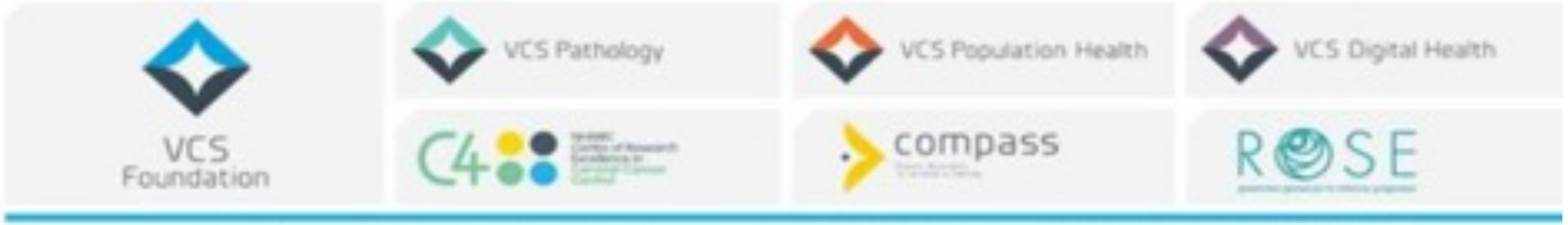
HPV-ASSOCIATED GLANDULAR LESIONS OF THE CERVIX

Dr Karen Talia FRCPA

Royal Women's Hospital & VCS Foundation

Melbourne, Australia

the women's
the royal women's hospital
victoria australia

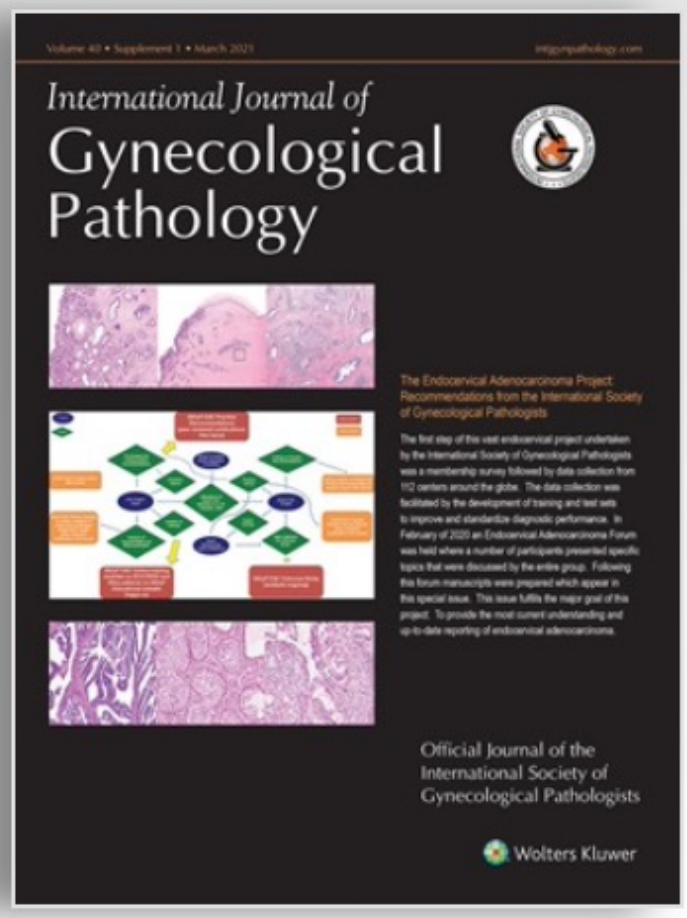


ISGyP Endocervical Adenocarcinoma Project

Aims:

1. Assess the spectrum of current practice in pathological evaluation - macroscopic handling, diagnosis, classification - via a member survey, review literature, examine controversial areas
2. Improve global reproducibility of classification and reporting
3. Assess prognostic significance of WHO/IECC classification and Silva pattern-based classification

ISGyP Endocervical Adenocarcinoma Project



March 2021 - Volume 40 - Issue 2, Supplement 1

Open access, 9 individual papers

Consensus recommendations, best practice guidelines

- Distinction of in situ from invasive adenocarcinoma
- Silva patterns of invasion
- Grading of endocervical adenocarcinoma
- Tumour typing including immunohistochemistry
- Staging
- Predictive biomarkers
- Intraoperative evaluation

Overview & Learning Objectives

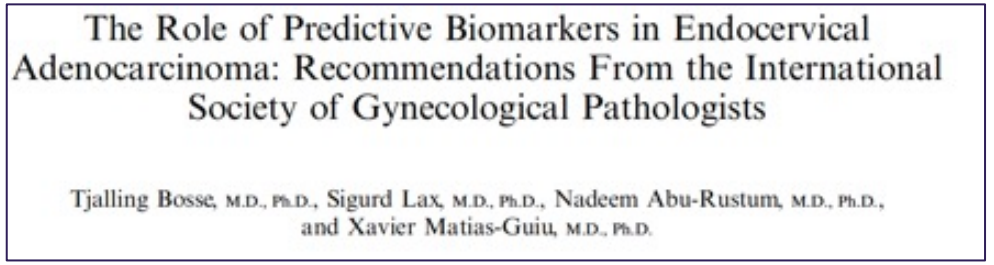
- Global perspective; HPV
- Classification; 2020 WHO
- Morphology & IHC
- Recently described variants
- Pattern-based classification

Topics not covered

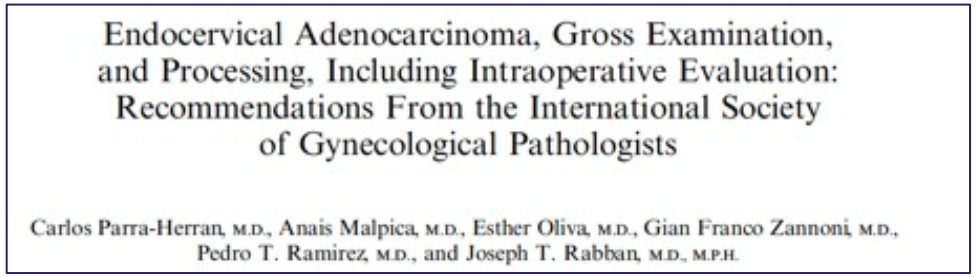
- Tumour staging
- Role of predictive biomarkers
- Intraoperative evaluation
- Neuroendocrine tumours

- **Podcast:** ISGyP Endocervical Adenocarcinoma Project, Part 1: Grossing and Intraoperative consultation
  - Joe Rabban (USA) (Moderated by: Carlos Parra Herran (USA))
  - August 25 at 12:00 US Eastern time

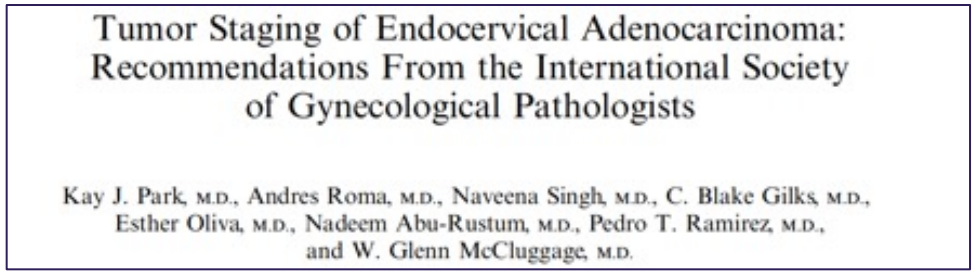
- **Podcast:** ISGyP Endocervical Adenocarcinoma Project, Part 2: Staging recommendations
  - Kay Park (USA) (Moderated by: Carlos Parra Herran (USA))
  - September 29 at 12:00 US Eastern time


The Role of Predictive Biomarkers in Endocervical Adenocarcinoma: Recommendations From the International Society of Gynecological Pathologists

Tjalling Bosse, M.D., Ph.D., Sigurd Lax, M.D., Ph.D., Nadeem Abu-Rustum, M.D., Ph.D., and Xavier Matias-Guiu, M.D., Ph.D.


Endocervical Adenocarcinoma, Gross Examination, and Processing, Including Intraoperative Evaluation: Recommendations From the International Society of Gynecological Pathologists

Carlos Parra-Herran, M.D., Anais Malpica, M.D., Esther Oliva, M.D., Gian Franco Zannoni, M.D., Pedro T. Ramirez, M.D., and Joseph T. Rabban, M.D., M.P.H.


Tumor Staging of Endocervical Adenocarcinoma: Recommendations From the International Society of Gynecological Pathologists

Kay J. Park, M.D., Andres Roma, M.D., Naveena Singh, M.D., C. Blake Gilks, M.D., Esther Oliva, M.D., Nadeem Abu-Rustum, M.D., Pedro T. Ramirez, M.D., and W. Glenn McCluggage, M.D.

Open to all live, archives available to ISGyP members only.

Website: www.isgyp.ca

GLOBAL PERSPECTIVE

CERVICAL CANCER

- Globally, major public health problem, significant disease burden
- 4th most common cancer in women
- >300 000 deaths in 2018
- ≈ 90% of deaths in low and middle-income countries; cancer with the largest variation in mortality based on geography
- Leading cause of cancer death in women in much of Africa and other resource poor countries

- 90-99% HPV associated
- **Most will be impacted by HPV vaccine**

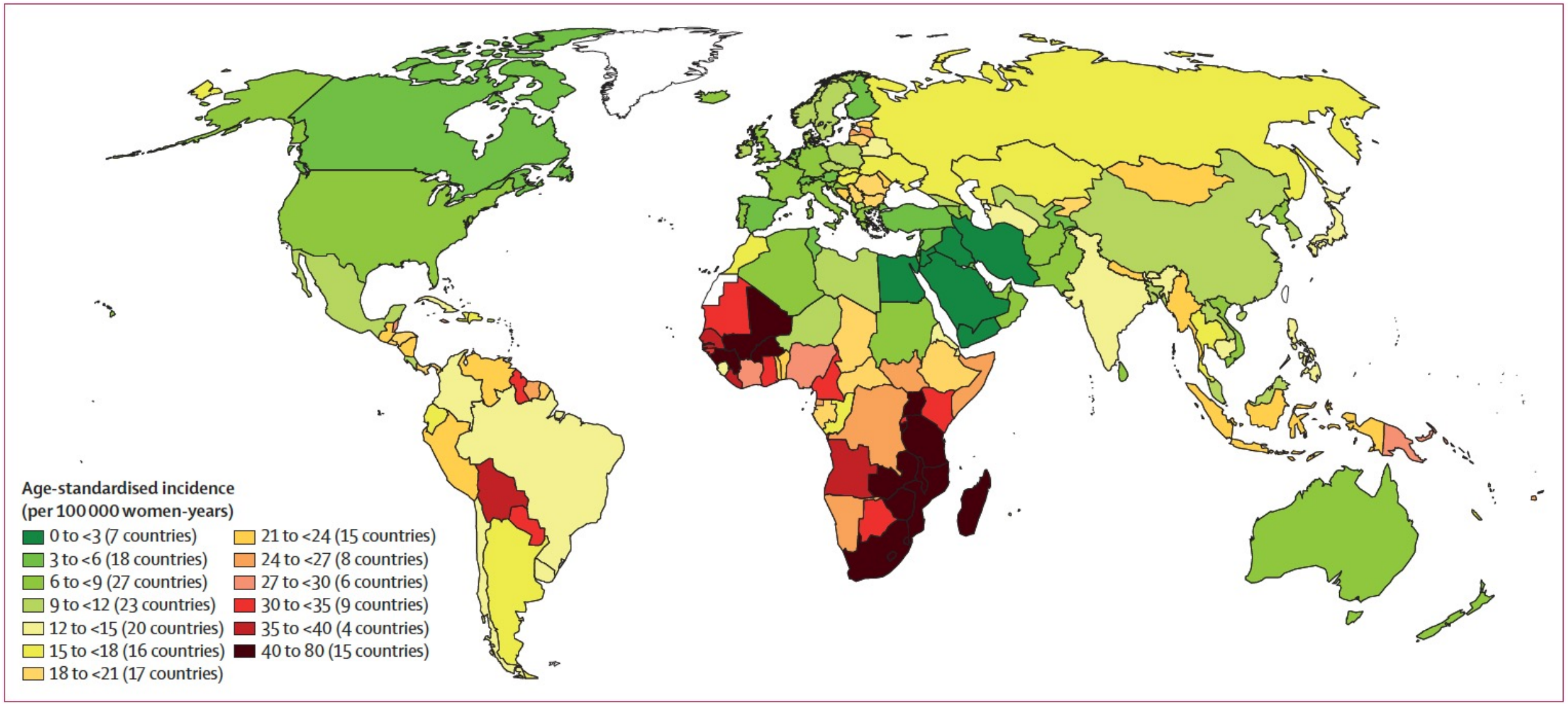


Figure 1: Geographical distribution of world age-standardised incidence of cervical cancer by country, estimated for 2018

The Lancet Global Health
2020;8:E191-E203

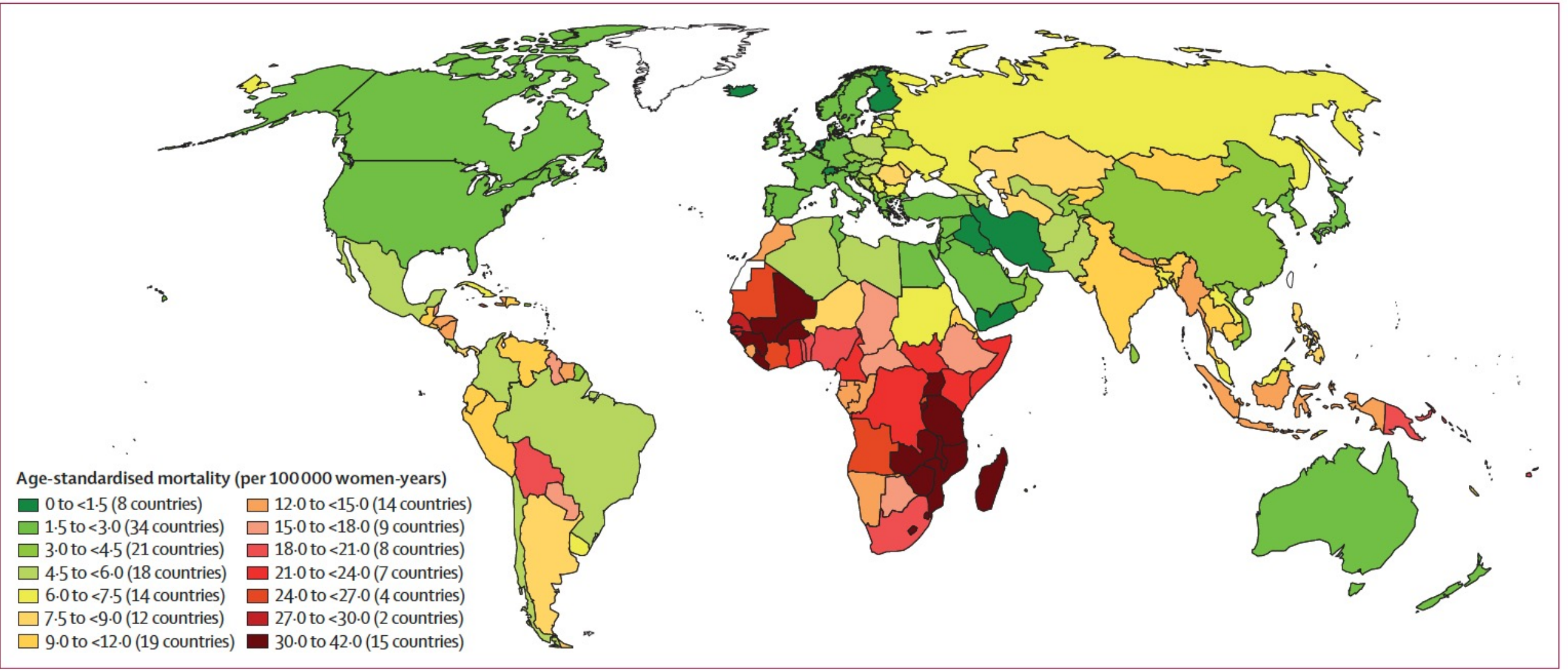


Figure 2: Geographical distribution of world age-standardised mortality rate of cervical cancer by country, estimated for 2018

The Lancet Global Health
2020;8:E191-E203

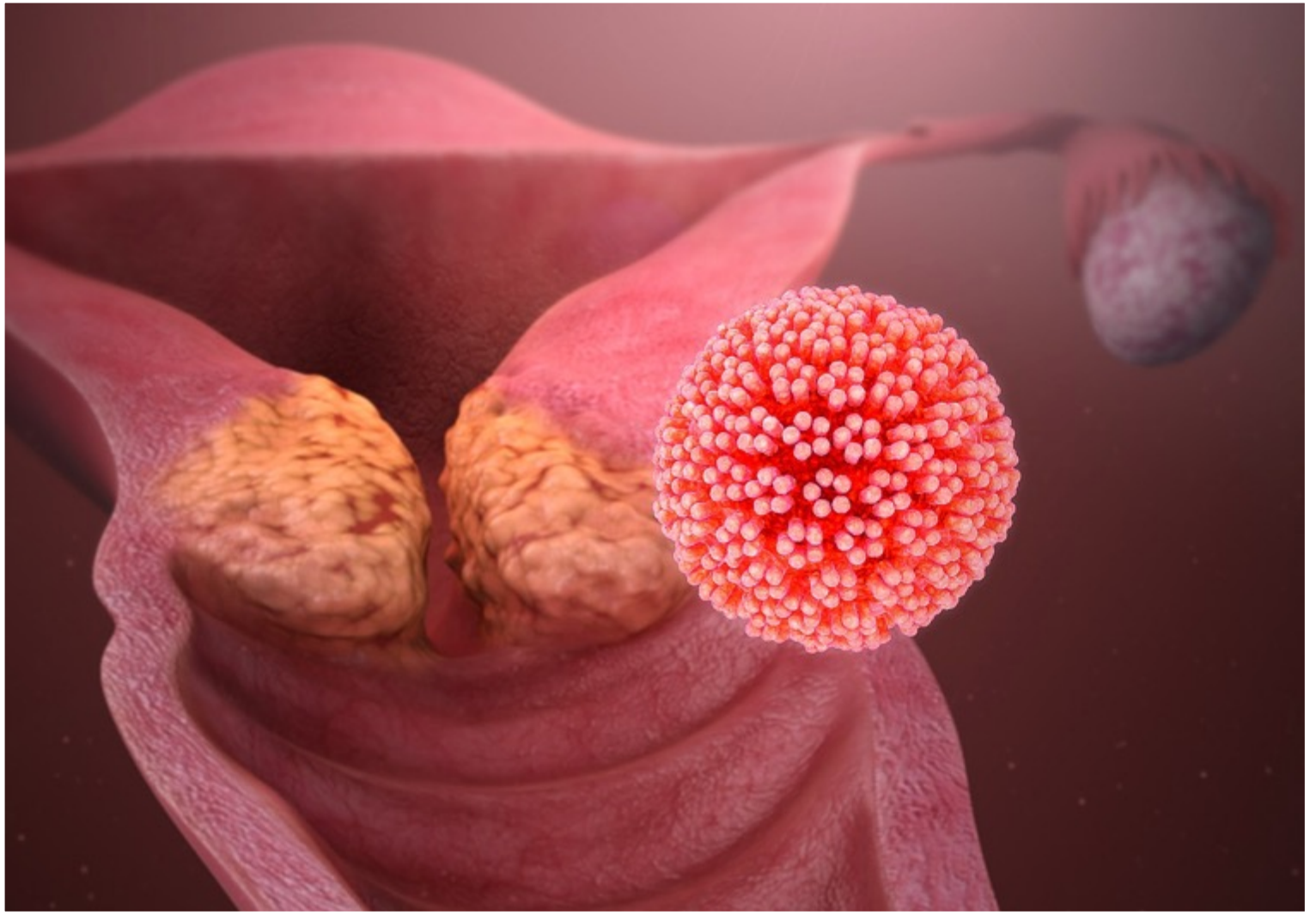
HPV

Cervical epithelial pathology dominated by the neoplastic consequences of HPV infection

- Over 200 HPV genotypes recognised
- At least 12 definite and 13 probable/possible oncogenic types

Commonest causing cancer:

- HPV16 and 18, followed by 31, 33, 35, 39, 45, 51, 52 and 58
- Also the most prevalent
- Glandular neoplasia is dominated by HPV 18, 16, 45



Source:	www.scientificanimations.com, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons

WHO global cervical cancer elimination initiative, 2018

World Health Organization

- **Eliminate cervical cancer as a public health problem when all countries reach an incidence < 4 cases per 100 000 women years**
- Aim: Within the lifetime of today's young girls

3 pillars:

Prevent

Screen

Treat

To reach elimination by the end of the century, targets for 2030:

- **90%** coverage HPV vaccination of girls (by 15 y.o)
- **70%** coverage of screening with a high-precision test (35-45 y.o)
- **90%** treatment of precancerous & invasive lesions

WHO global cervical cancer elimination initiative, 2018

World Health Organization

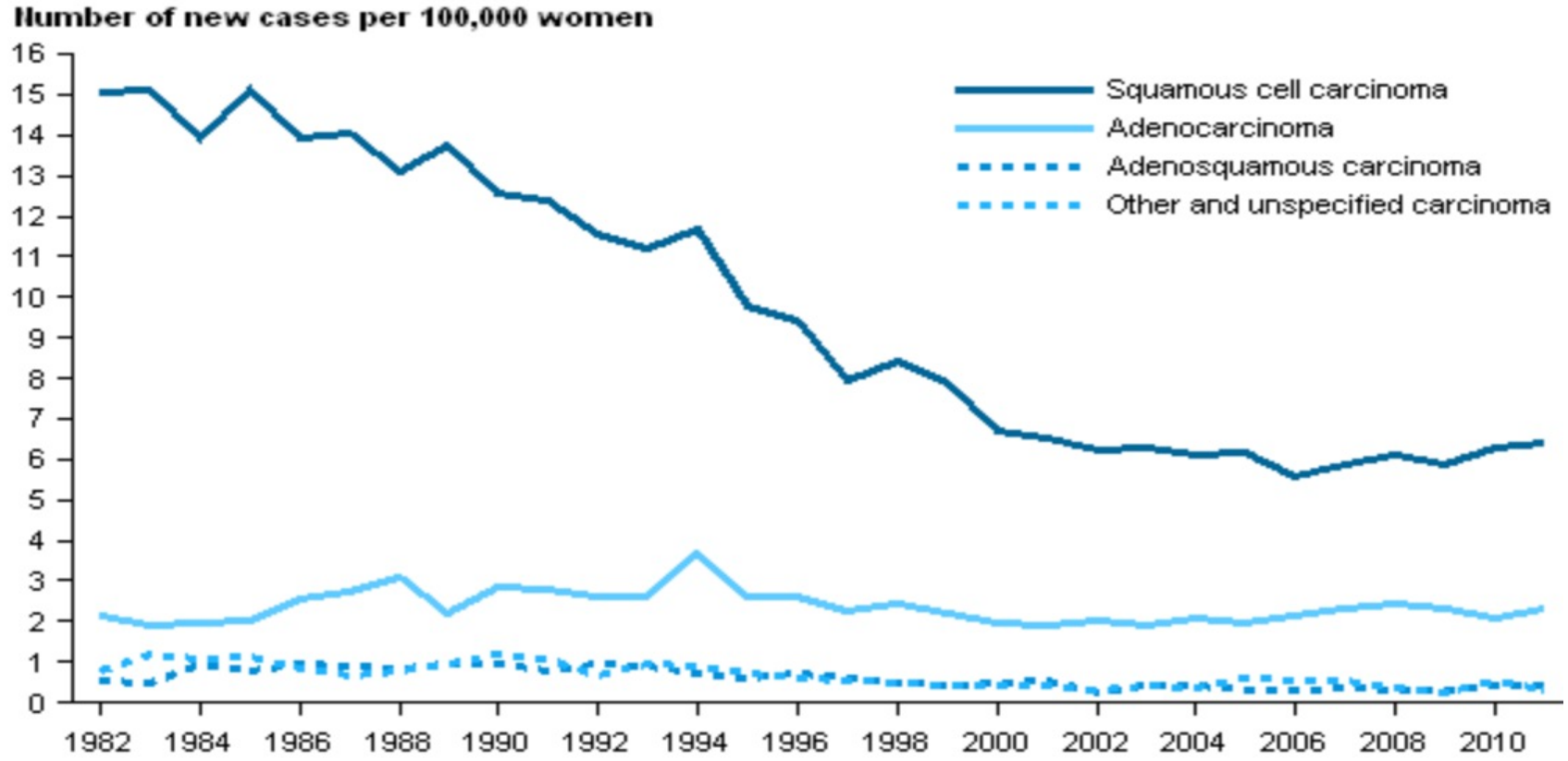
Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries

Marc Brisson*, Jane J Kim*, Karen Canfell*, Mélanie Drolet, Guillaume Gingras, Emily A Burger, Dave Martin, Kate T Simms, Élodie Bénard, Marie-Claude Boily, Stephen Sy, Catherine Regan, Adam Keane, Michael Caruana, Diep T N Nguyen, Megan A Smith, Jean-François Laprise, Mark Jit, Michel Alary, Freddie Bray, Elena Fidarova, Fayad Elsheikh, Paul J N Bloem, Nathalie Broutet, Raymond Hutubessy

Lancet 2020;395:575-590

- High rates of HPV vaccination of girls can lead to cervical cancer elimination in most low- and middle-income countries by the end of the century
- A high uptake of twice-lifetime screening will be necessary to achieve elimination in countries with the highest disease burden

Incidence carcinoma cervix in Australia



SQUAMOUS

89% (1982)

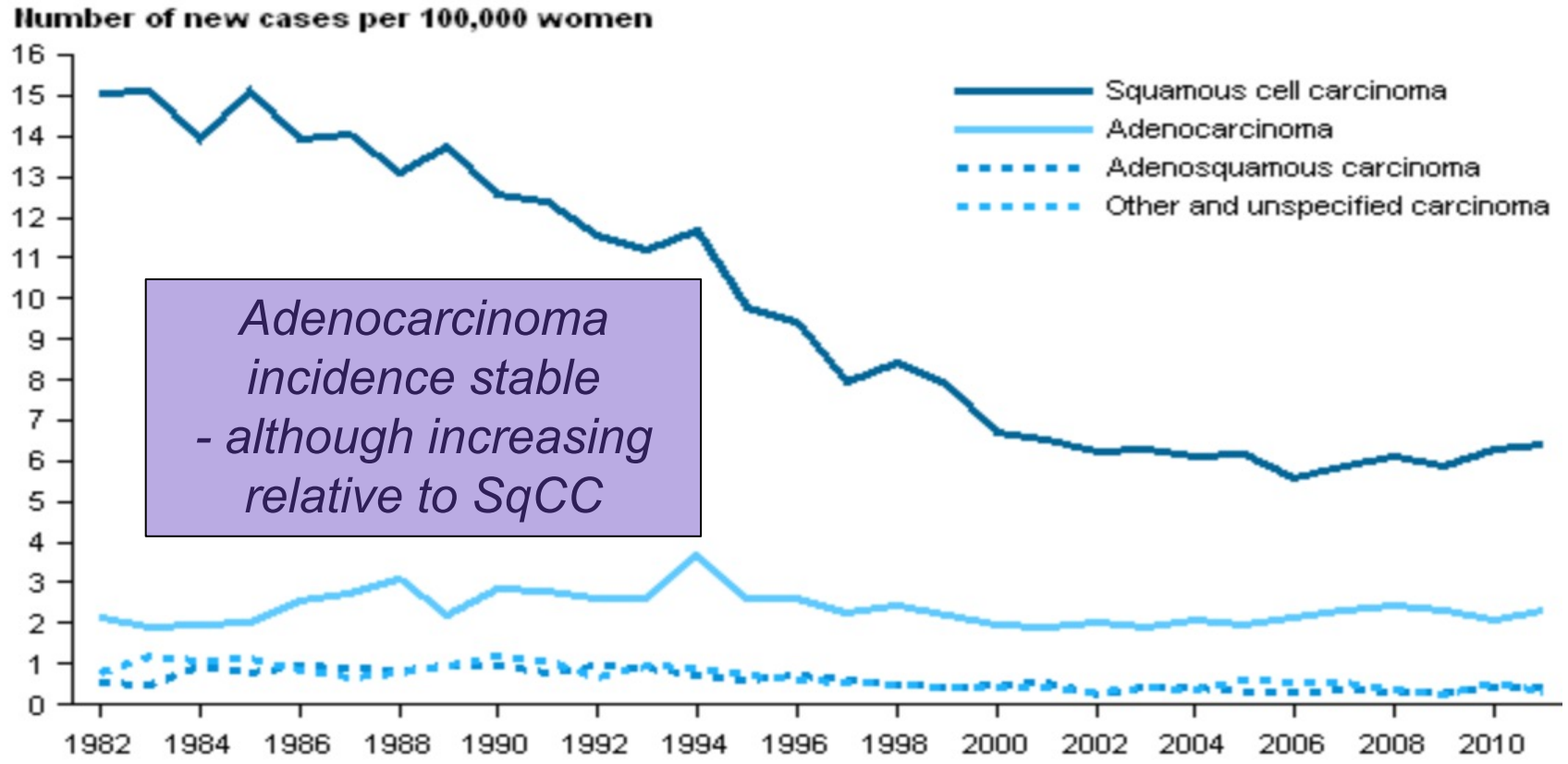
↓

68% (2019)

% of all cancer cervix

AIHW analysis of the Australian Cancer Database 2011

Incidence carcinoma cervix in Australia



ADENOCARCINOMA

RARE

↓

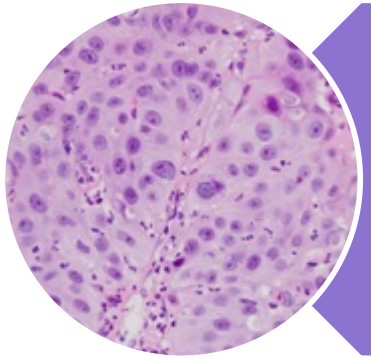
24% (2019)

.....

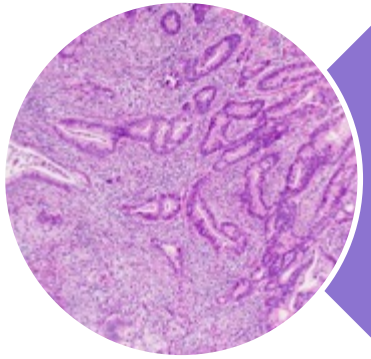
Not impacted by cervical screening

AIHW analysis of the Australian Cancer Database 2011

Worldwide since 1970s



SCC



Adenoca

up to 25%
all cx cancer

Increased incidence adenocarcinoma particularly in women <55

- **INCREASED EXPOSURE TO HPV**
  - Birth-cohort effect, post 1960s
- **INCREASED DETECTION**
  - Improved endocervical sampling devices
  - Increased recognition of AIS cytologically
  - LBC – greater sensitivity for glandular lesions
  - Improved histological Dx → Better data

Smith et al. Gynecol Oncol 2000;78:97-105

Shiliang et al. CMAJ 2001;164:1151-1152

Wang et al. Cancer 2004;100:1035-44

Bray et al. Cancer Epidemiol Biomarkers Prev 2005;12:2191-9

Adegoke et al. J Womens Health 2012;21:1031-37

Van der Horst et al. Cancer Medicine 2017;6:416-2

Epidemiology will continue to change

Australia 2017: Renewal of National Cervical Screening Program

- HPV based primary screening with partial genotyping - more sensitive test
- *Increased detection of HPV-associated glandular lesions*

HPV vaccine

- 2007: 4-valent women 12-26; boys from 2013; 9-valent 2018
- Decreased prevalence of HSIL <20, 20-24, 25-29 y.o.

Brotherton et al Cancer Causes Control 2015;26:953-954

- Decreased in incidence of AIS in women 21-24 recently reported

Cleveland AA et al Int J Cancer 2020;146:810-818

- *Anticipate decrease in prevalence of HPV-associated adenocarcinoma*

CLASSIFICATION

HPV

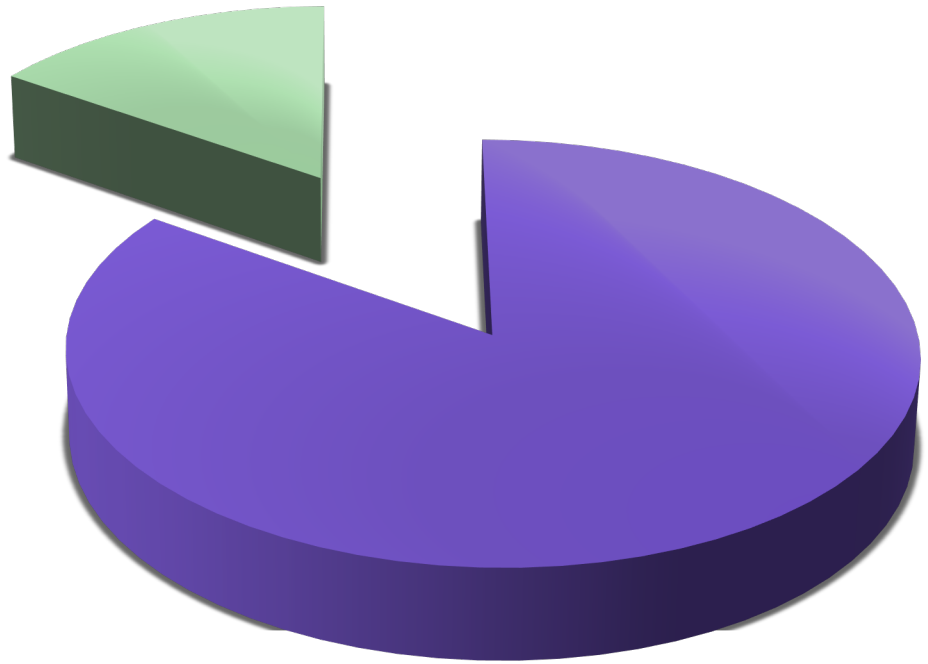
SCC:

- Almost all HPV-A
- Rare HPV-I SCC described
- No evidence that an HPV-I squamous precursor exists

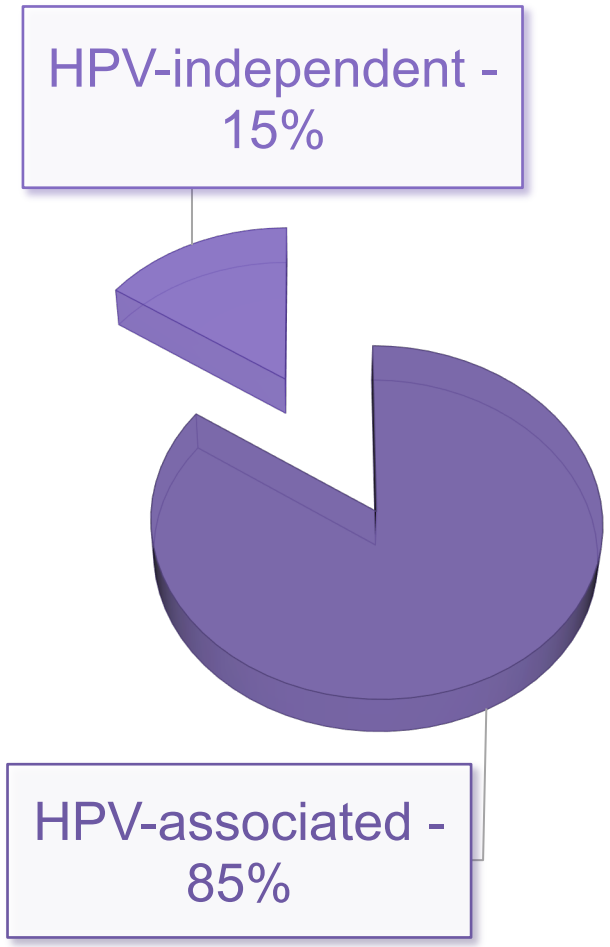
Adenocarcinoma:

- Most HPV-A
- Significant minority are NOT

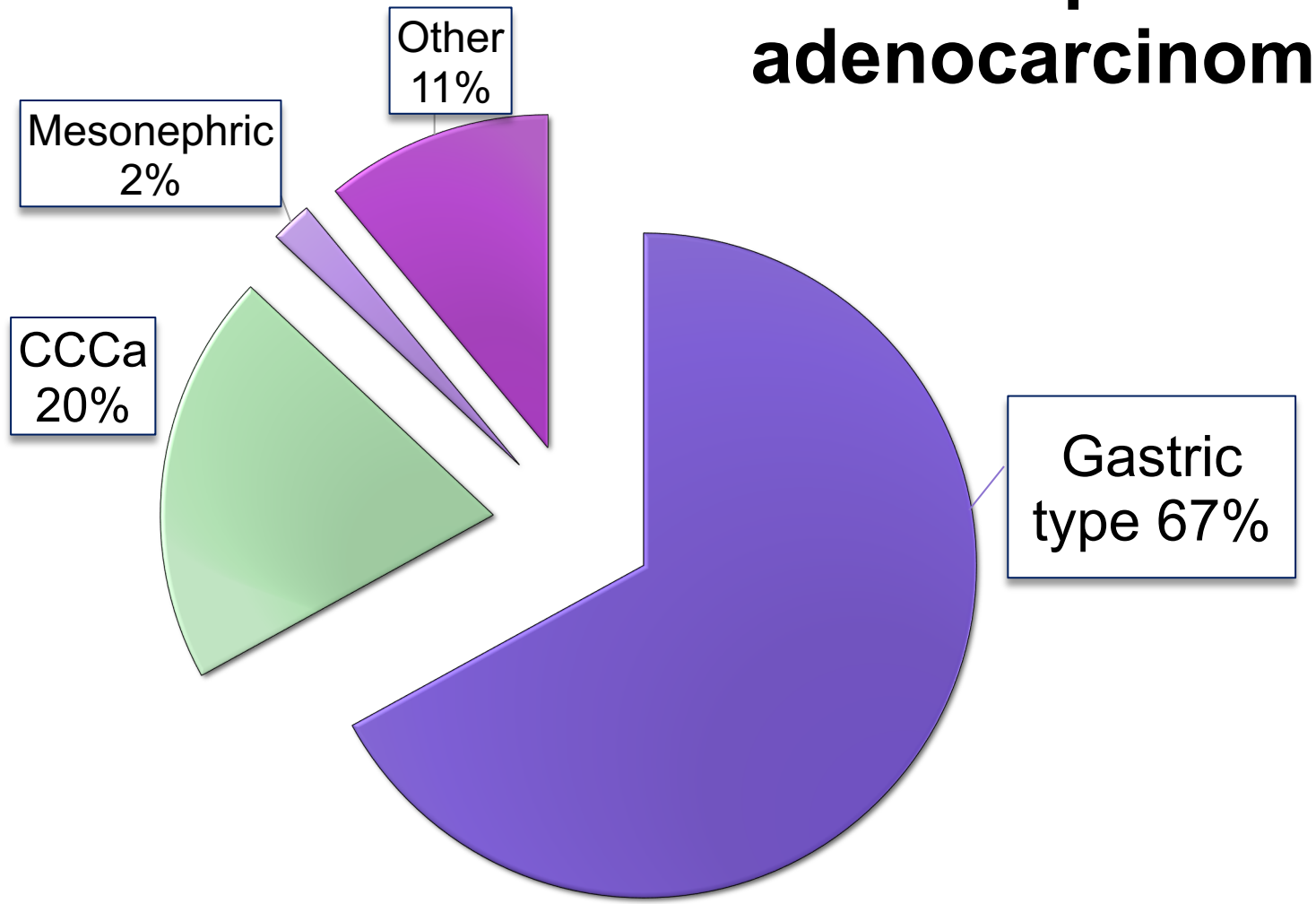
As in other body sites these HPV-independent carcinomas are generally more aggressive than HPV-associated



All adenocarcinoma

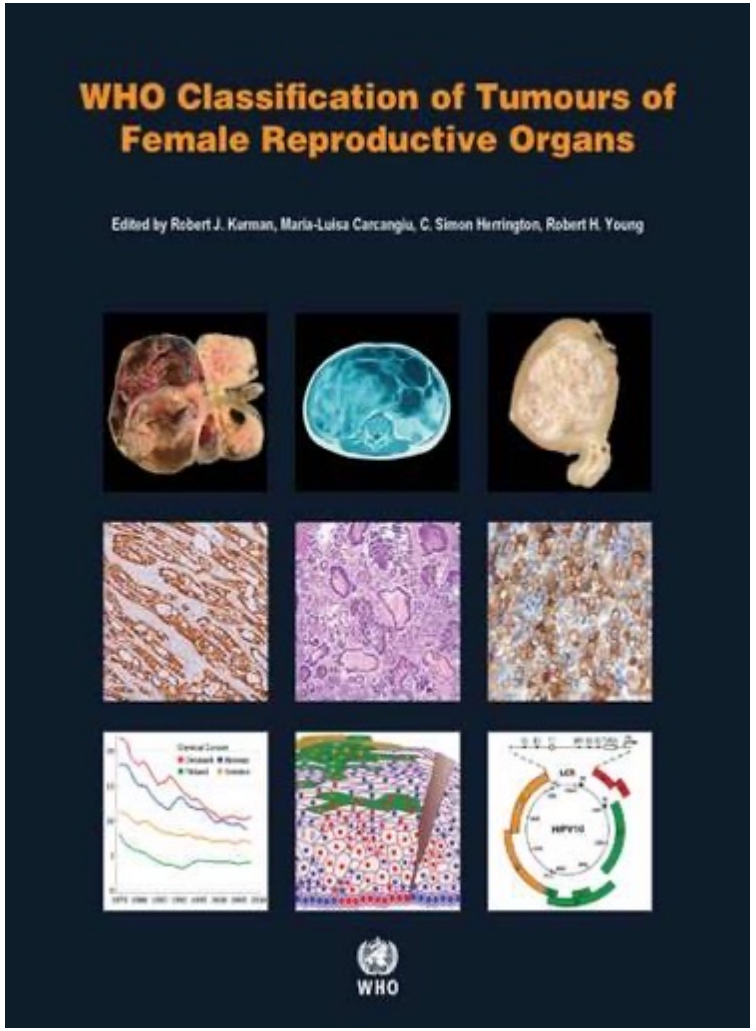


HPV-independent adenocarcinoma



Stolnicu et al
AJSP 2018;42:214-226

WHO 2014



Epithelial tumours

Adenocarcinoma

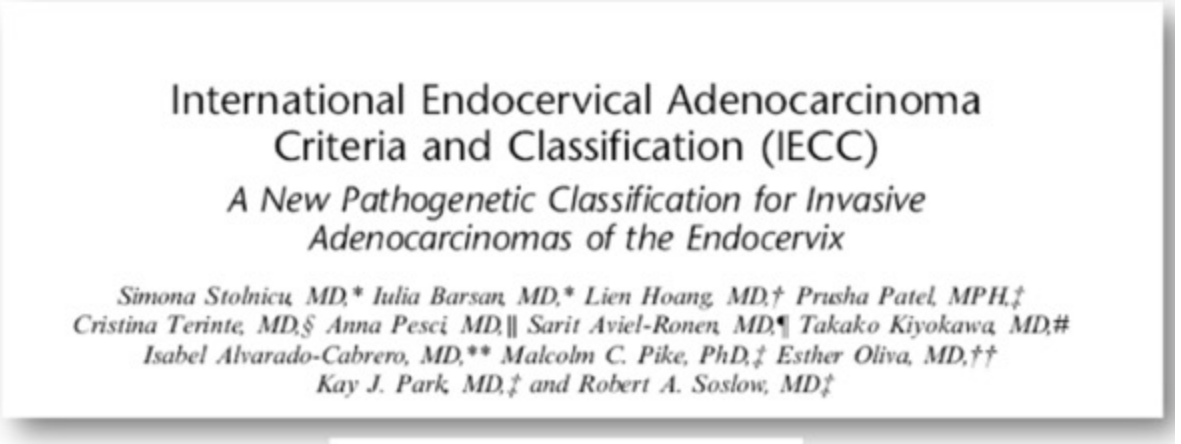
-
-
-
-
-
-
- Adenocarcinoma admixed with neuroendocrine carcinoma

Based on morphology – architecture, mucin

Not very reproducible

Lacks clinical relevance

International Endocervical Criteria and Classification (IECC) & 2020 WHO



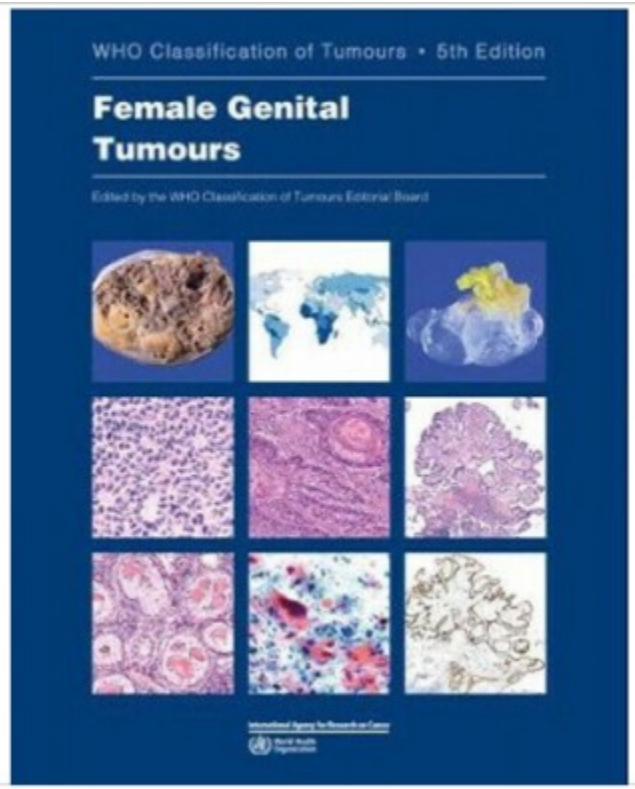
International Endocervical Adenocarcinoma Criteria and Classification (IECC)

A New Pathogenetic Classification for Invasive Adenocarcinomas of the Endocervix

Simona Stolnicu, MD, Iulia Barsan, MD,* Lien Hoang, MD,† Prusha Patel, MPH,‡ Cristina Terinte, MD,§ Anna Pesci, MD,‖ Sarit Aviel-Ronen, MD,¶ Takako Kiyokawa, MD,# Isabel Alvarado-Cabrero, MD,** Malcolm C. Pike, PhD,‡ Esther Oliva, MD,†† Kay J. Park, MD,‡ and Robert A. Soslow, MD‡*

