

HPV-associated and HPV-independent precursors and carcinomas of the vulva and cervix

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HPVA and HPVVI tumors of the vulva and cervix

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Outline

- Endocervical adenocarcinomas (HPVA and HPV)
- HPV vulvar squamous carcinoma precursors and carcinomas
- HPV cervical squamous carcinoma precursors and carcinomas

Take home messages

- HPV1 neoplasms are uncommon and under-recognized, and can be difficult to diagnose
- HPV1 neoplasms are more aggressive compared to HPVAs (squamous carcinomas and precursors, and adenocarcinomas)
- HPV1 cervical squamous carcinomas and precursors are gaining more attention

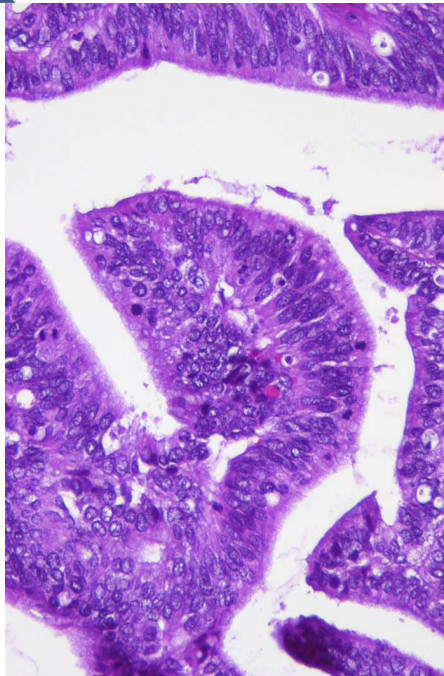
Endocervical adenocarcinoma WHO 2020

Easily identified apical mitoses and apoptosis?

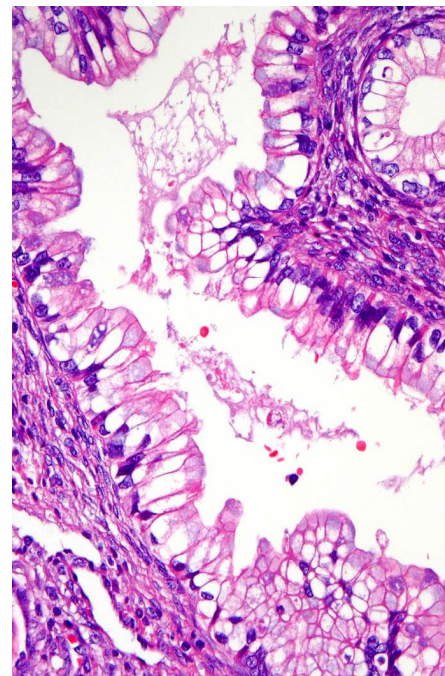
YES

NO

HPVA



HPVI



WHO 2014 classification

- Endocervical, usual type
- Mucinous carcinoma, NOS
 - Gastric type
 - Intestinal type
 - Signet-ring cell type
- Villoglandular
- Clear cell
- Mesonephric
- Endometrioid
- Serous

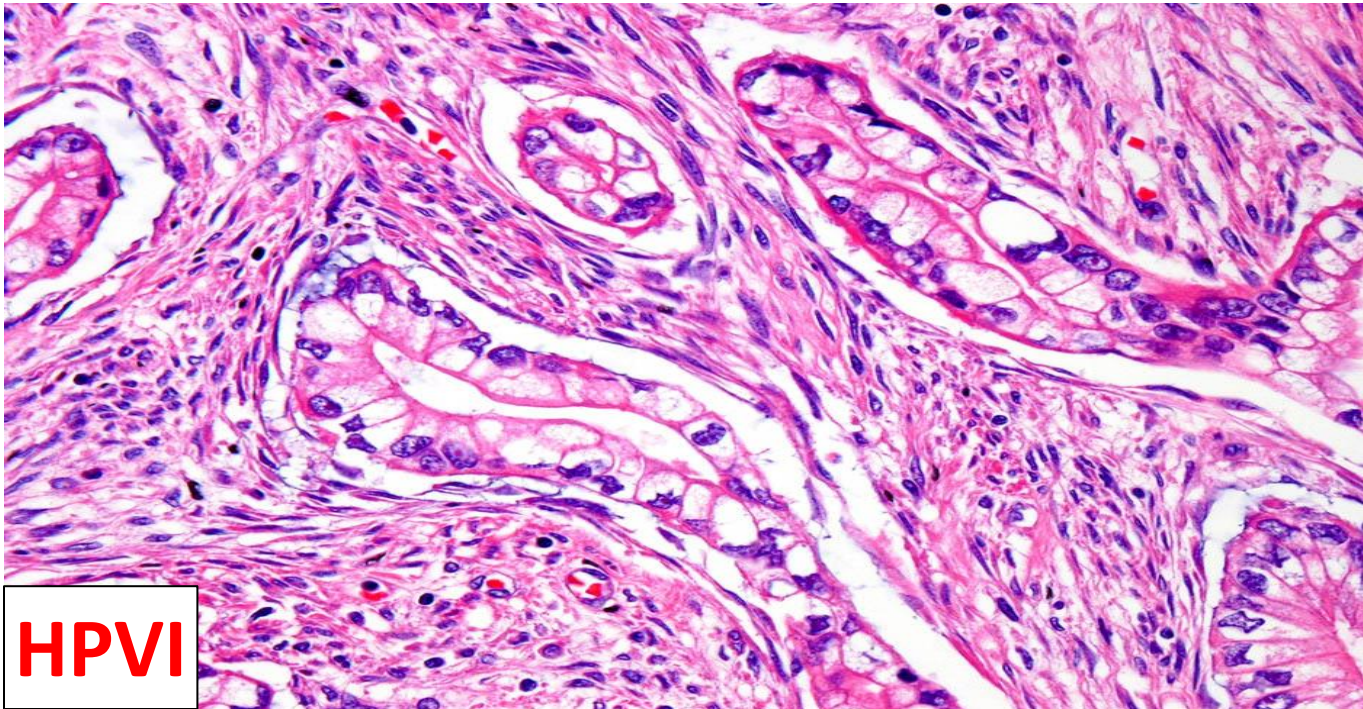
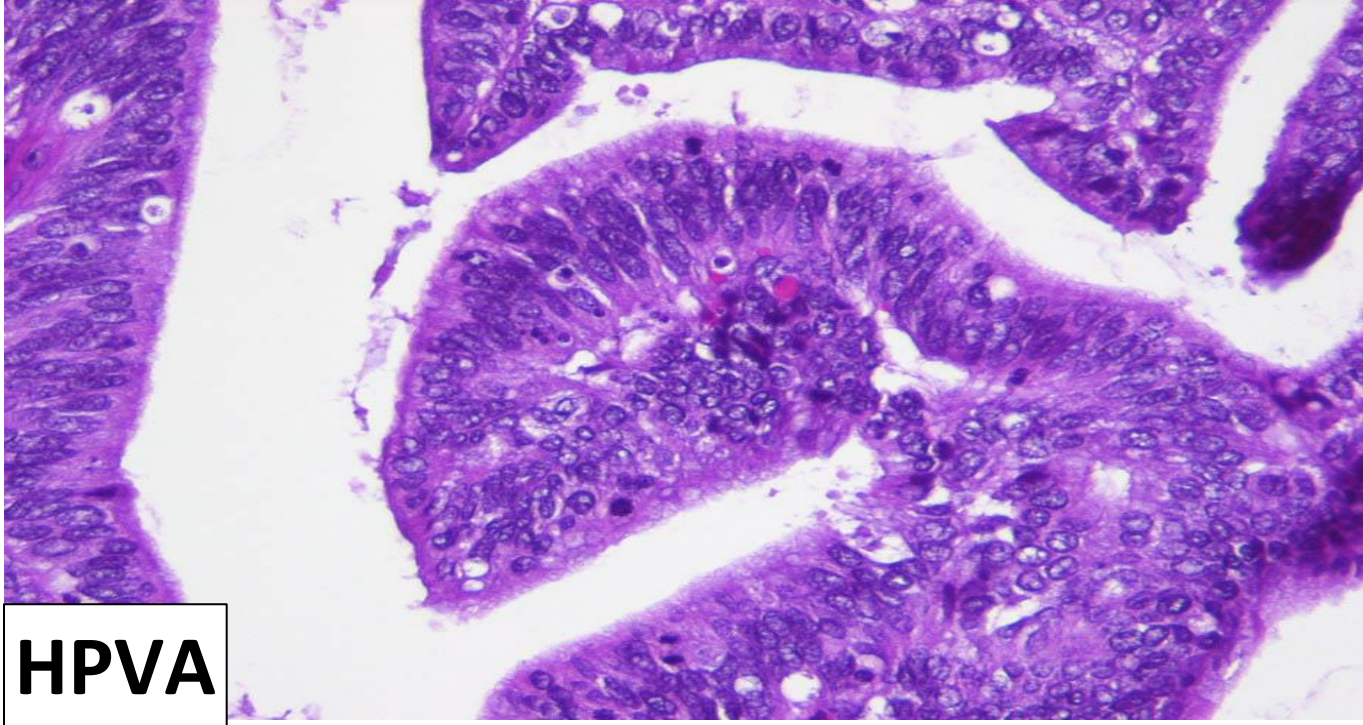
GREEN: HPV-associated

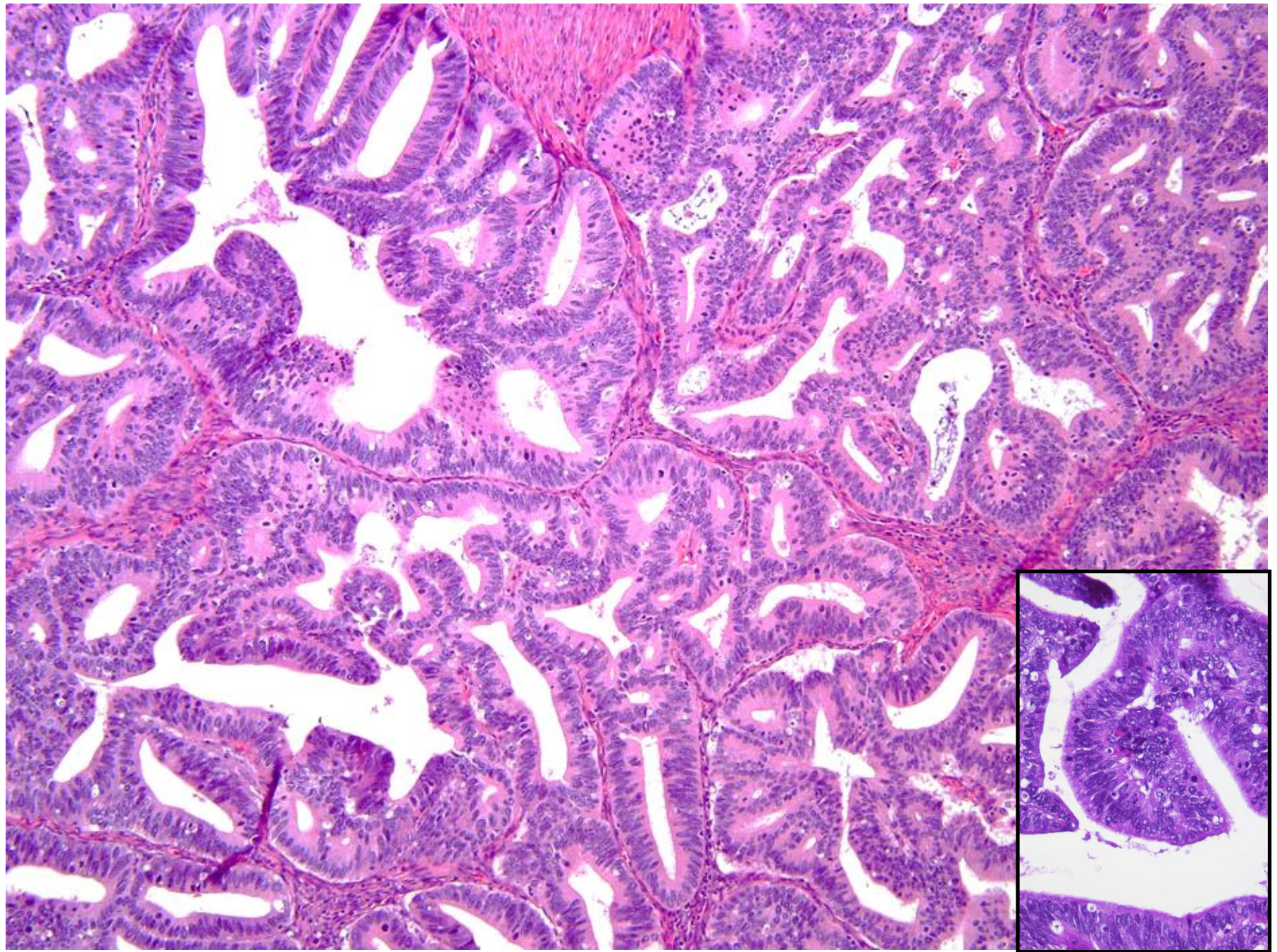
PURPLE: HPV-associated or unassociated

RED: Unassociated with HPV

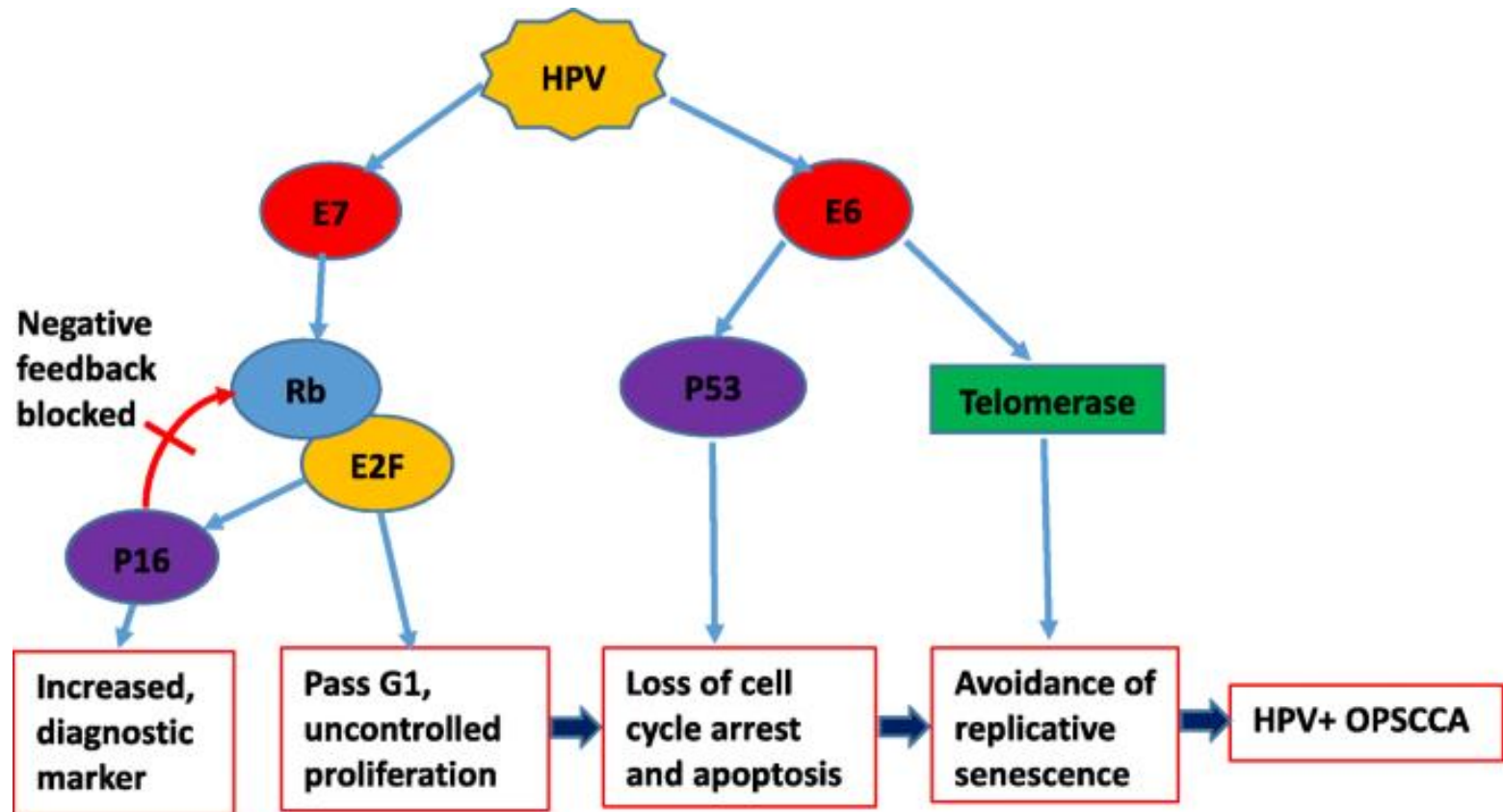
WHO 2020 classification

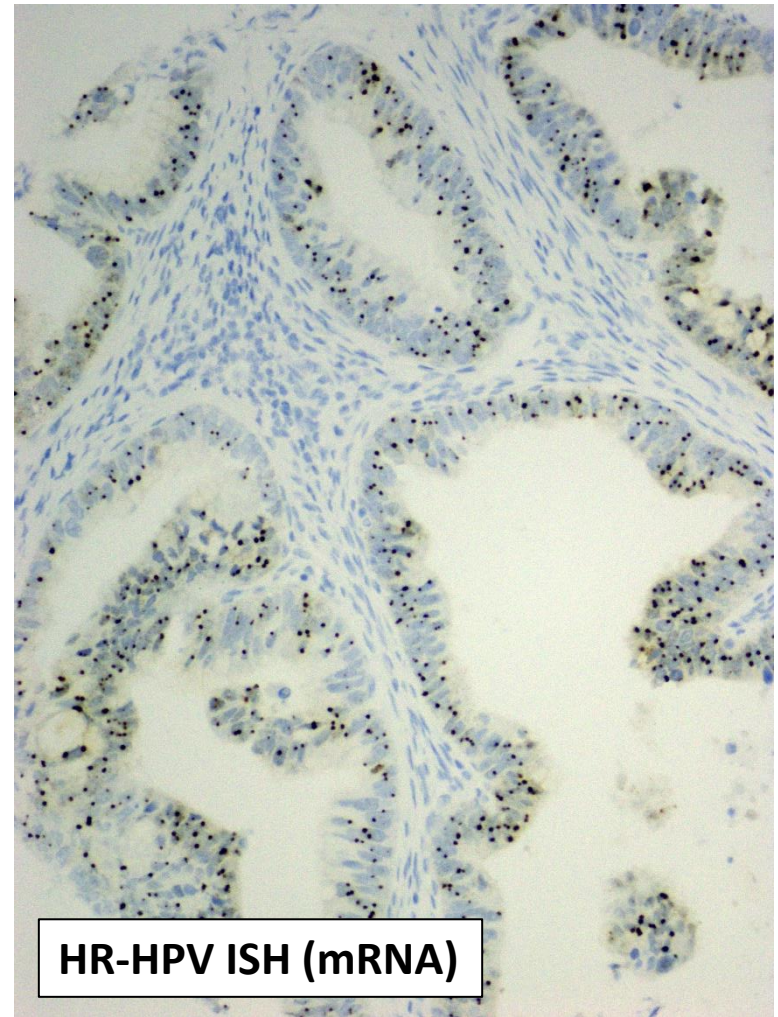
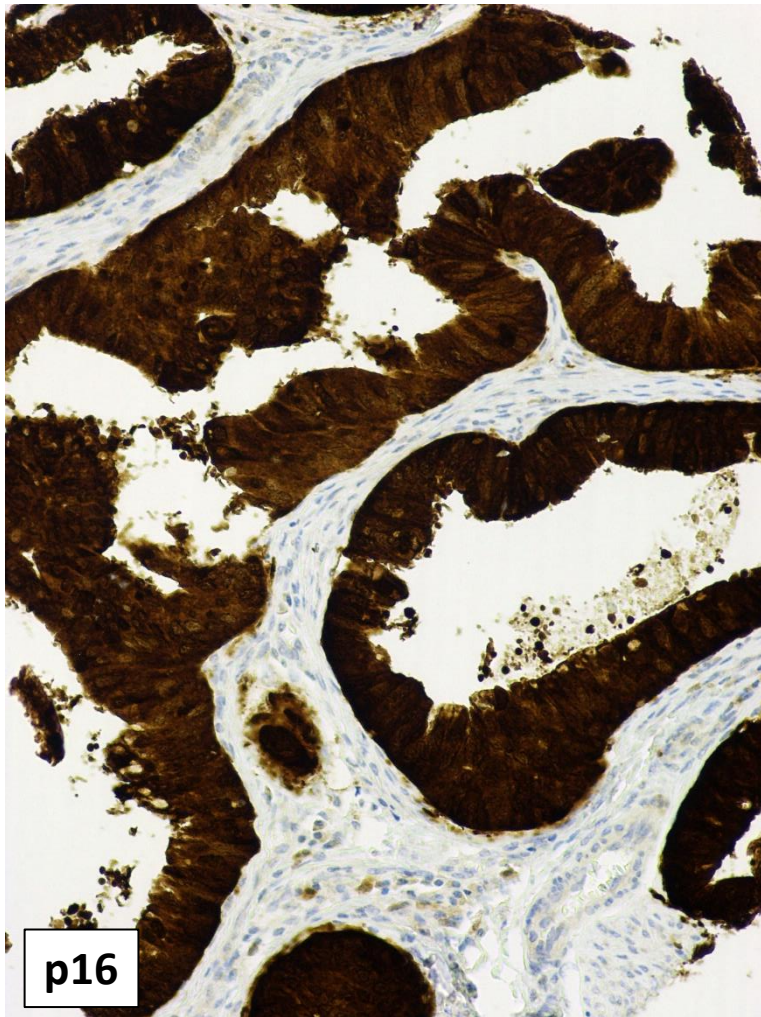
- HPV-associated endocervical adenocarcinoma (HPVA) (85%)
- HPV-independent endocervical adenocarcinoma (HPVI) (15%)
 - Gastric type (including adenoma malignum) (10% of total)
 - Clear cell (<5%)
 - Mesonephric (<5%)
 - NOS (<5%)
- Really rare or non-existent entities
 - Endometrioid
 - Serous





p16 and HPV



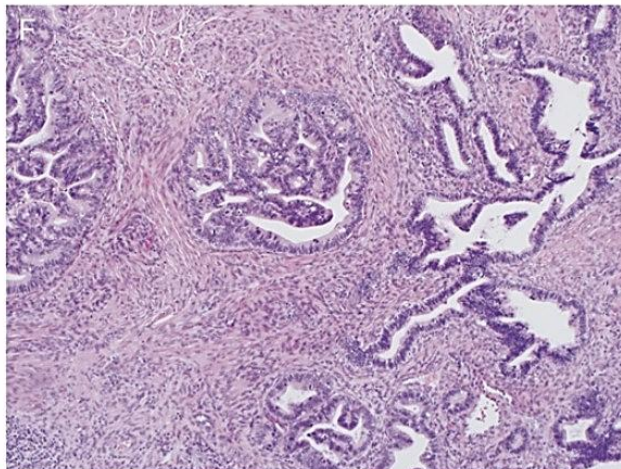
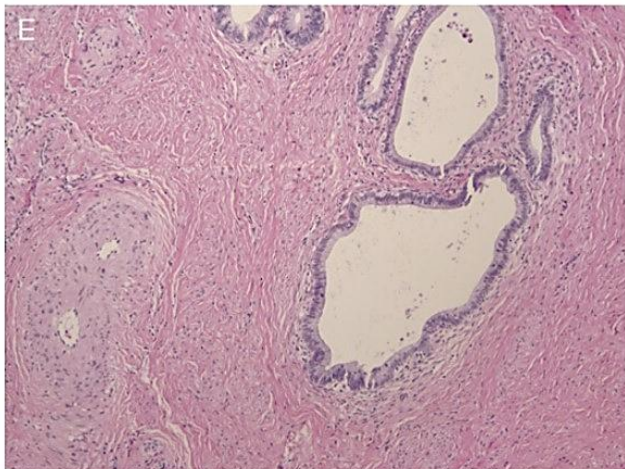
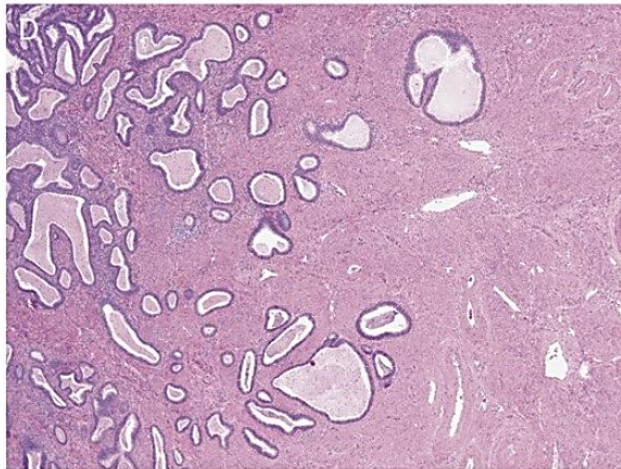
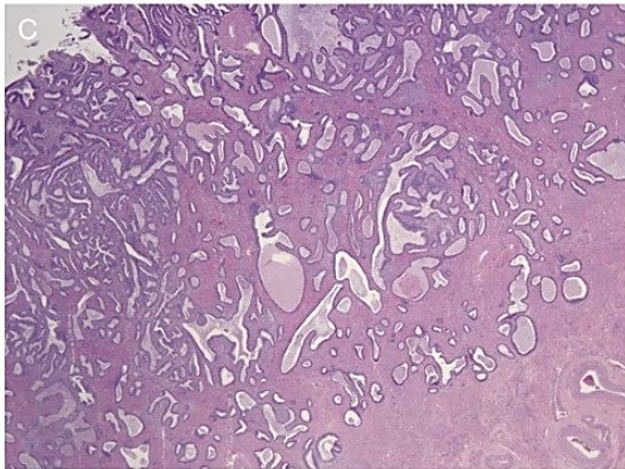
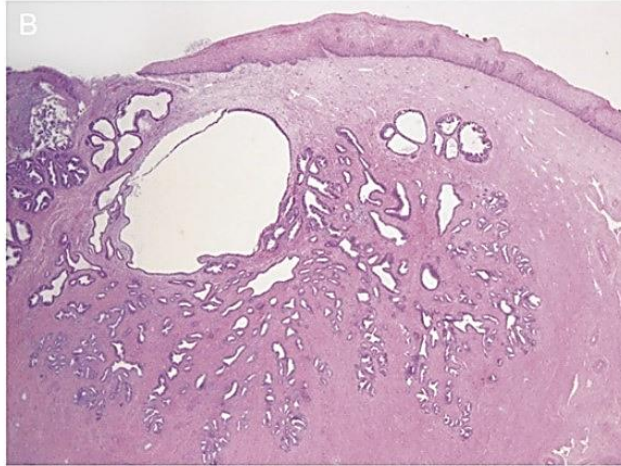
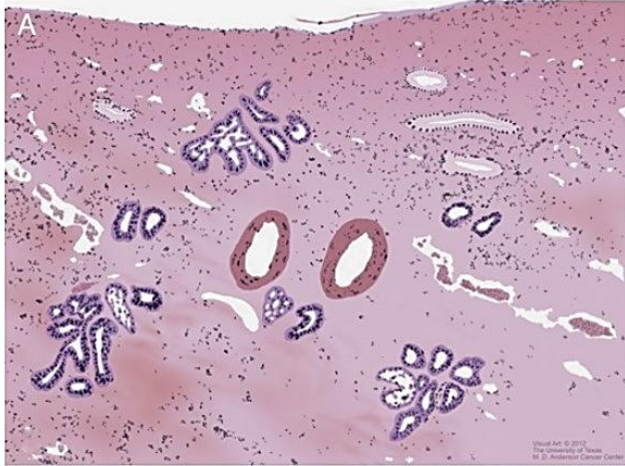


HPVA endocervical adenocarcinoma: patterns with clinical significance

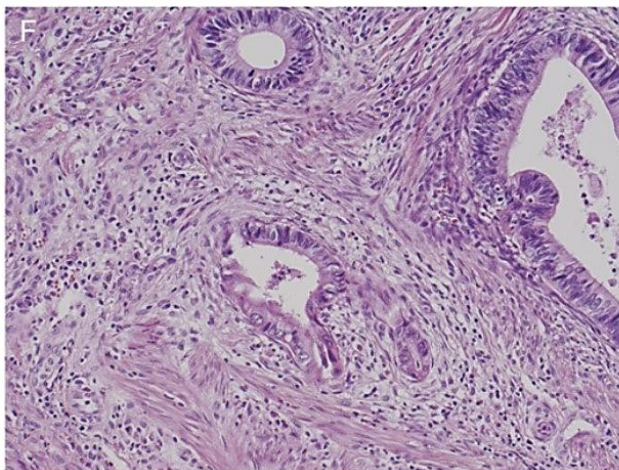
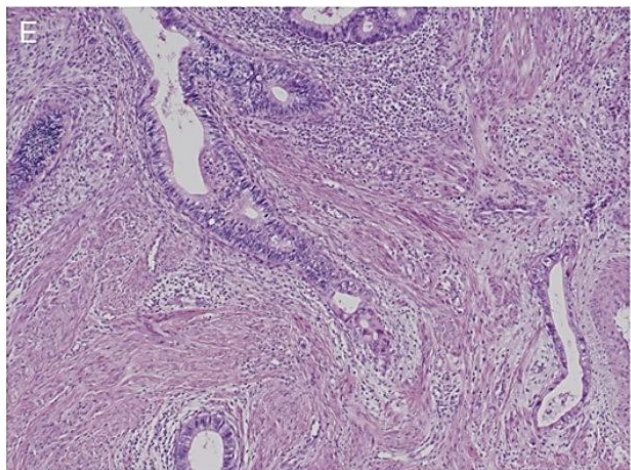
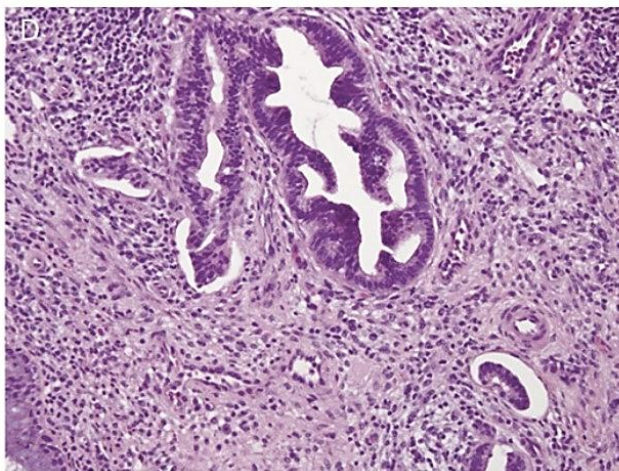
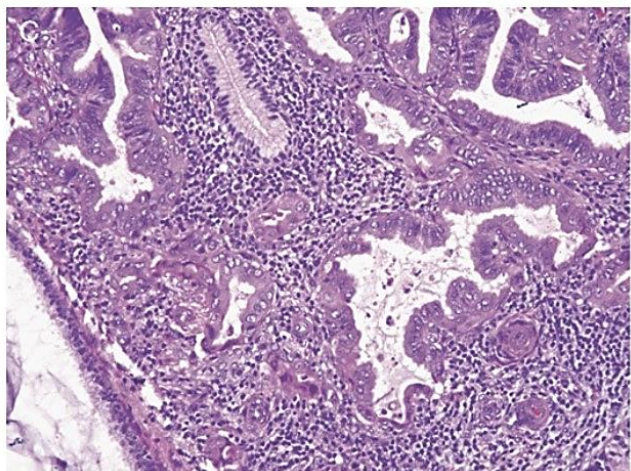
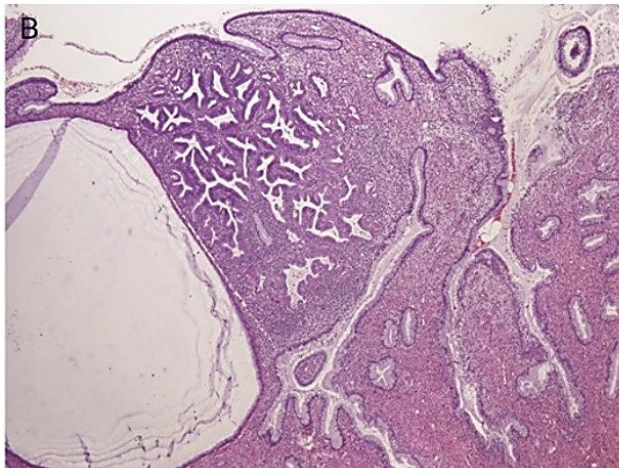
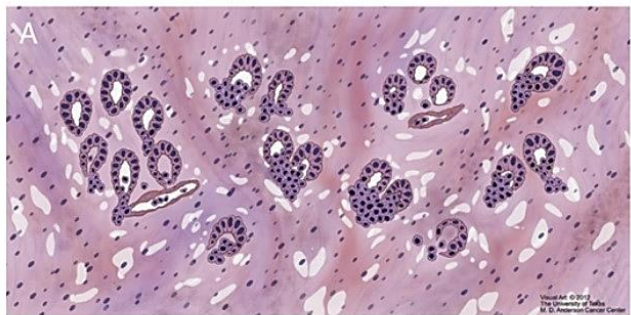
- Superior outcomes
 - No destructive invasion (Silva pattern A)
- Possibly worse outcomes
 - Mucinous, NOS
 - Stratified mucinous (ISMC)
- Worst outcomes
 - Micropapillary
 - Signet ring

Silva invasion patterns (HPVA)

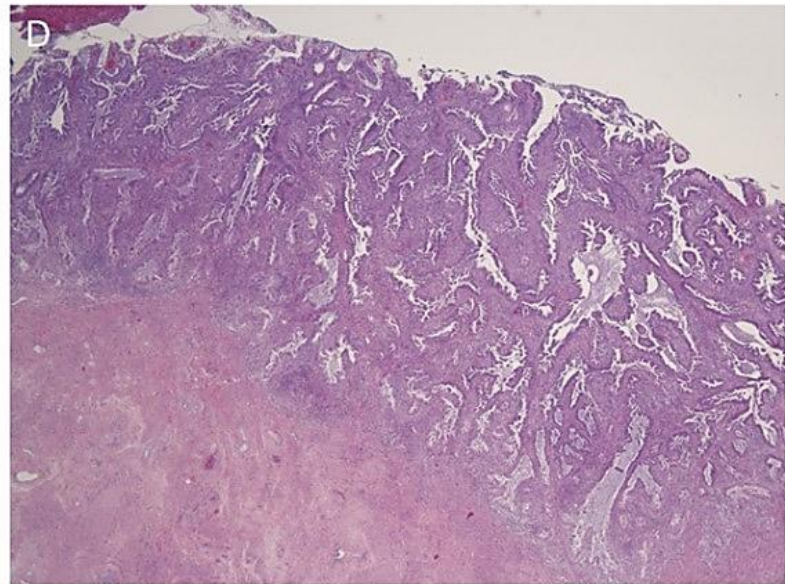
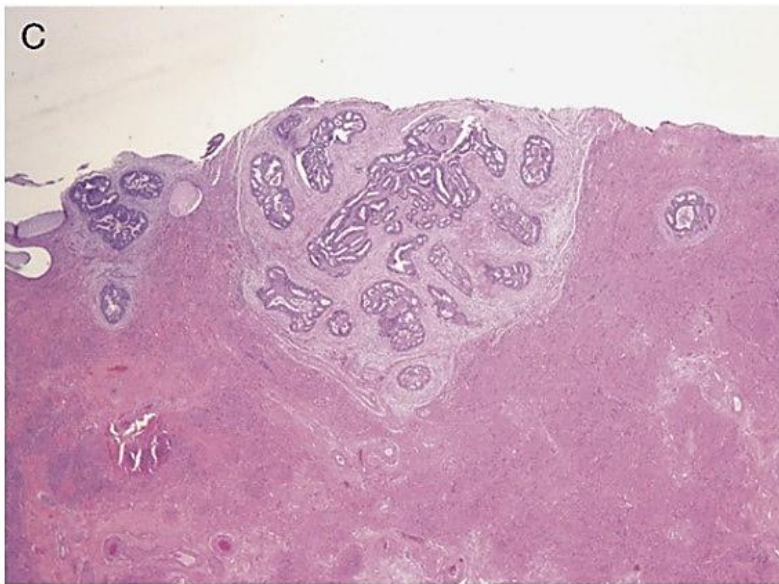
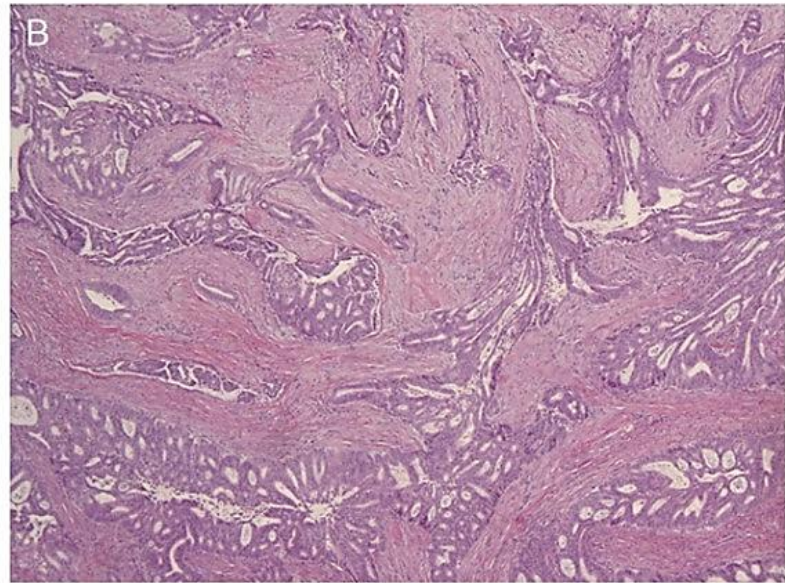
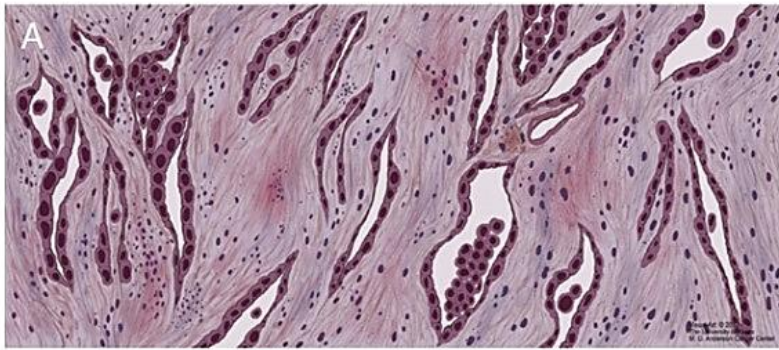
- Silva invasion pattern is more informative about clinical outcomes and LN status compared to depth of invasion in resectable carcinomas
 - i.e. FIGO IB1 carcinoma, Silva pattern A: 0% LN metastasis
- Silva A: no stromal desmoplasia/no LVI (non-destructive invasion)
- Silva B: focally destructive invasion, <5mm
- Silva C: extensive destructive invasion, >5mm
- Low-risk : Silva A or B, no LVI
- High-risk: Silva C and/or LVI

