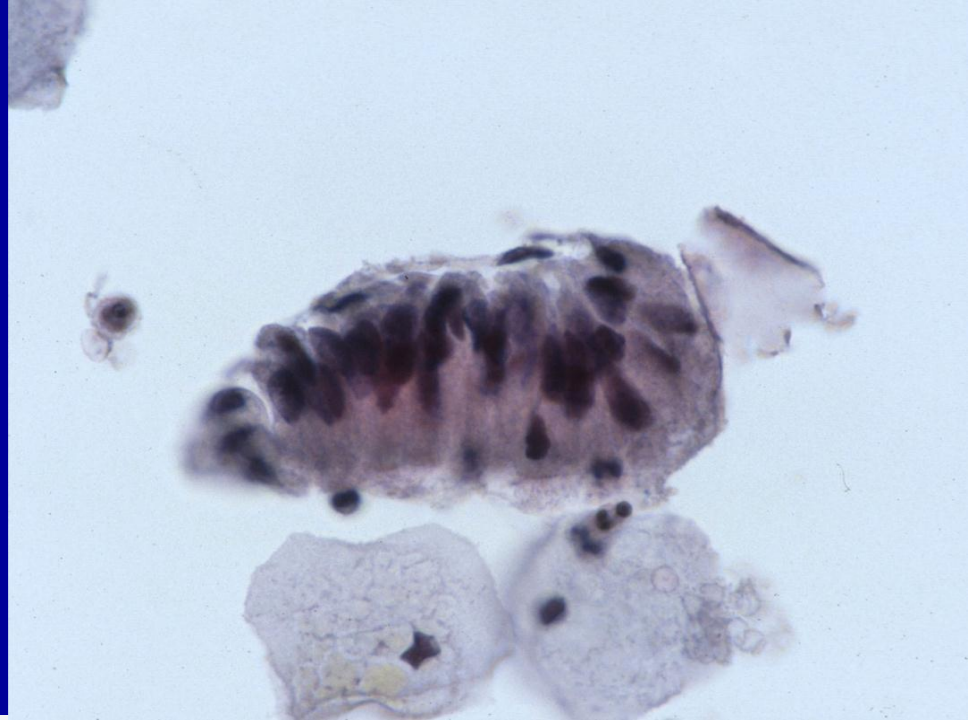
Endocervical AIS: Pitfalls

Tube-Endometrioid Metaplasia

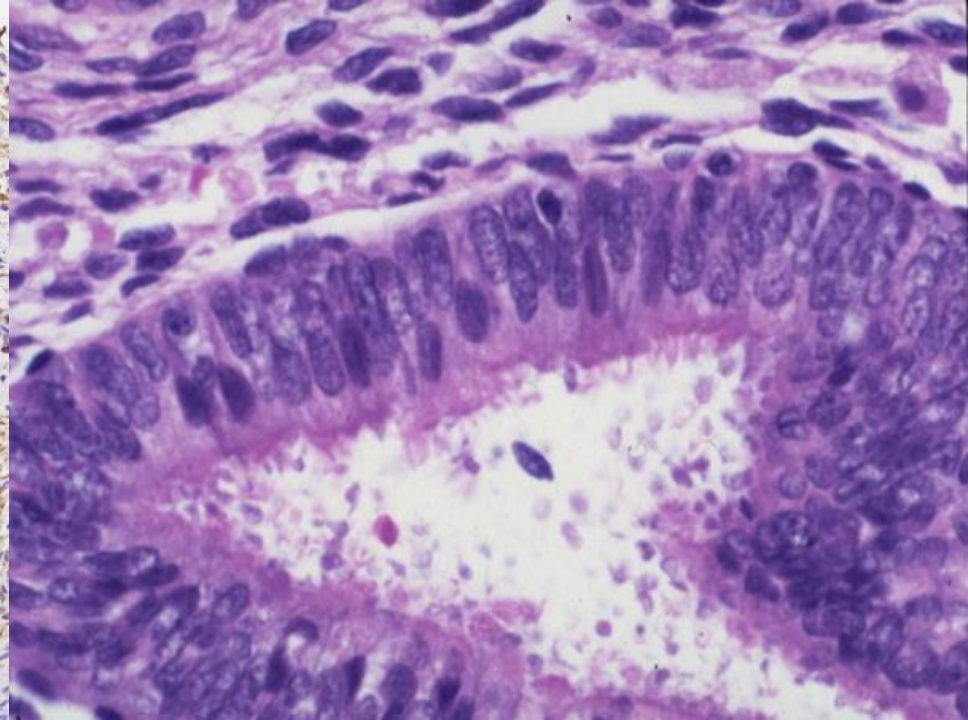
A diagnostic pitfall in ECCs

May give rise to AGUS

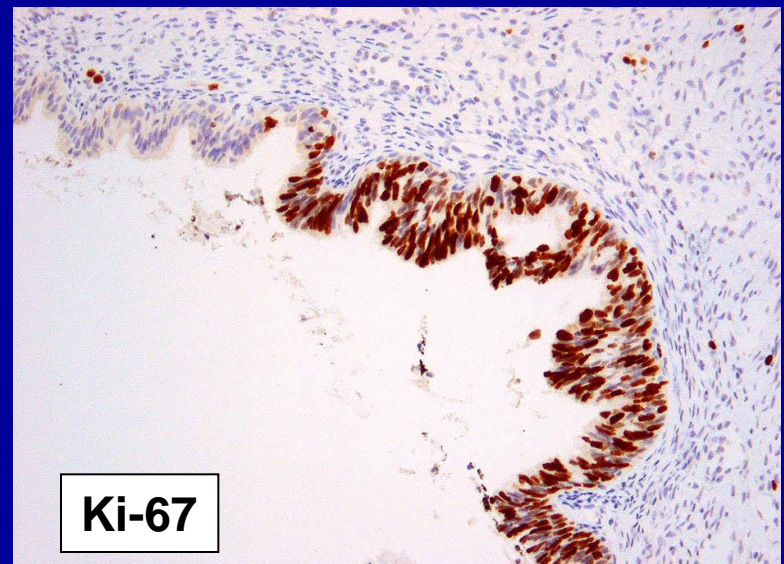
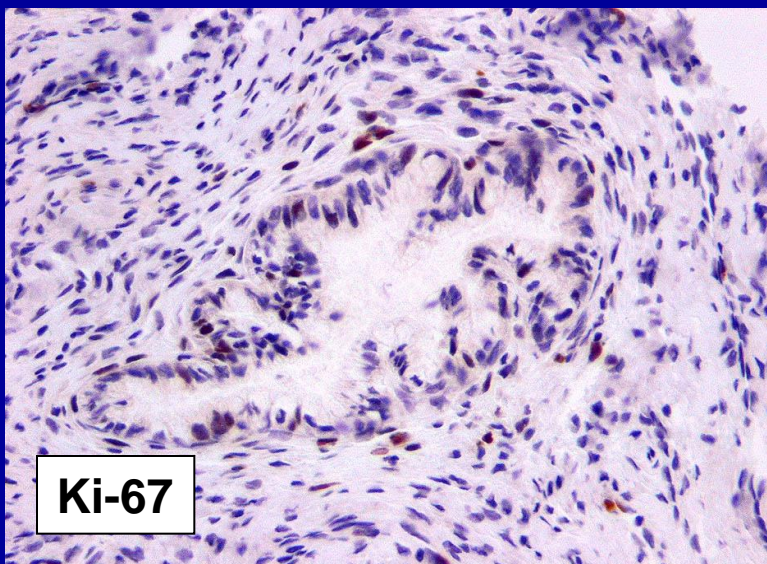
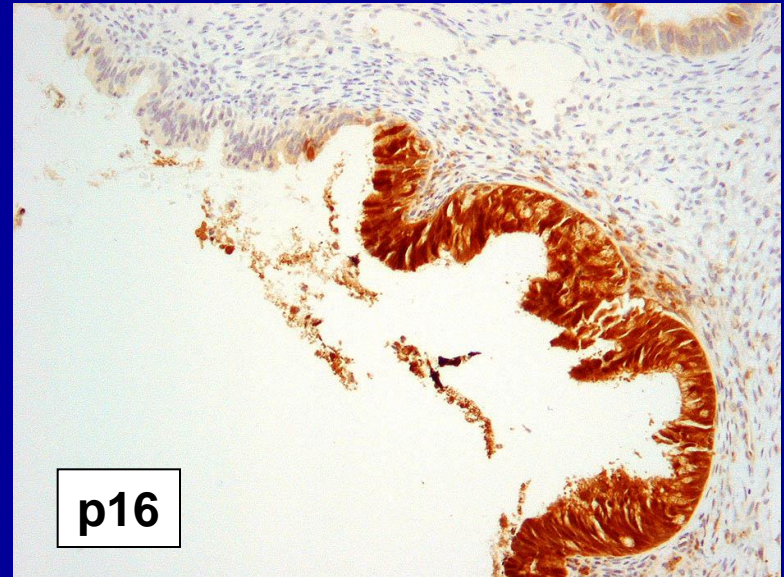
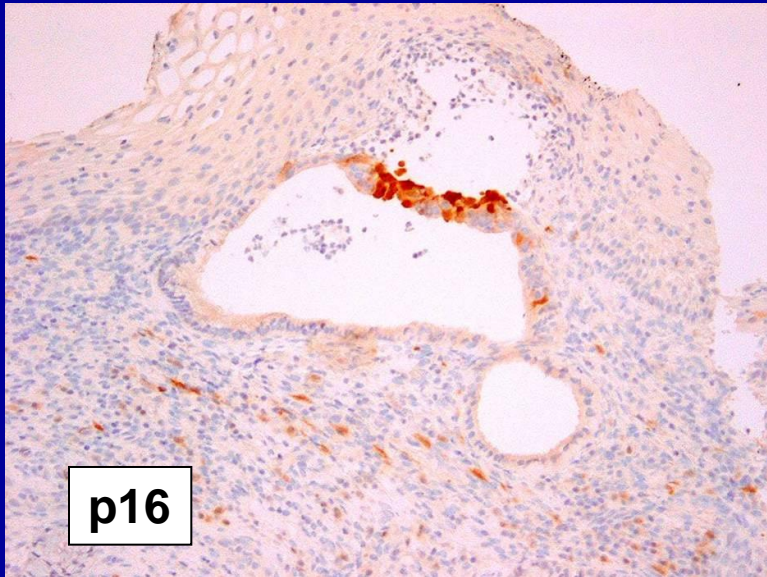
Worrisome appearance on cytology, ECCS, and biopsies



TM - Vimentin



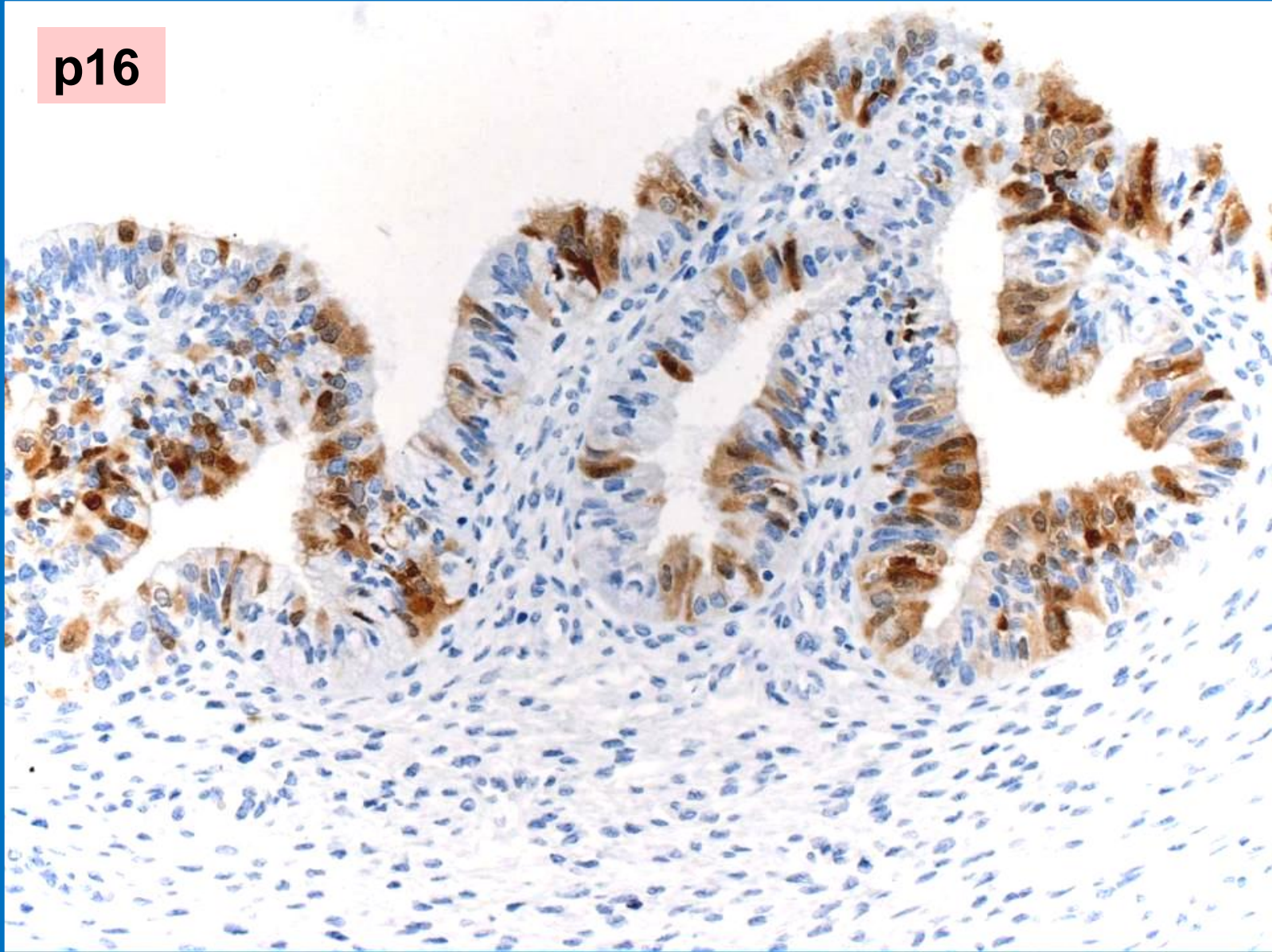
Tubal Metaplasia vs. AIS



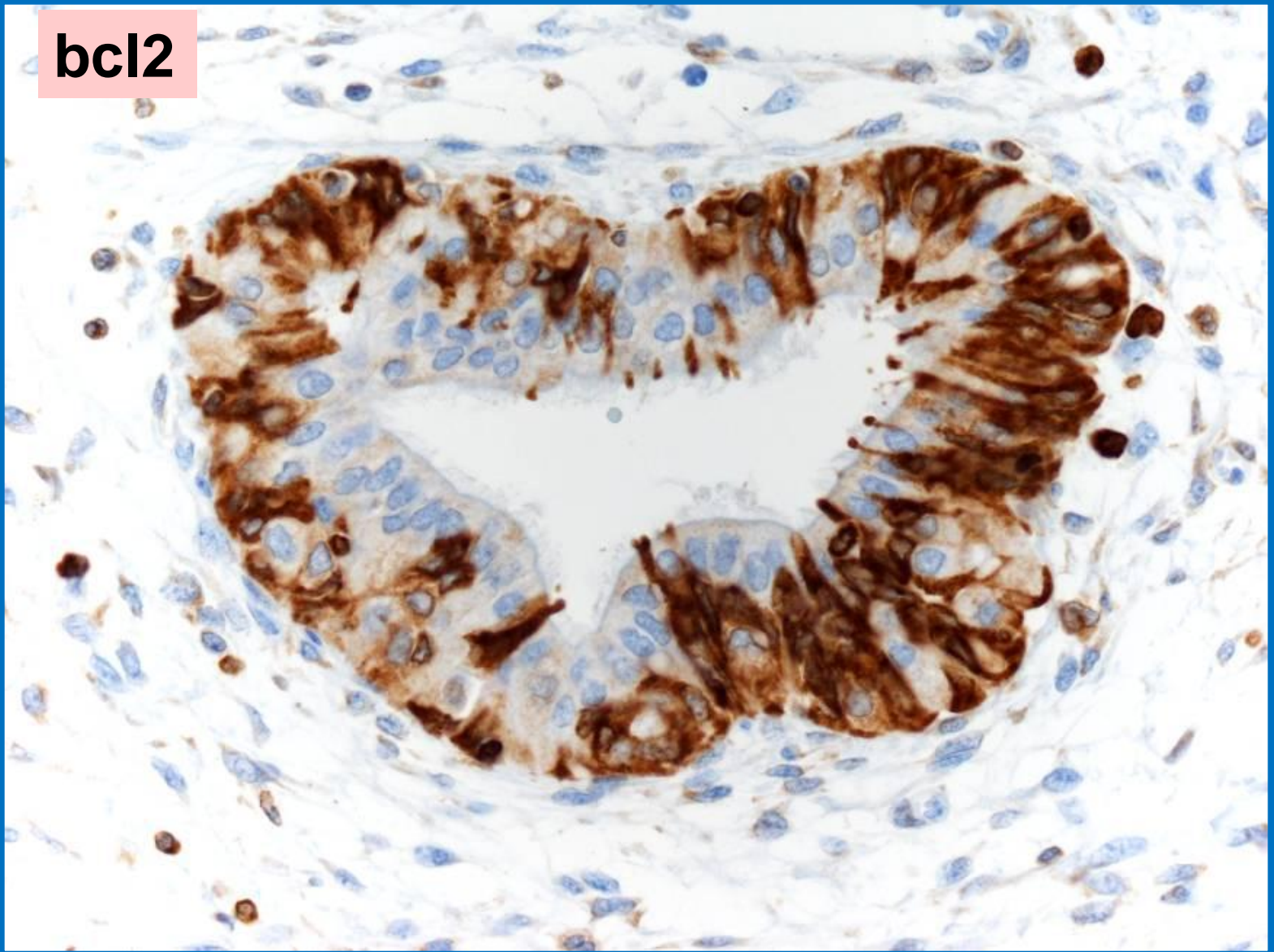
Tubal Metaplasia vs. AIS

	p16	Bcl-2	MIB- 1	ER, PR
Tubal metaplasia	Focal	+ cytoplasm	Less than 10%	+
AIS	100% Nuclear and cytoplasmatic	-	More than 30%	-

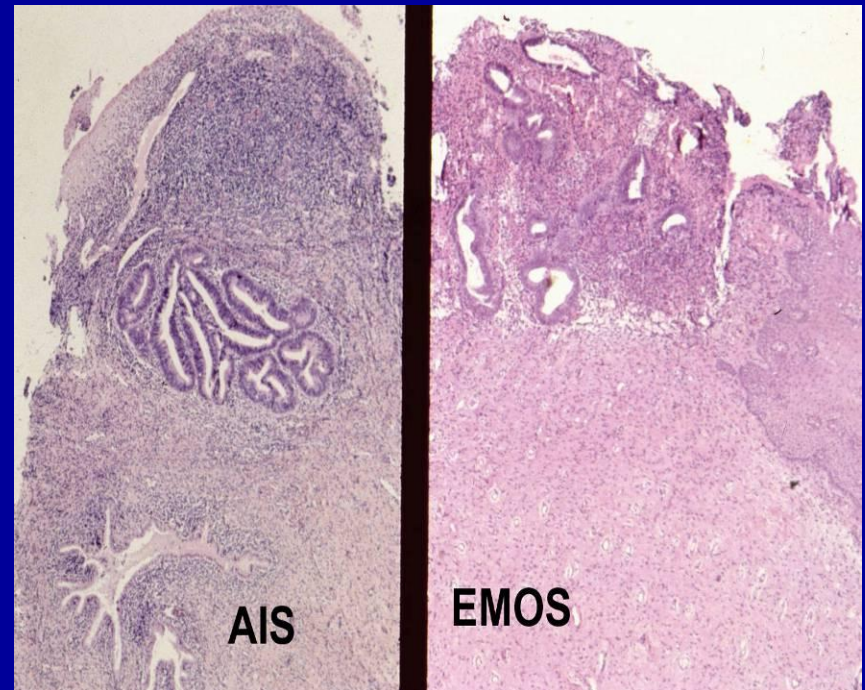
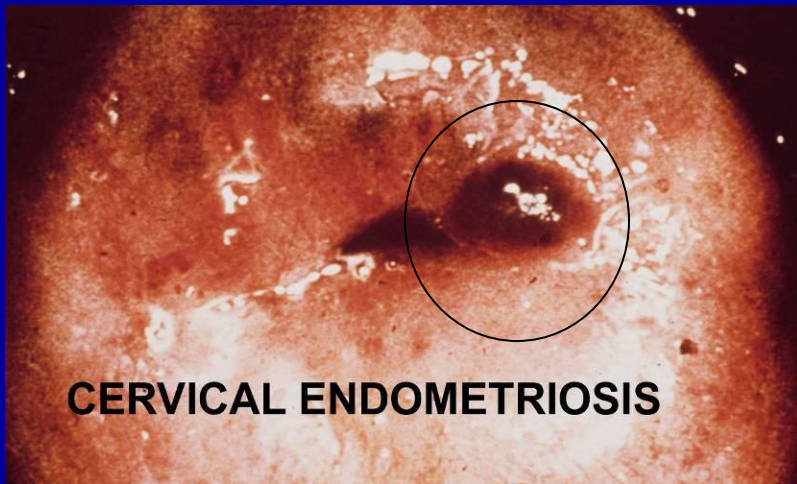
p16



bcl2

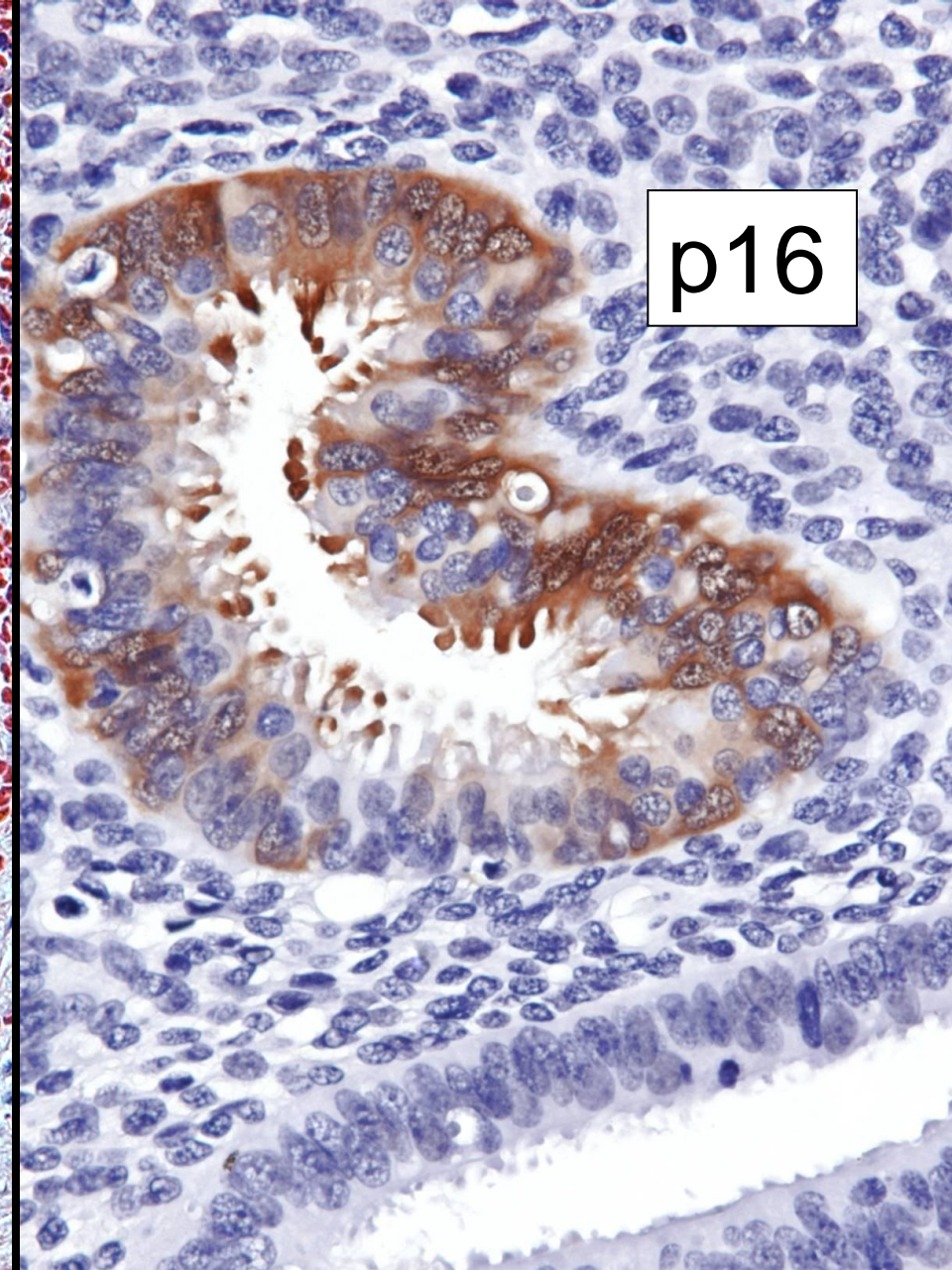
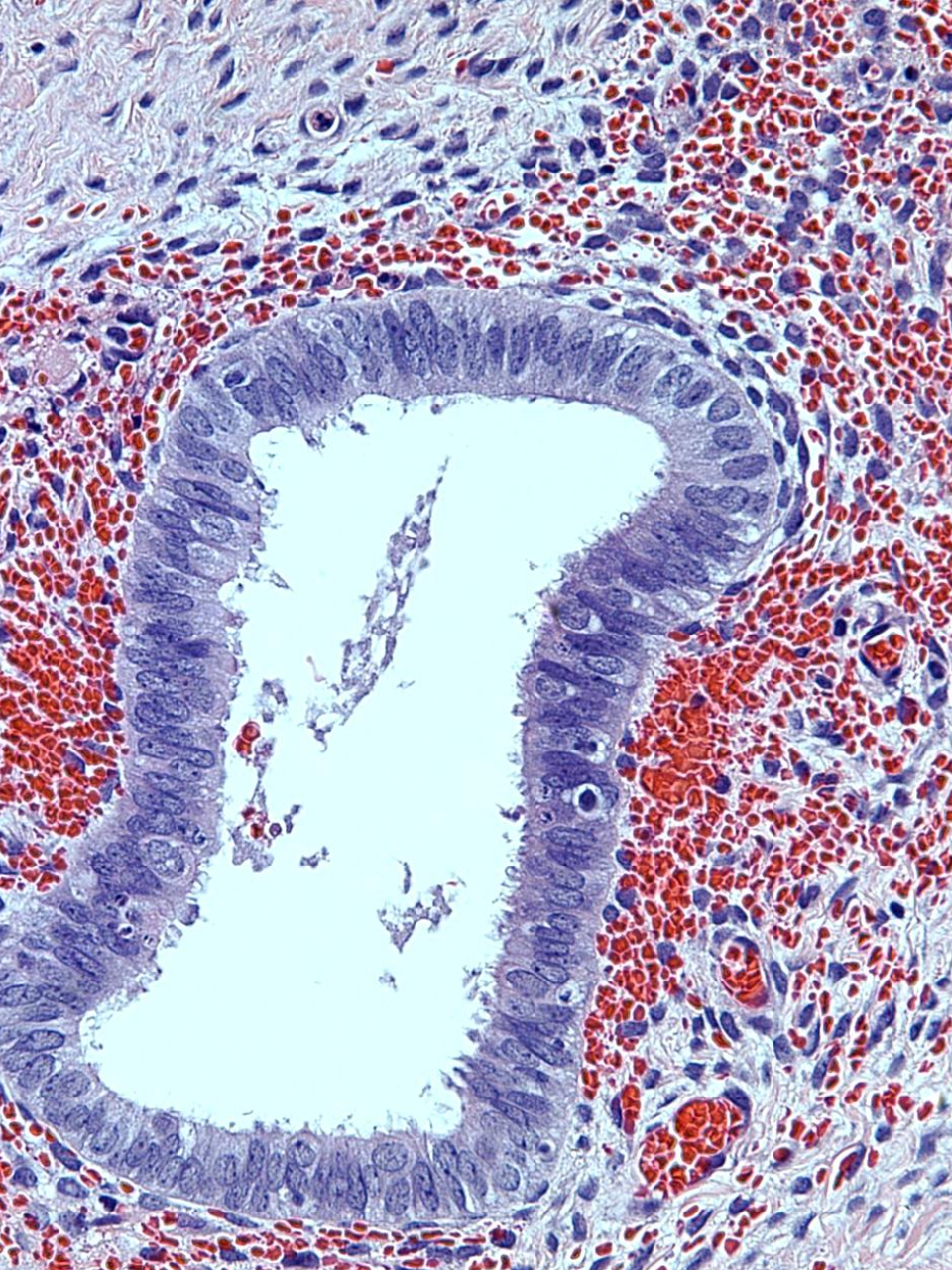


Cervical Endometriosis



- . A mimic of endocervical AIS
- Abnormal cervicovaginal smears due to endometriosis: a continuing problem.