Am J Surg Pathol • Volume 42, Number 2, February 2018

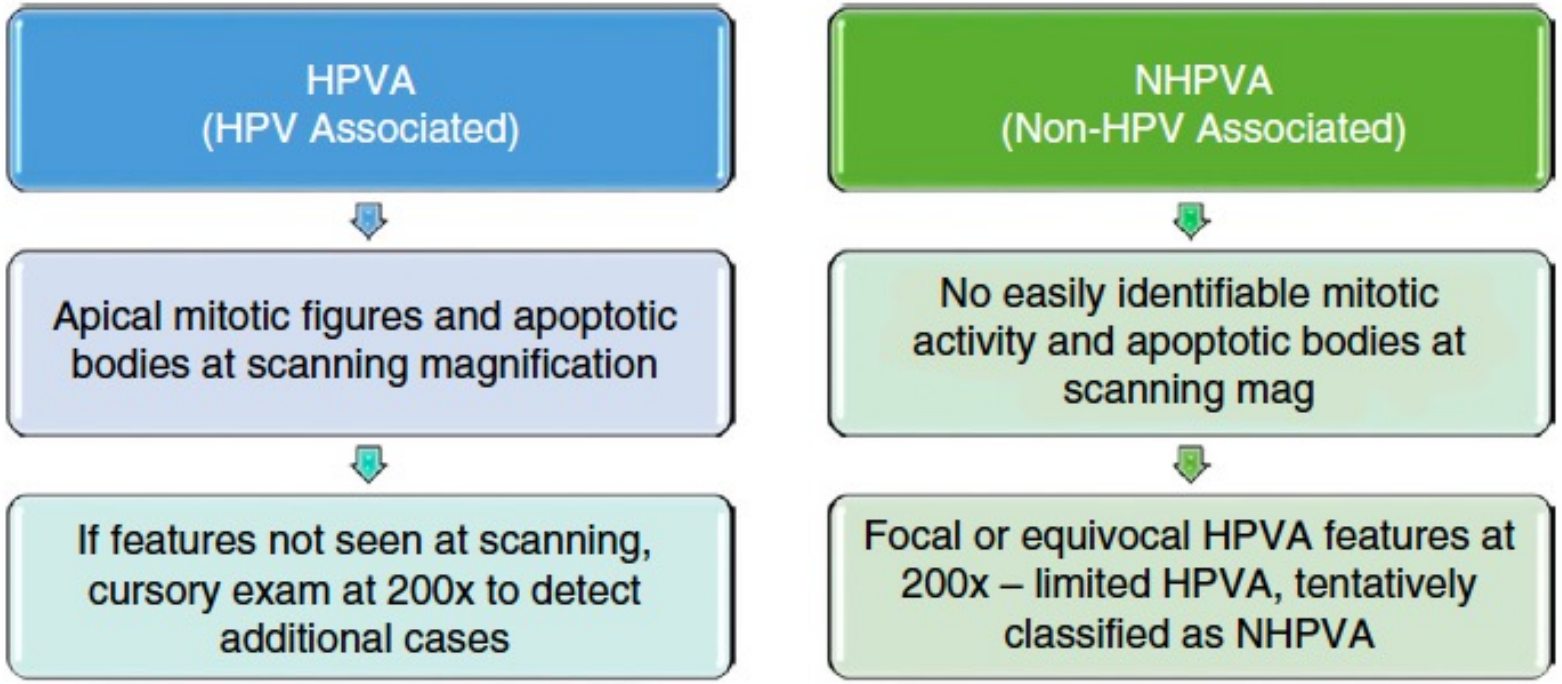
- Links etiology to morphology using presence of luminal mitoses and apoptoses as surrogate markers of an HPV-related tumour
  - Correlates with p16, HPV status
  - Correlates with clinical - prognosis, response to Rx
- Superior interobserver agreement among pathologists



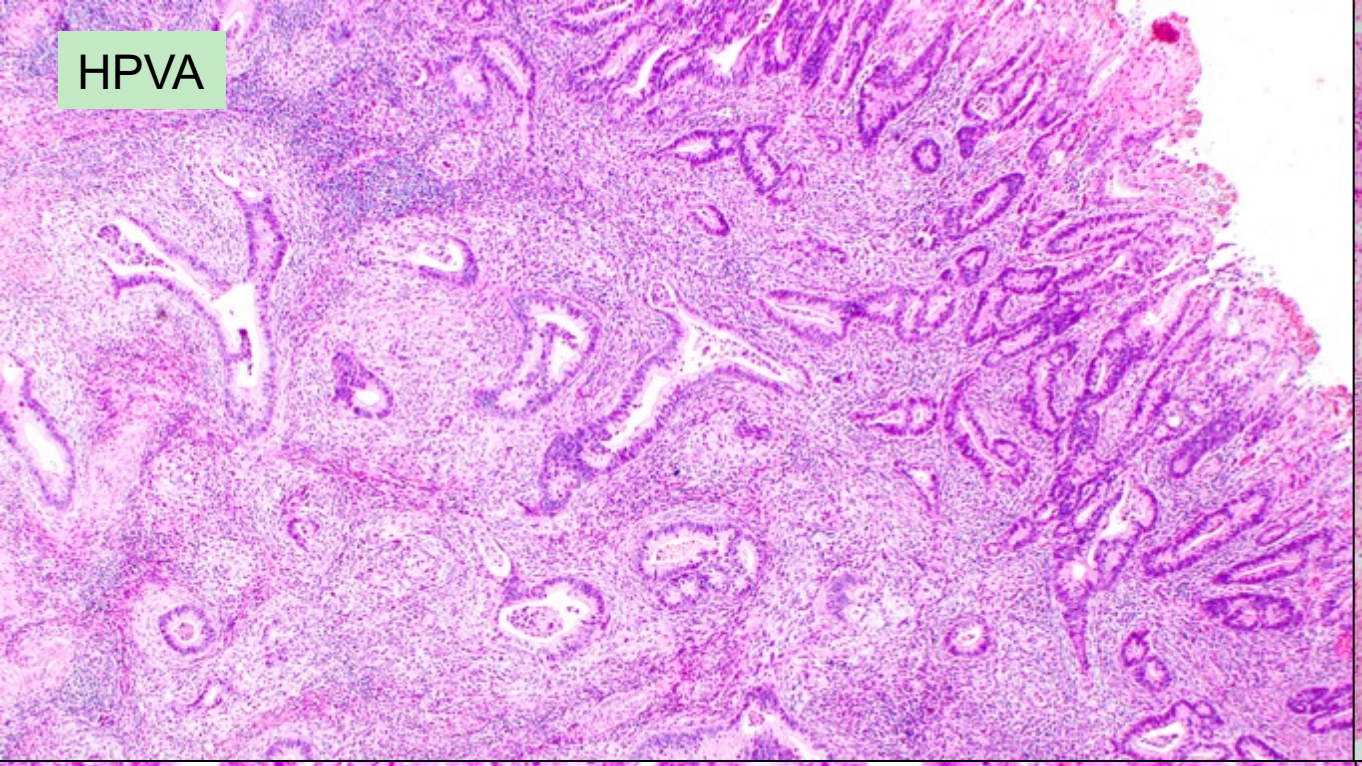
More biologically significant and more relevant for treatment purposes

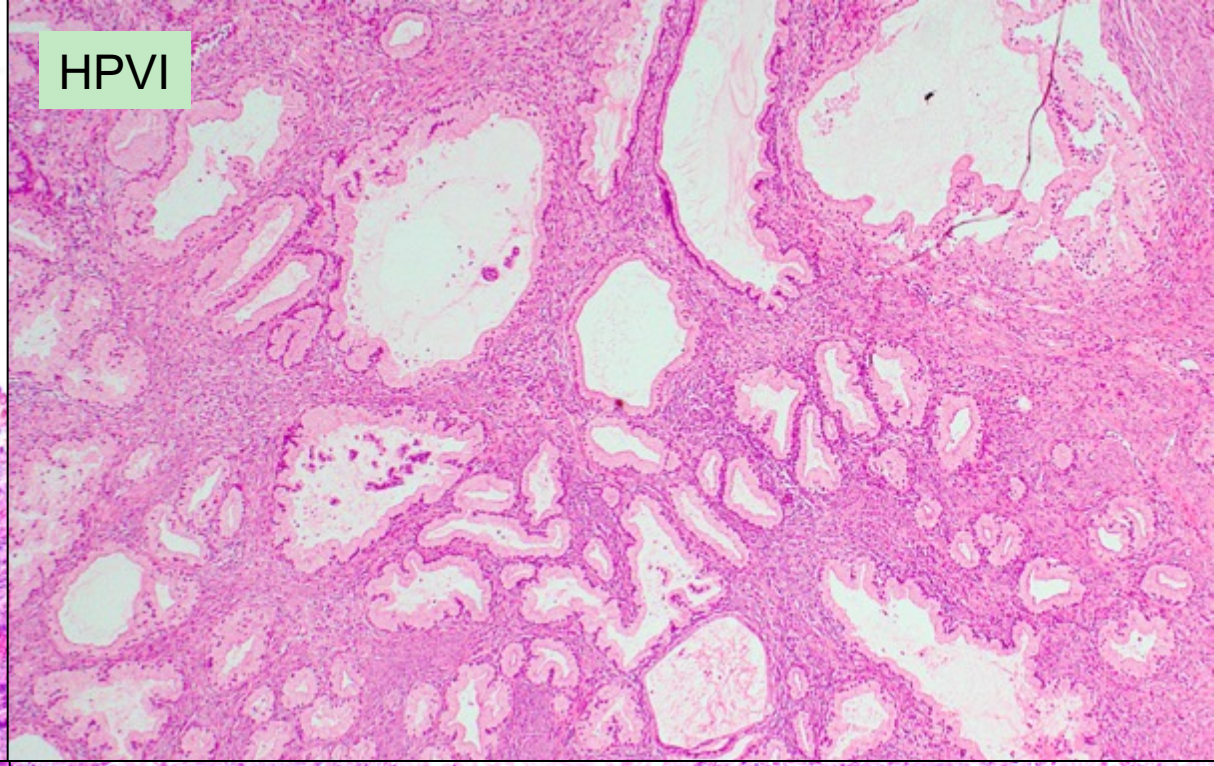
IECC

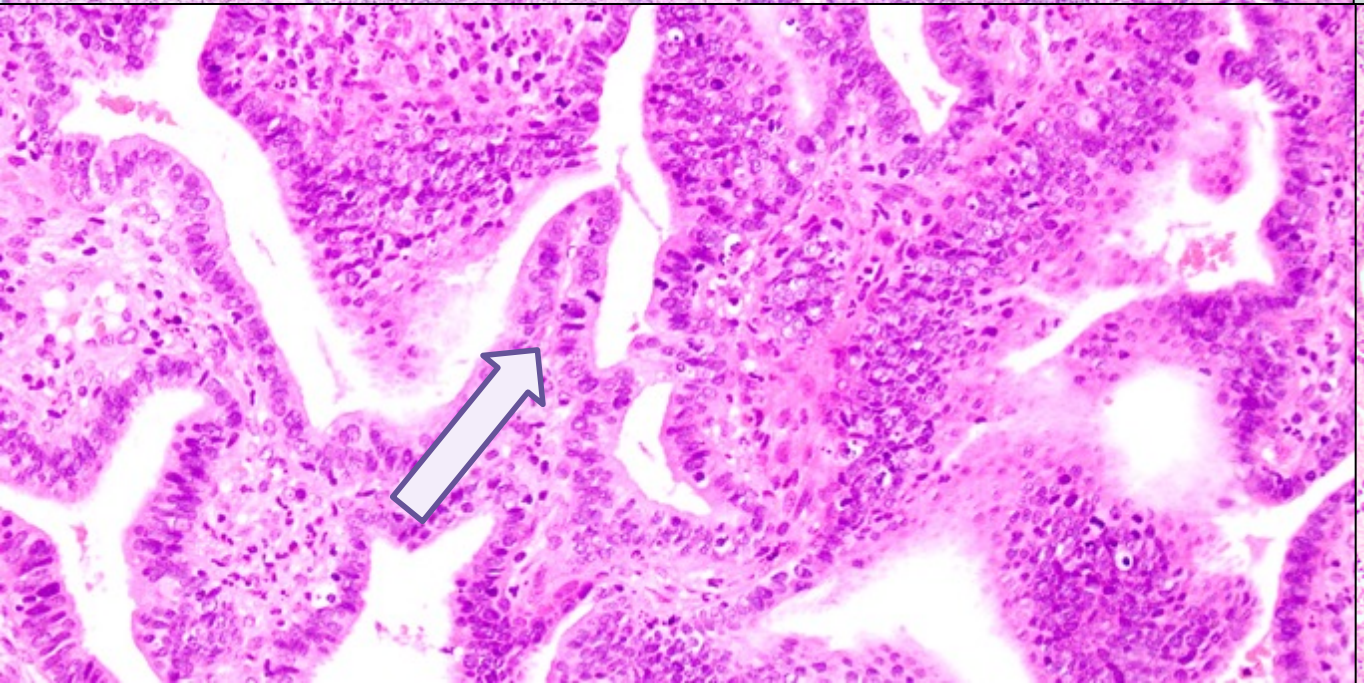
- Mitoses and apoptotic bodies identified using 4x - 10x objective
- If easily found, likely HPVA
- If absent or found with difficulty and at high magnification, likely HPVI

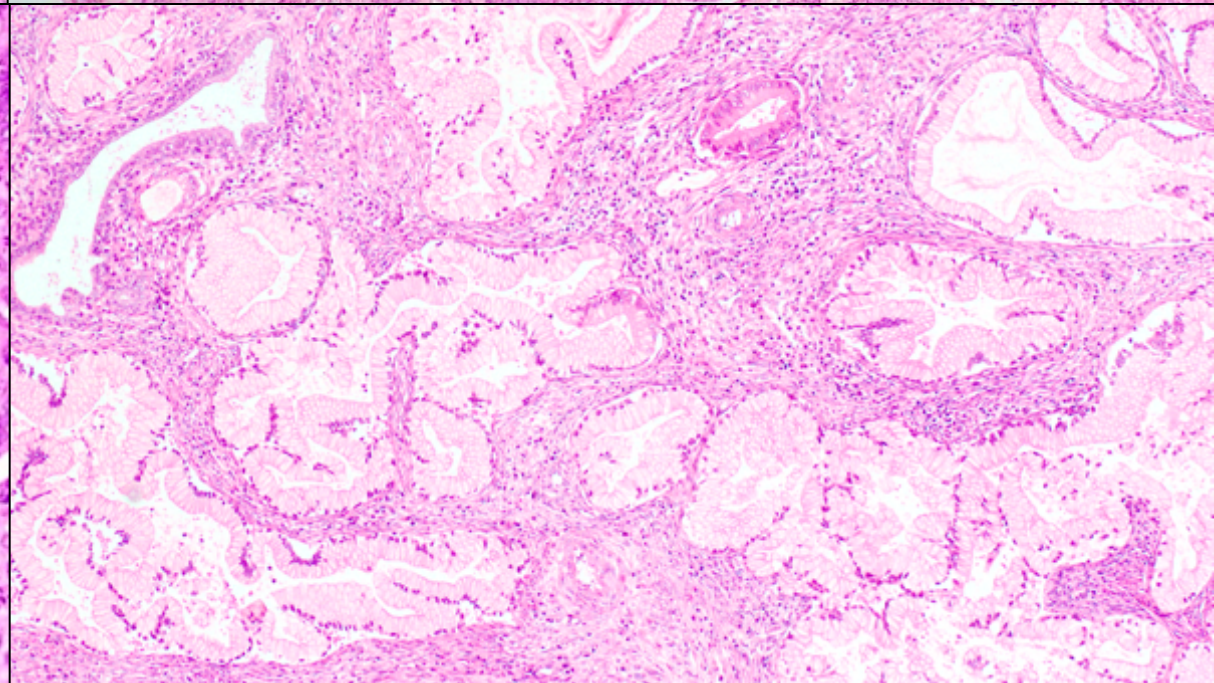


Park KY
Histopathology
2020;76:112-127


HPVA


HPVI





2020 WHO

HPV-associated adenocarcinoma	**HPV-independent adenocarcinoma**
Usual type ~ 75% all adenocarcinoma • Villoglandula Mucinous type • Mucinous NC • Intestinal adenocarcinoma • Signet-ring cell adenocarcinoma • Invasive stratified mucinous carcinoma	Gastric type ma ving cervix - Adenocarcinoma NOS

Neuroendocrine carcinoma and carcinoma admixed with NEC is now covered in a dedicated chapter

2020 WHO

HPV-associated adenocarcinoma - Usual type

~ 75% all adenocarcinoma

Cells with cytoplasmic mucin constitute 0-50% of the tumour

- Includes the newly recognised “micropapillary adenocarcinoma”
- *Villoglandular variant*
  - Rare, characterised by exophytic papillary growth, minimal/absent invasion of underlying cervical stromal

2020 WHO

HPV-associated adenocarcinoma - Mucinous type

~ 10% all adenocarcinoma

Cells with intracytoplasmic mucin constitute ≥ 50% of the tumour

- *Mucinous NOS adenocarcinoma*
  - Mucinous cytoplasm resembling normal endocervix
- *Intestinal adenocarcinoma*
  - Goblet cells and or enteroendocrine cells ≥50% of the tumour
- *Signet-ring cell adenocarcinoma*
  - Signet ring cells ≥50% of the tumour
- *Invasive stratified mucinous carcinoma*
  - Invasive nests of stratified epithelium with cytoplasmic mucin

2020 WHO

HPV-associated AIS	**HPV-independent AIS**
AIS (usual type) SMILE Acceptable: *“High-grade cervical glandular intraepithelial neoplasia” / HCGIN* Avoid: *“Glandular atypia”* *“Glandular dysplasia” / LCGIN*	Gastric-type AIS Atypical LEGH

Recommendations for Classification

Classify according to WHO 2020, which incorporates IECC

- Both systems classify into HPVA and HPVI using morphology alone

Only H&E slides required, avoids need for additional tests

- Ancillary testing (such as p16) does not need to be reflexively performed as morphology tightly linked to HPV status; reserve for difficult / ambiguous cases
- RNA-based ISH for HRHPV is more sensitive and specific compared with HPV DNA PCR and may also have superior sensitivity, specificity and positive and negative predictive value compared with p16 in identifying HPVA endocervical adenocarcinoma

If interpretation is difficult, a diagnostic algorithm based on the amount of cytoplasmic mucin and other ancillary tests may be useful

Diagnostic Algorithmic Proposal Based on Comprehensive Immunohistochemical Evaluation of 297 Invasive Endocervical Adenocarcinomas

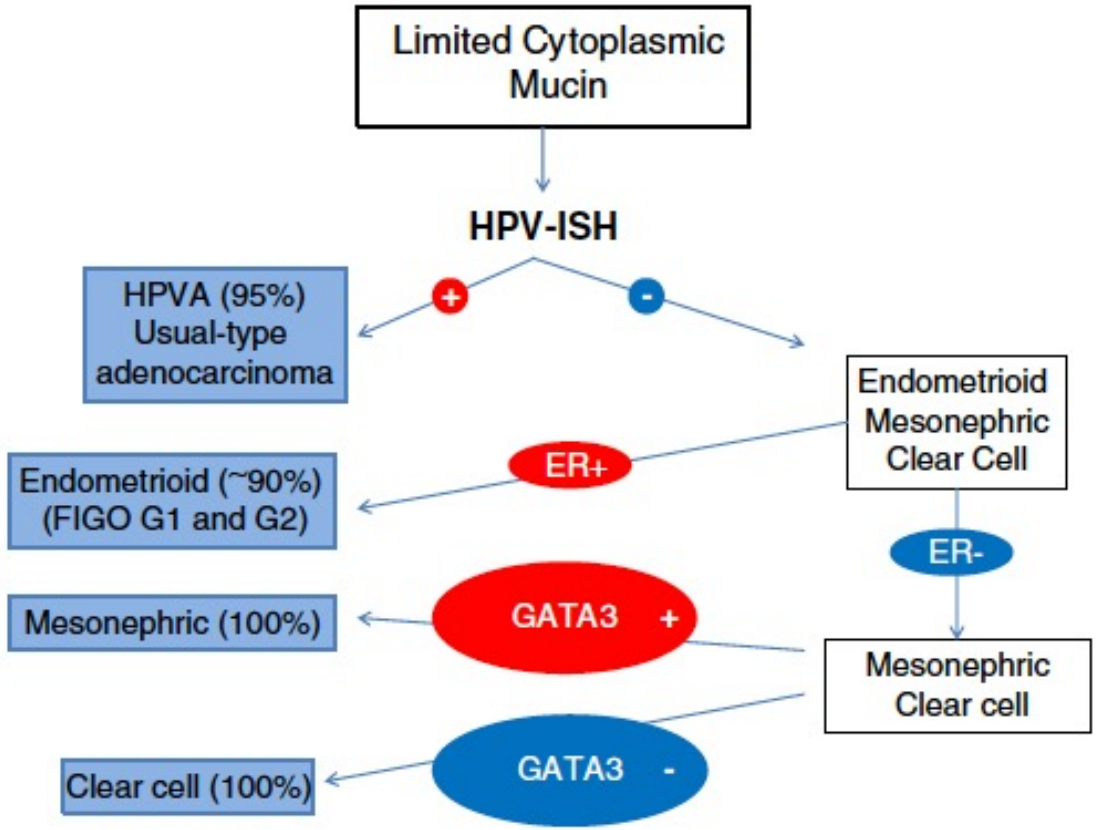


FIGURE 6. IHC algorithm for ECAs with limited cytoplasmic mucin. FIGO indicates International Federation of Gynaecology and Obstetrics.

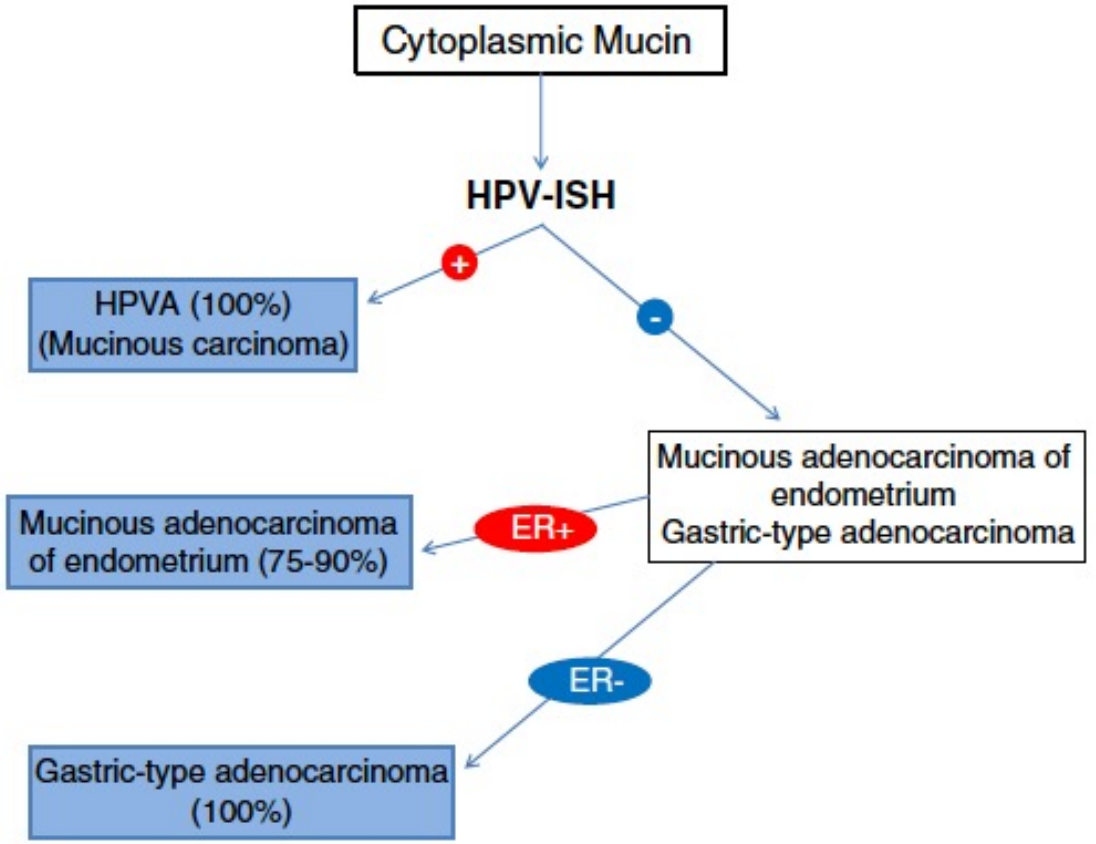
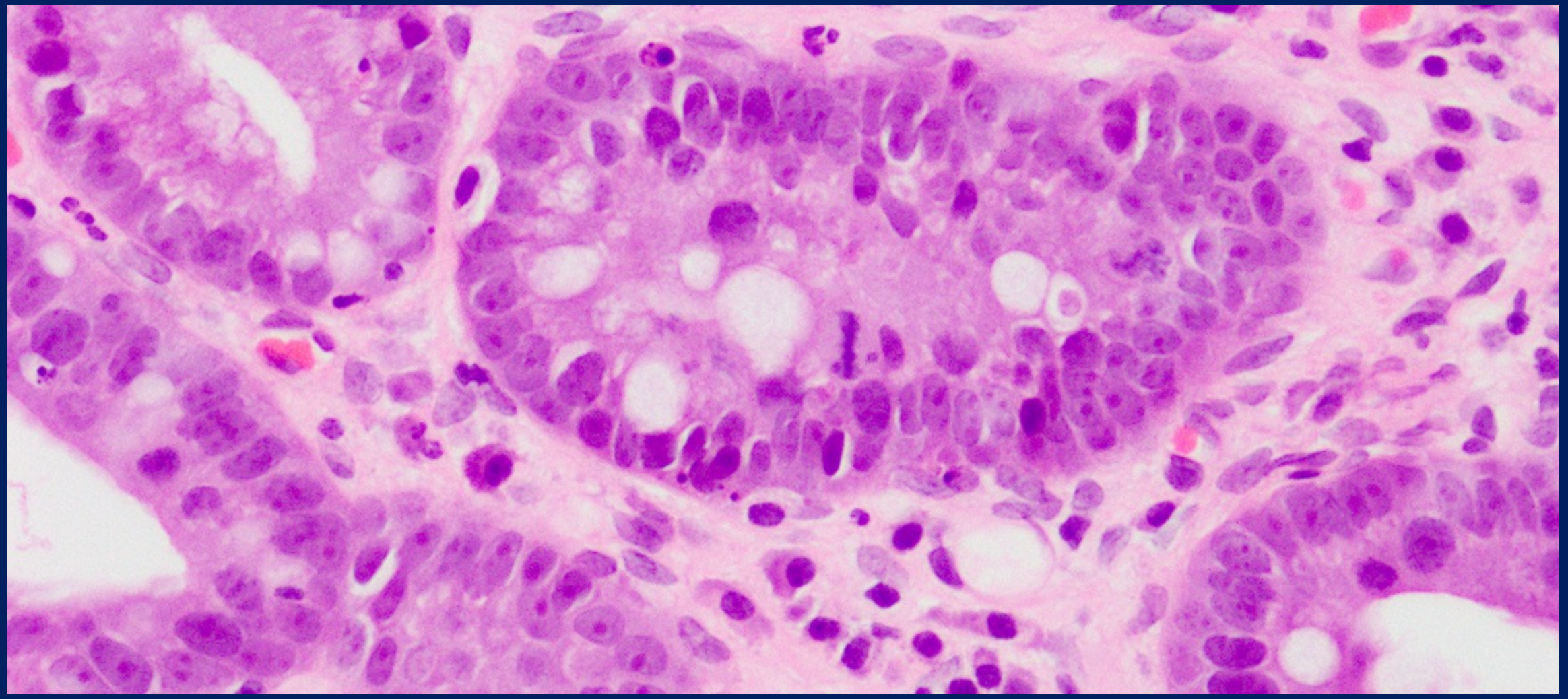


FIGURE 7. IHC algorithm for ECAs containing obvious cytoplasmic mucin.

MORPHOLOGY

HPV associated AIS

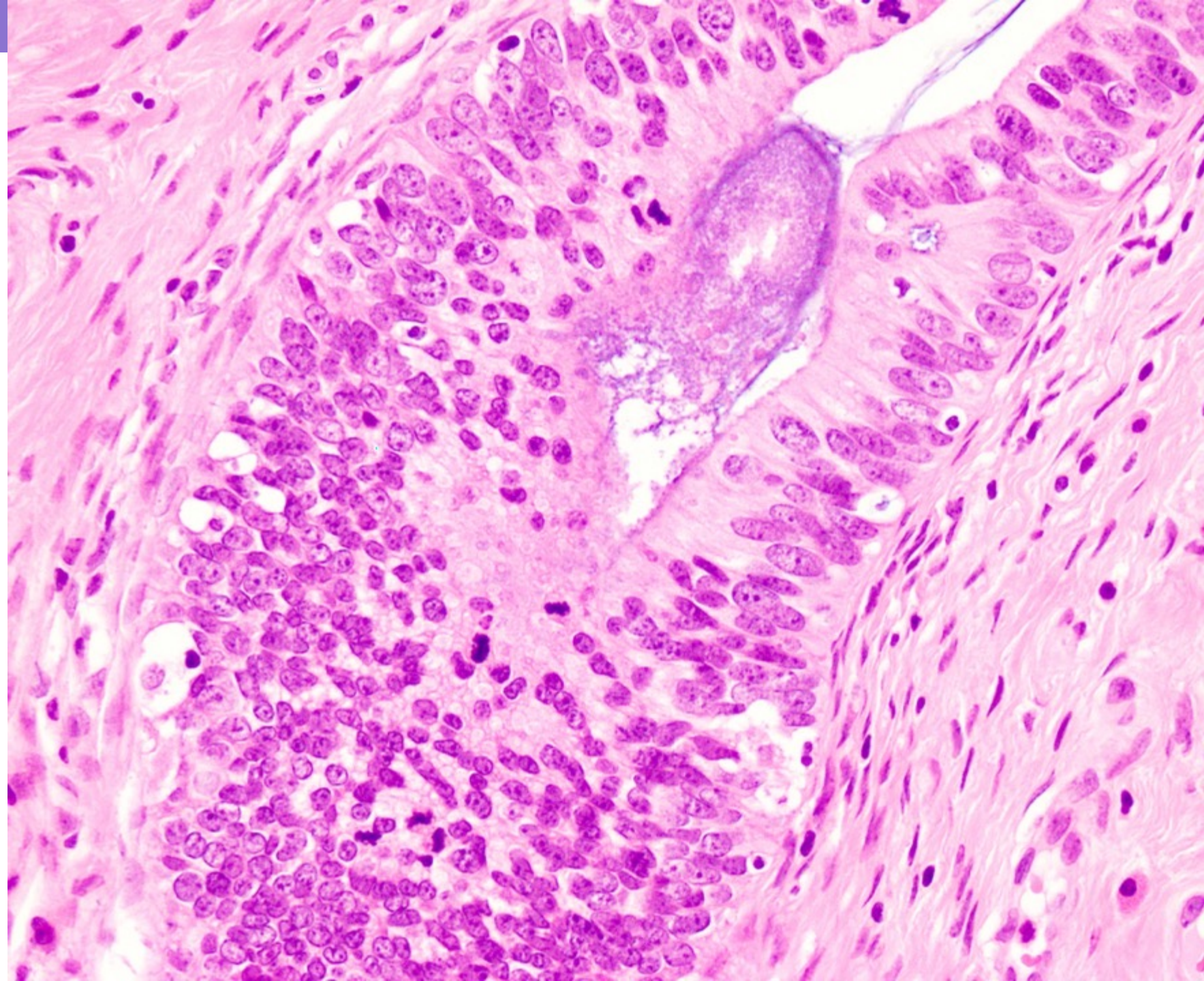


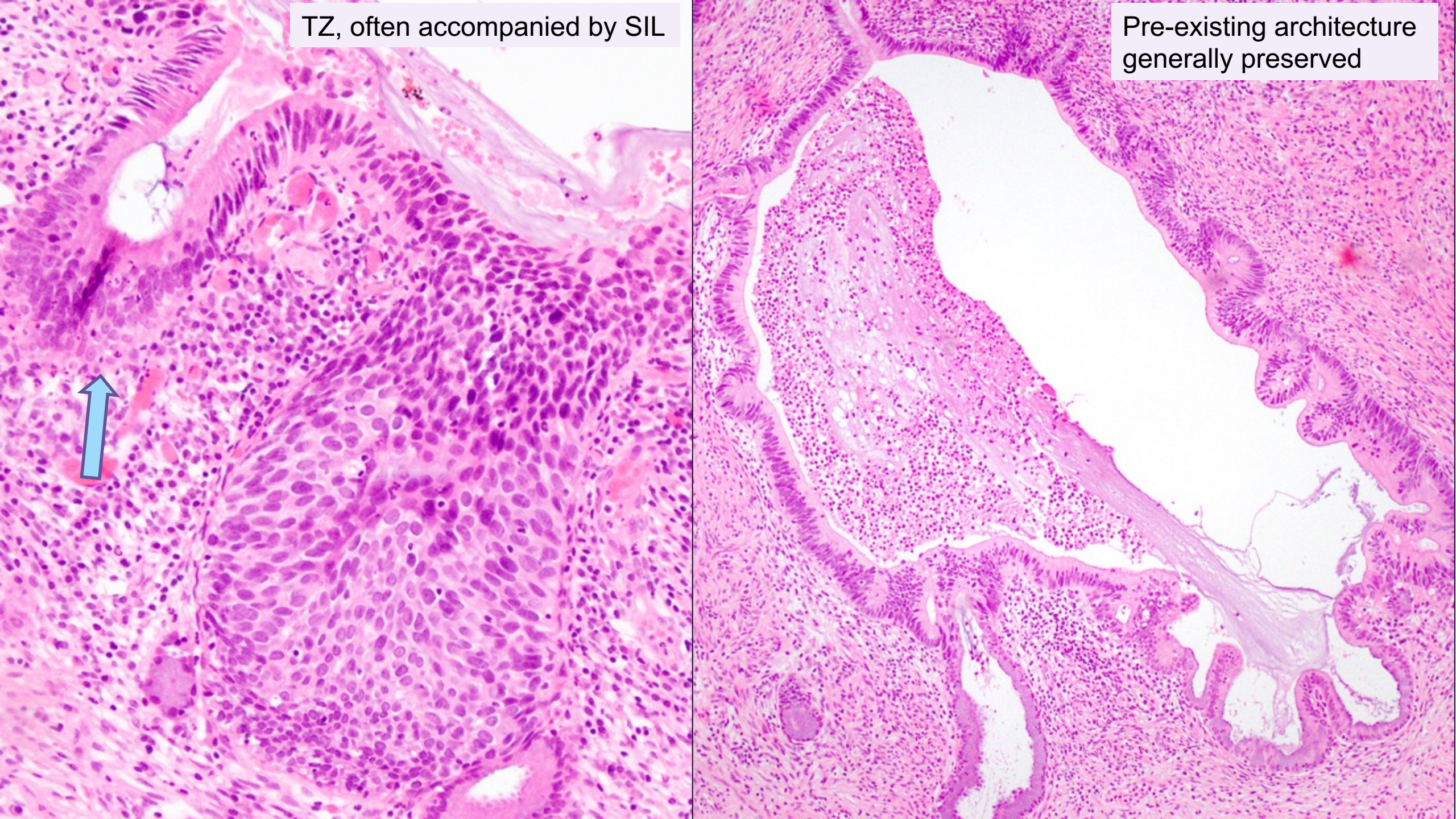
Clinical

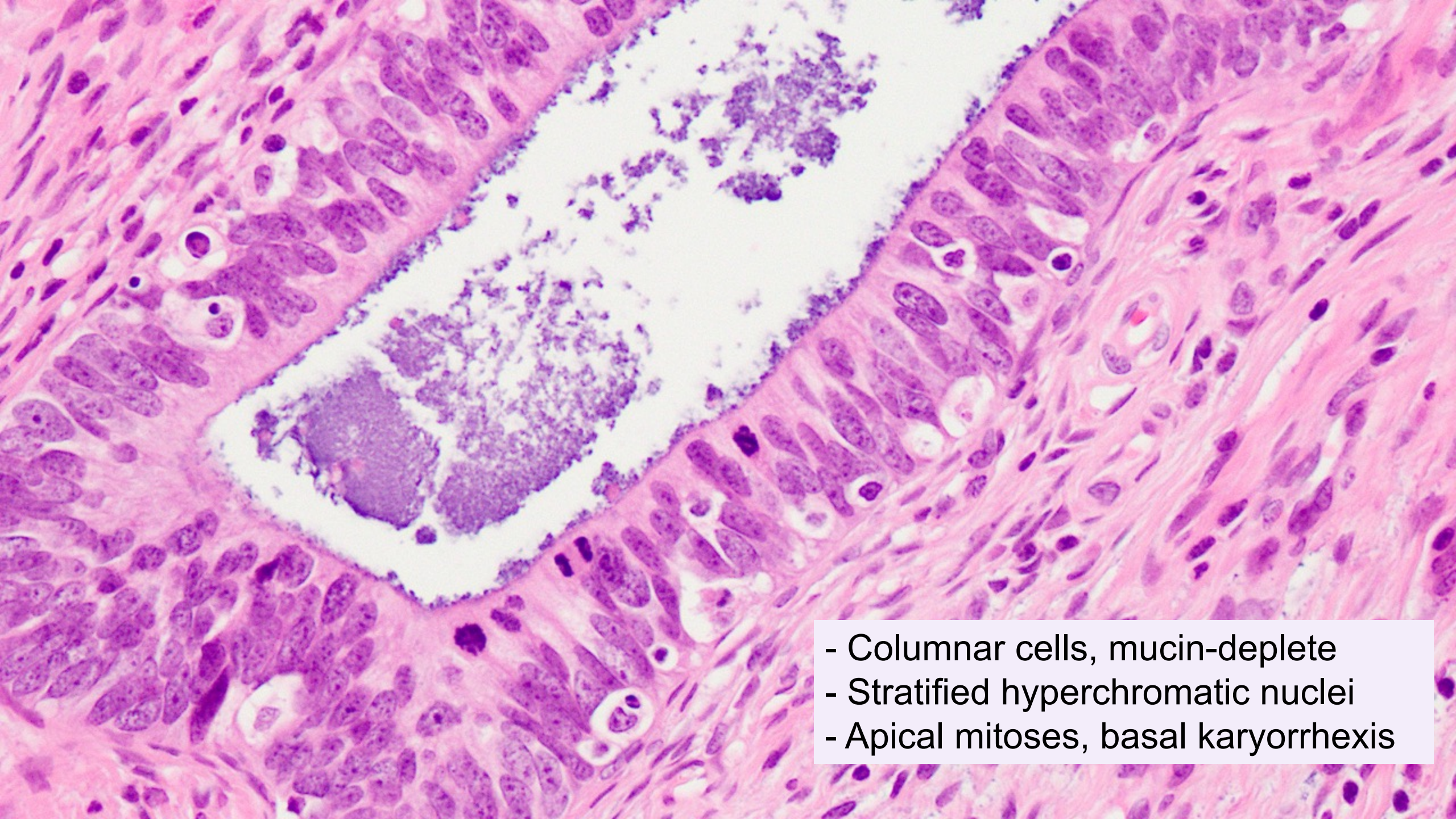
- Mean 40 years
- Usually asymptomatic, detected at cervical screening
- Often associated HSIL

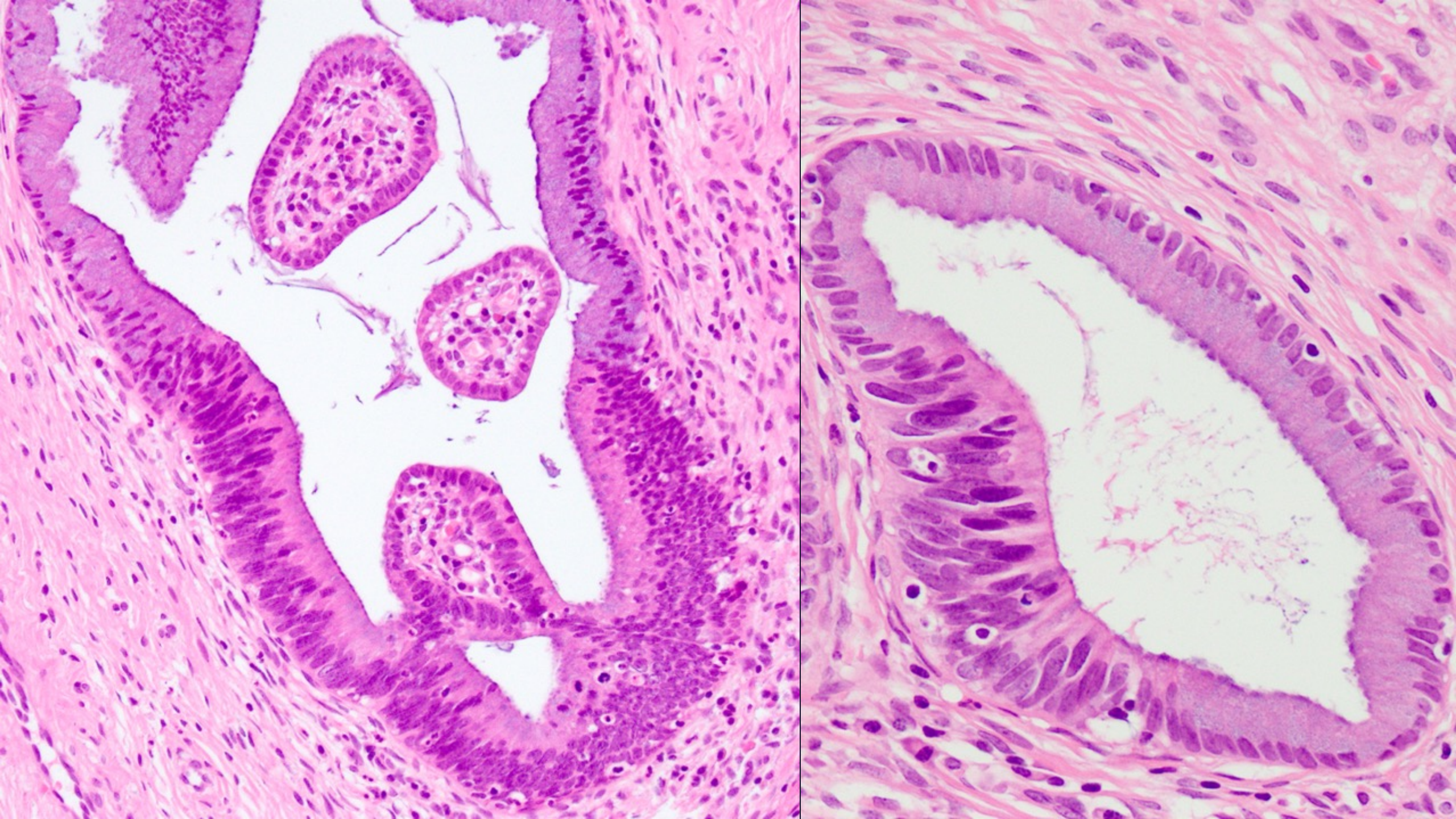
Aetiology

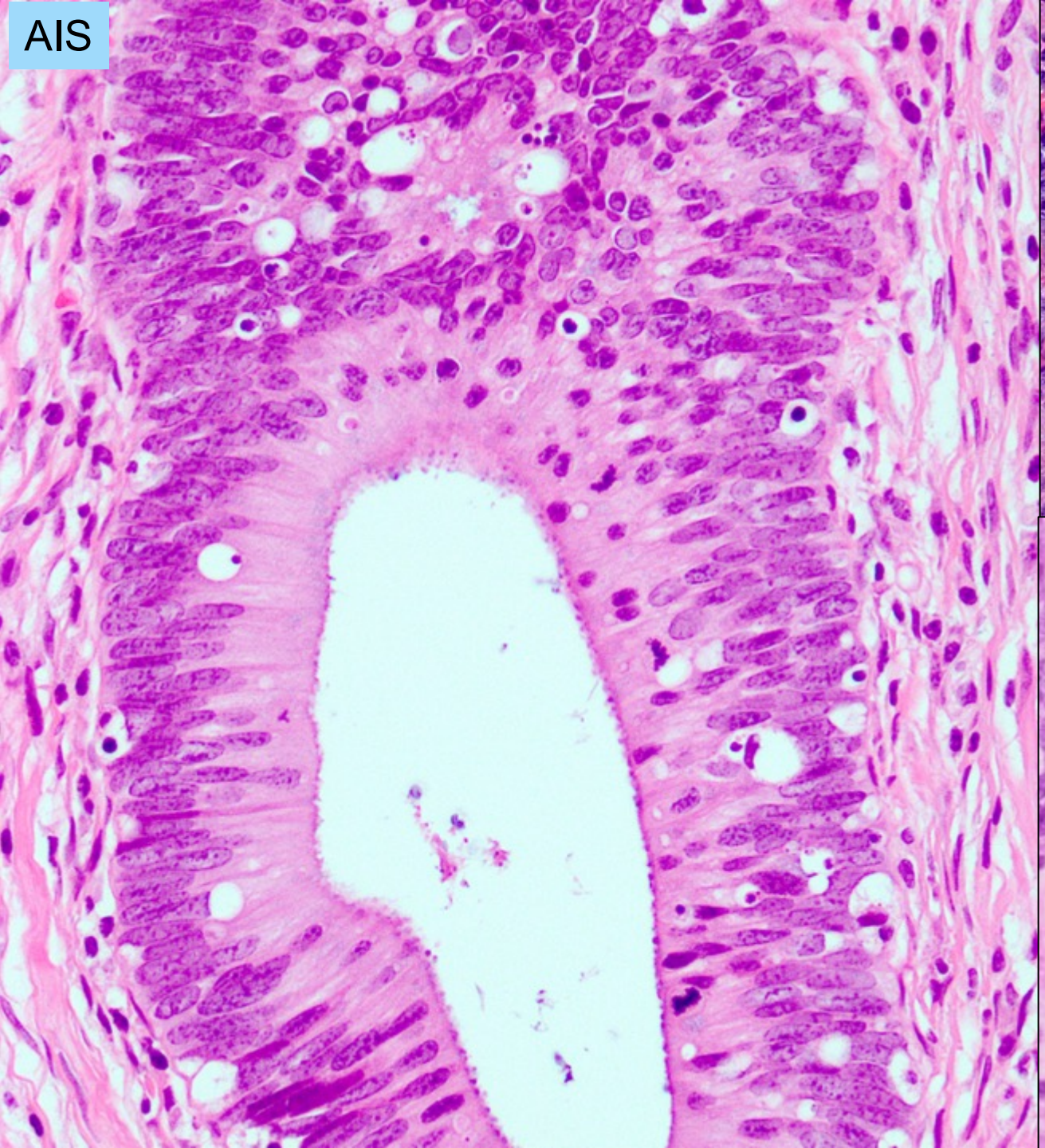
- HRHPV: 16,18 > 45
- Greater prevalence HPV 18 compared with squamous precursors