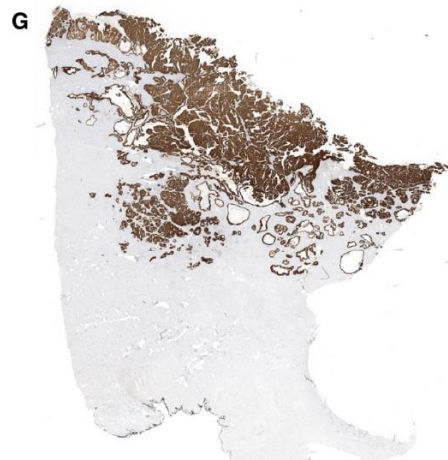
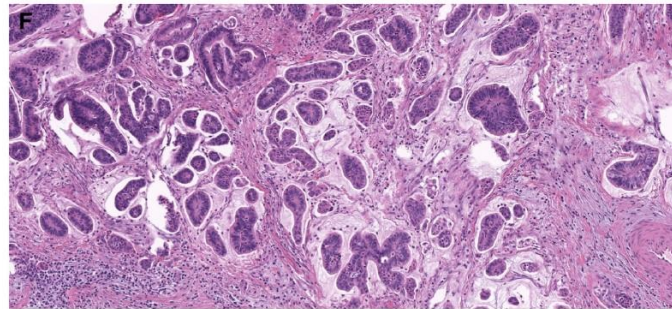
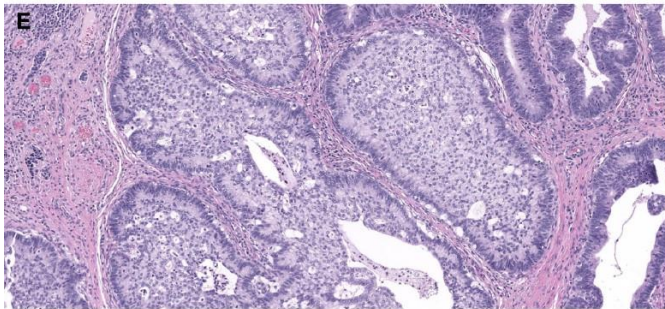
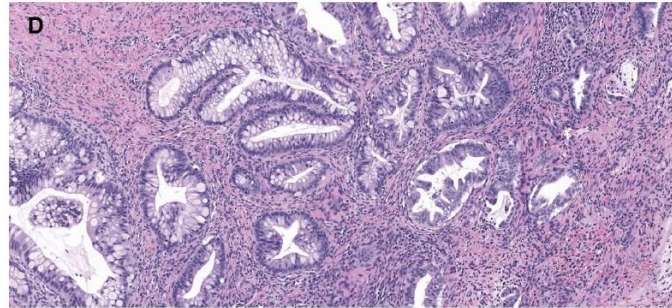
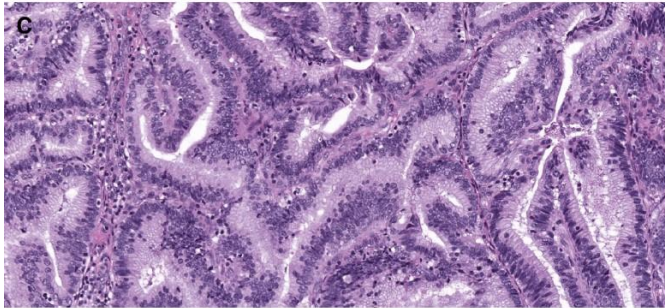
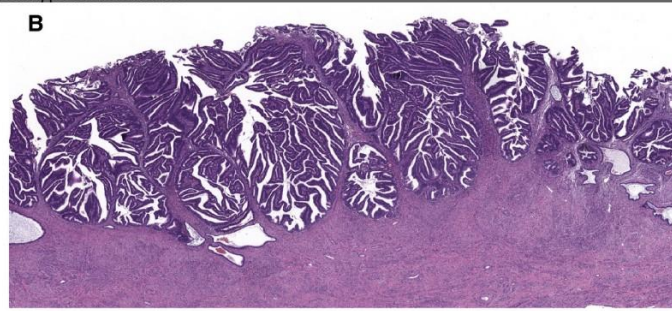
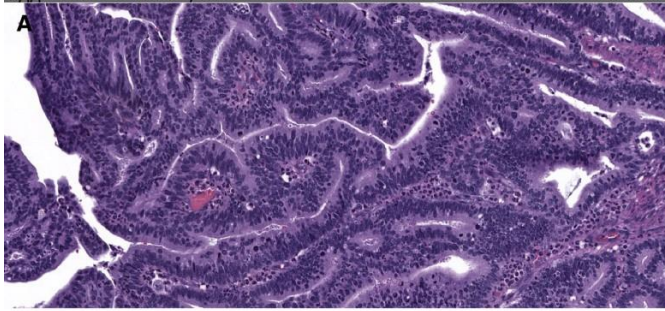


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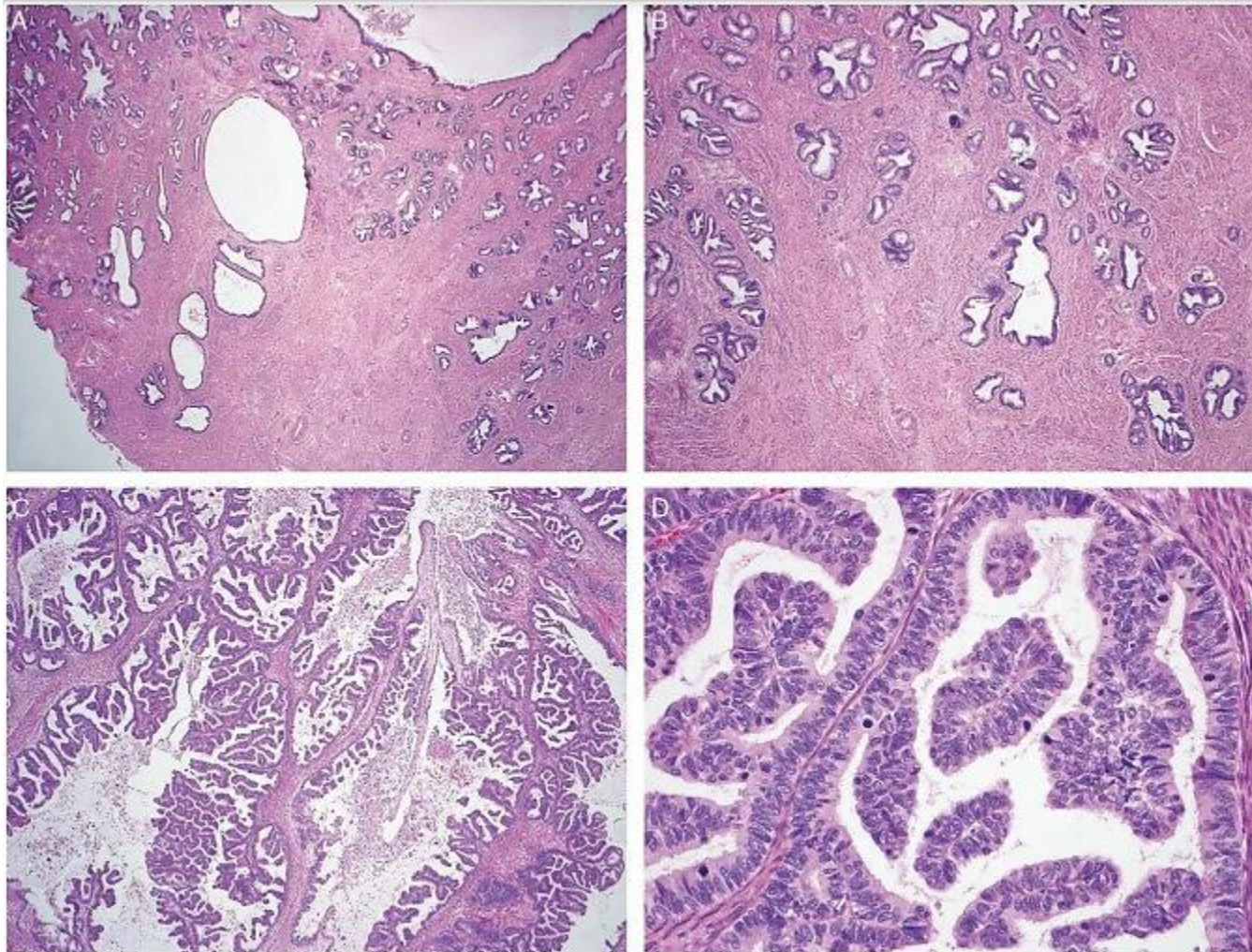
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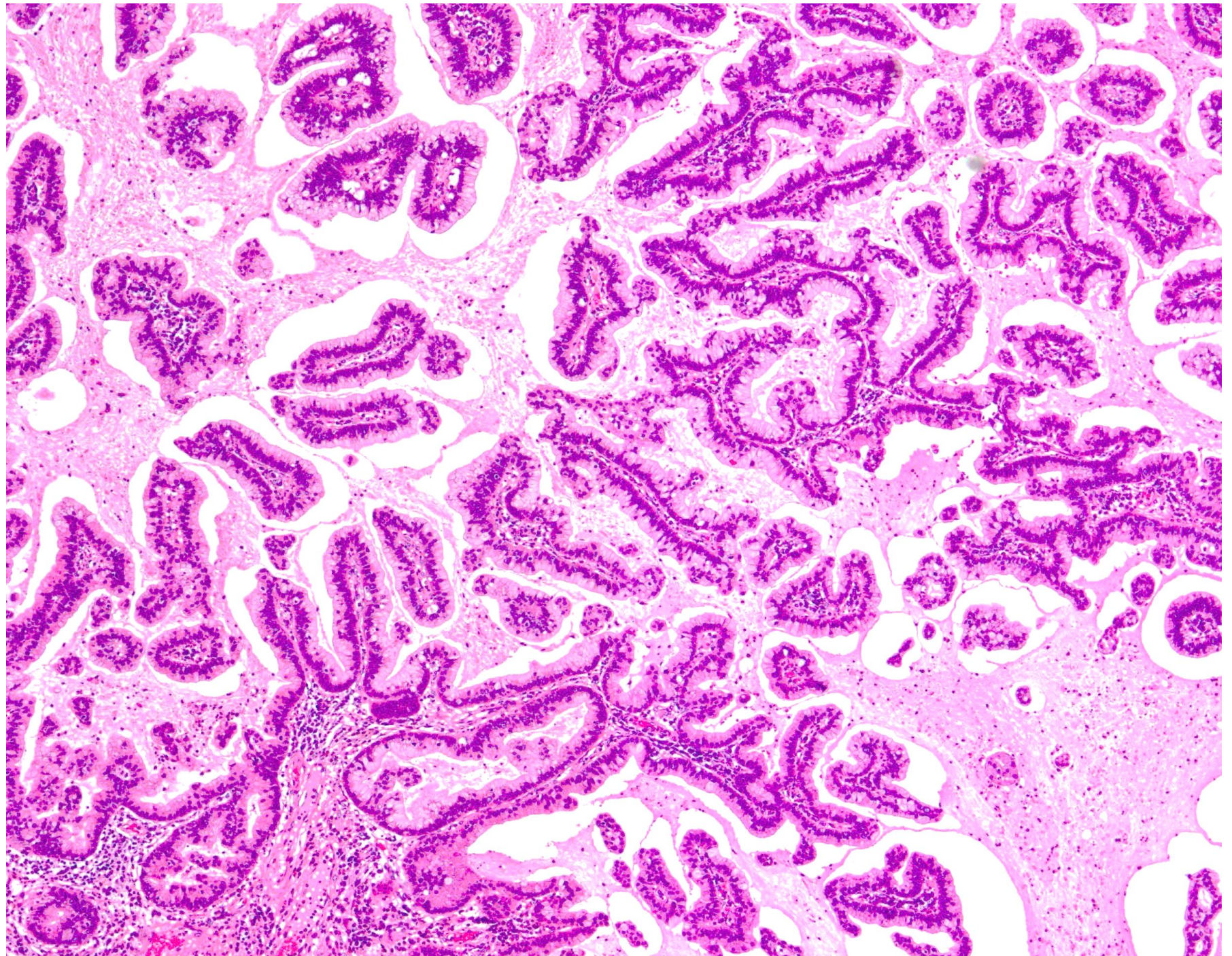


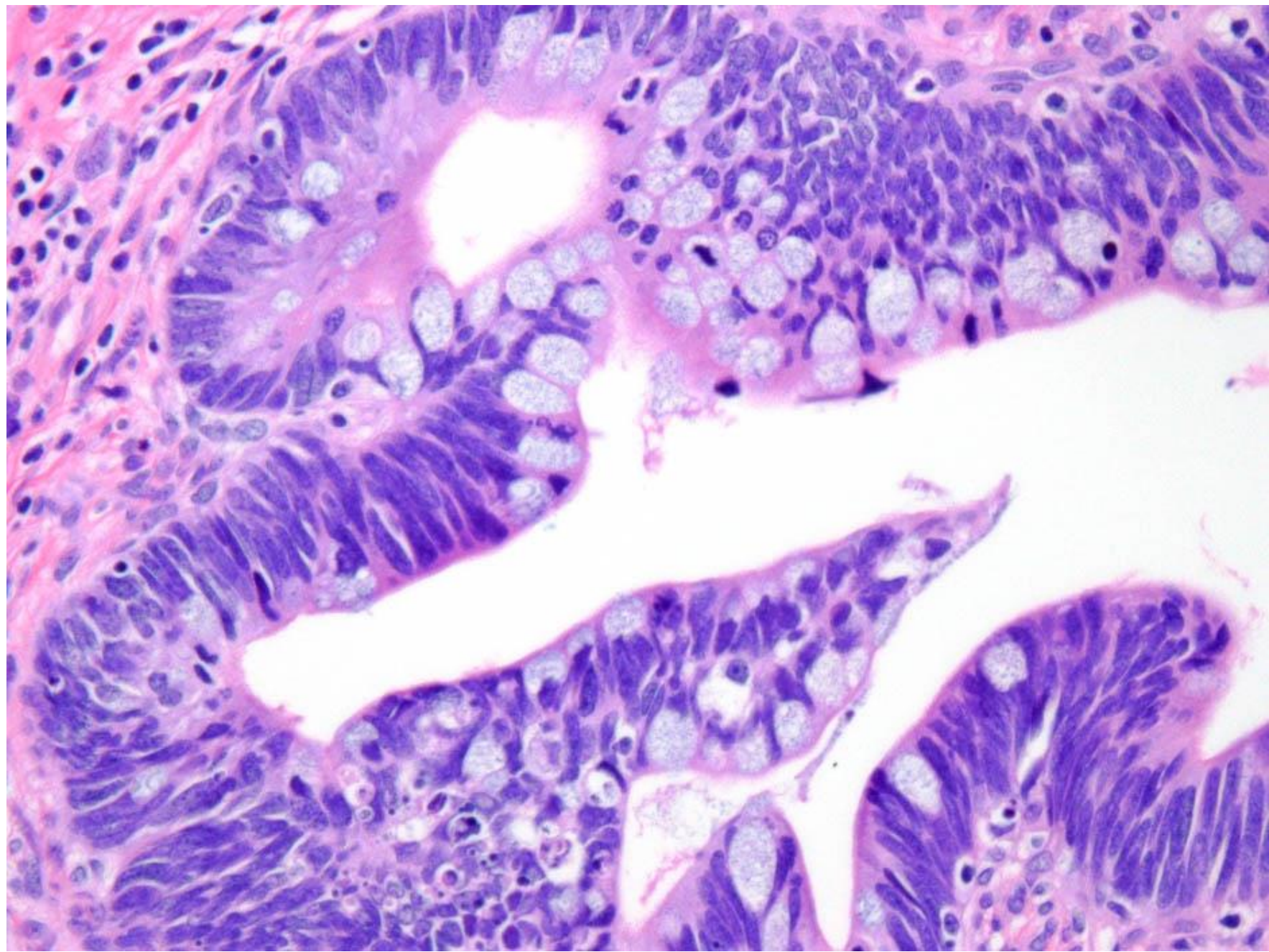


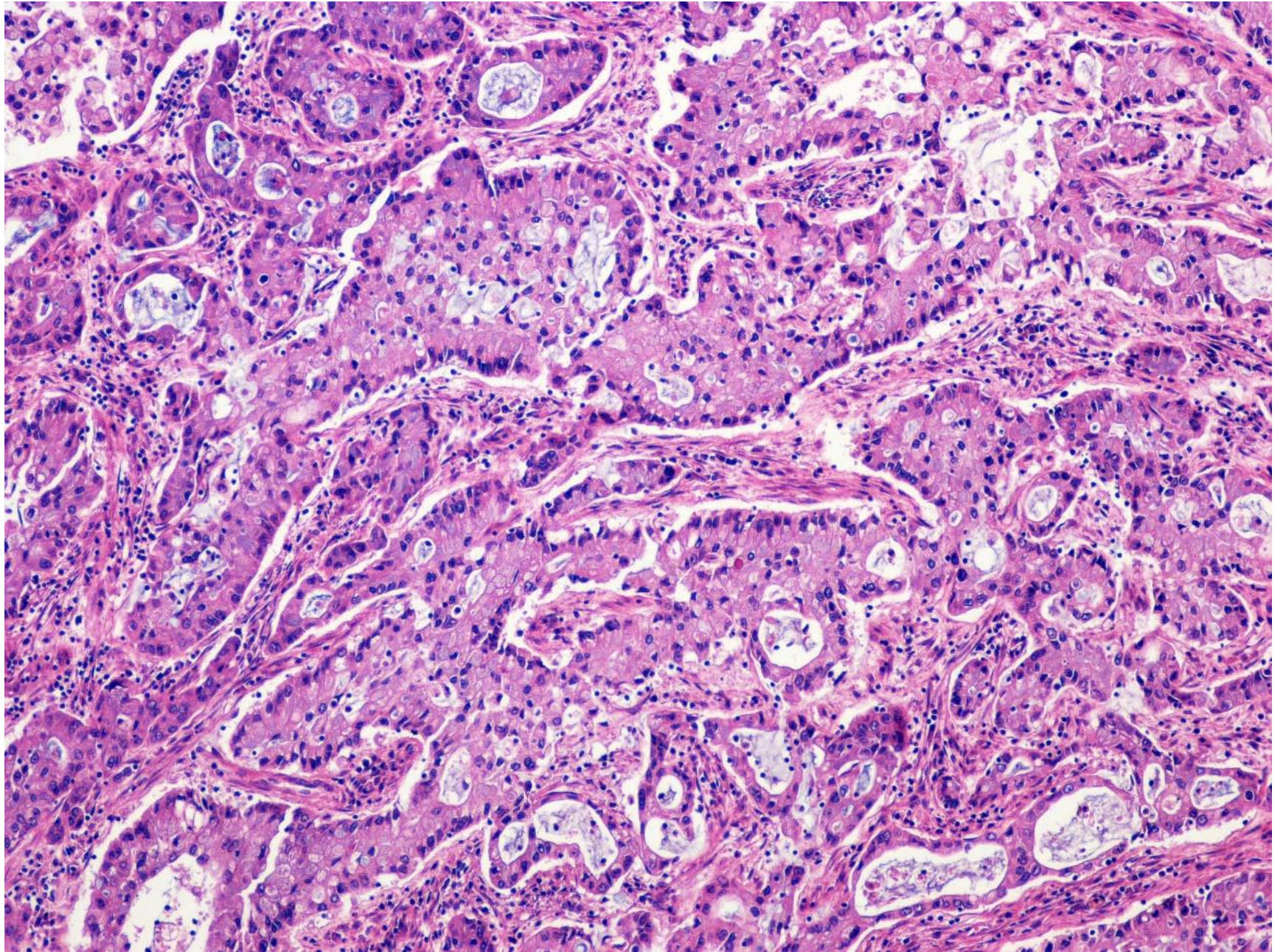
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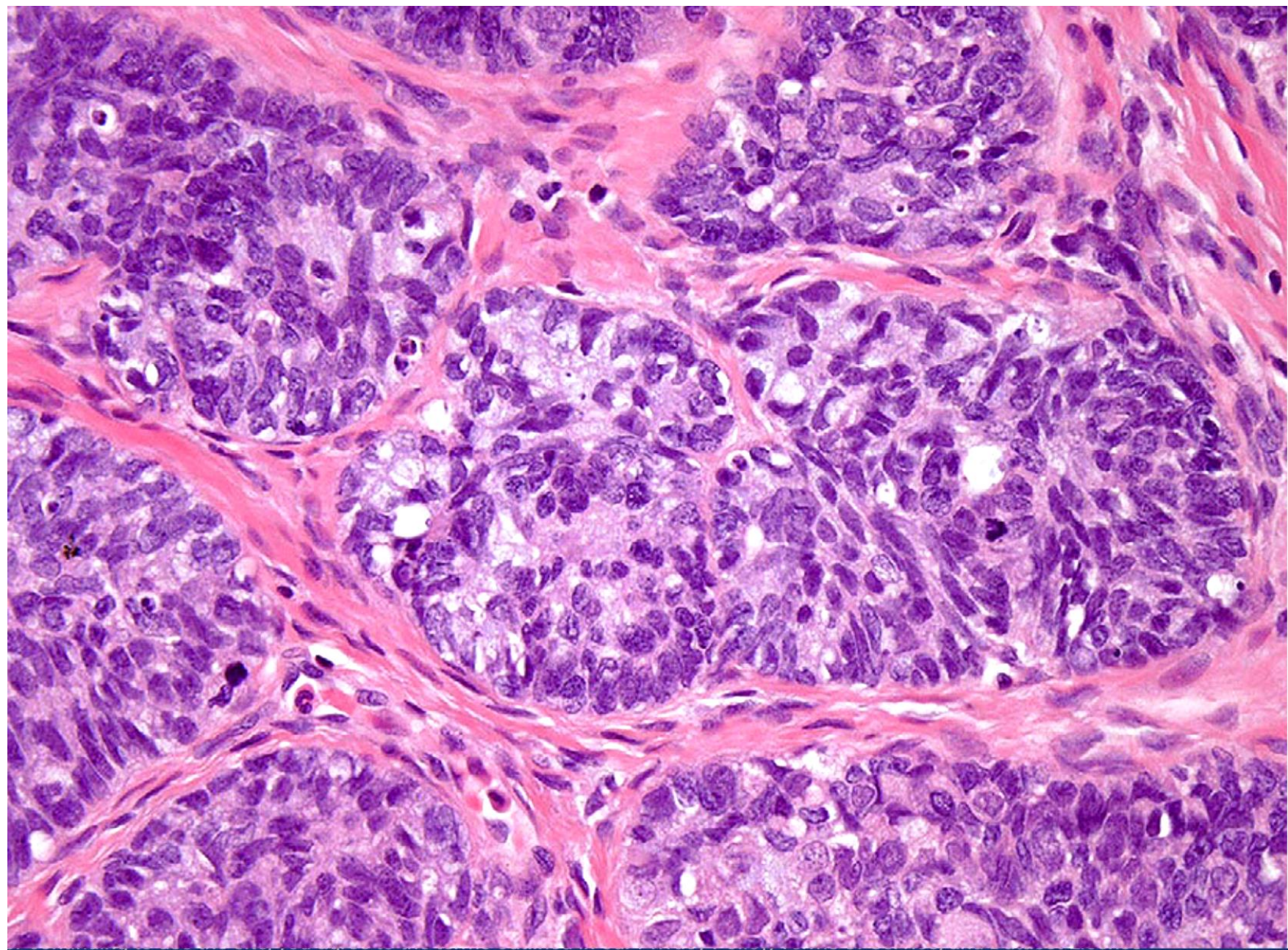
Pattern A: ovarian metastasis

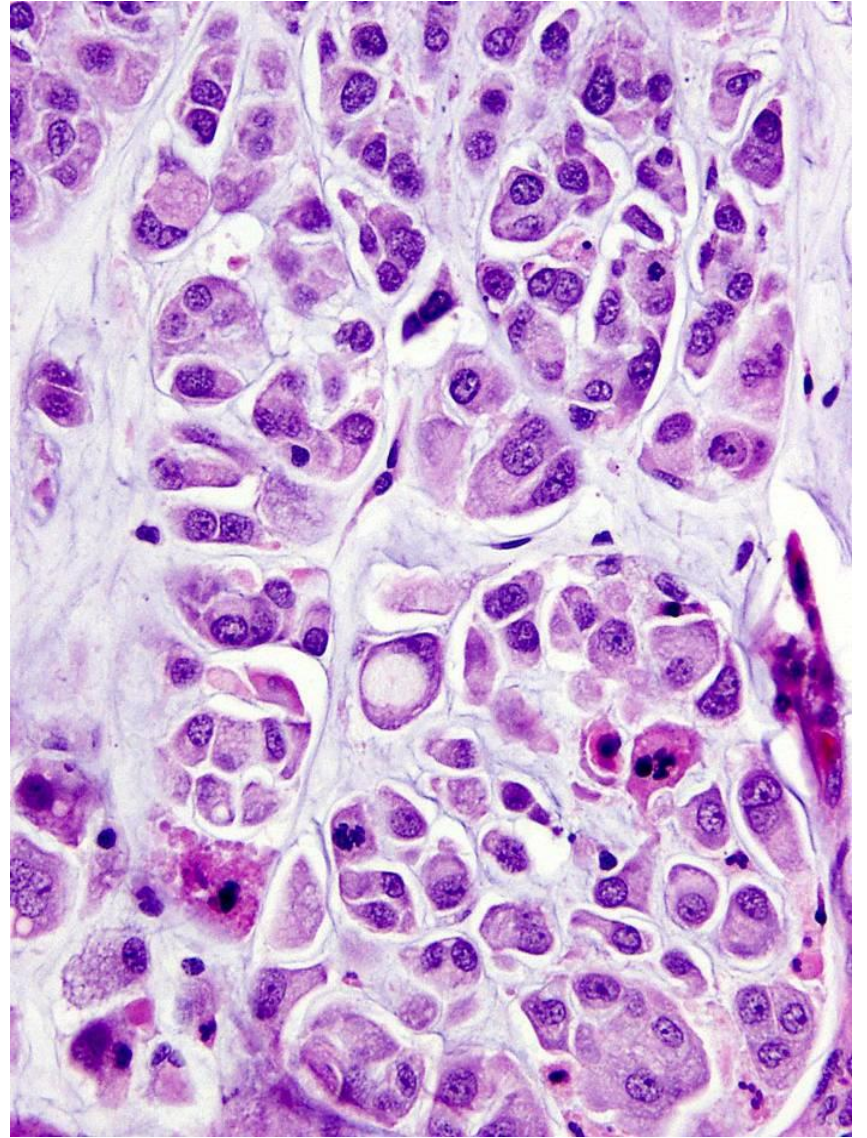
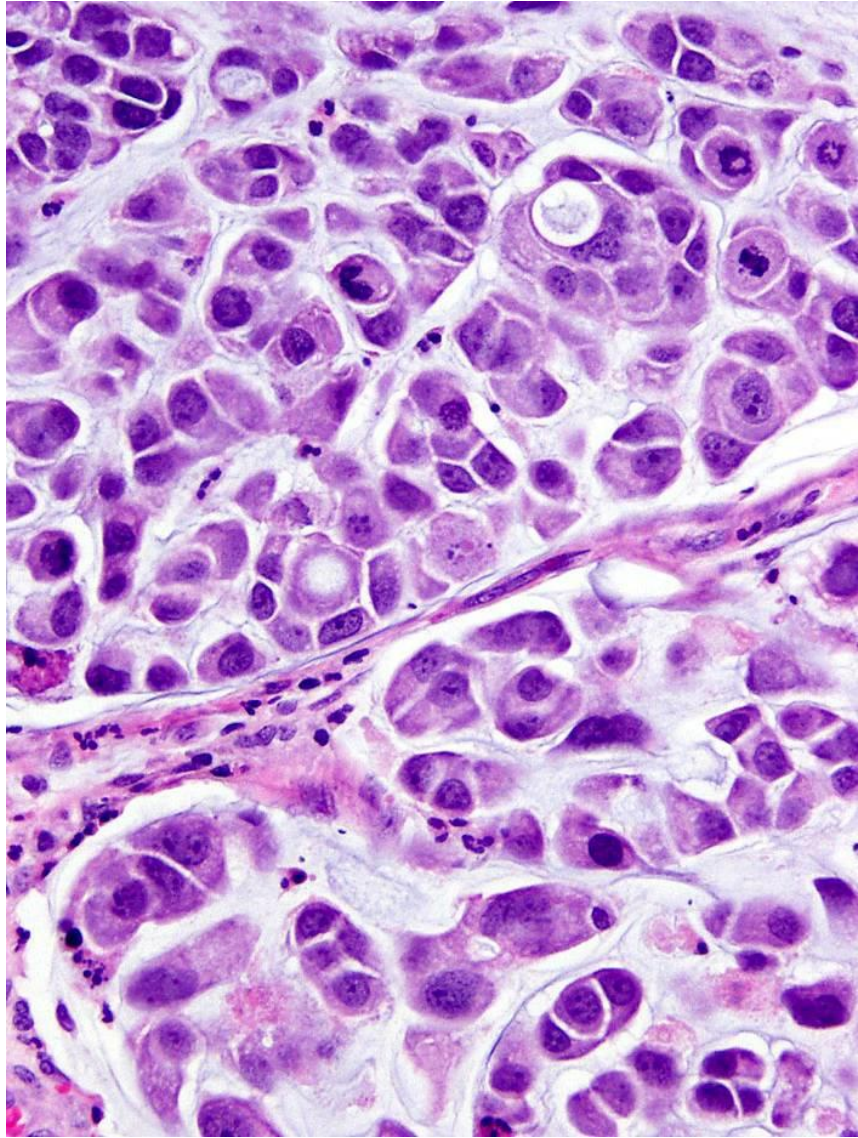








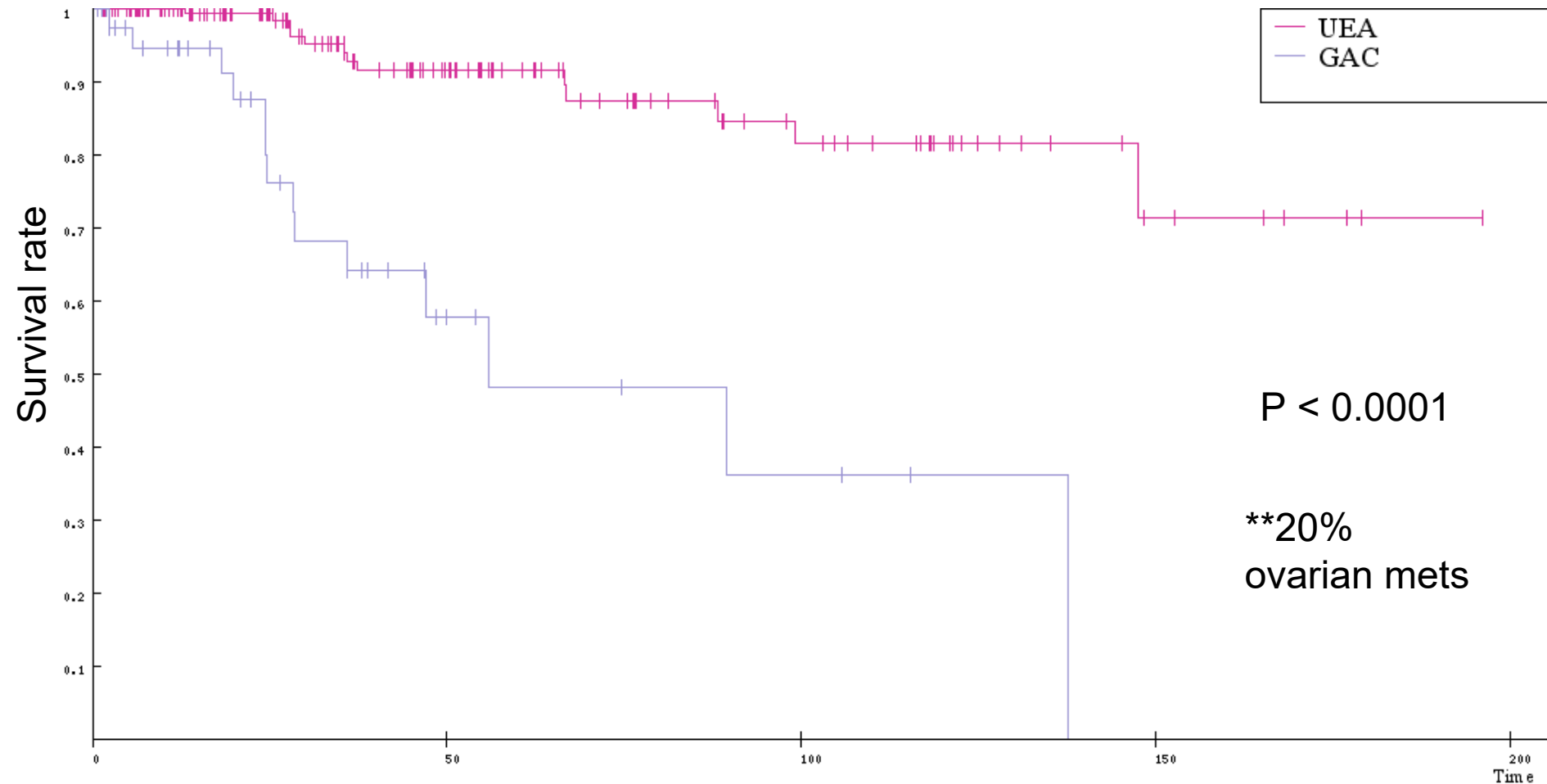




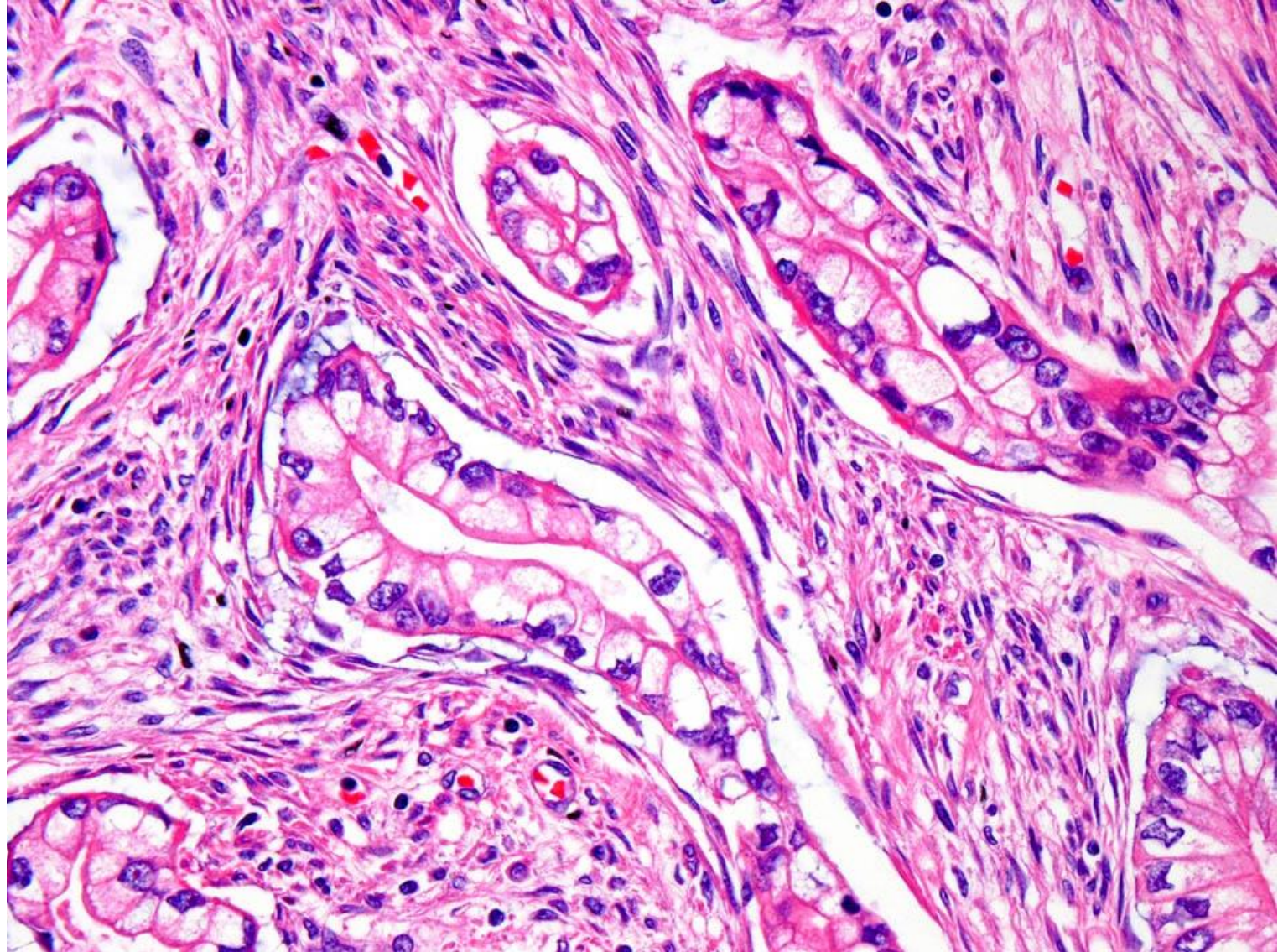
Crucial differences between HPVI and HPVA

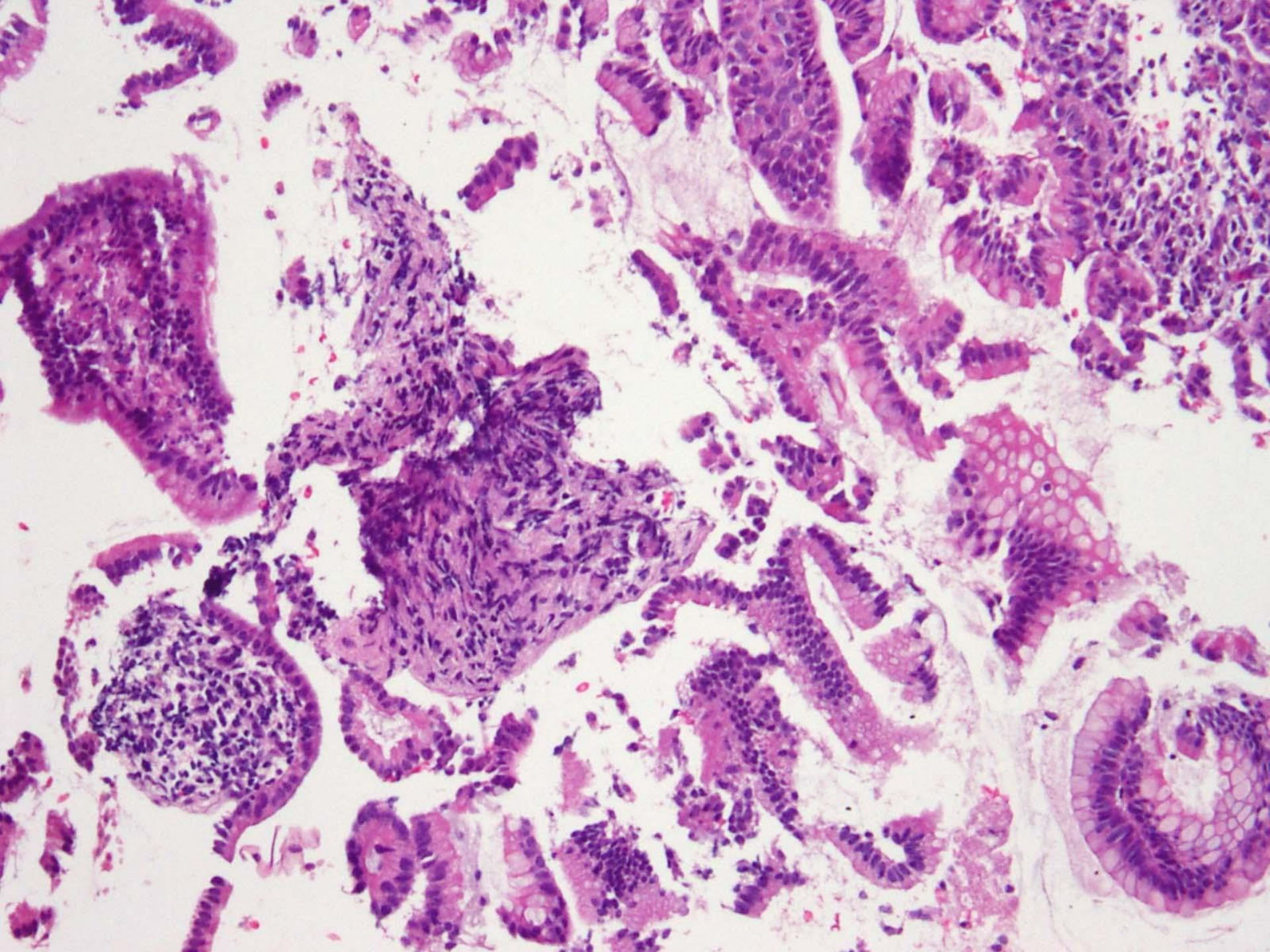
- Higher stage at presentation
 - 66% HPVI vs 12% HPVA
- Higher incidence of disease recurrence
 - 34% HPVI vs 4% HPVA
- Higher incidence of distant metastases including abdominal
 - 19% HPVI vs 3% HPVA
- Higher mortality rate
 - 39% HPVI vs 8% HPVA