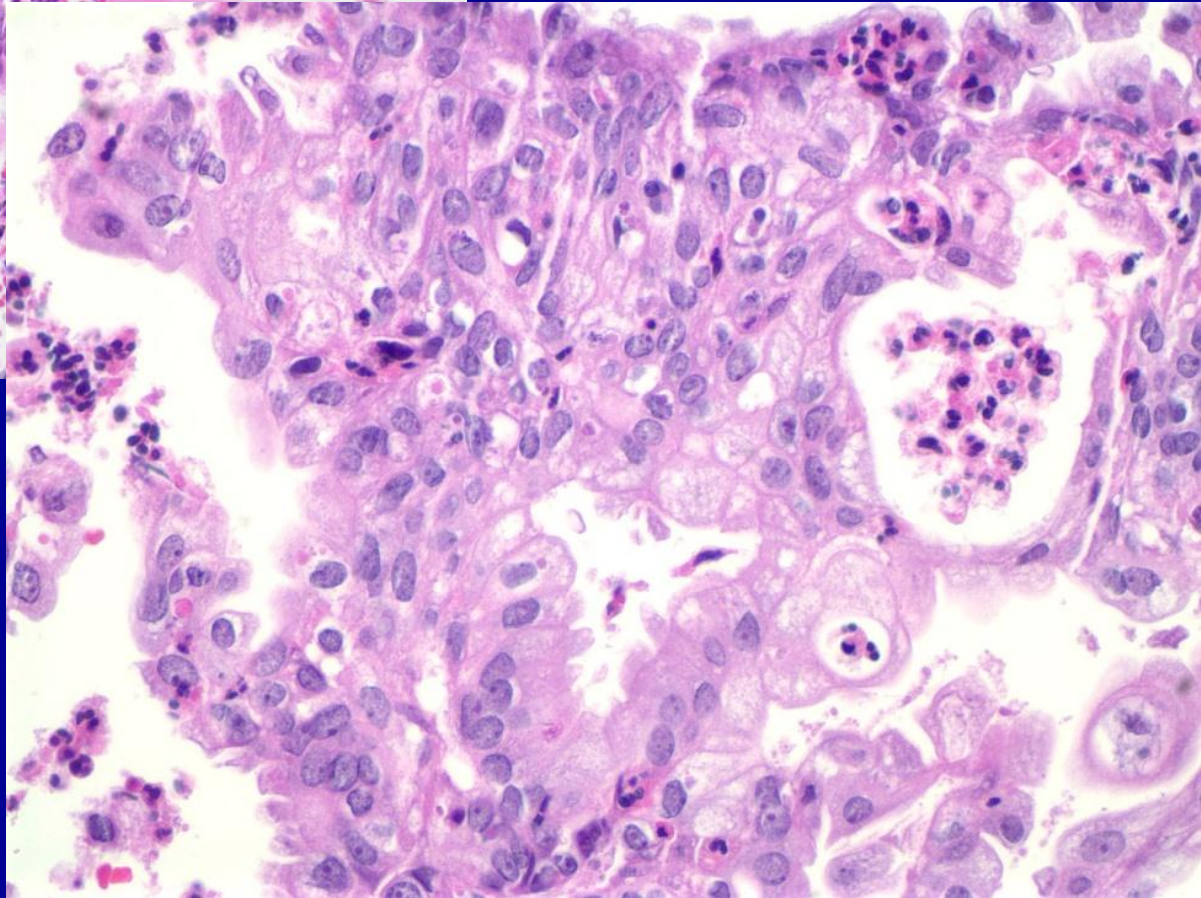
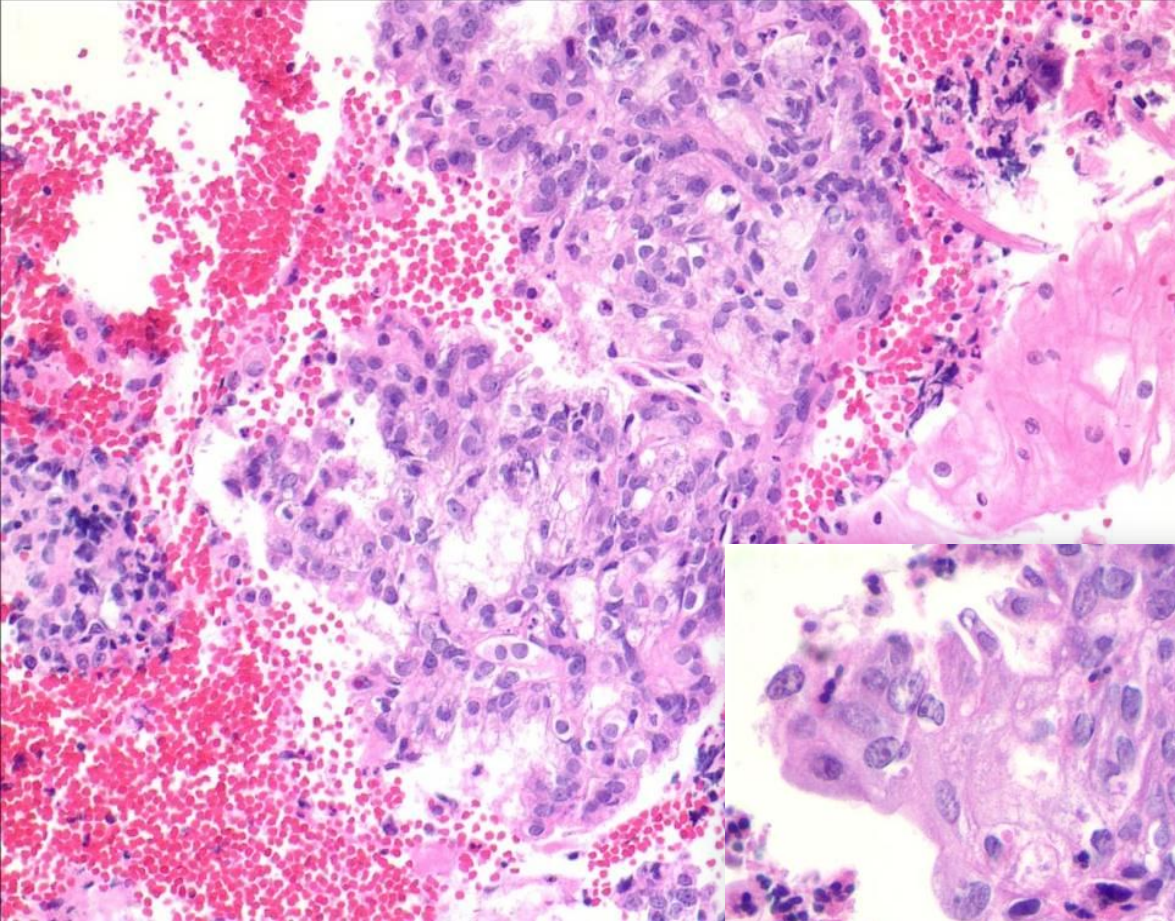
Diagn Cytopathol. 2002 Jan;26(1):35-40



p16

Cervical Endometriosis

Endocervical Microglandular Hyperplasia



Wolffian Fauna in the cervix



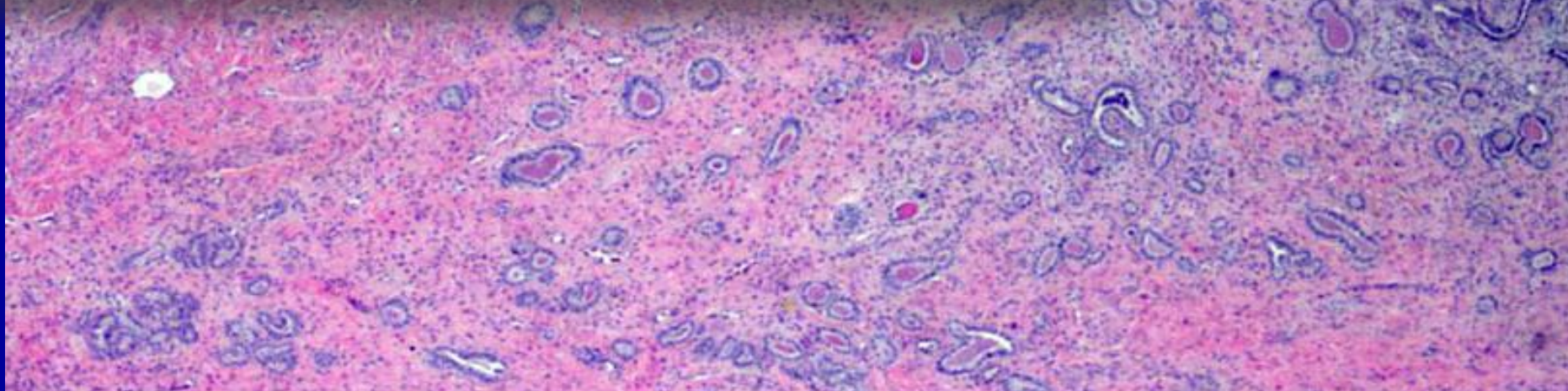
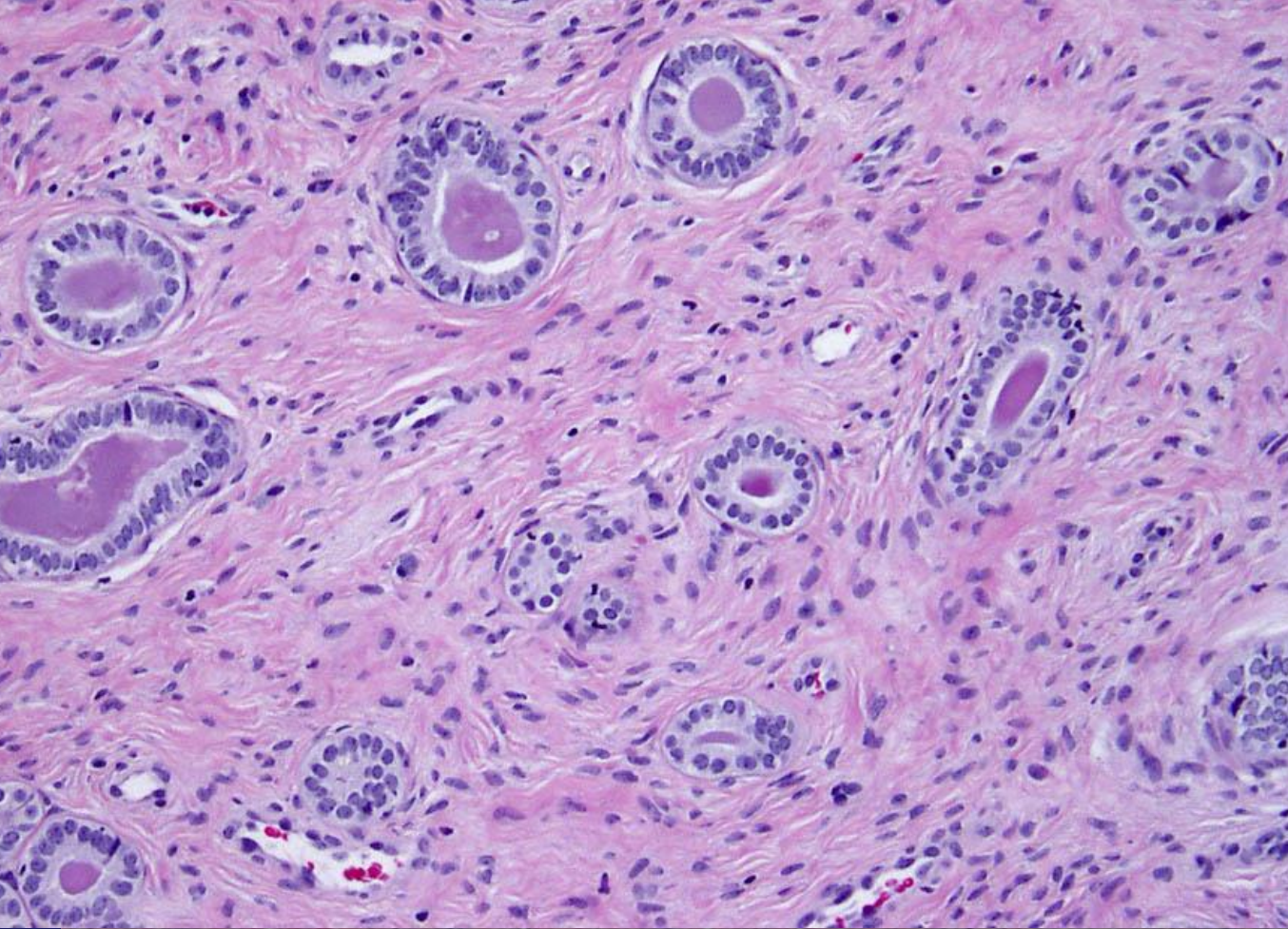
“NORMAL”

MESONEPHRIC
REMNANTS

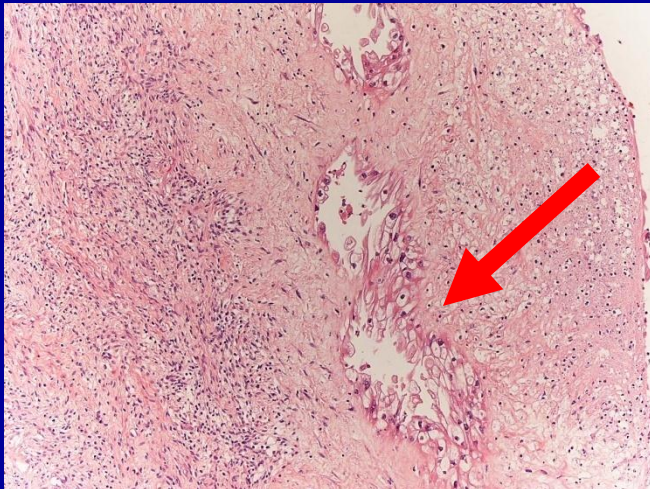
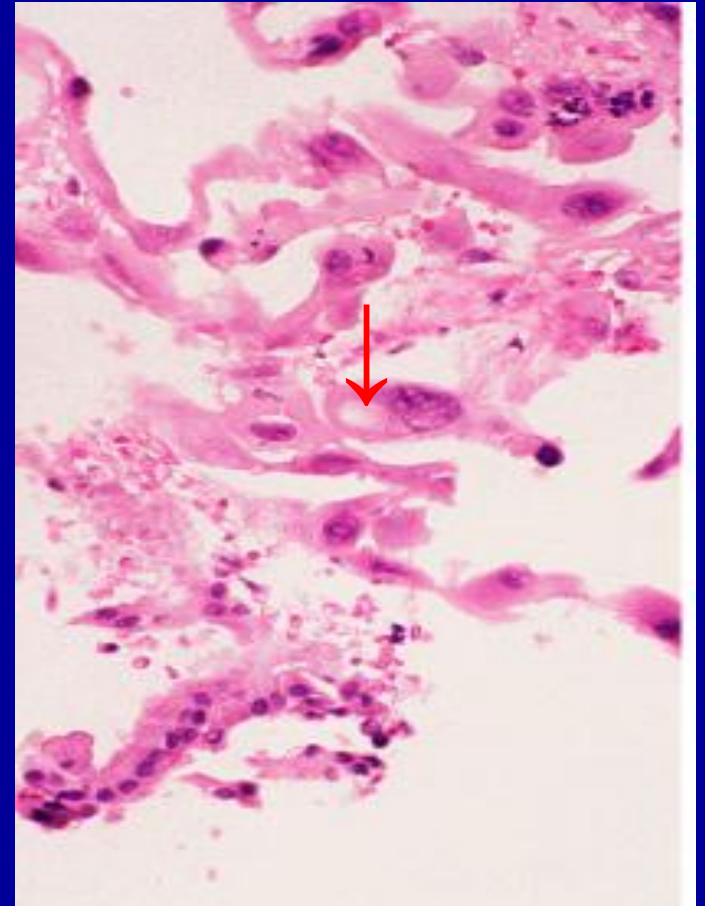
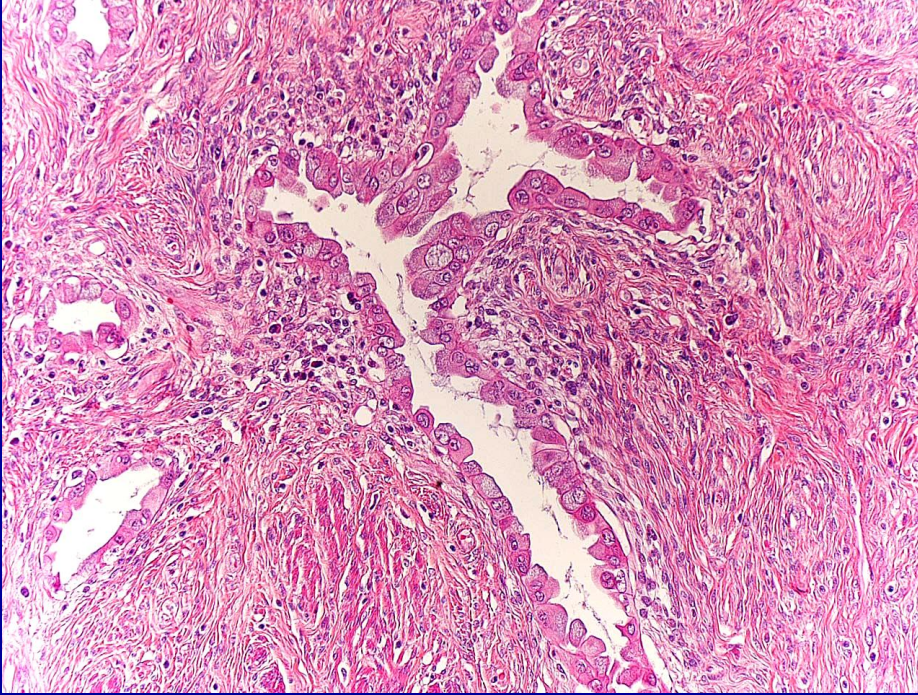
(FLORID)

MESONEPHRIC
HYPERPLASIA

MESONEPHRIC
CARCINOMA



Radiation induced Atypia



Management of Endocervical AIS

Hysterectomy - Preferred

Conservative Management

Acceptable if future fertility desired

Margins Involved OR
ECC Positive

Margins Negative

Re-excision
Recommended

Re-evaluation*
@ 6 mos - Acceptable

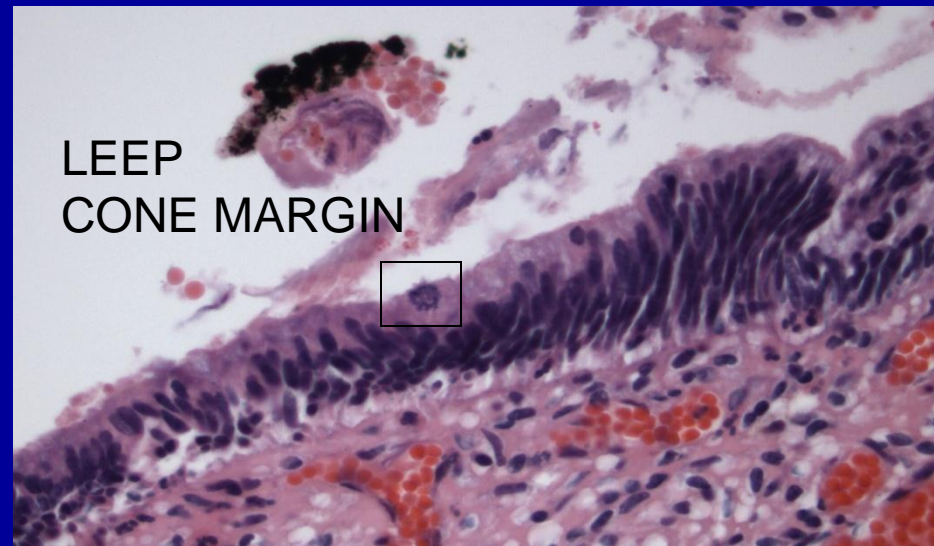
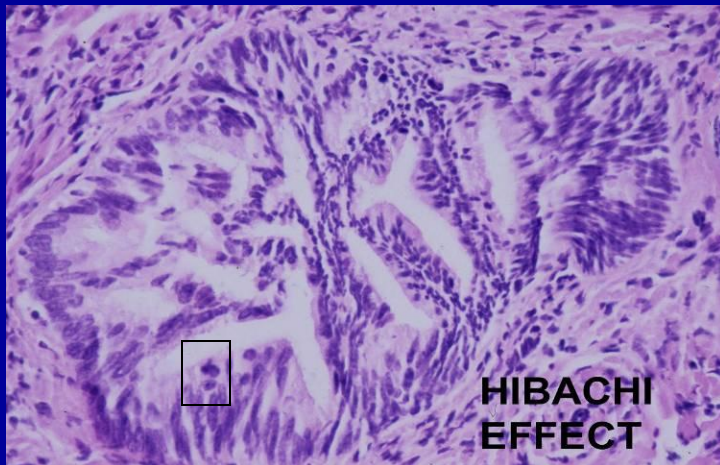
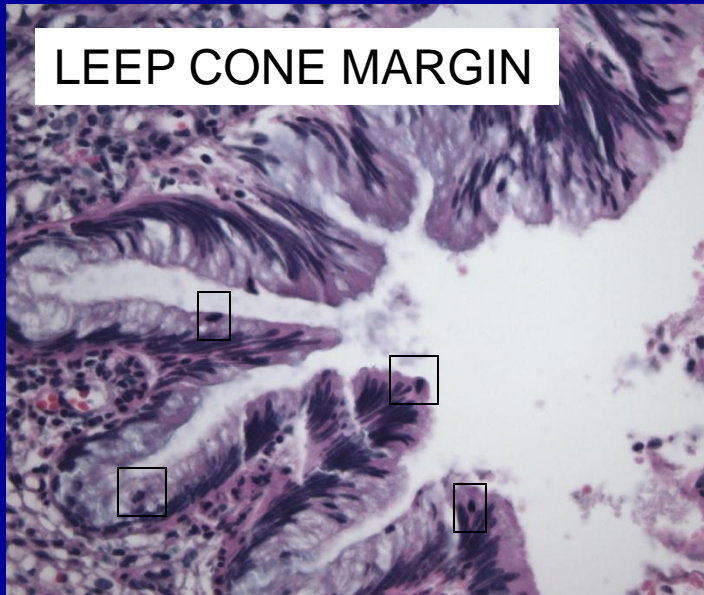
Long-term
Follow-up