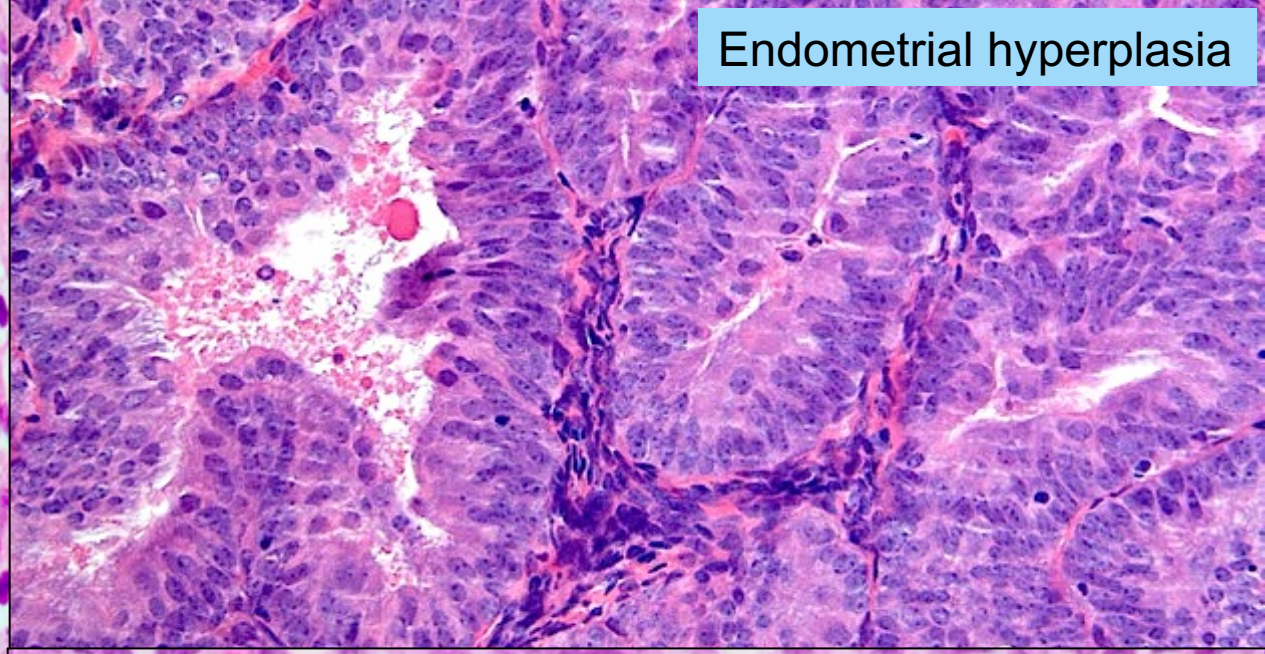


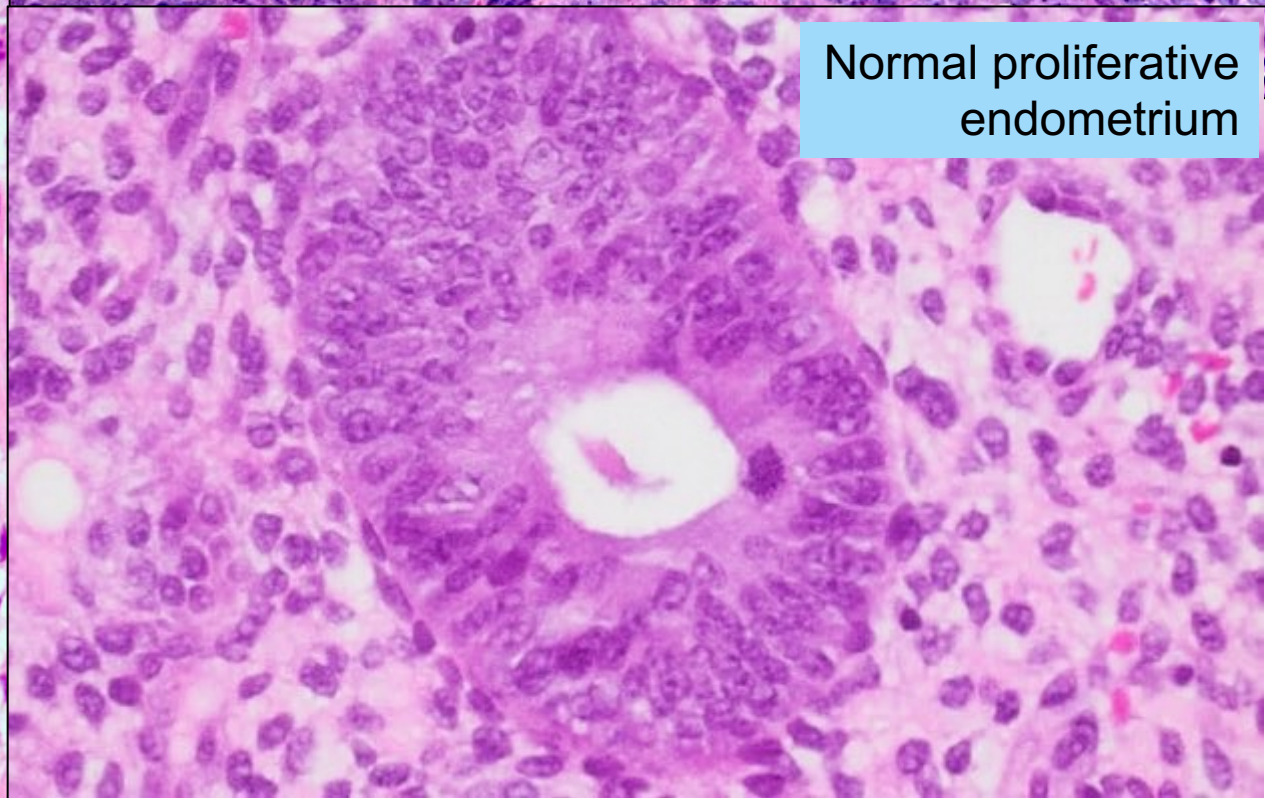

TZ, often accompanied by SIL
Pre-existing architecture generally preserved

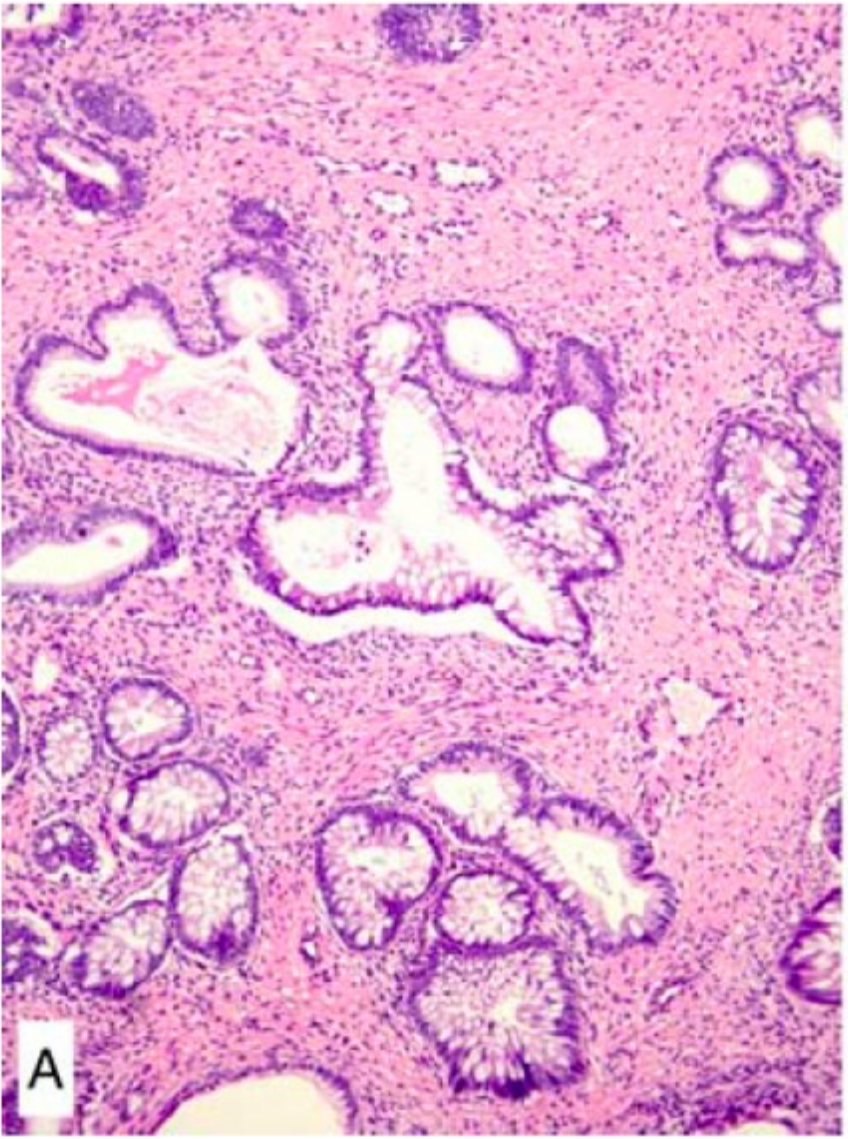

- Columnar cells, mucin-deplete
- Stratified hyperchromatic nuclei
- Apical mitoses, basal karyorrhexis

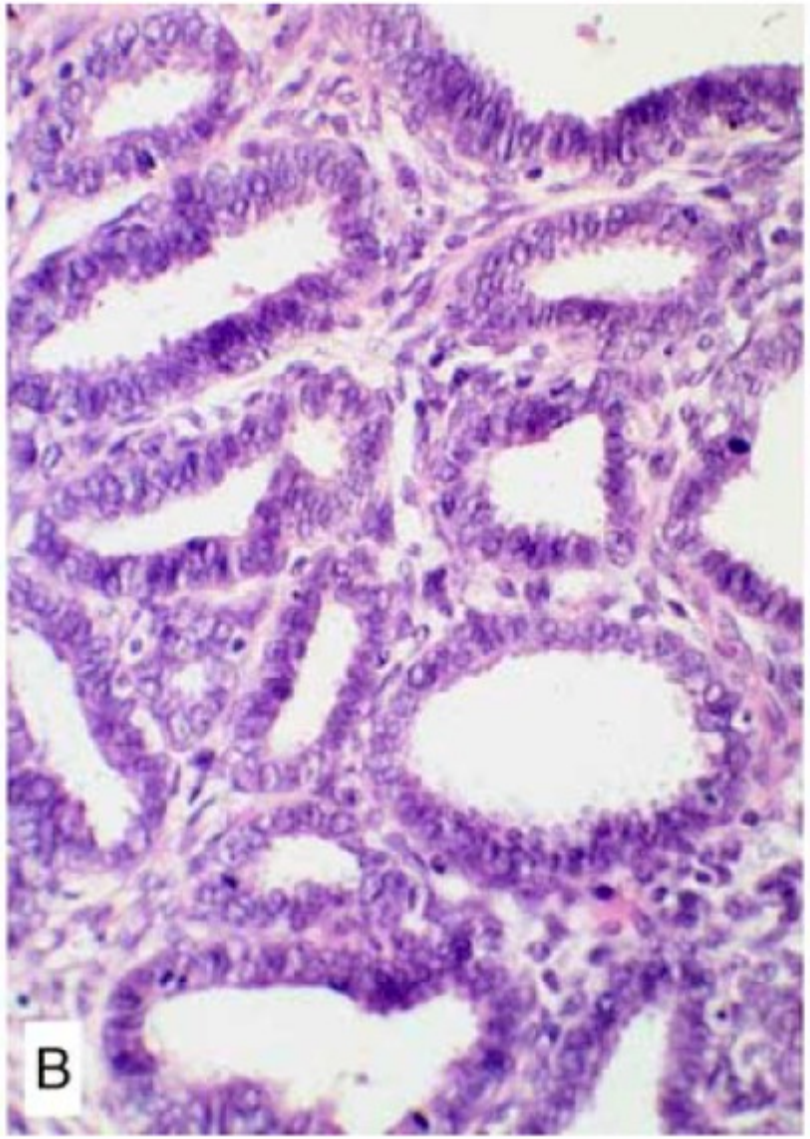


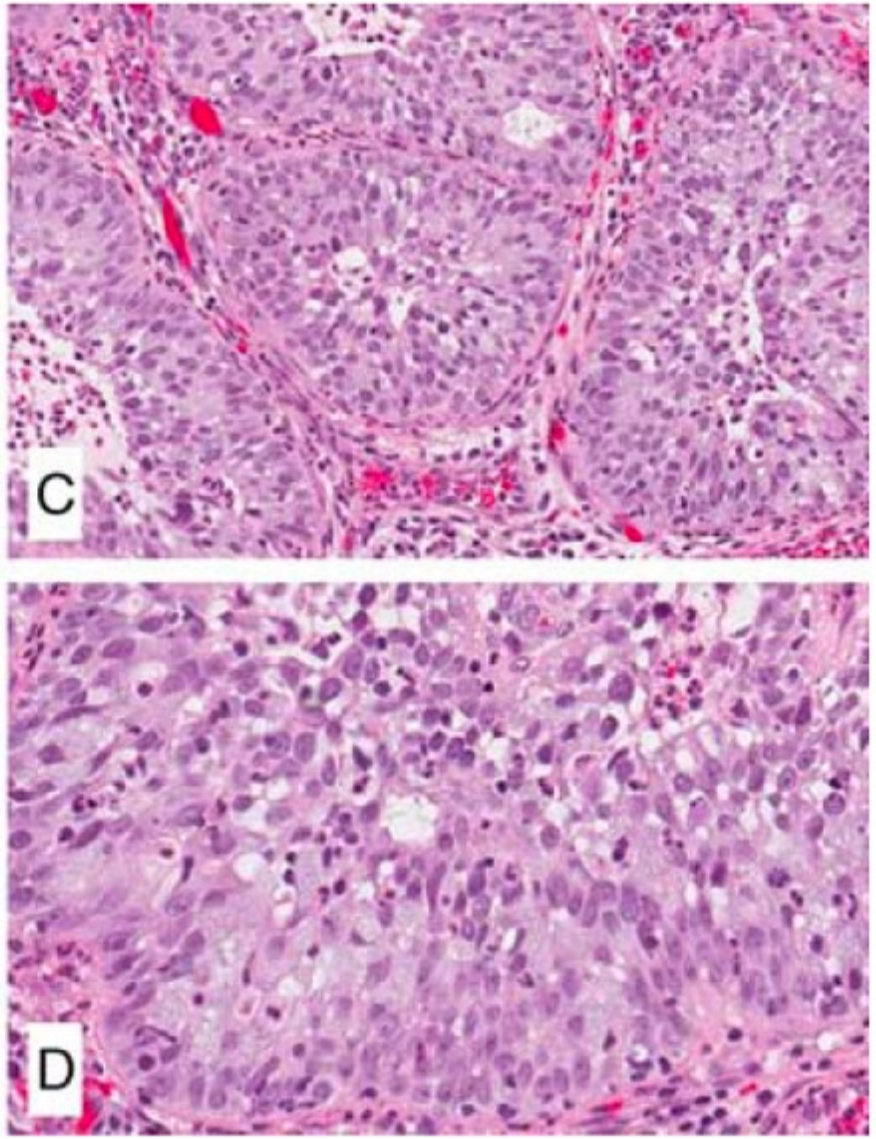

AIS


Endometrial hyperplasia


Normal proliferative endometrium



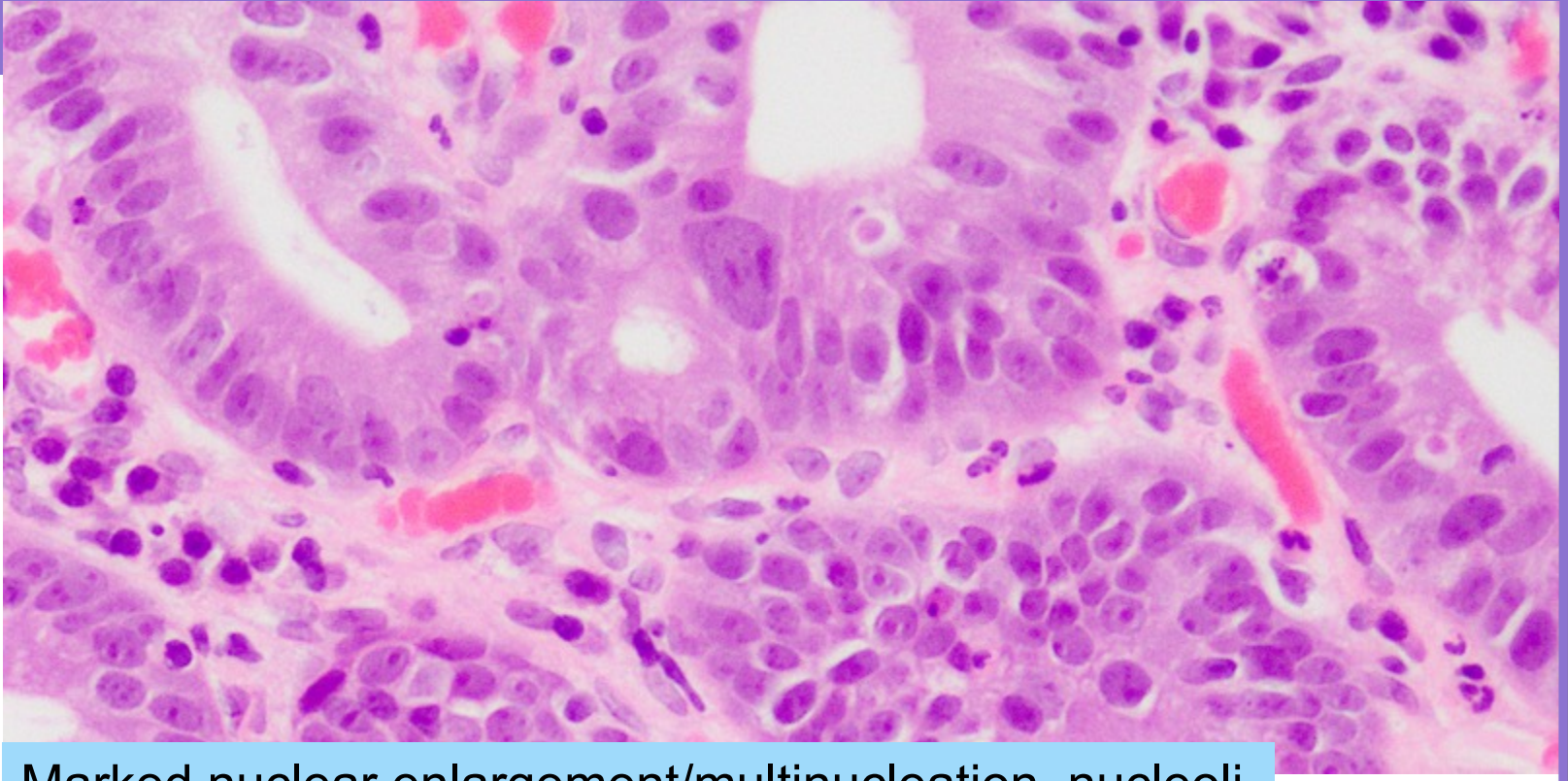




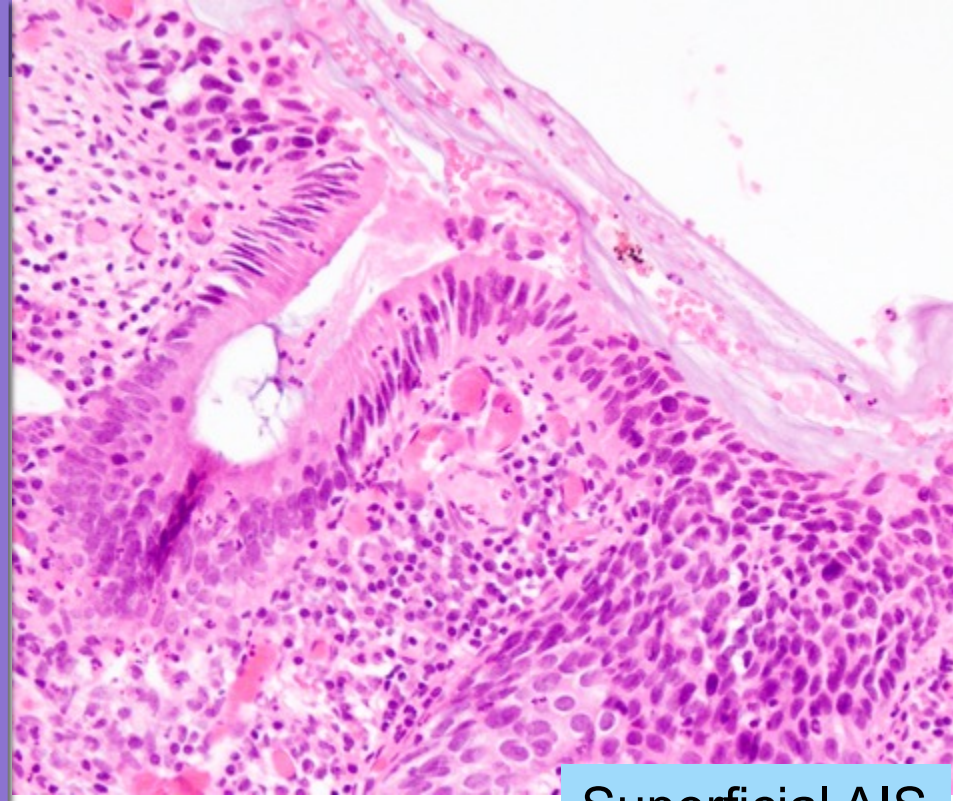
Intestinal/goblets

Ciliated/tubal

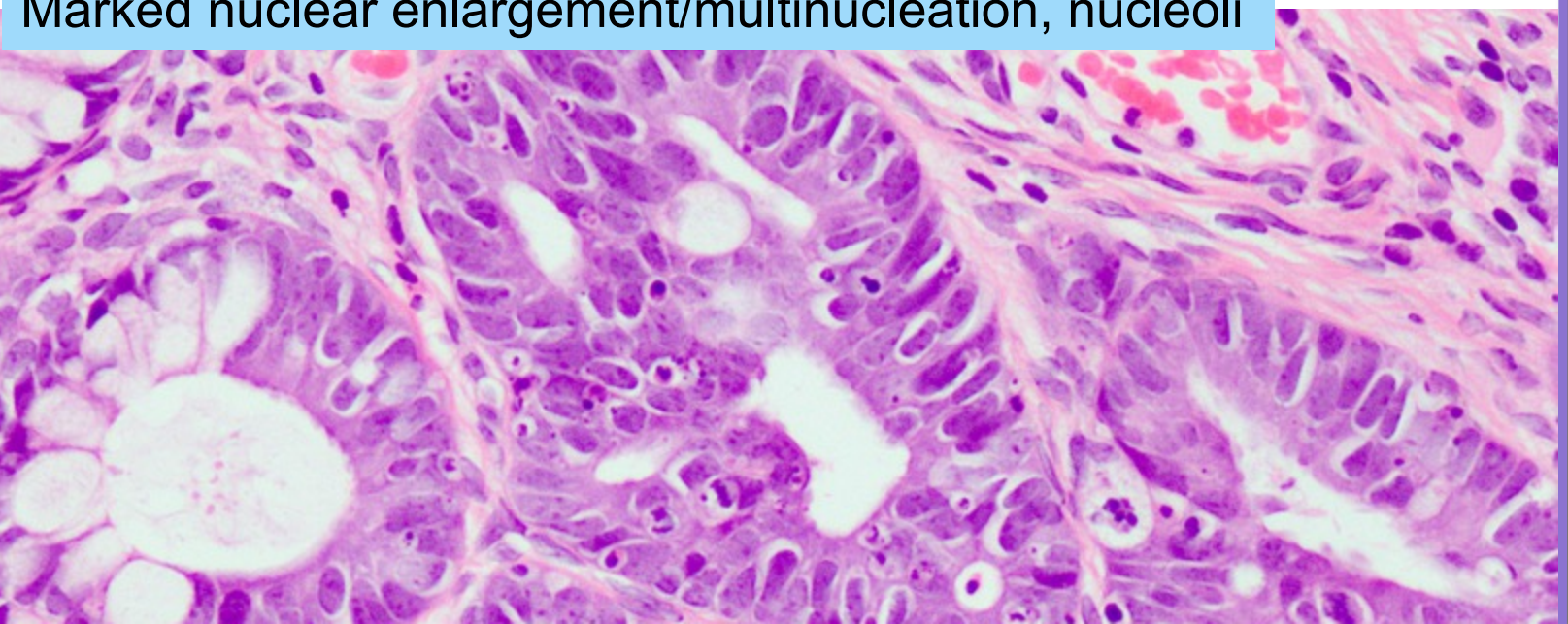
SMILE

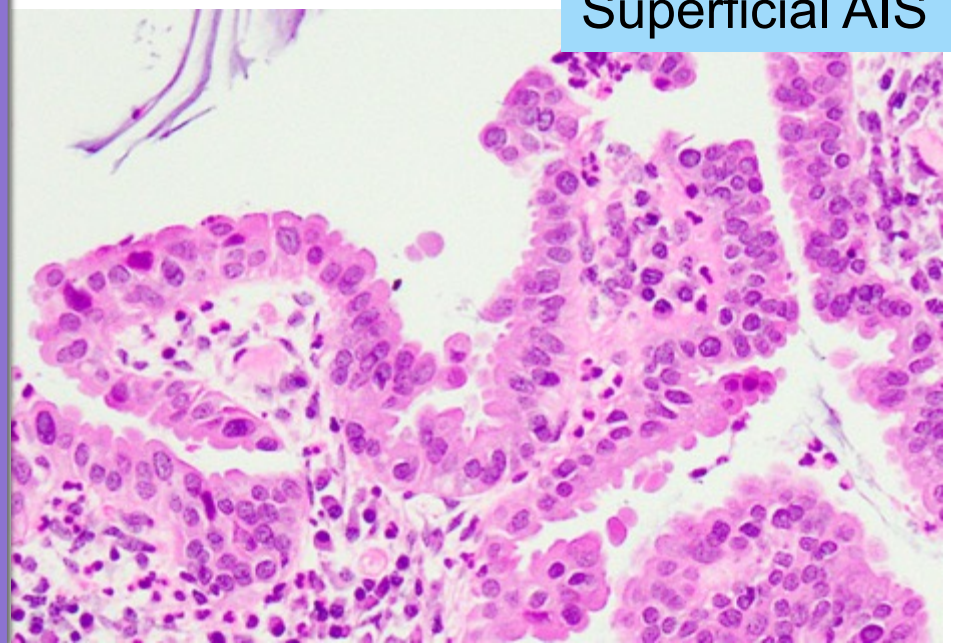


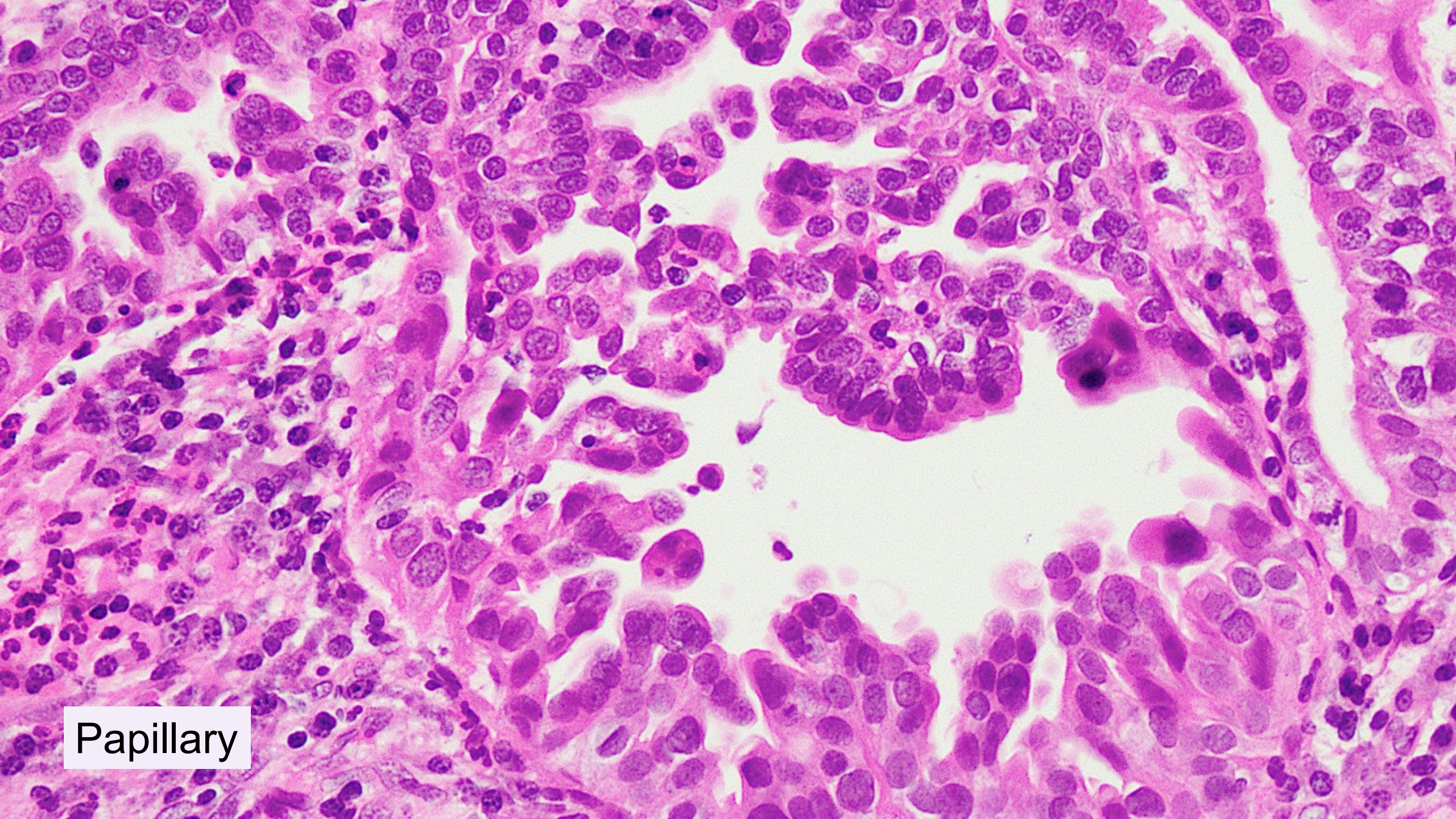
Marked nuclear enlargement/multinucleation, nucleoli

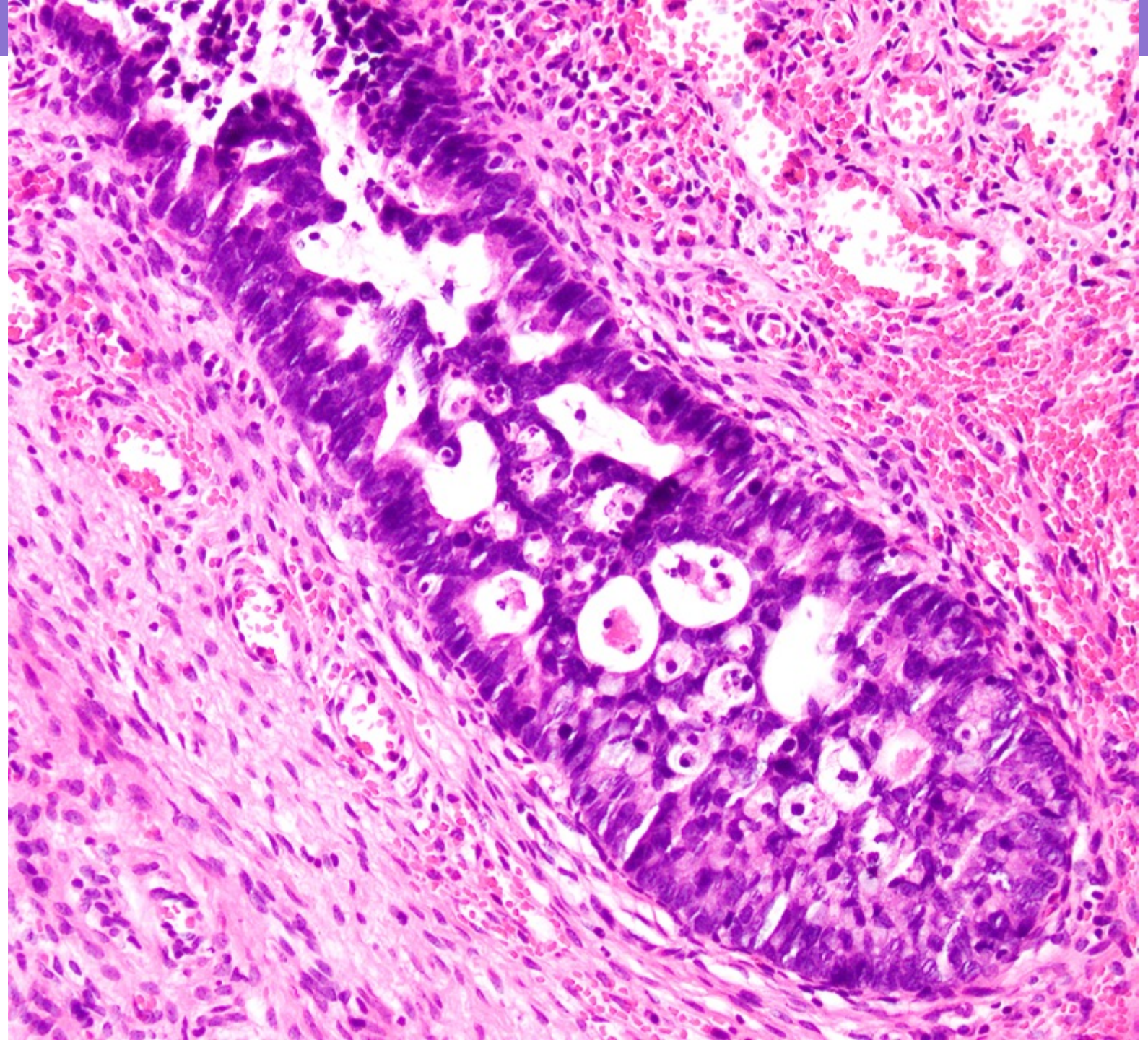


Superficial AIS






Papillary



Cribriform

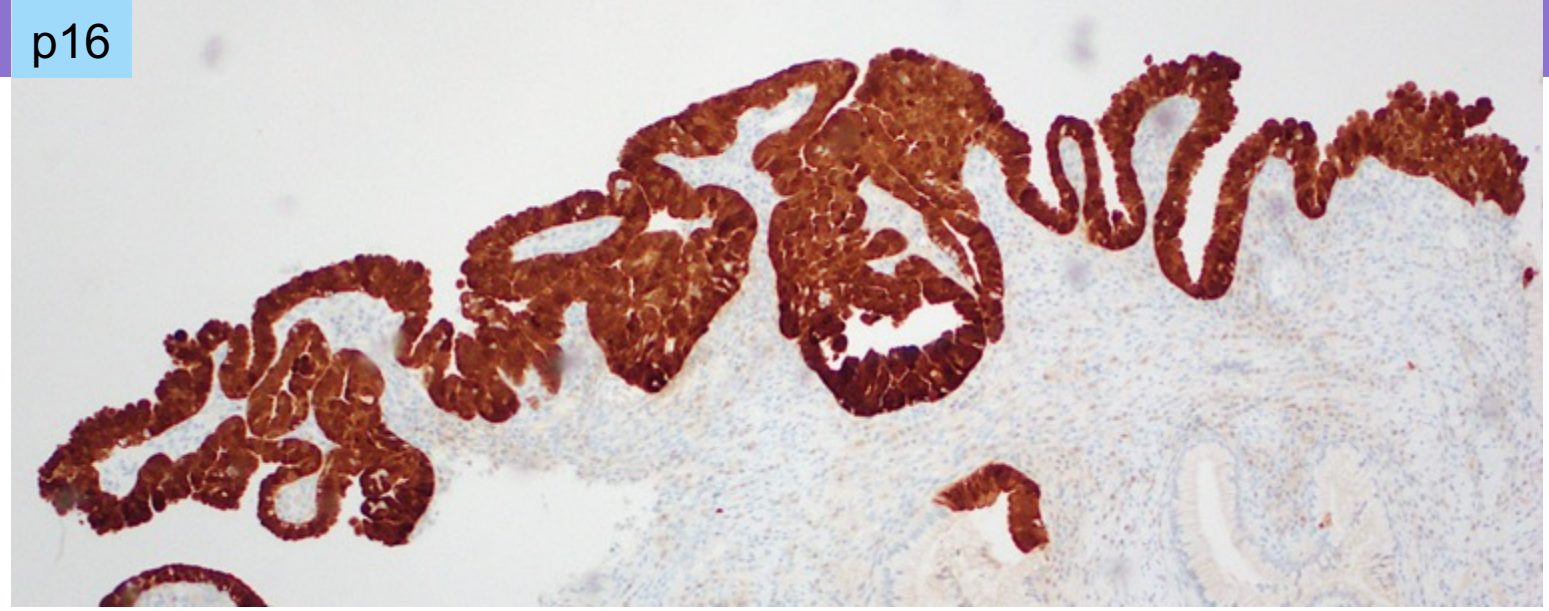
IHC

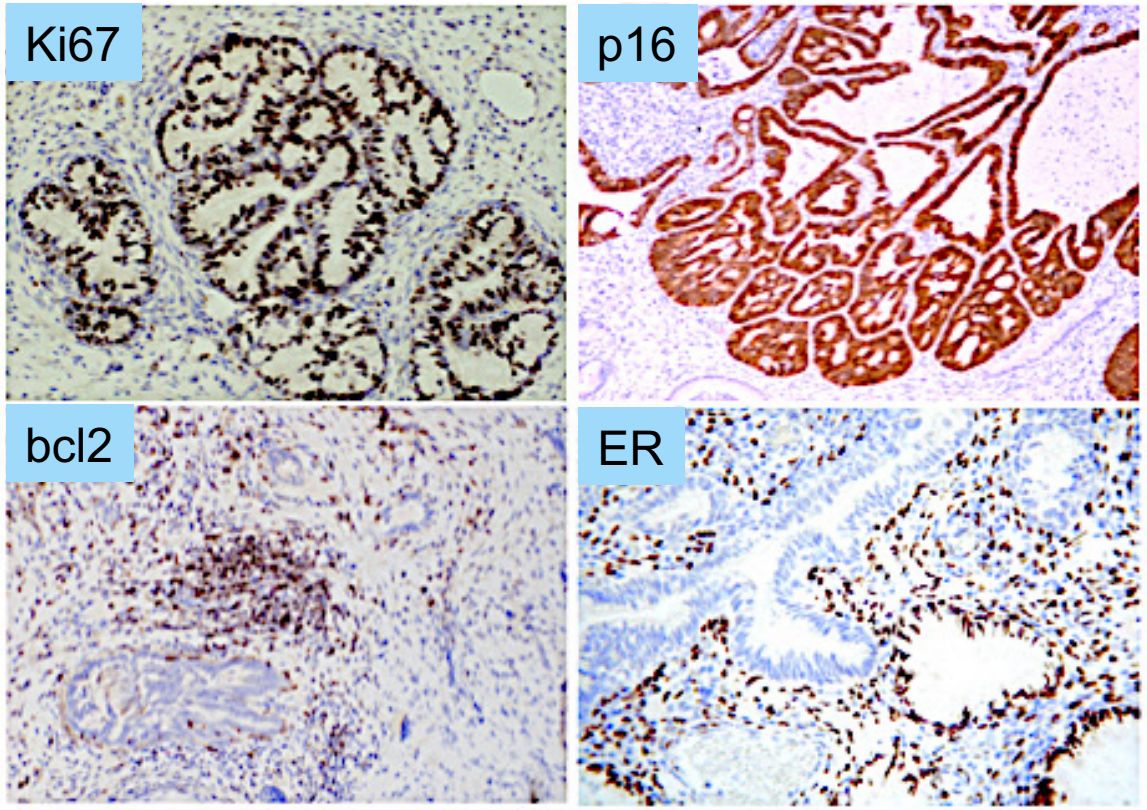
P16
- Diffuse, nuclear and cytoplasm
- HPV ISH positive

ER/PR, Vimentin, bcl2
- Usually negative
- Benign mimics ER/PR positive

Ki-67
- Increased, >30% in most
- <10% in benign glandular lesions

CEA
- Often positive





Broad differential

Benign

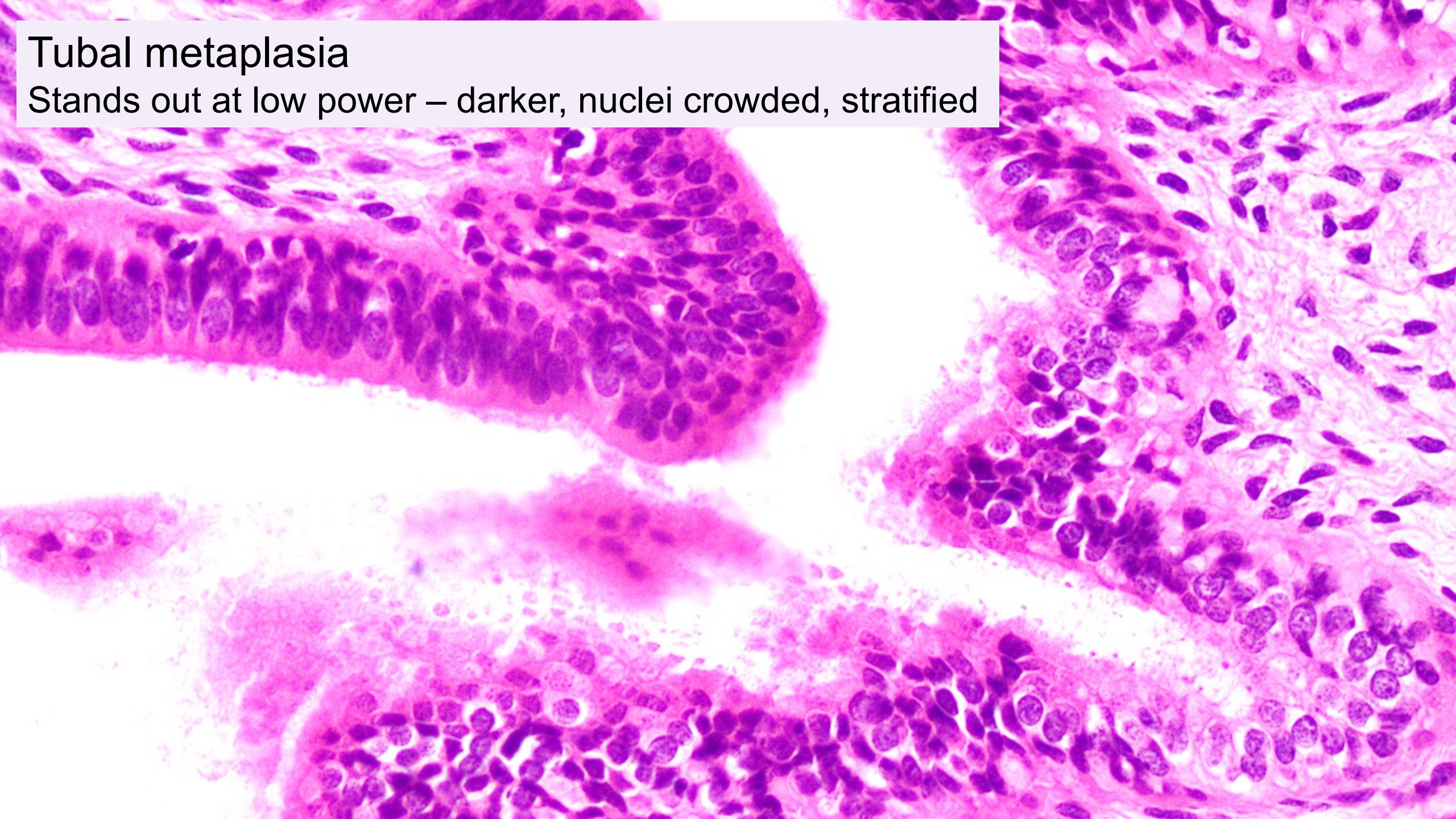
- Tuboendometrial metaplasia and superficial endometriosis
  - p16, bcl2, Ki-67, ER/PR, Vimentin, CEA
- Microglandular hyperplasia
- Mesonephric hyperplasia
- Arias-Stella reaction
- Radiation-induced atypia

Malignant/pre-malignant

- Gastric-type AIS
  - IHC: p16
- Cervical involvement by endometrial carcinoma – endometrioid, serous
  - IHC: p16, ER/PR, Vimentin, CEA, p53
- Metastasis to cervix from adnexal primary – eg serous carcinoma