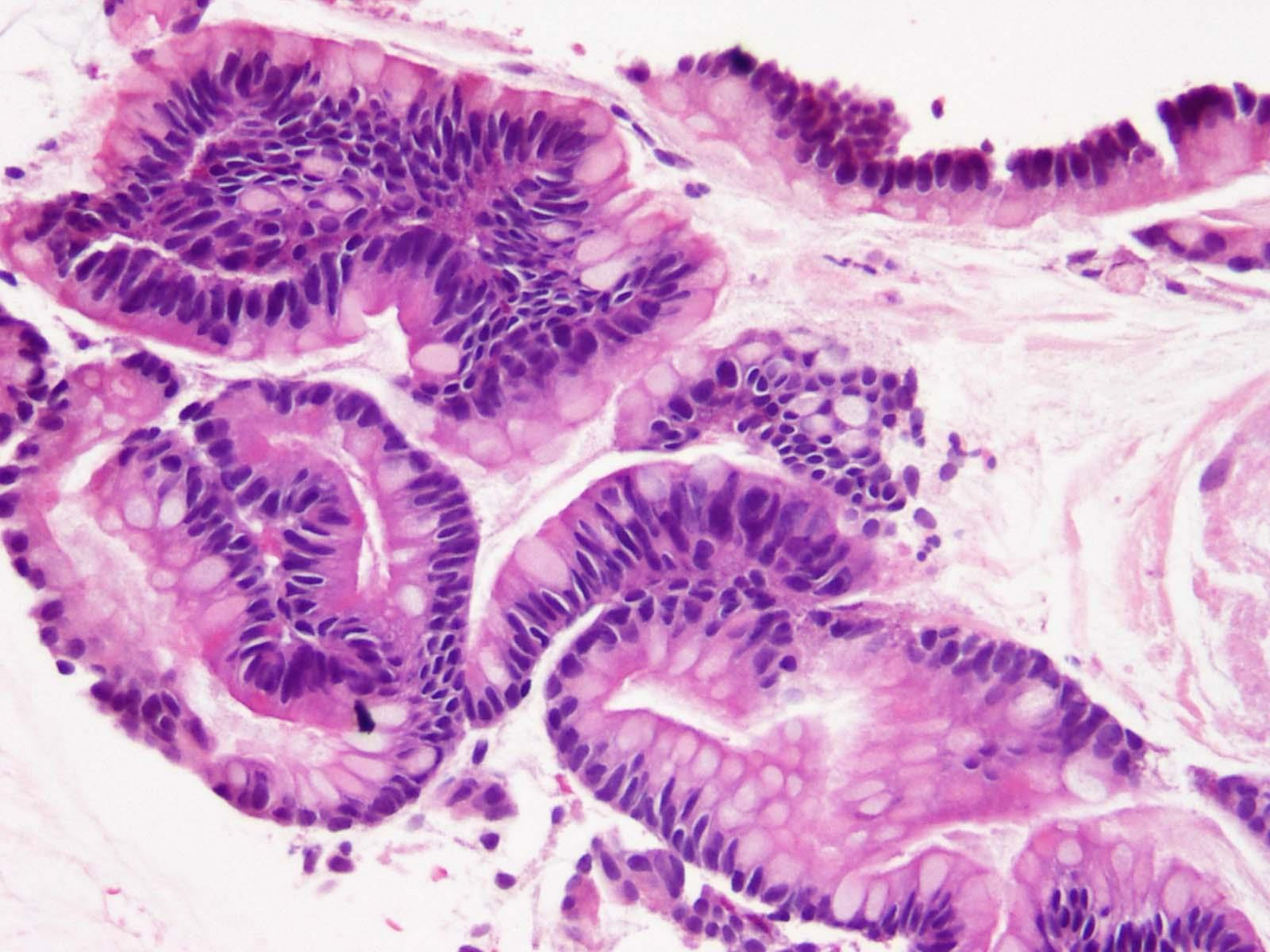
Disease-specific survival

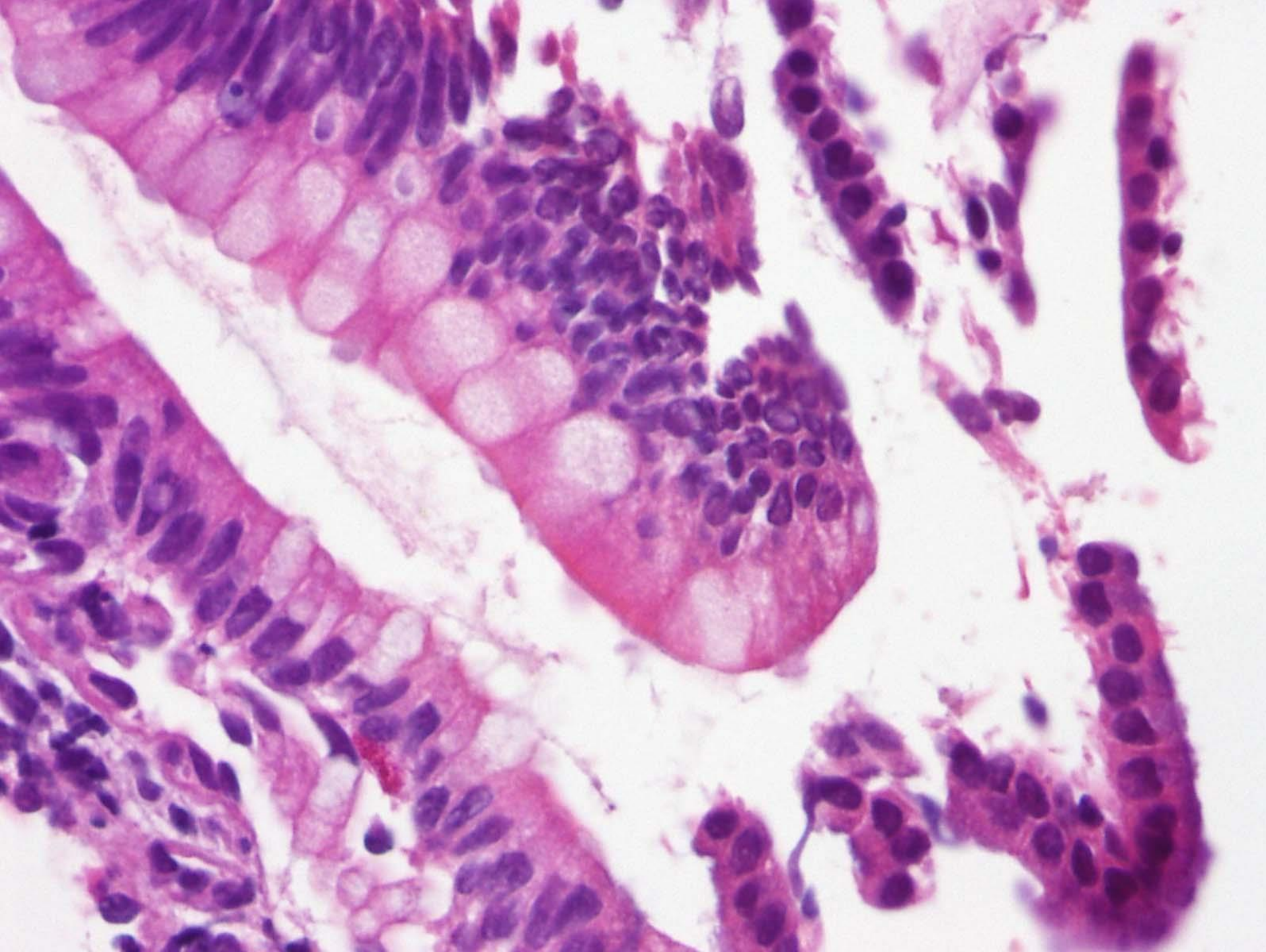


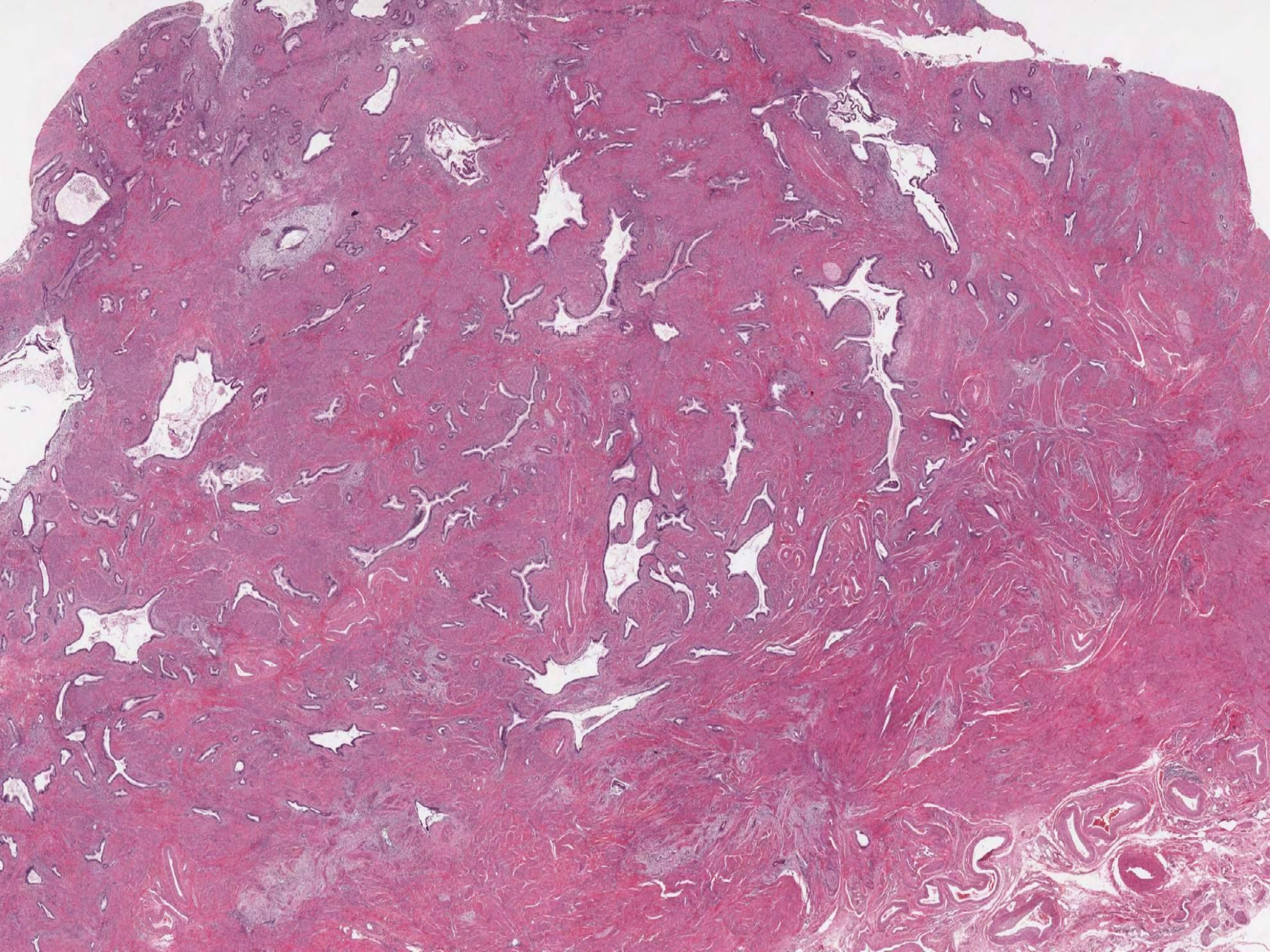
Gastric-type carcinoma (HPVI)

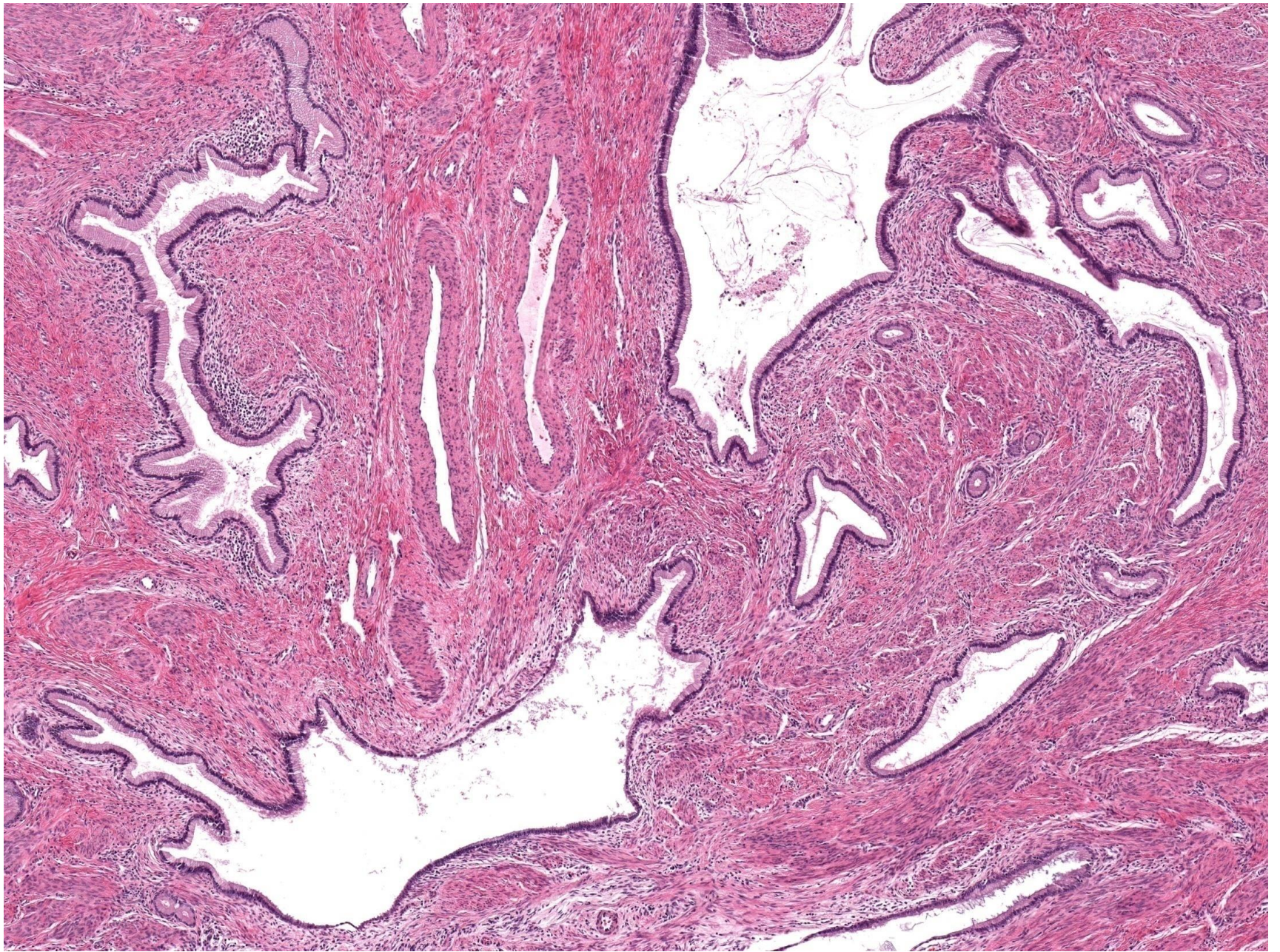


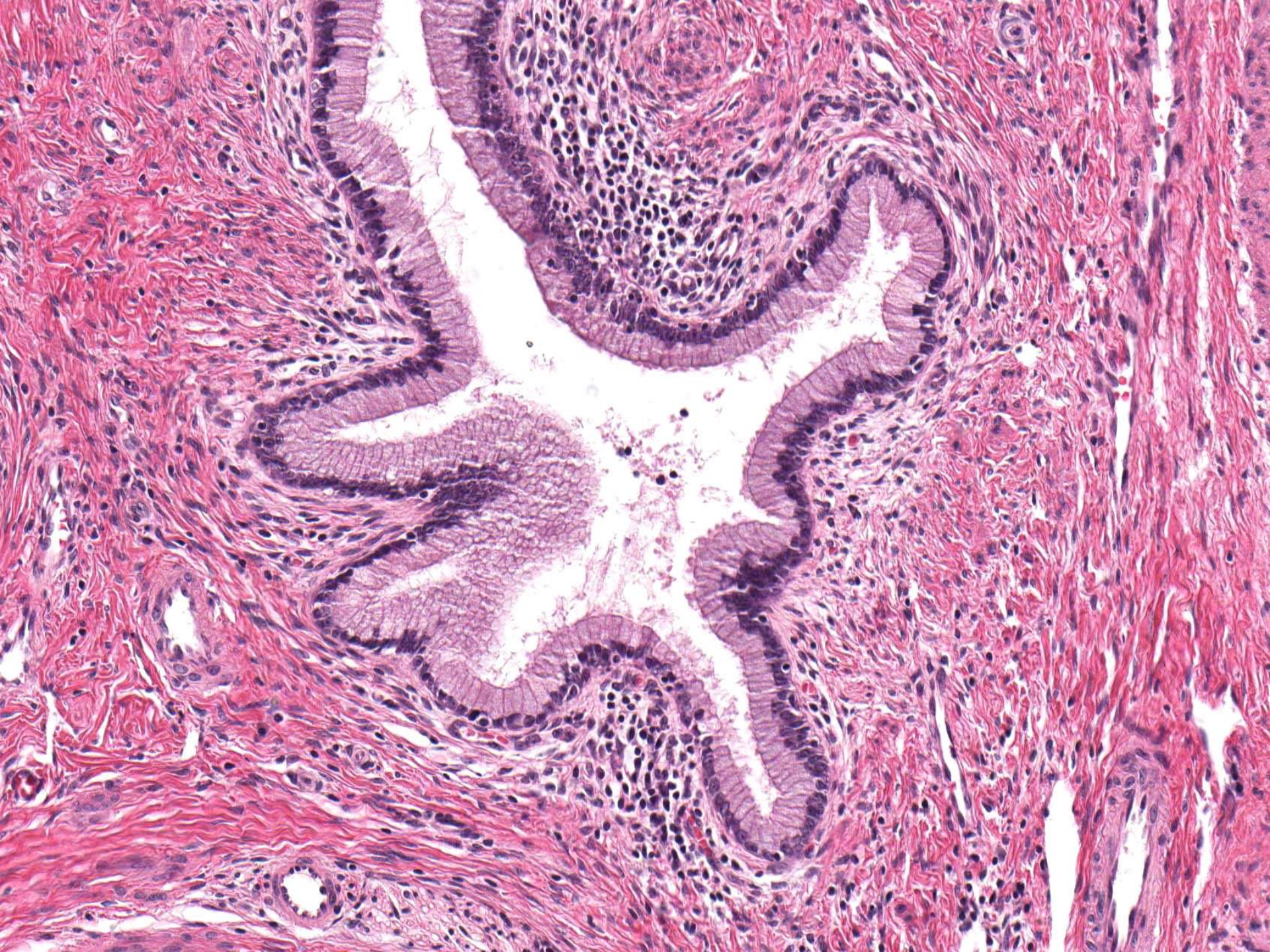


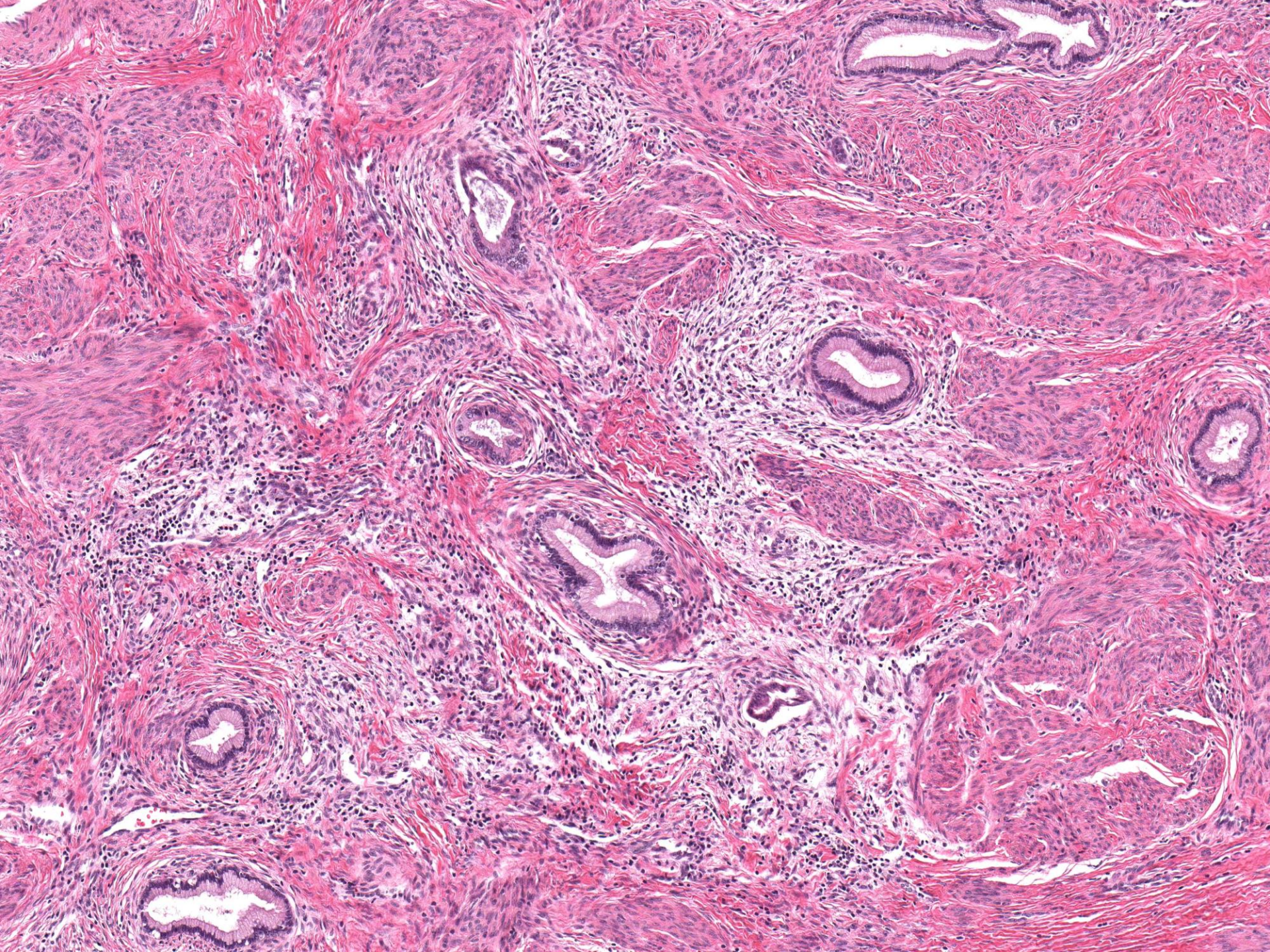


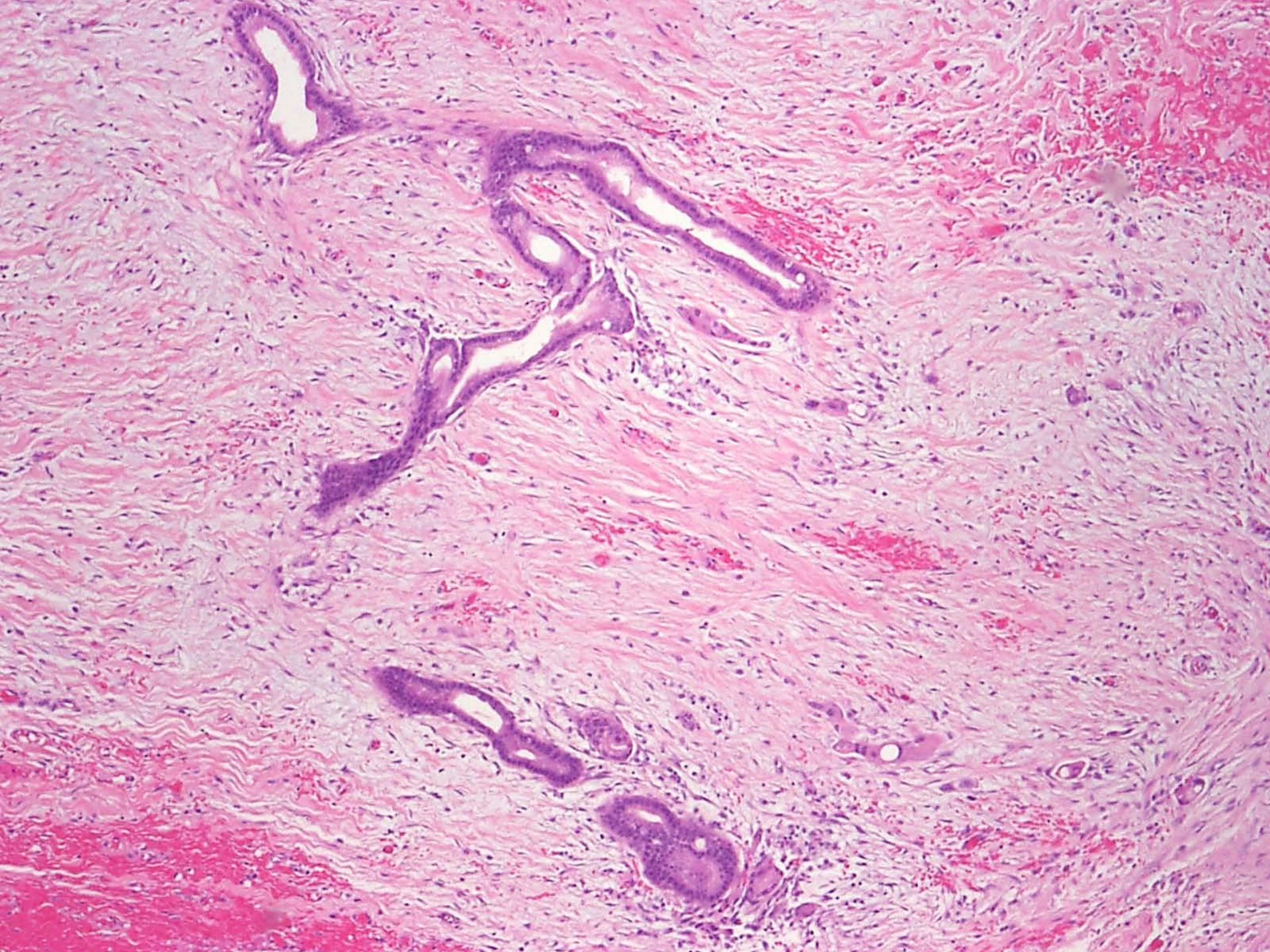


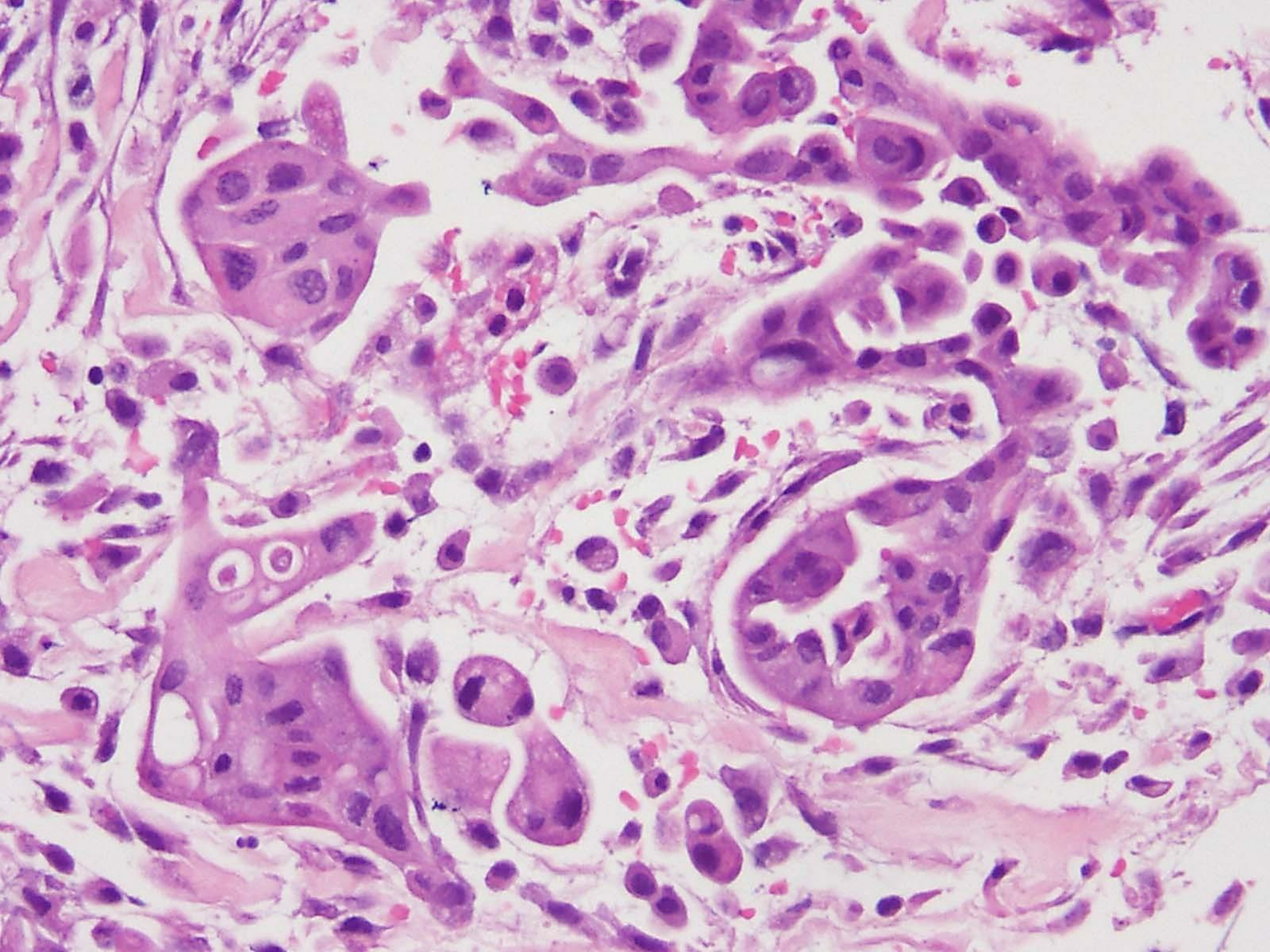


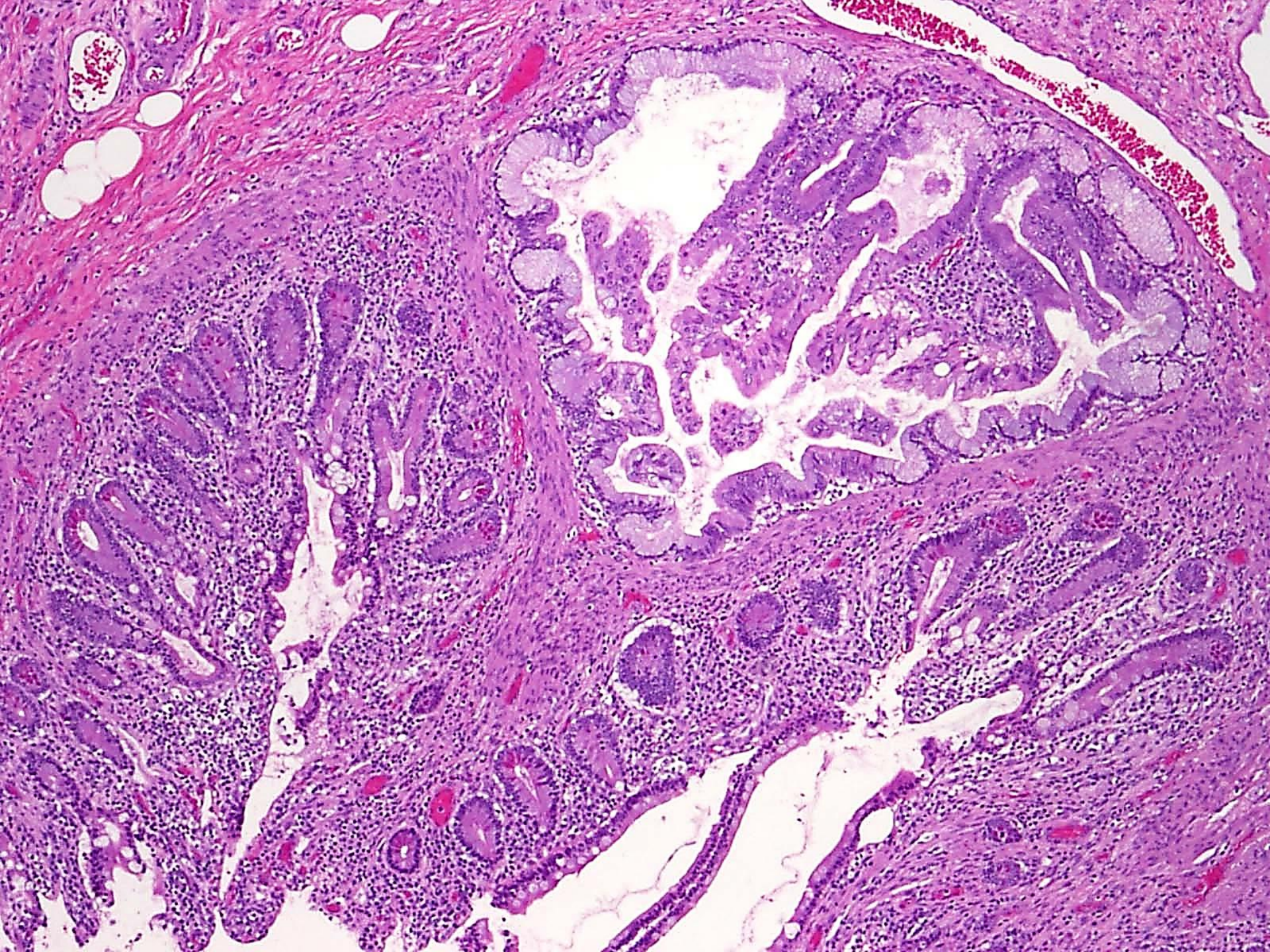




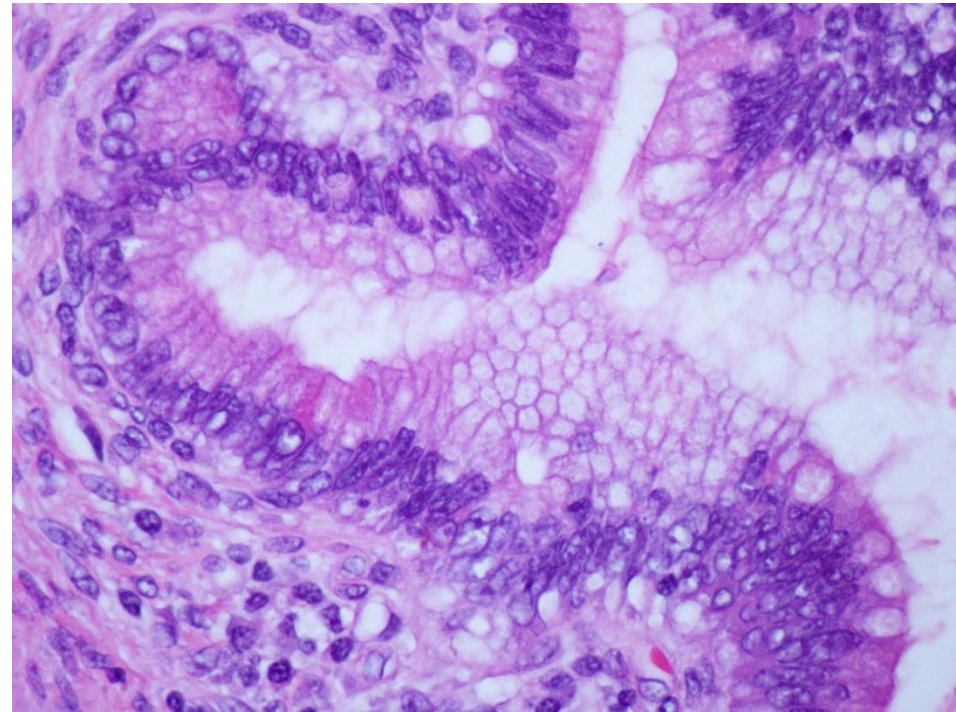
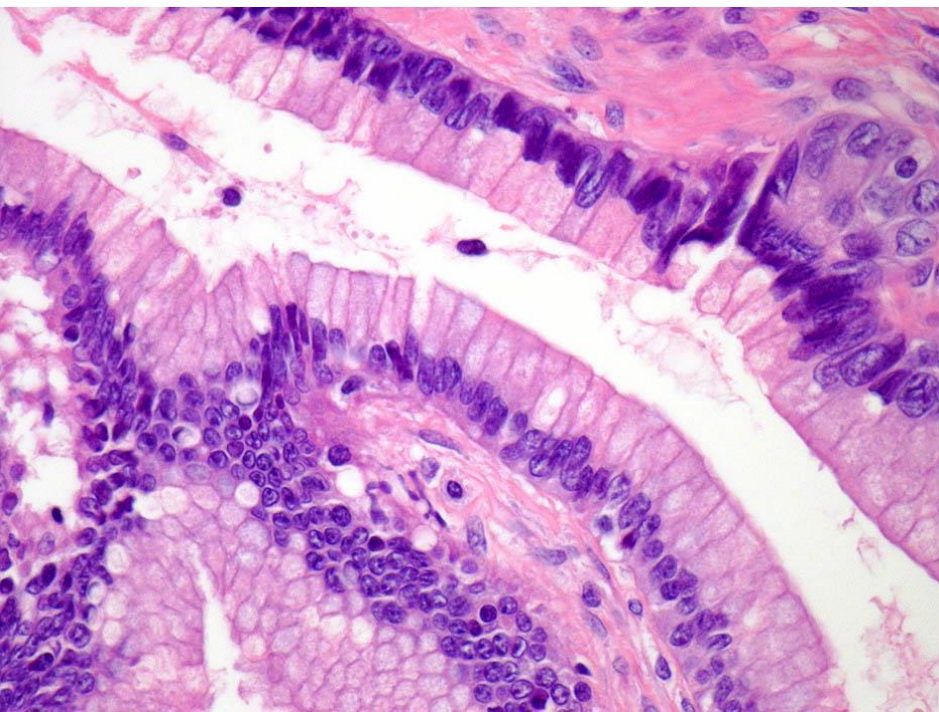
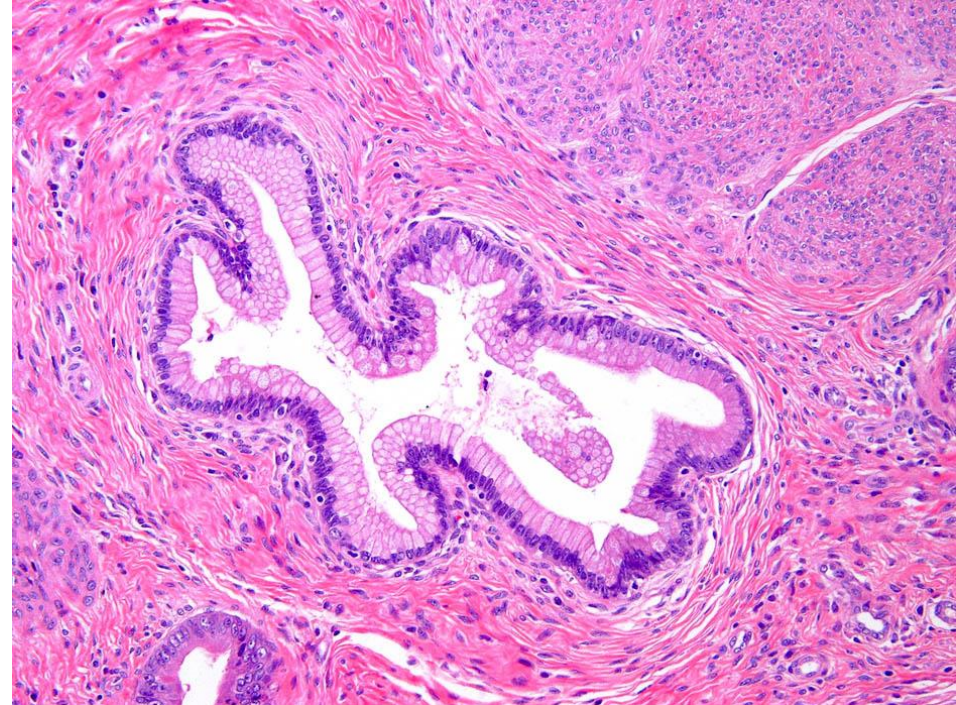
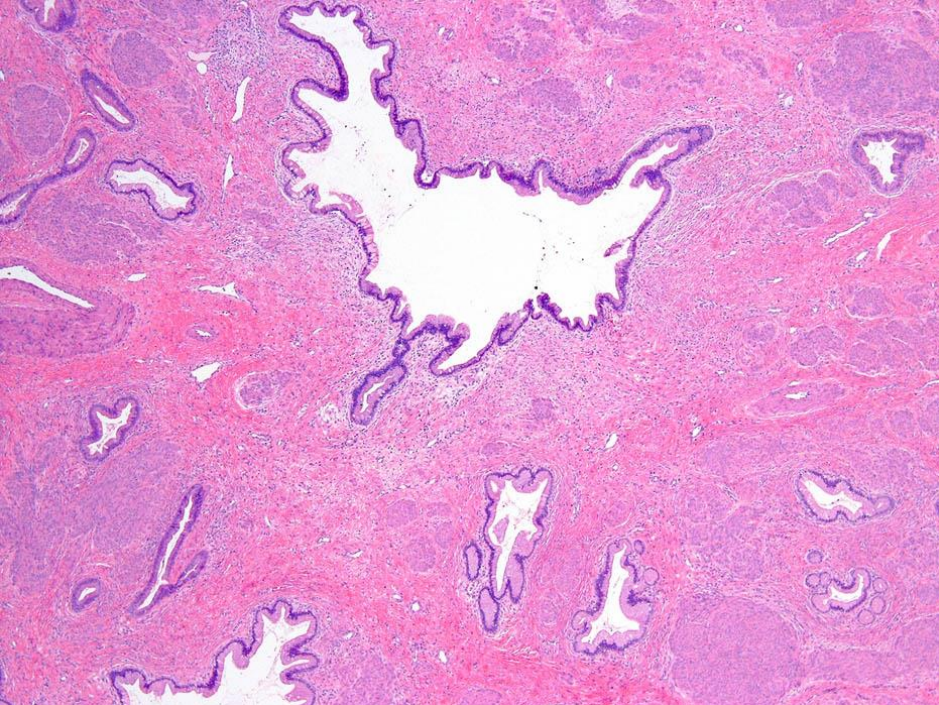