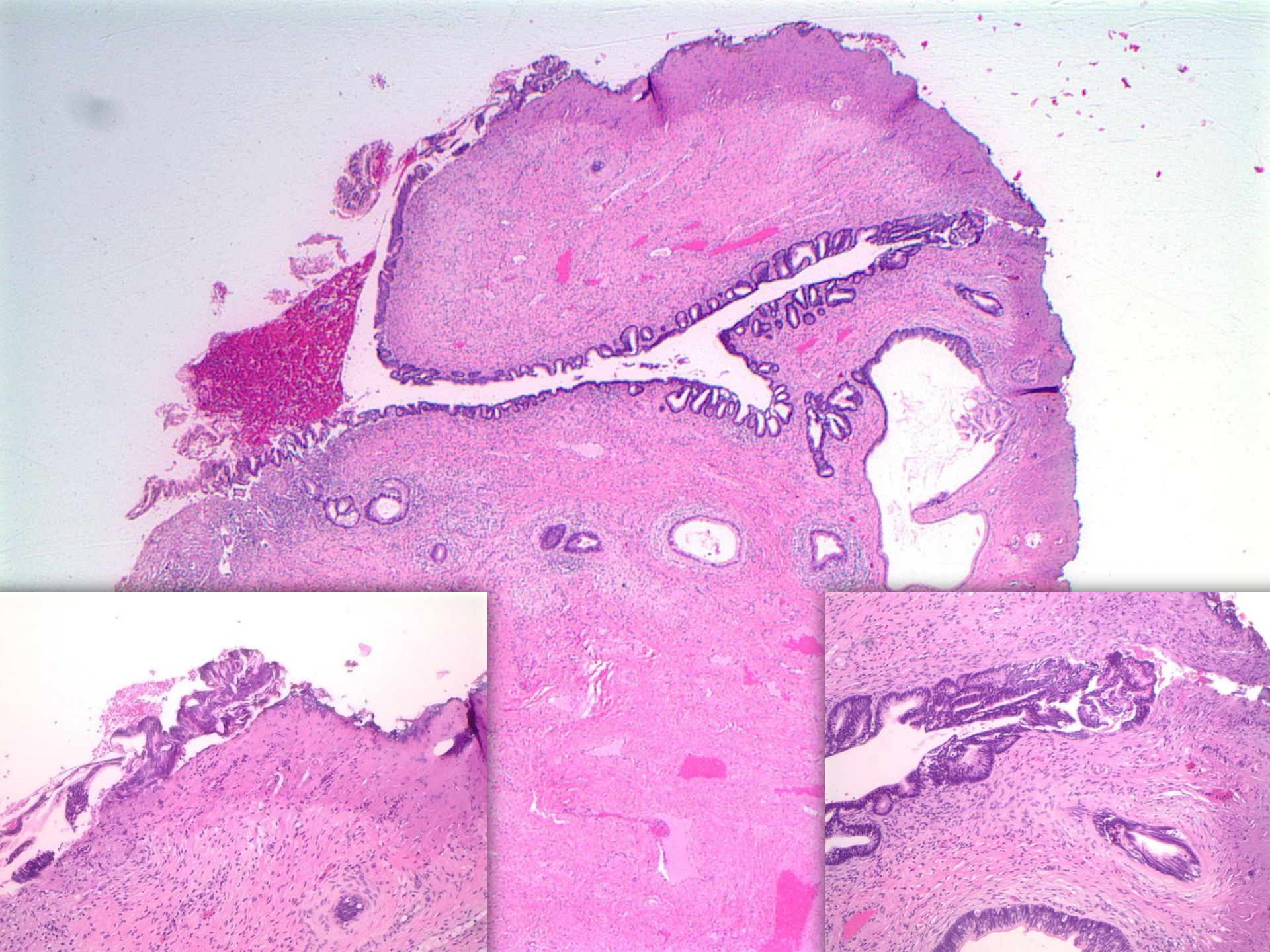
Histologic AIS

Margins Status and Persistence

- ◆ In a review of 1101 women undergoing conization for AIS:
 - Risk of residual disease at hysterectomy was 55% with (+) margins, 23% with (–) margins
 - Risk of recurrence among 560 women managed conservatively was only 7%
 - Including 1 with invasive cancer (0.2%)
 - Risk of +margin lower after CKC than LEEP
 - *Young JL et al. AJOG 2007;197:195.*

Thermal artifact on LEEP:



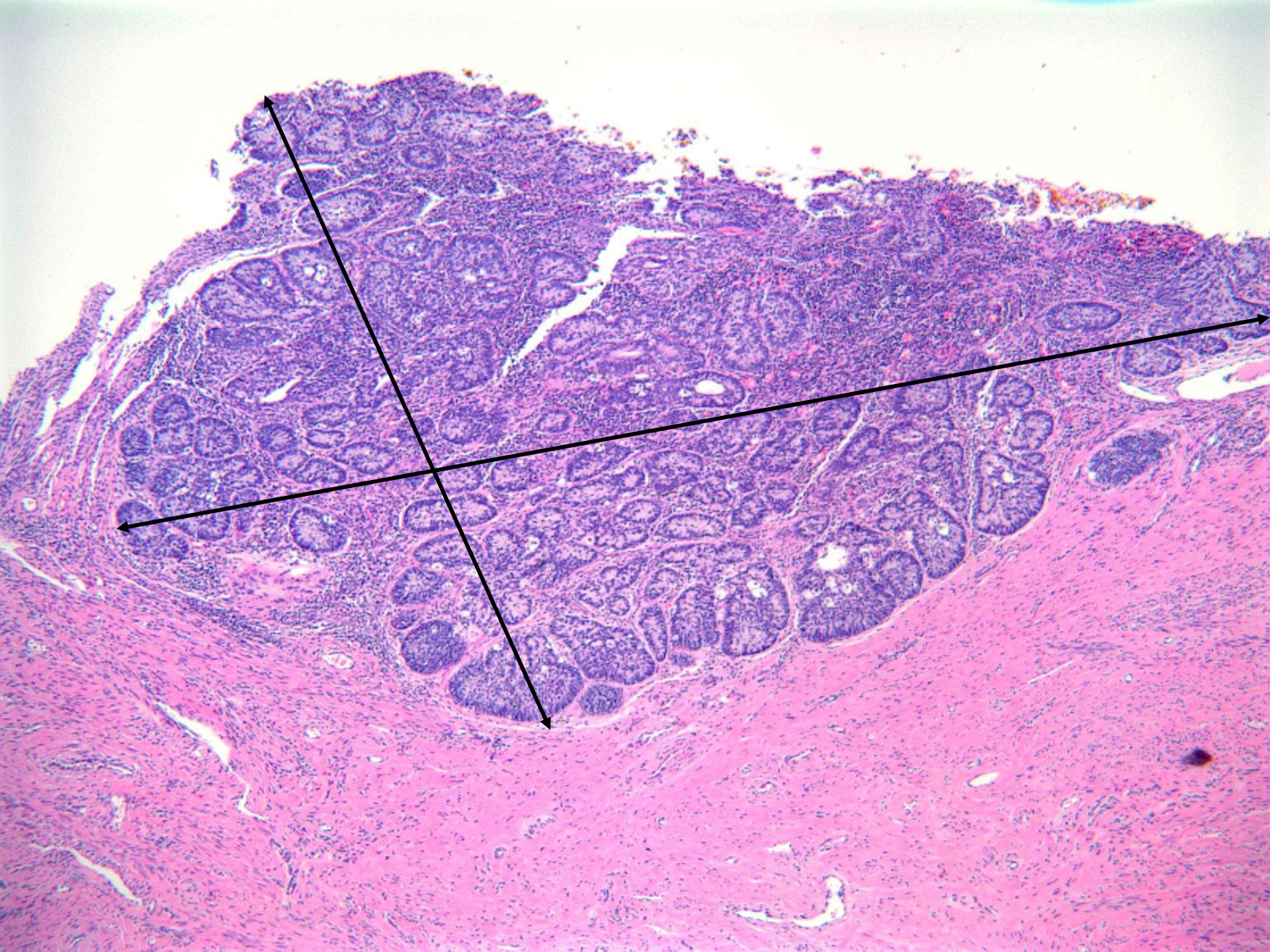


Early Invasive Endocervical Ca

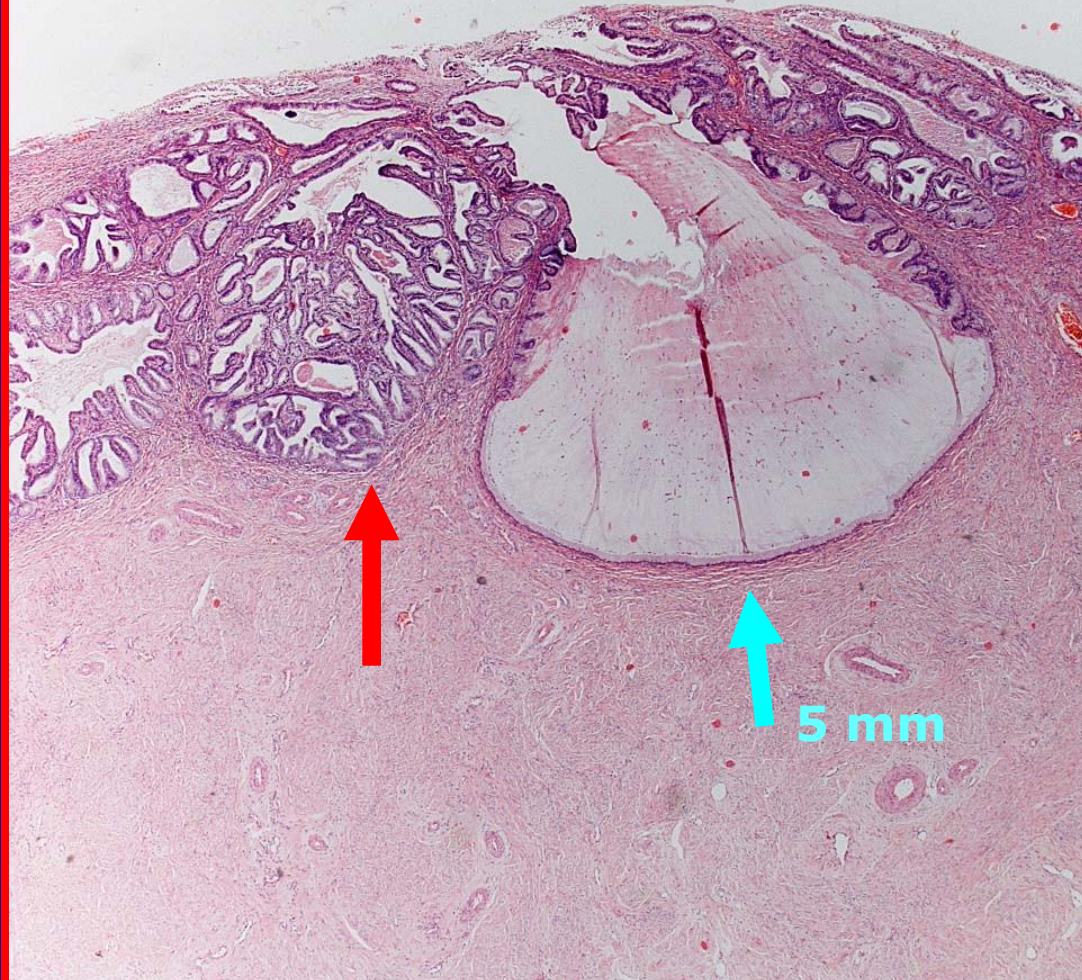
- Usually occurs in T-zone but sometimes higher in canal
- Particularly difficult to diagnose in small biopsies
- Two types of early invasion:
 - Destructive type with sharp borders
 - Expansile, confluent, pushing borders.

MACROSCOPY OF EARLY INVASIVE ADENOCARCINOMA



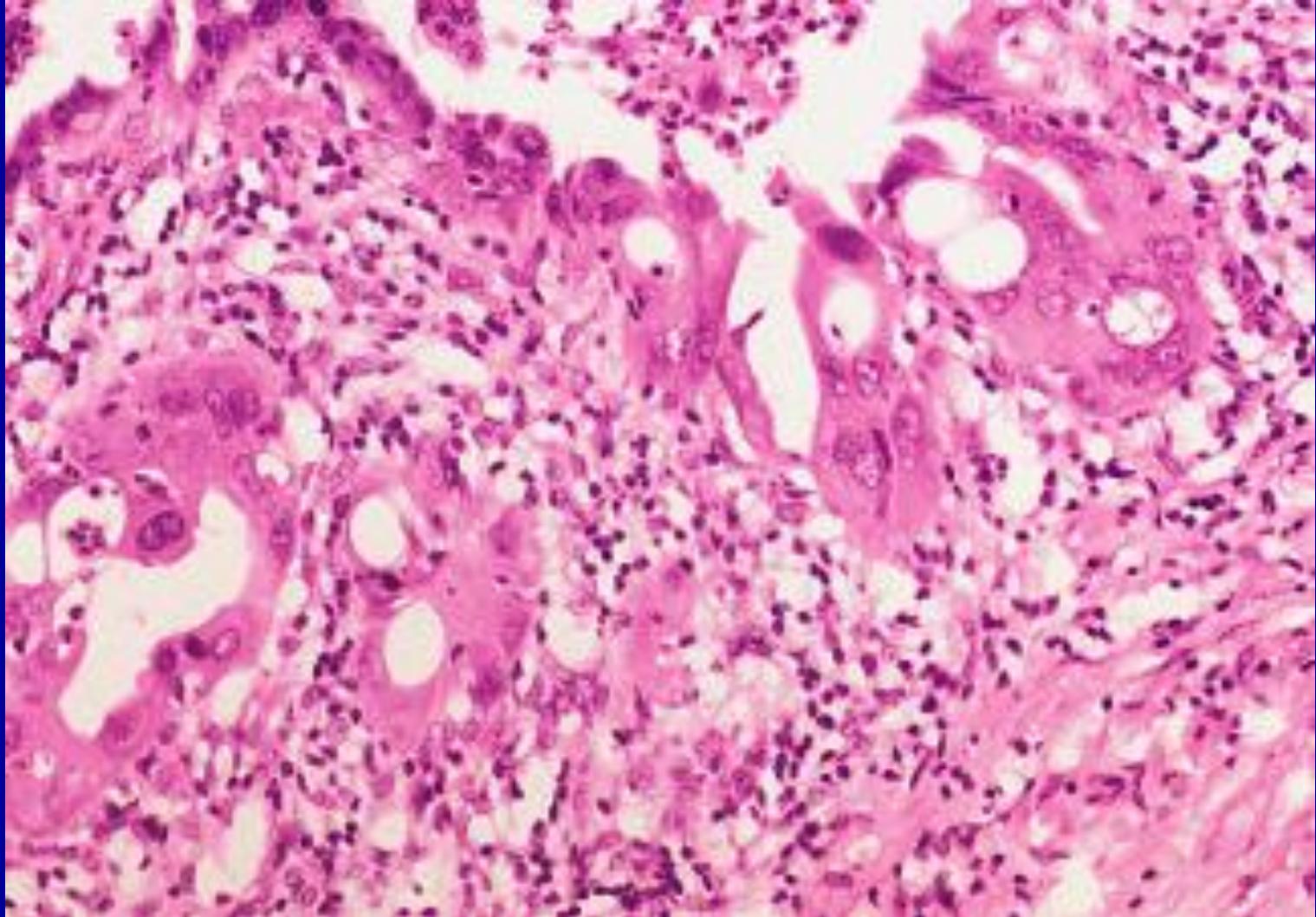


**expansile
pattern**



Well circumscribed glands extend deeper into the stroma as a compact unit rather than separate infiltrative glands. No stromal reaction

EARLY INVASIVE ADENOCARCINOMA

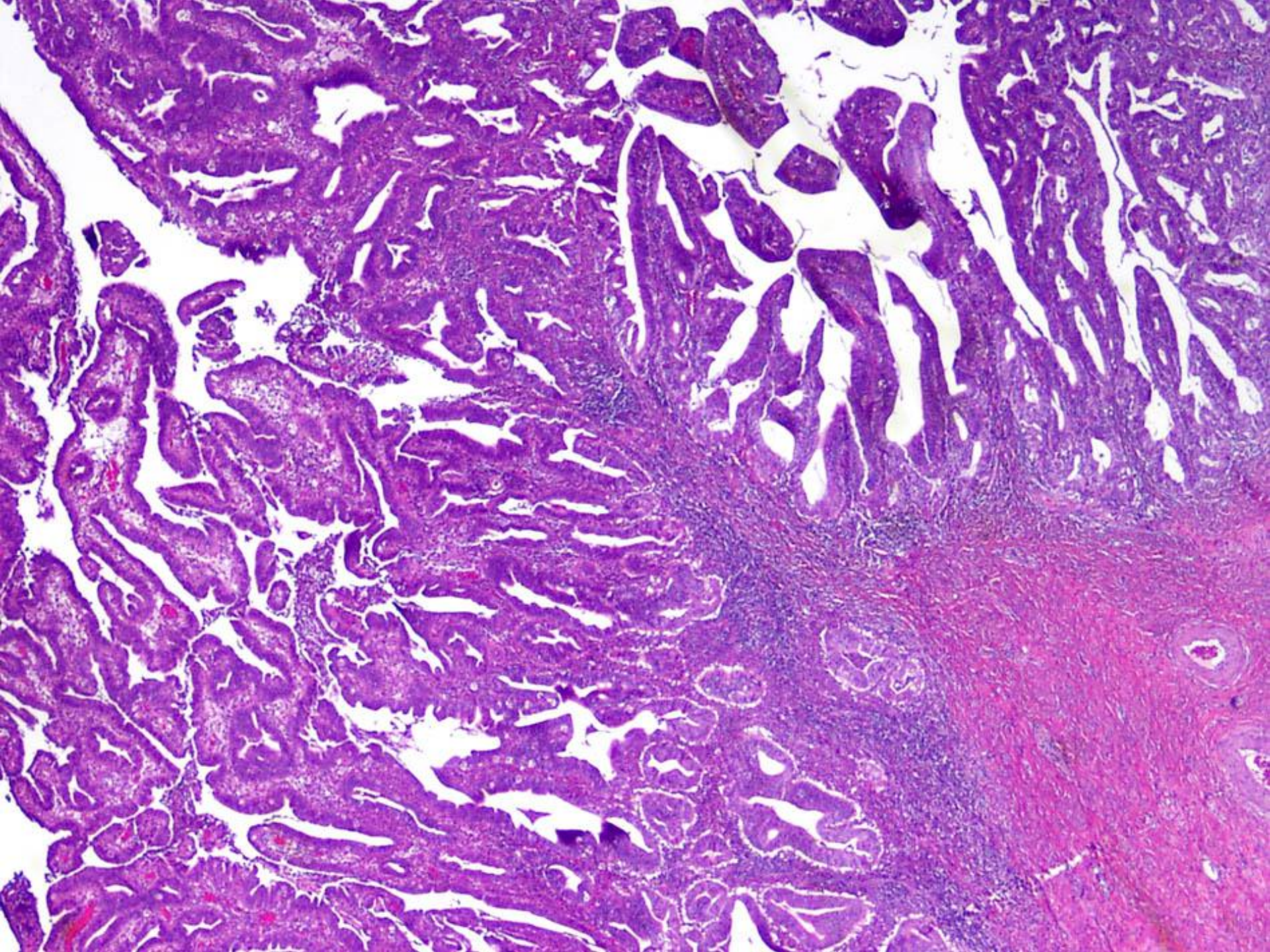


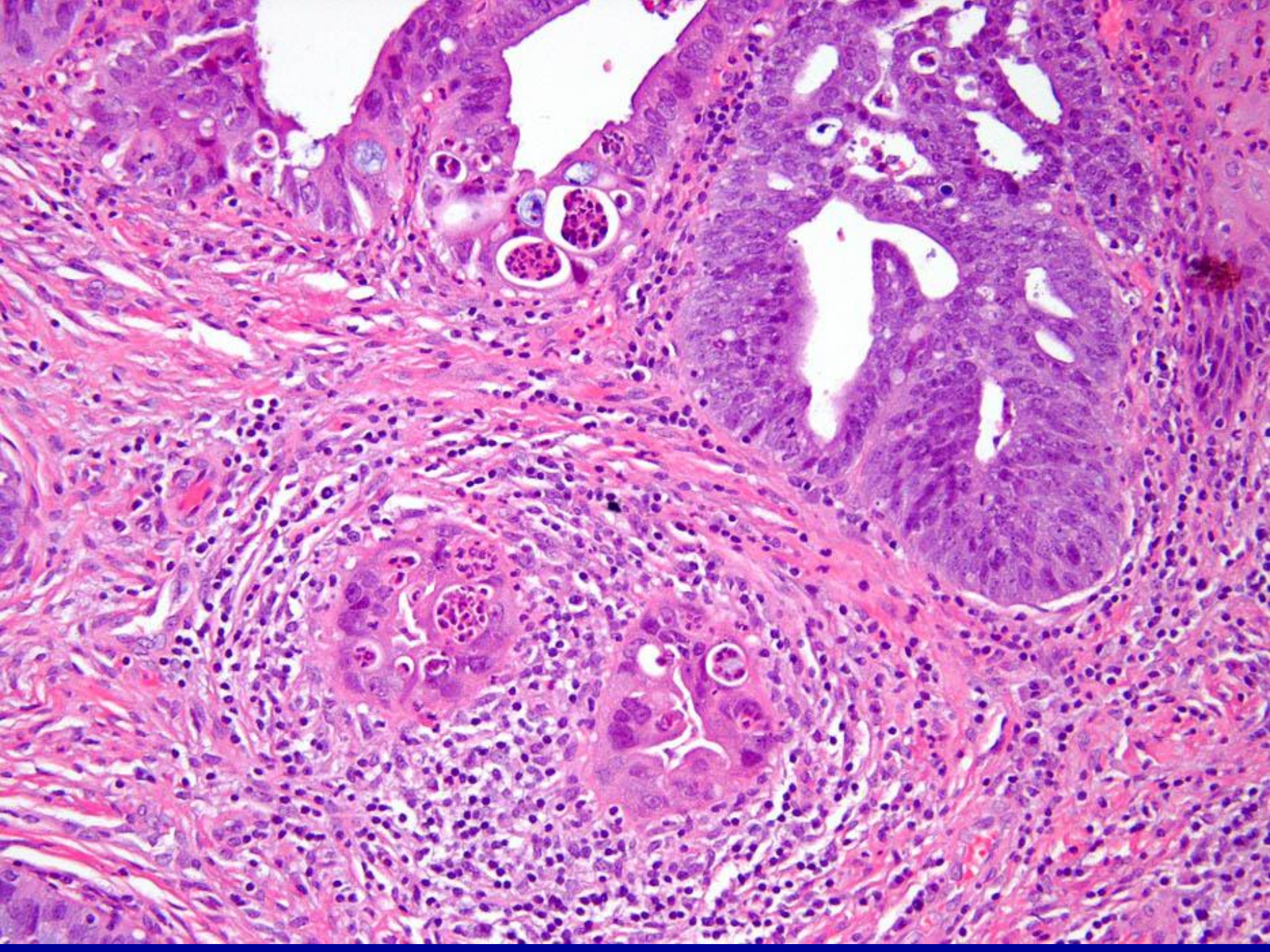
The Problem

- Is it invasive?
- How deep?
- How do you measure it?