Tubal metaplasia

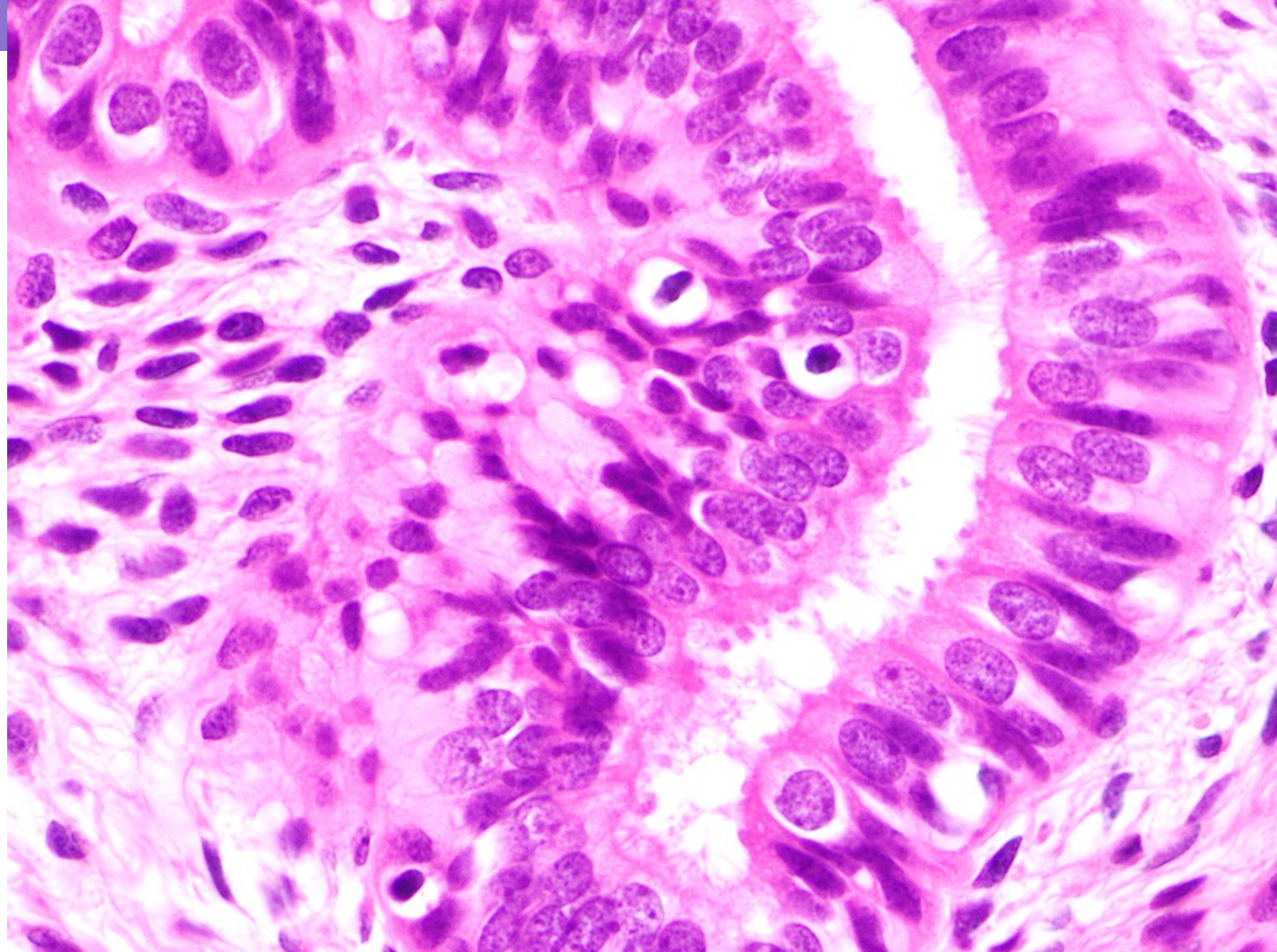
Stands out at low power – darker, nuclei crowded, stratified



Tubal metaplasia

- Mix of ciliated, secretory & peg cells

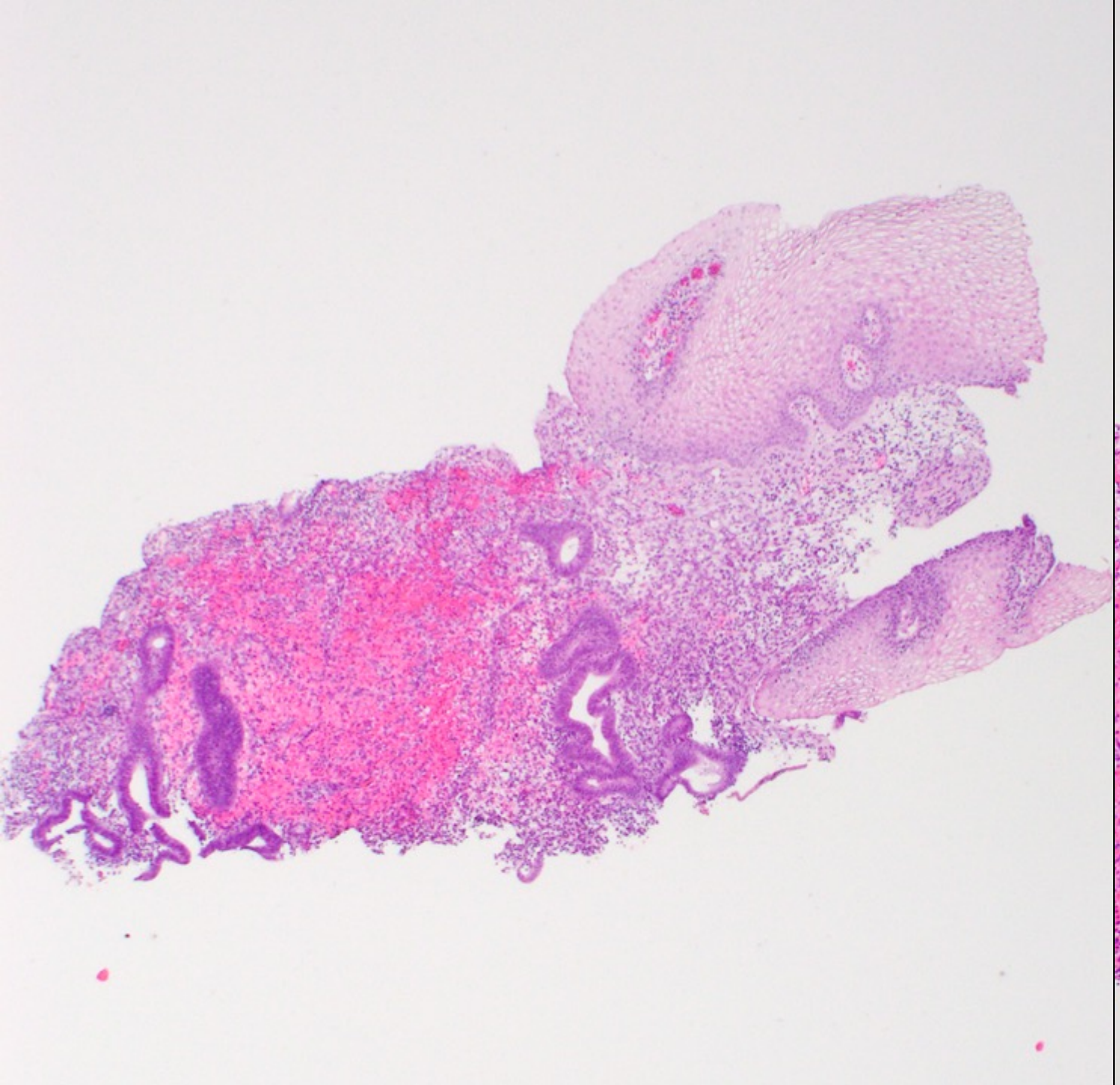
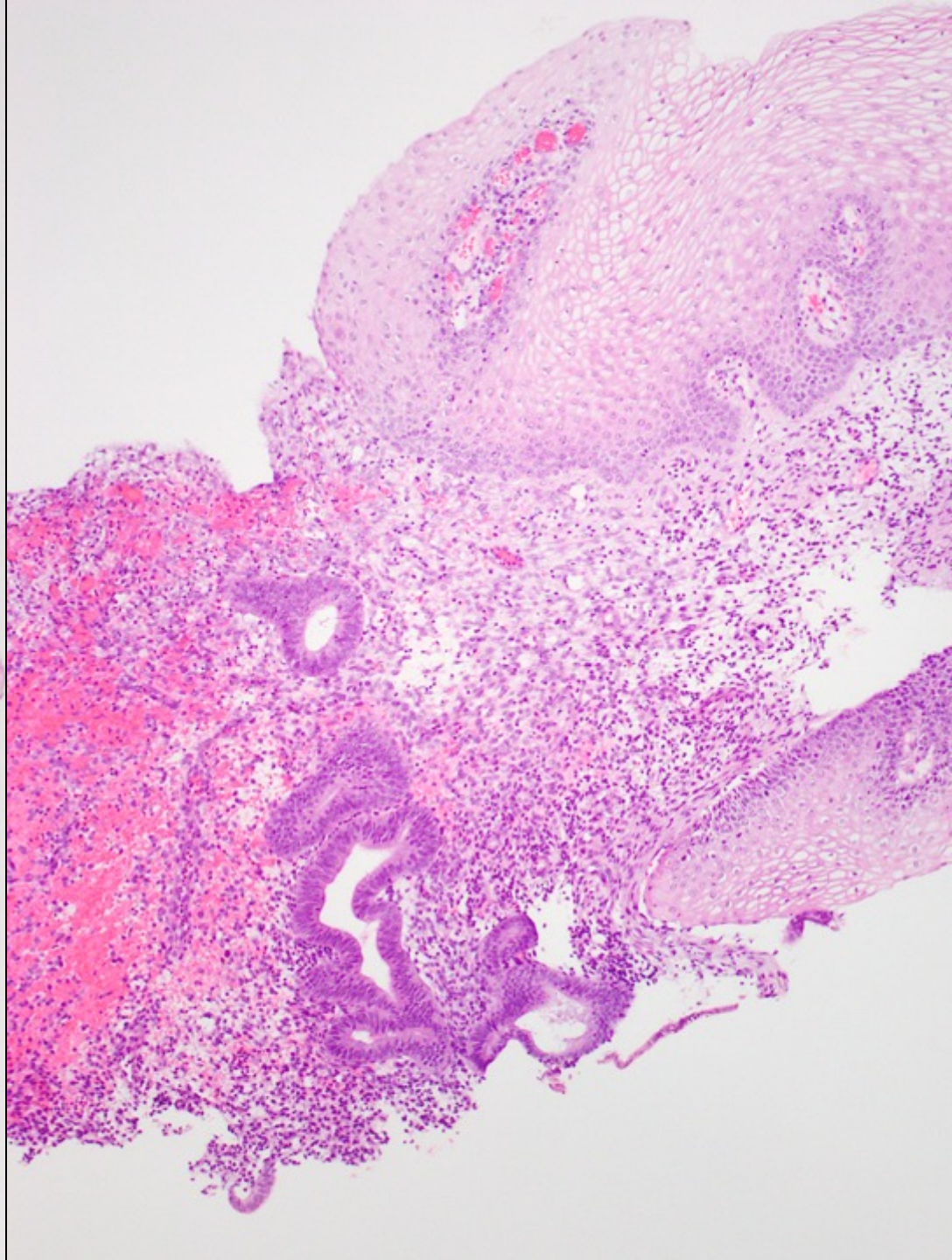
- Upper endocervix
- Post-excision



	Adenocarcinoma In Situ	Tuboendometrial Metaplasia/Superficial Endometriosis
p16	Diffuse (block-type) positive	Negative or focally (mosaic-type) positive
bcl2	Negative	Diffuse positive
MIB1	> 30%	< 30%
vimentin	Negative	Diffuse positive
ER/ PR	Negative	Diffuse positive
CEA	Diffuse positive (cytoplasmic)	Negative or luminal staining

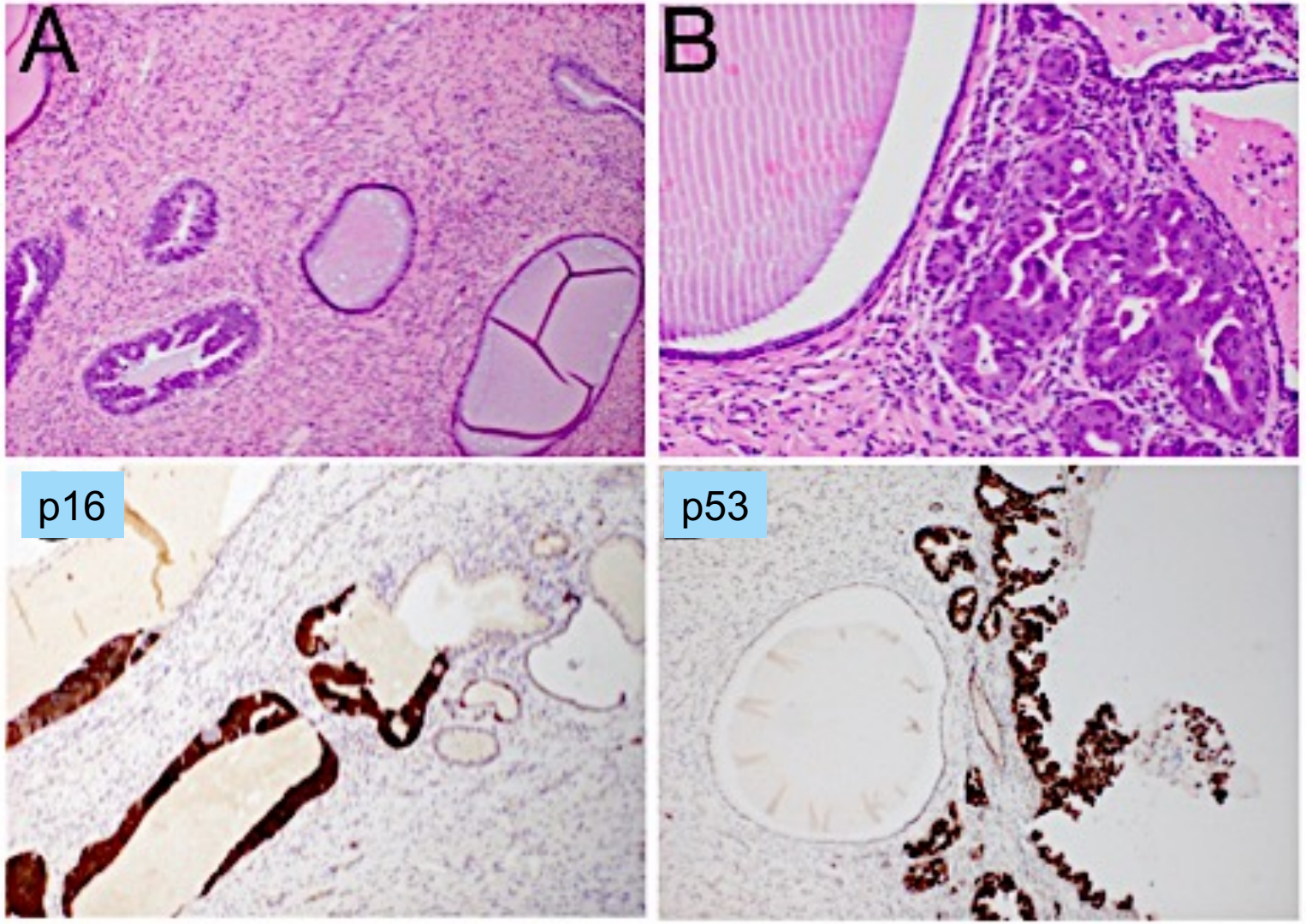
This table lists the usual staining reactions, but aberrant staining patterns may occur in individual cases.

Stolnicu S et al, Adv Anat Pathol 2020;27:278-293

Superficial endometriosis
Lacks atypia, apoptoses

Serous carcinoma involving cervix vs. AIS



Stolnicu S et al,
Adv Anat Pathol 2020;27:278-293

IJGP 2009;28:107-113

Is p16 staining truly positive?

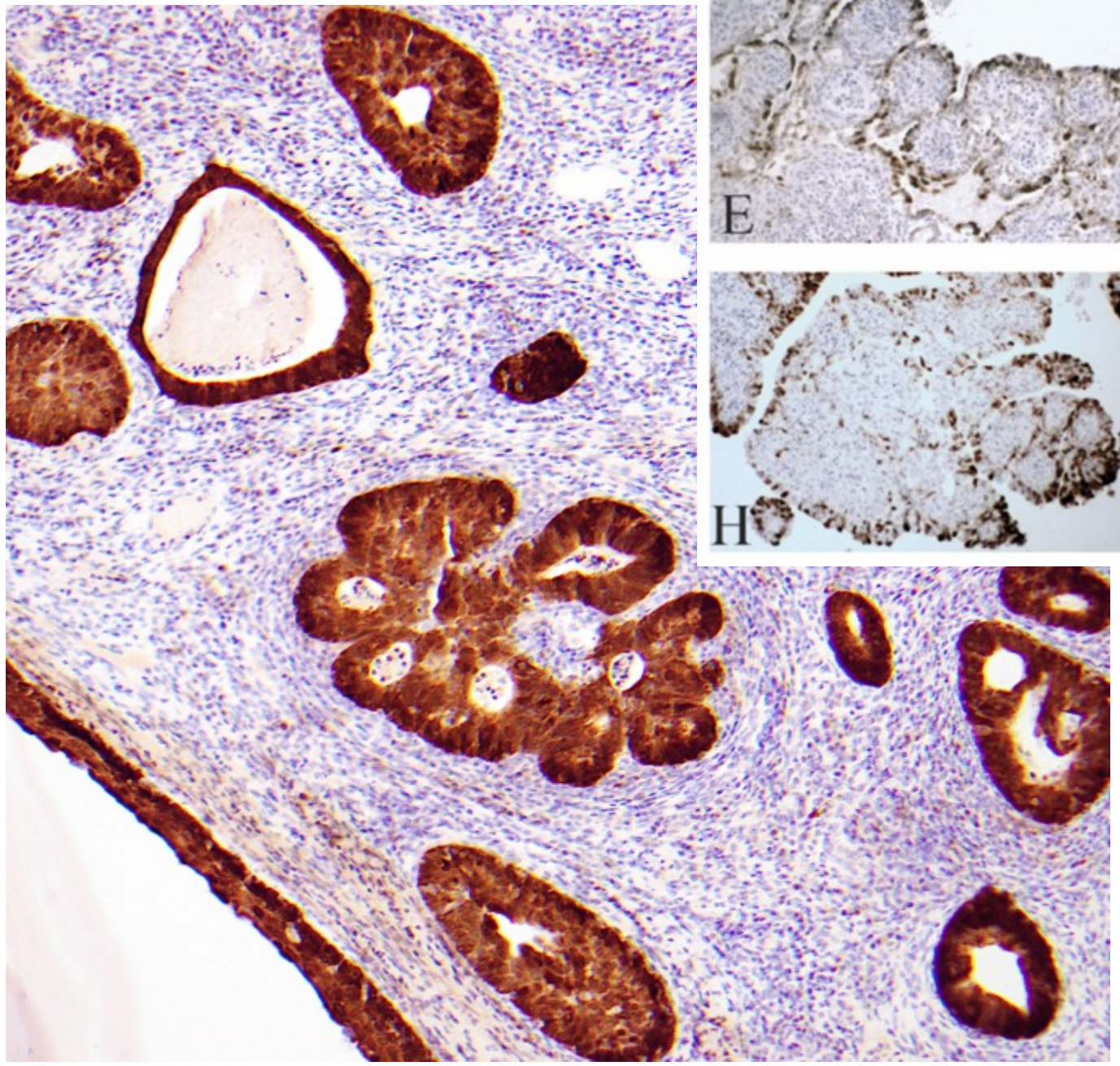
- Must be diffuse, every cell
- Mimics show patchy staining
- *BEWARE uterine serous ca (>95%),*
- *HG endometrioid ca (1/3), CCCa (1/3)*

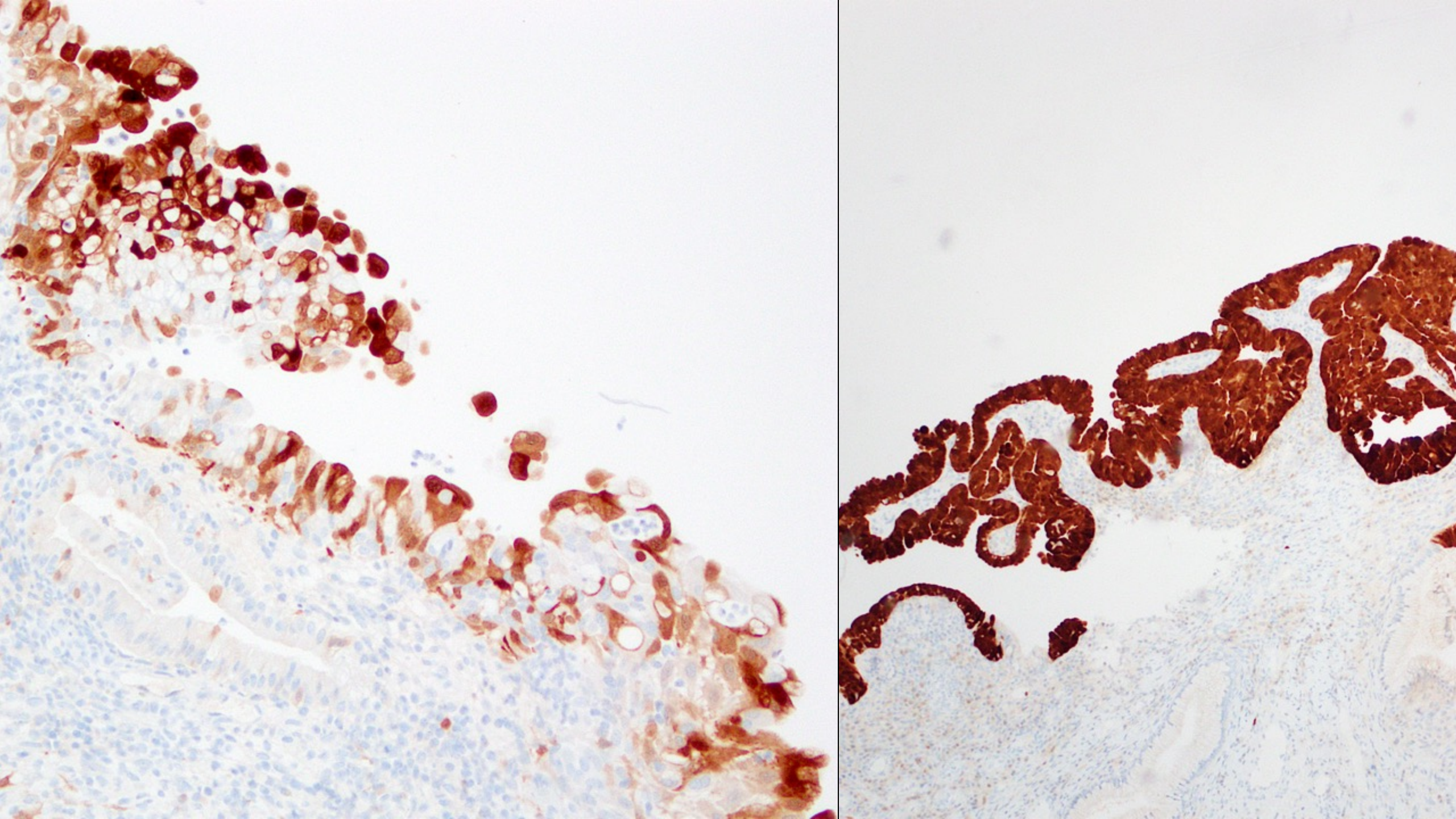
ER/PR

- Most benign: Positive
- Most pre/malignant: Negative

Look at the history

- HPV status?
- HPV-associated AIS/adenoca unlikely if HPV neg





HPV-A glandular lesion: in situ or invasive?

PATTERNS OF INVASION

- **Infiltrative/destructive growth:** Glands with irregular or angulated contours, desmoplastic stromal reaction, individual cells / buds / nests
- **Complex confluent growth:** Anastomosed, fused, interconnected glandular elements with scant to no stroma in between, complex cribriform, labyrinth-like or solid growth occupying a 4x field (5 mm diameter)

HPV-A glandular lesion: in situ or invasive?

"Non-destructive" or "AIS-like" pattern of growth also classified as a form of invasion

- **Increased gland density:** Glandular crowding that deviates from the normal distribution of crypts; tight clustering of small glands, sometimes with lobulated appearance
- **Deep glandular proliferation:** Glands in a haphazard distribution deep within the cervical stroma, close proximity to large BVV

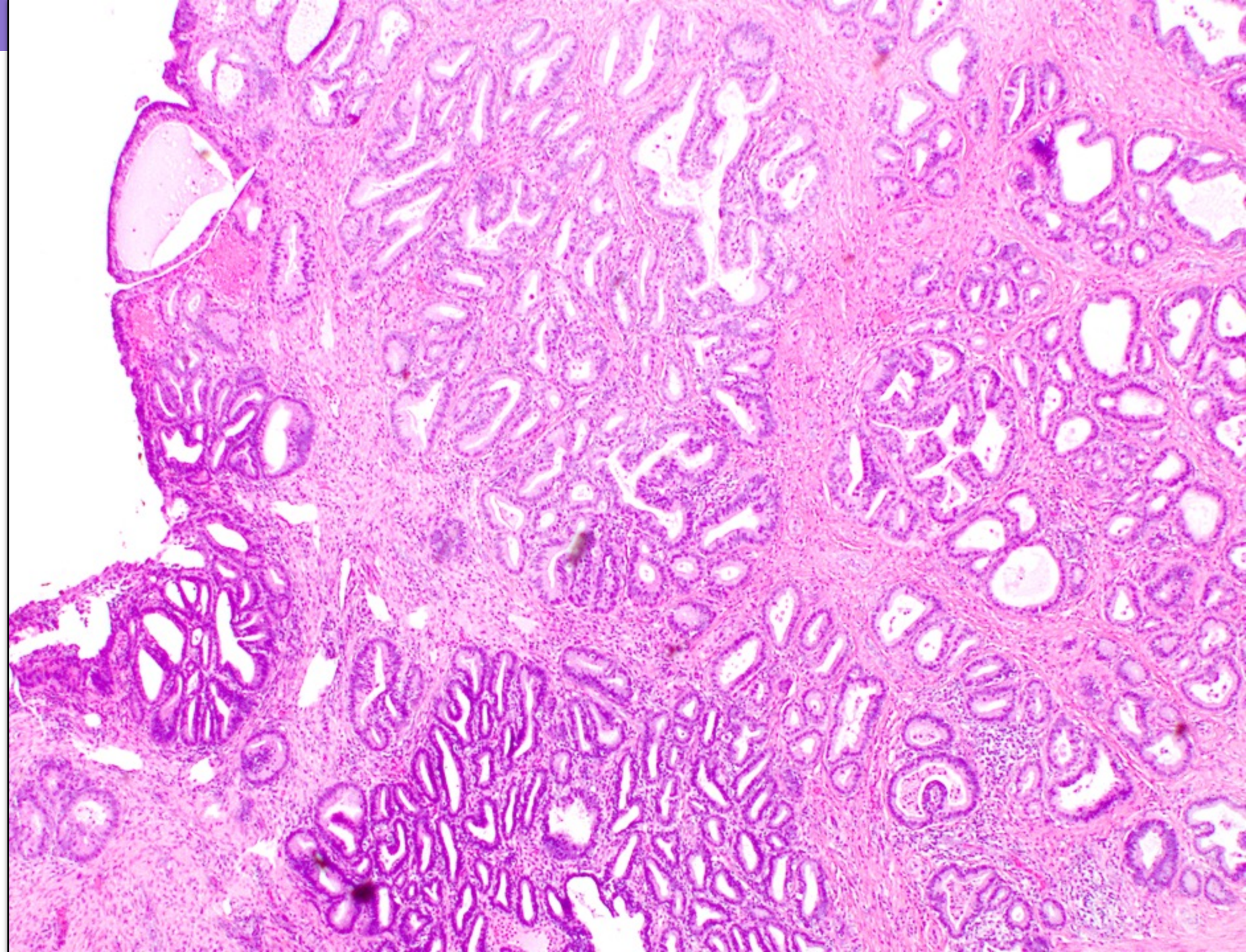
Non-destructive /AIS-like pattern of growth

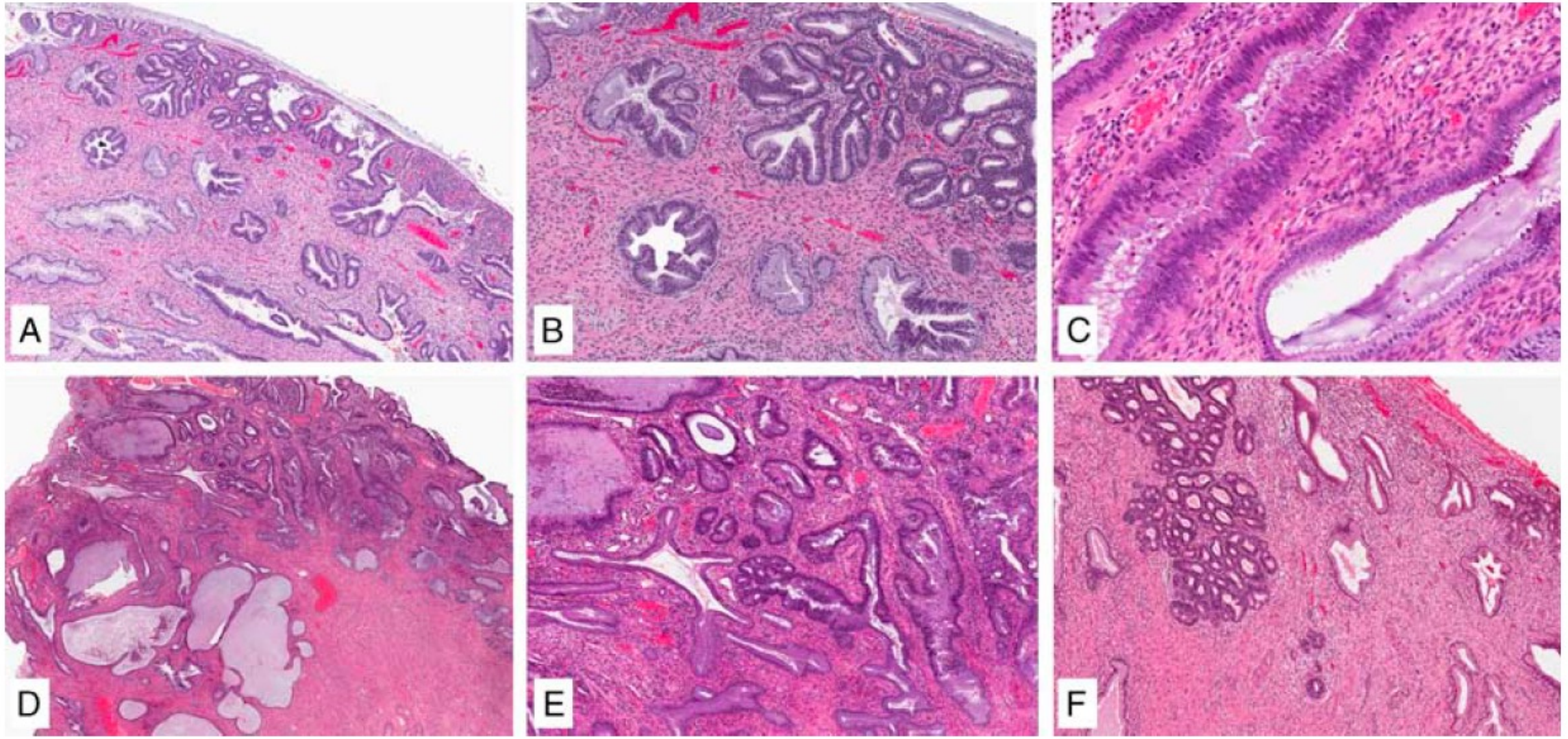
Increased gland density

Architecture “too complex” for benign

Tight lobules
Labyrinth-like
Cribriform, papillary

Helpful to compare with normal glands





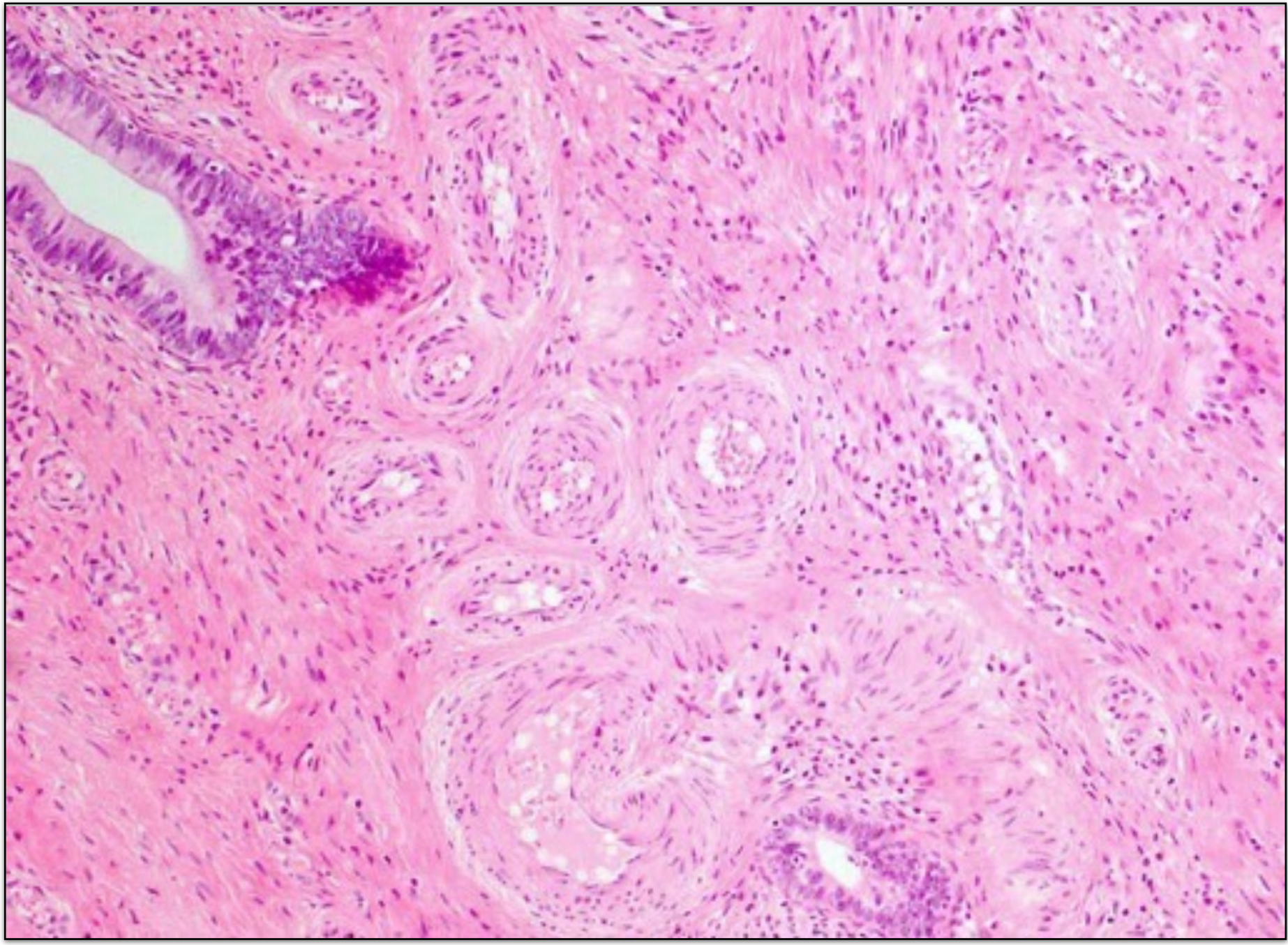
Just AIS

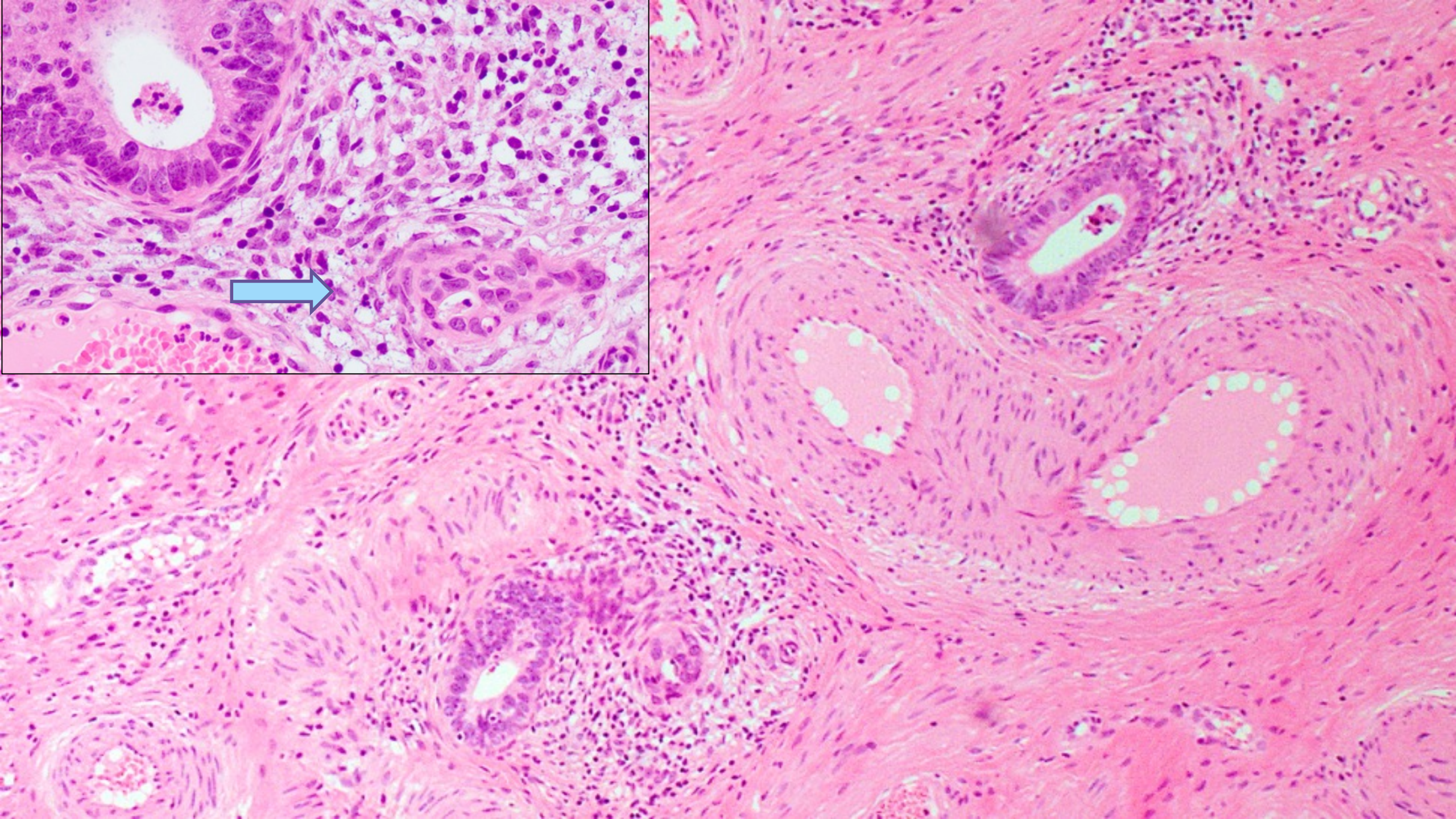
Non-destructive /AIS-like pattern of growth

Deep glandular proliferation

Angulated ‘claw-like’ invasive glands deep in the cervical stroma by lacking stromal response

- “Naked” pattern invasion
- Proximity to thick-walled BVV, glands deeper than normal glandular field
- ?LVSI may assist

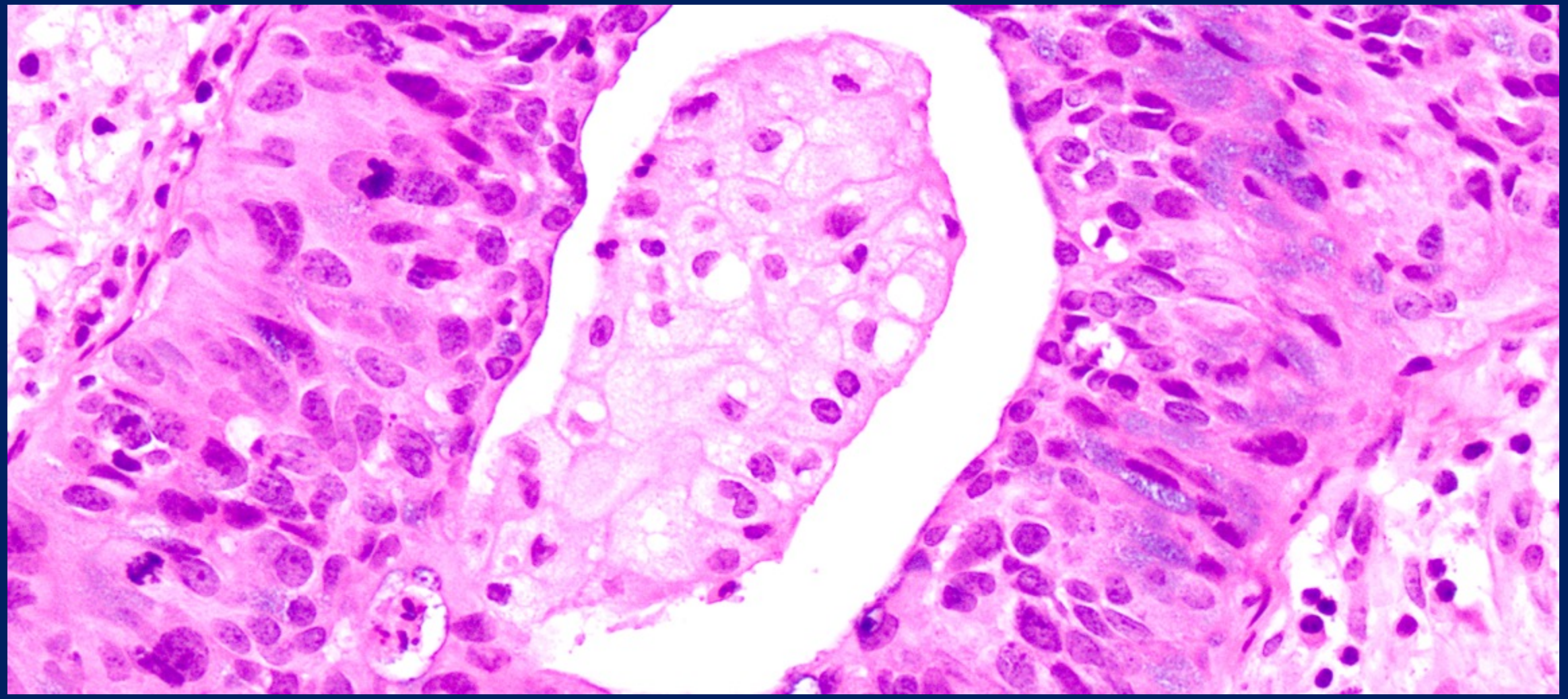




AIS or Non-destructive adenocarcinoma?
Difficult, poorly reproducible

If cannot reliably determine:
Call it Pattern A adenocarcinoma (non-destructive invasion)

HPV associated AIS - SMILE



SMILE

First described 2000 *PMID11023104*

WHO 2014: Subtype of AIS

- HG reserve cell dysplasia
- Adenosquamous CIS

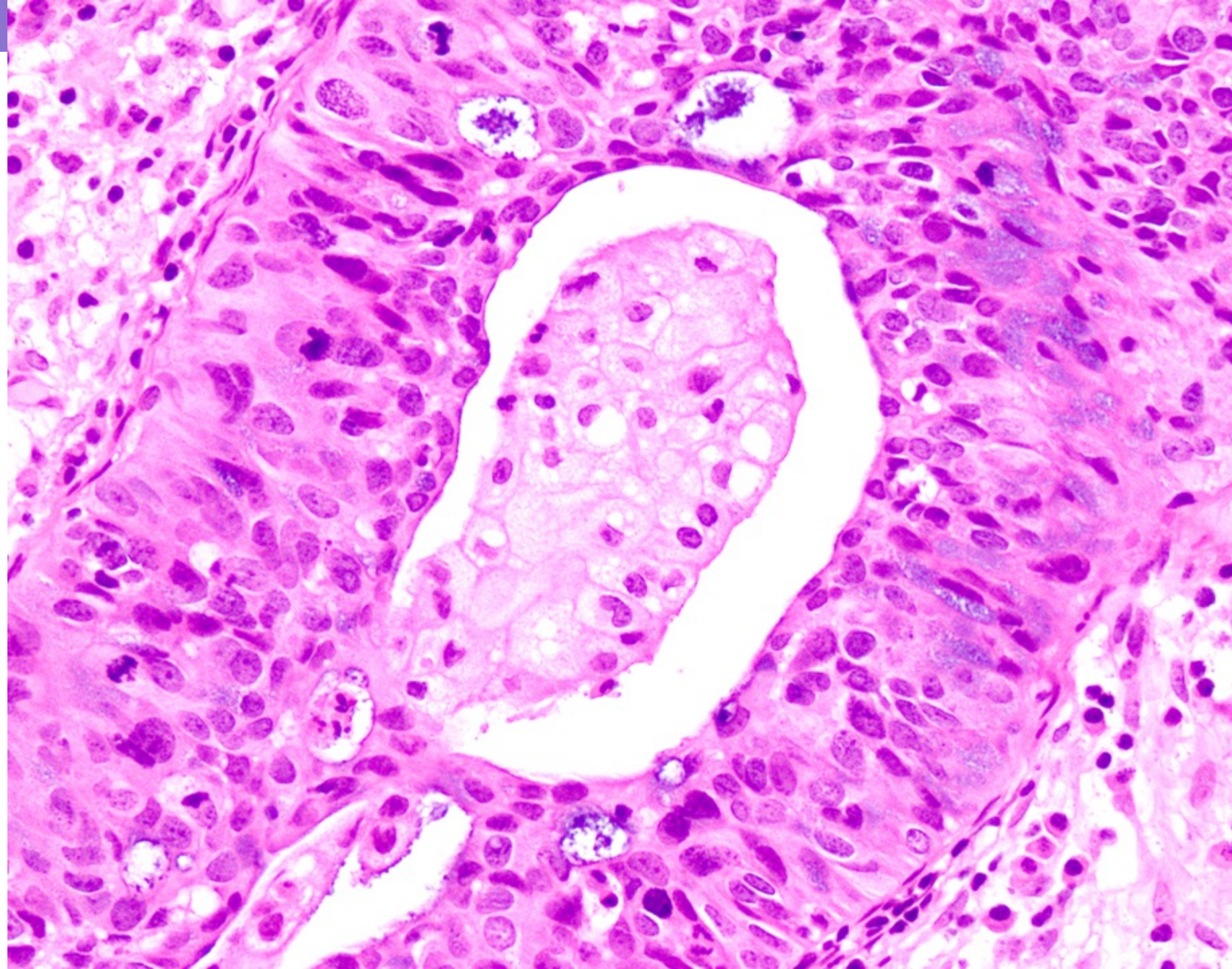
No specific HPV type known

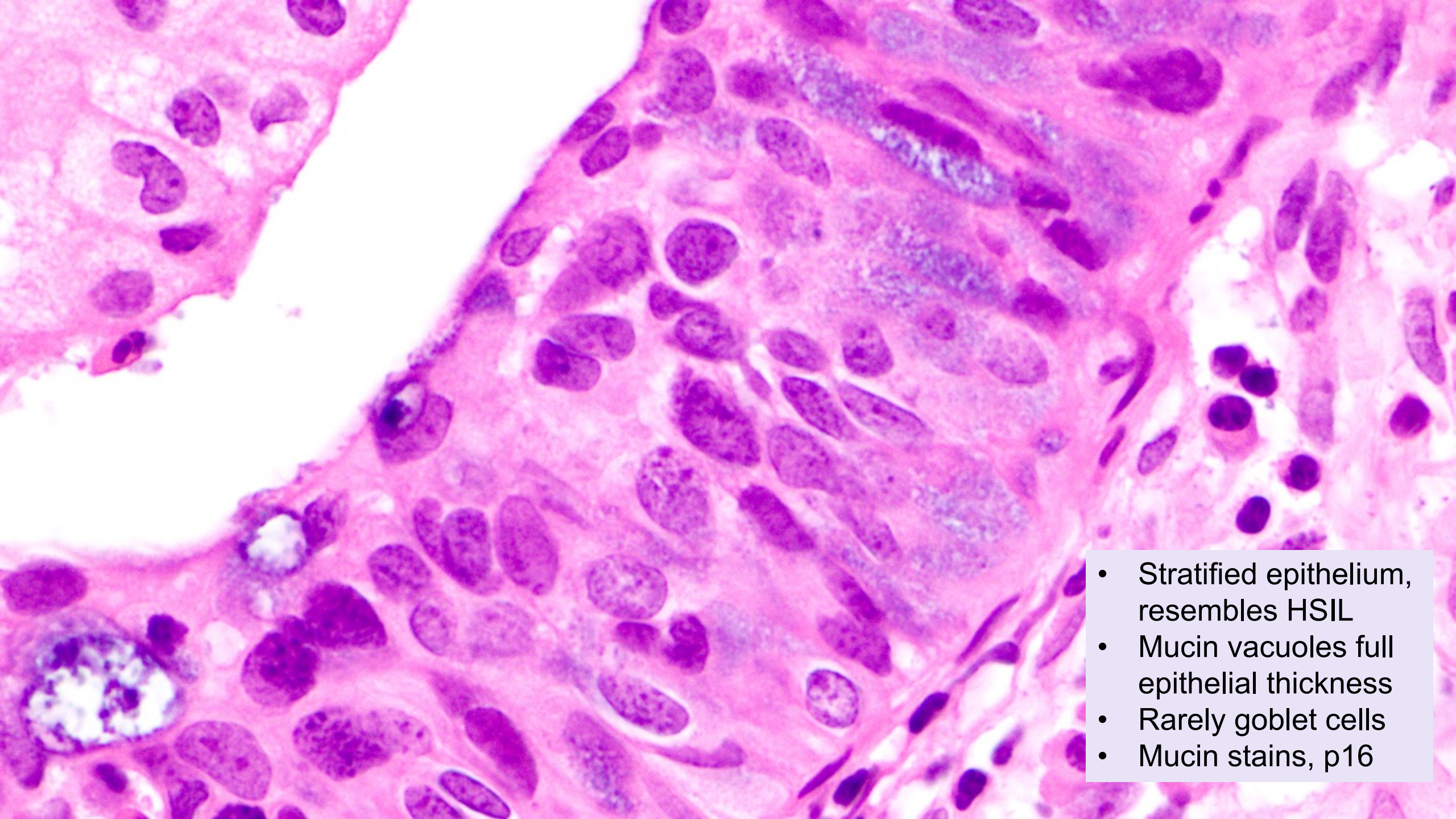
Uncommon

Study of 69 cases:

- Seldom in pure form
- Associated SIL 93%
- Usual AIS 42%
- Invasive carcinoma 10%
- Pure SMILE 4%

Boyle & McCluggage Histopathol 2015





- Stratified epithelium, resembles HSIL
- Mucin vacuoles full epithelial thickness
- Rarely goblet cells
- Mucin stains, p16

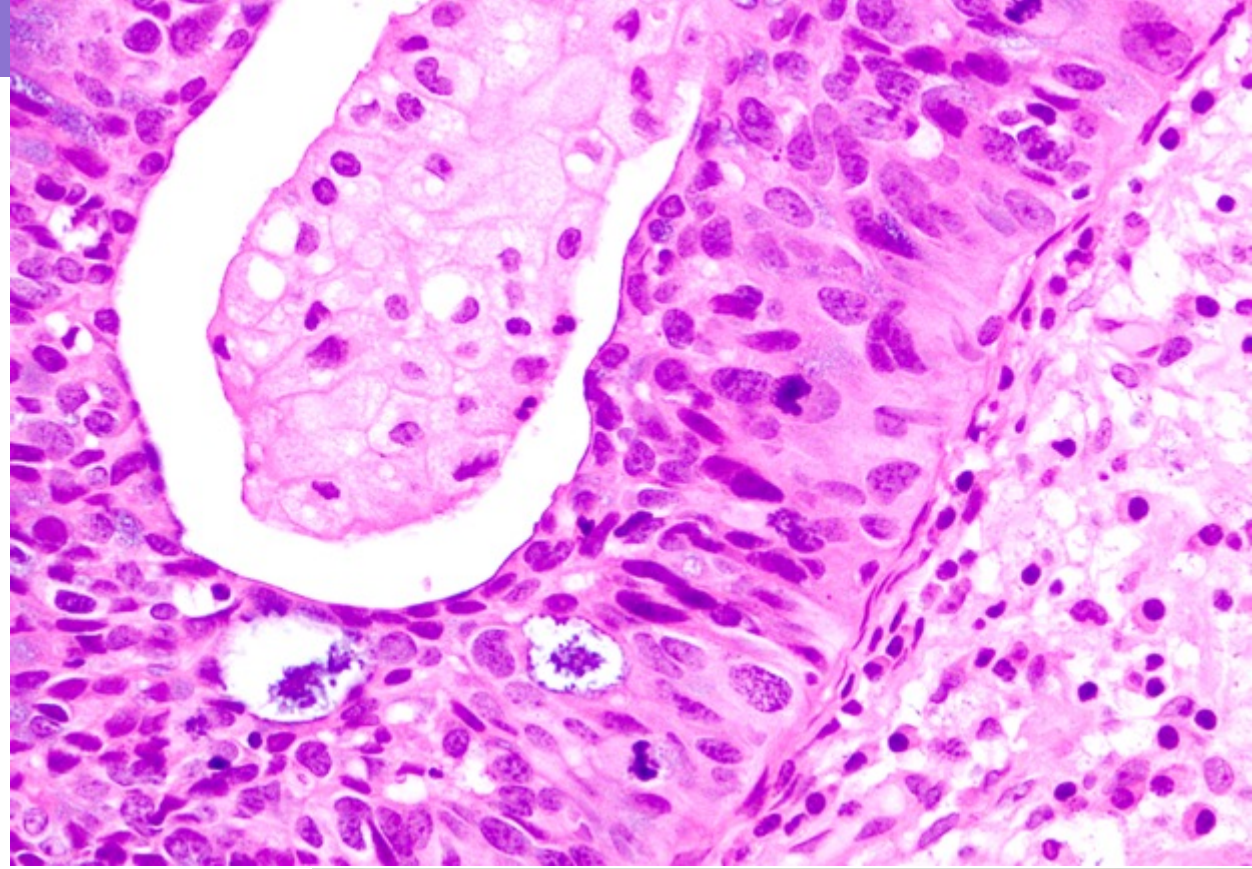
SMILE

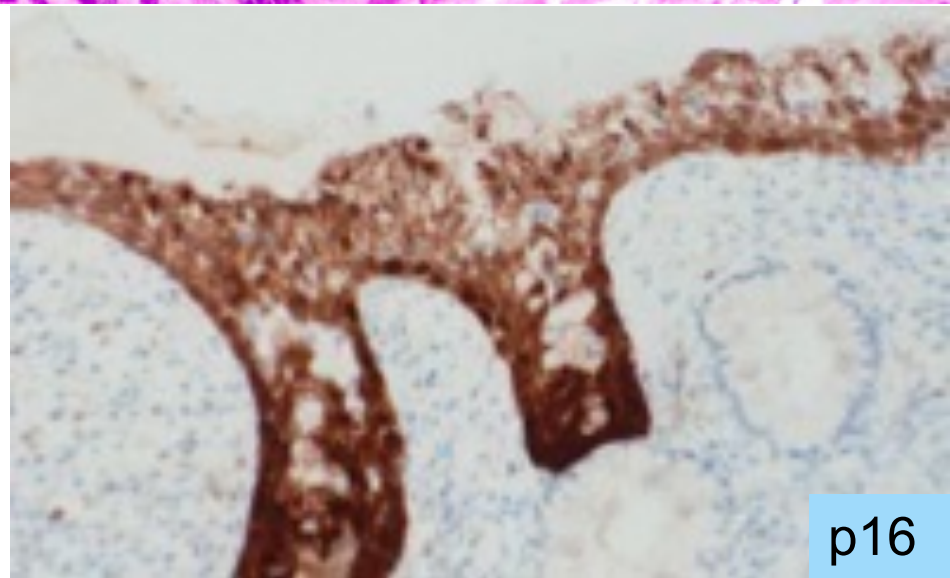
- Likely over-diagnosed
- Morphology should be unequivocal, p16 block positive

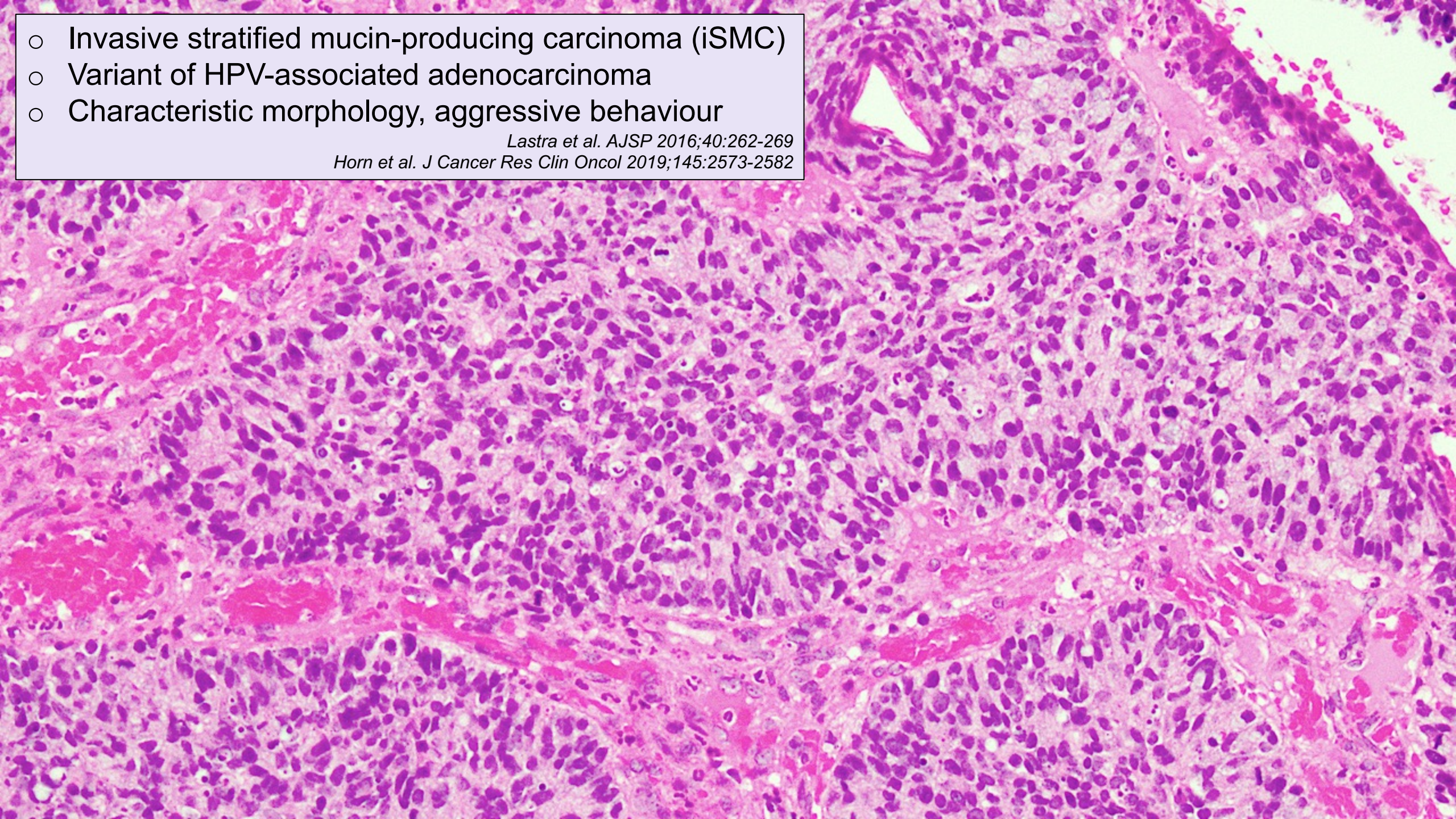
Differential:

- HSIL involving immature squamous metaplasia or endocervical glands
  - ➢ Mucin vacuoles confined to surface rather than full epithelial thickness

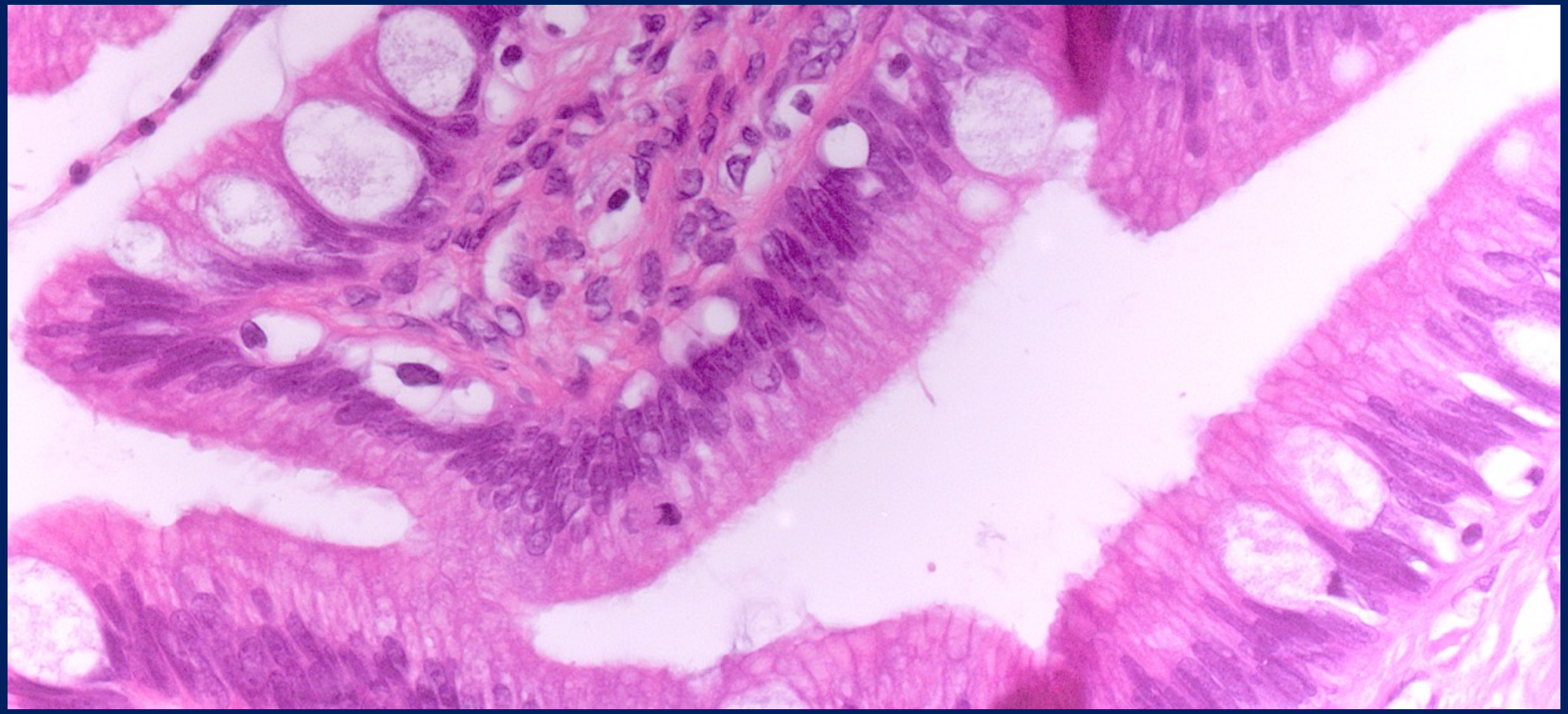
Treat as usual AIS – complete excision

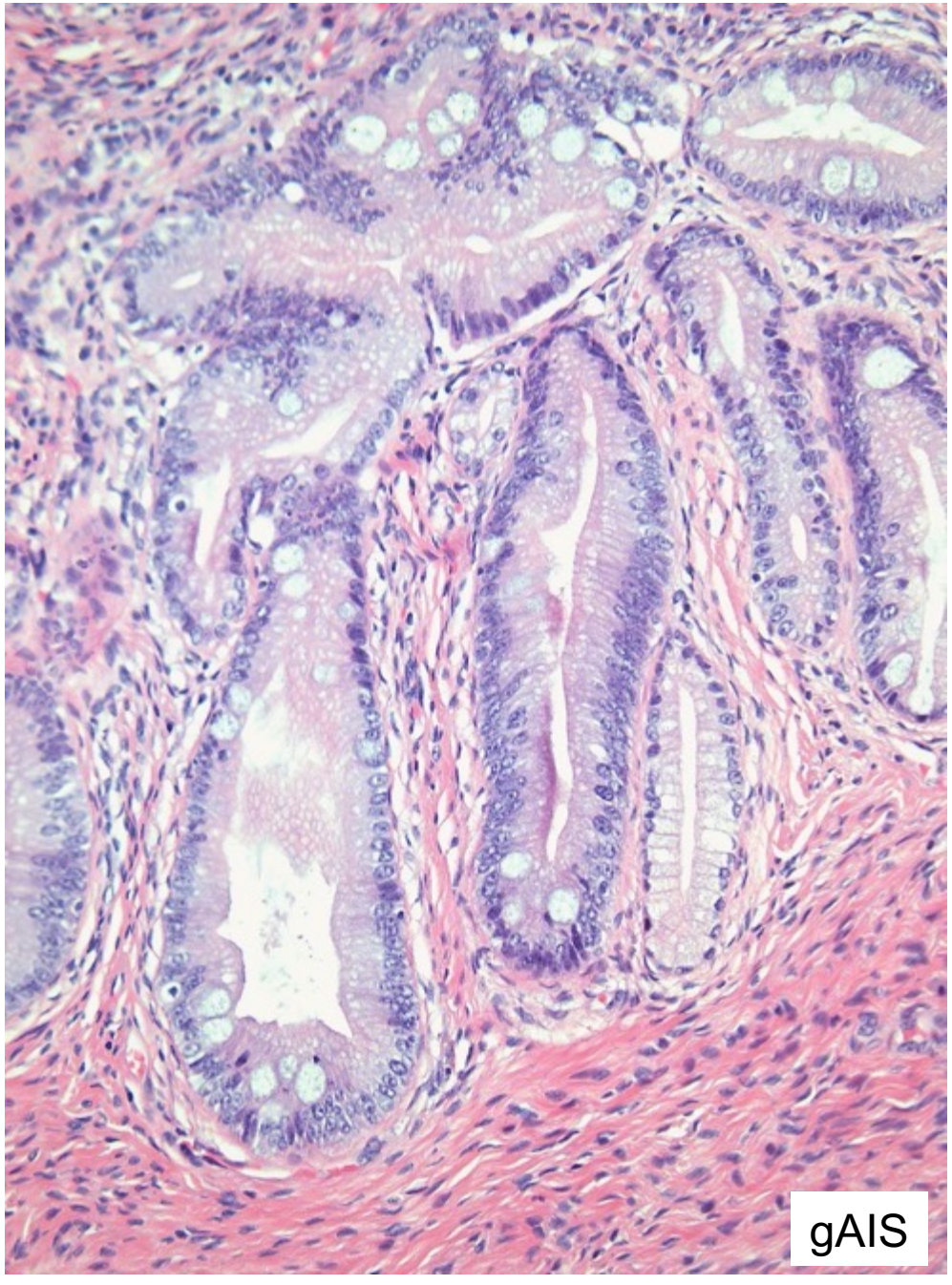





Invasive stratified mucin-producing carcinoma (iSMC)
Variant of HPV-associated adenocarcinoma
Characteristic morphology, aggressive behaviour
Lastra et al. AJSP 2016;40:262-269
Horn et al. J Cancer Res Clin Oncol 2019;145:2573-2582

“Intestinal-type” AIS





Intestinal differentiation

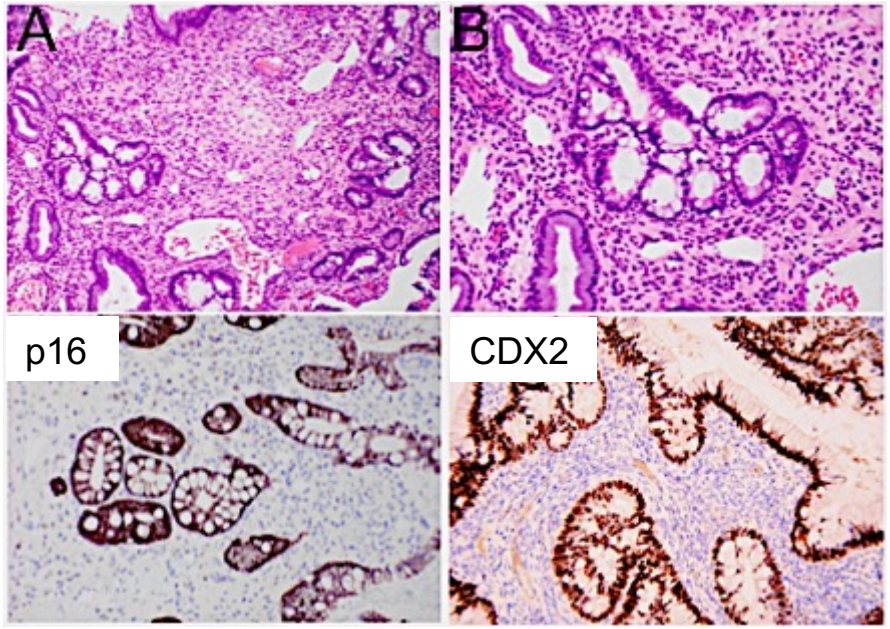
- Goblet cells, neuroendocrine cells, rarely Paneth cells
- CDX2 & CK20 expression

- Occurs in both HPV-associated and HPV-independent (gastric-type) AIS

- Previously “intestinal-type AIS” but this encompasses both HPV-associated and HPV-independent

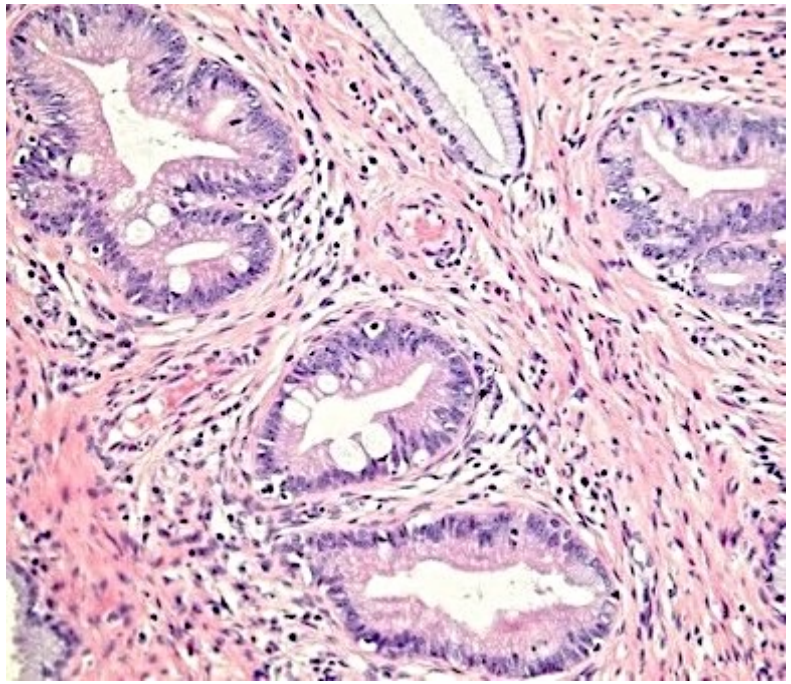
Recommended terminology

HPV-associated AIS with intestinal differentiation



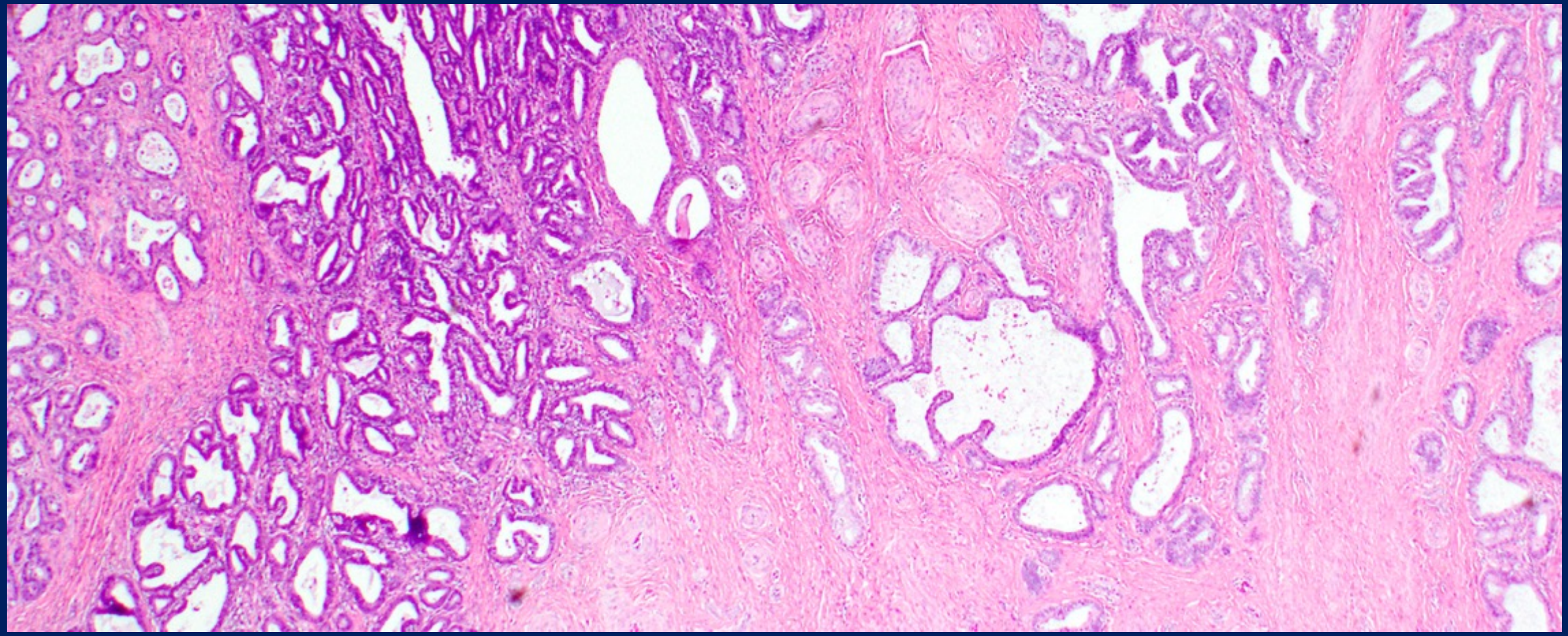
- Nuclear atypia may be subtle due to compression by cytoplasmic mucin
- Easily identifiable mitotic and apoptotic activity
- Block-type p16, HR-HPV ISH positive

Gastric-type AIS



- Abundant eosinophilic/clear cytoplasm, basal nuclei, subtle nuclear atypia
- Low mitotic and apoptotic activity
- p16 negative / non-block staining, HPV ISH neg

HPV-associated adenocarcinoma



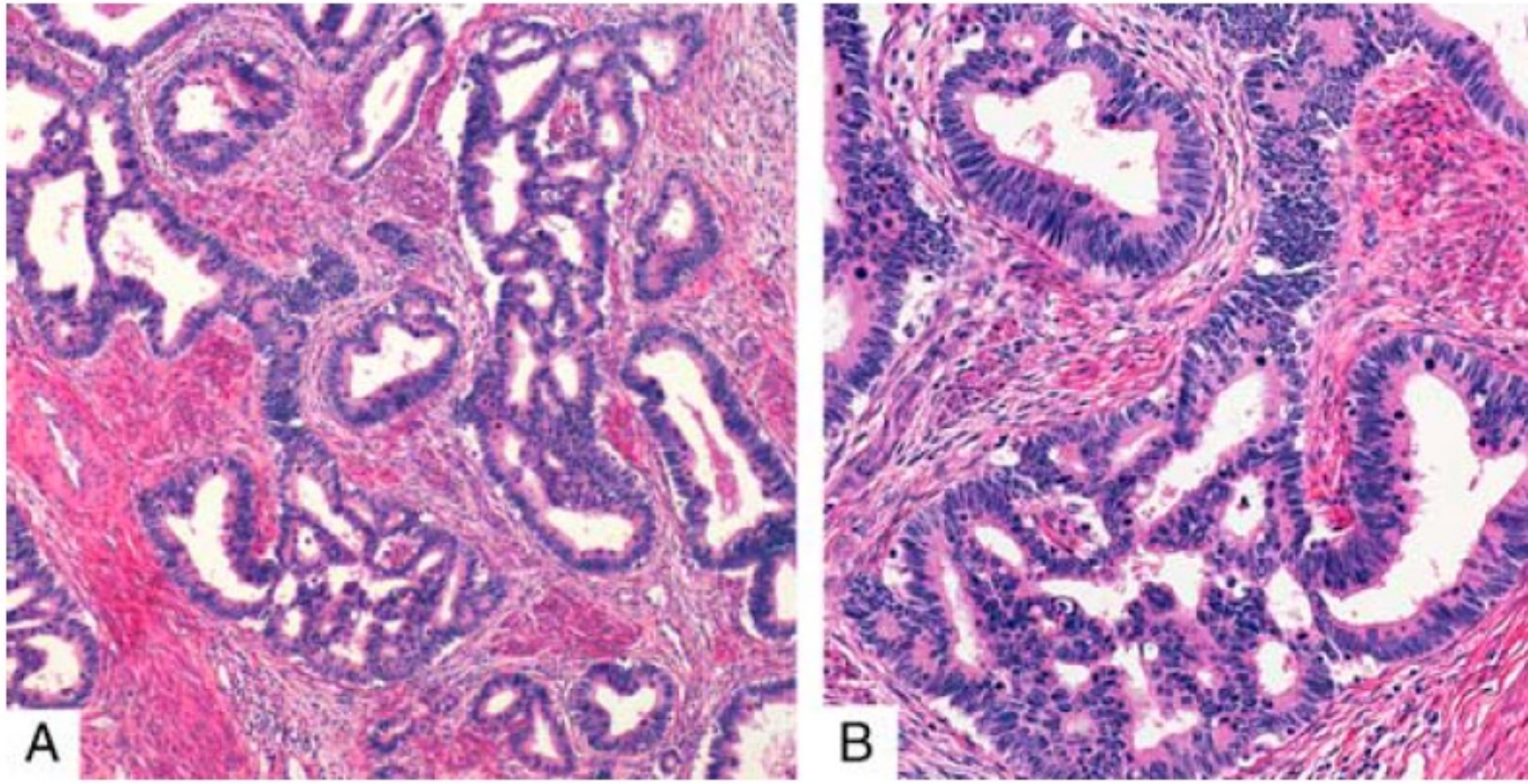
Usual type

- Most common
- 75-80% of all endocervical adenocarcinomas

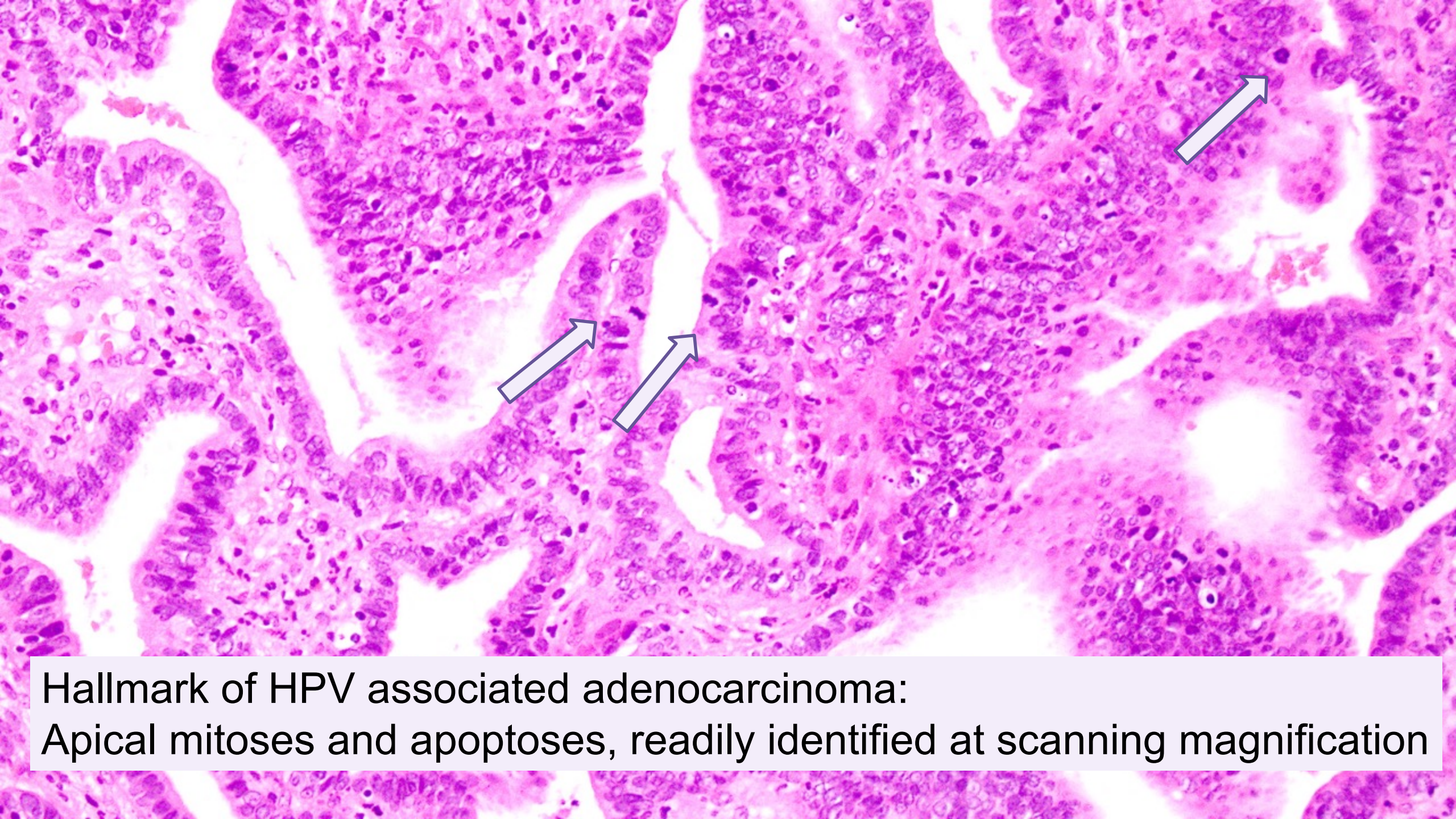
- Previously:

"*endocervical type*"
if obvious cytoplasmic mucin

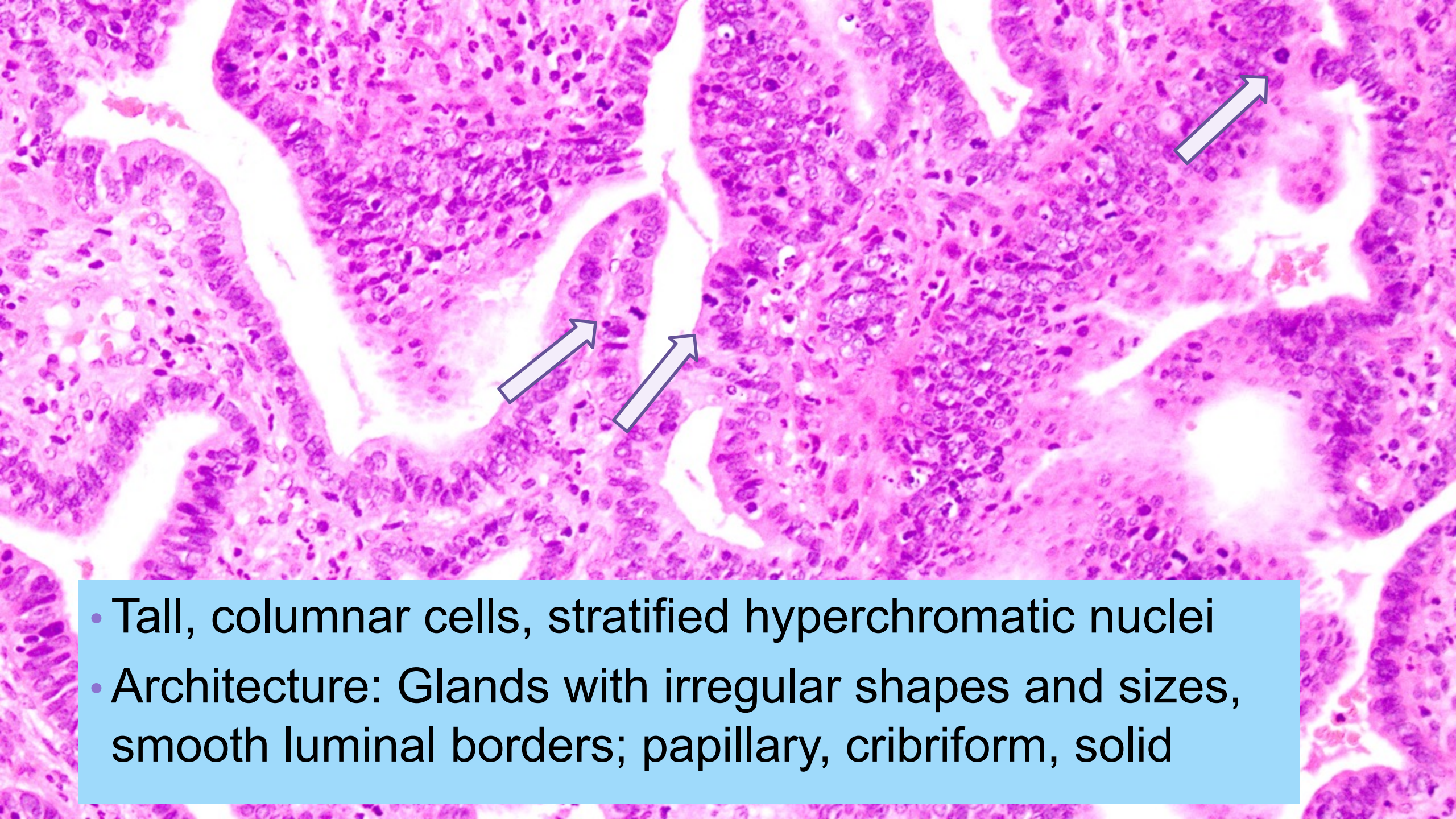
"*endometrioid type*"
if mucin-deplete



ISGyP consensus issue



Hallmark of HPV associated adenocarcinoma:
Apical mitoses and apoptoses, readily identified at scanning magnification

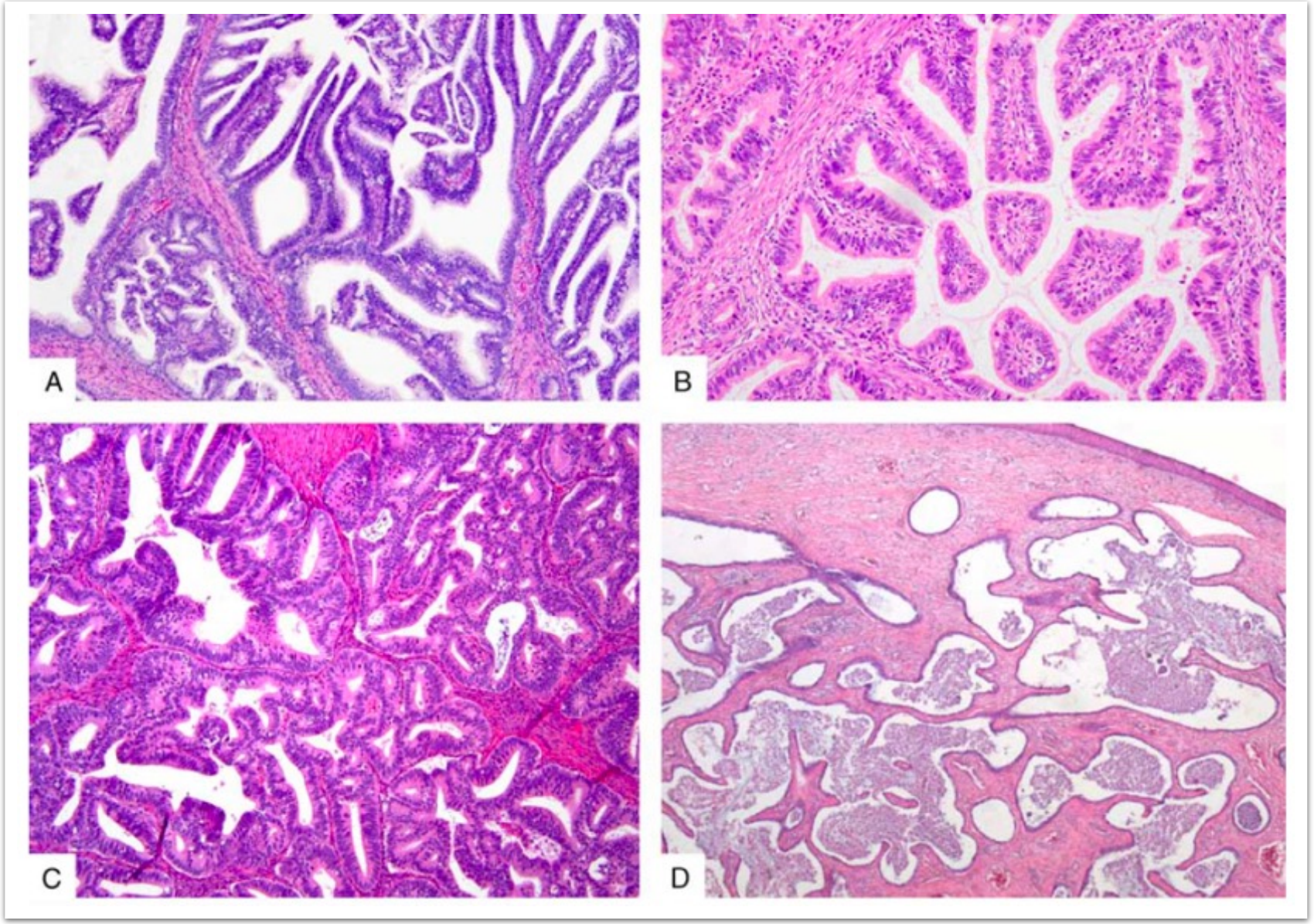


- Tall, columnar cells, stratified hyperchromatic nuclei
- Architecture: Glands with irregular shapes and sizes, smooth luminal borders; papillary, cribriform, solid

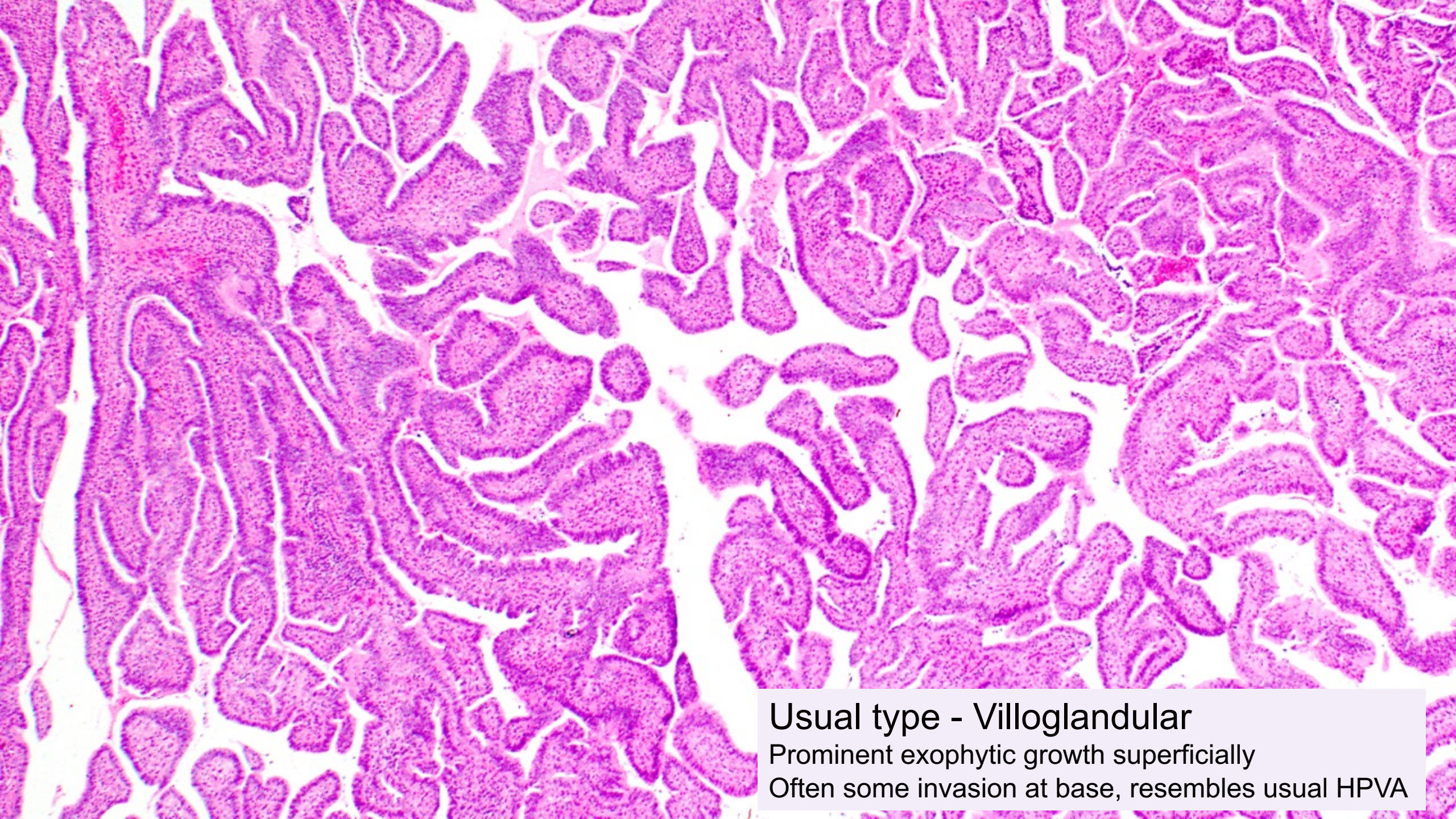
Usual type

Less common architectural features

- Villoglandular
- Micropapillary
- Macrocystic
- Microcystic
- Trabecular
- Single cell