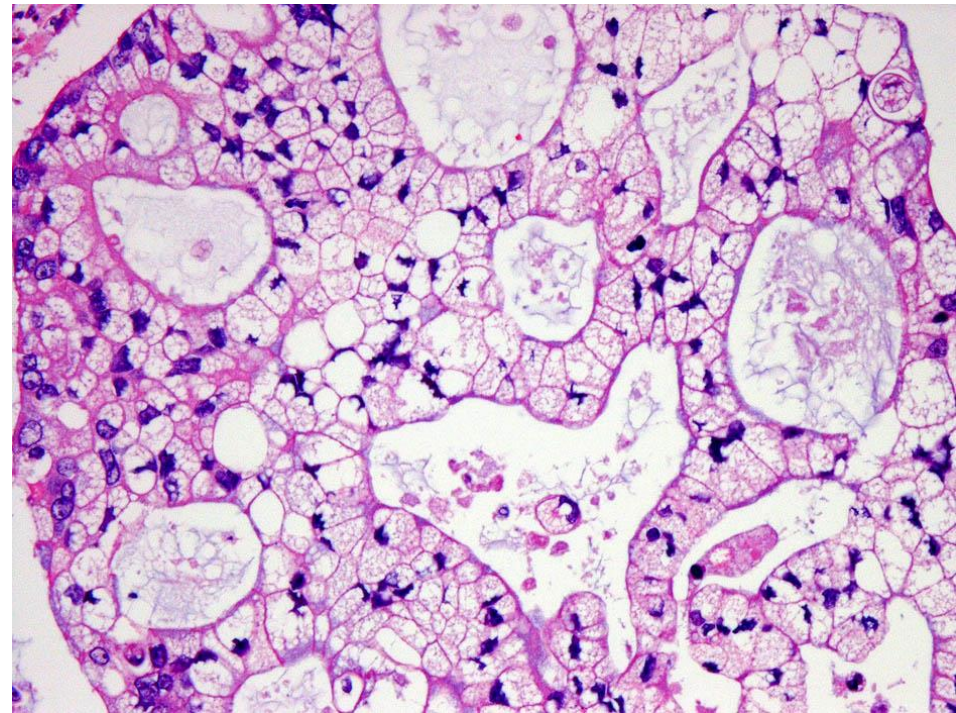
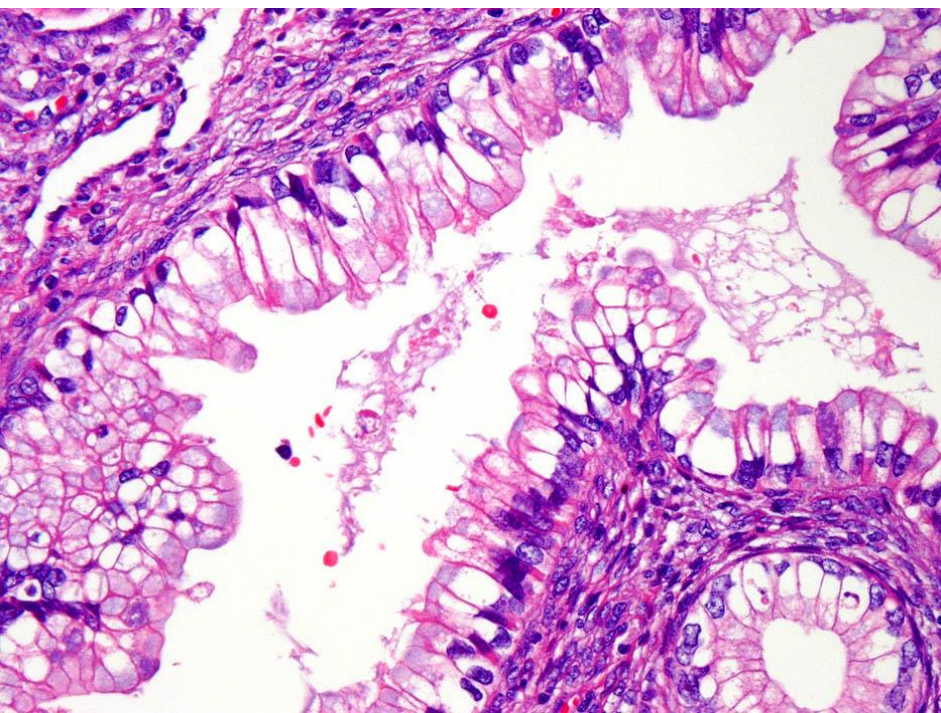
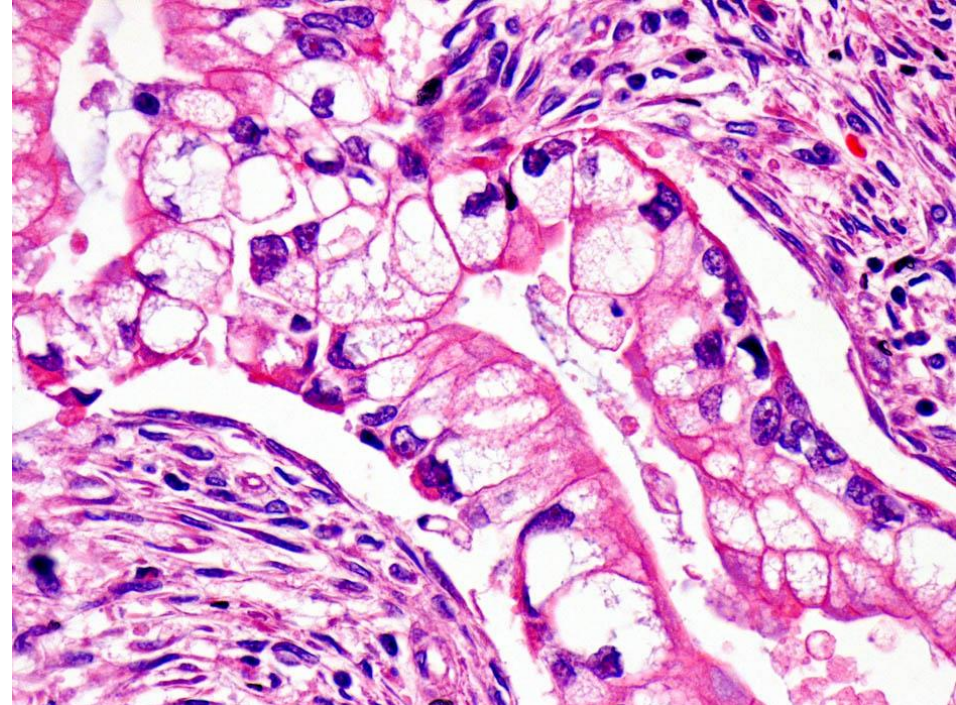
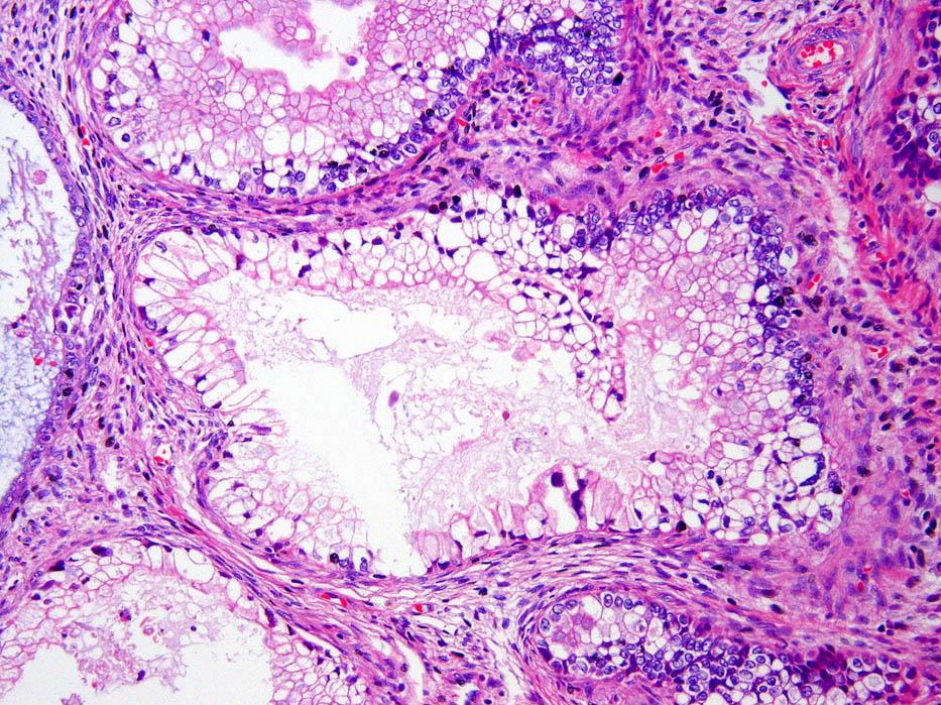




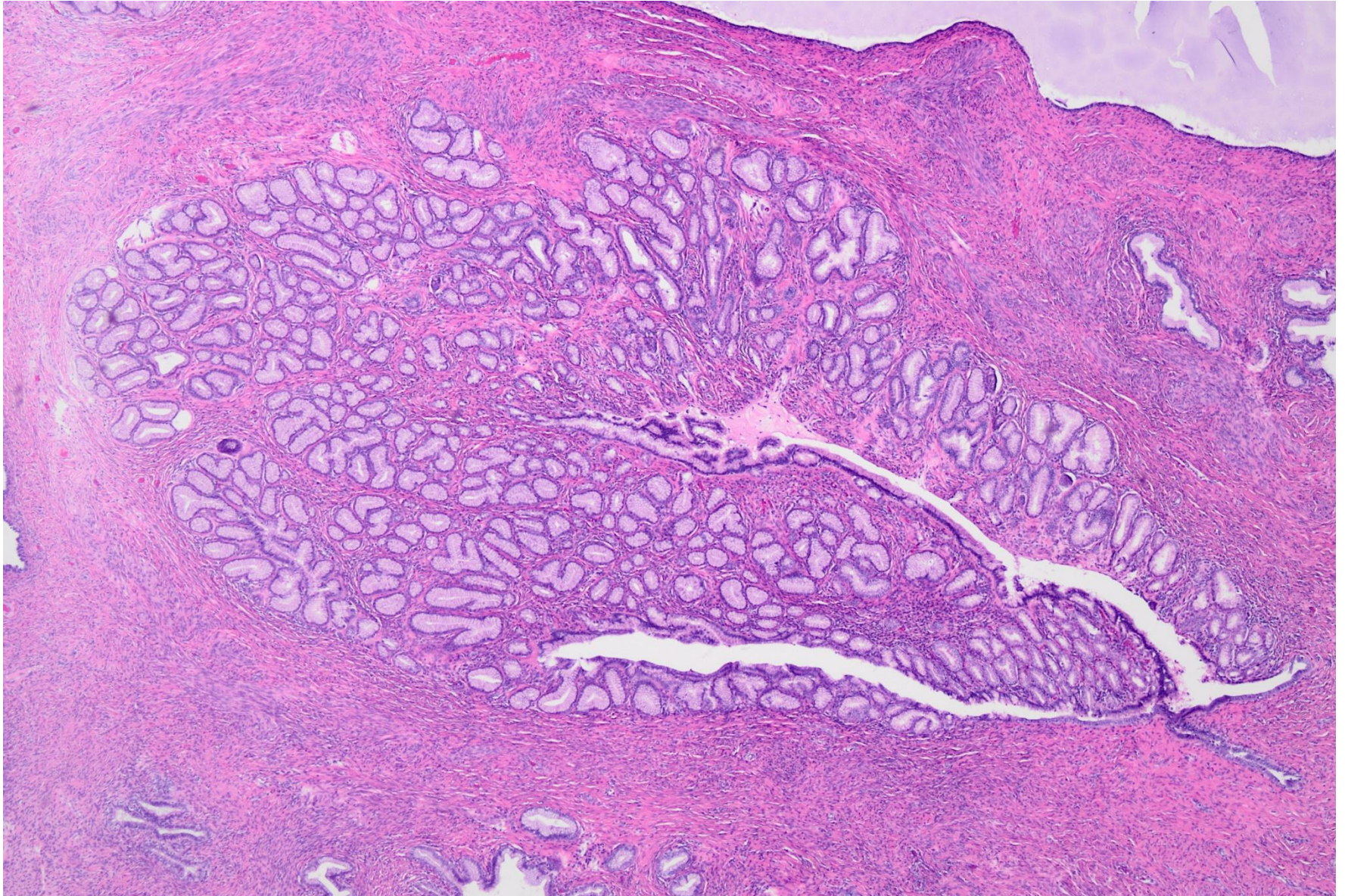




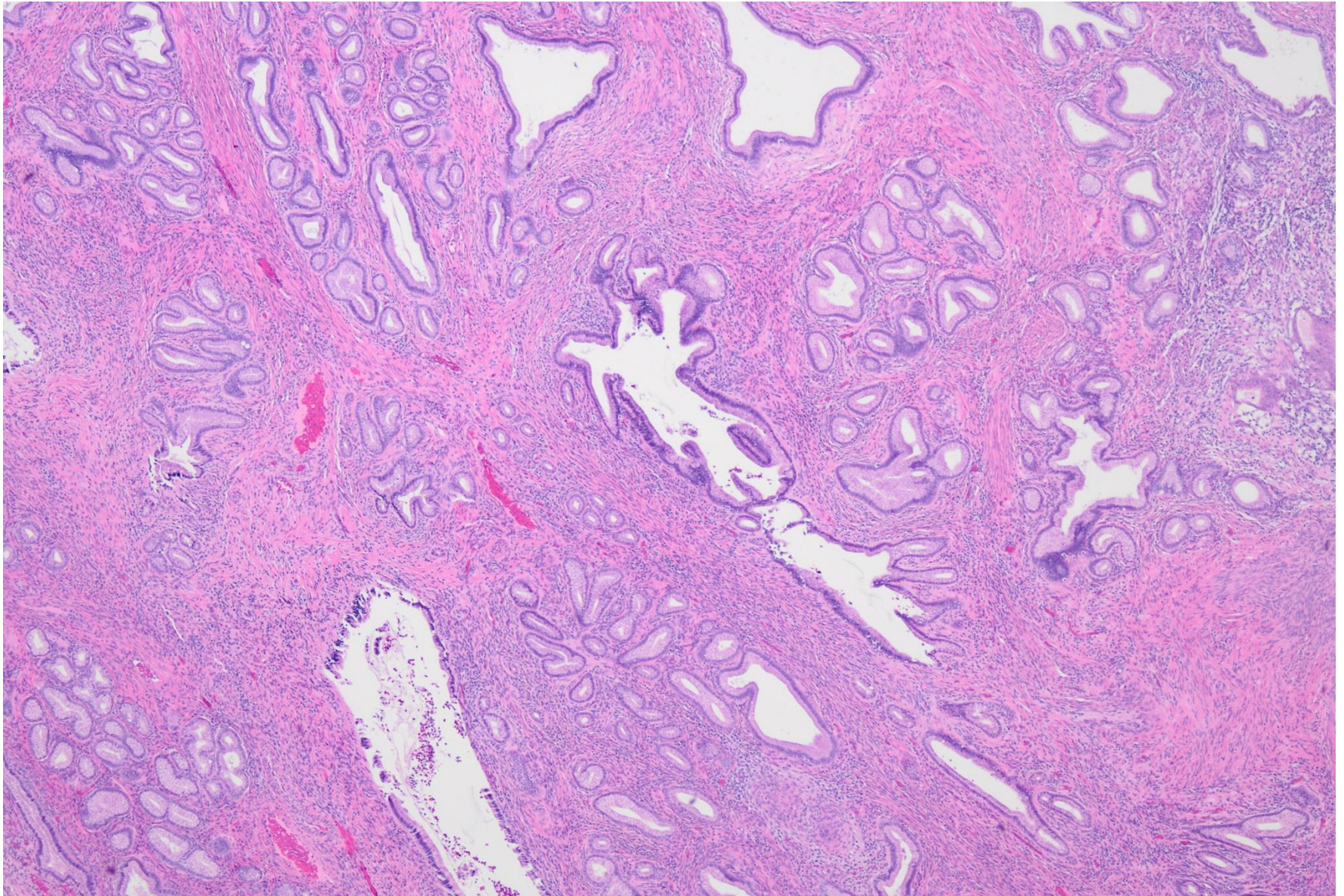


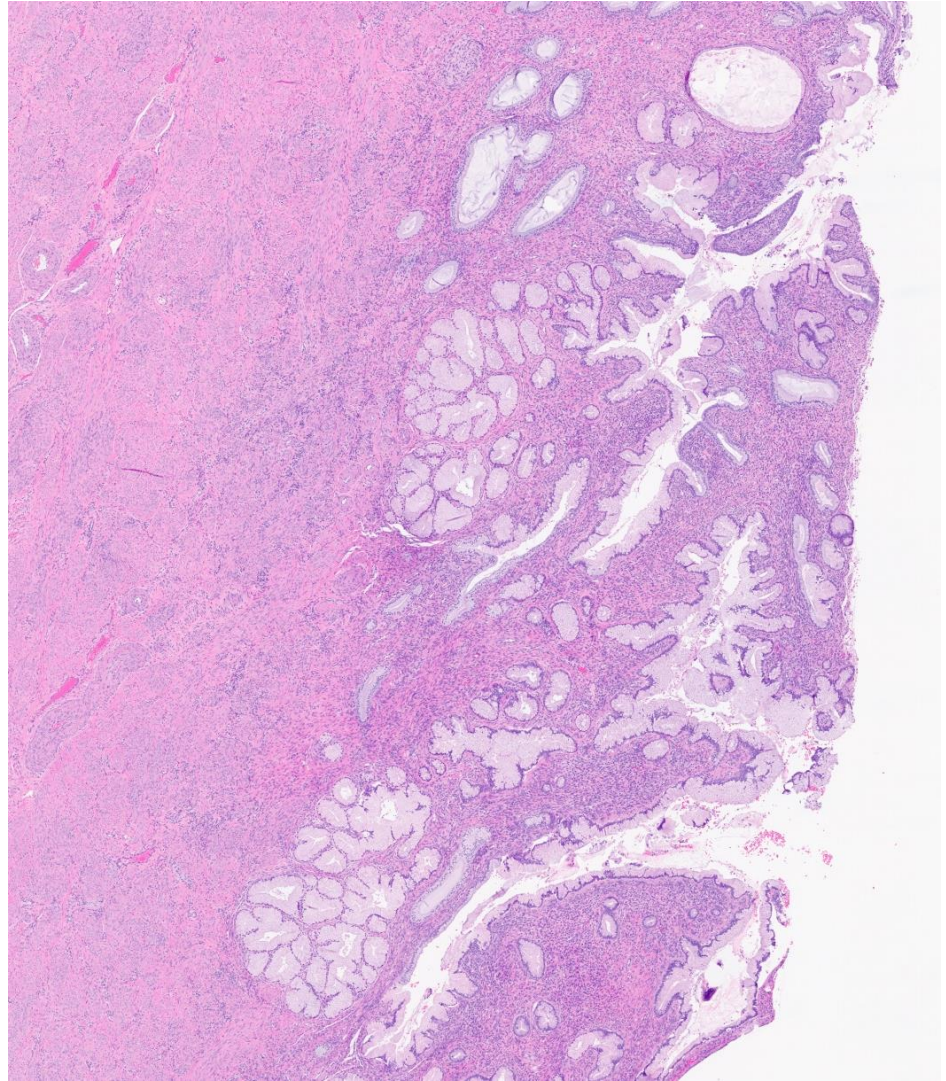
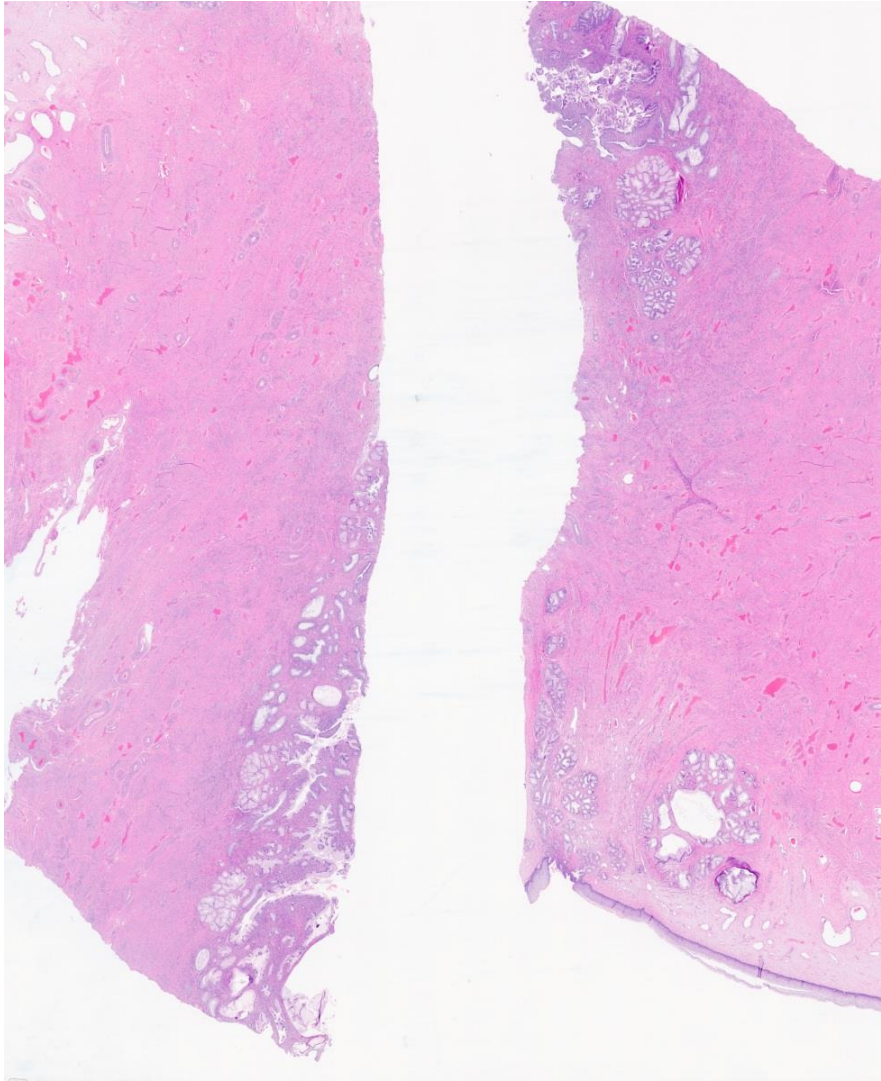


Lobular endocervical glandular hyperplasia (LEGH)

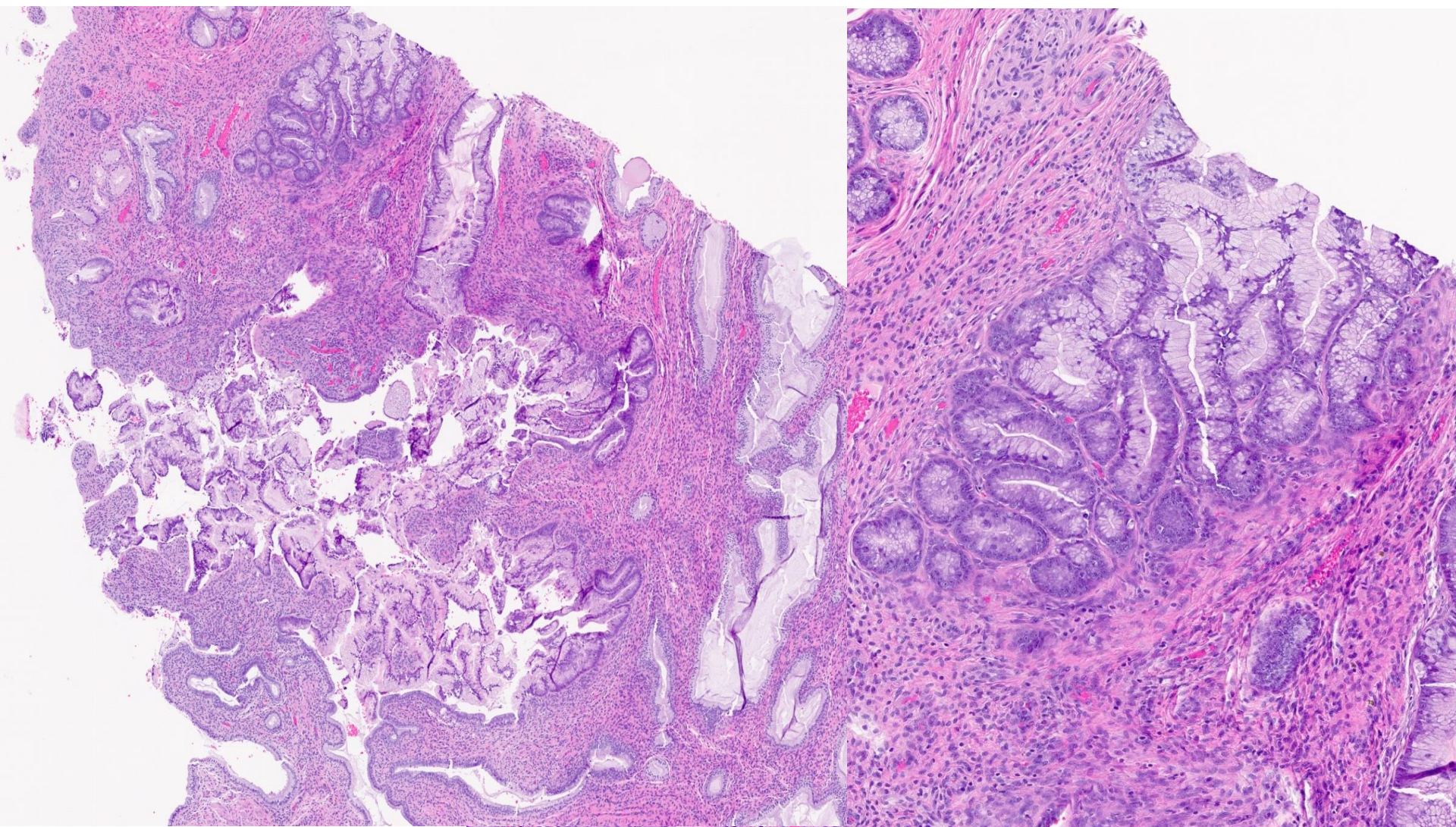


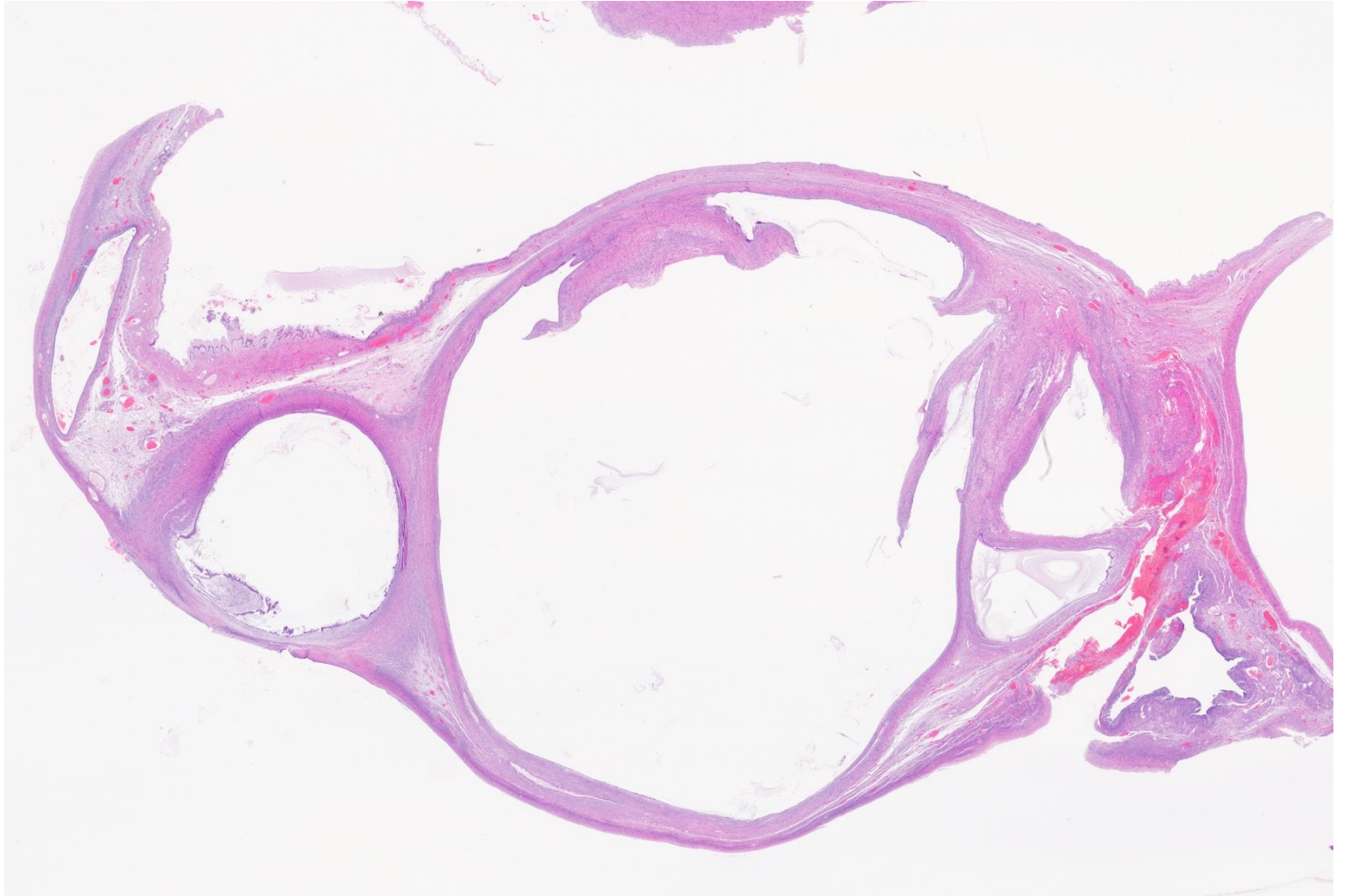
Atypical LEGH



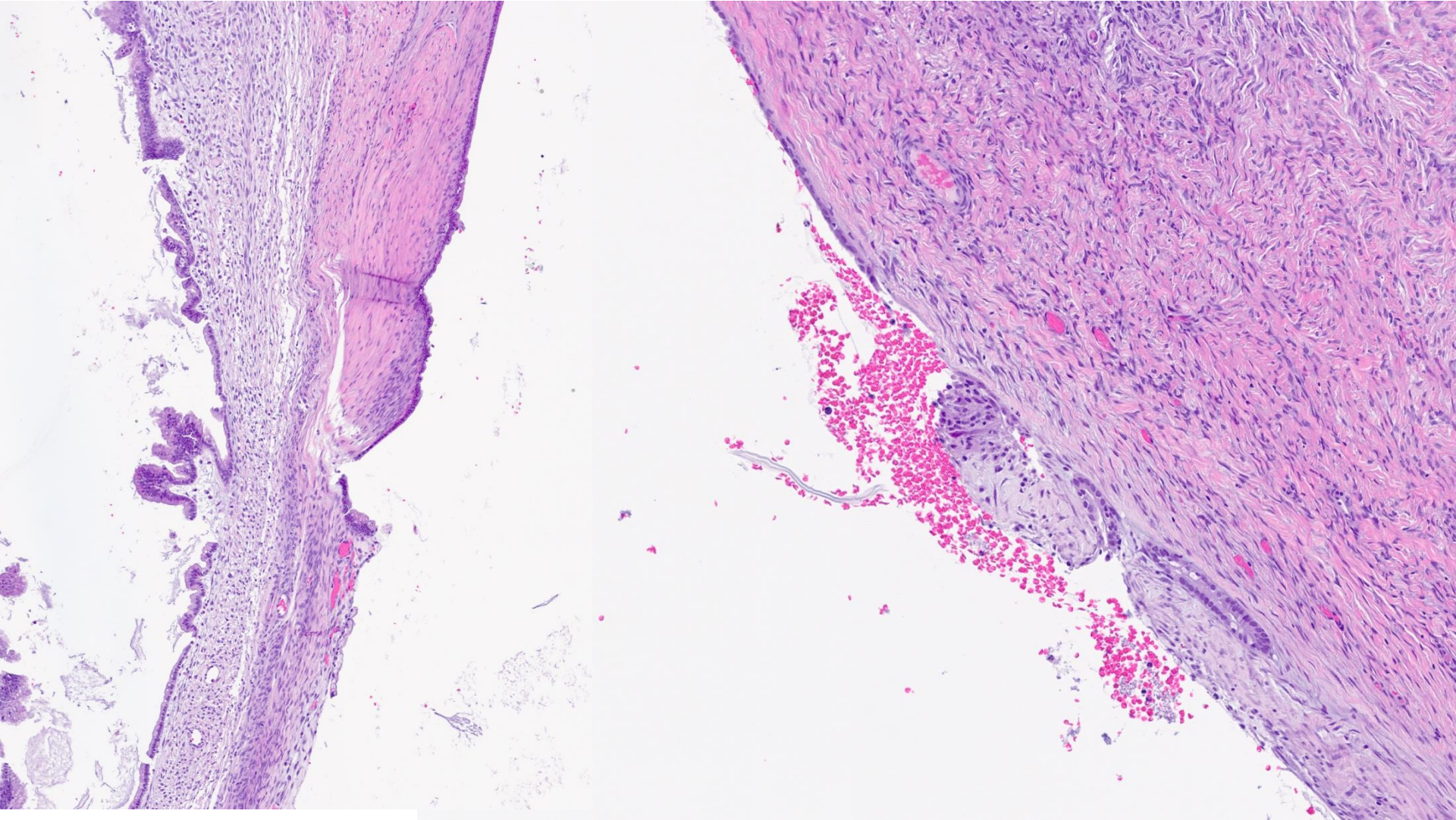


Gastric-type adenocarcinoma in situ





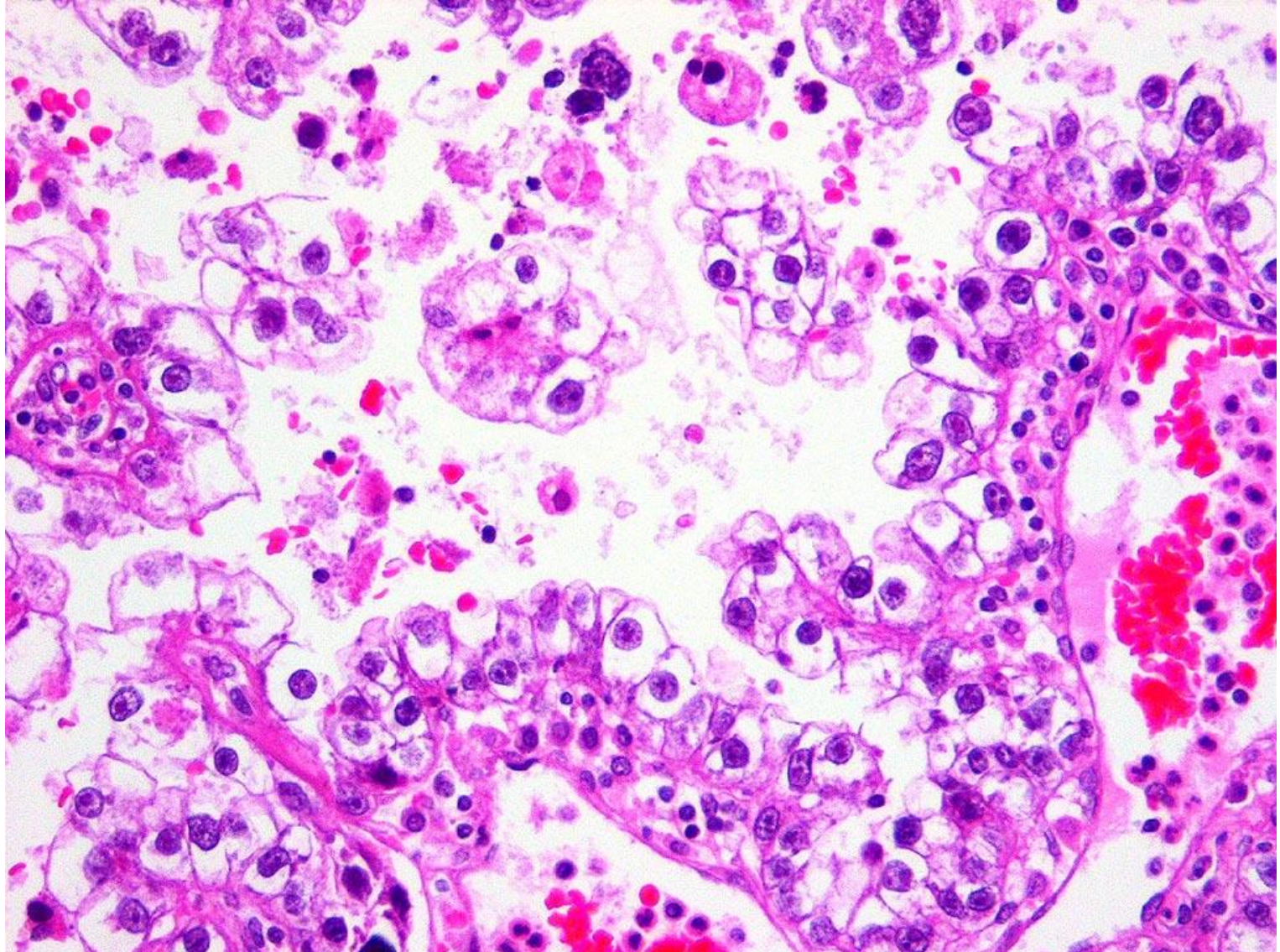
Metastatic gastric-type carcinoma



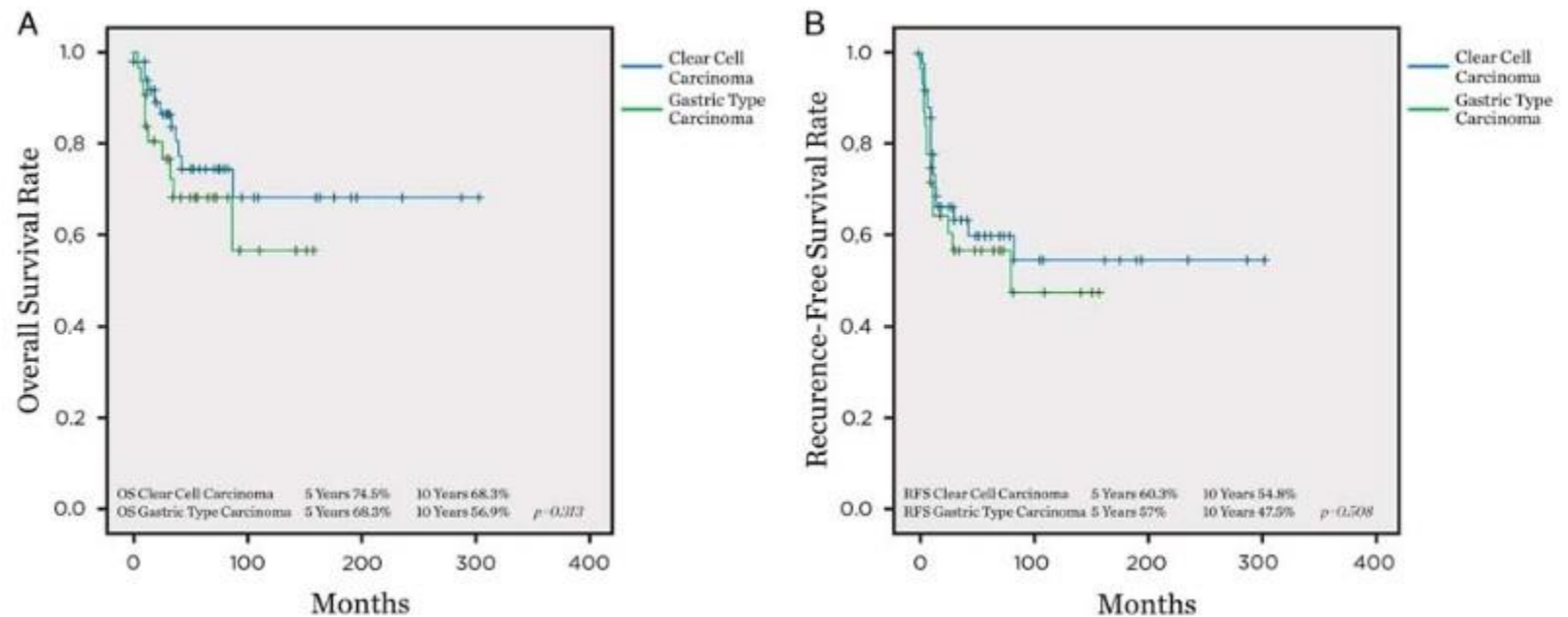
Gastric-type immunohistochemistry

	p16	HR-HPV (ISH)	Claudin 18 (strong)	p53	PR
<i>Gastric-type</i>	<i>10%</i>	<i>0%</i>	<i>96%</i>	<i>50%</i>	<i>0%</i>
Usual (HPV)	>90%	95%	7%	3%	10%
Clear cell	45%	0%	0%	10%	0%