AIS vs. Invasive Adenocarcinoma

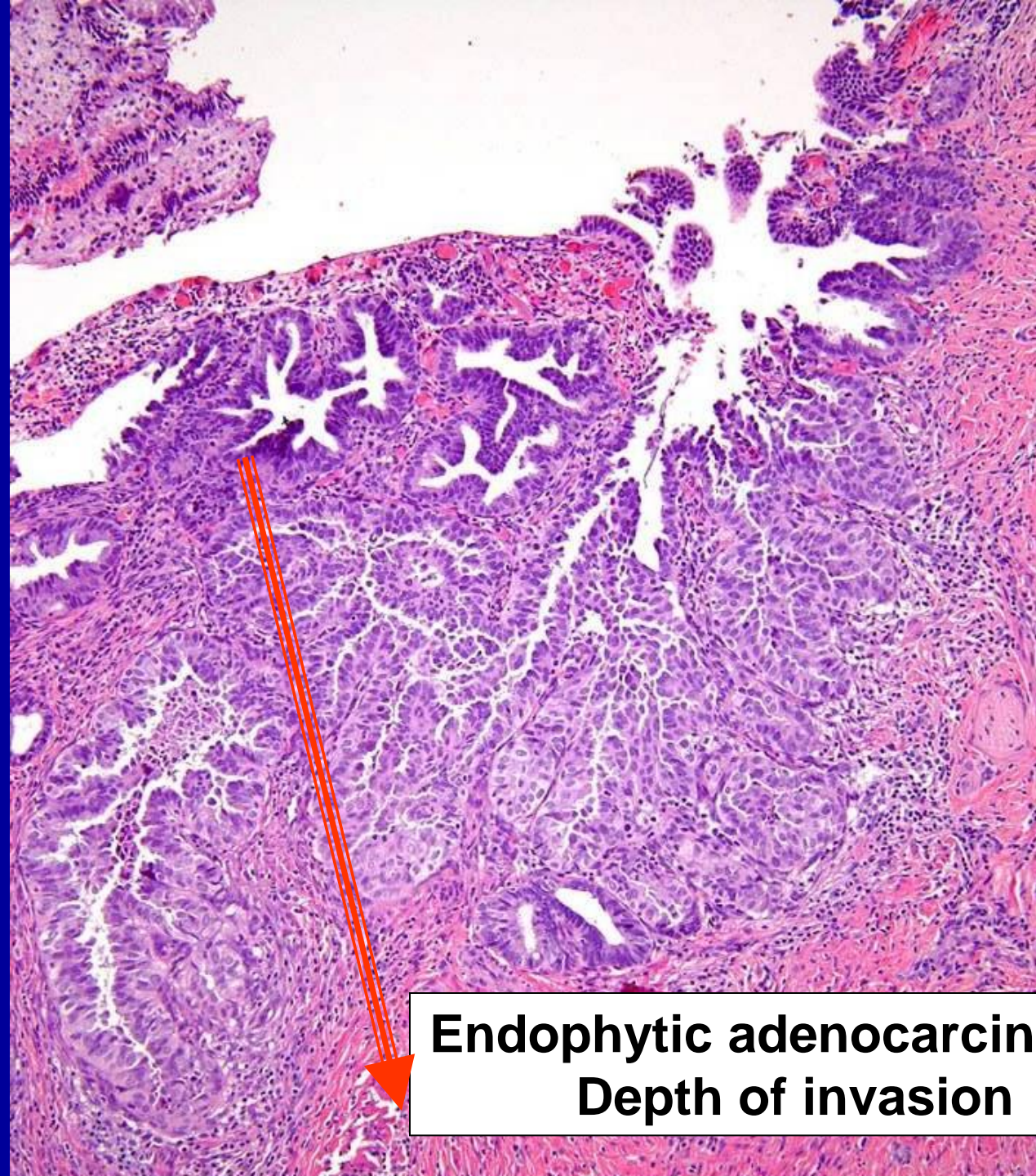
- **Morphologic features favoring invasive carcinoma**
 - **Stromal reaction**
 - **Loss of lobular contour; strikingly increased gland density**
 - **Extensive intraglandular architectural complexity**
 - **Cytologic change from AIS**
 - **Deep extension; perivascular invasion**
- **Immunohistochemistry: not contributory**



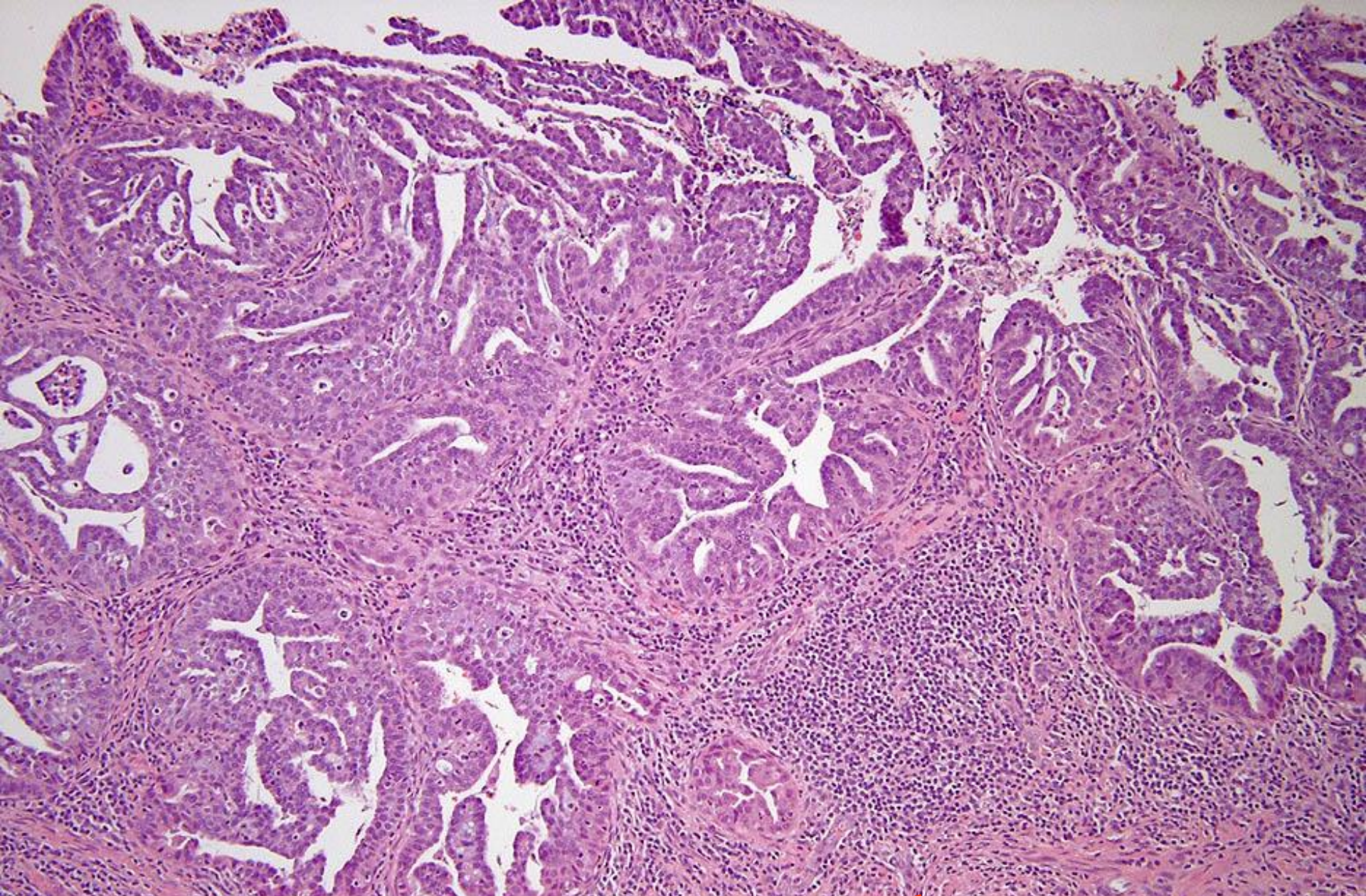


AIS vs. Invasive Adenocarcinoma

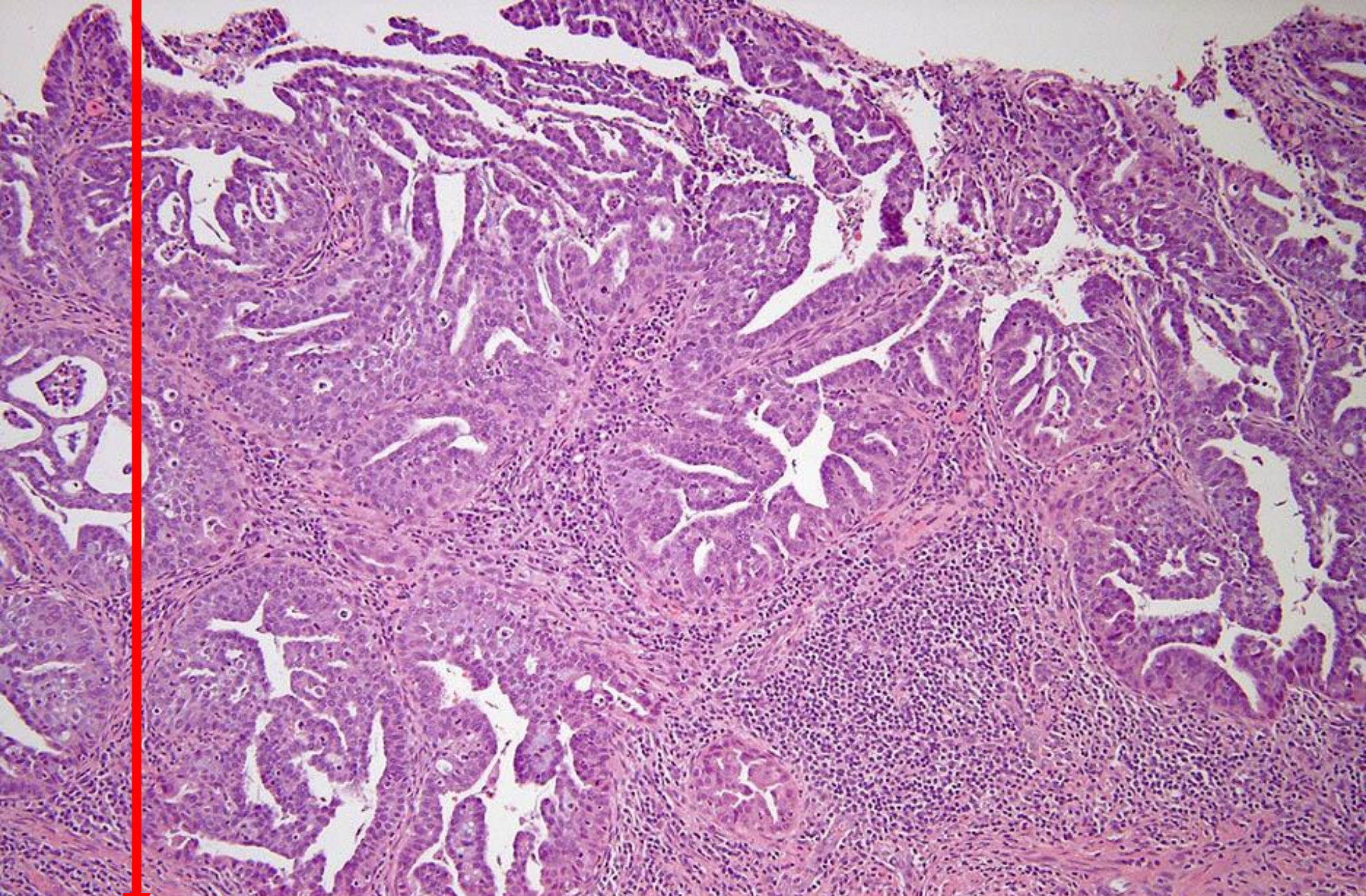
- **Sometimes you have to equivocate**
 - **Measure greatest extent of possibly invasive carcinoma**
 - **Search for lymphovascular invasion**



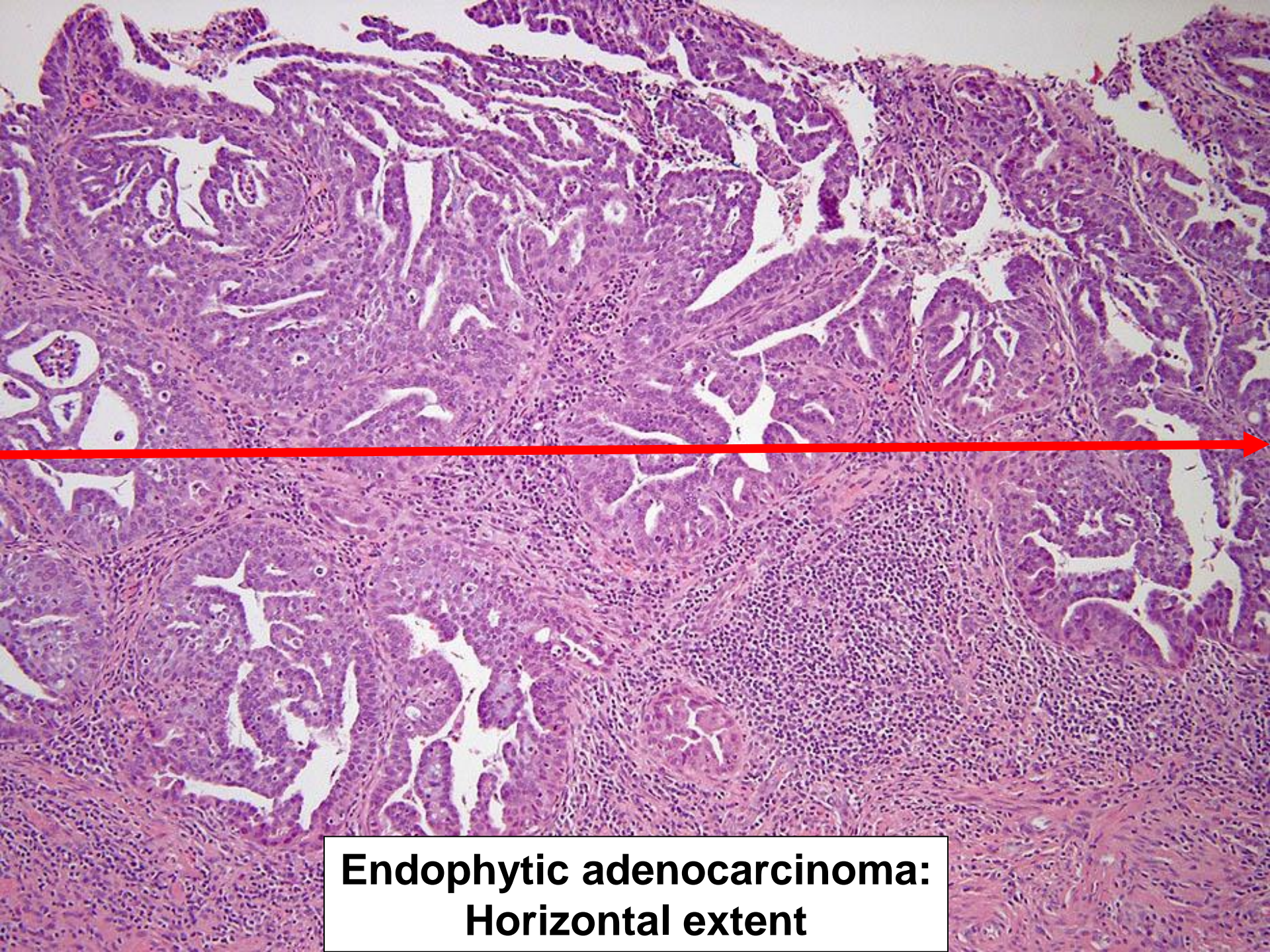
**Endophytic adenocarcinoma:
Depth of invasion**



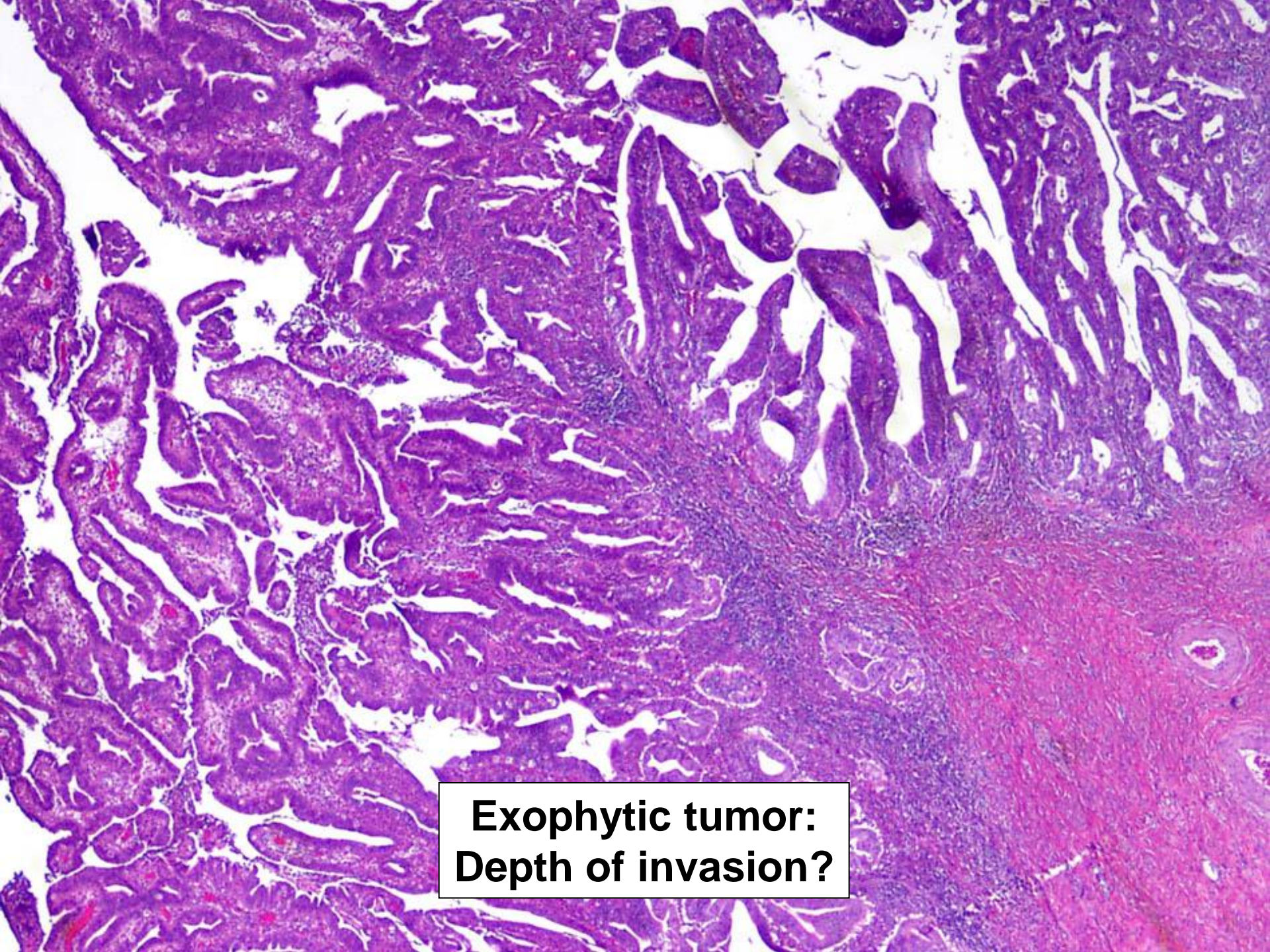
**Endophytic adenocarcinoma:
Depth of invasion?**



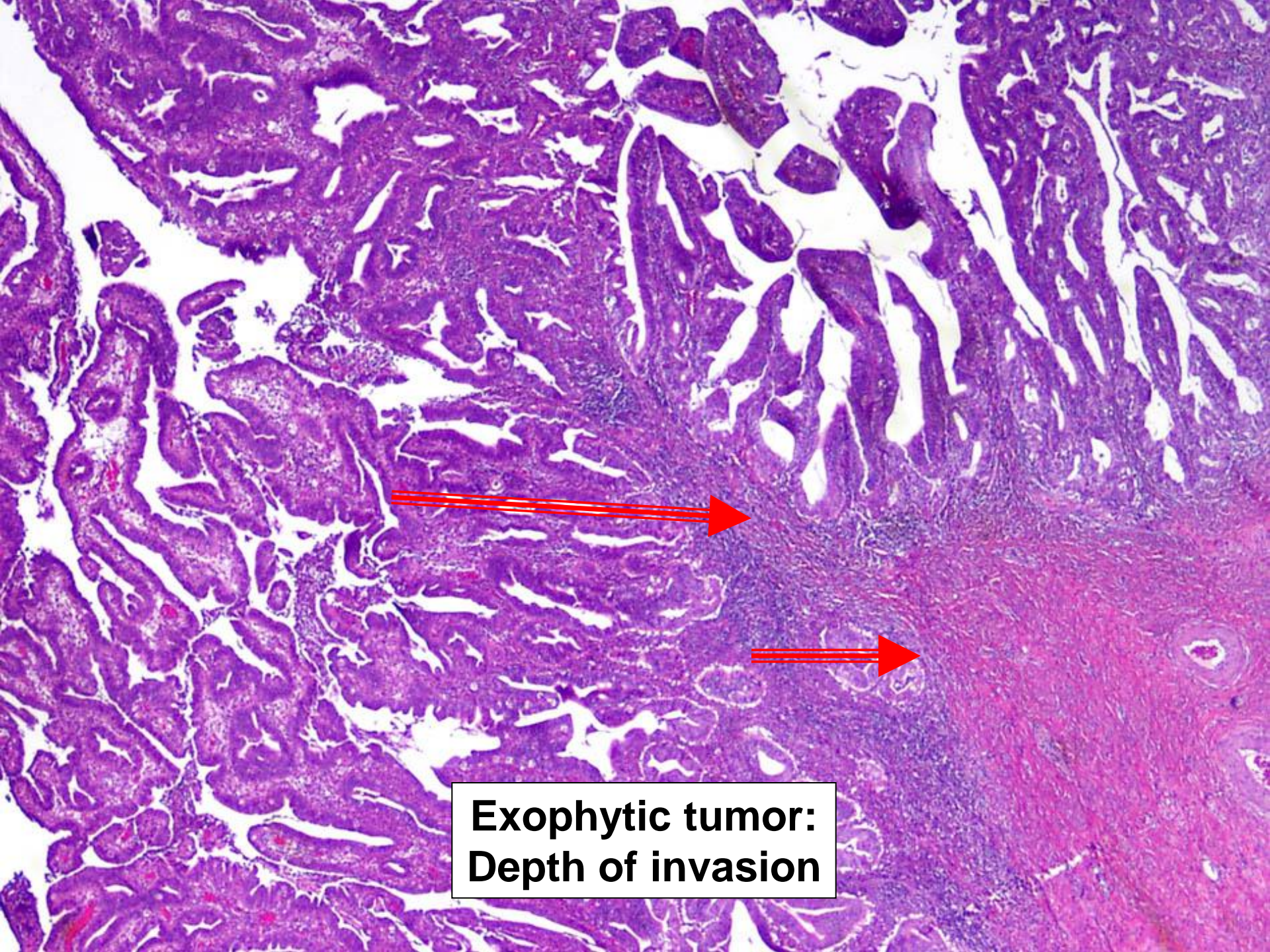
**Endophytic adenocarcinoma:
Lesion THICKNESS**



**Endophytic adenocarcinoma:
Horizontal extent**



**Exophytic tumor:
Depth of invasion?**



**Exophytic tumor:
Depth of invasion**

Cervical Cancer Staging

- **Microscopically detected invasive carcinoma**
 - **Stage IA1:** depth \leq 3 mm AND horizontal extent \leq 7 mm: conservative therapy

Cervical Cancer Staging

- **Microscopically detected invasive carcinoma**
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 - **Stage IA2:** depth ≤ 5 mm AND horizontal extent ≤ 7 mm: radical therapy > conservative therapy

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- **Microscopically detected invasive carcinoma**
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Cervical Cancer Staging

- **Microscopically detected invasive carcinoma**
 - **Stage IA1:** depth \leq 3 mm AND horizontal extent \leq 7 mm: conservative therapy
 - **Stage IA2:** depth \leq 5 mm AND horizontal extent \leq 7 mm: radical therapy > conservative therapy
 - **Stage IB1:** microscopically detected invasive carcinoma exceeding Stage IA2: radical therapy

Cervical cancer staging

- **Small, confined clinically visible lesion**
 - **Stage IB1: incisional biopsy followed by radical surgery**

Management

- **Cone biopsy is curative if:**
 - **Stage IA1**
 - **Margins are negative**
 - **No lymphovascular invasion**

CA—what's important to mention in the report?

- Cervical biopsy
 - Establish invasive carcinoma for a grossly visible lesion

CA—what's important to mention in the report?

- Cone biopsy or LEEP
 - Establish invasive carcinoma for a microscopic lesion
 - Determine invasive carcinoma's extent and presence of LVI
 - Depth of invasion (exophytic adenocarcinoma)
 - Thickness of invasive carcinoma (adenocarcinoma)
 - Horizontal extent of invasive carcinoma

CA—what's important to mention in the report?