ISGyP consensus issue



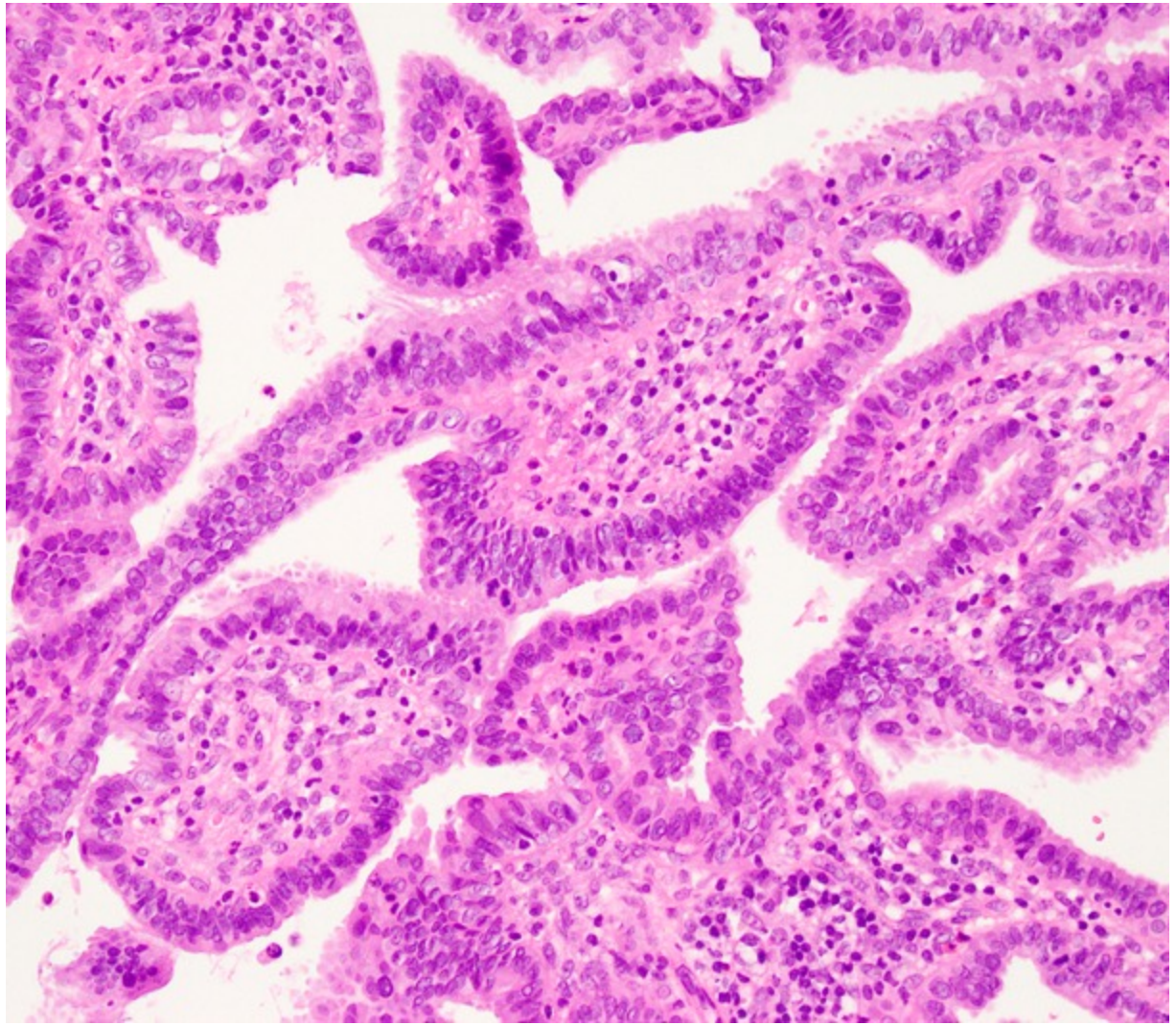
Usual type - Villoglandular

Prominent exophytic growth superficially

Often some invasion at base, resembles usual HPVA

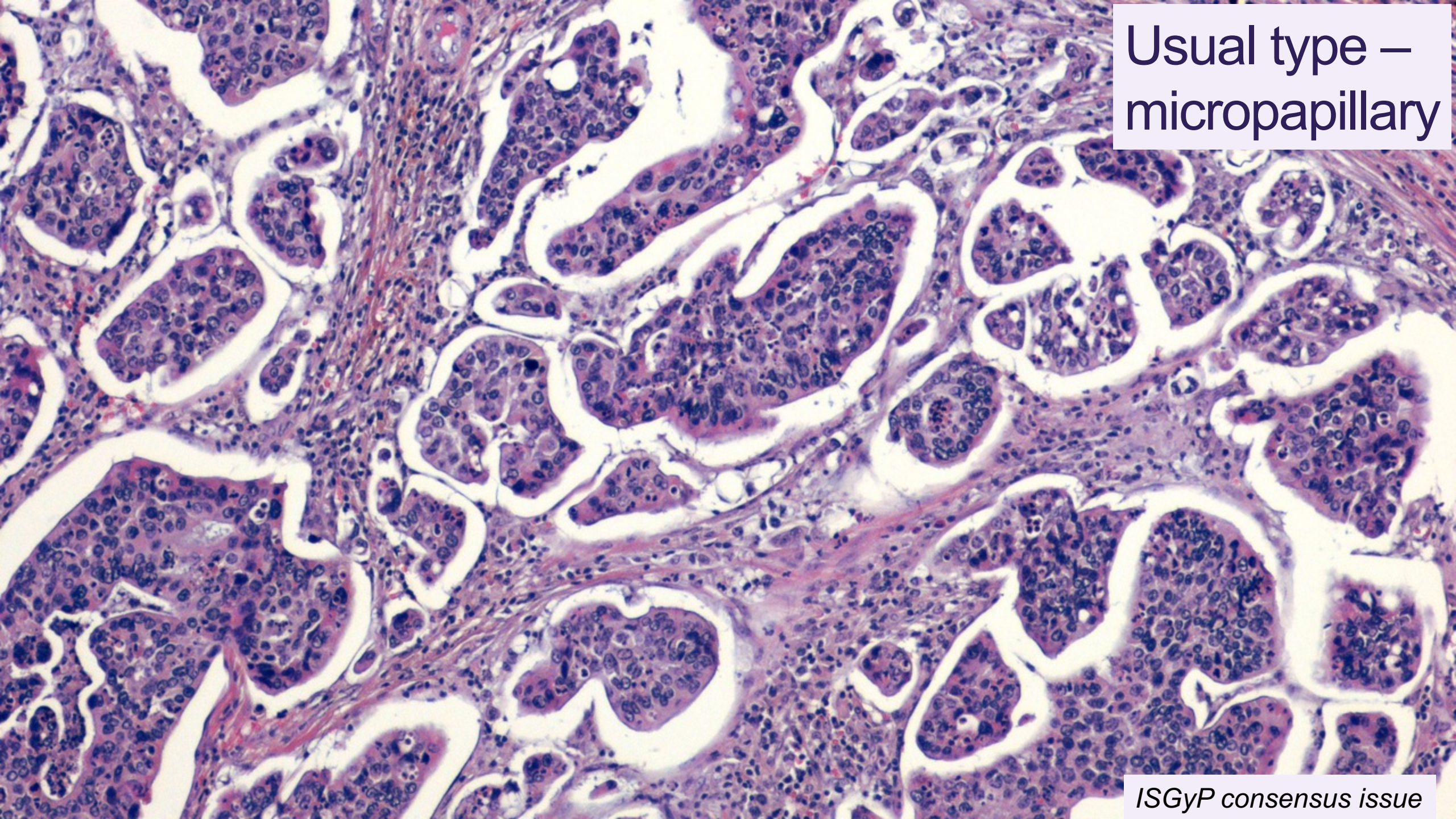
Usual type - villoglandular

- Atypia is usually low-grade
- Characteristic apical mitoses, apoptotic bodies, IHC same as usual tumours so *not a separate tumour type*



If this growth patten prominent: "HPVA endocervical adenocarcinoma with villoglandular architecture"

Usual type – micropapillary



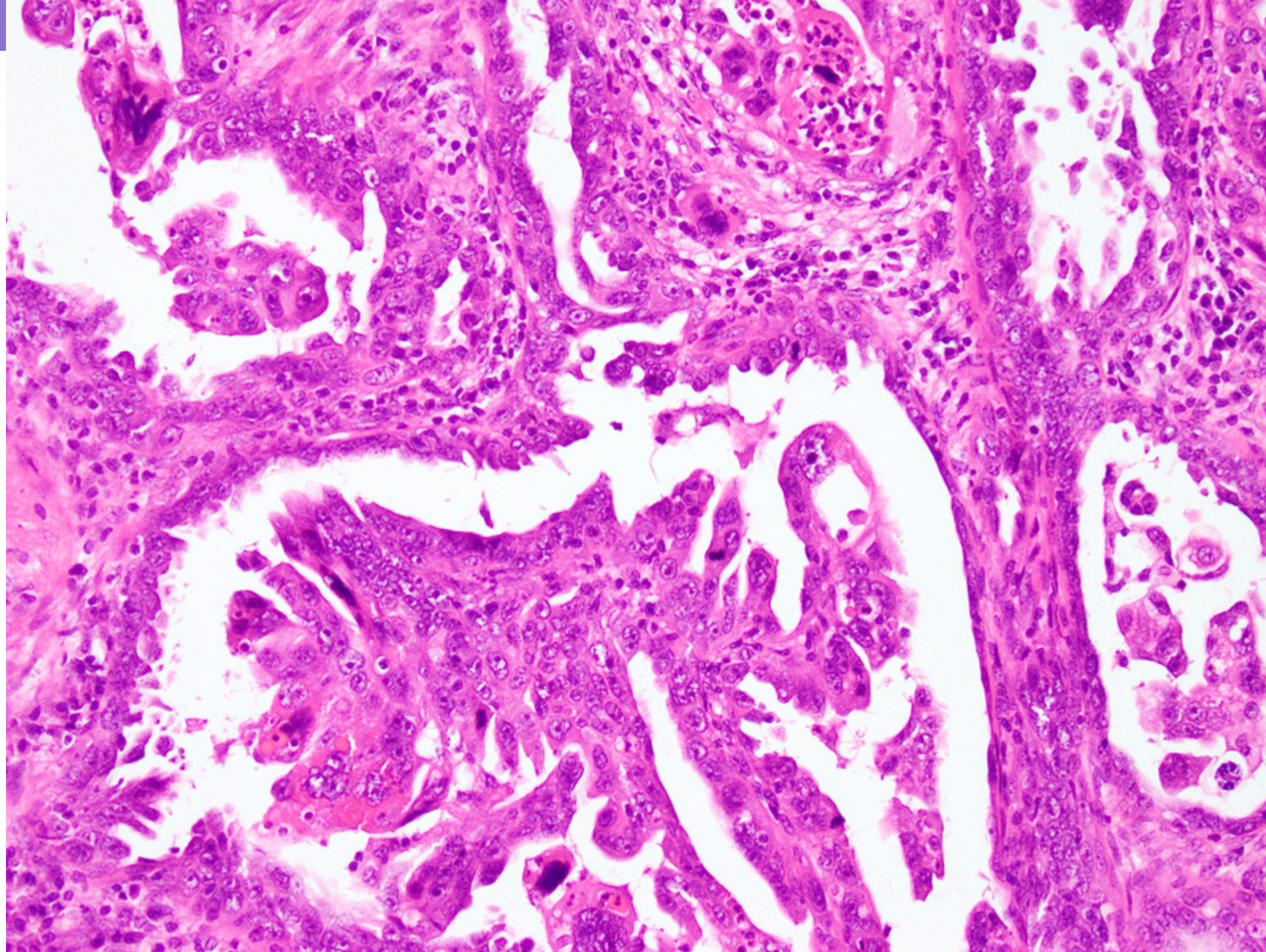
ISGyP consensus issue

Serous carcinoma?

Usual HPVA adenocarcinoma with papillary or micropapillary architecture

versus

Serous carcinoma - direct spread or drop metastasis from uterine or tubo-ovarian primary



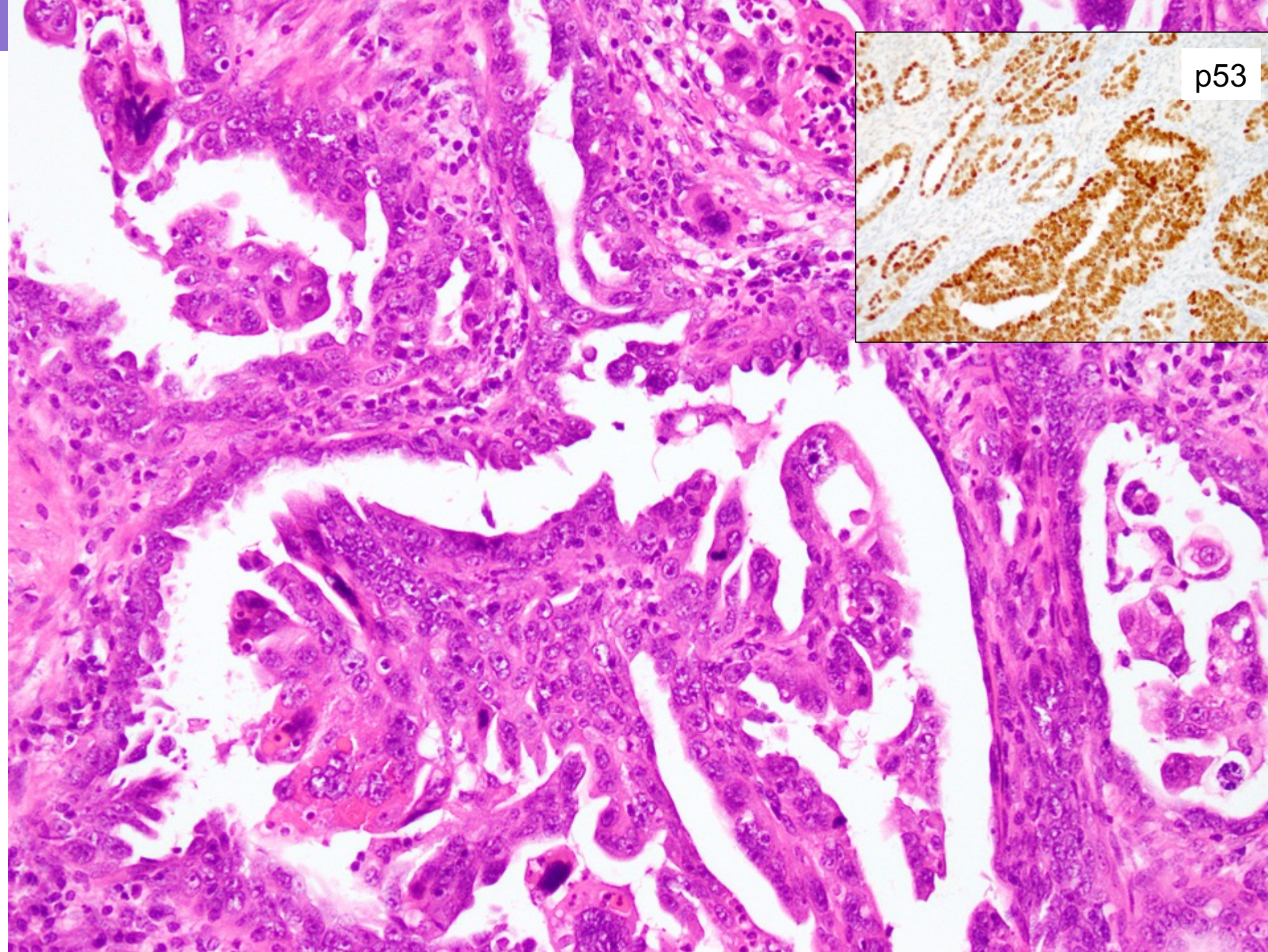
Serous carcinoma?

p16: Positive in both

p53: Mutation-type staining favours serous from uterus or adnexa

p53: Wild type staining seen in most HPVA

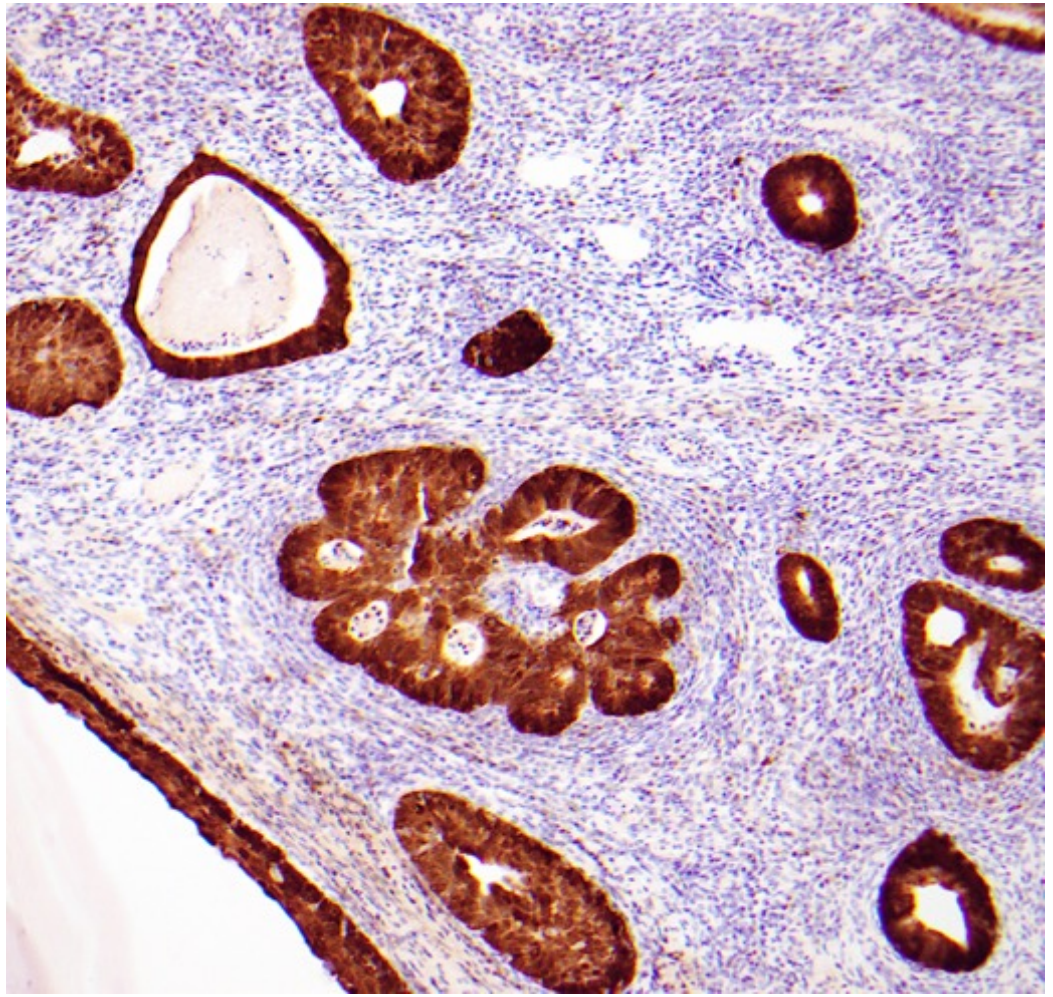
No longer accept serous ca as a primary tumour type in the cervix.



Ancillary studies – Typical usual-type adenoca

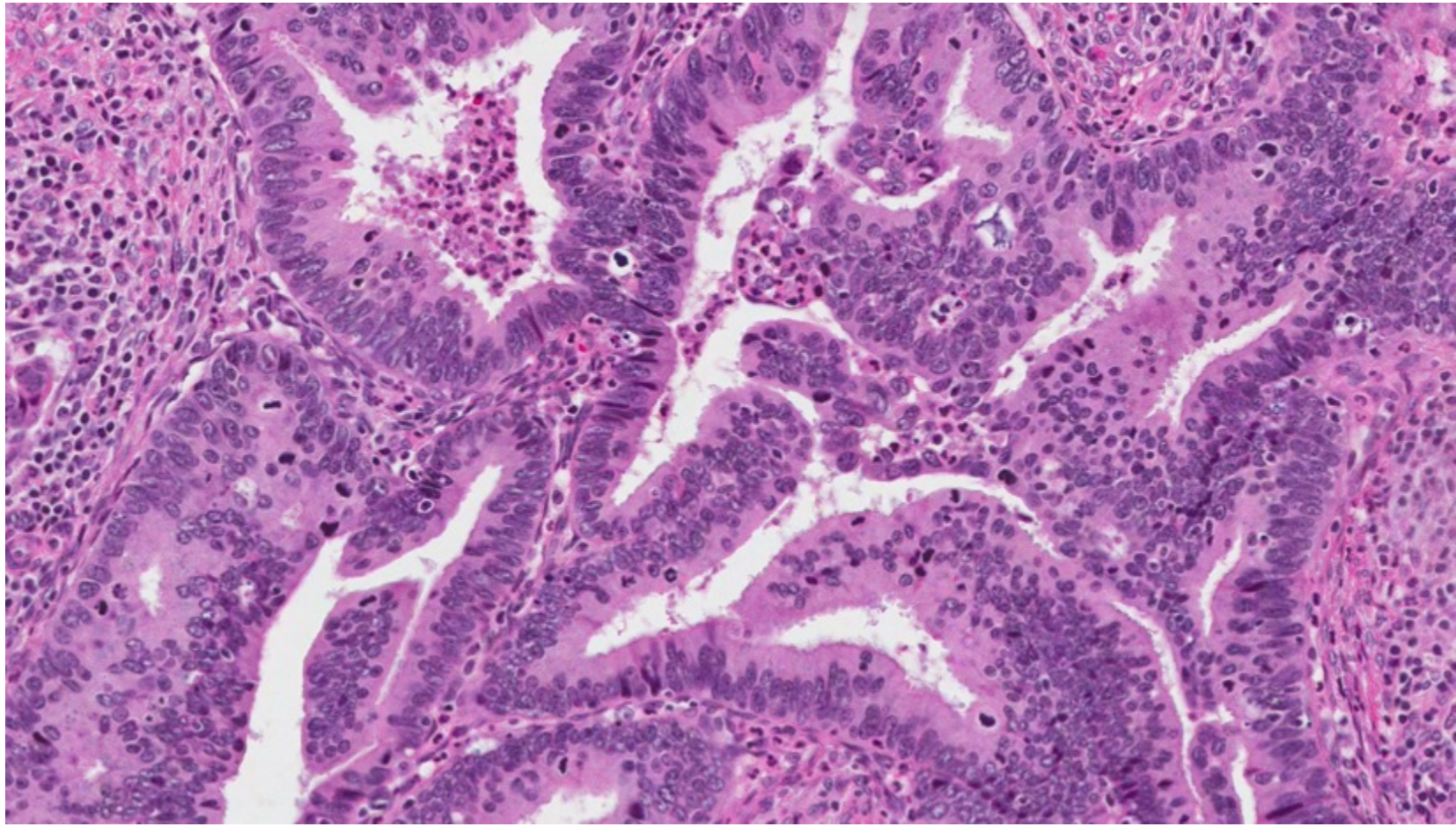
- **p16:** Diffuse positive staining, essentially every cell; anything less than block-type staining is not supportive of a HRHPVA adenoca
- **ER/PR** negative
- **Vimentin** negative
- MUC6, HNF1beta, NapsinA, GATA3, AR, HER2 negative
- **P53** wild-type

Occasional positive/aberrant staining



Usual type

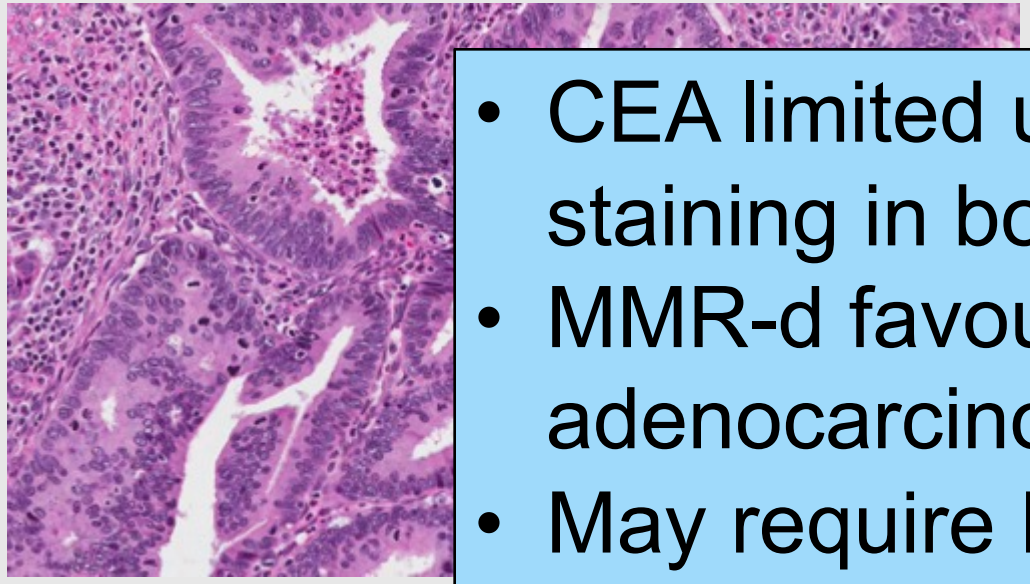
- Mucin deplete appearance may suggest endometrioid adenocarcinoma of endometrial origin
- Don’t call a mucin deplete adenocarcinoma endometrioid if there are apical MF and apoptoses



2020 WHO Blue book;
Source: C Parra-Herran

Cervical endometrioid adenocarcinomas very rare, likely arise in endometriosis, HPV-negative

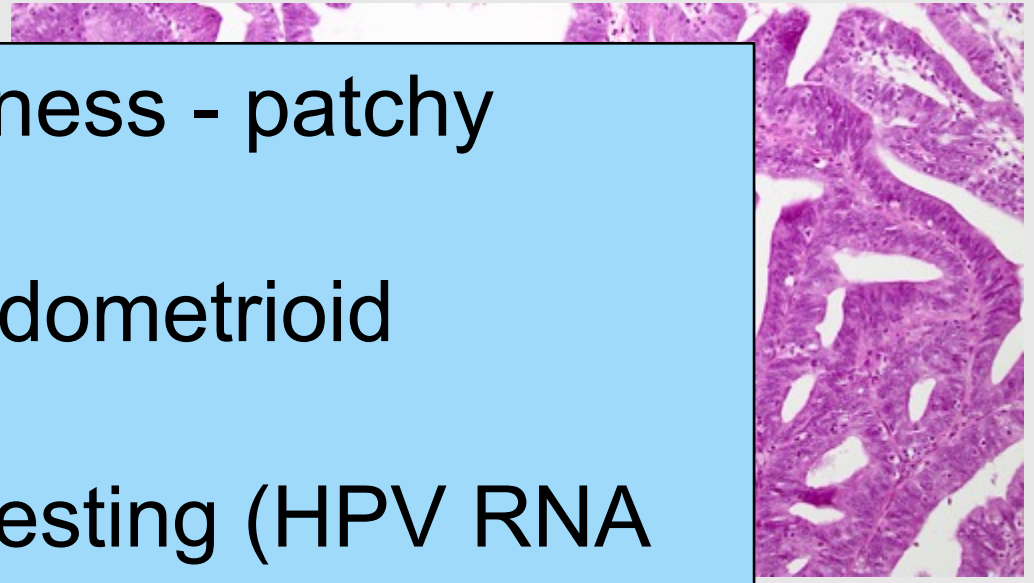
HPVA cervical adenocarcinoma



ER, PR: Usually negative
VIMENTIN: Usually negative
p16 diffuse positive

Caveat: Rare exceptions – positive staining

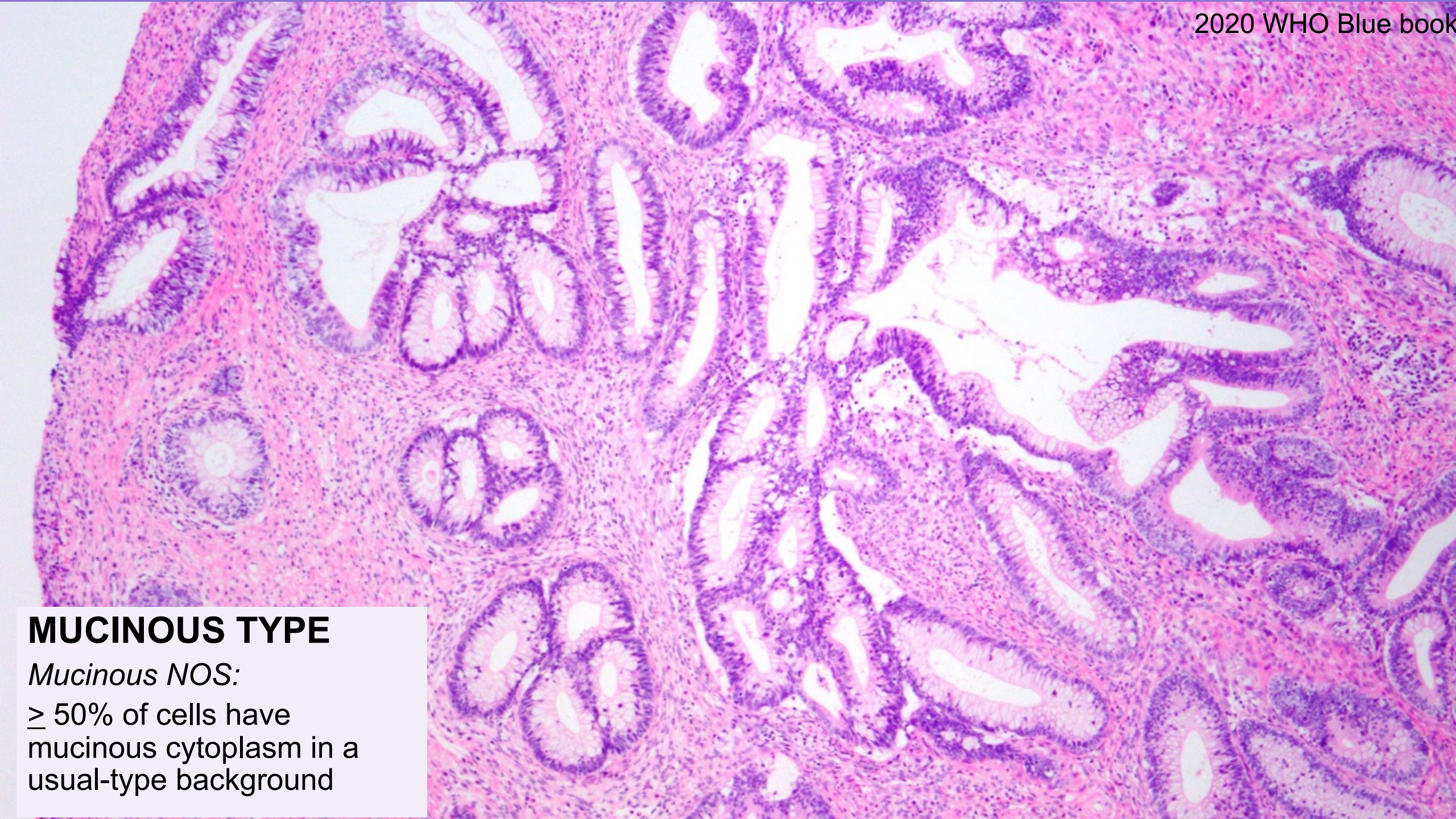
Endometrial endometrioid adenocarcinoma



VIMENTIN: Usually positive
p16 patchy/negative

Caveat: HG endometrioid adenoca may be negative for ER/PR and p16 block positive

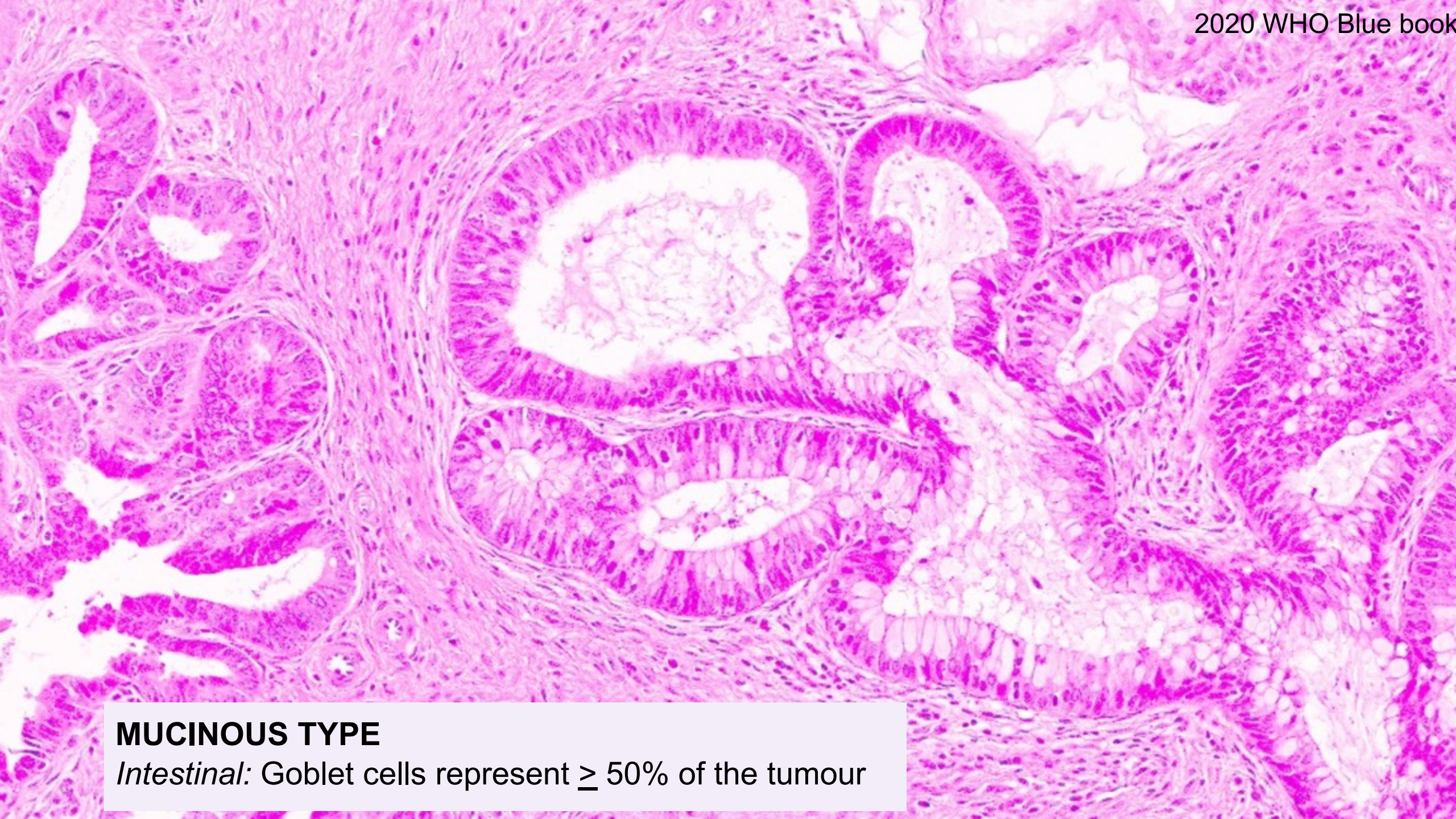
- CEA limited usefulness - patchy staining in both
- MMR-d favours endometrioid adenocarcinoma
- May require HPV testing (HPV RNA ISH) to resolve difficult cases



MUCINOUS TYPE

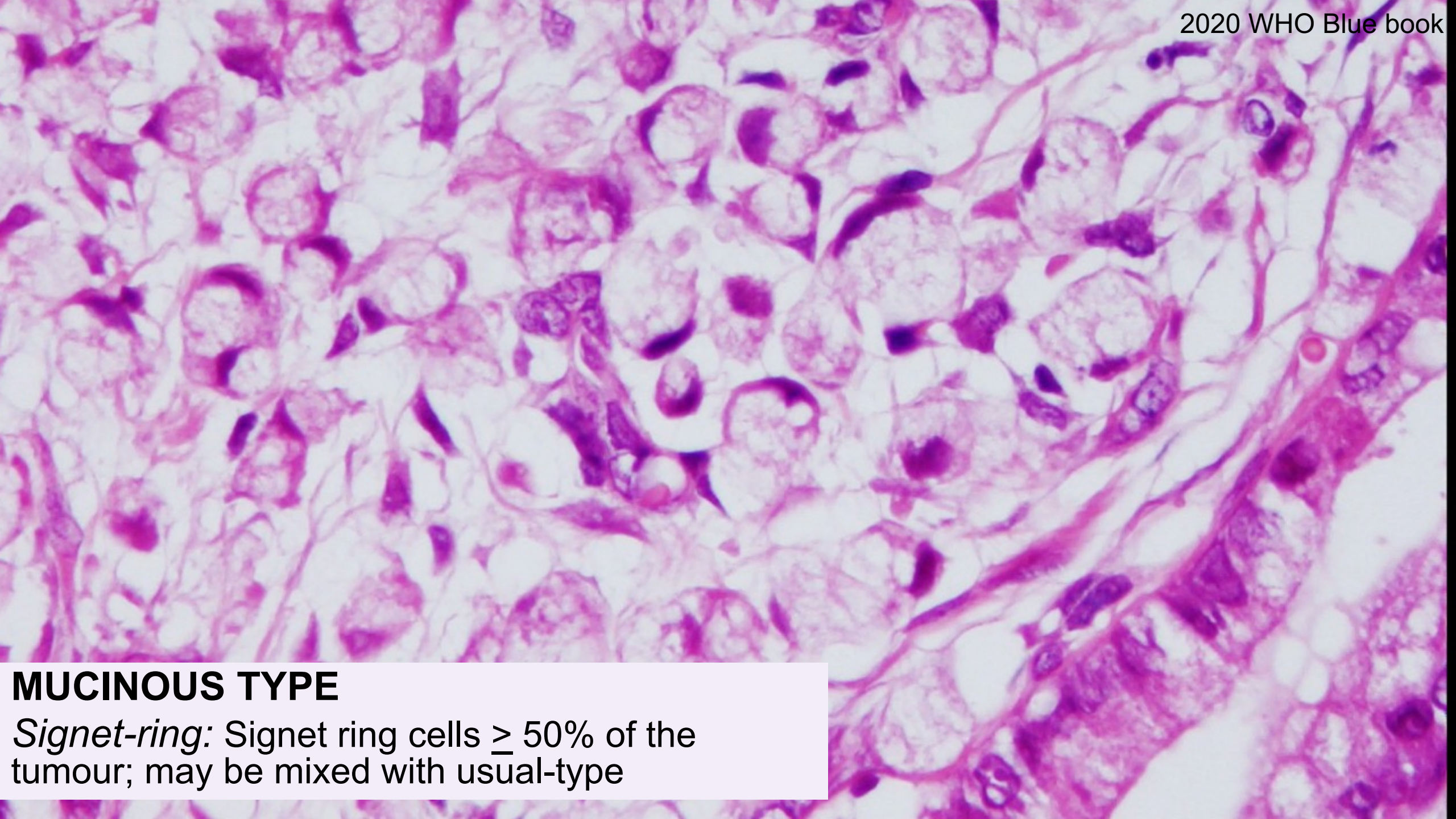
Mucinous NOS:

≥ 50% of cells have mucinous cytoplasm in a usual-type background



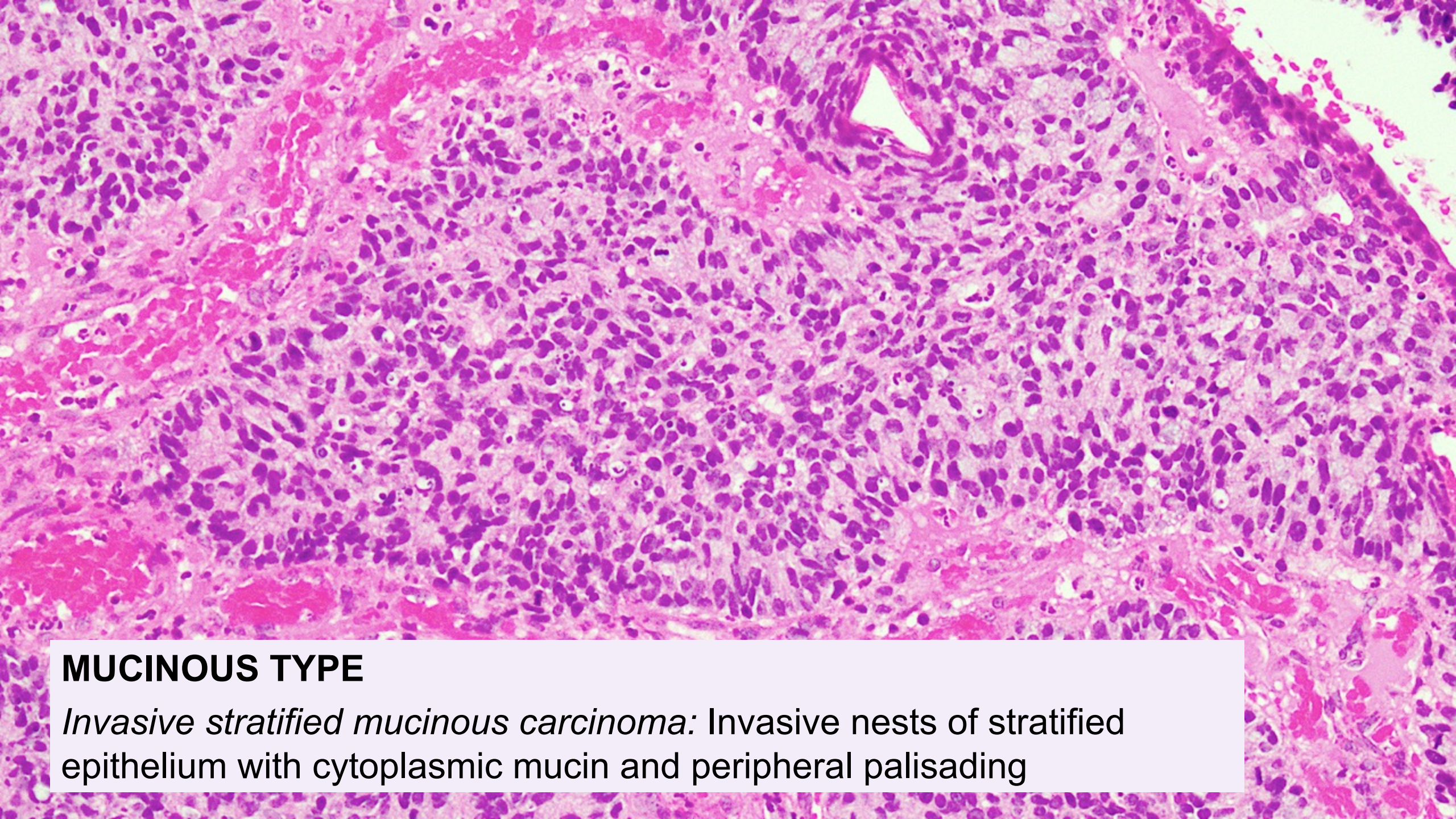
MUCINOUS TYPE

Intestinal: Goblet cells represent ≥ 50% of the tumour



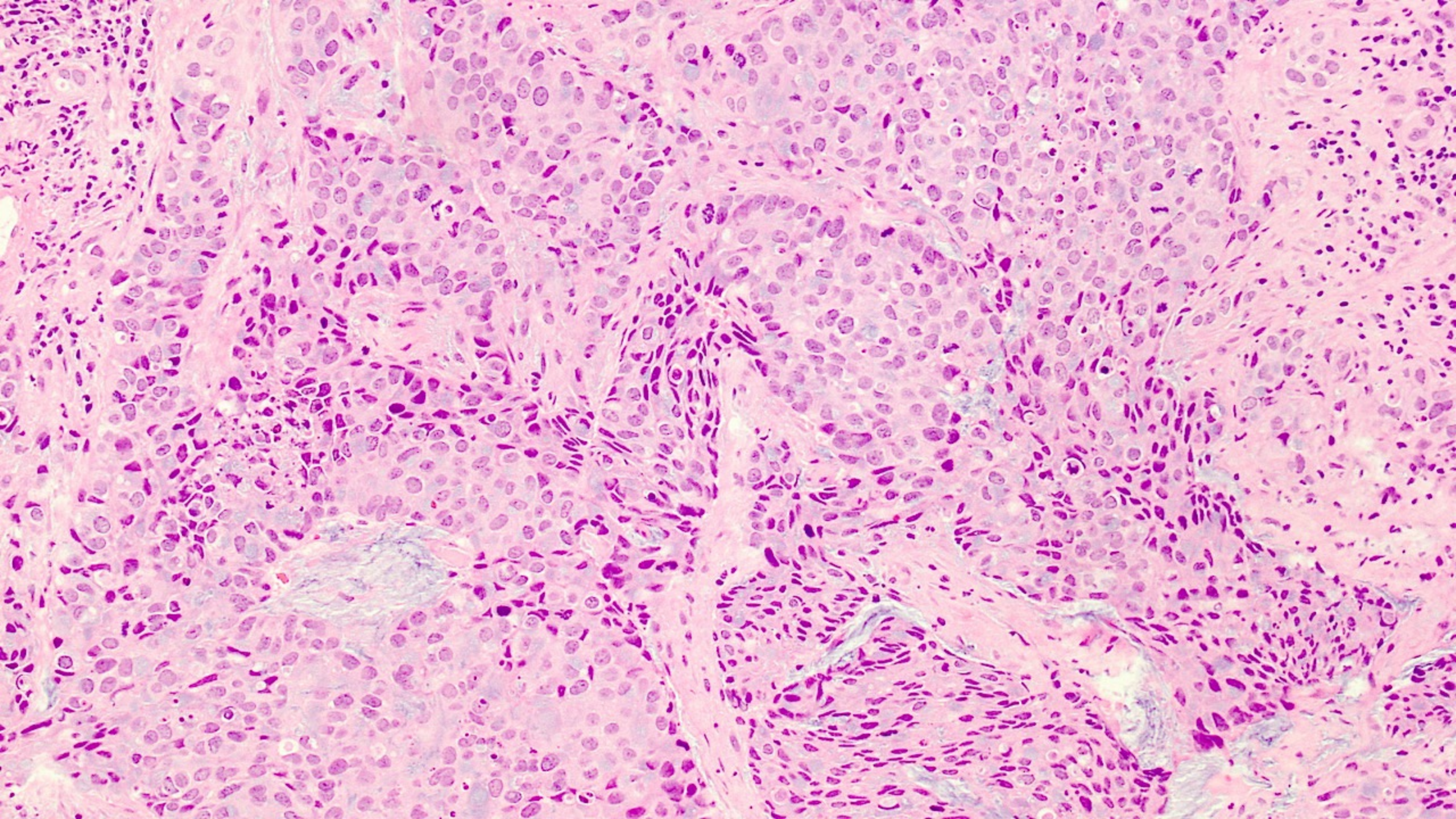
MUCINOUS TYPE

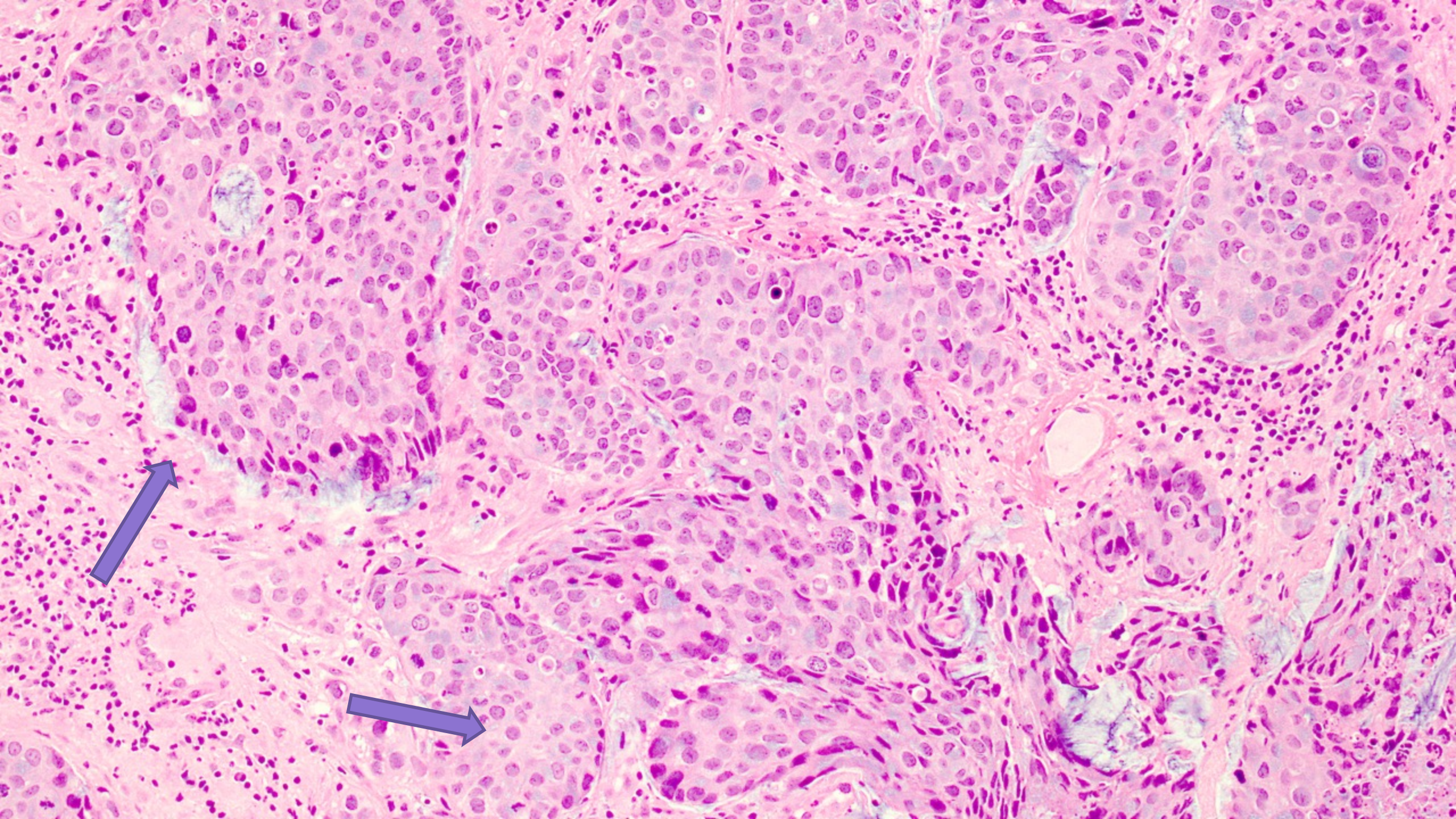
Signet-ring: Signet ring cells ≥ 50% of the tumour; may be mixed with usual-type