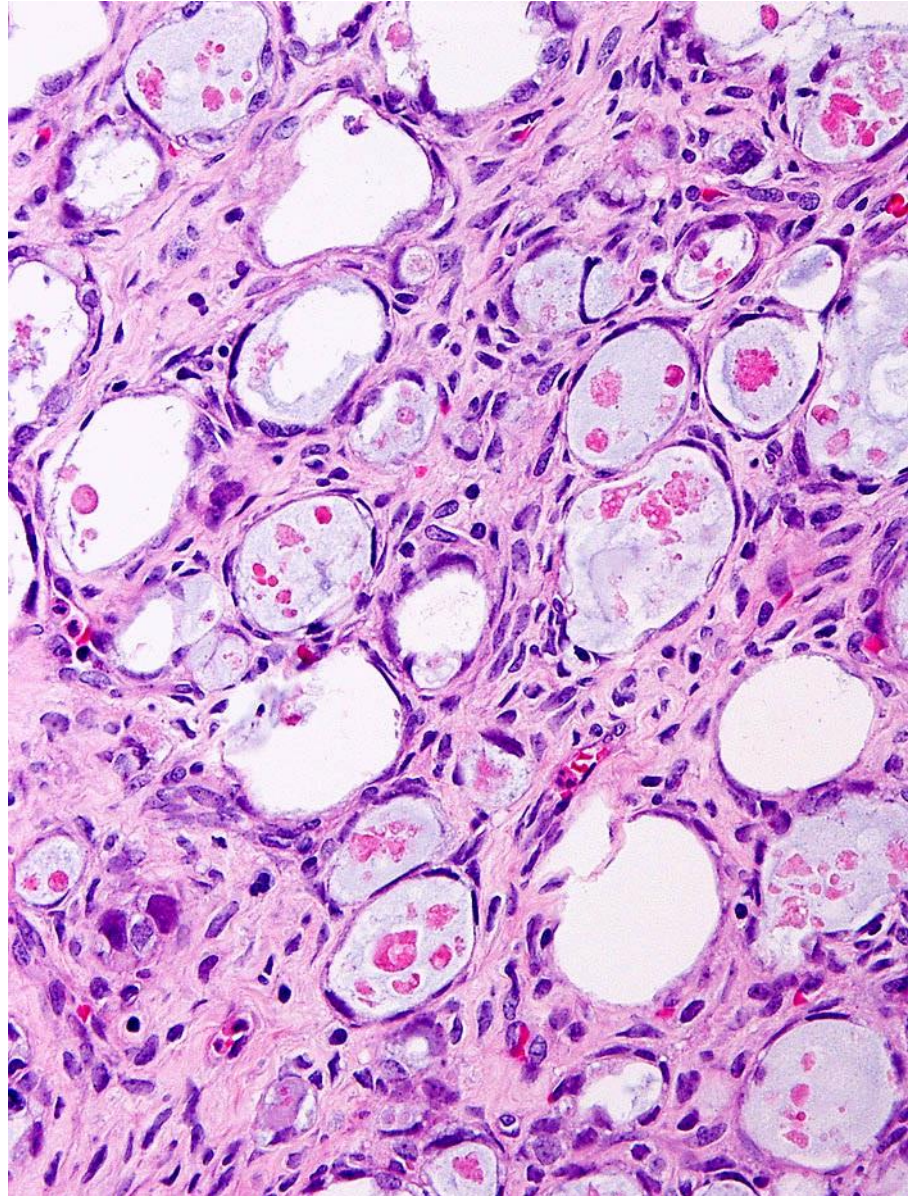
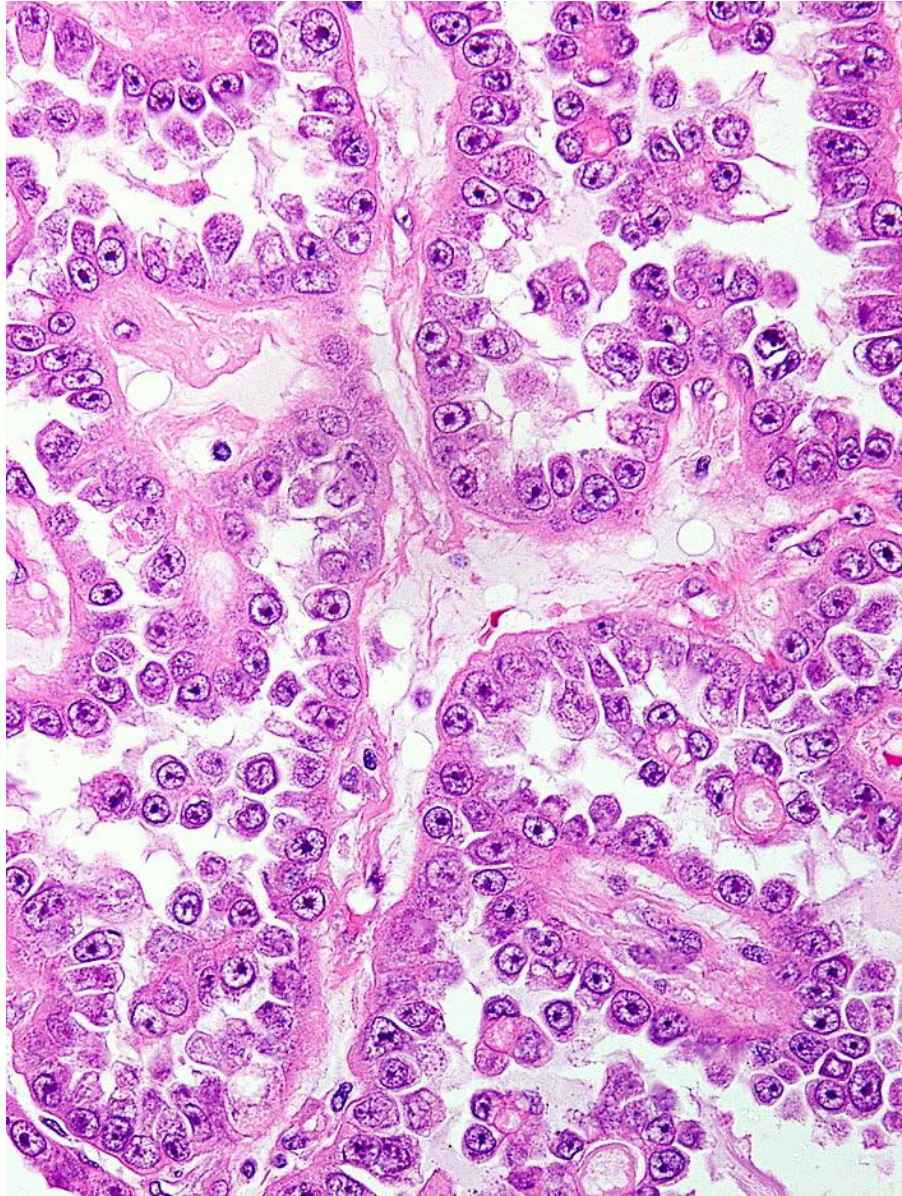
Clear cell carcinoma



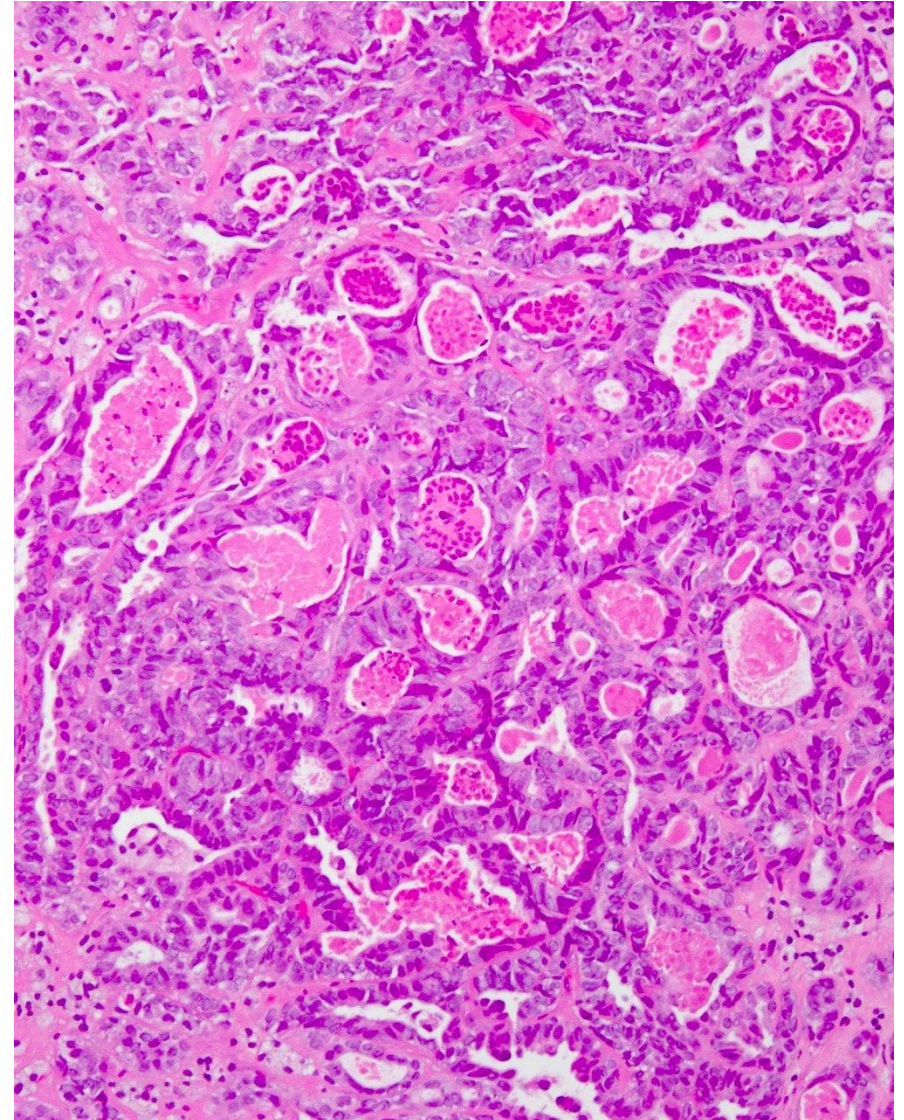
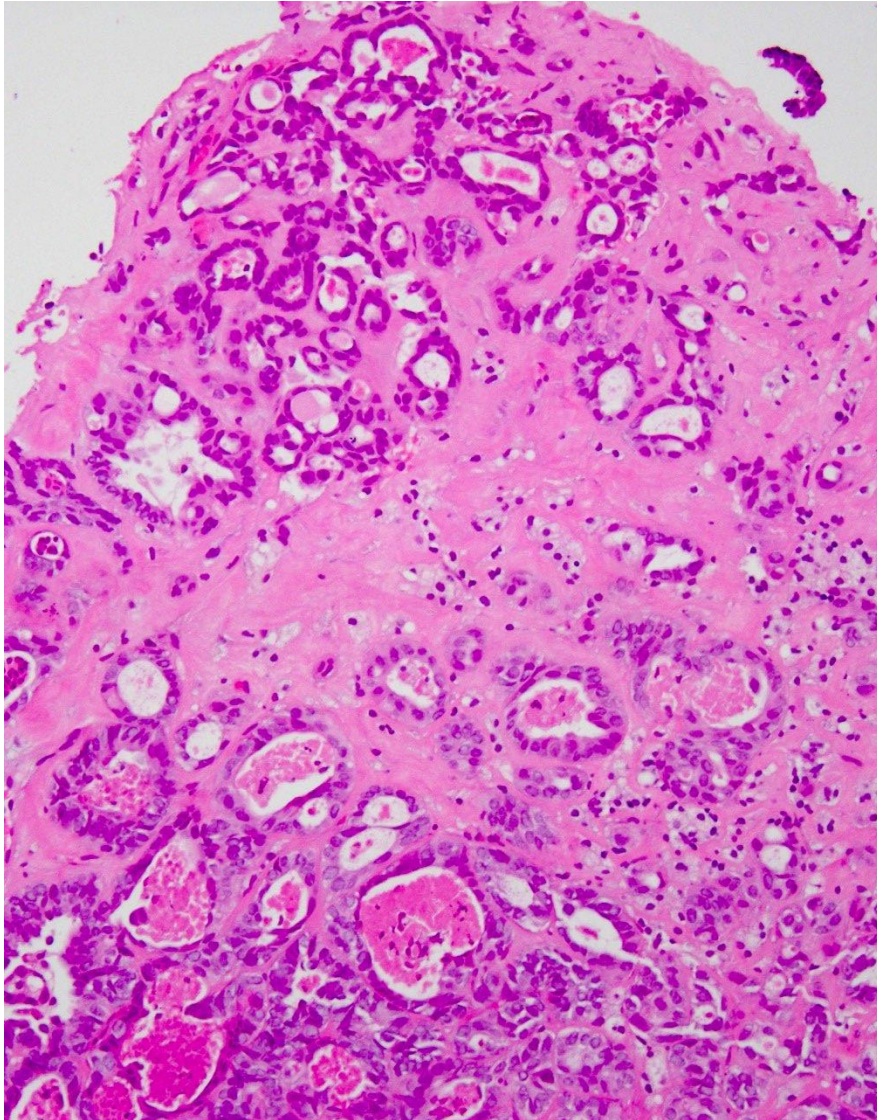
Survivals: gastric-type vs clear cell

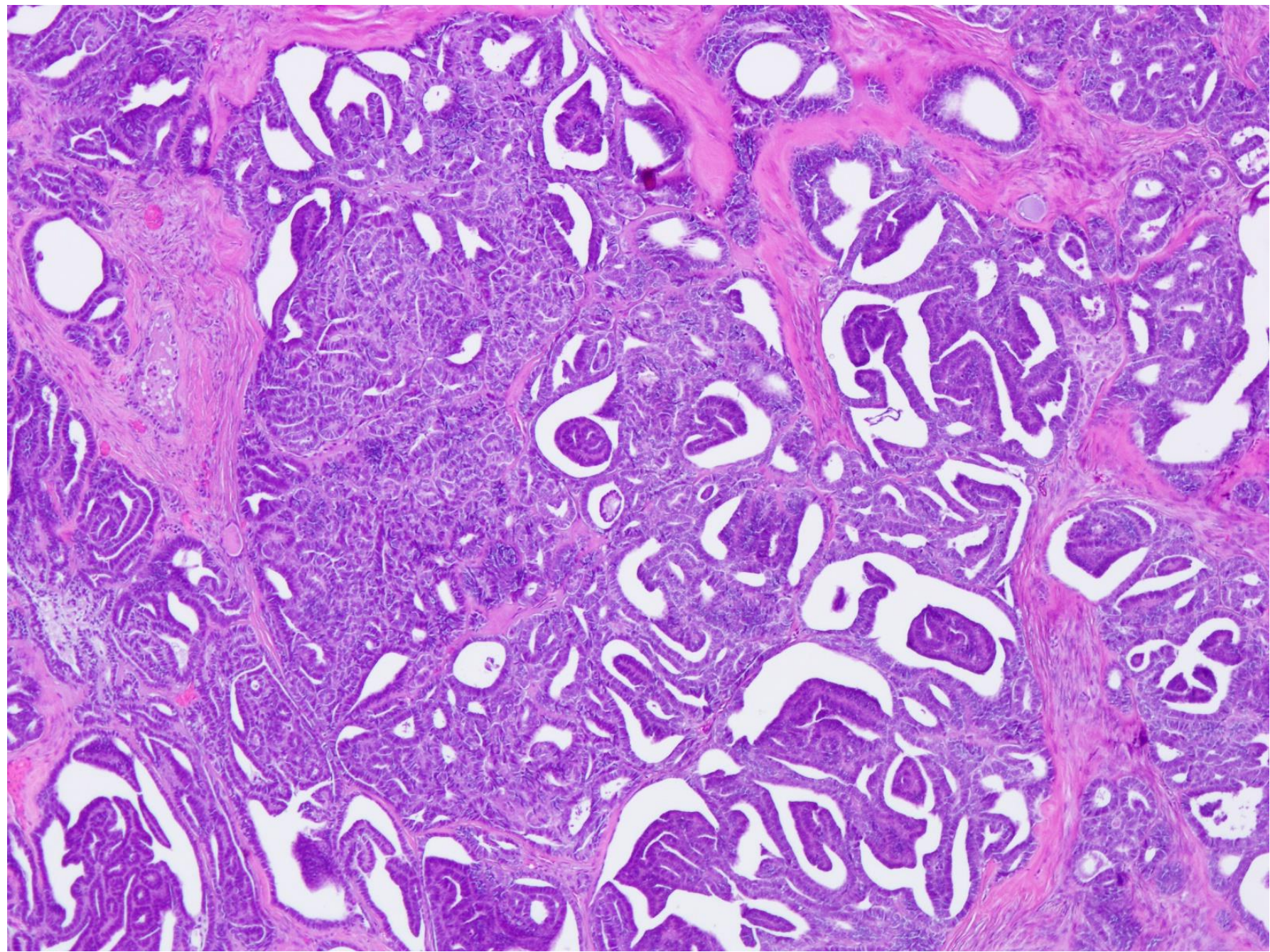


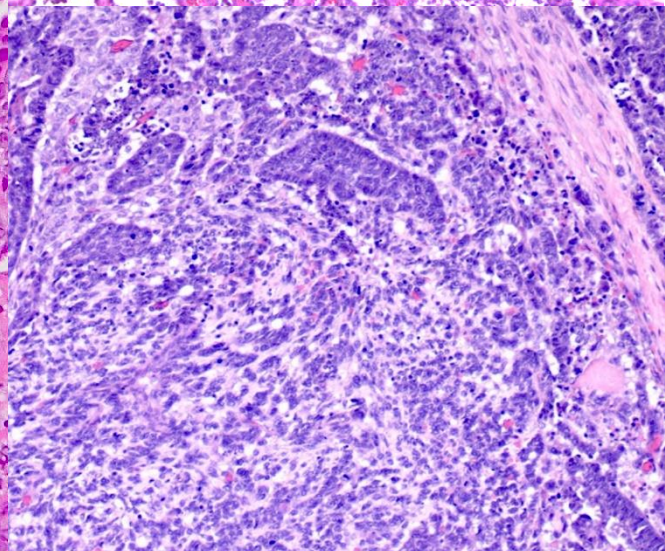
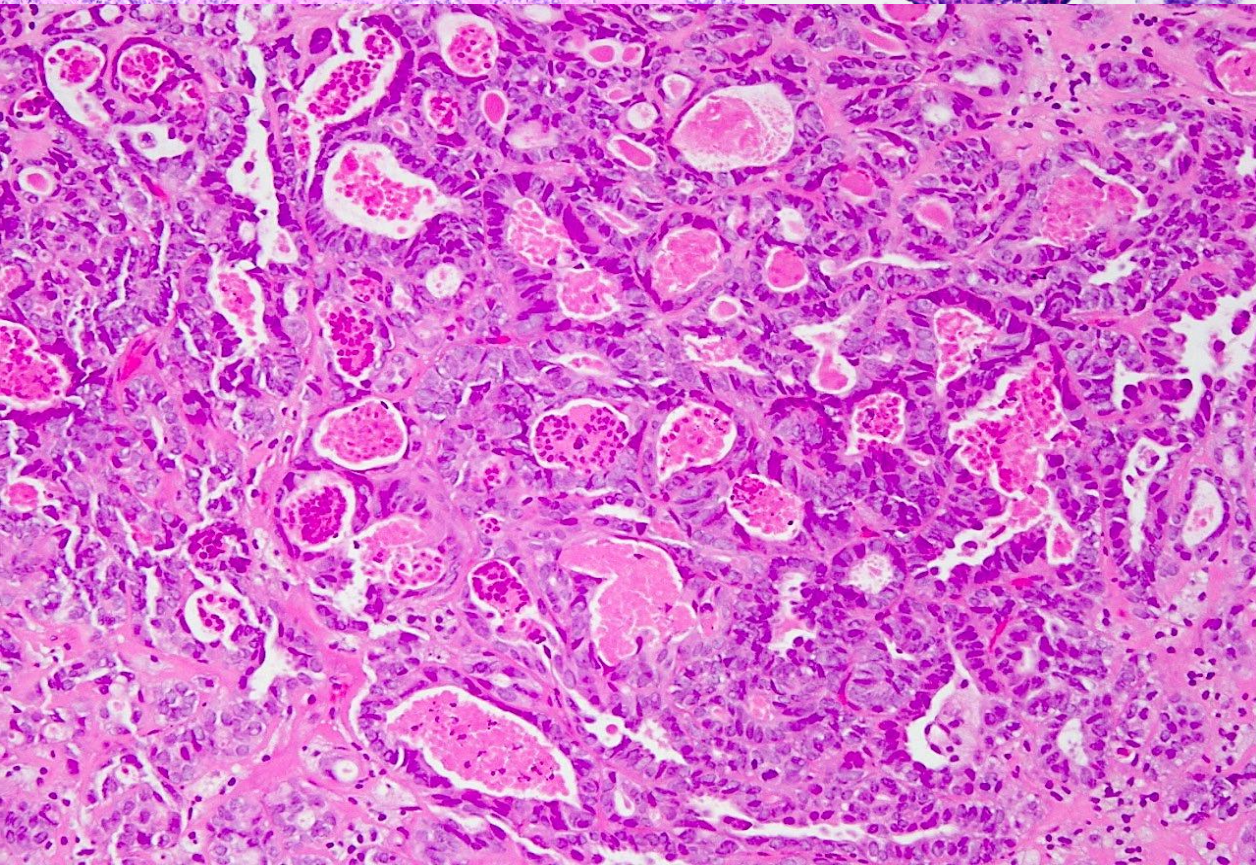
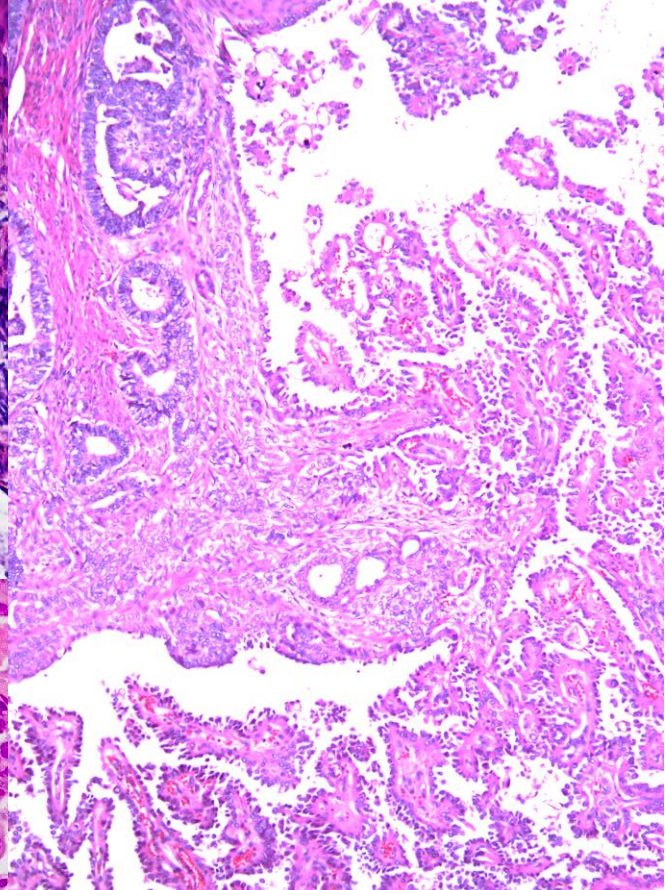
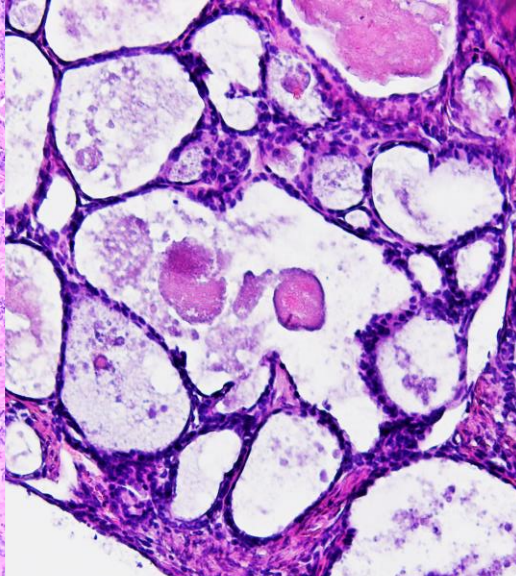
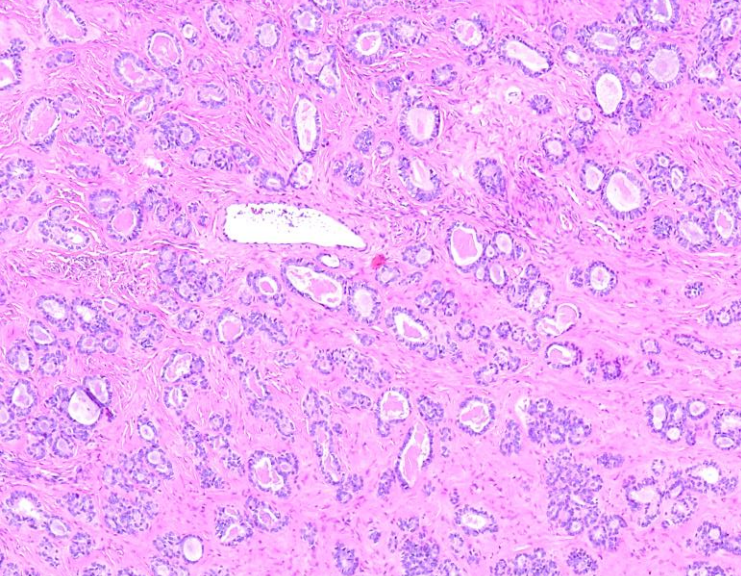
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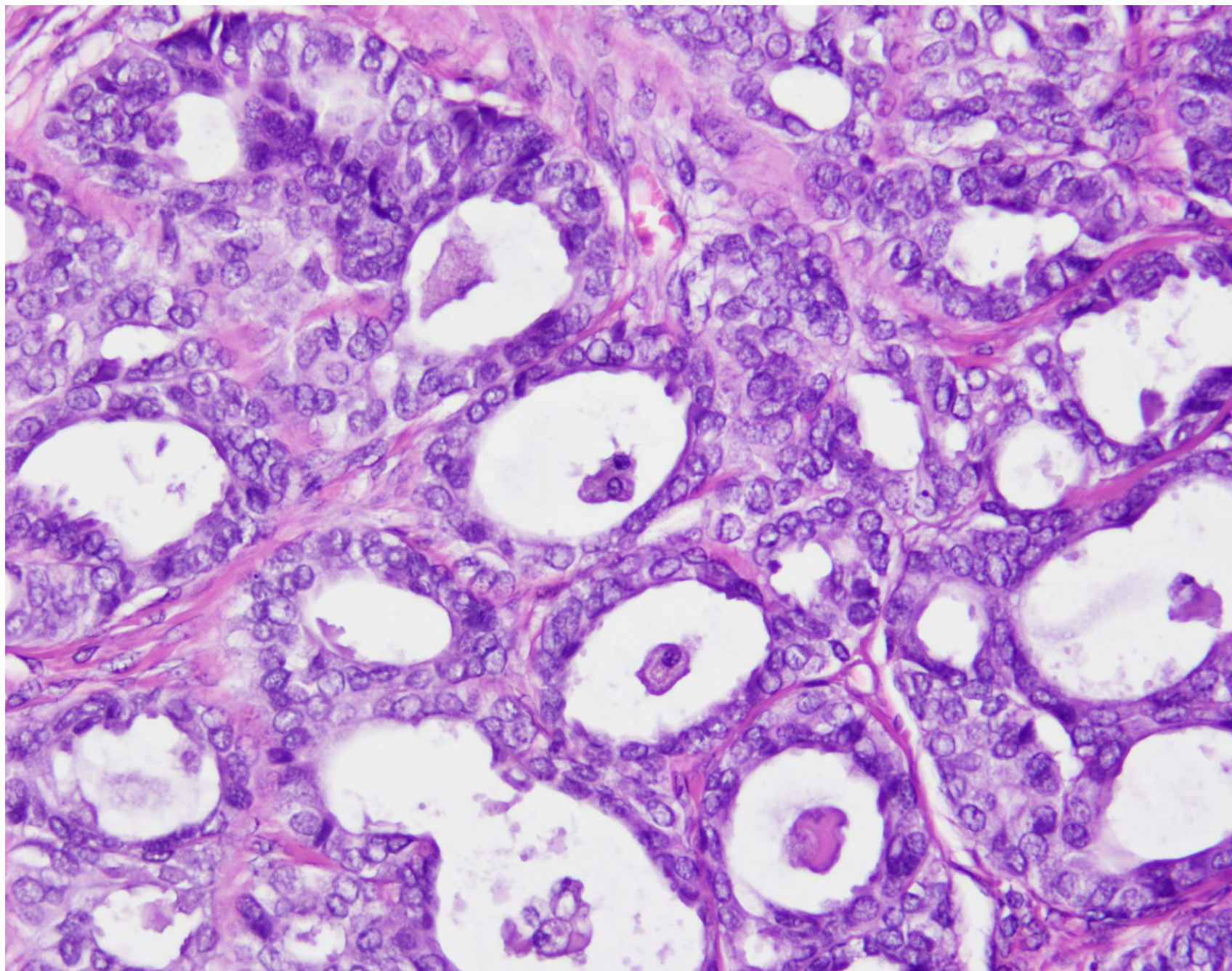


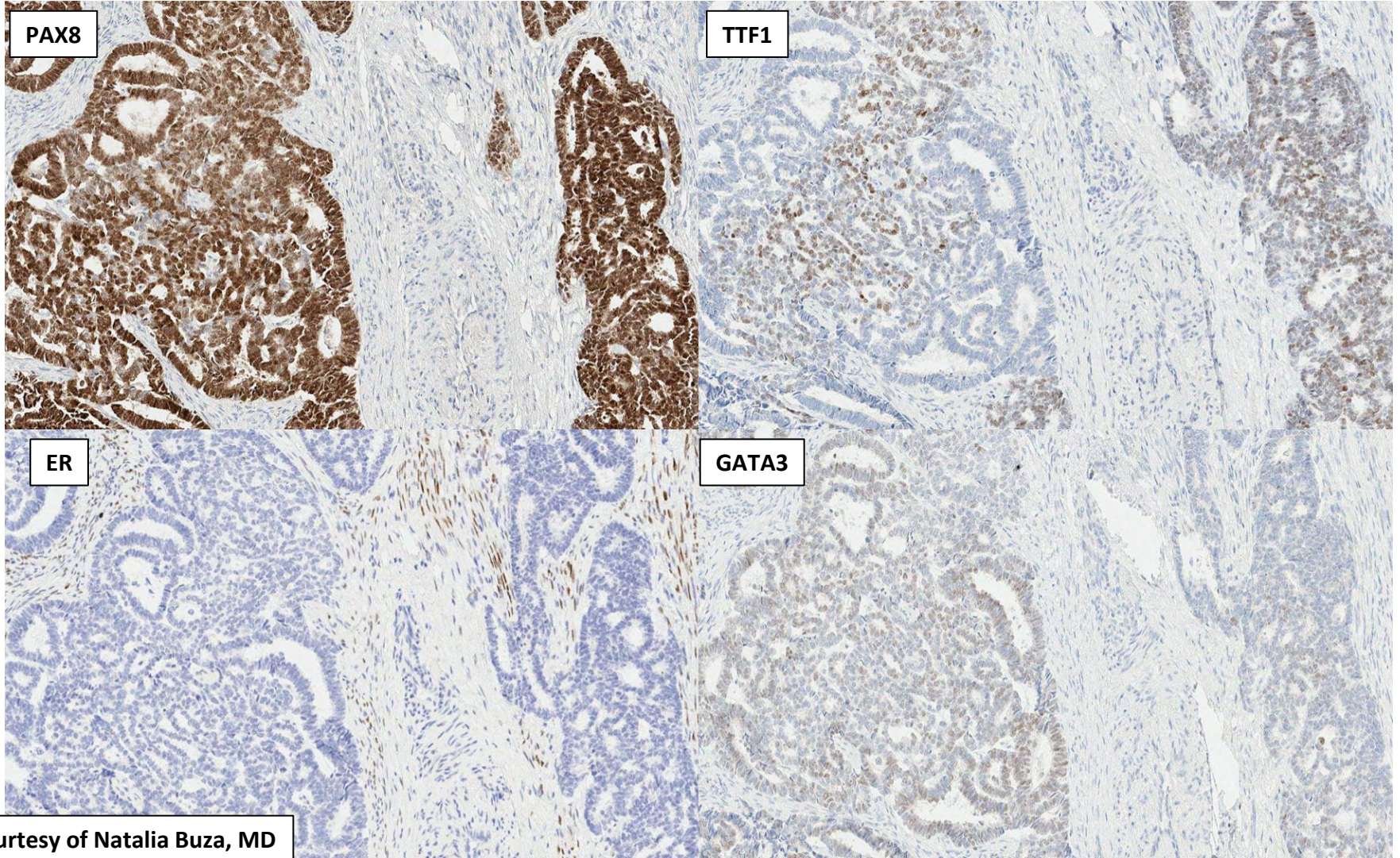
Mesonephric carcinoma









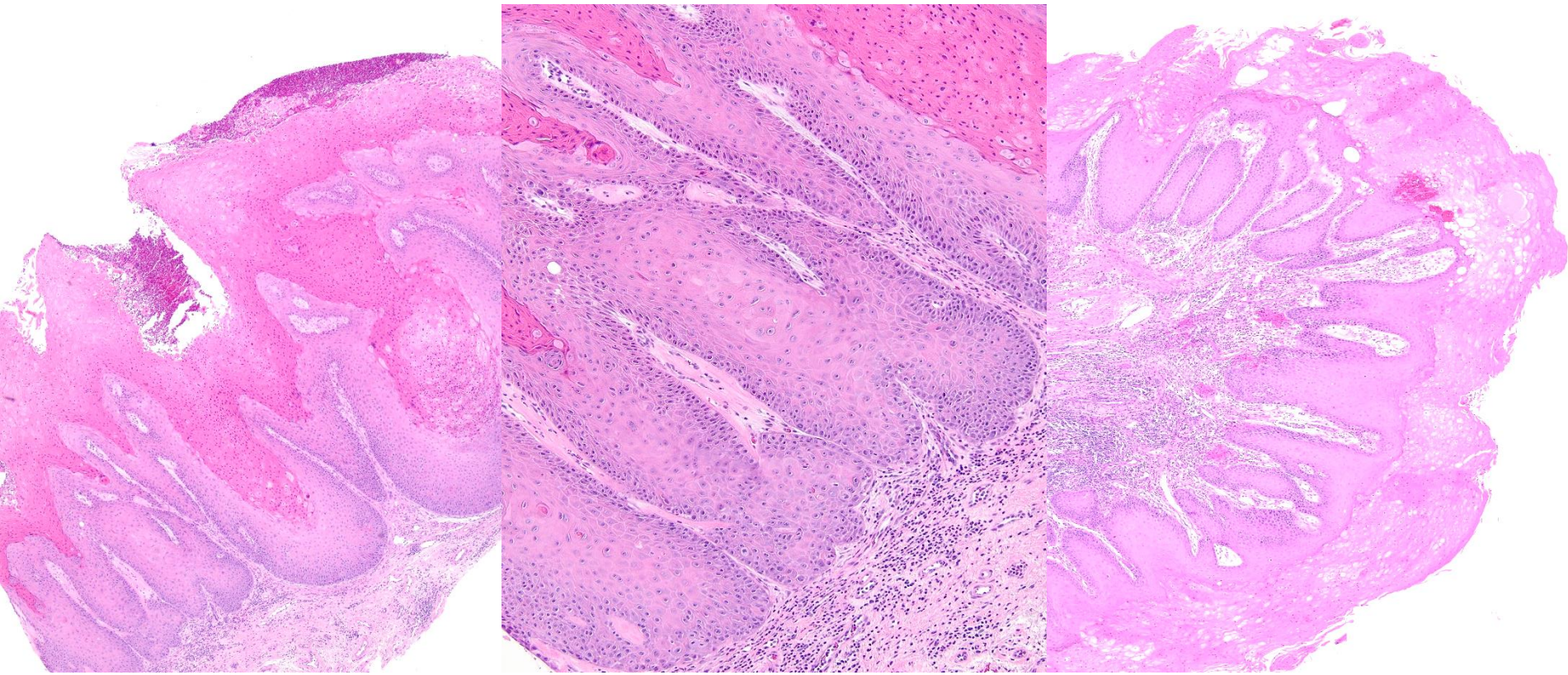


Courtesy of Natalia Buza, MD

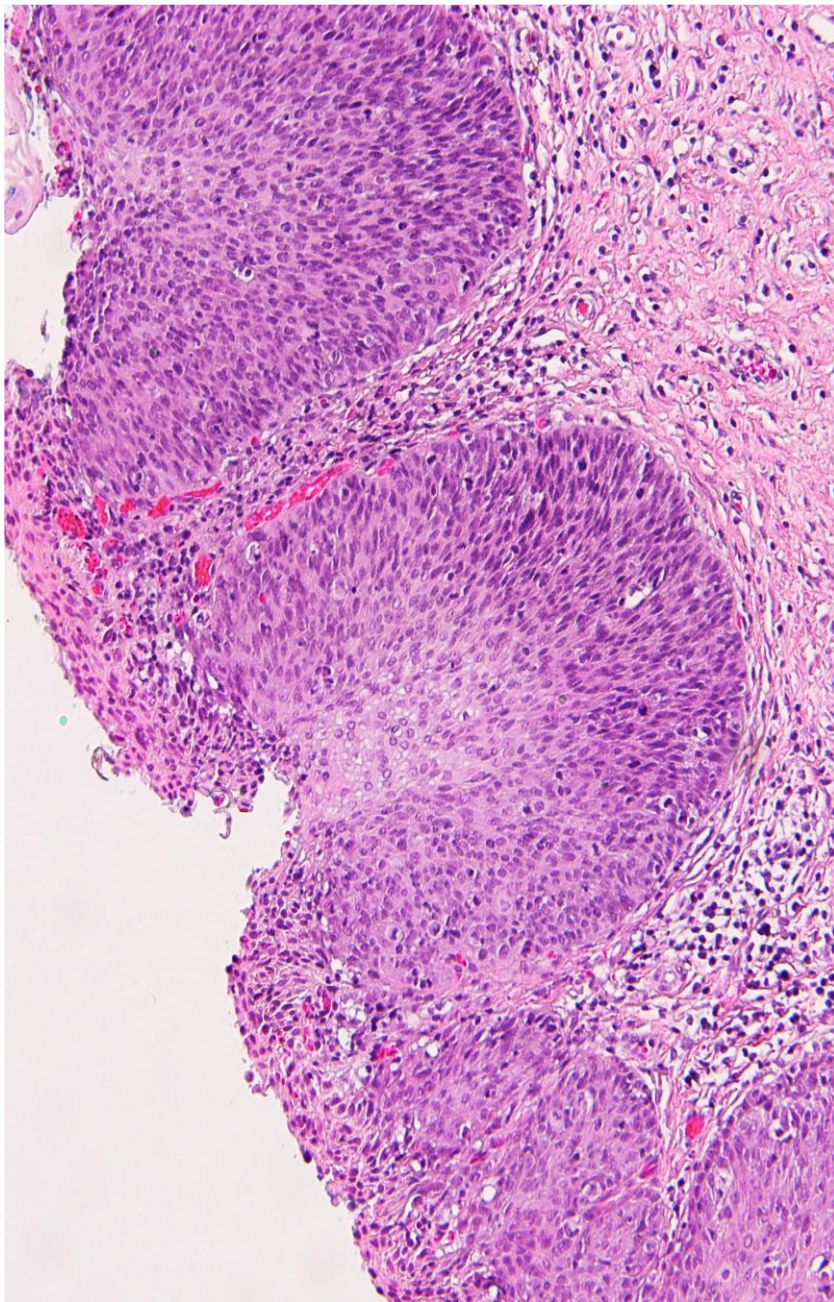
HPV-independent (HPVI) vulvar intraepithelial neoplasia