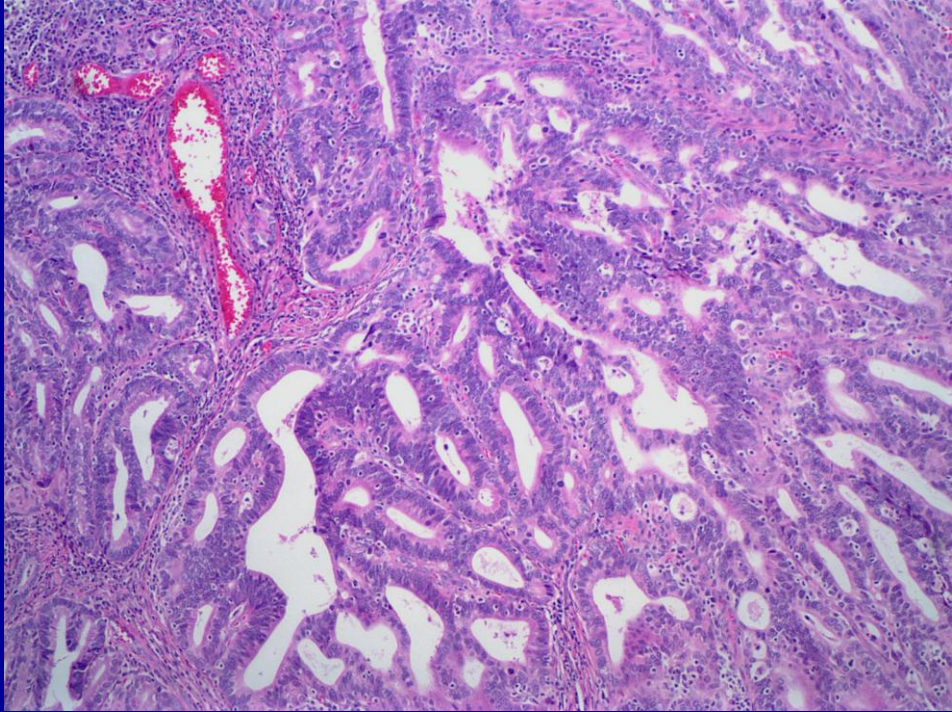
- Hysterectomy
 - Determine pathologic factors that influence decision for adjuvant therapy
 - Parametrial invasion (if radical)
 - Margin involvement
 - Lymph node metastasis
 - Gross lesion size
 - Depth or thickness of cervical wall invasion
 - LVI

Endocervical adenocarcinoma histologic subtype

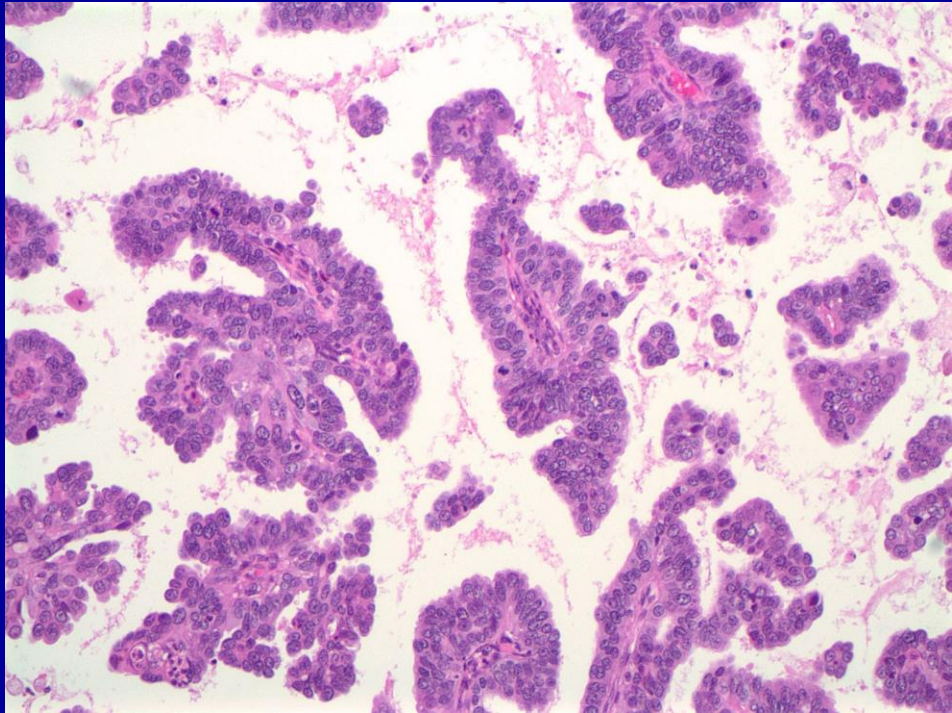
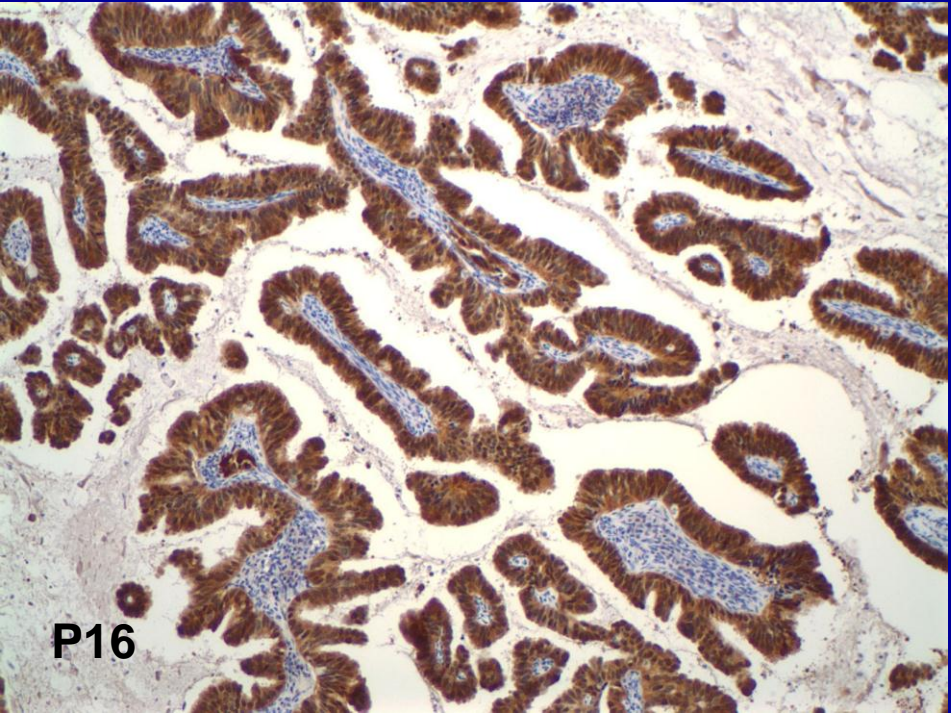
**HPV positive endocervical
adenocarcinomas**

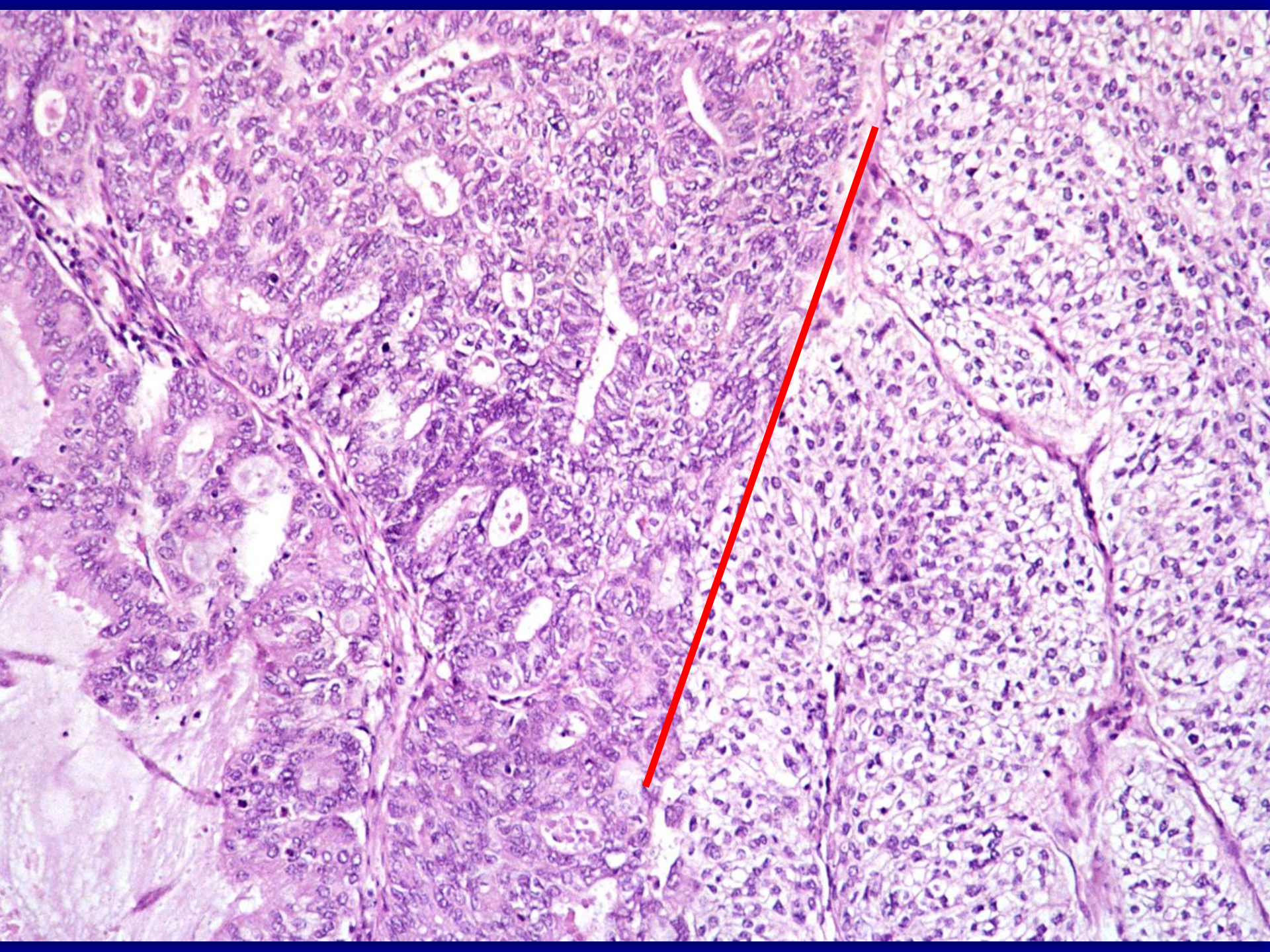
Usual endocervical adenocarcinoma type

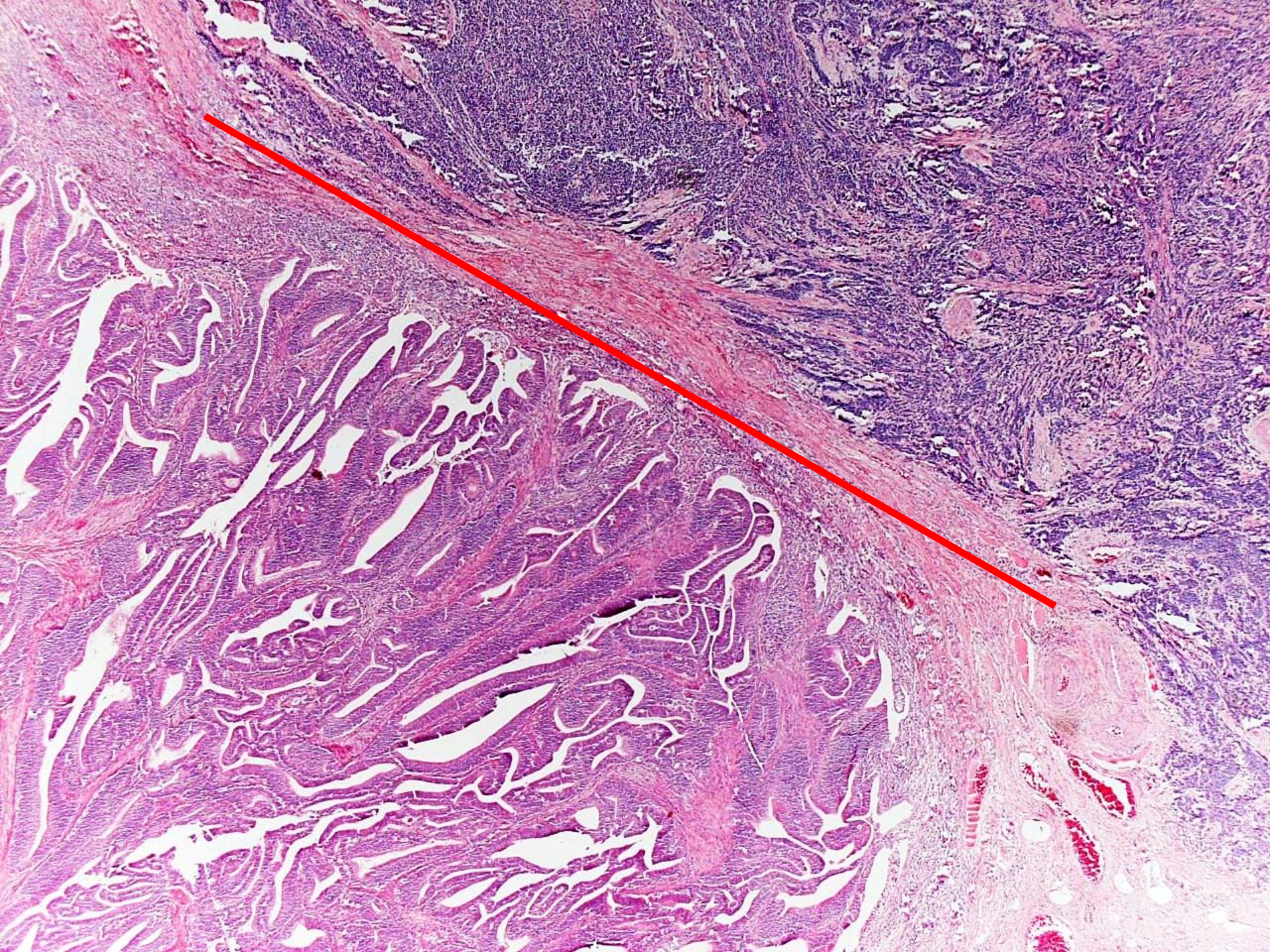
Usual
endocervical
adenocarcinoma
type



Villoglandular
adenocarcinoma







Unusual Endocervical Adenocarcinomas: An Immunohistochemical Analysis With Molecular Detection of Human Papillomavirus

Kay J. Park, MD, Takako Kiyokawa, MD,† Robert A. Soslow, MD,* Colleen A. Lamb, MD,‡
Esther Oliva, MD,‡ Oliver Zivanovic, MD,§ Margrit M. Juretzka, MD,|| and Edyta C. Pirog, MD¶*

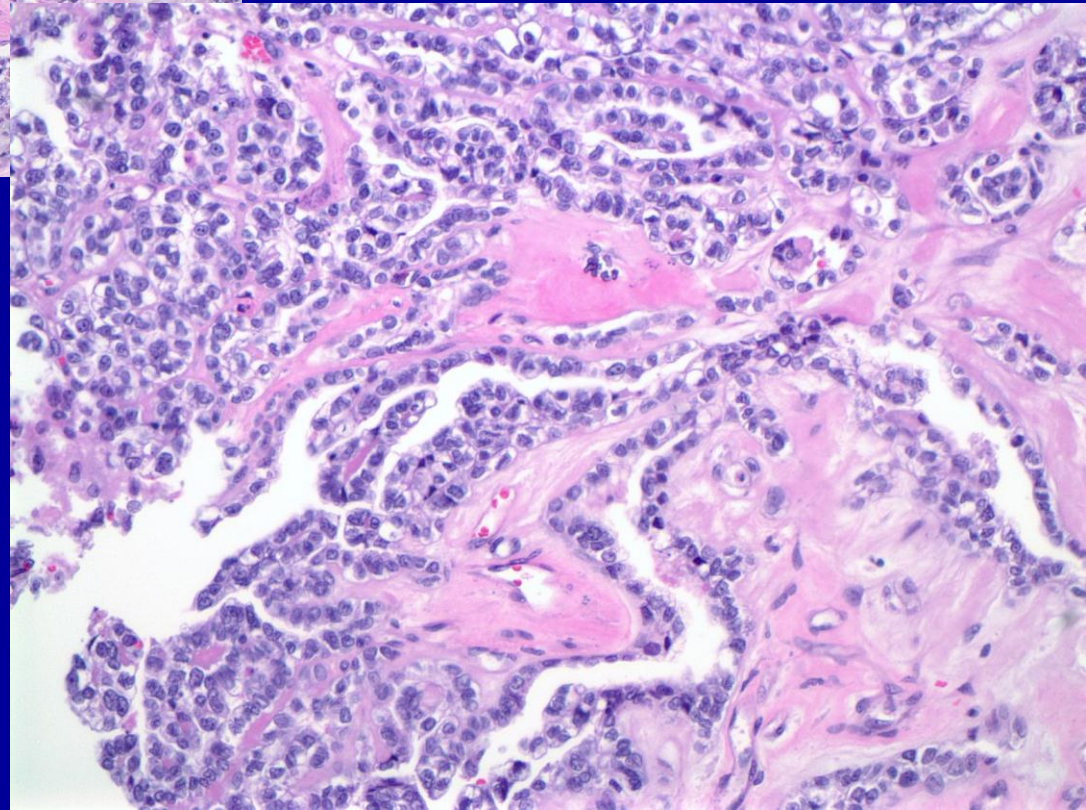
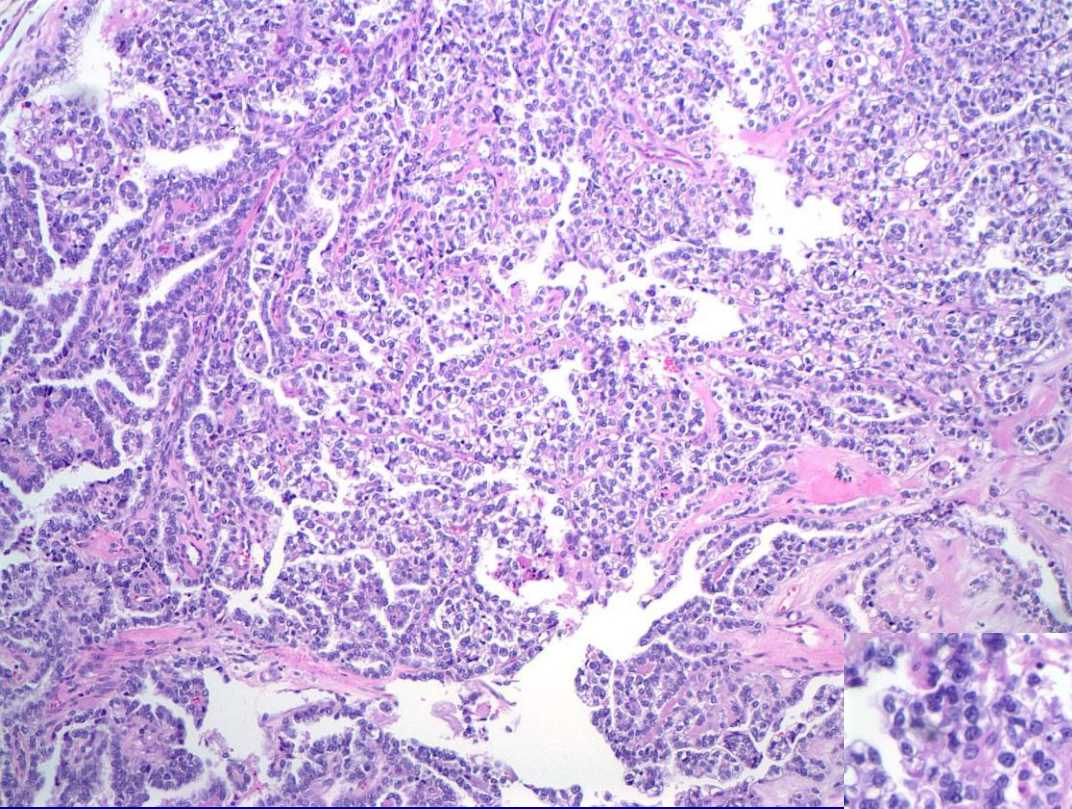
Conclusions: Unusual variants of endocervical adenocarcinoma are not related to HPV infection, with only rare exceptions, and p16 overexpression in non-UEA does not correlate with HPV status. Negative staining for PR and ER may serve as a general marker of endocervical neoplasia. GAS/MDA may be differentiated from all other adenocarcinomas with either positive HIK1083 stain or negative/focal p16 stain. Positive CEA stain differentiates GAS/MDA from CCC and negative PR and ER stains differentiate GAS/MDA from benign endocervical glands. CCC may be distinguished from all other adenocarcinomas, except MSN, with a negative CEA stain. Strong and diffuse p53 positivity in SER may be useful in differentiation from UEA. MSN may be identified with negative CEA, ER, and PR stains.

Endocervical adenocarcinoma histologic subtype

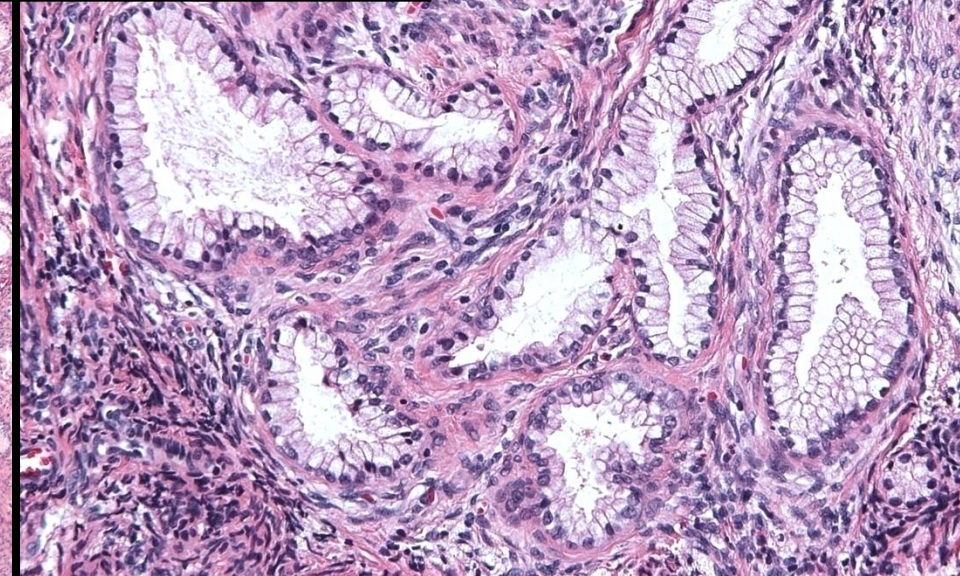
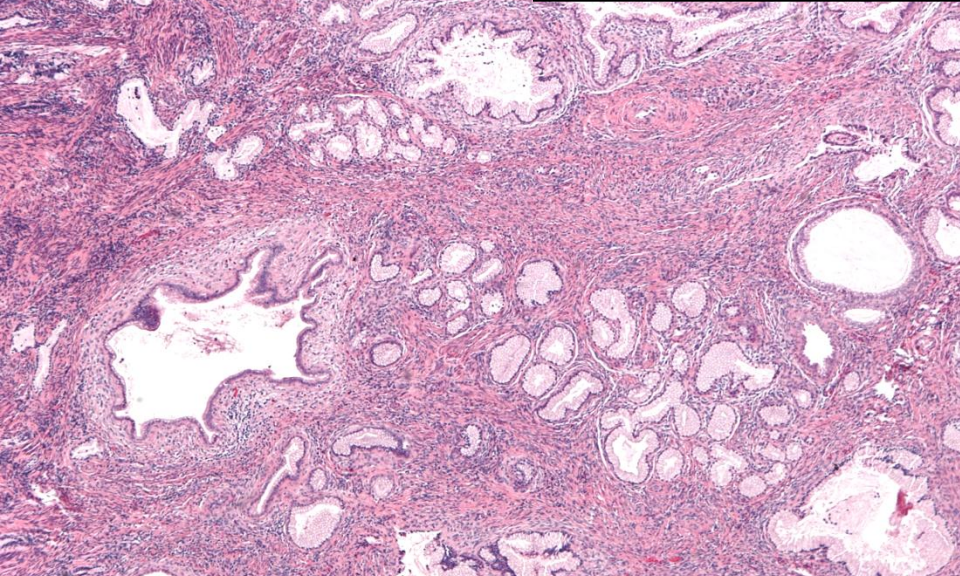
- Clear cell
- Adenoma malignum (minimal deviation)
- Mesonephric

- Endometrioid?
- Serous?
- Adenoid cystic?