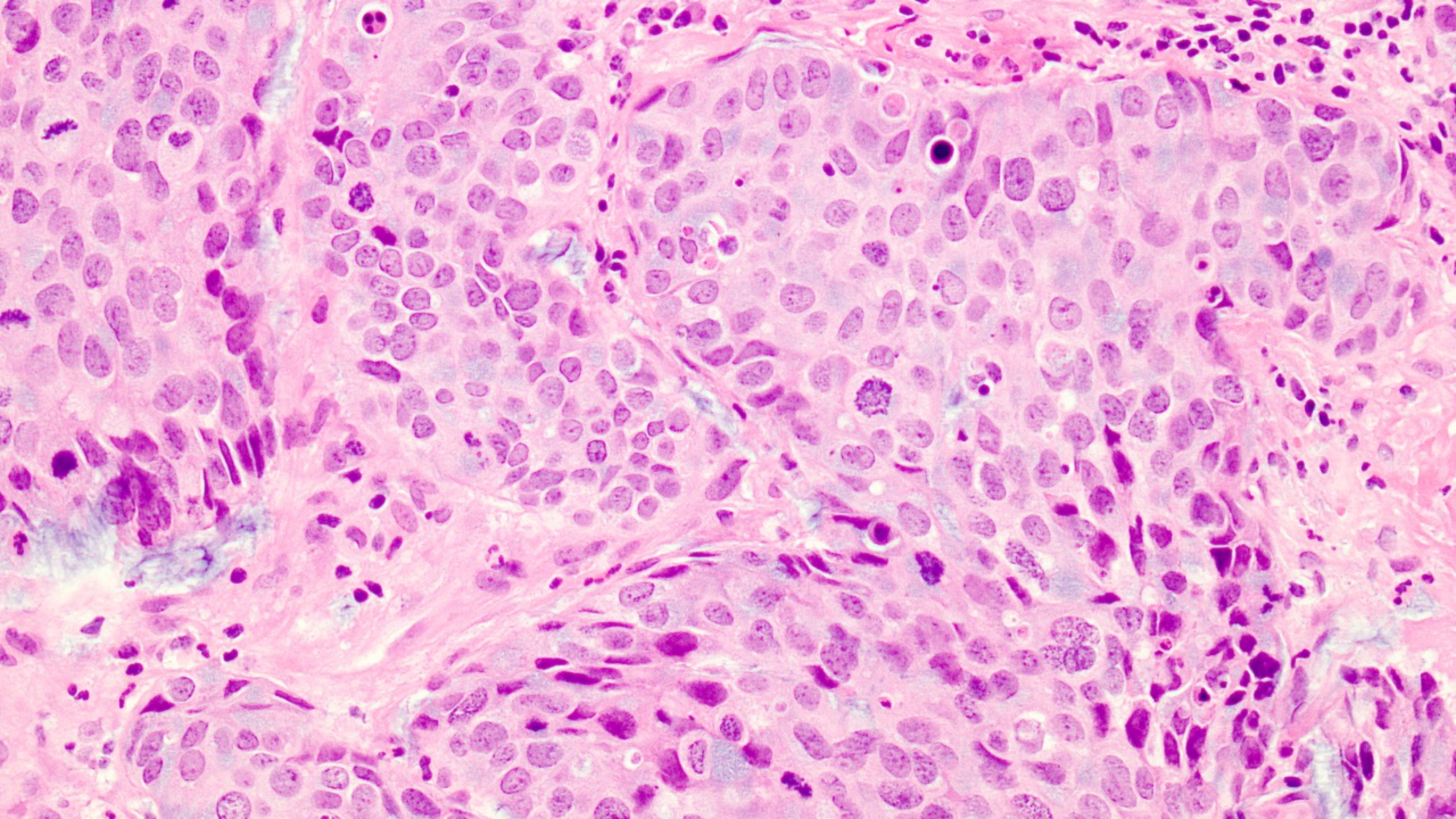


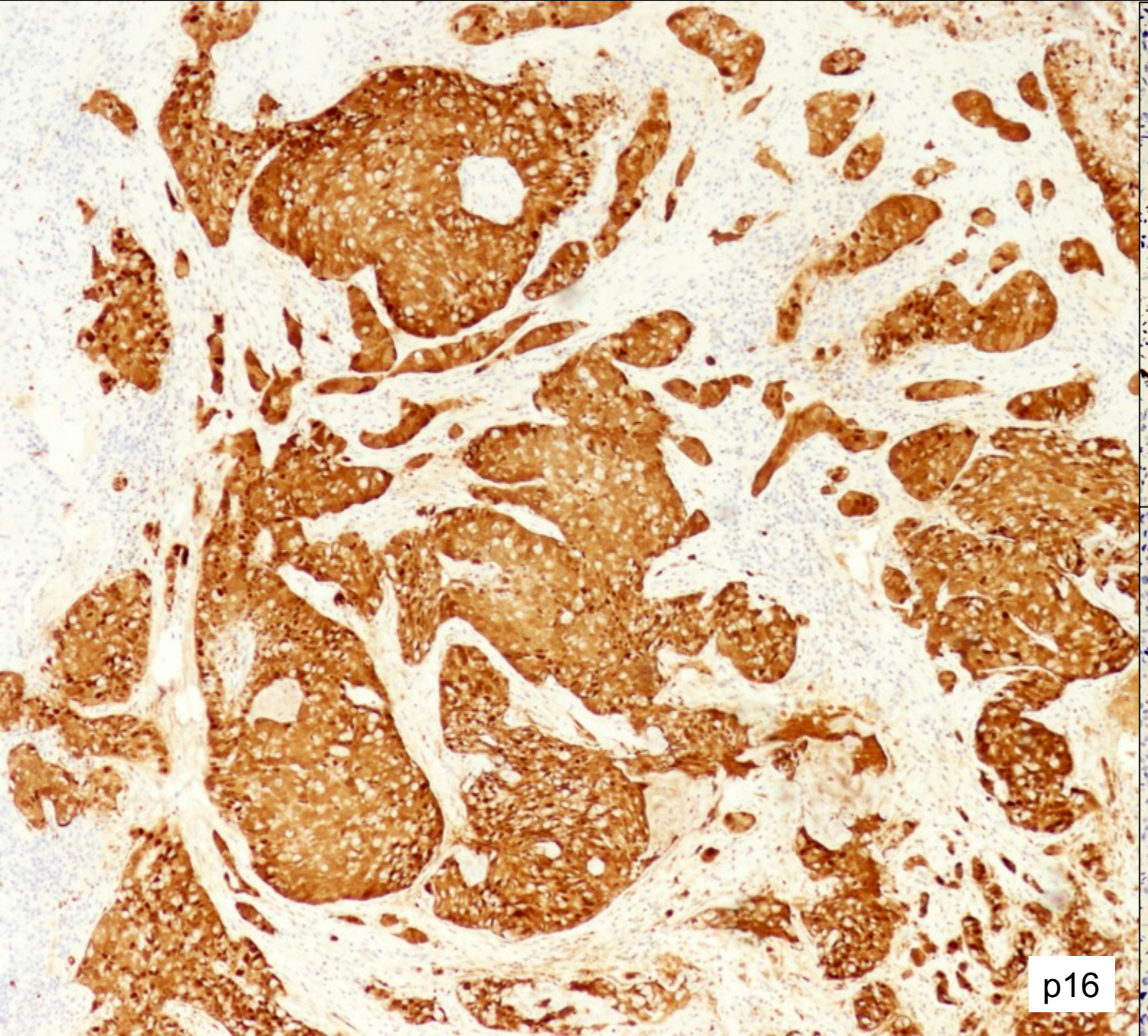
MUCINOUS TYPE

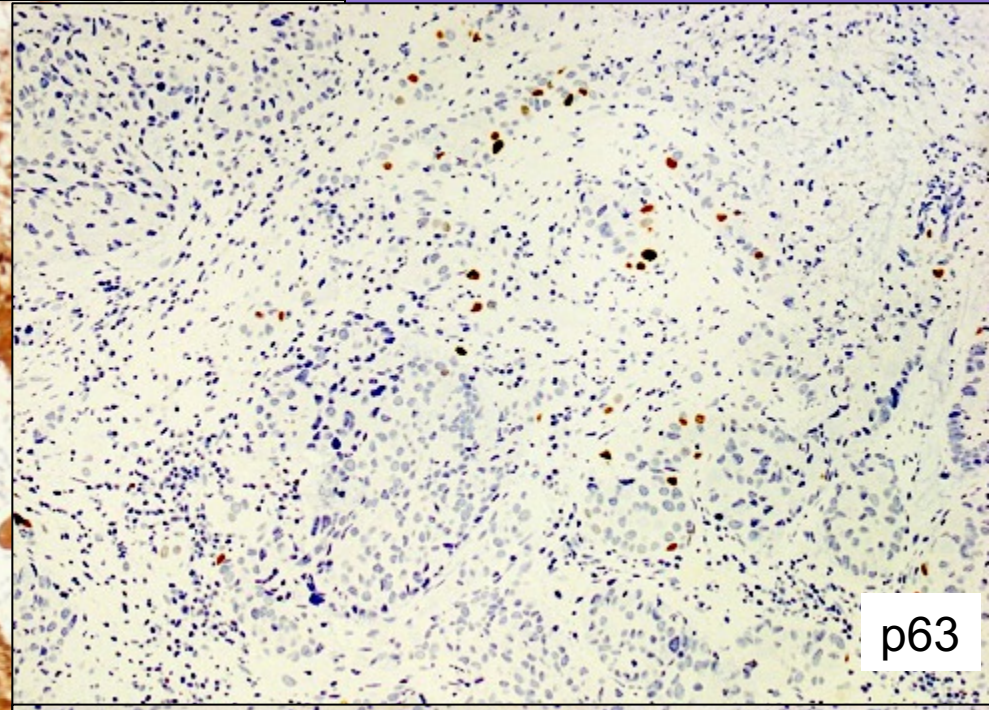
Invasive stratified mucinous carcinoma: Invasive nests of stratified epithelium with cytoplasmic mucin and peripheral palisading

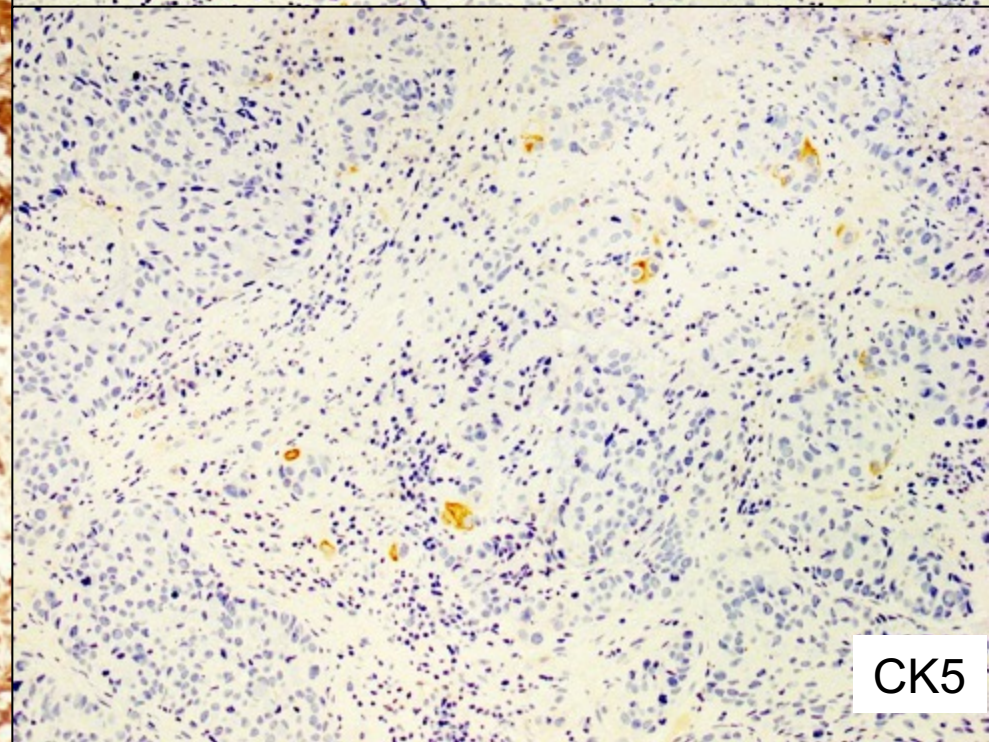







p16


p63


CK5

Invasive stratified mucinous carcinoma

- Pure or mixed with other HPVA carcinoma – glandular / squamous / neuroendocrine

Morphological diversity

- Architecture:
  - Insular, glandular, solid, papillary, trabecular, micropapillary, single cell
- Cytology:
  - Mucin rich vs. mucin poor, cytoplasmic clearing, glassy cell like, histiocytoid, signet ring-like, bizarre atypia, squamoid +/- keratinization, neutrophilic infiltrates

Unlike other HPV-A tumours, iSMC may show mutation-type p53 staining, less PAX8

Stolinicu et al,
AJSP 2020;44:873-880

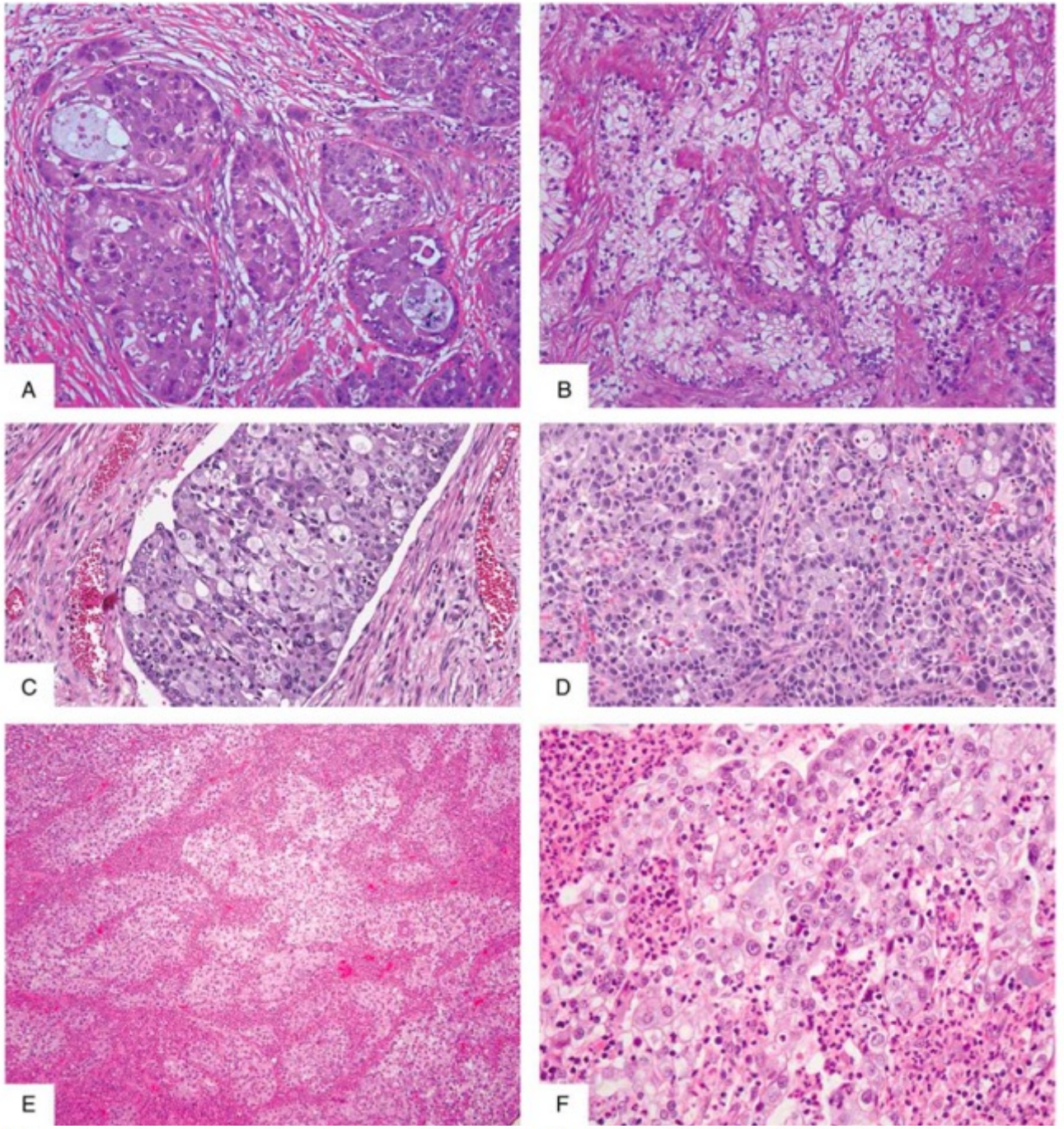
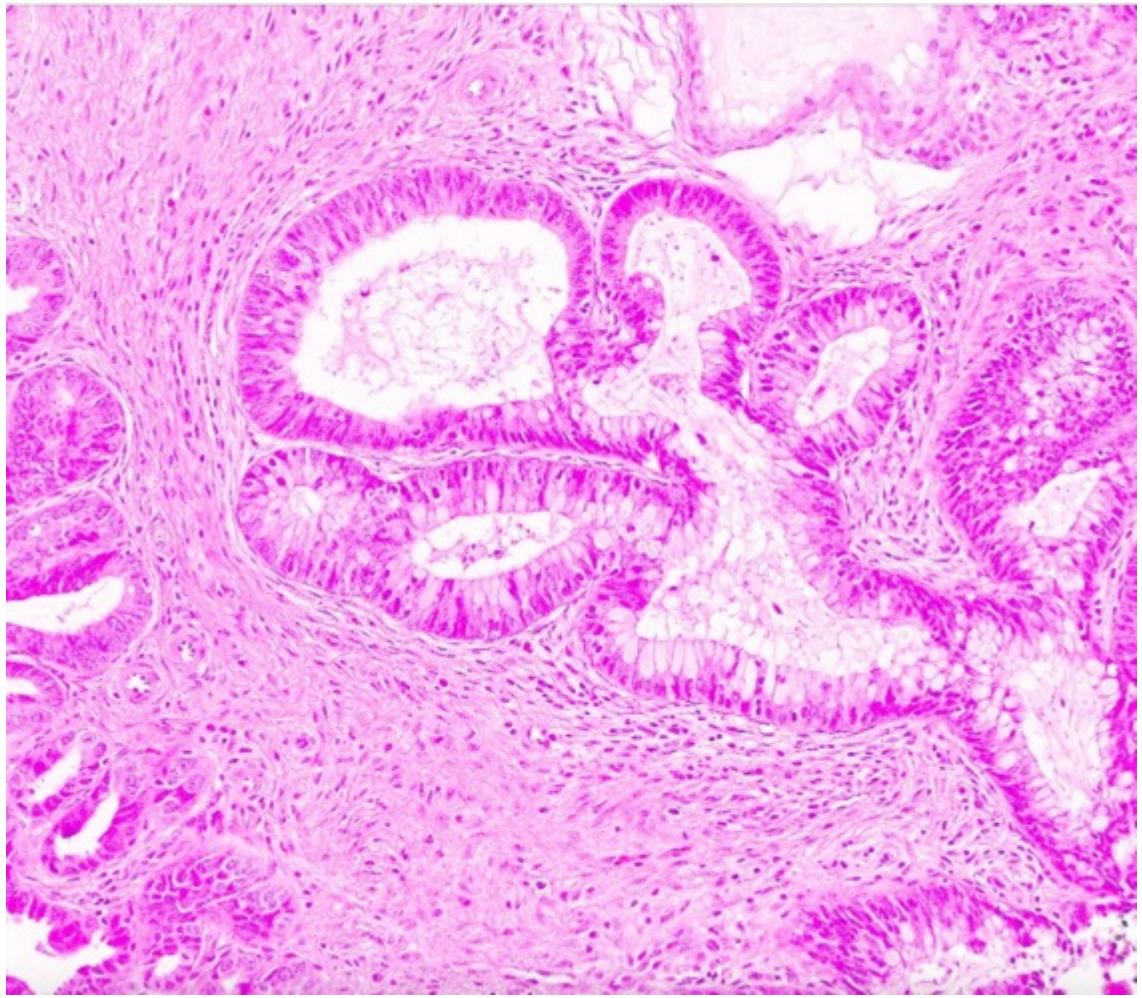


FIGURE 3. ISMC with cytologic diversity: eosinophilic cytoplasm (A), cytoplasmic clearing (B), histiocytoid features (C), signet ring-like features (D), glassy cell-like features with infiltrating neutrophils and eosinophils (E, F).

Mucinous type HPV-A adenocarcinoma

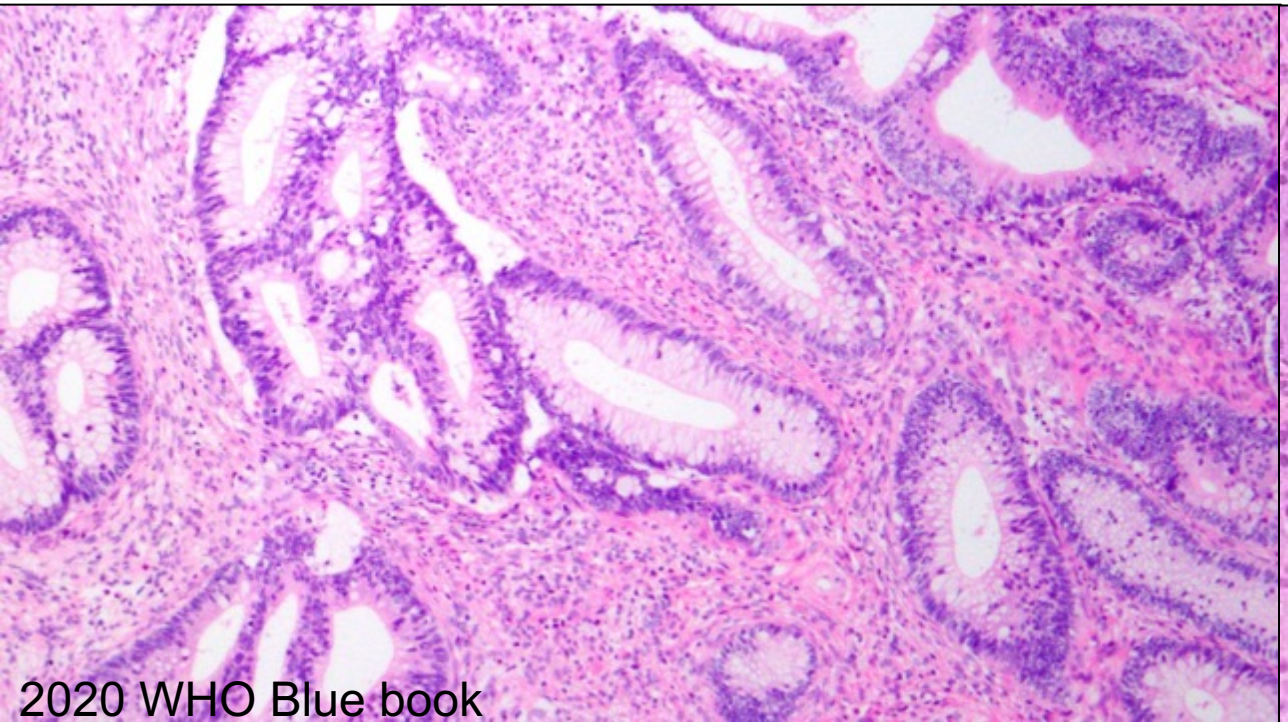
DIFFERENTIAL DIAGNOSES

- ? Endometrioid adenocarcinoma with mucinous differentiation
- ? HPV-I gastric-type adenocarcinoma
- ? Metastatic carcinoma

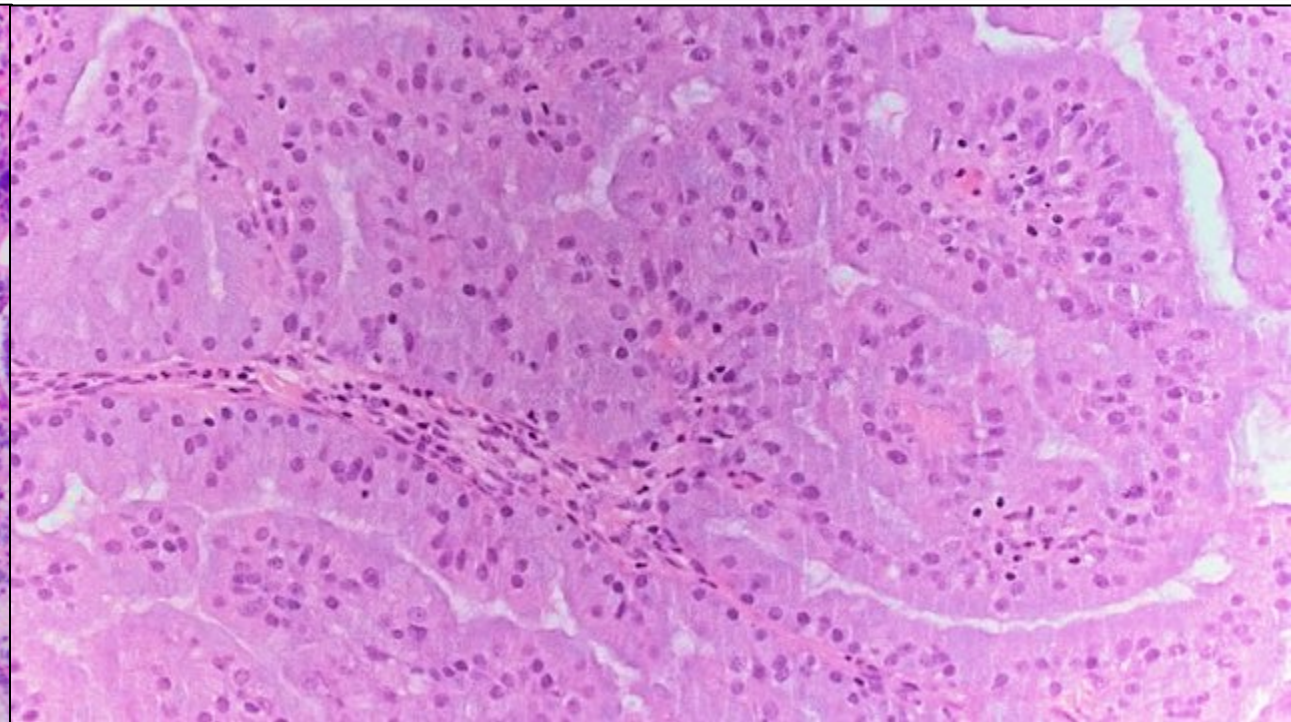


2020 WHO Blue book

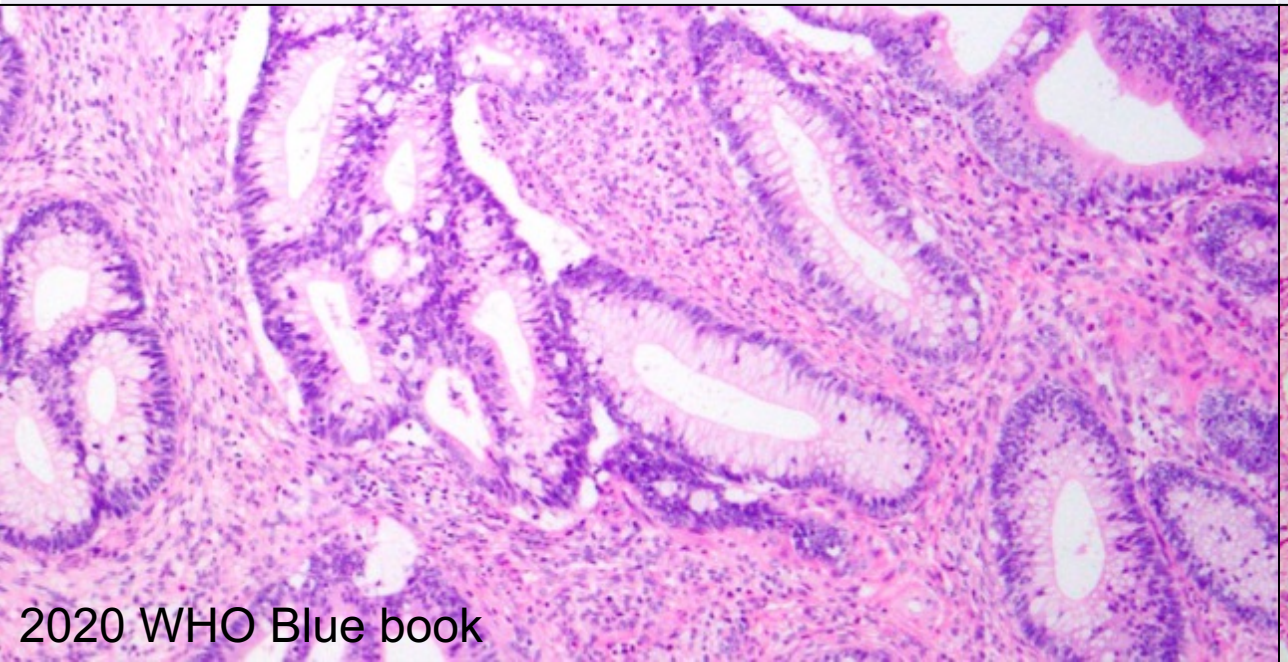
HPV-A mucinous carcinoma	Endometrioid adenocarcinoma with mucinous differentiation
Apical mitoses, apoptoses at low power	Less prominent
P16 block type, HPV positive	P16 mosaic/patchy
ER/PR, Vimentin negative	ER/PR, vimentin positive
HSIL / AIS	Atypical hyperplasia



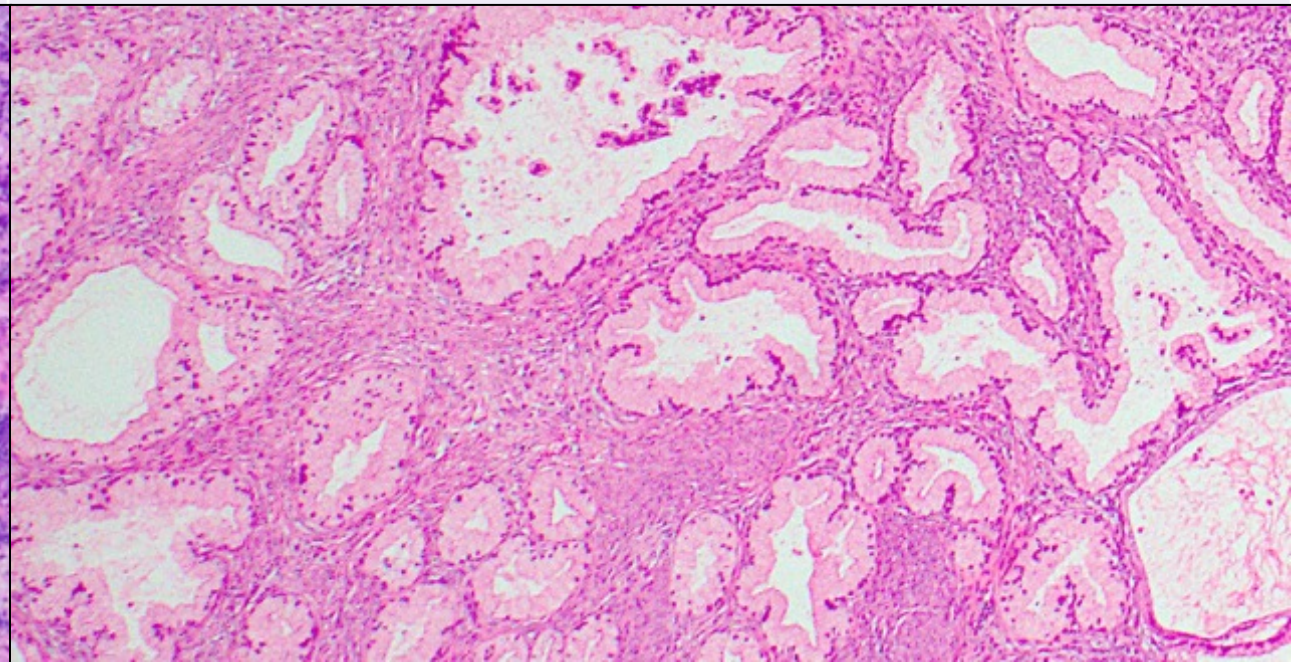
2020 WHO Blue book



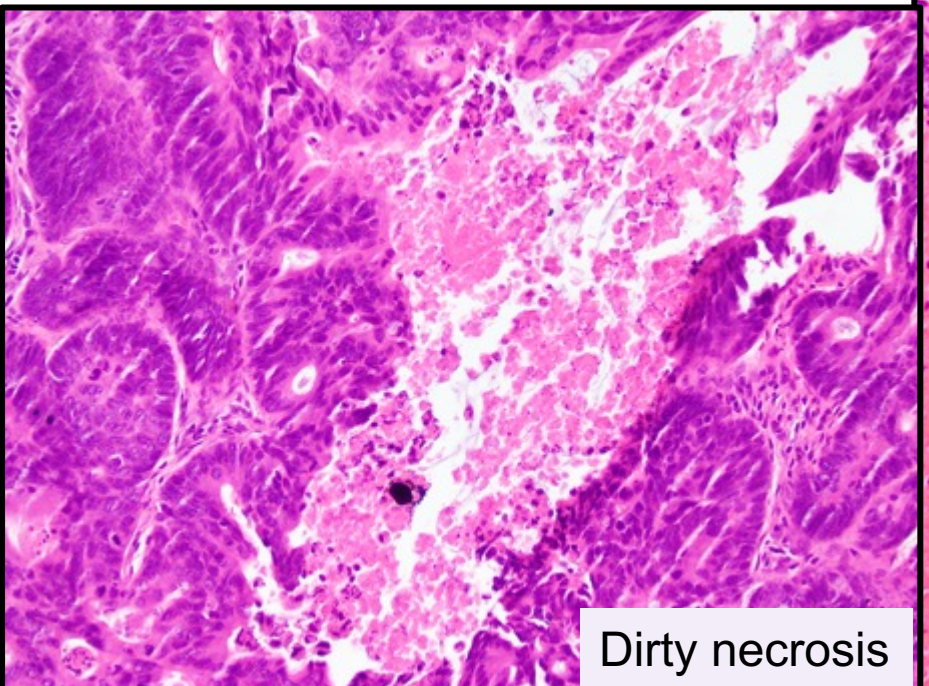
HPV-A mucinous carcinoma	HPV-I gastric type adenocarcinoma
Apical mitoses, apoptoses at low power	Less prominent
Intestinal differentiation	Intestinal differentiation
P16 block type, HPV positive	Rarely, p16 positive; MUC6, HIK1083
HSIL / AIS	Atypical LEGH or gAIS



2020 WHO Blue book



- Tumour of extrauterine origin metastatic to or directly invading the cervix
- Cervical primaries with intestinal differentiation can be positive for CDX2
- Clinical correlation, Broader IHC panel – p16



Dirty necrosis

Metastasis to the cervix

Genital tract origin

- Endometrial or adnexal primary – usually direct extension or drop metastasis

Extragenital origin

- Breast, especially lobular carcinoma
- Colorectal carcinoma
- Gastric carcinoma, signet-ring type
- Kidney
- Melanoma

Suspect a metastasis if:

- **The lesion doesn't resemble any primary pathology at that site**
- **Lack of an in-situ component**
- **Signet ring morphology**
- **Extensive LVI**

Immunohistochemistry and clinical history required to resolve. Beware IHC pitfalls; use a panel.

Recommendations for Dx of HPV-A endocervical adenocarcinoma

- Usual-type tumours lacking cytoplasmic mucin should not be diagnosed as endometrioid
- HPV-A endocervical adenocarcinoma with villoglandular and micropapillary patterns can be designated as usual-type tumours but these patterns should be noted on the pathology report
- A diagnosis of primary cervical serous ca should not be made when you see serous-like morphology; most will represent an HPV-A endocervical adenocarcinoma with serous-like morphology OR a metastasis from the uterine corpus or adnexa
- A micropapillary or iSMC component of any percentage has a propensity for aggressive behaviour and should be reported
- Mucinous-type tumours are likely associated with a worse survival compared with usual type tumours so keeping these 2 categories distinct is recommended until further studies are conducted
- In the absence of block-type p16 staining or HPV, a diagnosis of HPV-A endocervical adenocarcinoma should be questioned

PATTERN-BASED CLASSIFICATION

INTERNATIONAL JOURNAL OF GYNECOLOGY OBSTETRICS FIGO WILEY

Box 1 FIGO staging of carcinoma of the cervix uteri (2018).

Stage I:

The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)

- **IA** Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
  - **IA1** Measured stromal invasion <3 mm in depth
  - **IA2** Measured stromal invasion ≥3 mm and <5 mm in depth
- **IB** Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
  - **IB1** Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
  - **IB2** Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - **IB3** Invasive carcinoma ≥4 cm in greatest dimension

For low stage tumours, the staging and ultimate management of the patient is determined by pathologist;

- Depth of invasion < 3, 3-5 or > 5 mm?