VULVAR SQUAMOUS INTRAEPITHELIAL NEOPLASIA		
HPV-ASSOCIATED VULVAR INTRAEPITHELIAL NEOPLASIA High Grade Squamous Intraepithelial Lesion (HSIL)	HPV-INDEPENDENT p53 MUT VULVAR INTRAEPITHELIAL NEOPLASIA Differentiated VIN (dVIN)	HPV-INDEPENDENT p53 WT VULVAR INTRAEPITHELIAL NEOPLASIA Verruciform/Acanthotic VIN (vaVIN)
● Atypia extending to upper layers ● Large hyperchromatic nuclei ● Loss of polarity and organization ● Loss of maturation with basaloid appearance & brisk mitotic activity with extension beyond basal layers	● Atypia often confined to the basal layer ● Large nuclei with open chromatin ● Prominent nucleoli ● Retained but abnormal maturation with elongated and/or fused rete ridges, acantholysis & dyskeratotic cells	● No cytologic atypia ● Verruciform acanthosis with flat (VAAD) or exophytic growth pattern (DEVIL) ● Retained but altered maturation with hypogranulosis & cytoplasmic pallor (VAAD/DEVIL) or hypergranulosis (vLSC)
p16 = Overexpressed * p53 = Wild type (mid-epithelial) **	p16 = Negative or patchy p53 = Mutant pattern **	p16 = Negative or patchy p53 = Wild type (scattered) **

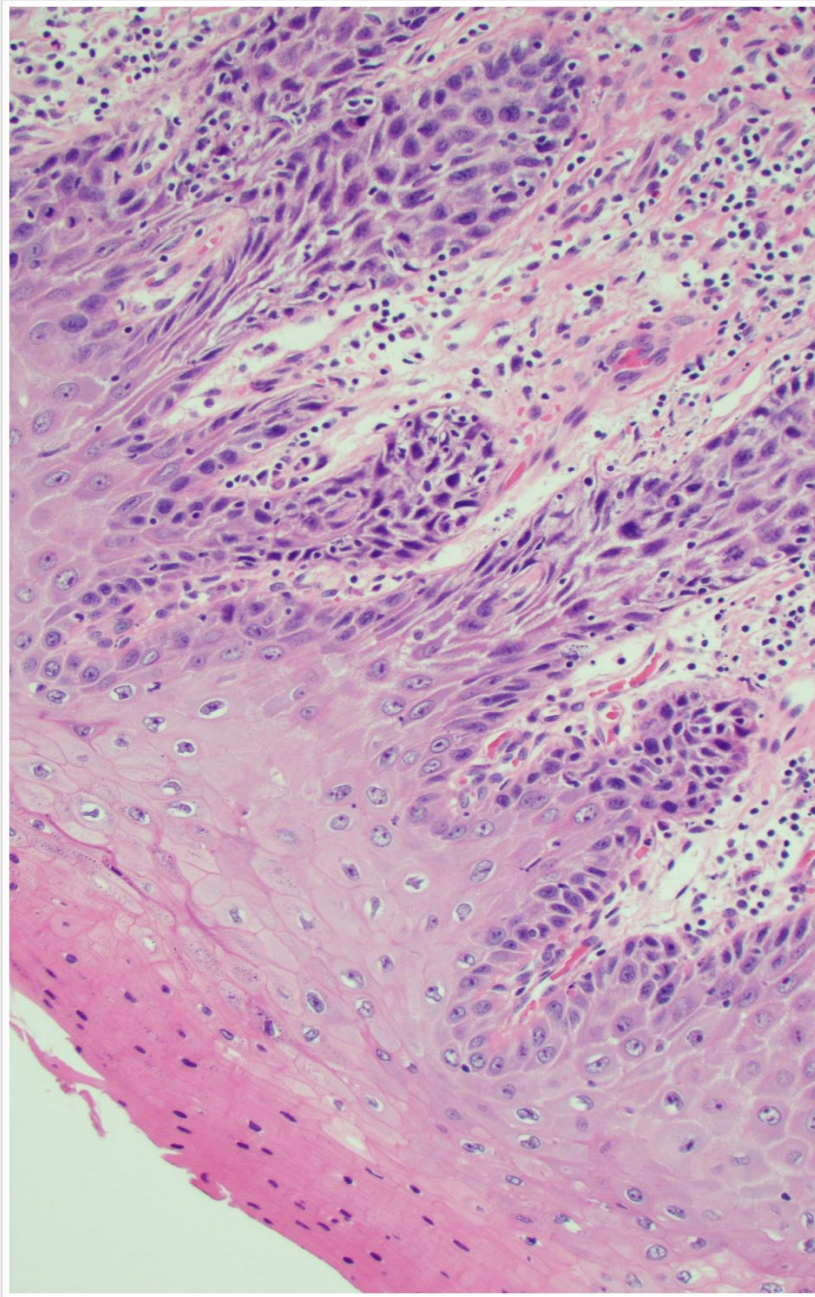
HPV-independent (HPVI) vulvar intraepithelial neoplasia



HSIL (HPVA)



HPVI p53 abnl VIN (dVIN)



dVIN features that differ from HSIL

Arises in a chronic inflammatory background (i.e. lichen sclerosis)

Excision may remove the incident lesion, but

- Chronic inflammatory background remains
- p53-abnormal epithelium can persist
- **Expected:** recurrence, multifocal disease, invasive carcinoma (HPVI), fatality

dVIN features that differ from HSIL

Arises in a chronic inflammatory background (i.e. lichen sclerosis)

Excision may remove the incident lesion, but

- Chronic inflammatory background remains
- p53-abnormal epithelium can persist
- **Expected:** recurrence, multifocal disease, invasive carcinoma (HPVI), fatality

- **Vulvar SCC risk**
- Up to 90%
- 13-32 months

HPVI p53-abnormal vulvar intraepithelial neoplasia

Differentiated VIN (dVIN)

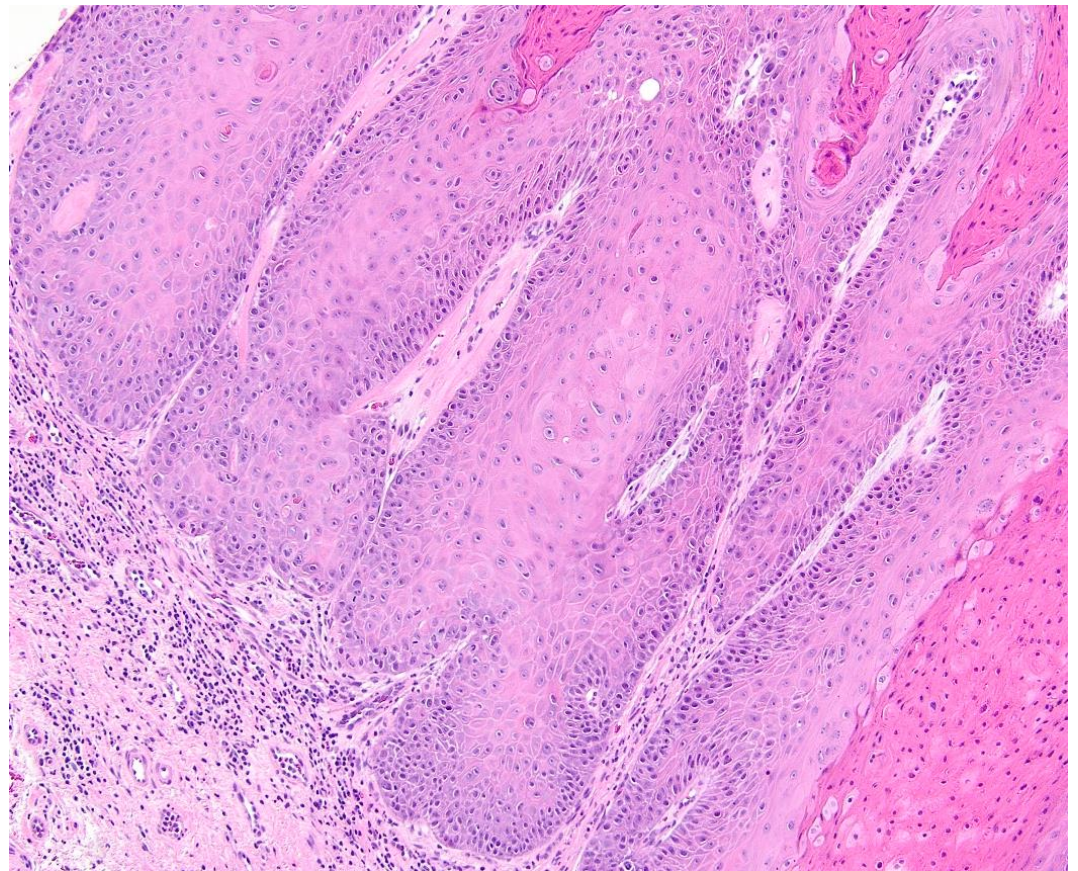
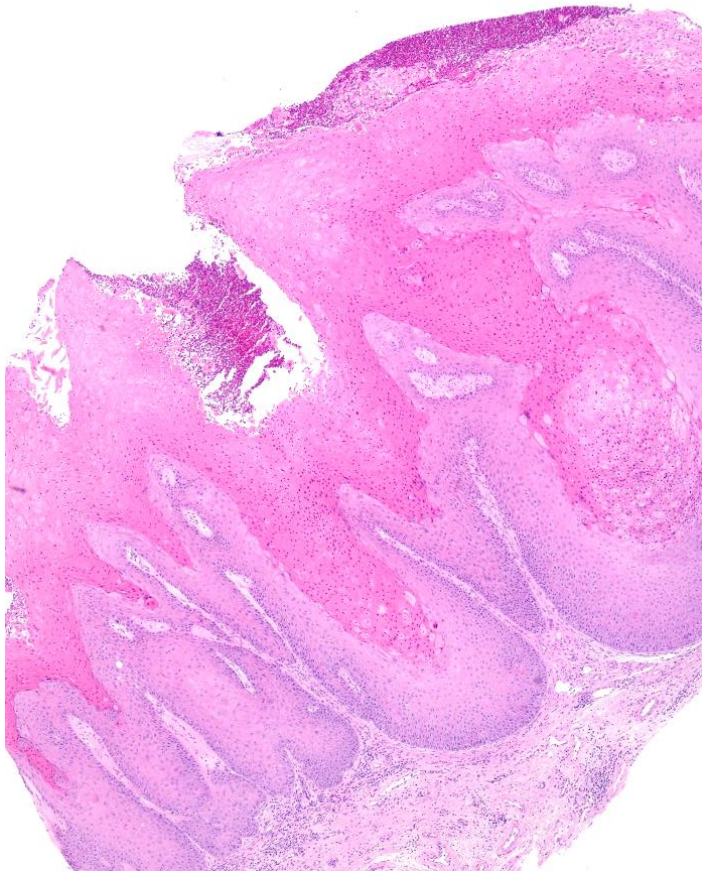
Required

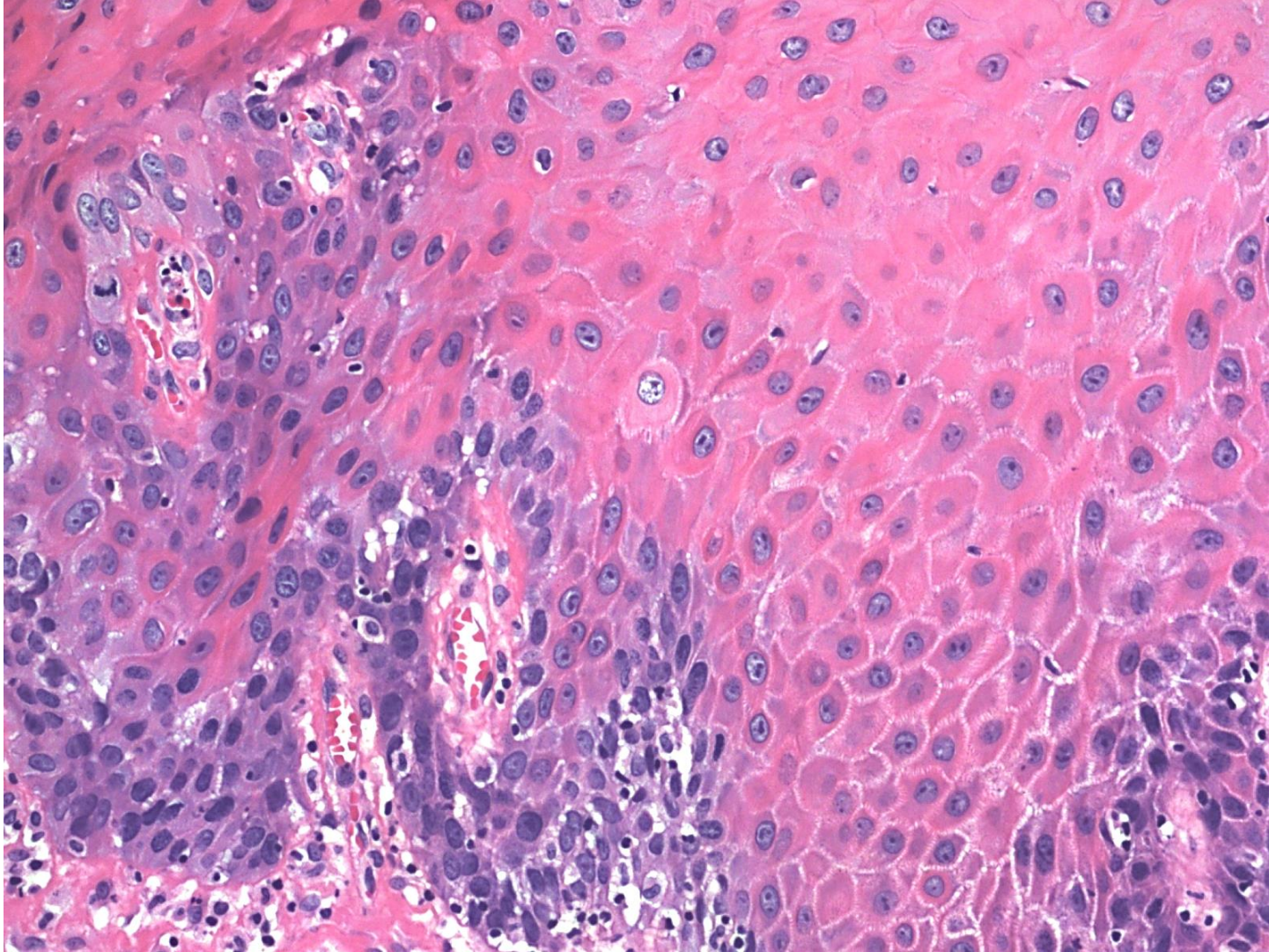
- HPV-independent
- Considerable basal atypia
- Exclude non-neoplastic
- p53 abnormal

Not required
but typical

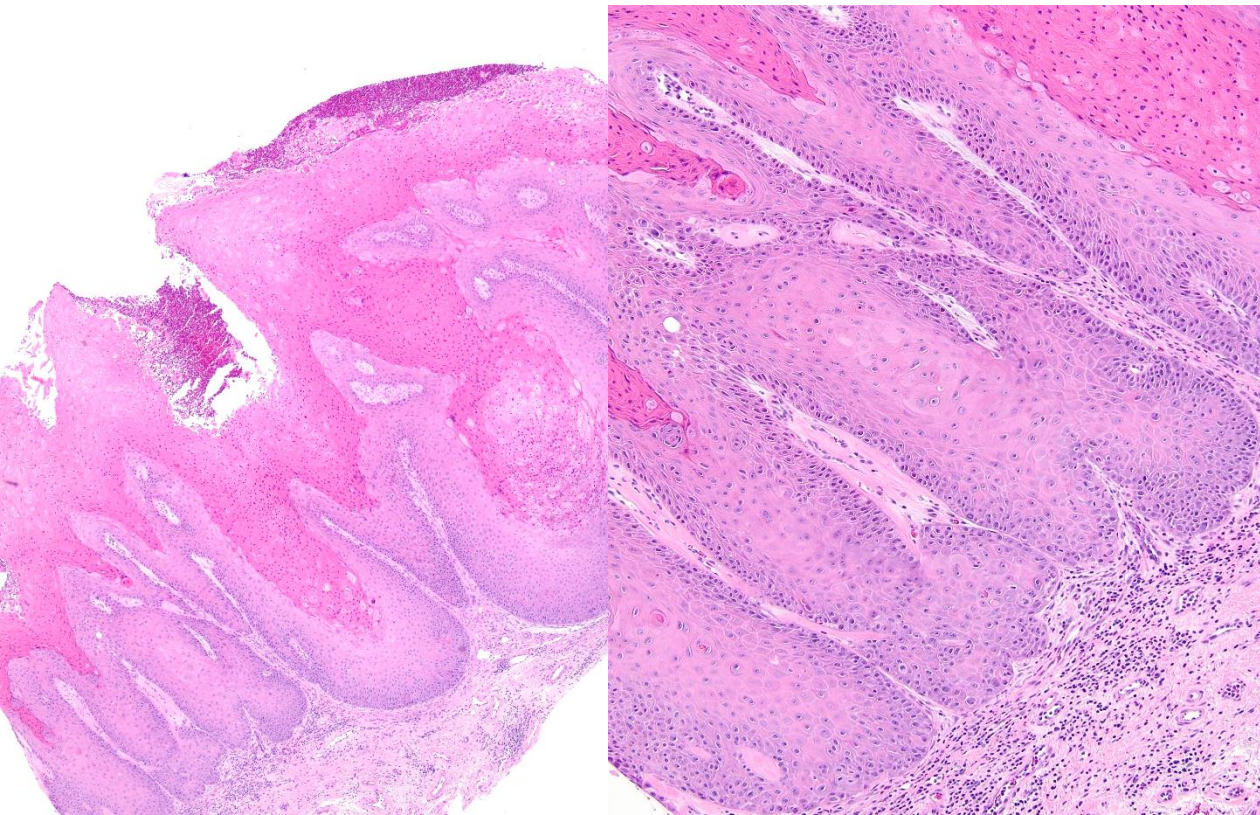
- Abnormal squamous maturation

64-year-old with white and thick patches on the labia minora

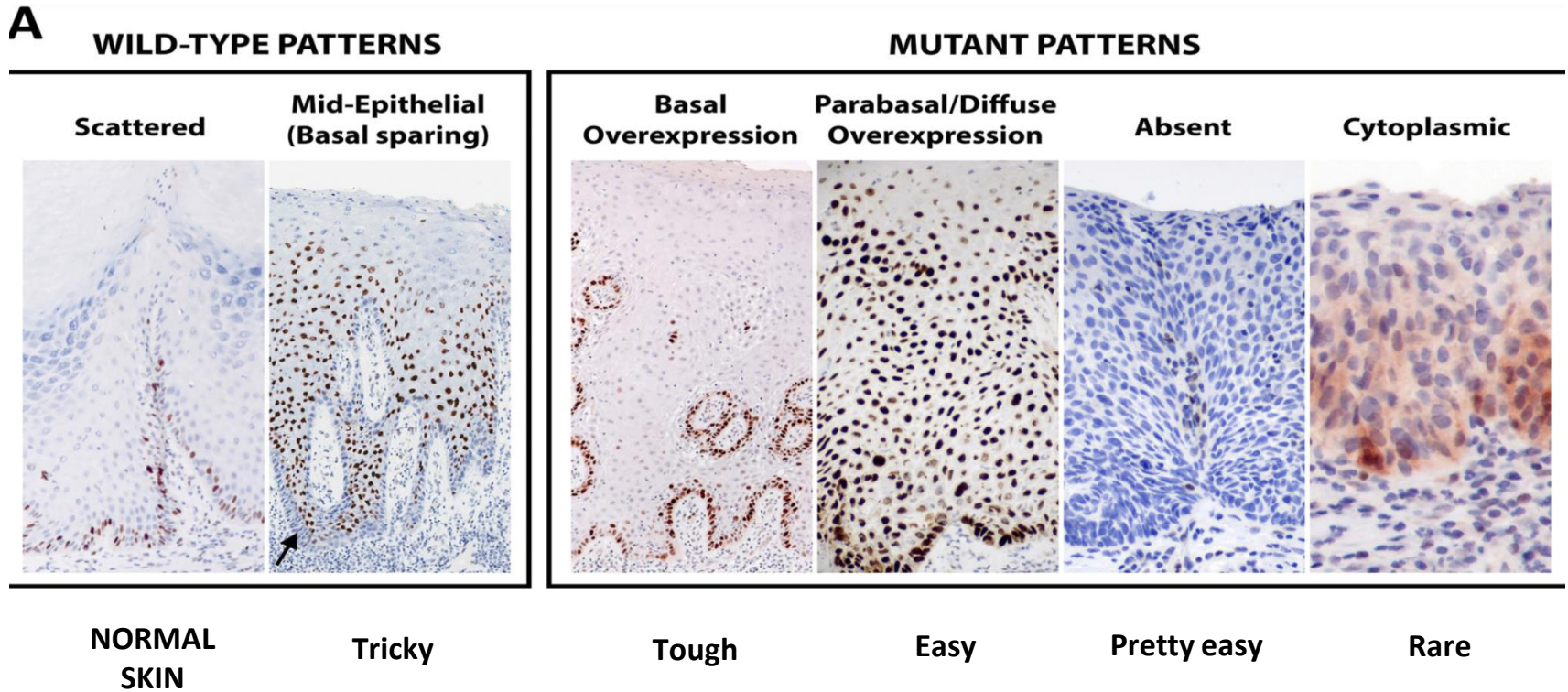




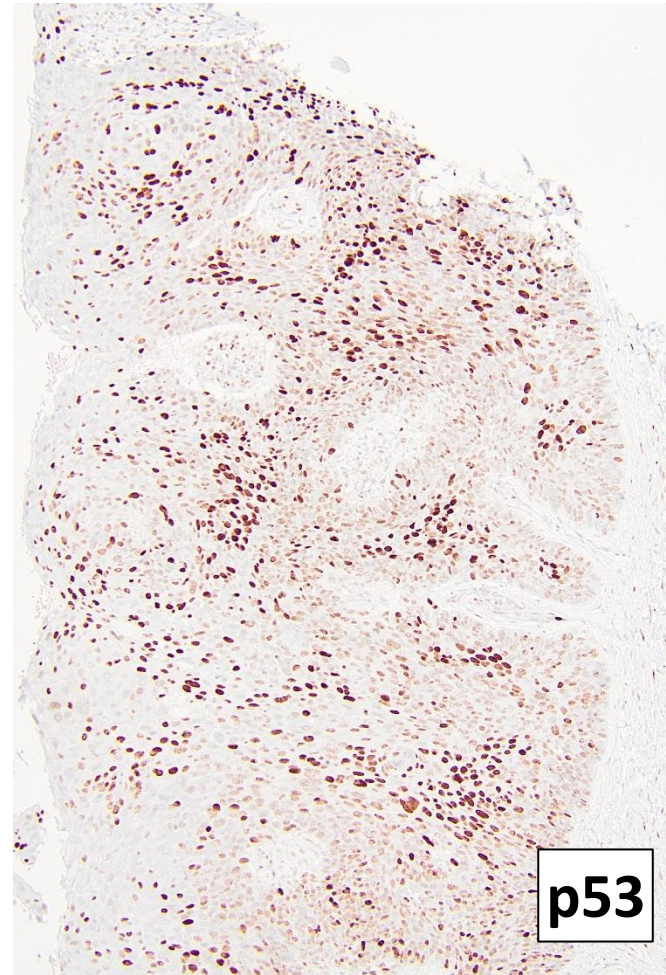
64-year-old with white and thick patches on the labia minora



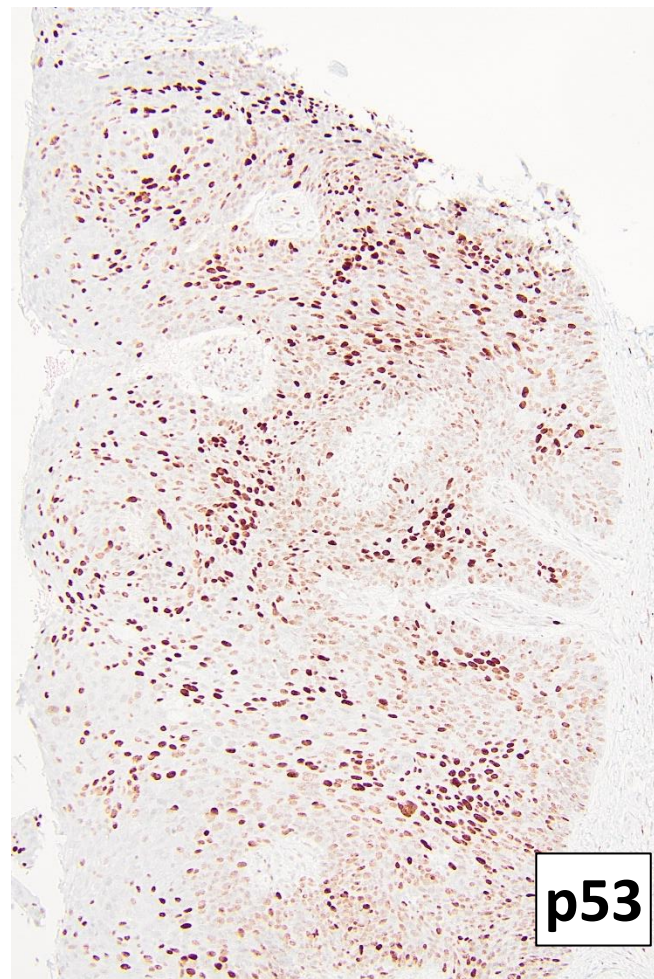
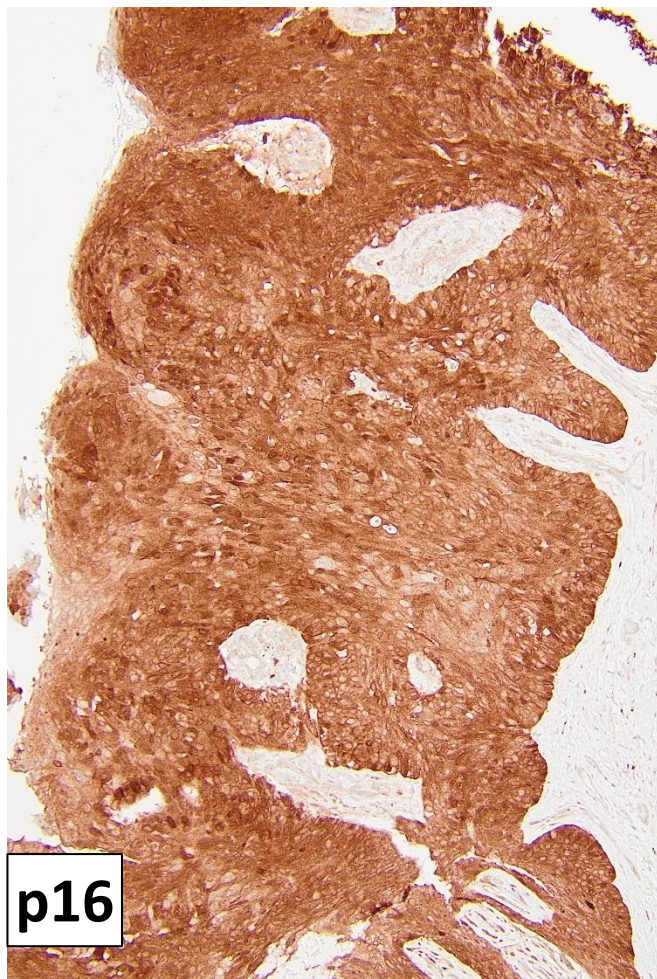
p53 immunohistochemistry

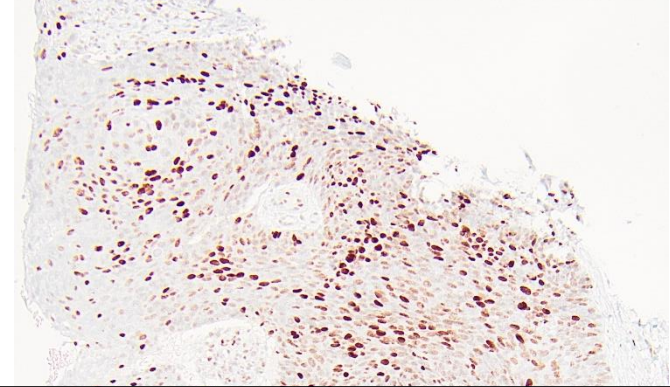
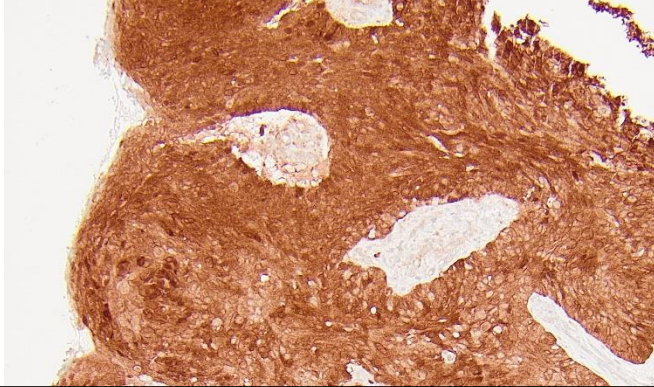


Tricky

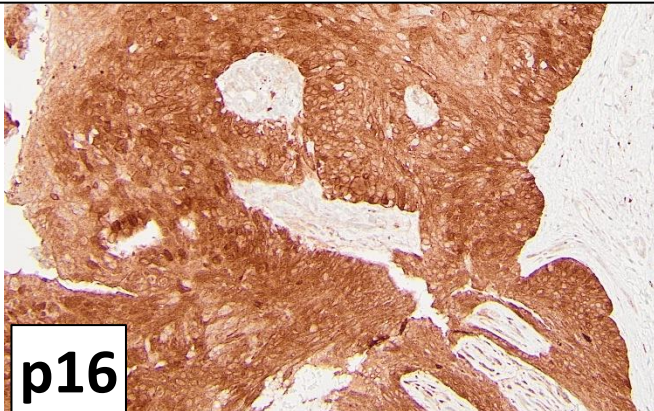


Tricky

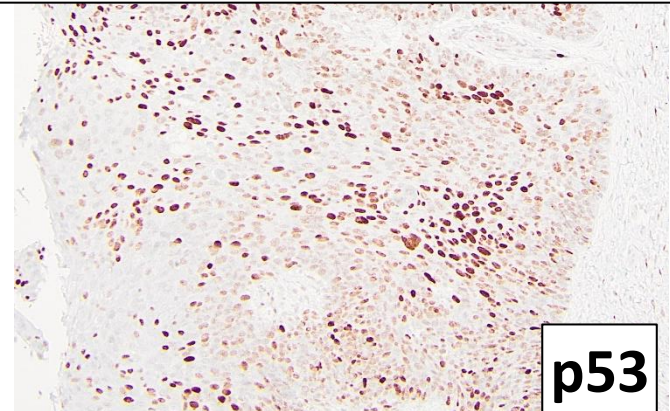




**Must consider p16 and p53 IHC
on all neoplastic biopsies in postmenopausal patients**

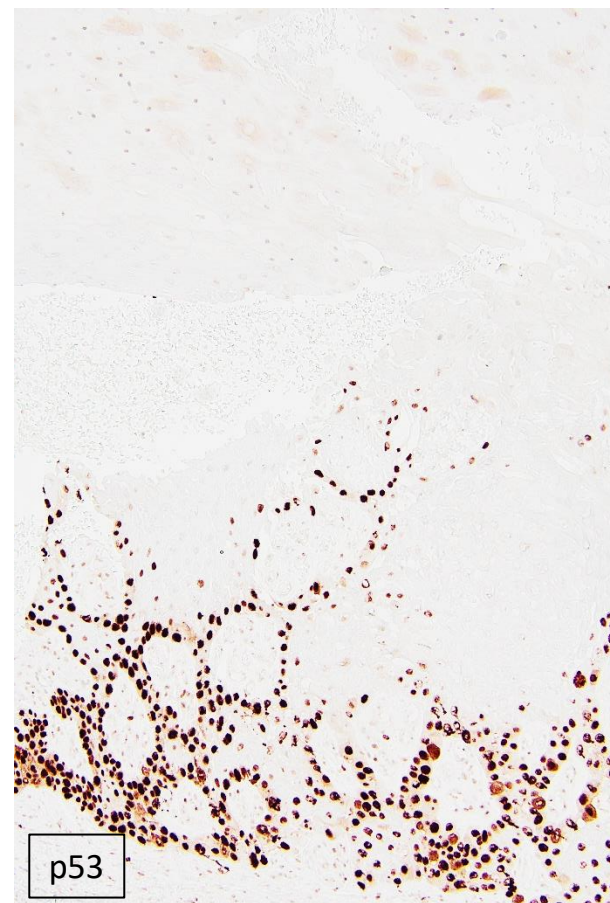
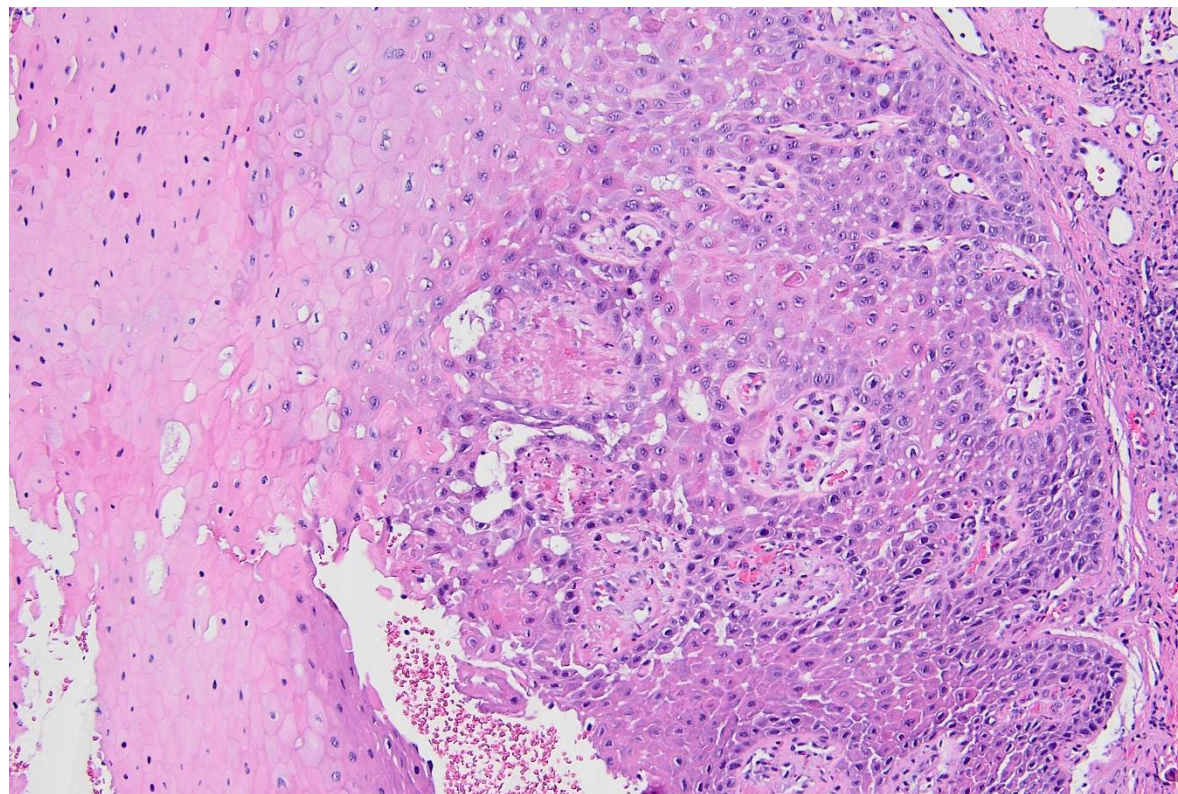