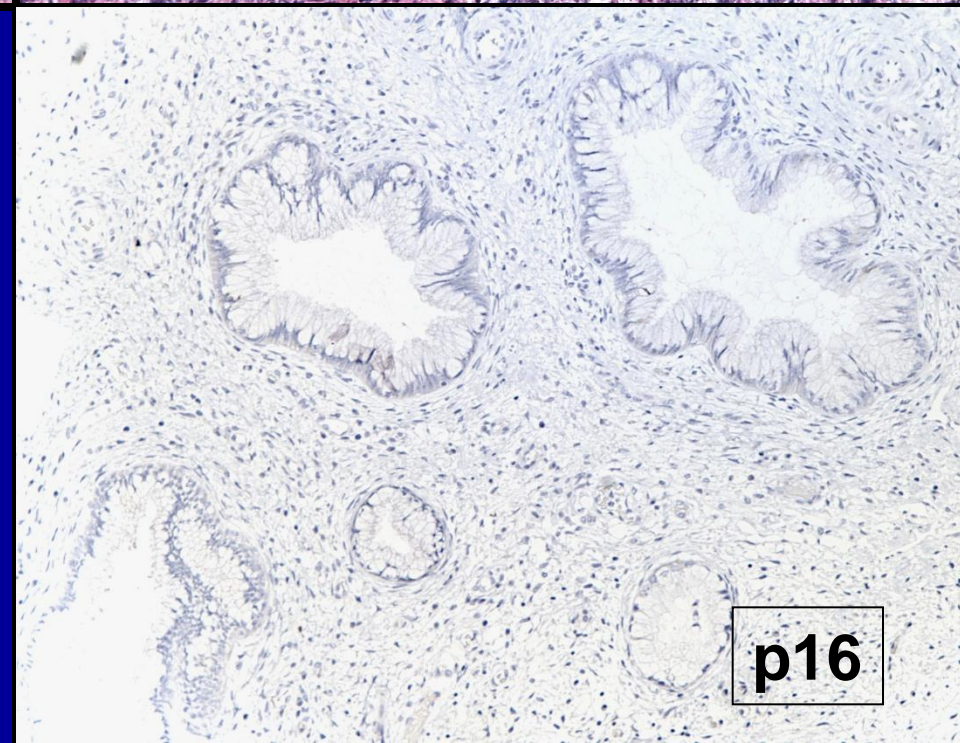
Clear cell



Adenoma Malignum

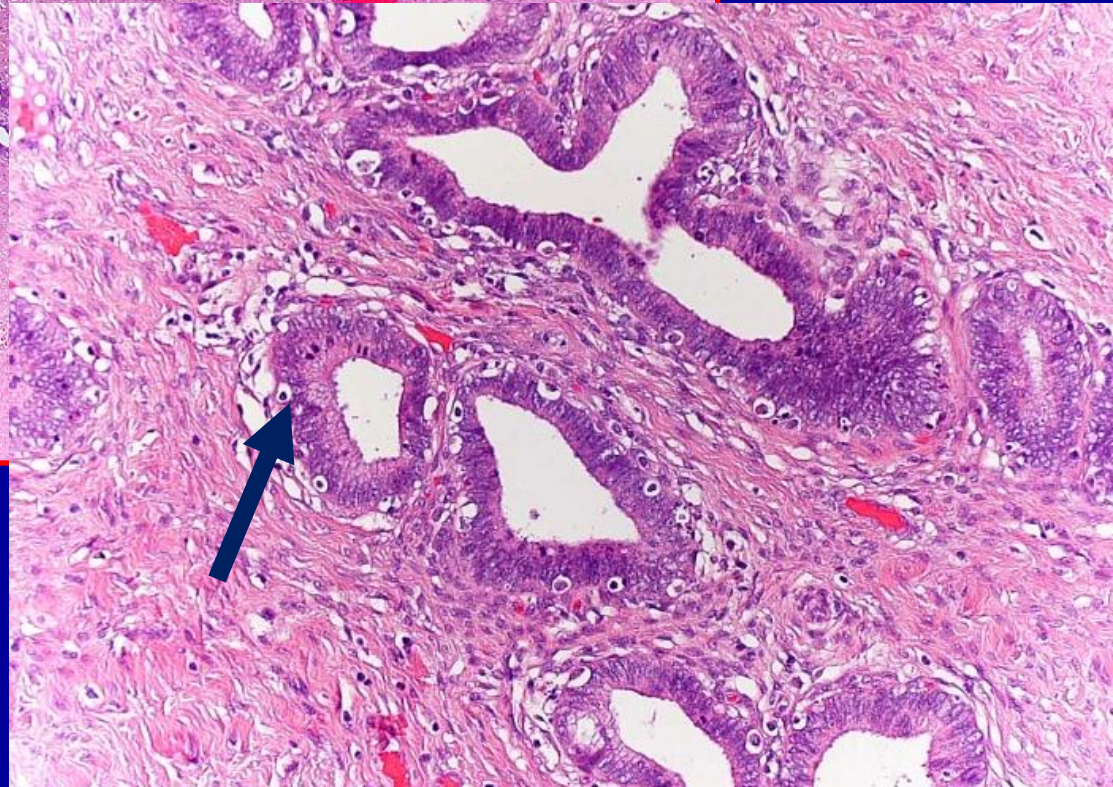
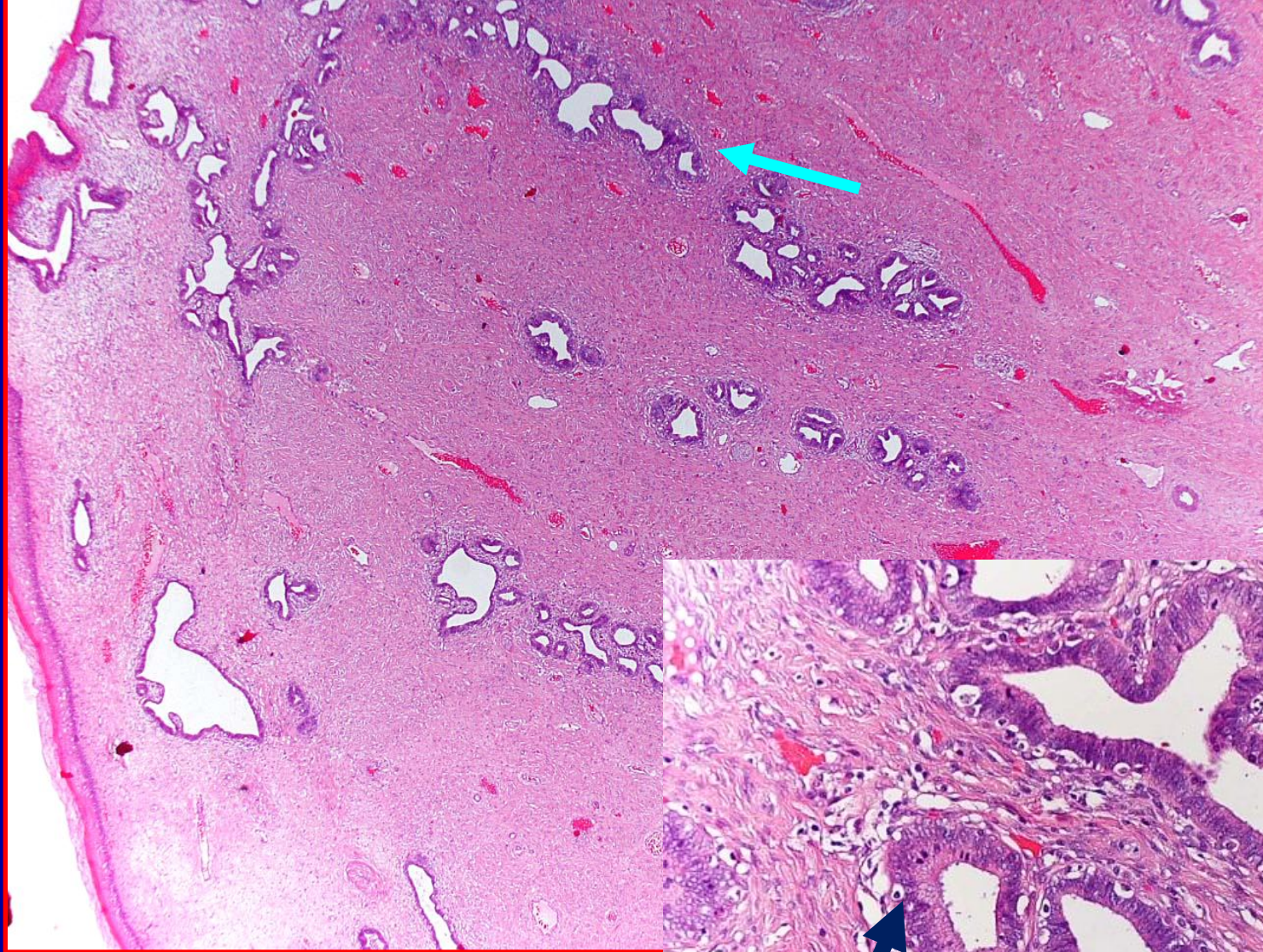


- Difficult diagnosis to make
- Well differentiated
- Deep invasion
- Advanced stage
- HPV negative



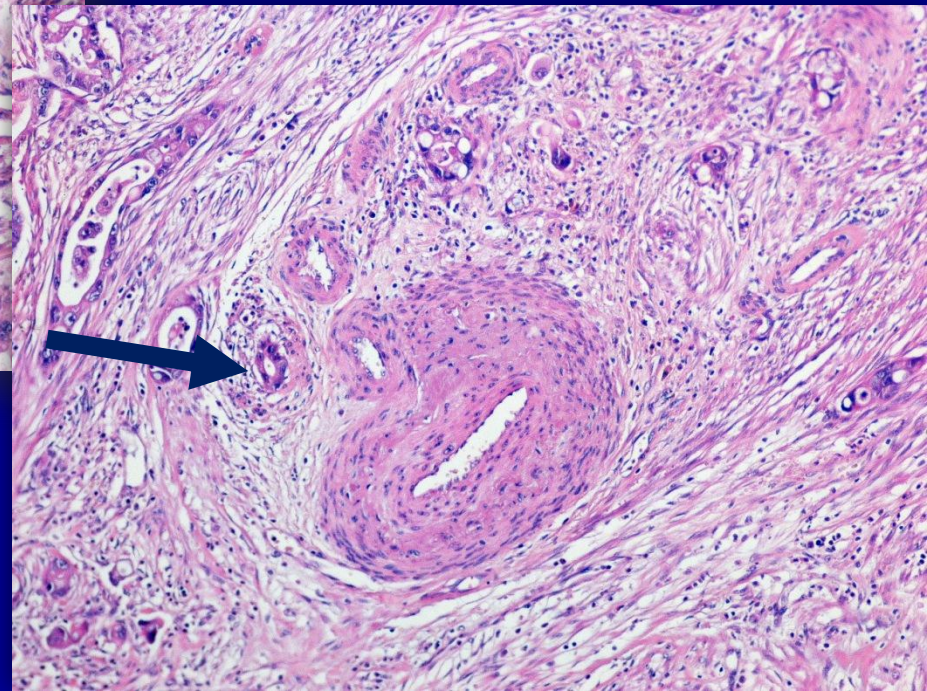
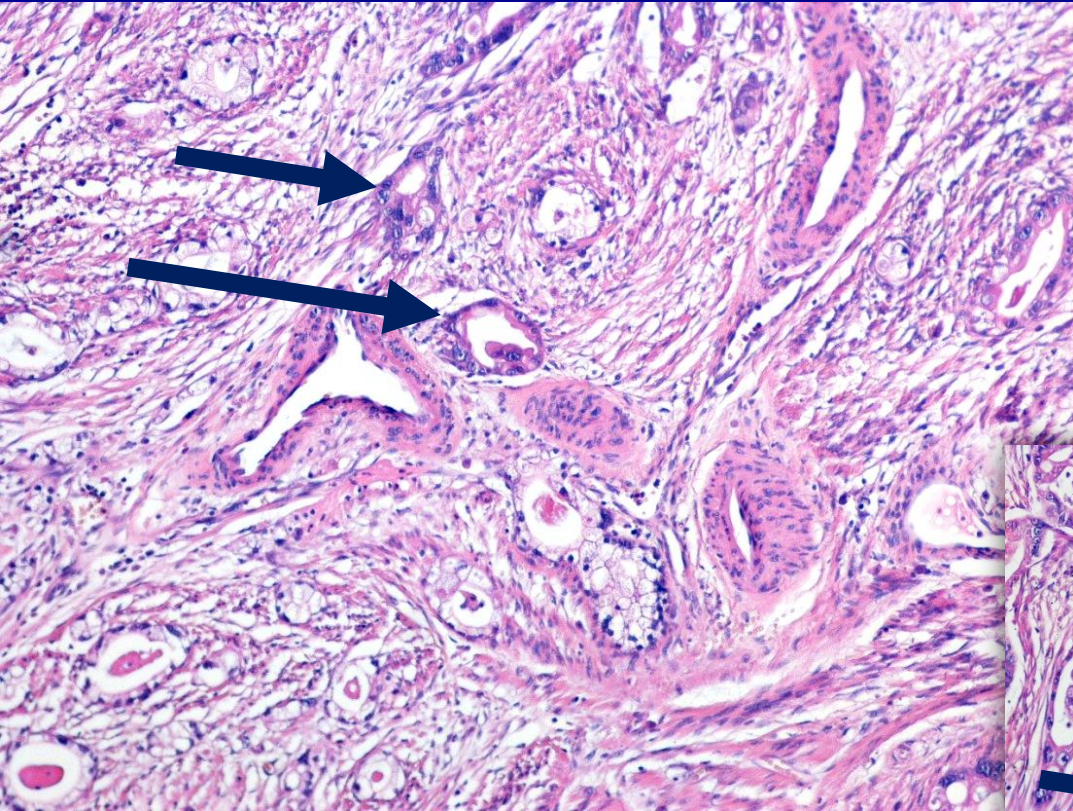
p16



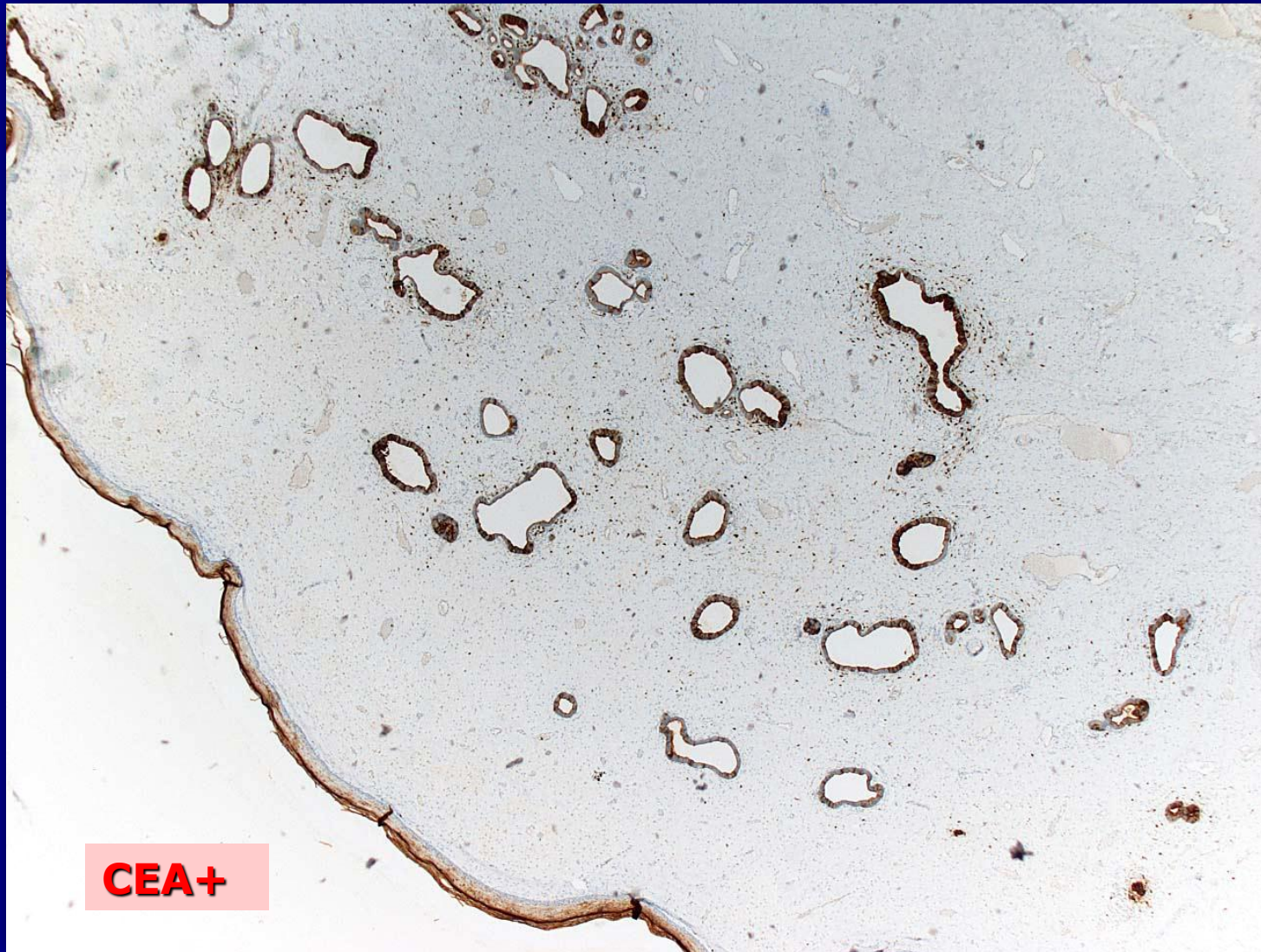


Adenoma malignum (minimal deviation)

-glands in proximity to blood vessel

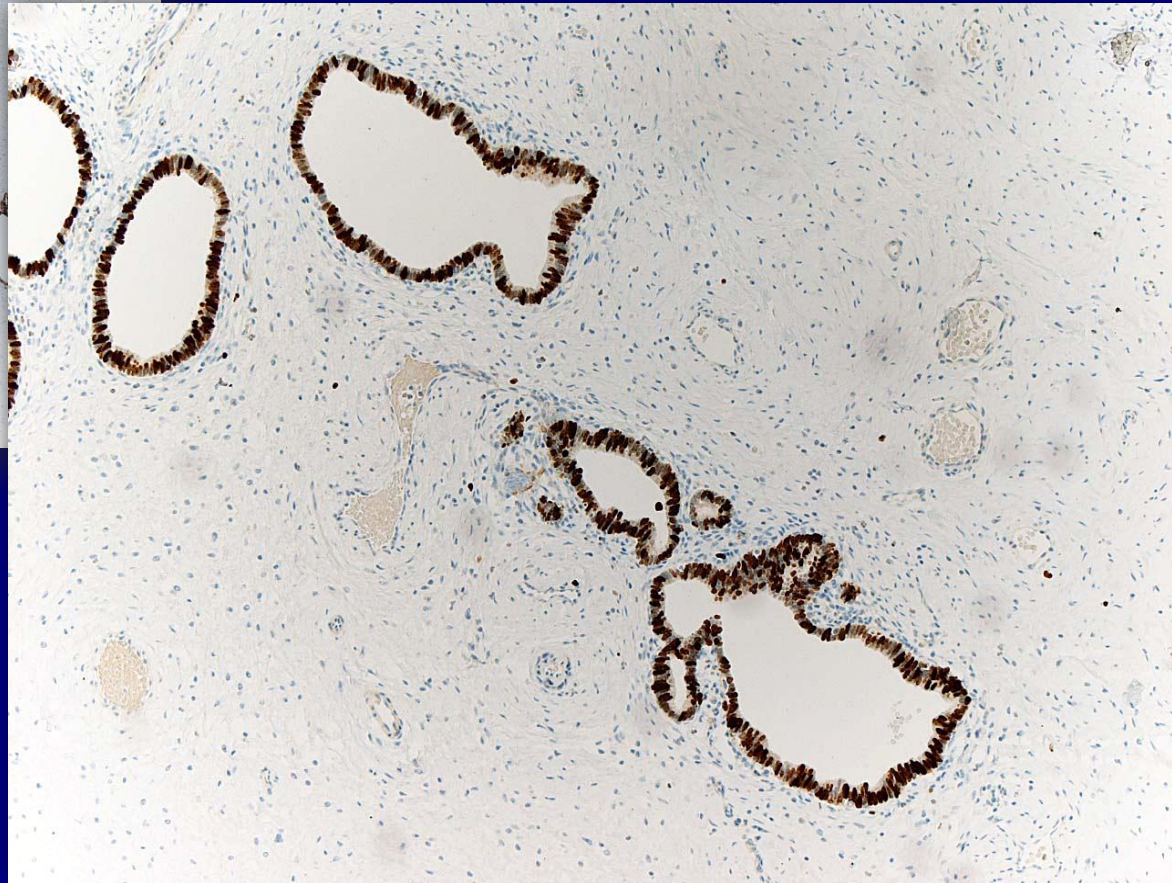
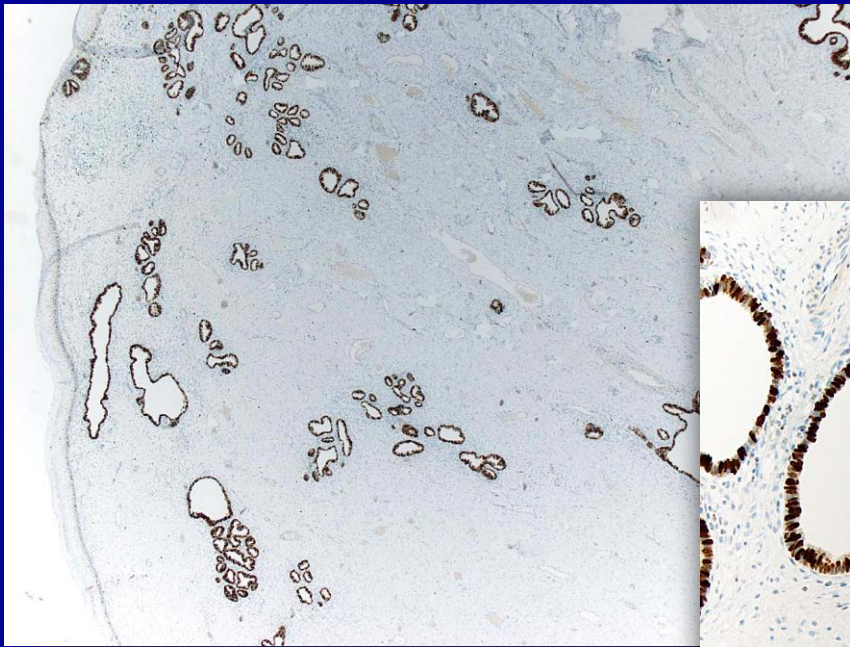


Adenoma malignum (minimal deviation)



Adenoma malignum (minimal deviation)

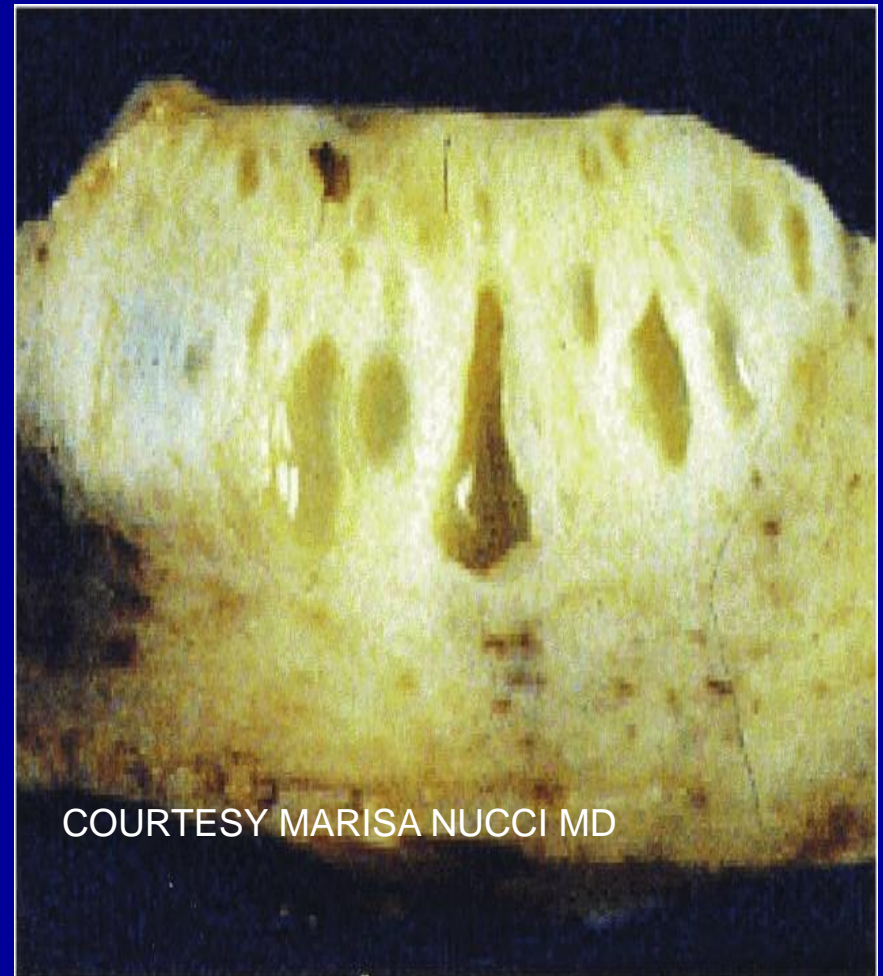
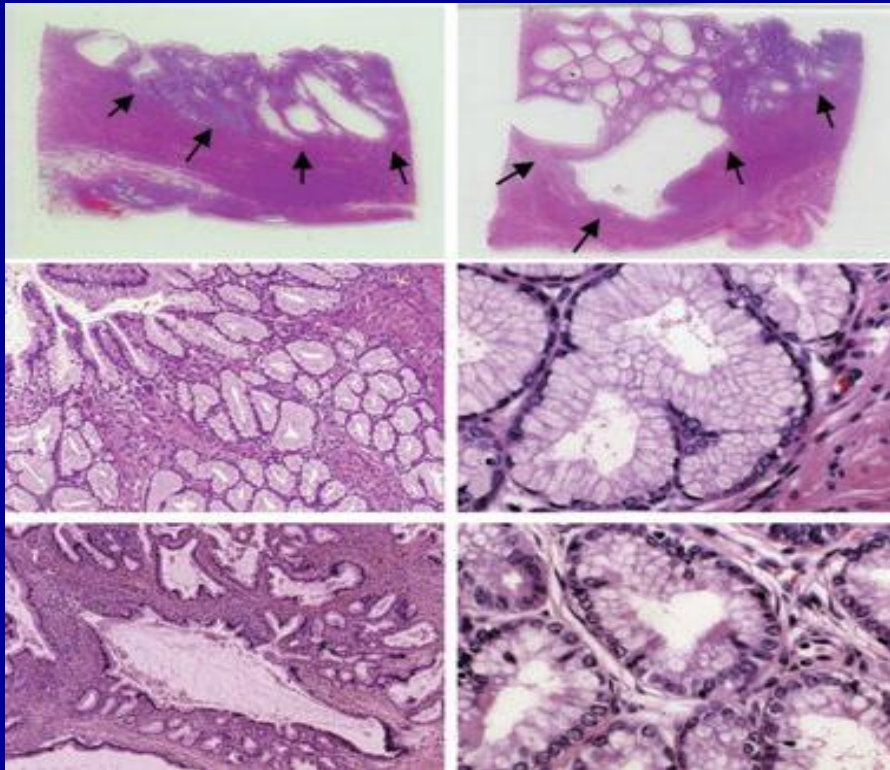
Ki 67 +