p16

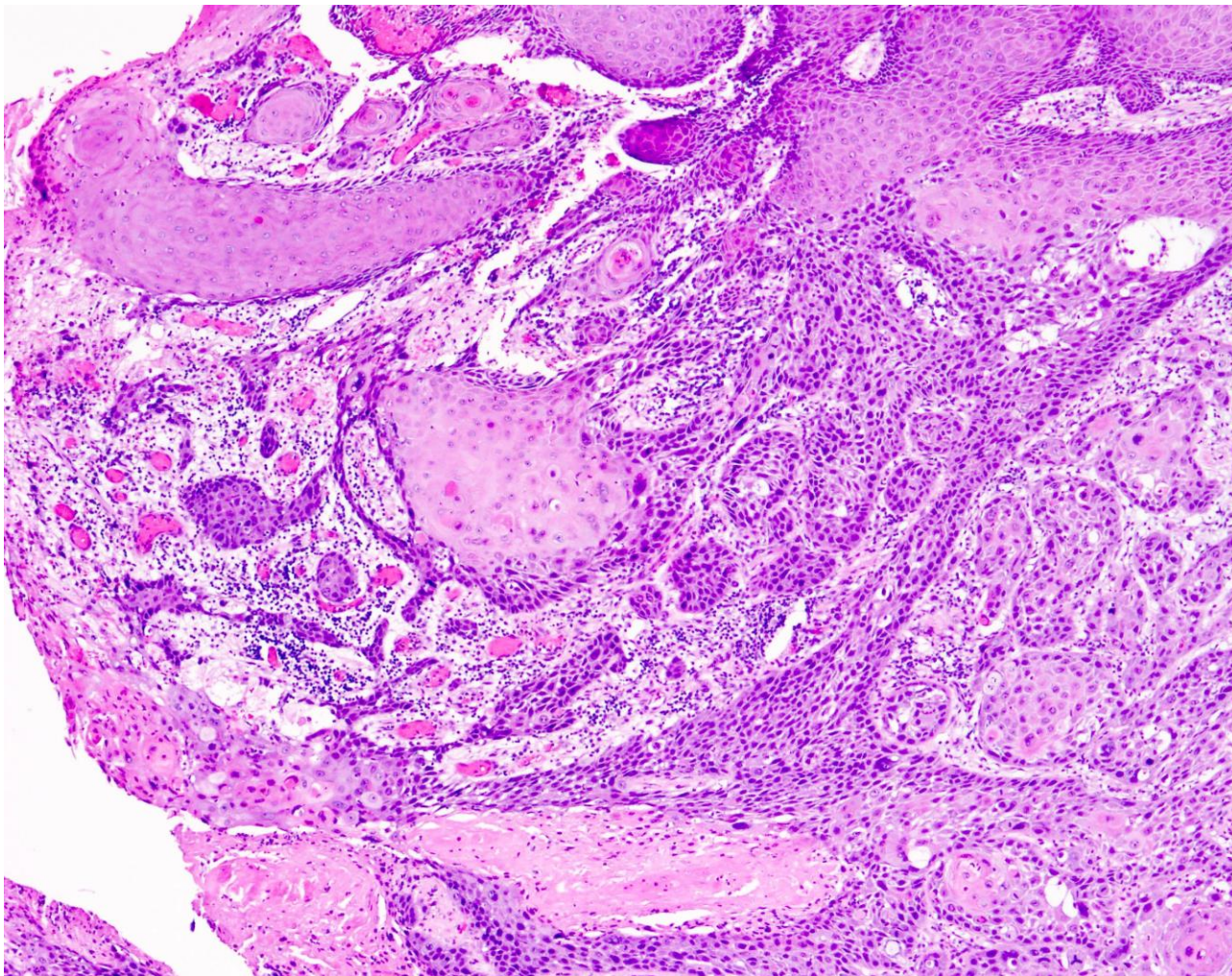


p53

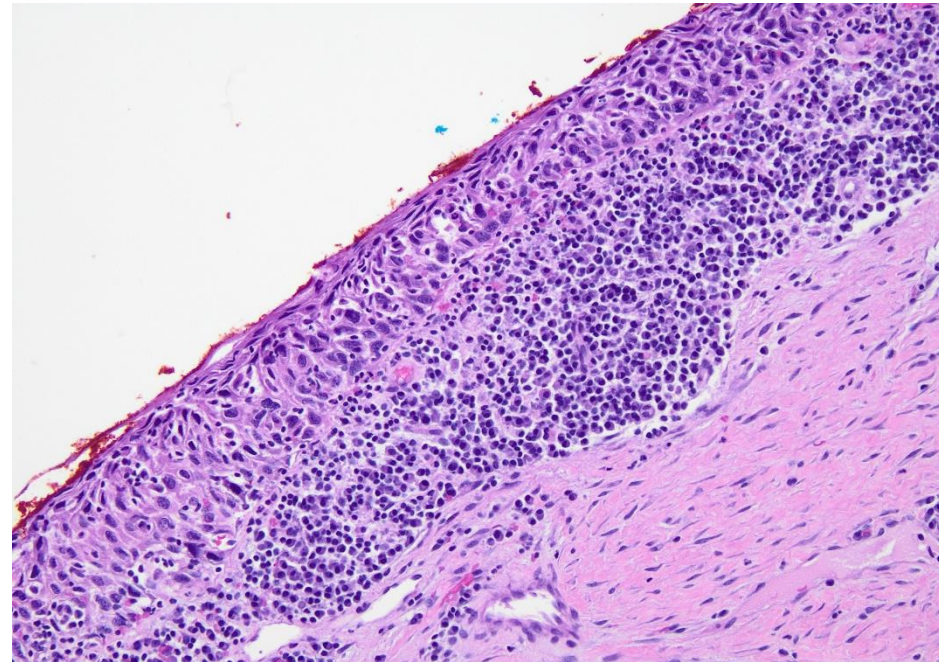
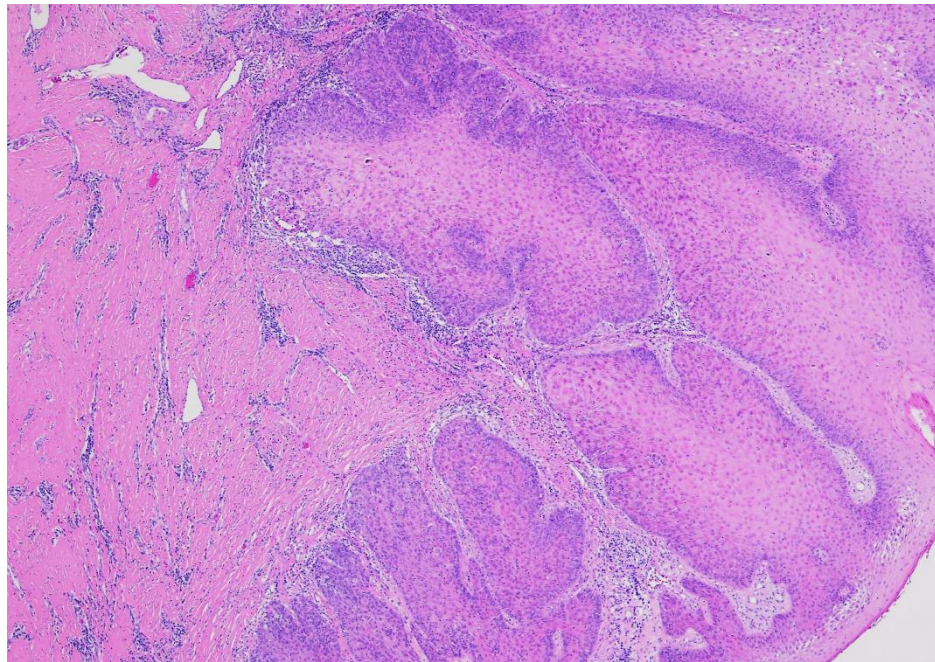
87-year-old with a 1.5 cm ulcer with a sclerotic border

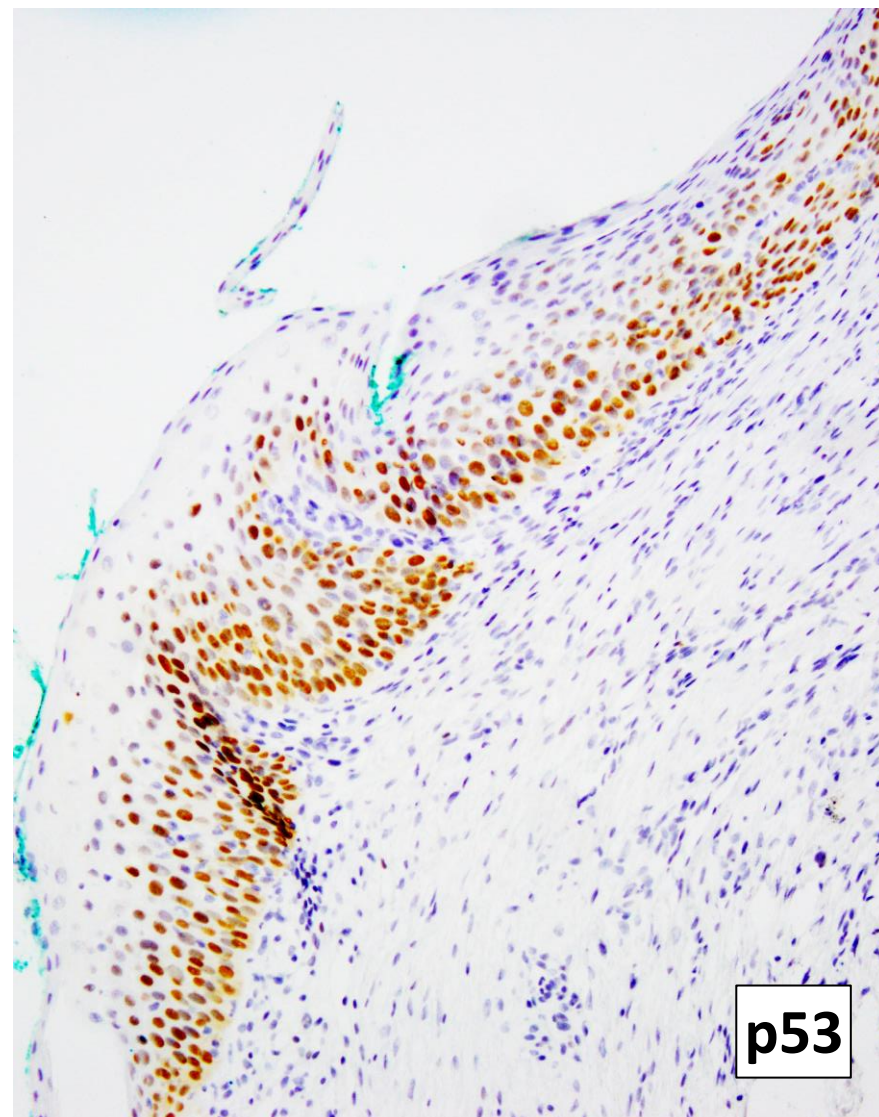
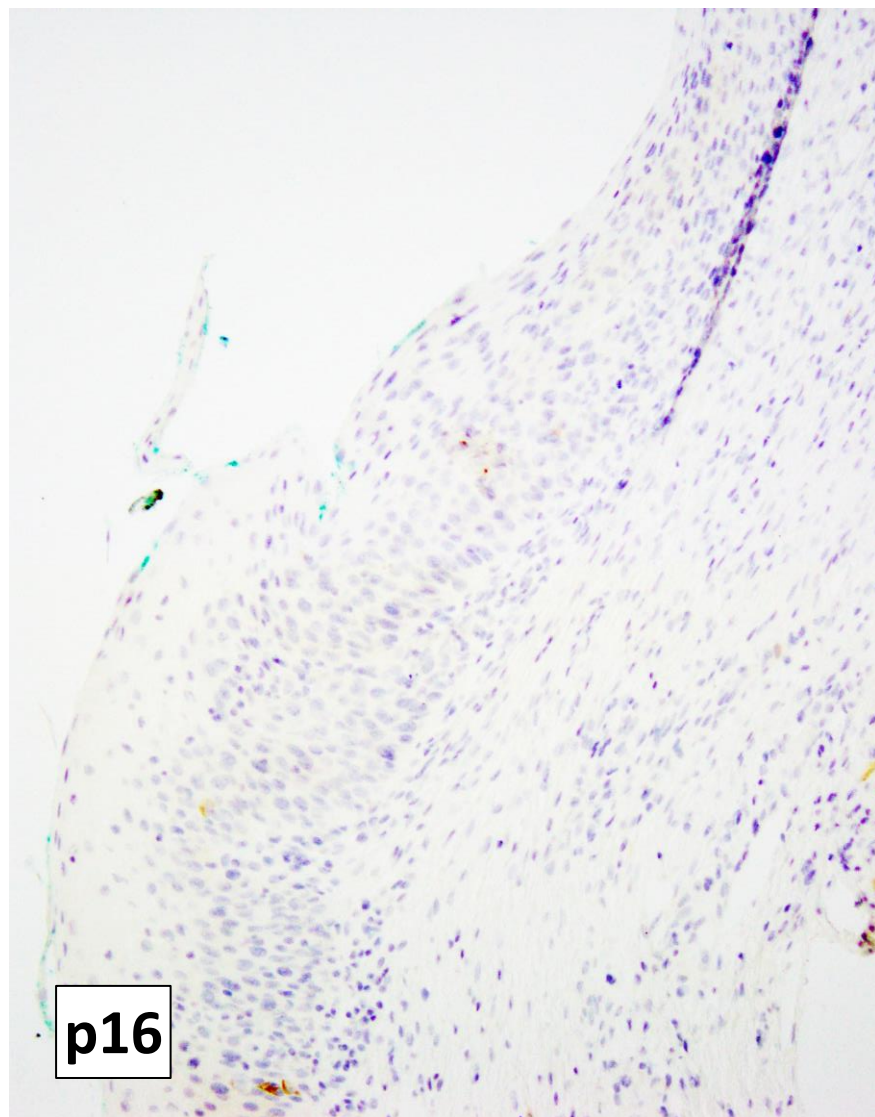


75-year-old with HPV1 invasive squamous cell carcinoma



75-year-old with a h/o HPV I invasive squamous cell carcinoma





Differential diagnosis for HPV1 p53- abnormal VIN (dVIN)

“Atypical lichen
sclerosus”

Lichen simplex
chronicus

Lichen planus

Radiation atypia

Psoriasis

p53 difficulties

Is it a mutational pattern (basal overexpression)?

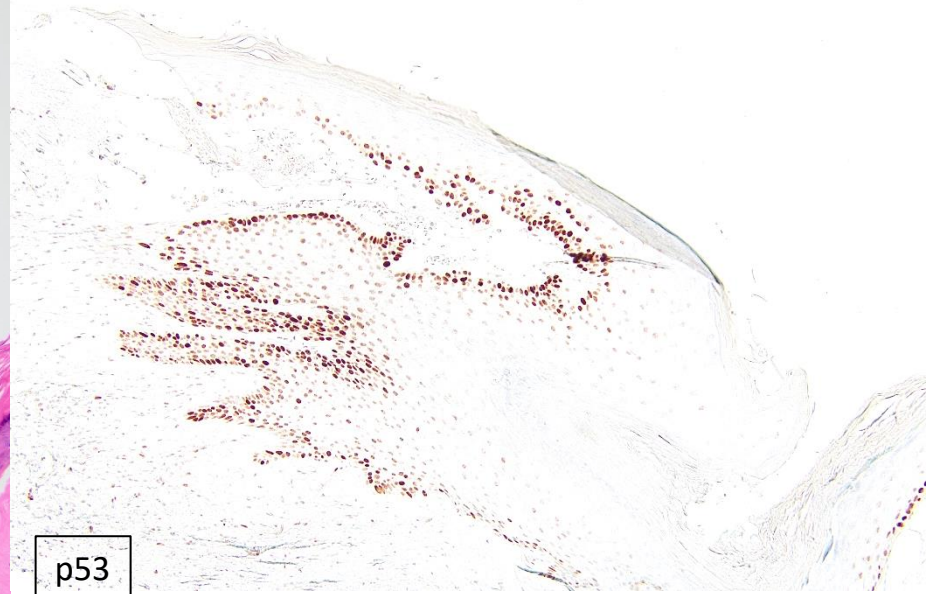
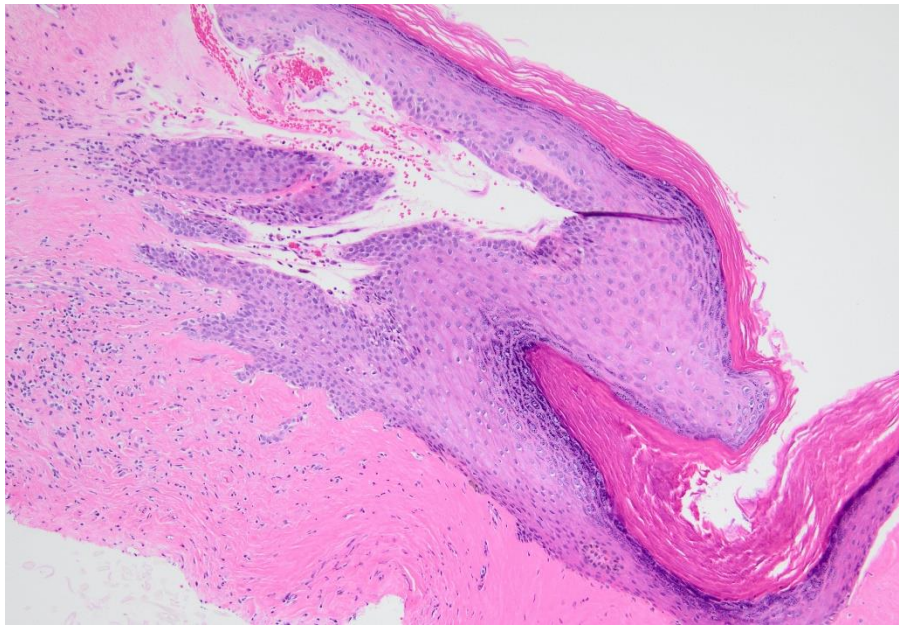
Discrepancy between pattern and H&E findings

LEAN ON THE H&E

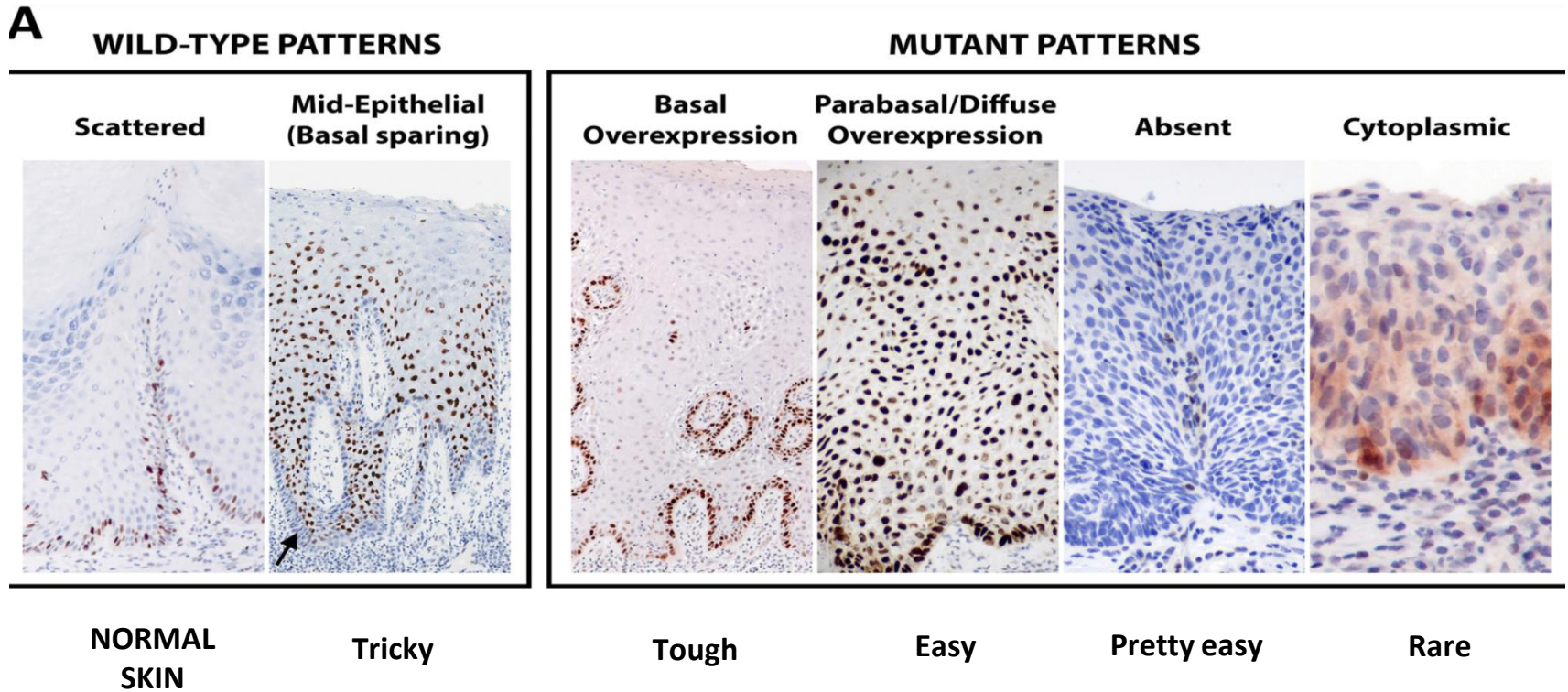
When does mutational pattern take precedence over H&E findings?

DEPENDS

56-year-old with a thickened and white plaque on the anterior vulva



p53 immunohistochemistry



Strategies when unsure

Consensus

Recommend excision if there is a lesion

Recommend very close clinical follow up

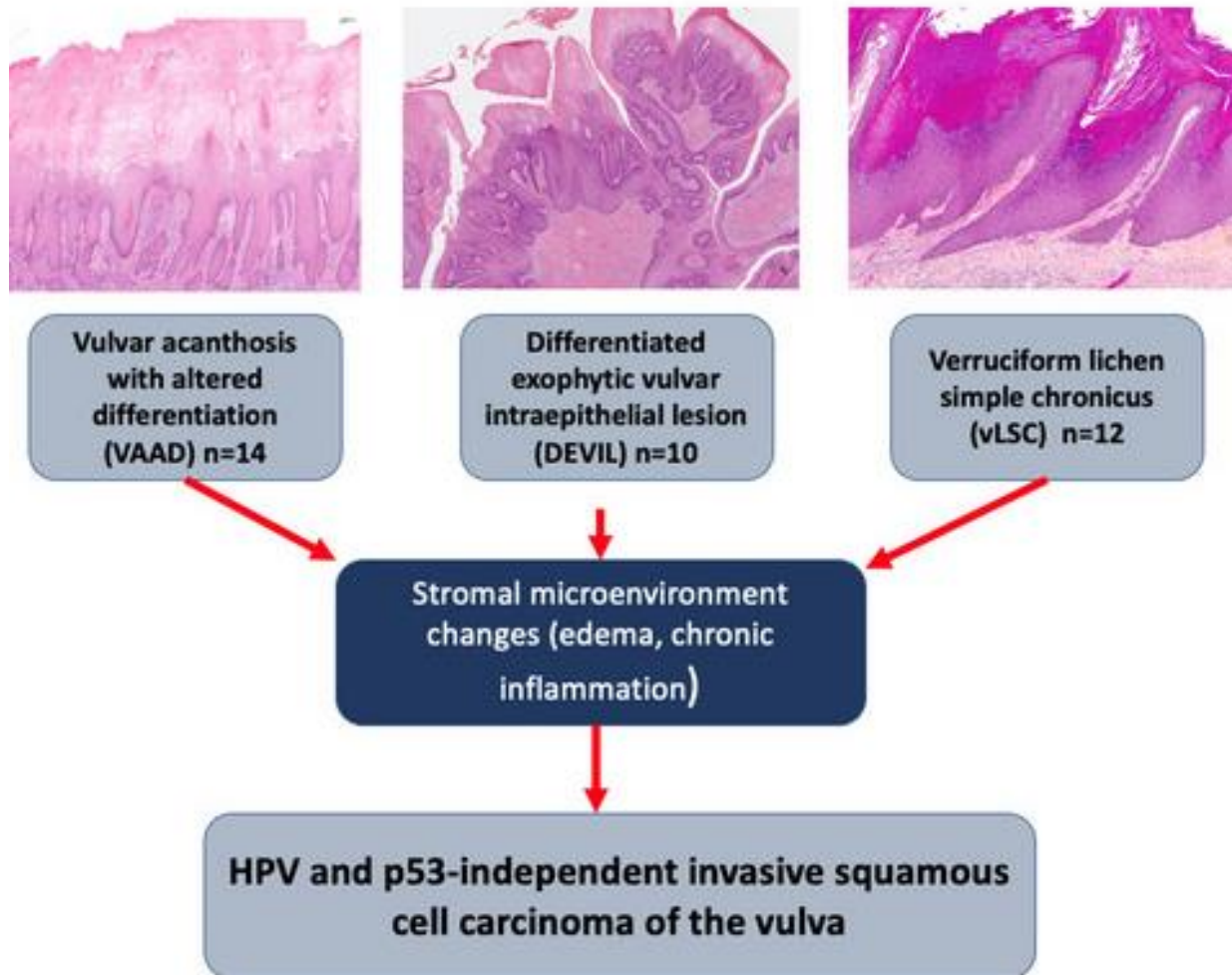
- Lichen sclerosis with possible or confirmed p53 abnormality

Consultation

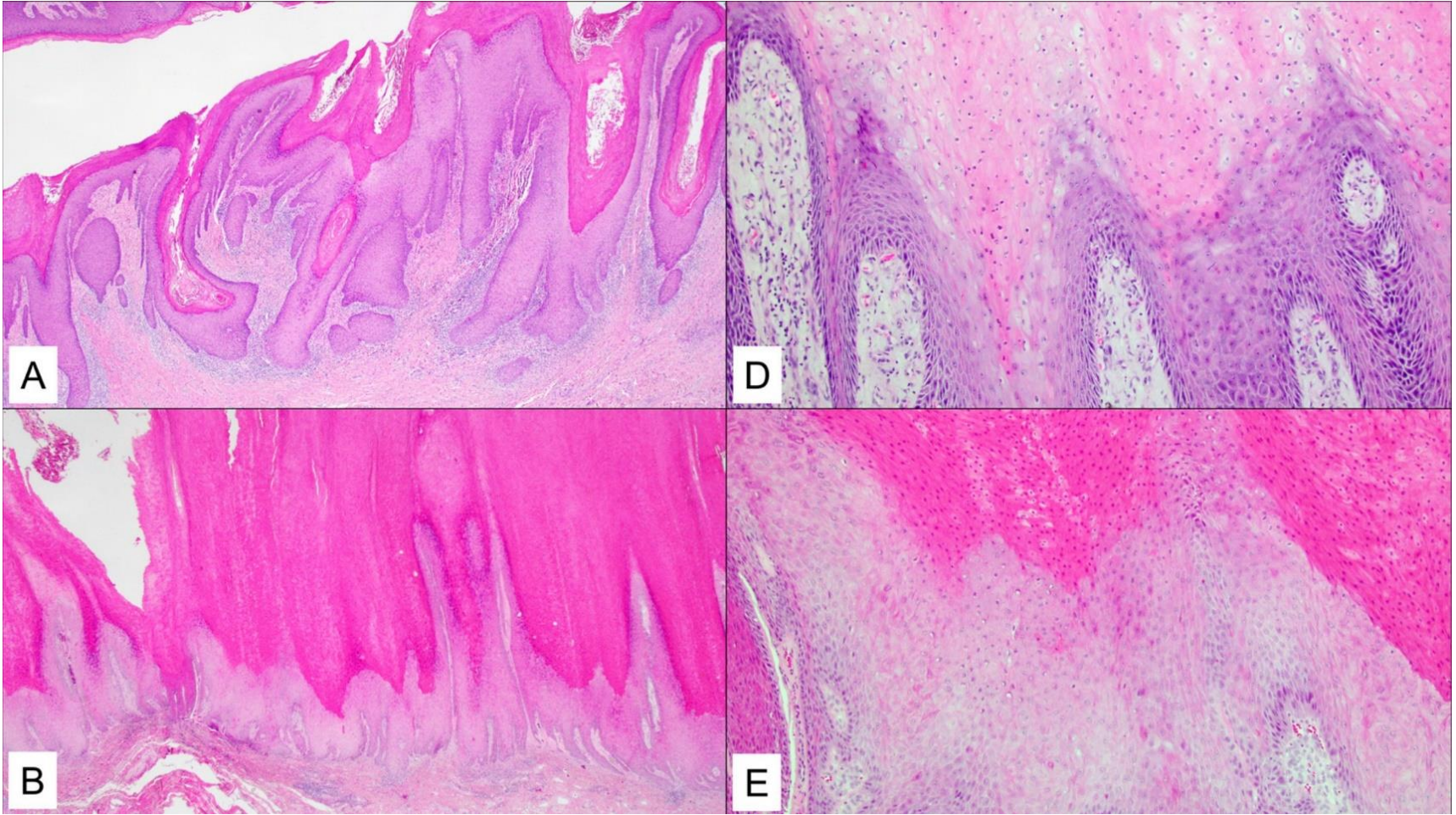
Immunohistochemistry (GLUT-1, GATA3, CK17, SOX2)

HPV1 *p53-wild type* VIN

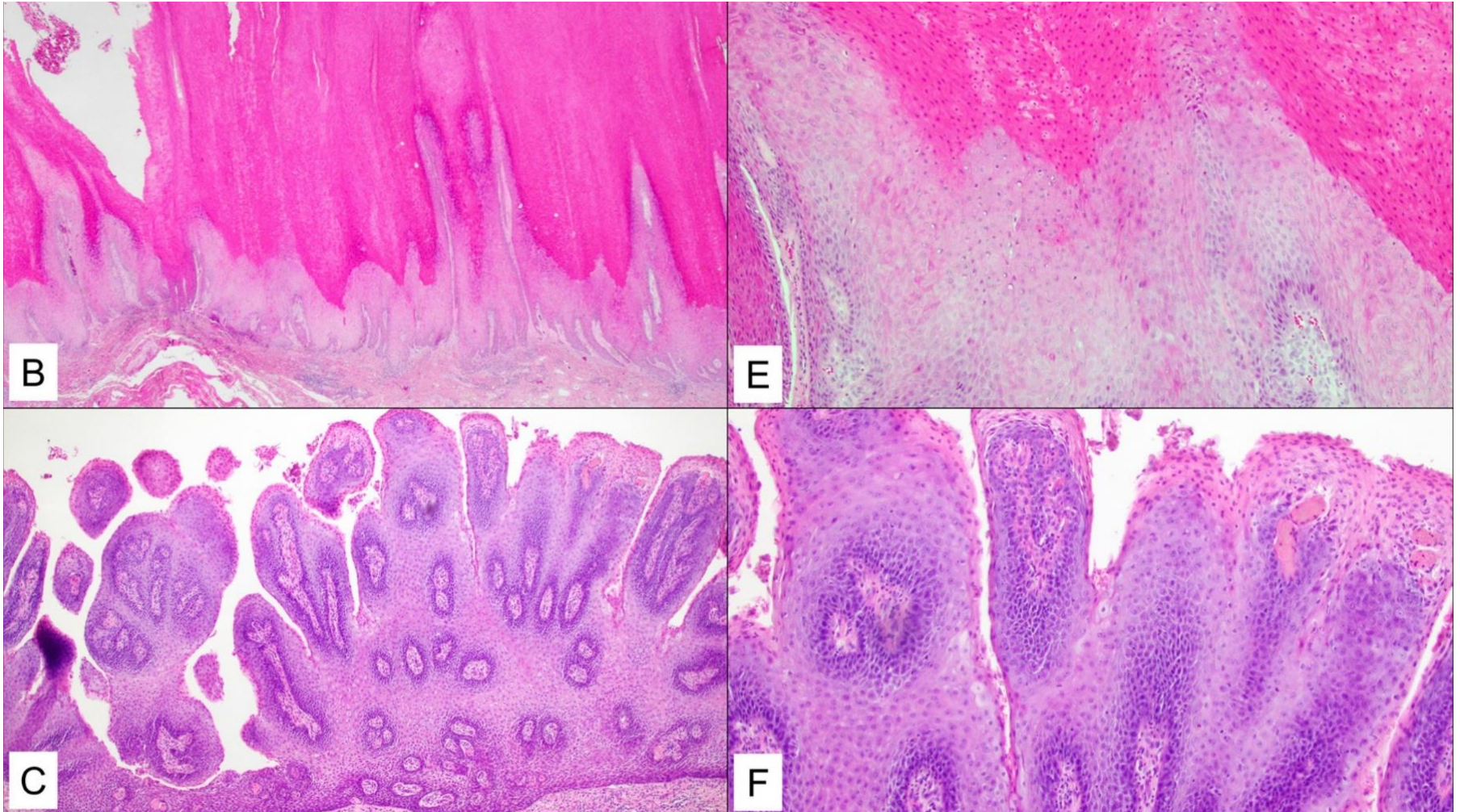
Verruciform acanthotic vulvar intraepithelial neoplasia (vaVIN)



HPV1 p53-wild type VIN



HPV1 p53-wild type VIN



HPV1 *p53-wild type* VIN

Grossly acanthotic or verruciform architecture, raised and discrete

Altered squamous differentiation (hyper- and parakeratosis, usually with hypogranulosis)

No cytologic atypia

Wild-type p53 staining; HPV-independent

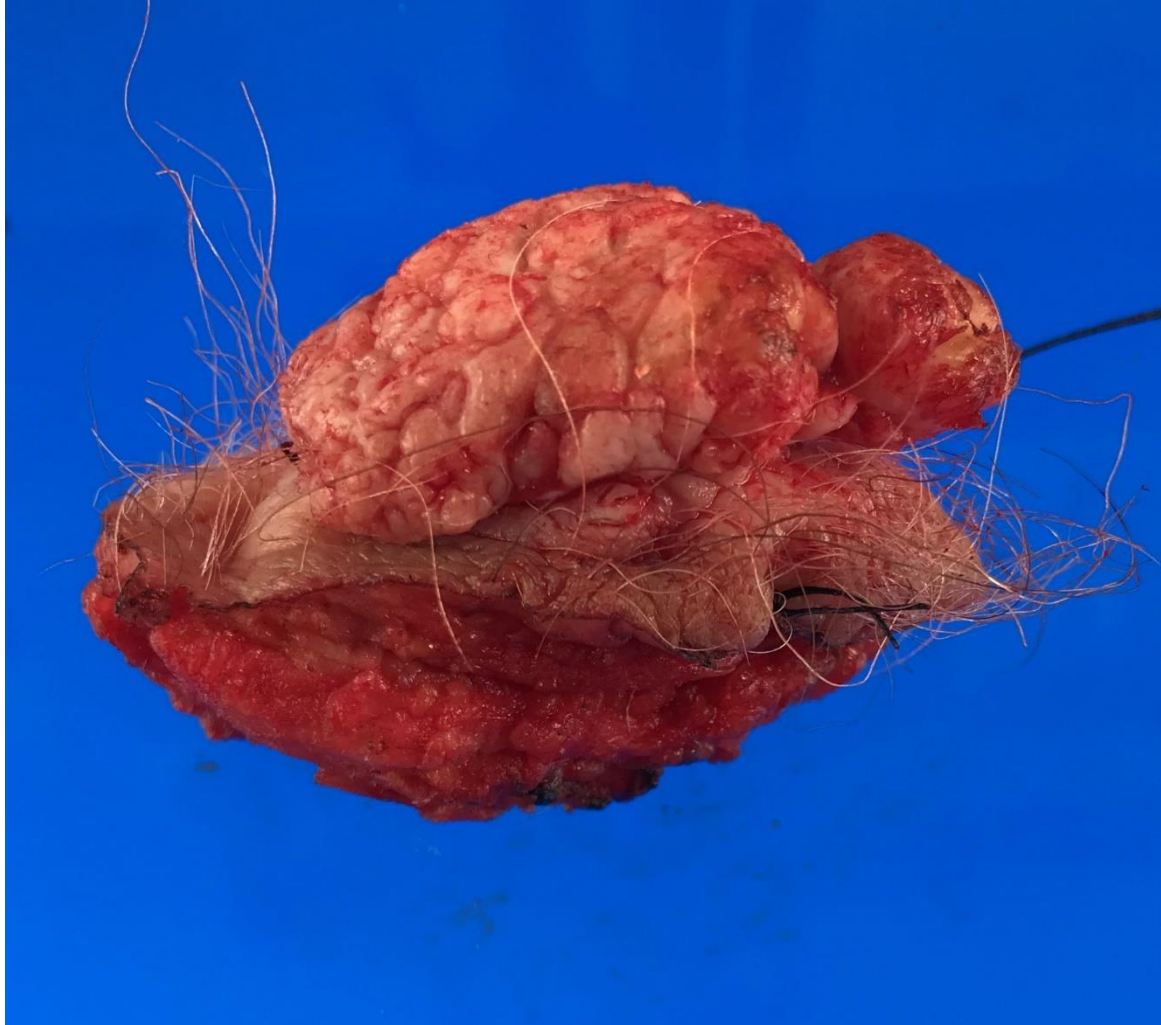
“It kinda looks like verrucous carcinoma but I’m not convinced it’s invasive”

HPV1 *p53-wild type* VIN

Slower and less frequent progression to invasion versus dVIN

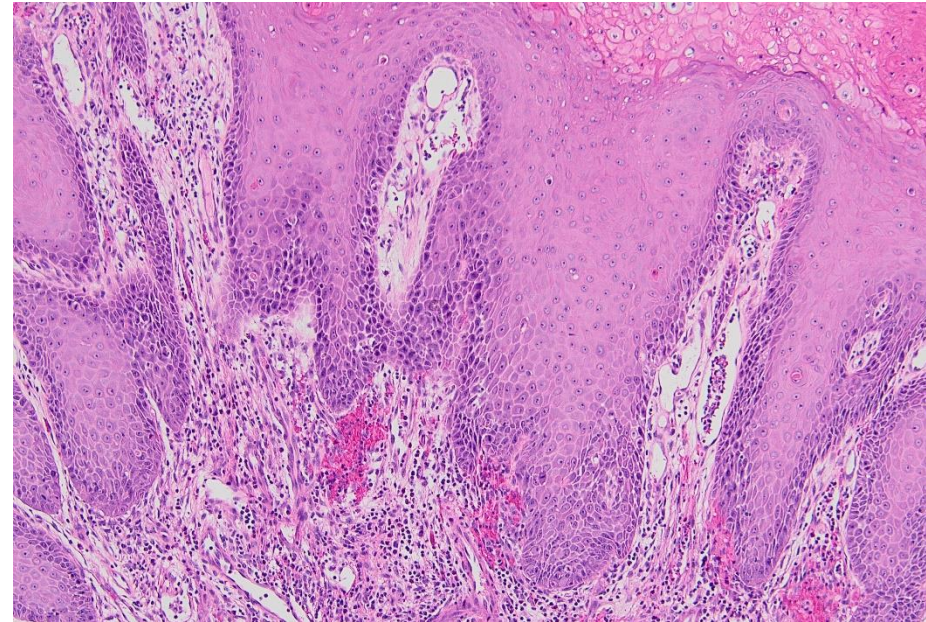
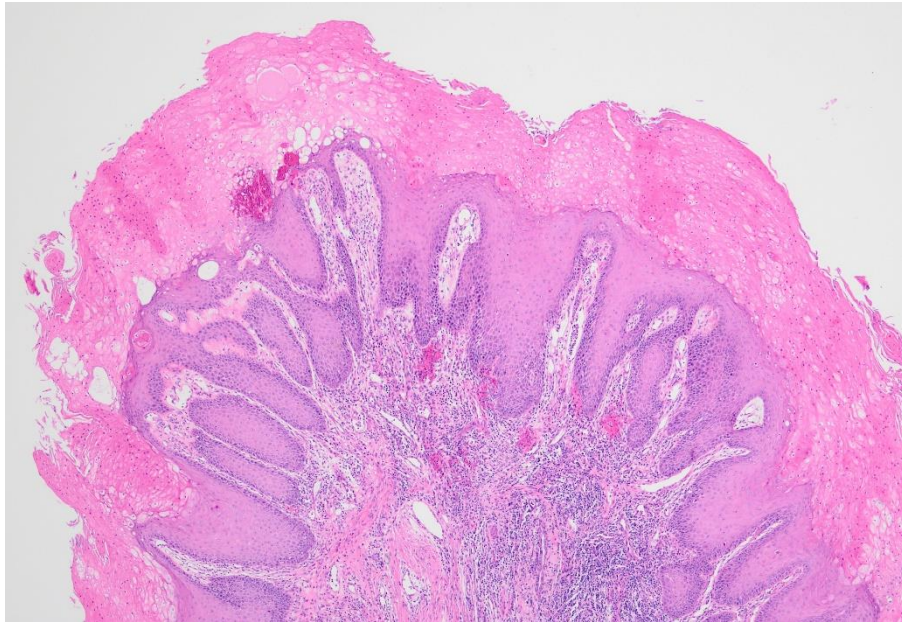
Vulvar SCC risk