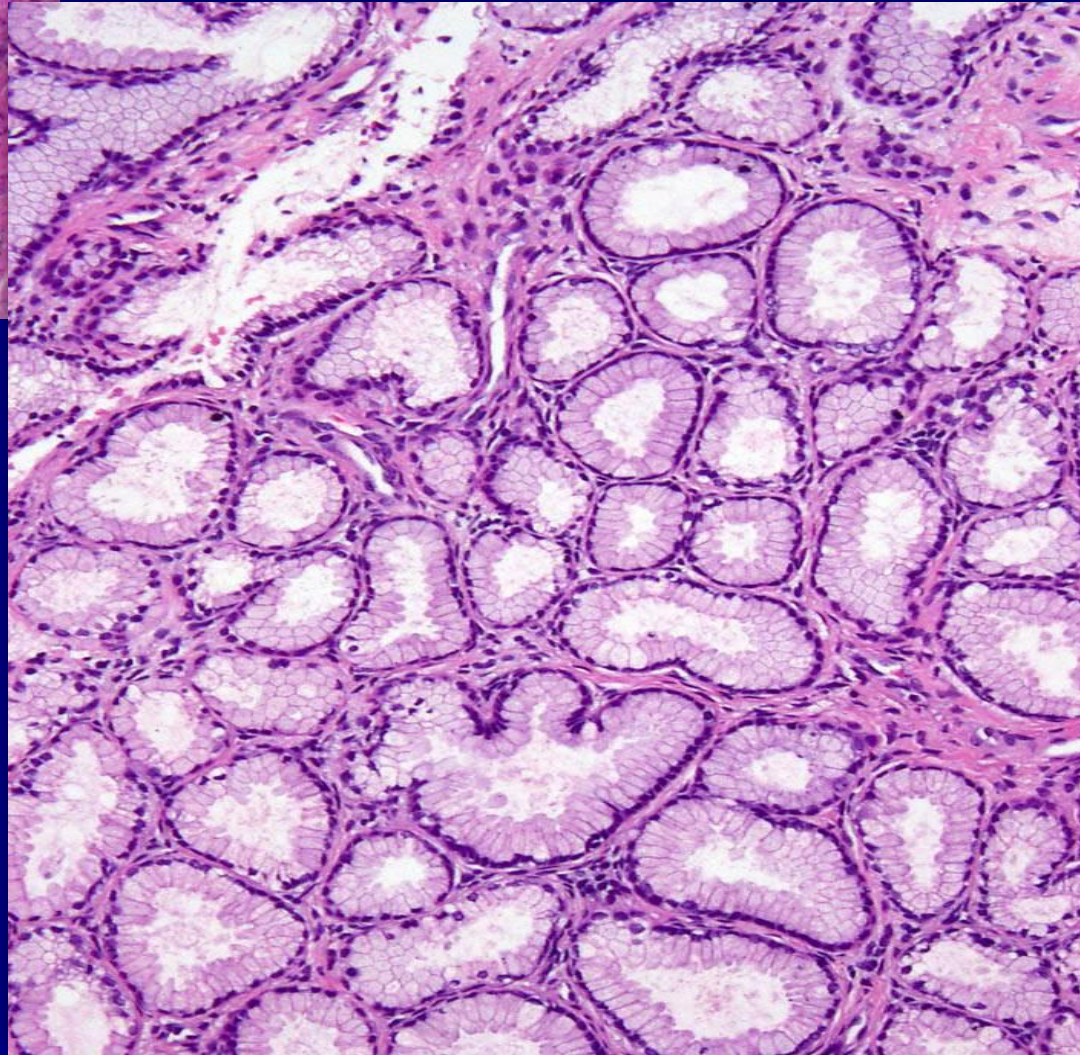
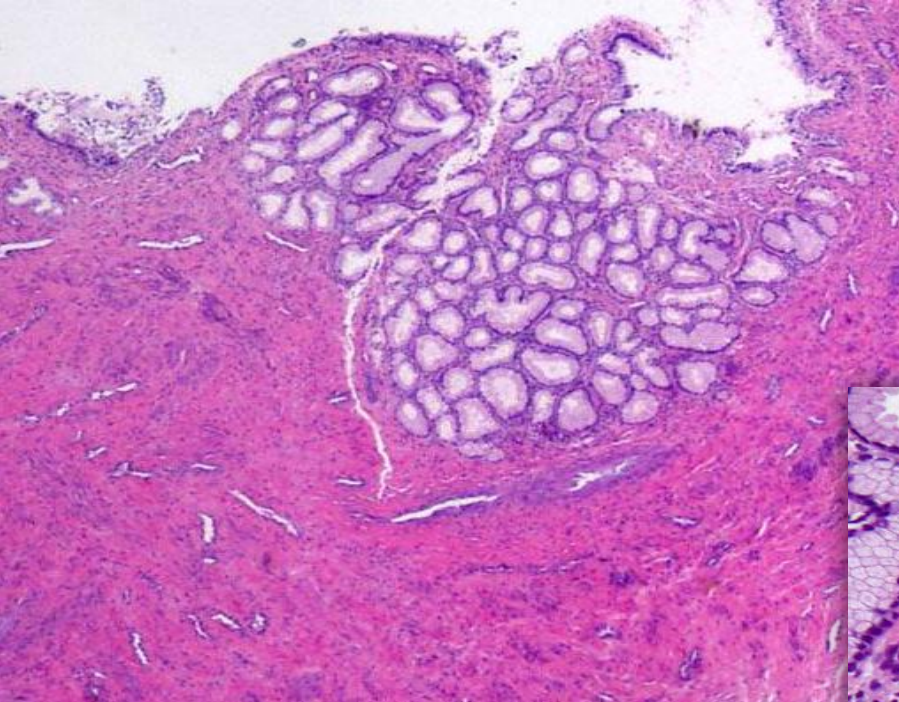
HPV- negative

Lobular Endocervical Hyperplasia

- A set-up for the misdiagnosis of adenoma malignum
- LEH often has gross appearance suggestive of tumor



Lobular Endocervical Hyperplasia



Is Lobular Endocervical Glandular Hyperplasia a Cancerous Precursor of Minimal Deviation Adenocarcinoma? *A Comparative Molecular-genetic and Immunohistochemical Study*

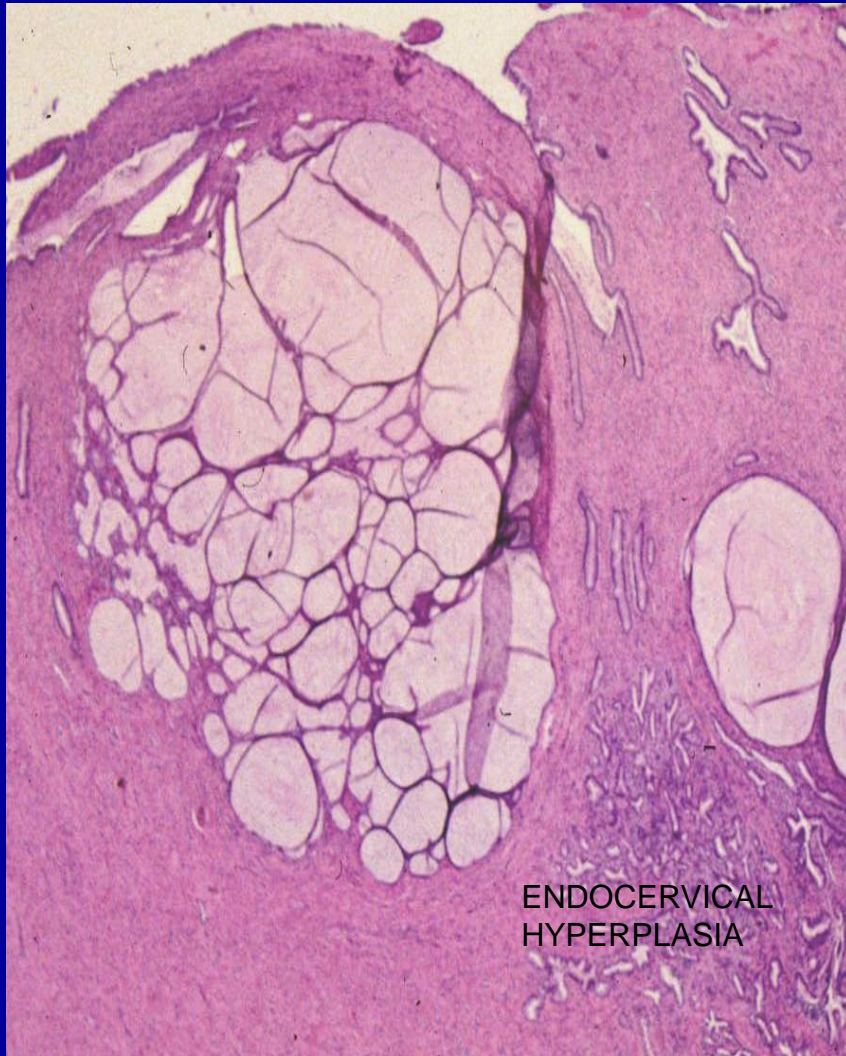
Shigeto Kawauchi, MD, Tomoko Kusuda, MD,* Xu-Ping Liu, MD,* Yutaka Suehiro, MD,†
Tsunehisa Kaku, MD,‡ Yoshiki Mikami, MD,§ Morishige Takeshita, MD,||
Motonao Nakao, PhD,* Yasuyo Chochi, MD,* and Kohsuke Sasaki, MD**

Abstract: Although lobular endocervical glandular hyperplasia (LEGH) was originally described as a distinct hyperplastic glandular lesion of the uterine cervix, recent studies have raised a question that LEGH may be a cancerous precursor of minimal deviation adenocarcinoma (MDA) and other mucinous adeno-

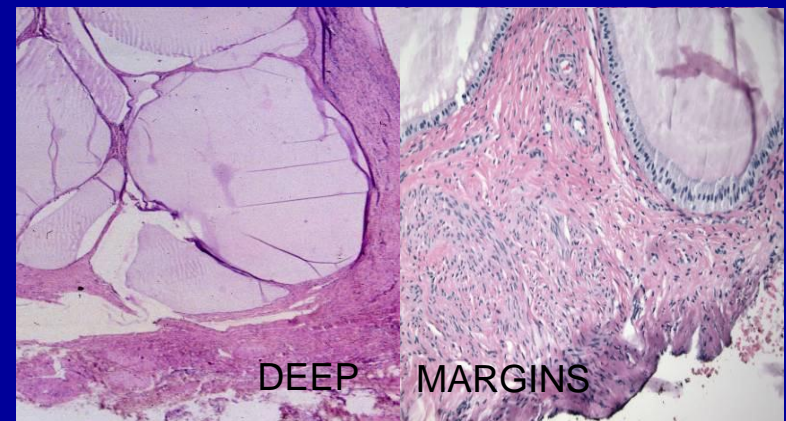
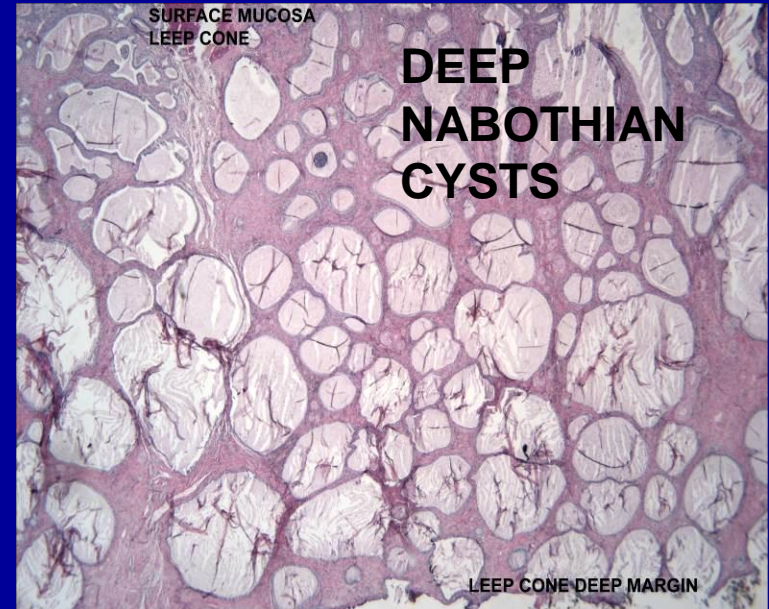
tive genomic hybridization, gastric pyloric-type mucin, human papillomavirus, microsatellite instability

(*Am J Surg Pathol* 2008;32:1807–1815)

“Tunnel Clusters” and Deep Nabothian Cysts: Mimics Of “Adenoma Malignum”



Tunnel Clusters



Endometrioid adenocarcinoma of endocervix

- **Controversial entity**
- **Statistically, an unusual lesion**
 - ER, PR+
 - Unassociated with HPV (p16-)
 - Association with endometriosis
 - If diagnosis confirmed, exclude endometrial primary

**Why is it important to distinguish
between endometrial and
endocervical carcinomas?**

Management

Endometrial Ca

- TAH + BSO

Endocervical Ca

- Radical hysterectomy
- + Pelvic lymphadenectomy
- +/- Radiotherapy

Endometrial Primary	Endocervical Primary
Post menopausal	Pre- or perimenopausal
EMC>ECC	ECC>EMC
Endometrial hyperplasia	AIS or squamous dysplasia (SIL) or Abnormal Pap smears
Stromal foam cells Squamous metaplasia	Large, elongate, pseudostratified, darkly stained nuclei Abundant mitotic activity, most obvious apically Abundant apoptotic bodies
Expression of ER, PR, vimentin	Diffuse expression of CEA and p16
Imaging and clinical exam favor corpus primary	Imaging and clinical examination favor cervical primary

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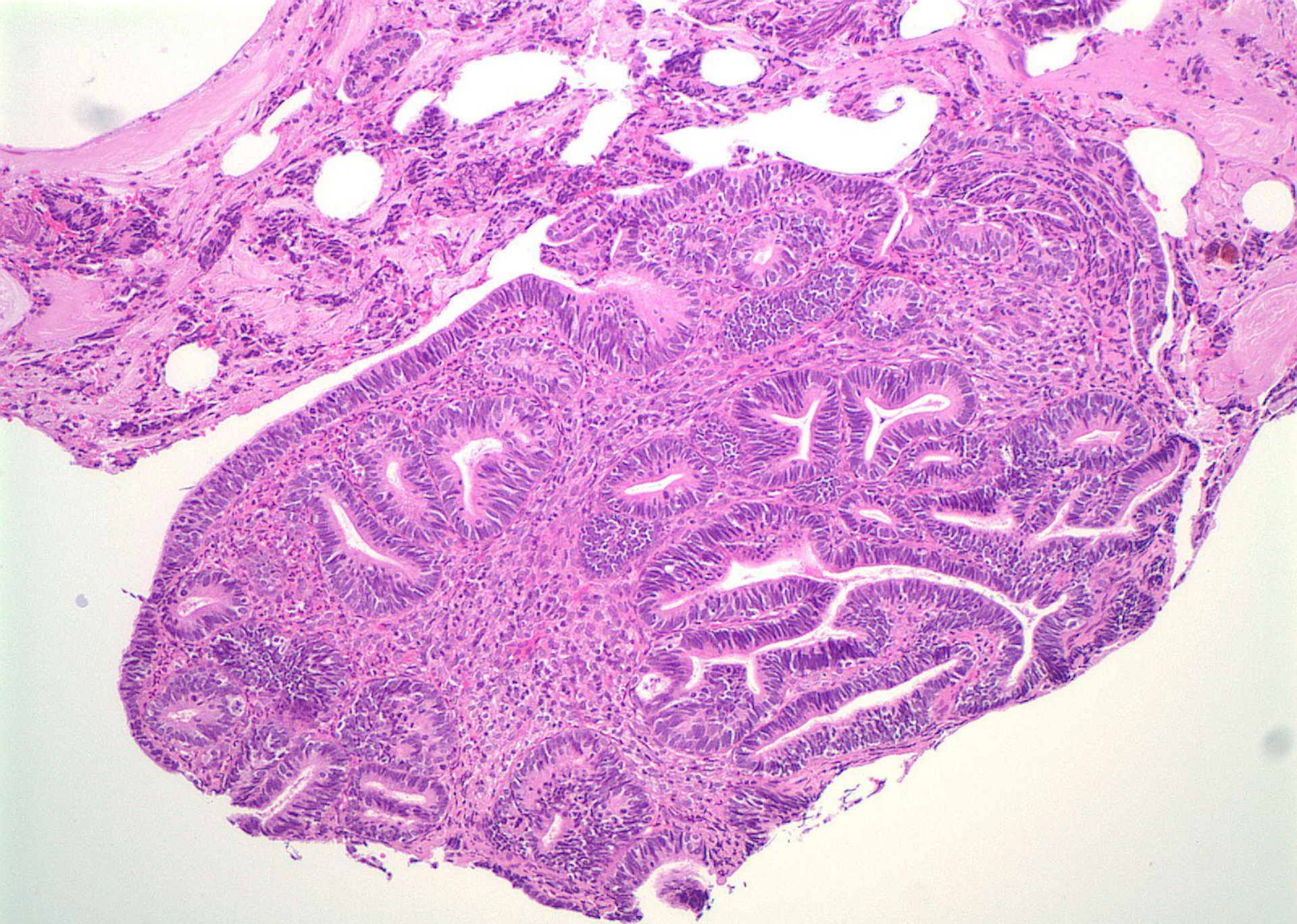
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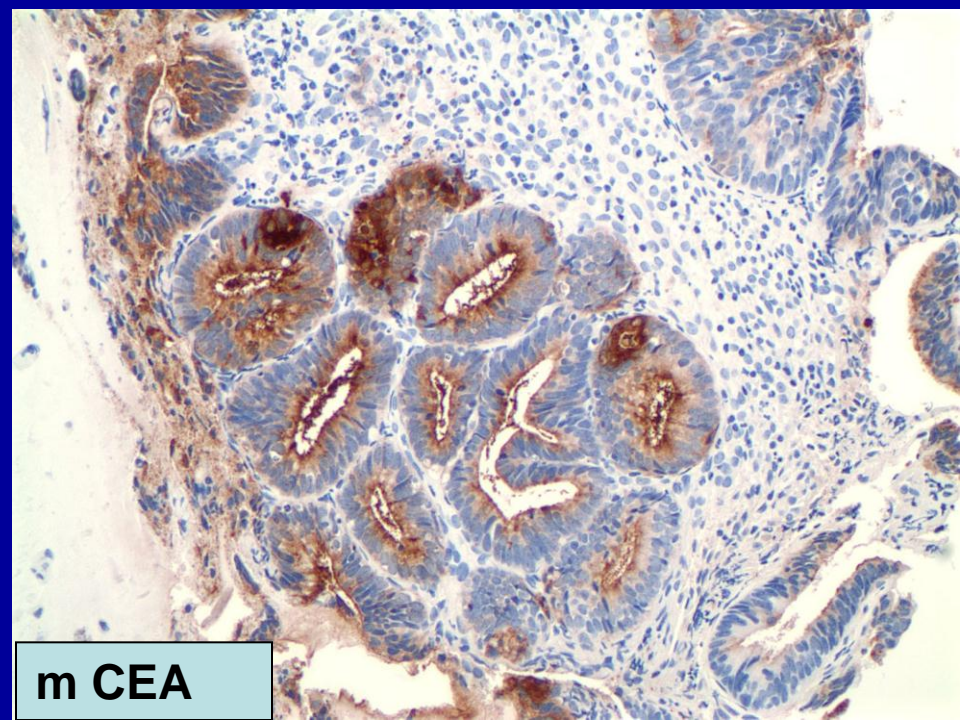
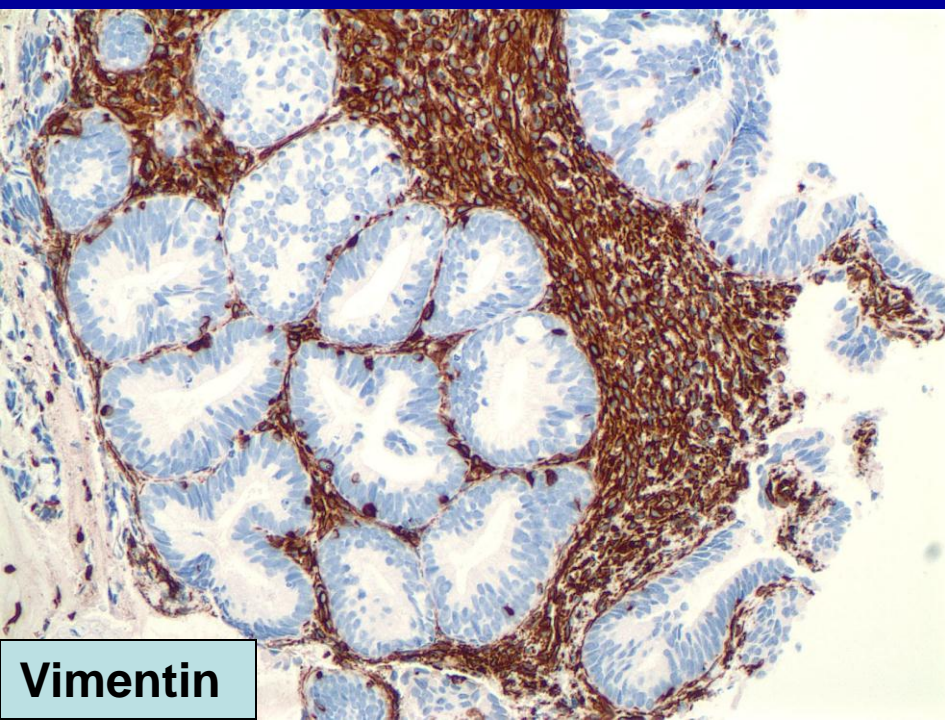
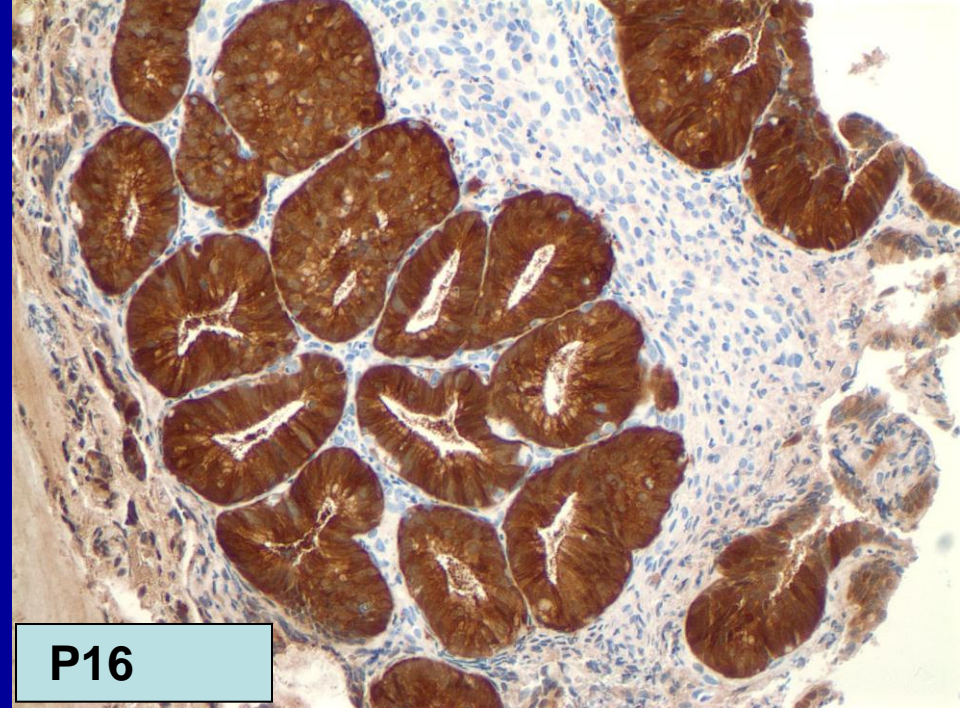
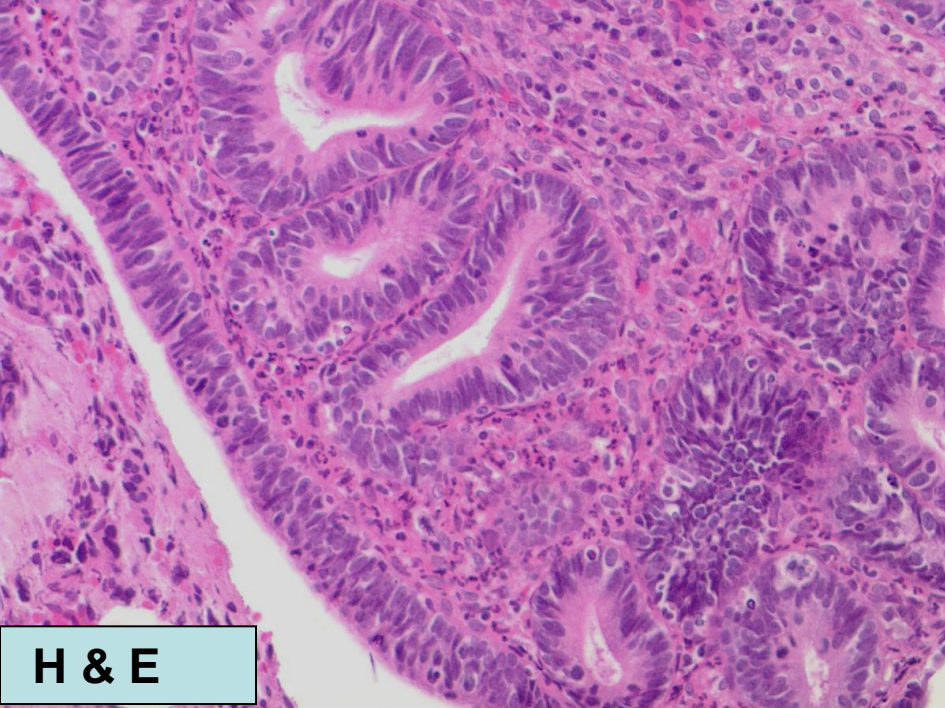
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“Endometrial vs endocervical”

	Endocervical	Endometrial
Vimentin	neg	pos
mCEA	pos	neg
ER	neg	pos
PR	neg	pos
P16	pos	neg
HPV	pos	neg





P16 in endometrium

	p16 (+)	ER (+)	PR (+)	mCEA (+)	vimentin (+)
FIGO 1	7%	45%	57%	7%	ND
FIGO 2&3	25	19	19	2.5	ND
Serous	92	38	50	13	93
Clear cell	45	9	45	18	100
MMMT	67	11	11	0	ND
p-value	<0.001	0.03	0.003	0.28*	0.44

ND: not done; *only 9 positive for mCEA.