- Up to 50%
- Median 60 months

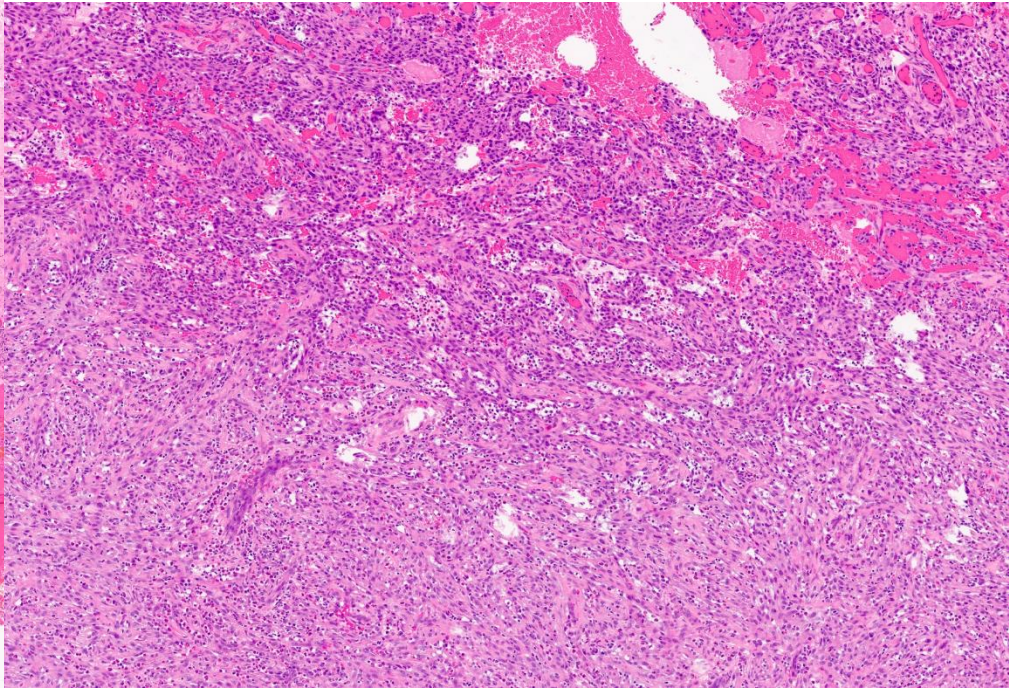
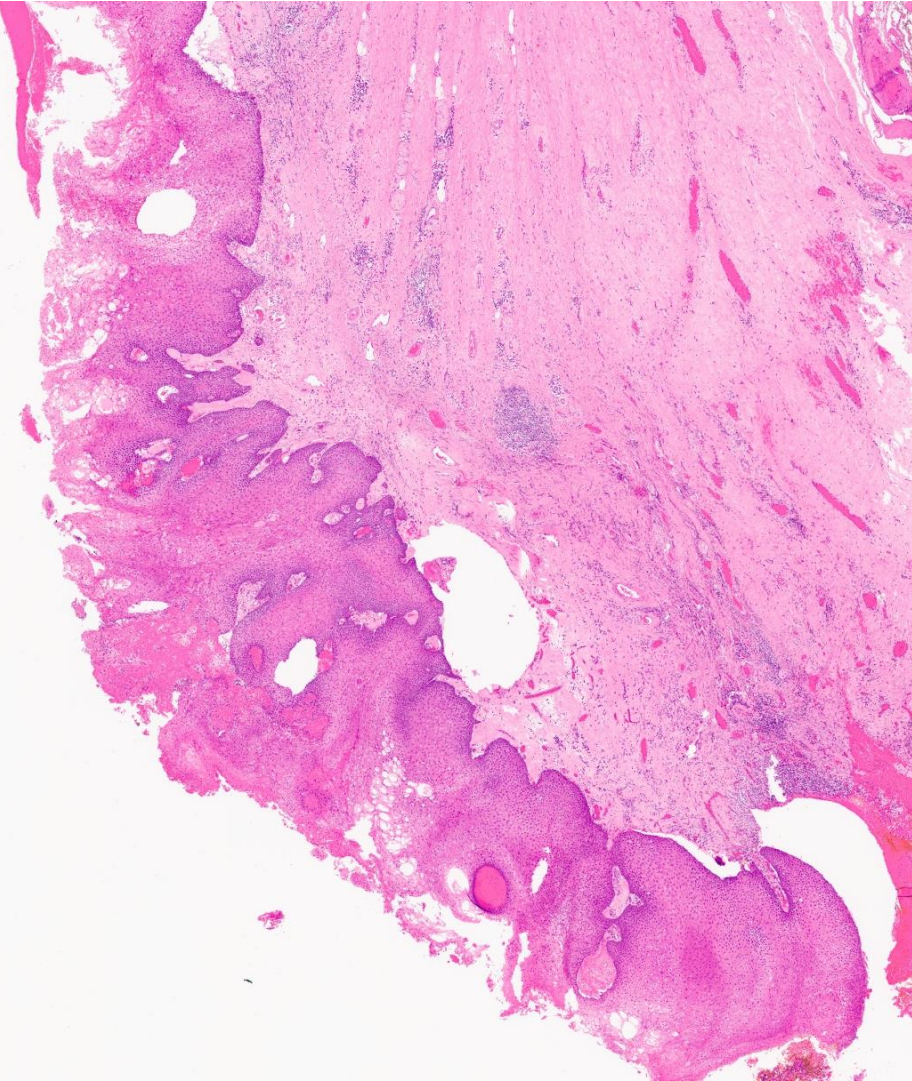


Courtesy of C. Blake Gilks, MD

67-year-old with a large vulvar mass extending to vagina



73-year-old with
a 3 cm vulvar mass



Differential diagnosis for HPV *p53*-wild type VIN

Seborrheic keratosis
and condyloma

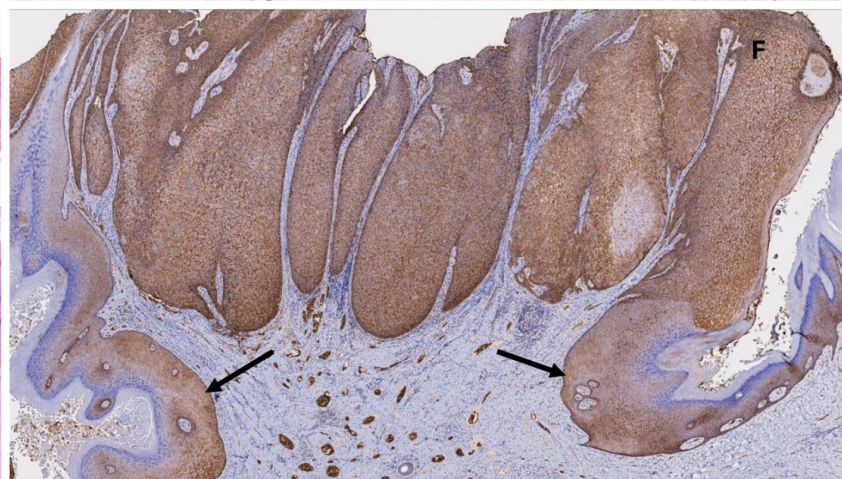
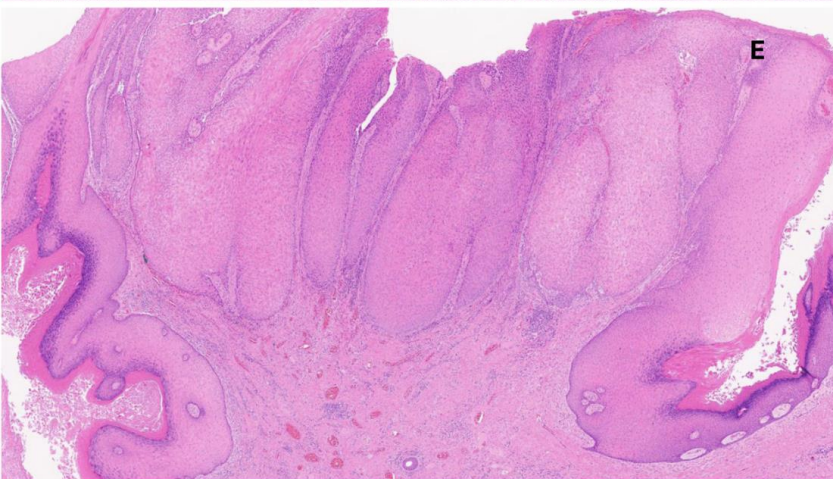
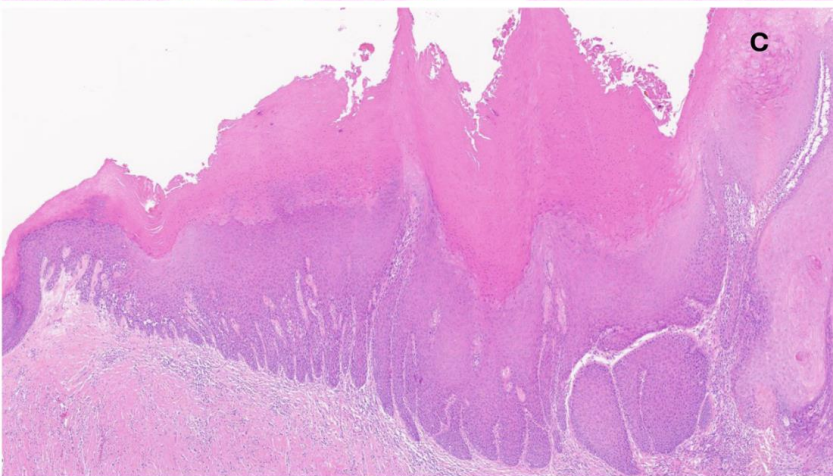
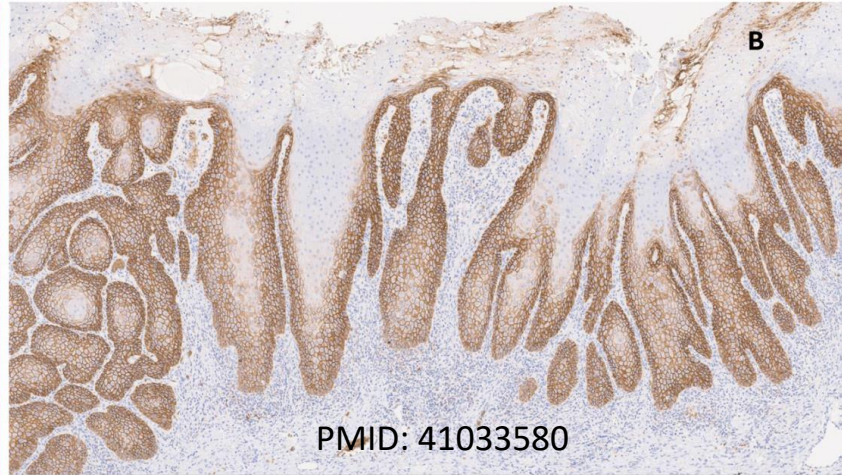
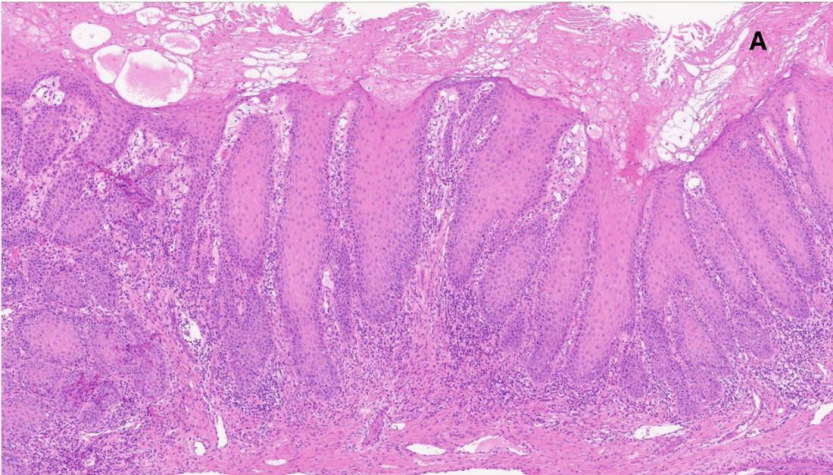
Lichen simplex
chronicus

Verruca vulgaris

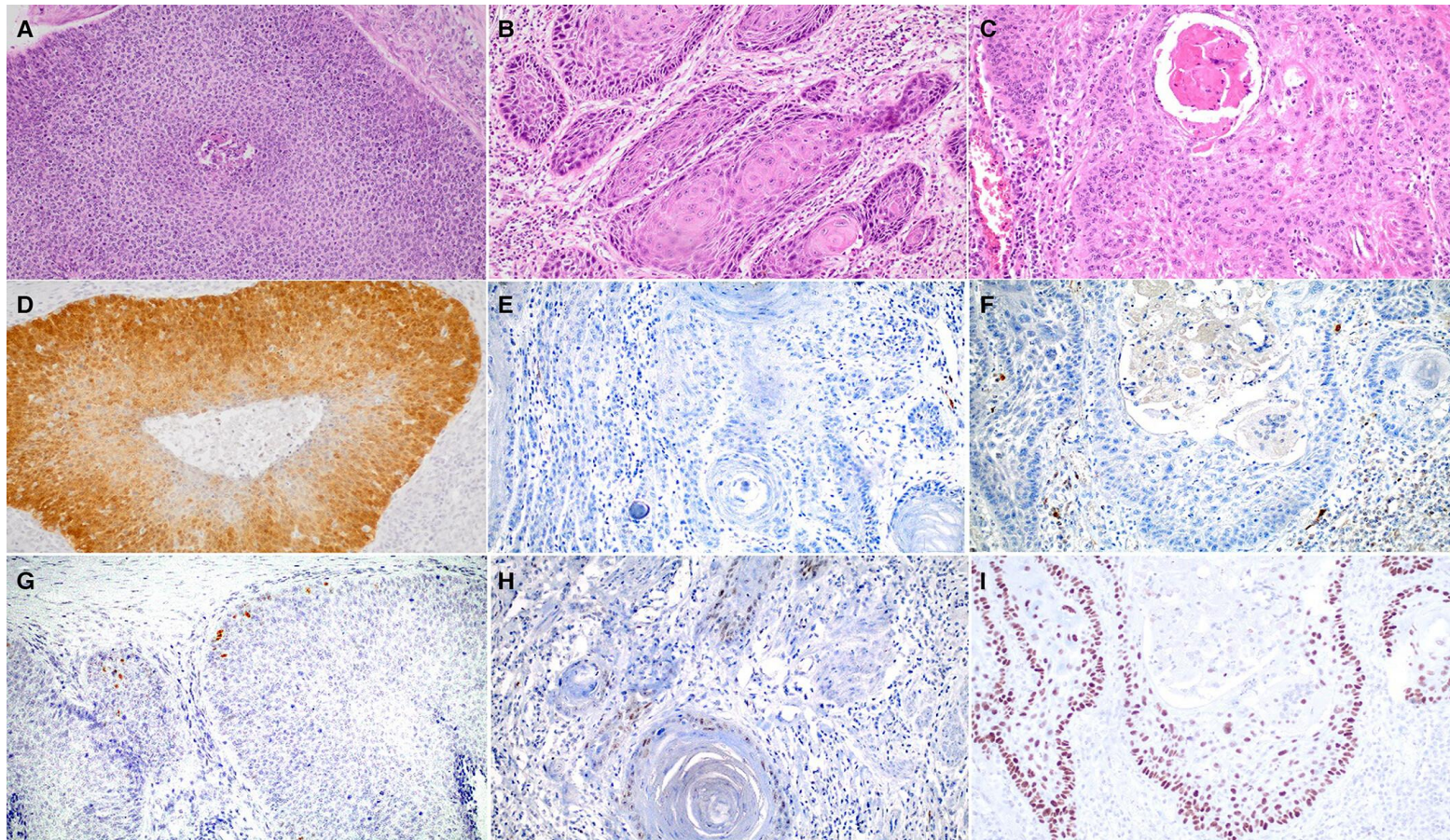
Pseudo-
epitheliomatous
hyperplasia

Verrucous carcinoma

GLUT-1 immunohistochemistry



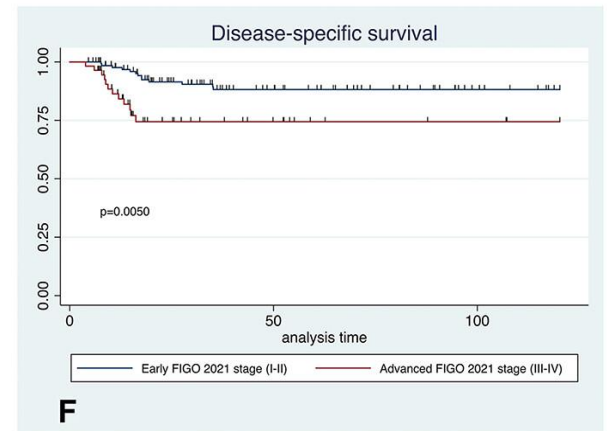
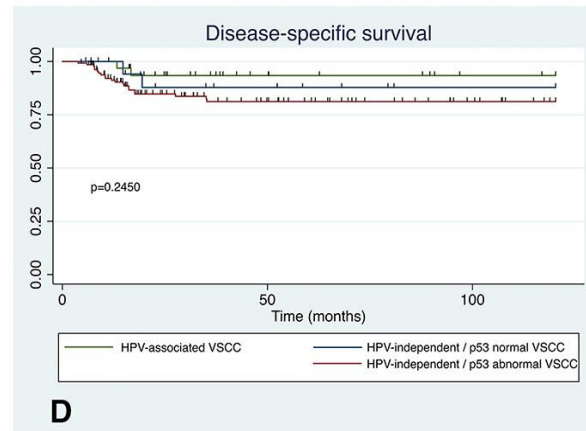
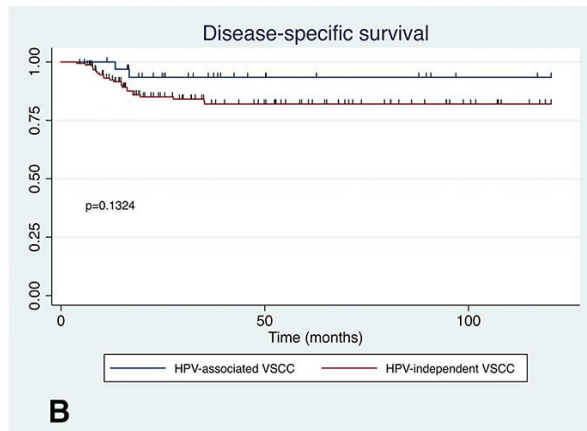
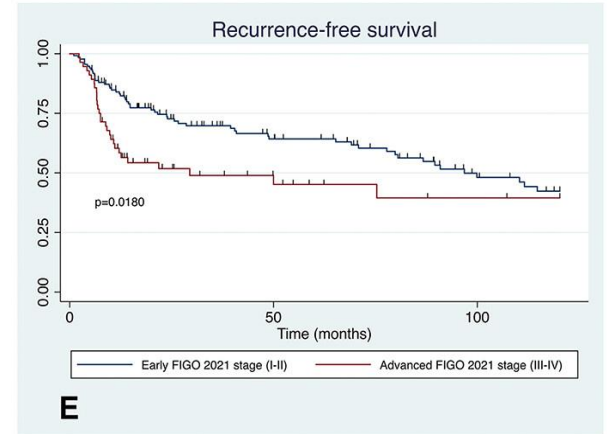
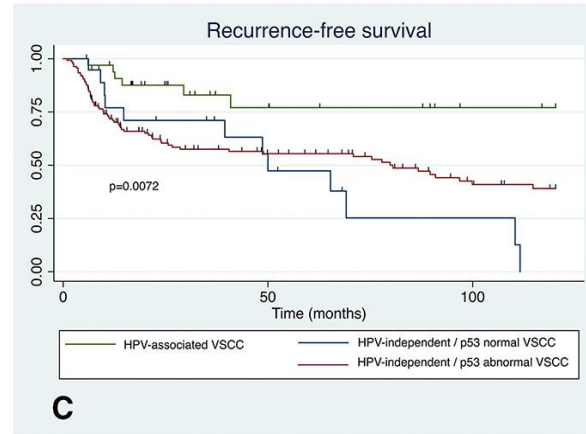
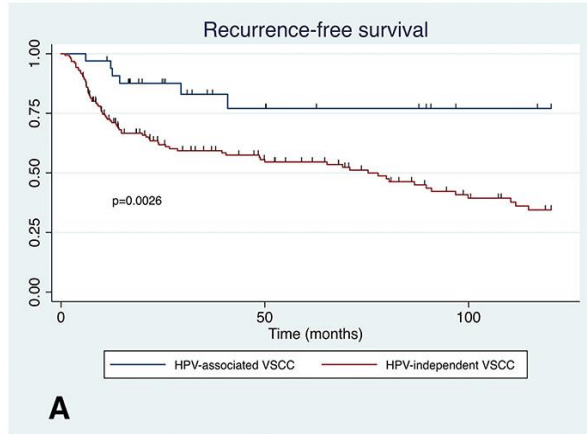
Three types of vulvar squamous cell carcinomas with distinct clinical, pathological, and prognostic features



p16

p53

Three types of vulvar SCC

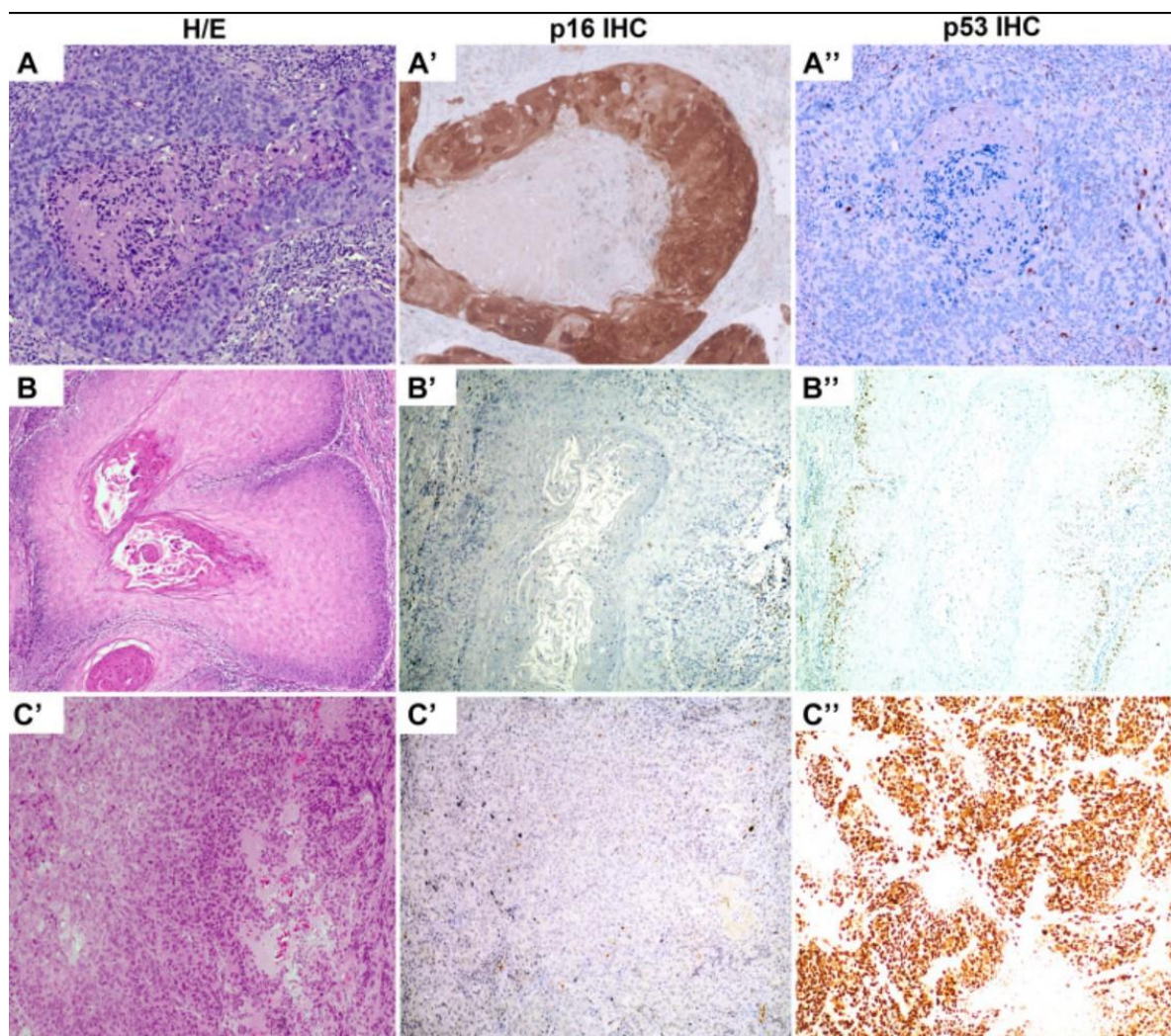


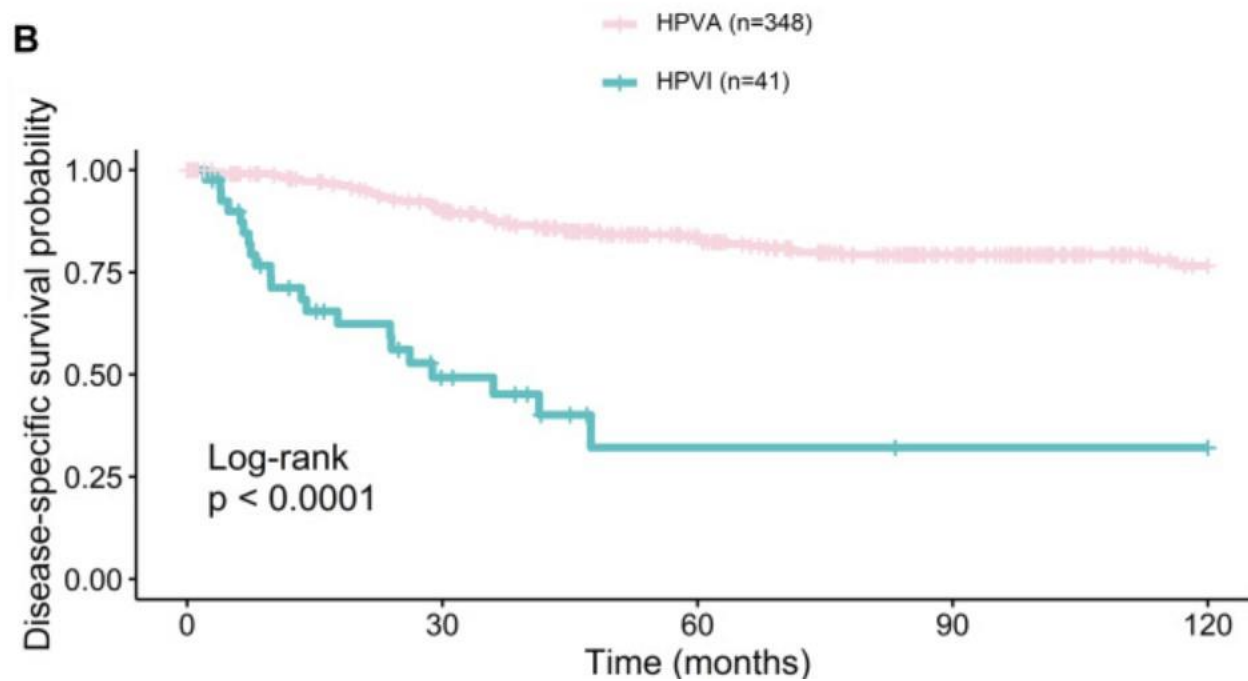
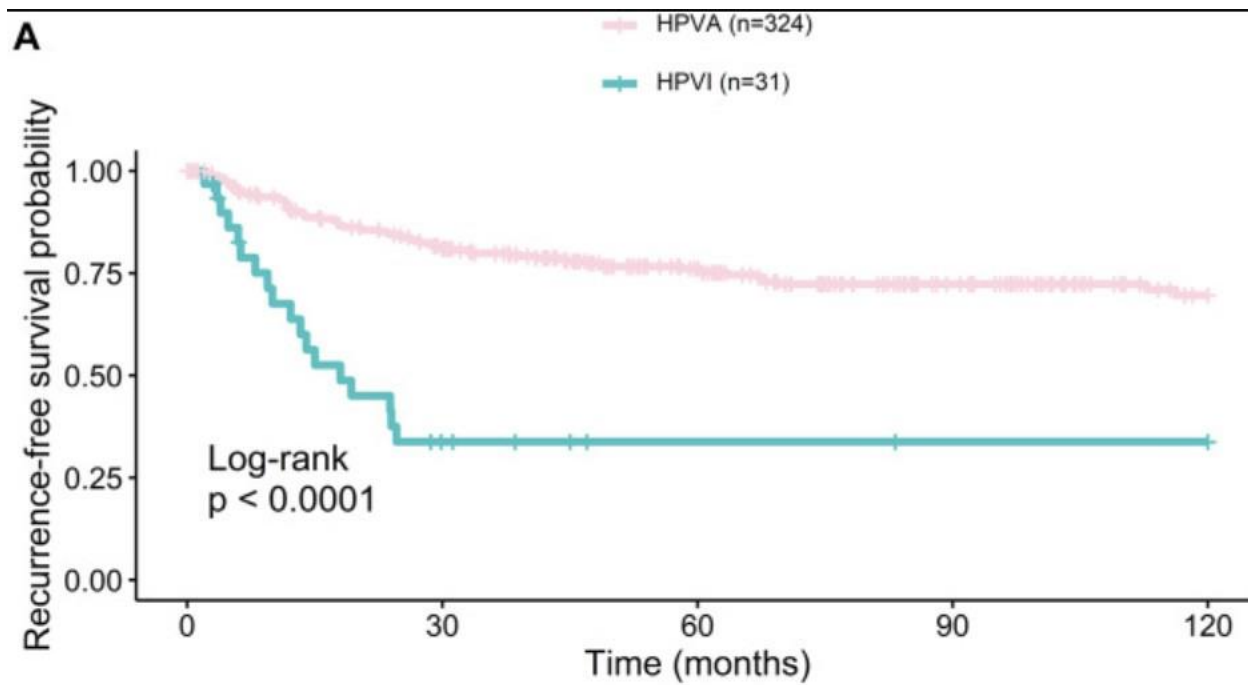
Low stage

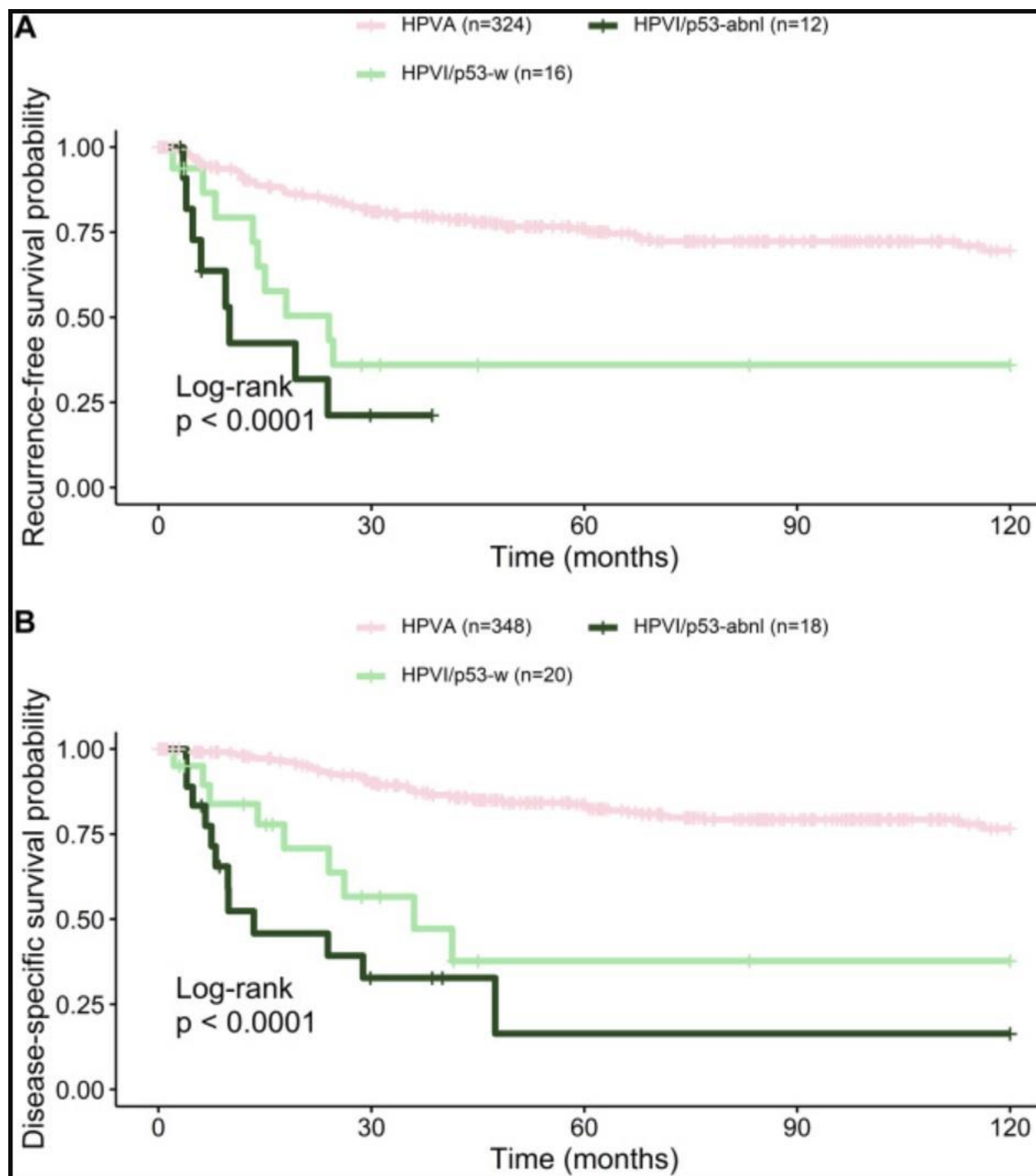
High stage

HPVI SCC of cervix: Emerging information

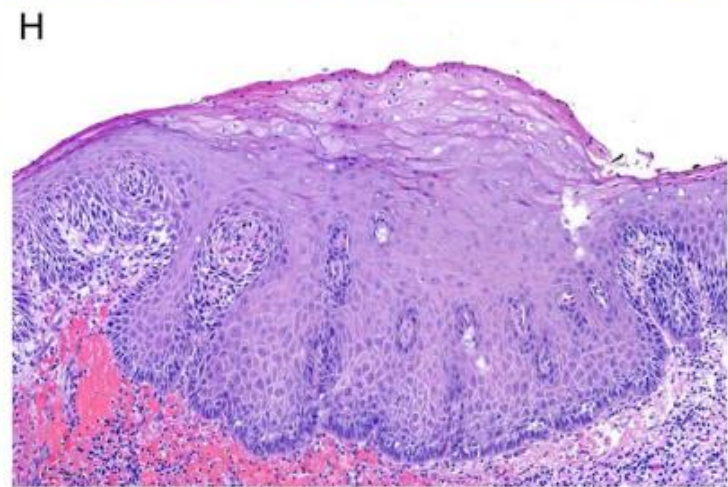
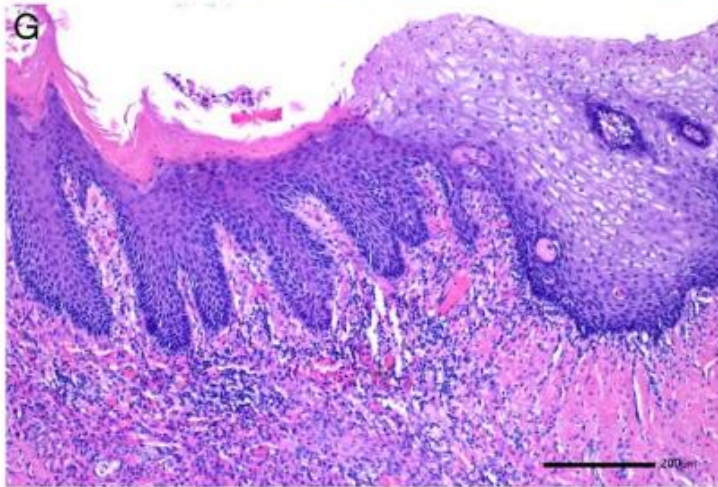
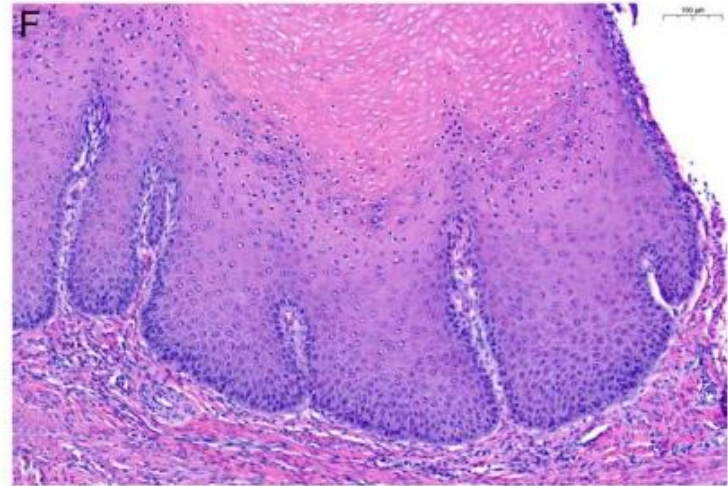
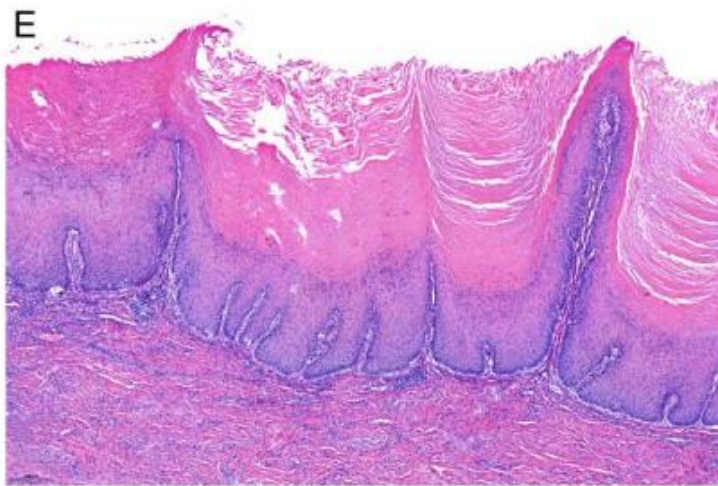
- Rare: 2-5% of cervical SCCs
- Older patients (> 60 years); >10-30% frequency
 - p16/HR-HPV evaluation when patient >60 years
- Uterine prolapse
- Large tumors
- Keratinizing histology
- p53 wild type and p53 mutated
- Aggressive clinical course







HPVI cervical squamous precursors



Summary

- Endocervix
 - HPV1 adenocarcinomas are clinically aggressive
 - Morphology is informative; p16 stains not usually necessary

Summary

- Vulva
 - HPV1 precursors and carcinomas are very aggressive, more aggressive than HPV1A, and relatively resistant to therapy
 - Two HPV1 precursors: dVIN and vaVIN
 - p16 and p53 stains recommended on all vulvar SCCs and precursors

Summary

- Cervix
 - Rare HPV1 SCC precursors and invasive carcinomas
 - p16 stains recommended in patients > 60 years
 - p53 status associated with clinical outcomes



PHOTO: SDOMINICK/GETTY IMAGES