P16 in endometrium

	p16 (+)	ER (+)	PR (+)	mCEA (+)	vimentin (+)
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~~“Endometrial vs endocervical”~~

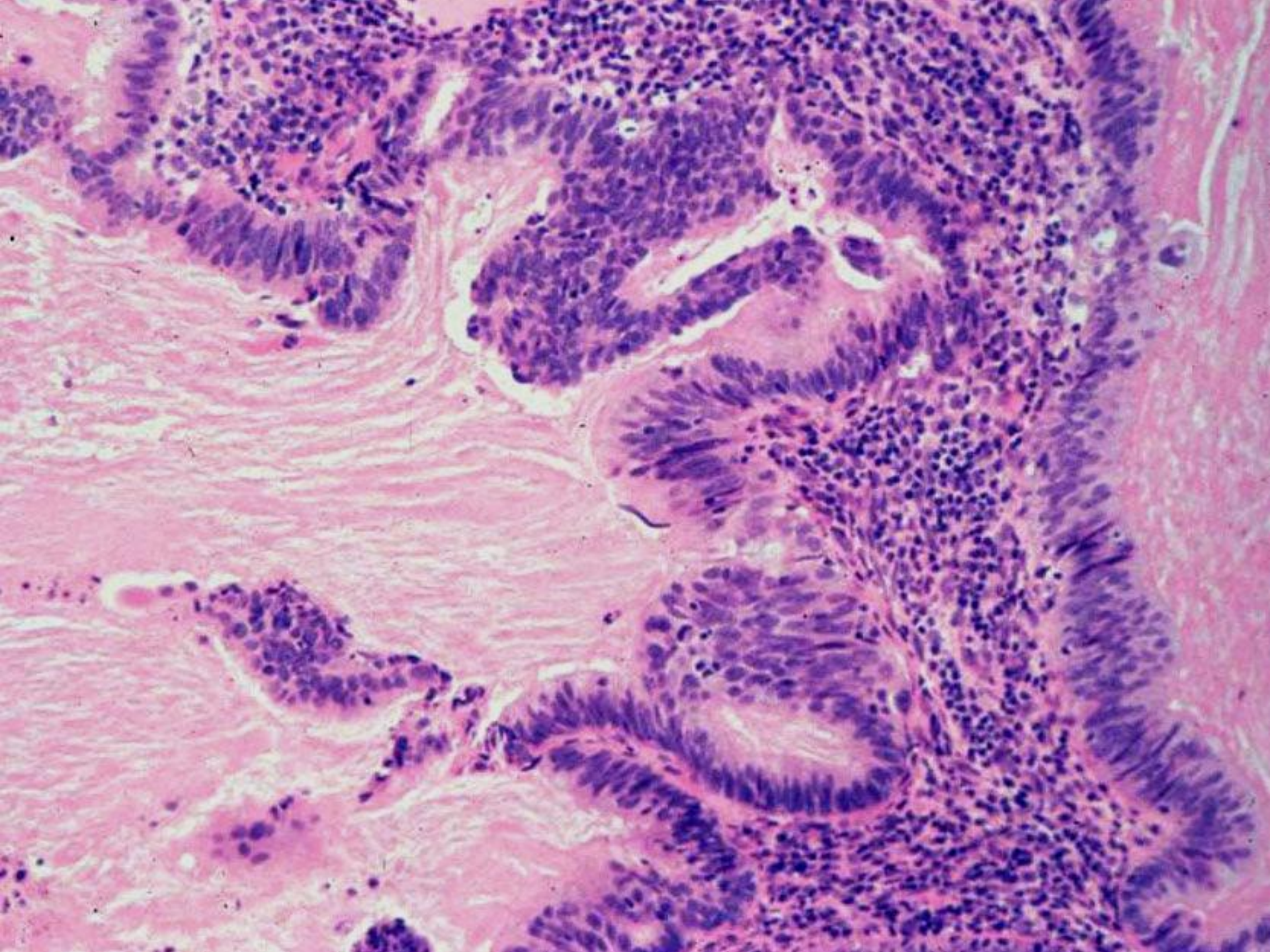
	Endocervix	Endometrial
Vimentin	neg	pos
mCEA	pos	neg
ER	neg	pos
PR	neg	pos
P16	pos	neg
HPV	pos	neg

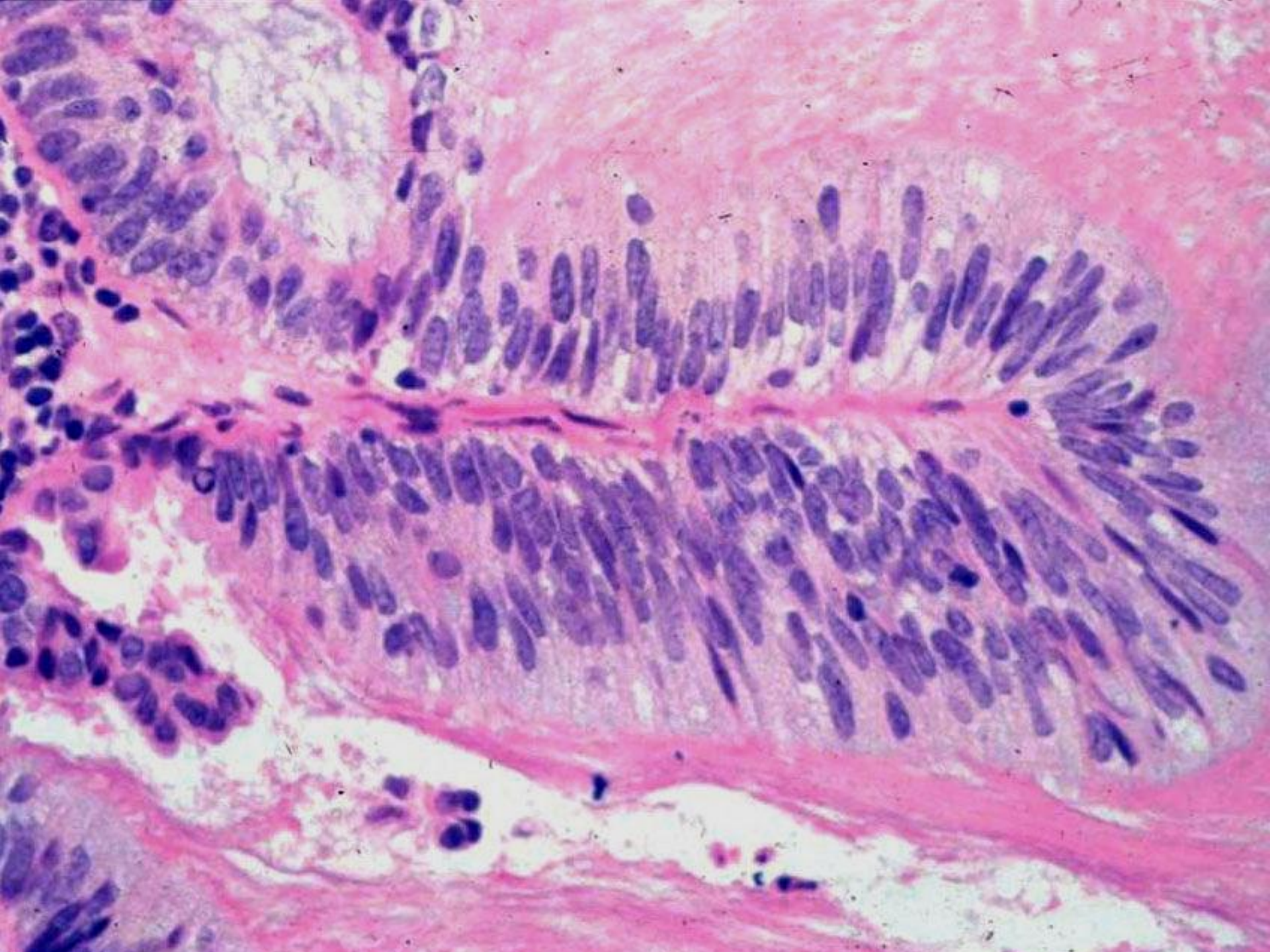
FIGO grade 1 uterine endometrioid vs endocervical (usual type)

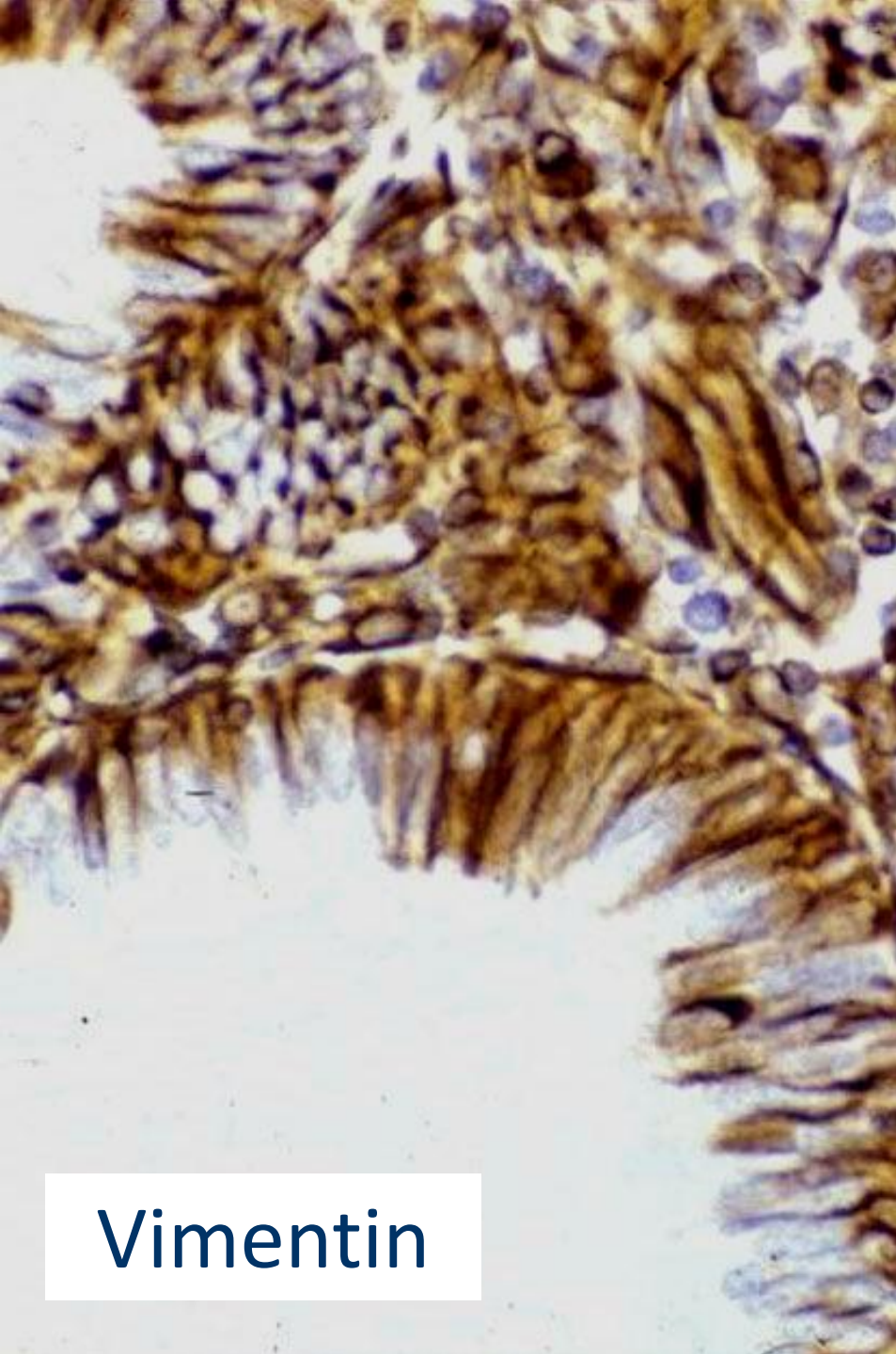
	Endocervix	Endometrioid
Vimentin	neg	pos
mCEA	pos	neg
ER	neg	pos
PR	neg	pos
P16	pos	neg
HPV	pos	neg

**Beware of mucinous
lesions.**

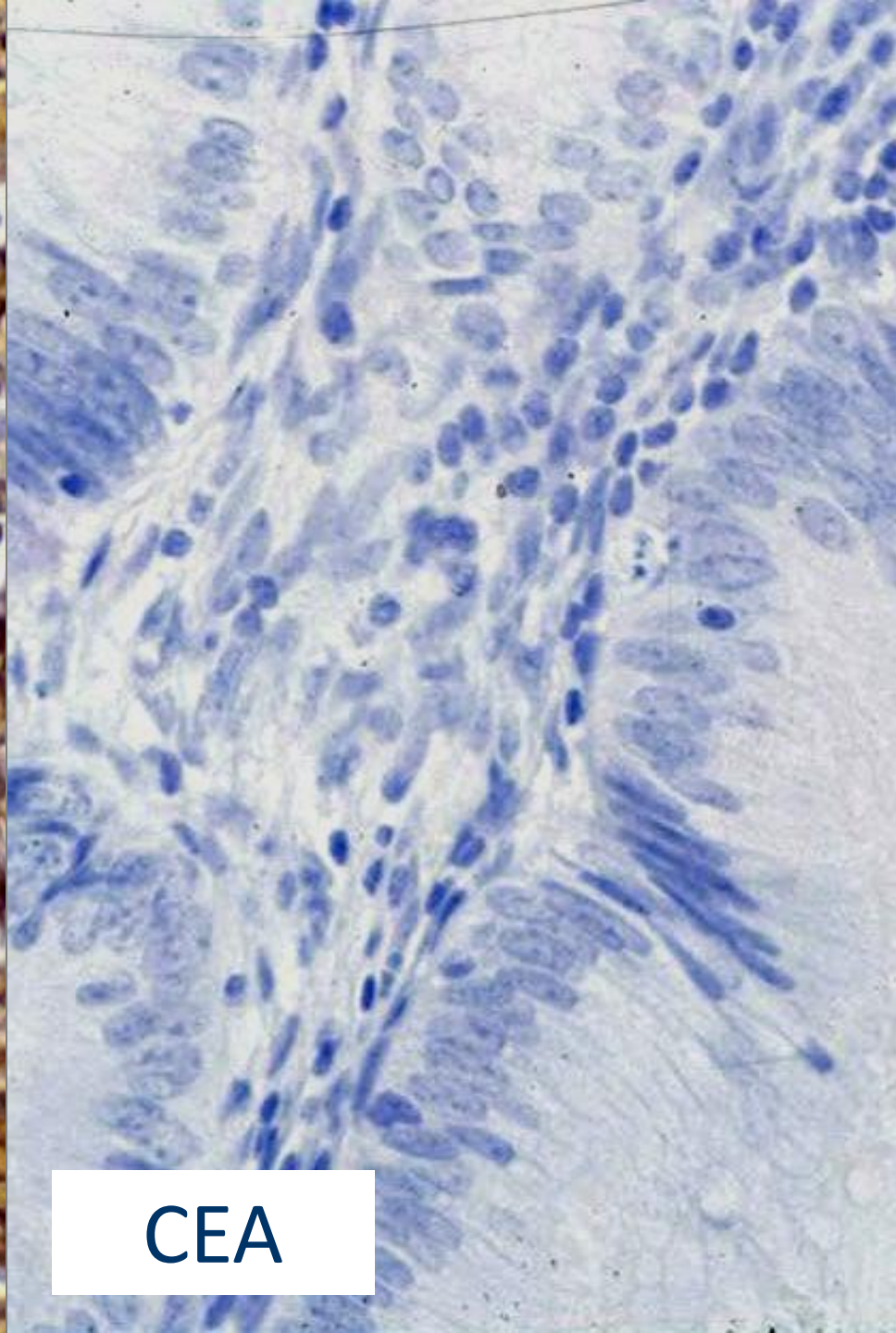
**They can be very
tricky.**







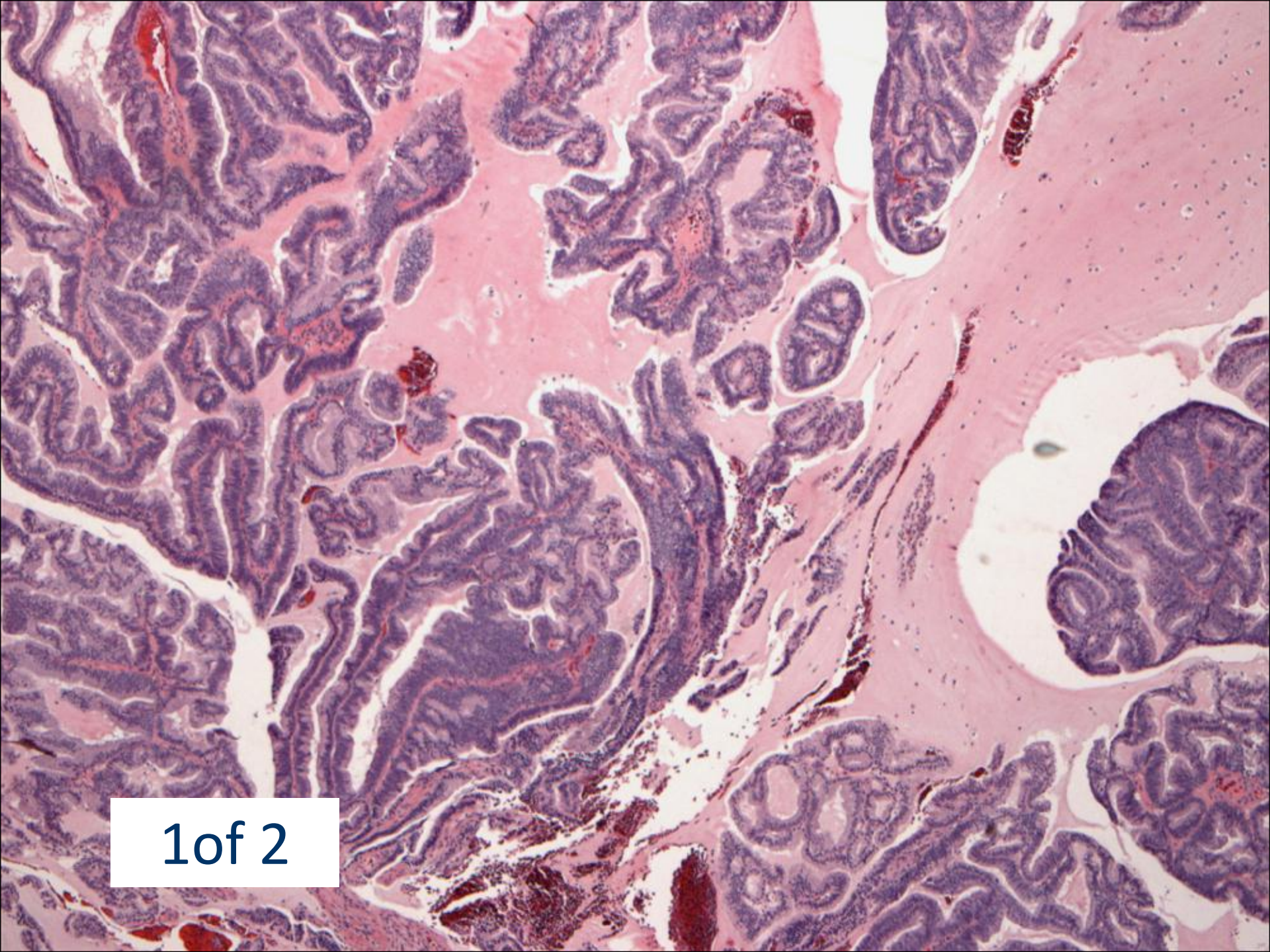
Vimentin



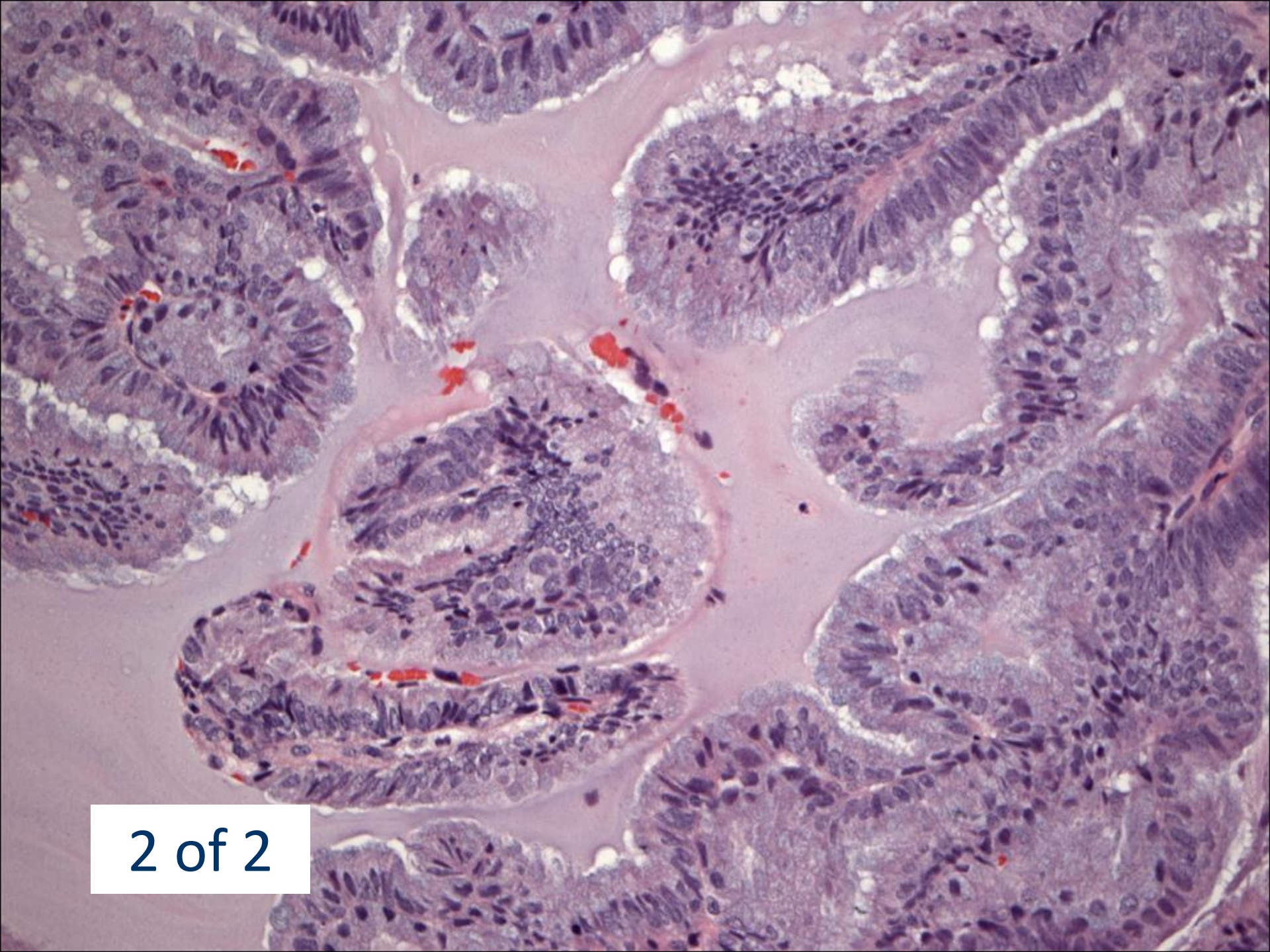
CEA

**Endocervical carcinomas may have
endometrioid morphology**

**Endometrioid carcinomas may have
mucinous histology**



1 of 2



2 of 2