Difficulty assessing DOI

- Well
- Poly
- Ulce

ction –
whe

Key tr

Cone

Many of these low stage tumours have good Px
Lymph node metastases seen in:
<1% of patients with IA1 tumours
~2% of patients with IA2

Gynecol Oncol 2016;141:36-42

Impetus for the Silva system:
Aims to improve risk-stratification for patients in order to avoid overtreatment

- Potential for significant treatment-related complications

Silva pattern-based classification

Diaz DeVivar A et al.
IJGP 2013;32:592-601
Roma AA et al.
AJSP 2015;39:667-72

Stratifies HPV-A endocervical adenocarcinoma into 3 patterns (A,B,C) based on:

- Presence or absence of destructive stromal invasion
- Degree of destructive invasion (if present)
- Presence or absence of LVI
- Tumour architecture and grade of cytological atypia

Does not take into account:

- Depth of invasion
- Relationship of tumour to large vessels in the cervical stroma

3 prognostic groups:

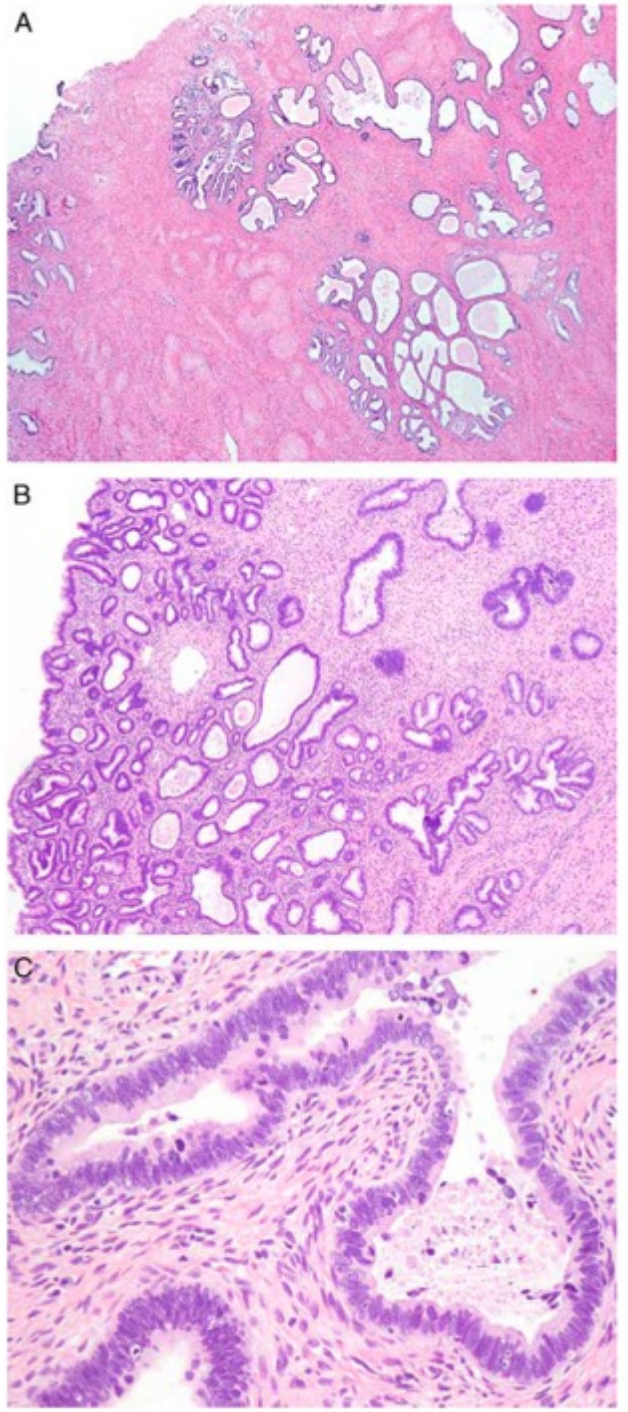
- Correlates with lymph node metastasis & clinical outcome

Pattern A

NO DESTRUCTIVE INVASION

- Well demarcated glands, round contours, sometimes lobulated
- Allow complex intra-glandular growth (<5 mm)
- “Pushing” invasion, any depth
- No desmoplasia; allow focal periglandular inflam
- No single cells or detached cell clusters in stroma
- No high-grade cytology
- No LVSI

Requires examination of the entire tumour – negative resection margins if a LEEP

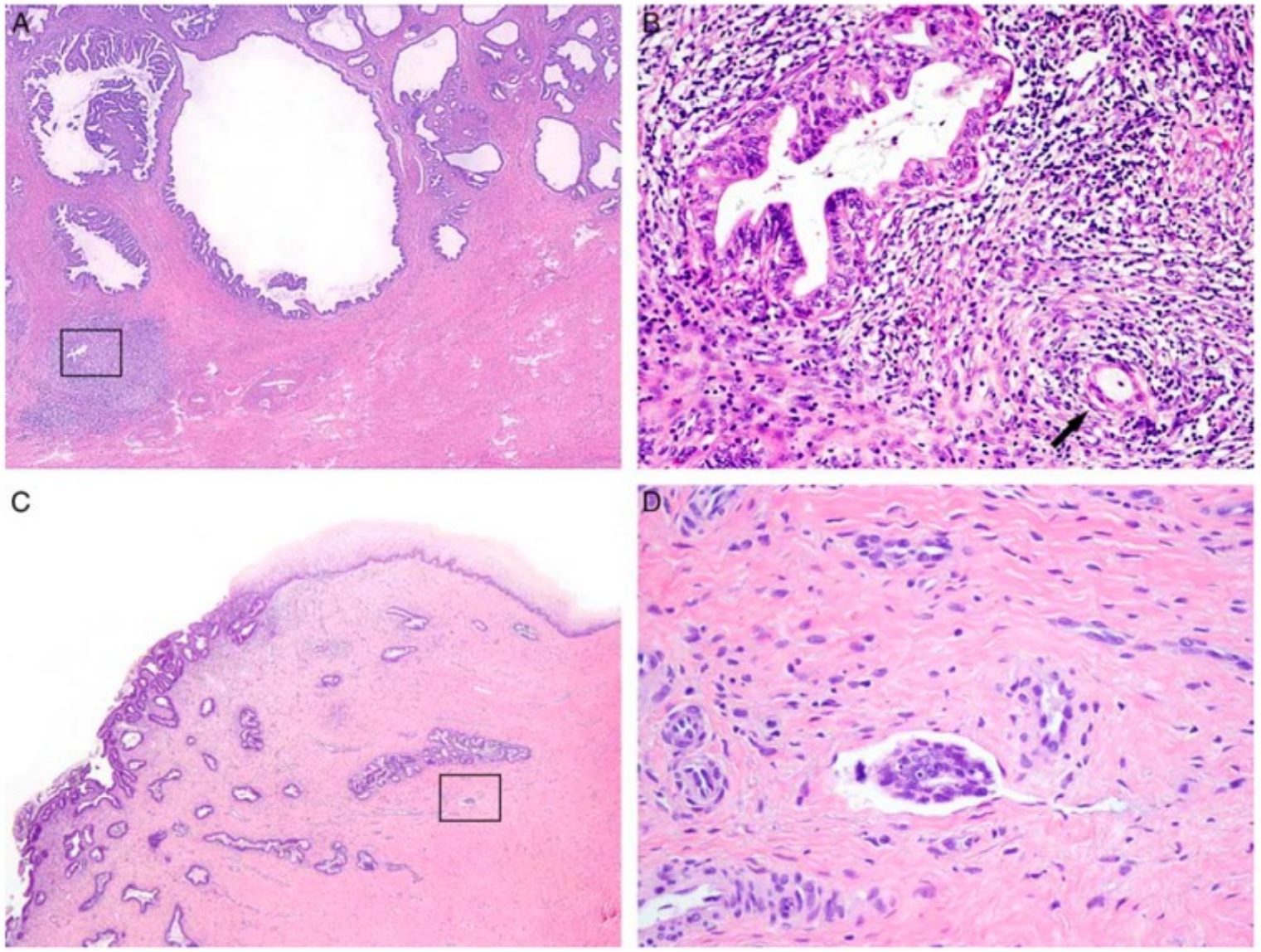


ISGyP Consensus issue

Pattern B

EARLY DESTRUCTIVE INVASION

- Pattern A-like glands with early / localised destructive stromal invasion
- Single cells, small clusters budding off Pattern A glands into desmoplastic or inflamed stroma
- Single or multiple foci, but must not fill a 4x field (5 mm)
- No solid growth
- LVSI ±

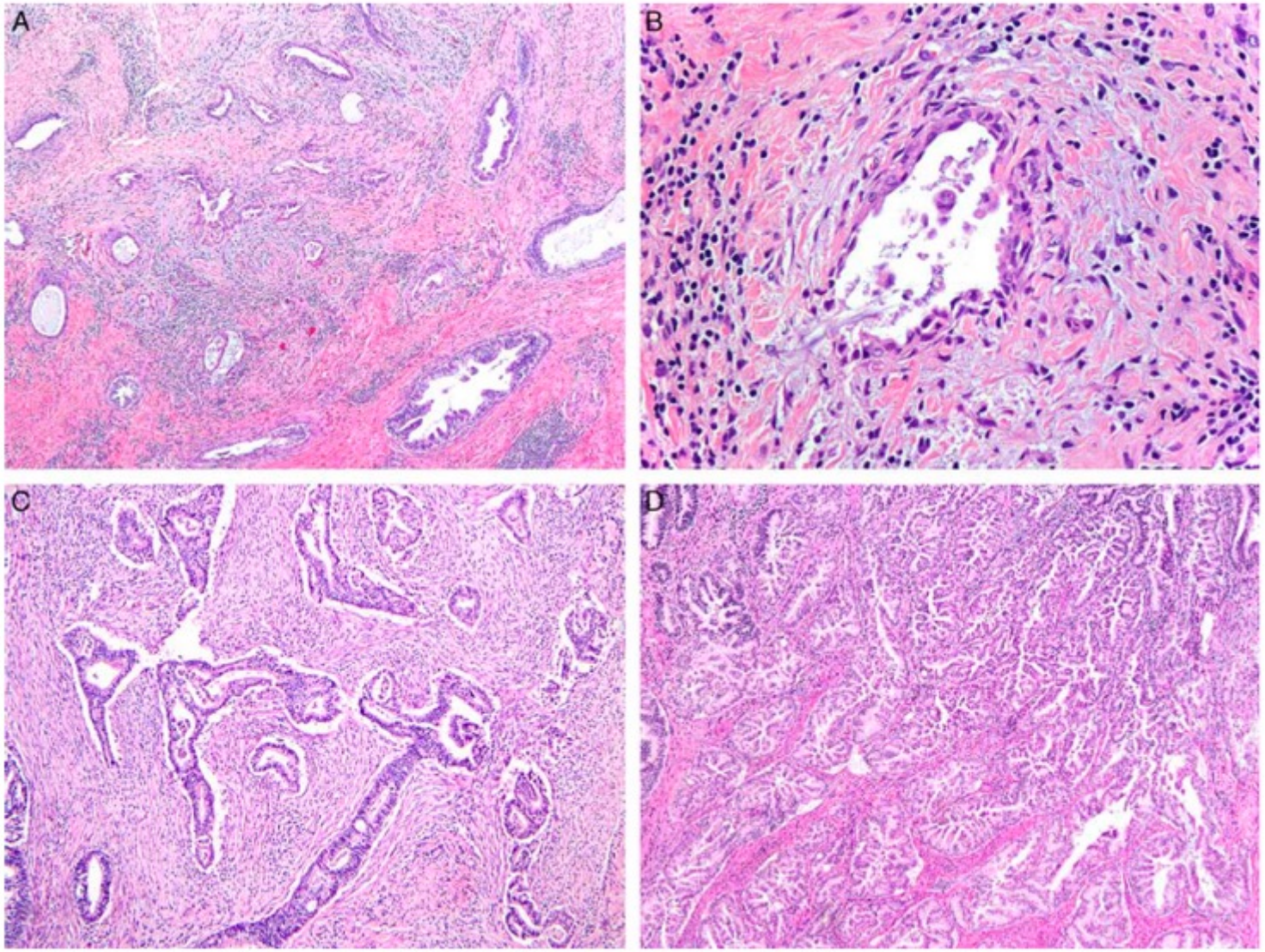


ISGyP consensus issue

Pattern C

DIFFUSE DESTRUCTIVE INVASION

- Infiltrating glands with varied architecture, often angulated, interconnected, extensive desmoplasia
- Confluent glands / papillae with minimal intervening stroma filling a 4x field (5 mm); must be endophytic
- Solid or micropapillary growth
- May be superficially invasive
- LVSI ±



ISGyP consensus issue

Pattern A (non-destructive invasion)

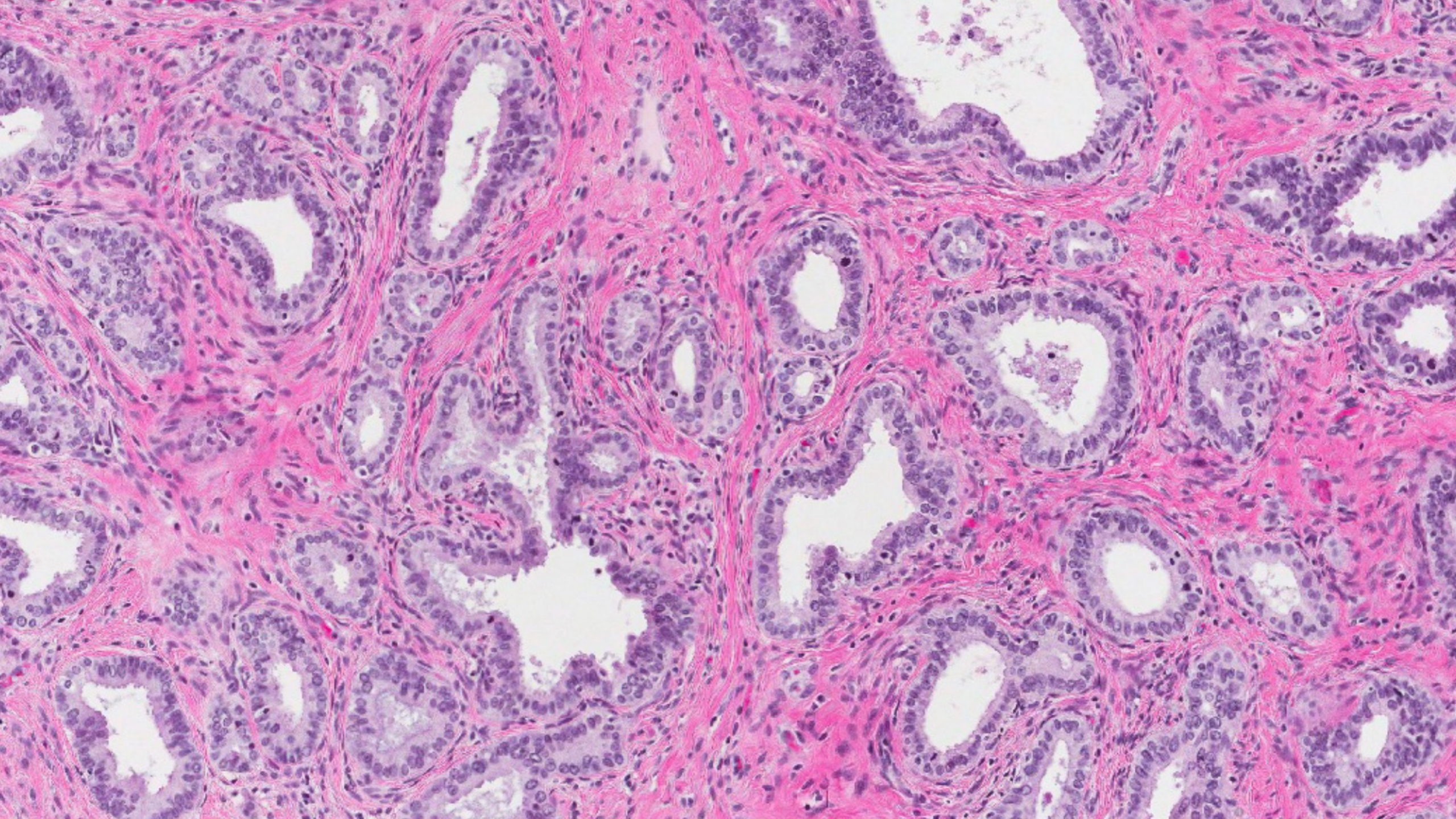
- Well-demarcated glands with rounded contours
- No lymphovascular invasion
- Complex intraglandular growth acceptable (i.e. cribriform growth, papillae)
- Lack of solid growth (i.e. architecturally well to moderately differentiated)

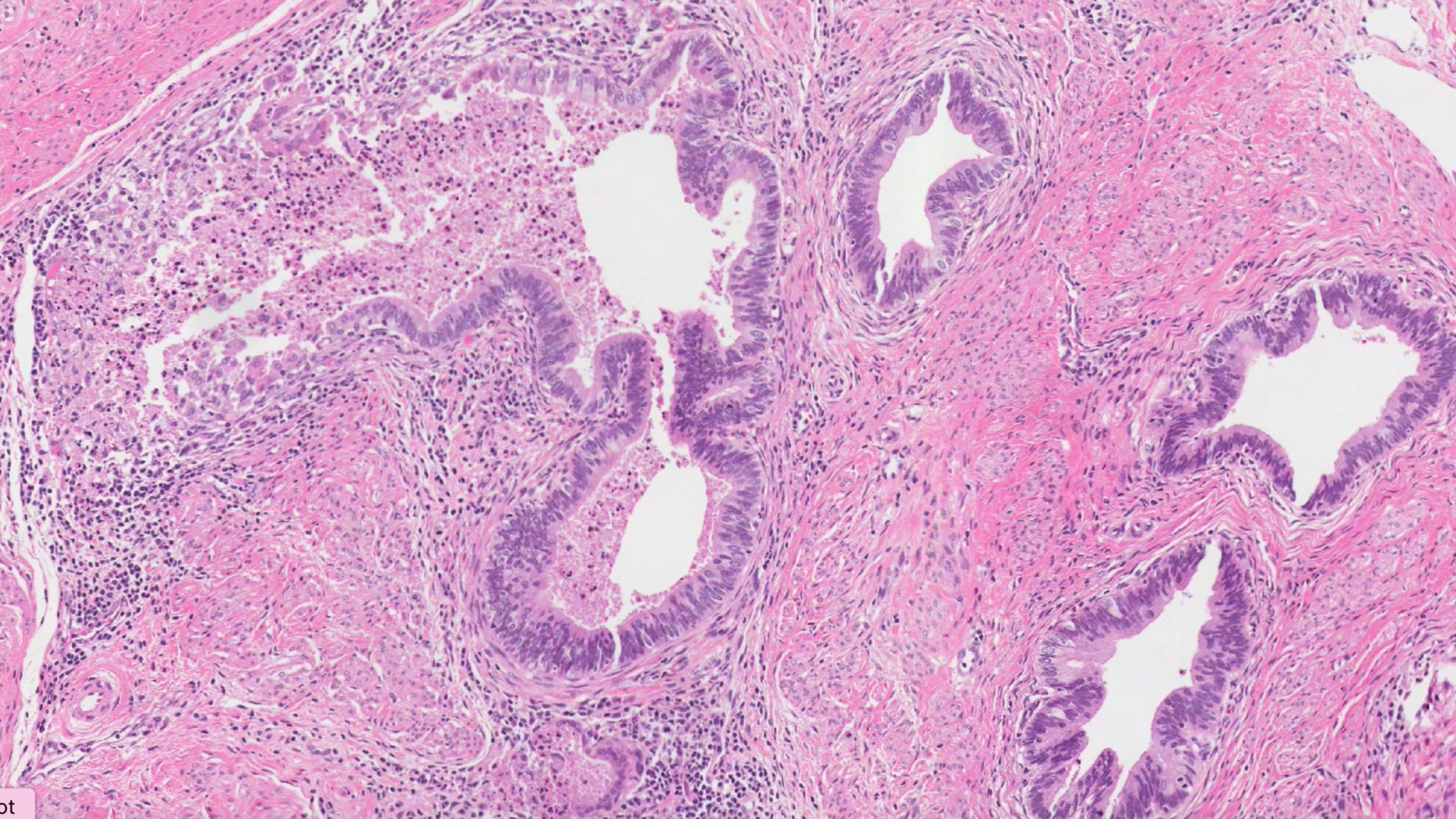
Pattern B (early / focally destructive invasion)

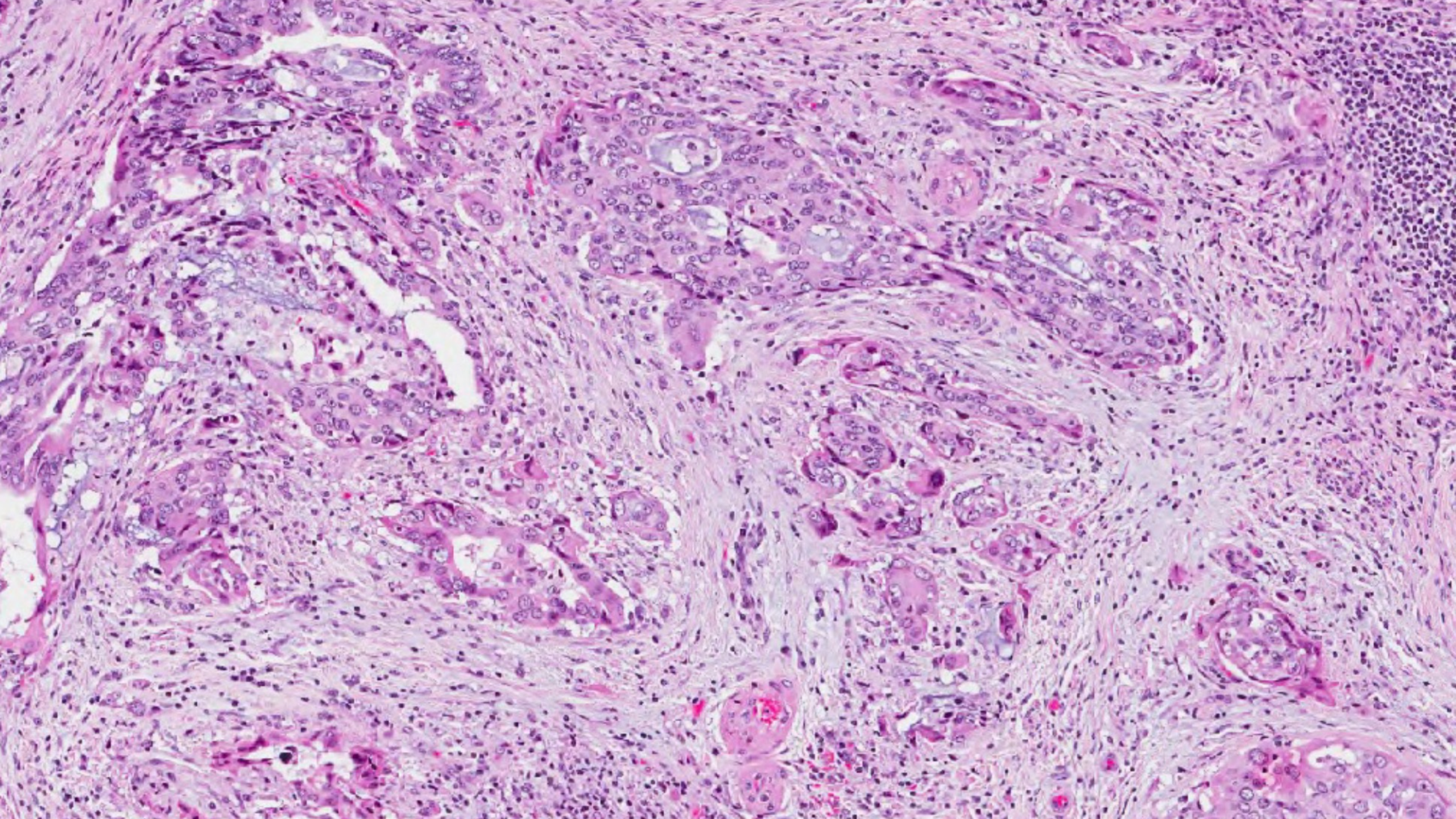
- Individual or small groups of tumour cells, separated from the rounded glands; focally desmoplastic or inflamed stroma
- Foci may be single, multiple, or linear at base of tumour
- Lymphovascular invasion +/–
- Lack of solid growth (i.e. architecturally well to moderately differentiated)

Pattern C (diffusely destructive invasion)

- Diffusely infiltrative glands with associated extensive desmoplastic response
- Glands often angulated or with canalicular pattern, with interspersed open glands
- Confluent growth filling a 4× field (5 mm): glands, papillae (stroma only within papillae), or mucin lakes
- Solid, poorly differentiated component (architecturally high-grade); nuclear grade is disregarded







Exophytic tumours

- Evaluate Silva pattern at the tumour base, in the cervical wall, not within the exophytic component

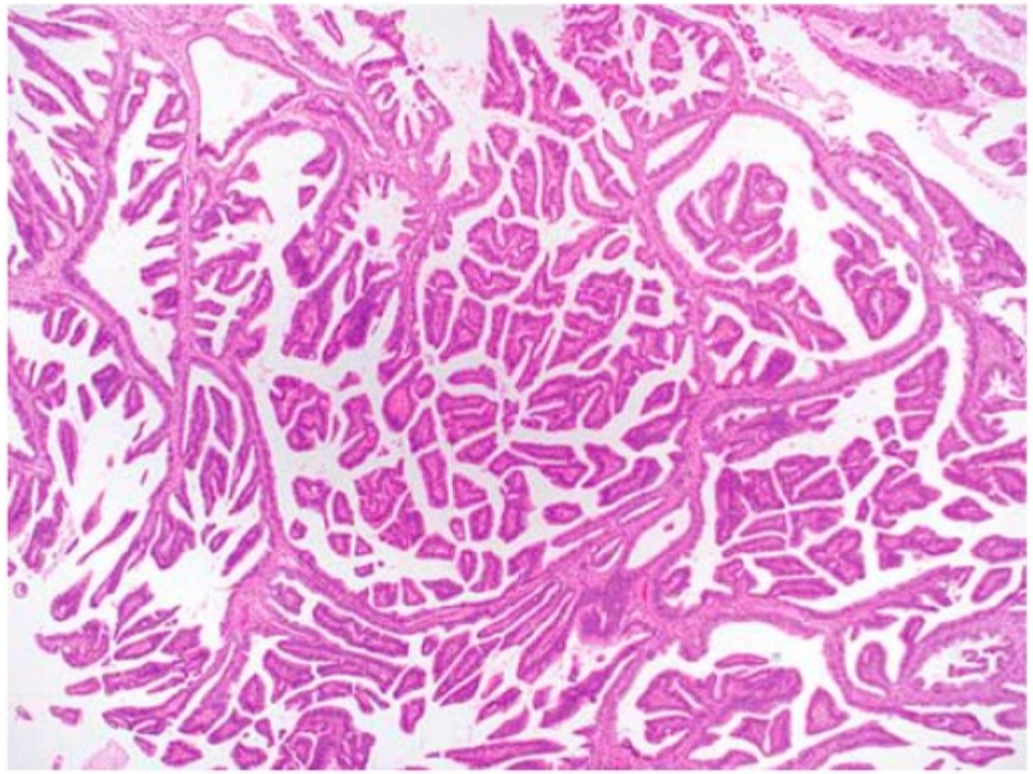


FIG. 6. Invasive human papilloma virus–associated adenocarcinoma, pattern C. Confluent villoglandular growth within the cervical stroma filling a 4× field (5 mm).

ISGyP consensus issue

Pattern based classification

Only applied for HPV-A adenocarcinomas
Stratifies into 3 prognostic groups
Correlates with lymph node metastasis & clinical outcome

Pattern A NO DESTRUCTIVE INVASION	Pattern B EARLY DESTRUCTIVE INVASION	Pattern C DIFFUSE DESTRUCTIVE INVASION
• 0% nodal metastases	• 5% nodal metastases	• 22% nodal metastases Different biological behavior; tendency to recur

Clinical impact

TABLE 4. *Cumulative clinico-pathologic features of patients with endocervical adenocarcinoma categorized according to the Silva pattern-based classification*

	Total	Pattern A	Pattern B	Pattern C
No. Pts	1319	253	262	804
LVI	543 (41%)	0	53 (20%)	490 (61%)
With LN mets	191 (14%)	0	14 (5%)	177 (22%)
With stage information	1102	224	241	637
Stage I	981 (89%)	222 (99%)	233 (97%)	526 (83%)
Stage II–IV	119 (11%)	2 (1%)	6 (3%)	111 (17%)
With F/U	776	201	216	359
F/U in months, mean (range)	62 (3–392)	62 (3–252)	69 (5–392)	55 (3–258)
With recurrences	77 (10%)	0	7 (3%)	70 (19%)
DOD	42 (5%)	0	3 (1%)	39 (11%)

DOD indicates dead of disease; F/U, follow-up; LN, lymph node.

ISGyP consensus issue

Conclusions: Pattern-based classification

Current evidence supports the use of the Silva classification to assist in clinical decision-making for HPV-A tumours

- Pattern A tumours are indolent with no risk of nodal mets and negligible risk of adverse outcome, mirroring AIS. Suggests can be treated conservatively with conization to obtain a negative margin and no LN dissection
- Follow-up still required; ovarian spread has ben reported in tumours with AIS-like growth; further studies are required to determine the prevalence of ovarian metastasis in patients with Pattern A tumours

Reproducibility studies:

- Acceptable reproducibility, improved with consensus review
- Especially good and distinguishing Pattern A from B & C
  - Poor agreement distinguishing between AIS and Pattern A

Recommendations: Pattern-based classification

- Include Silva pattern in the pathology report when diagnosing HPV-A adenocarcinoma
  - Do not apply to HPV-I tumours as most have pattern C invasion, even when well differentiated, and are associated with a poor prognosis
  - If Pattern C the presence of a micropapillary subtype should be mentioned
  - Pattern A diagnosis requires examination of entire tumour to exclude destructive invasion
- A pre-requisite is examination of the entire tumour – best done on a cone/LEEP with negative margins, hysterectomy, trachelectomy; *not on a biopsy specimen*
- LVI is not an independent prognostic factor in Pattern C but quantification of this finding may improve the prognostic value of this parameter: If $\geq$ 20 LV spaces involved, significantly higher rate of LN mets and recurrence
  - Still recommended to report as impacts management

Recommendations: Pattern-based classification

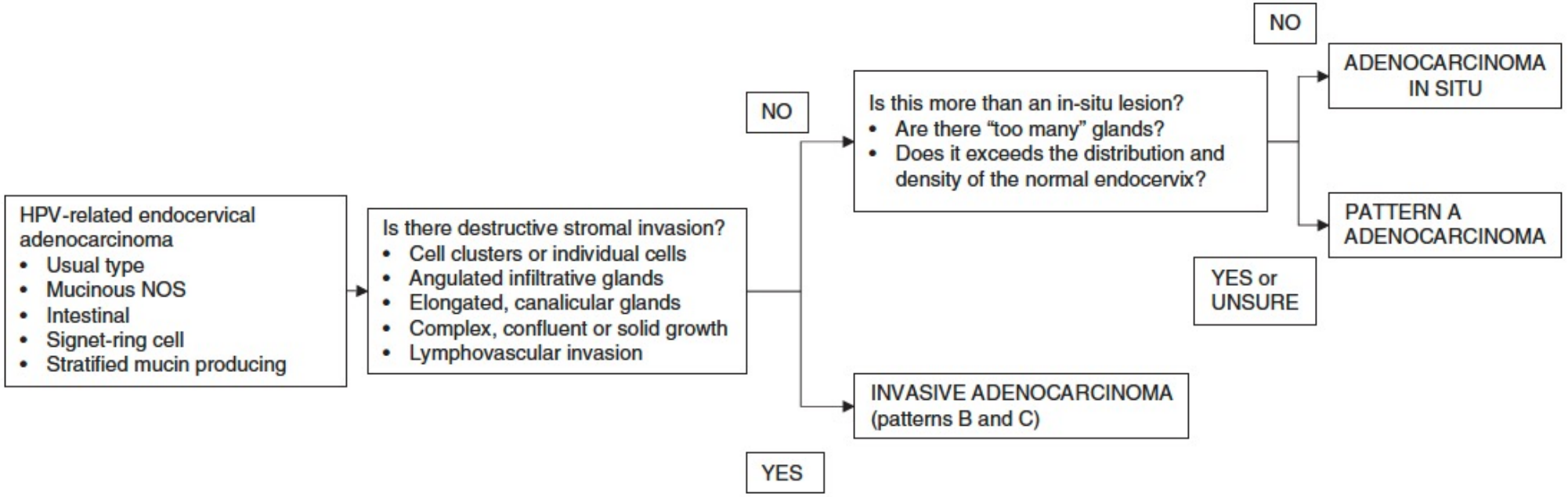


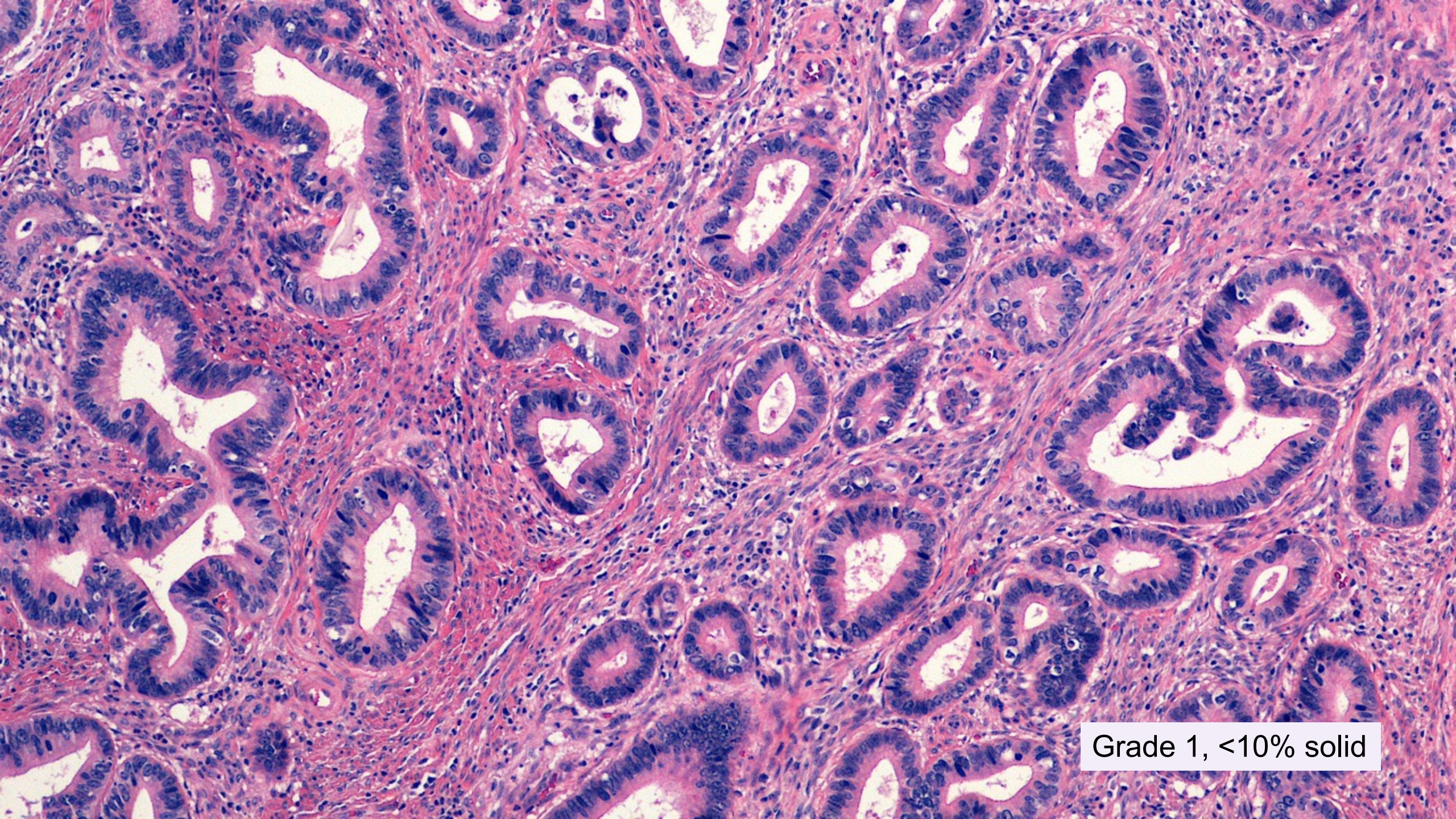
FIG. 11. Algorithmic approach to the distinction between in-situ and invasive HPV-associated endocervical adenocarcinoma. HPV indicates human papilloma virus; NOS, not otherwise specified.

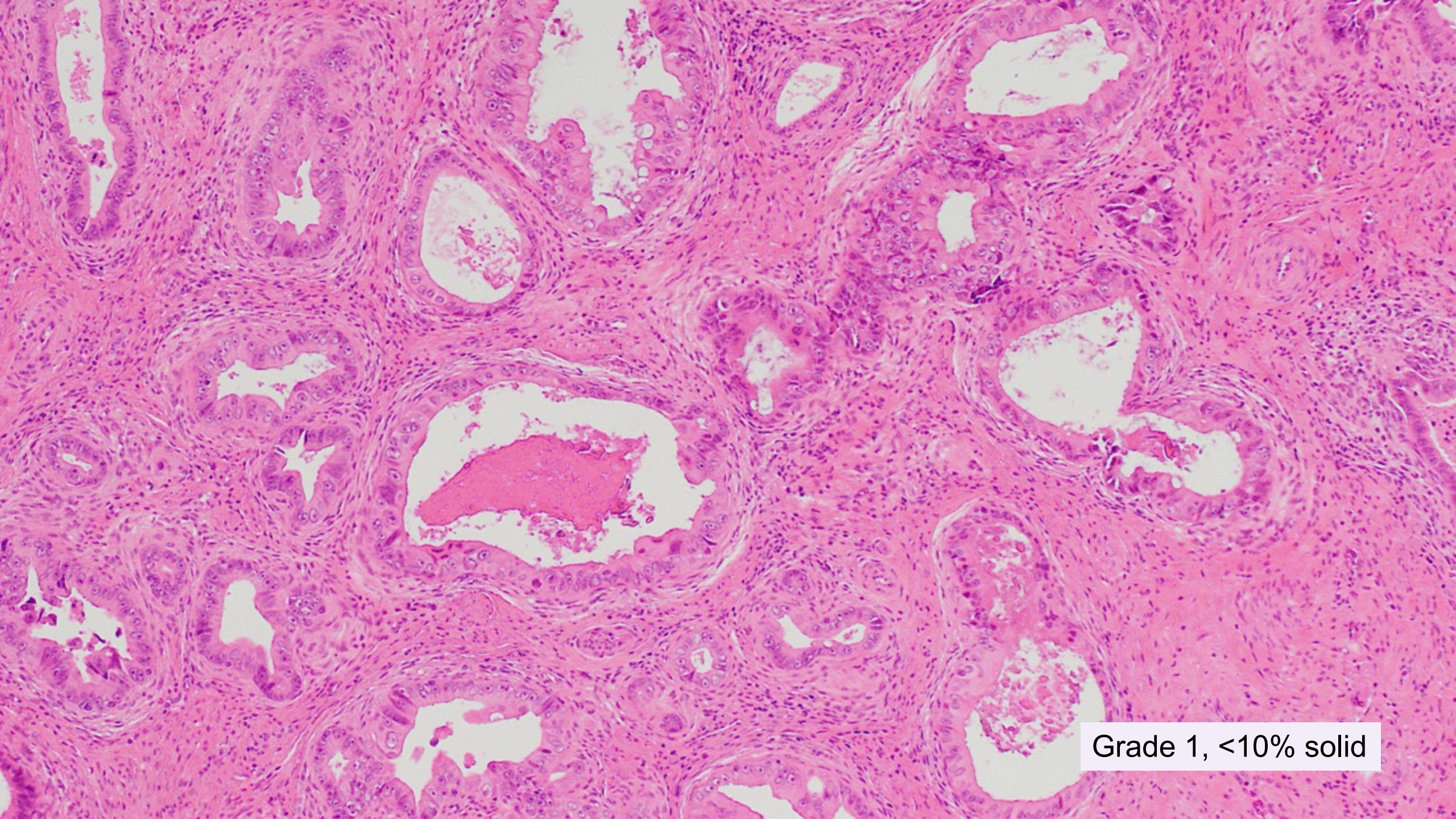
Also: ISGyP online learning module

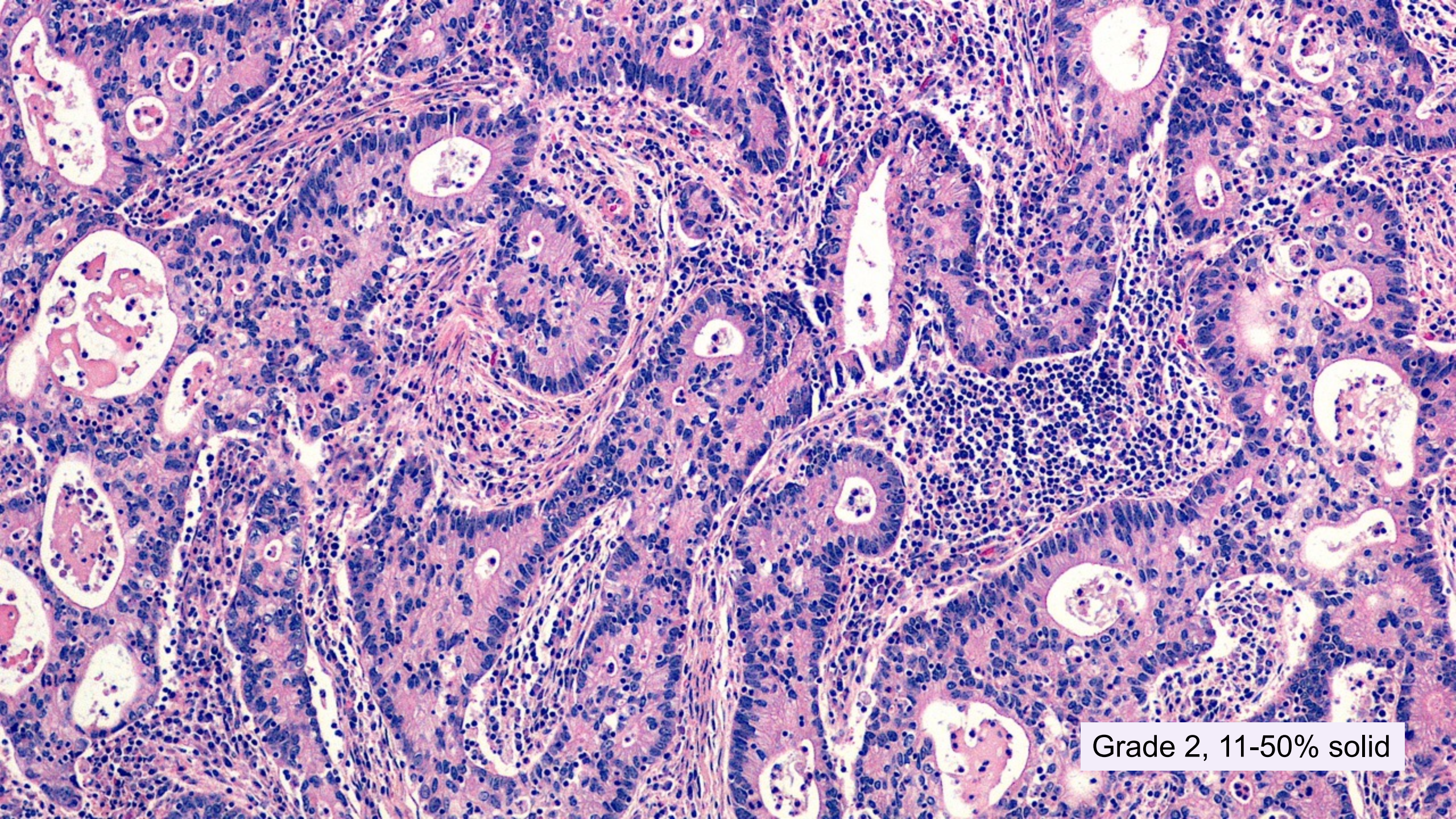
Grading of endocervical adenocarcinoma

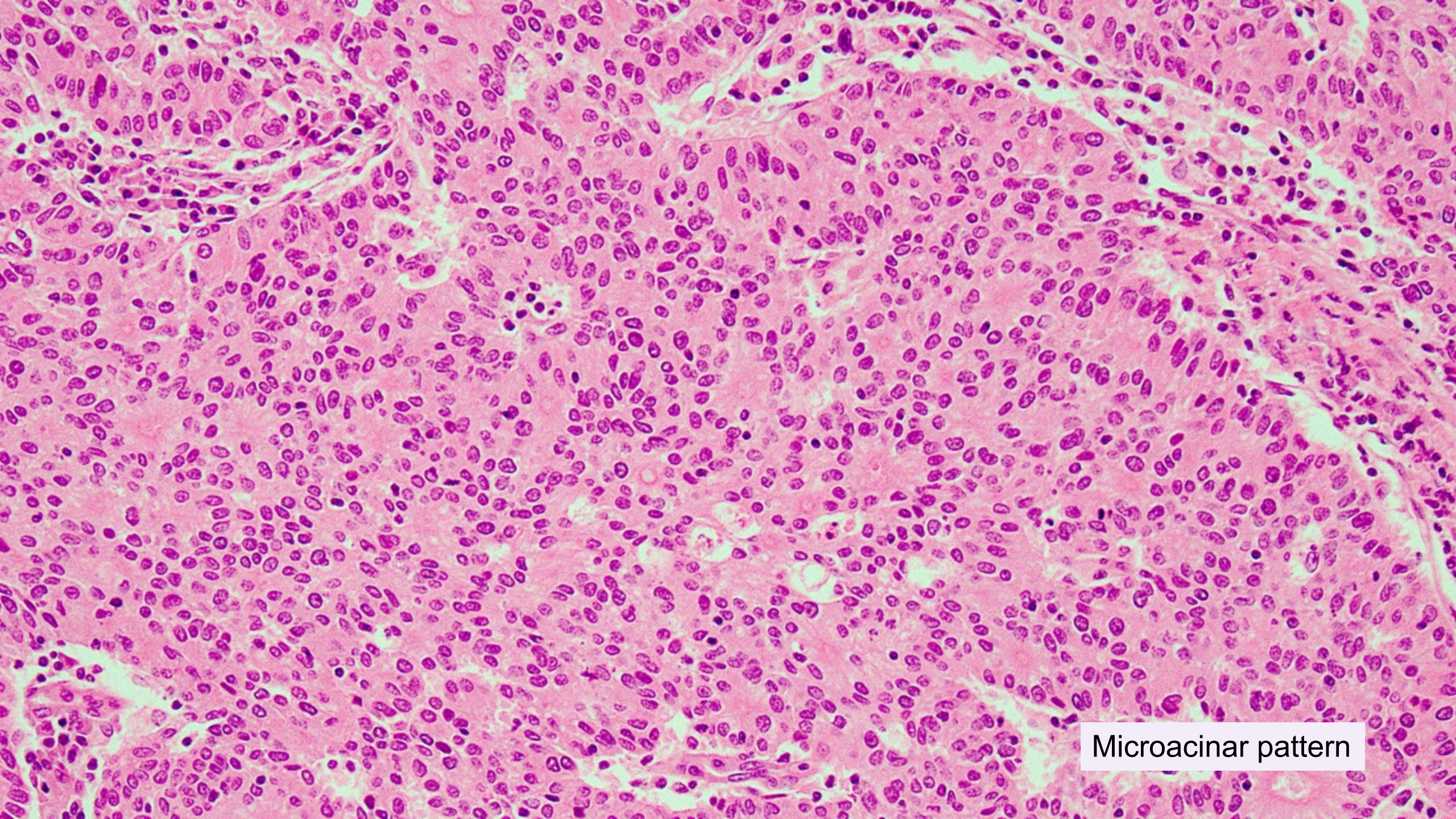
RECOMMENDATIONS

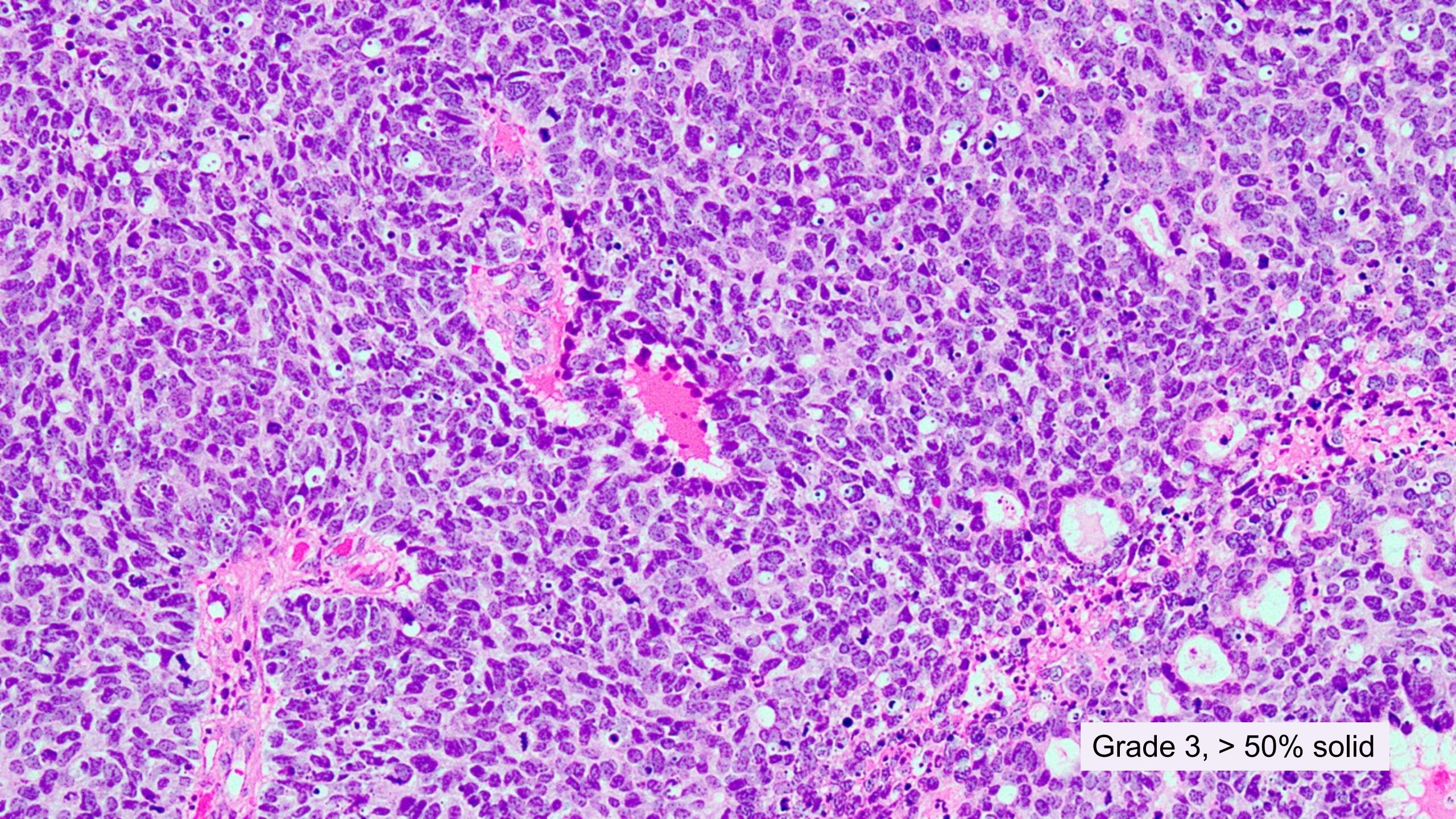
- HPVA endocervical adenocarcinomas (with some exceptions*) should be graded using a combination of architecture and cytology.
  - Exclude variants with a micropapillary, signet ring or ISMC component, as these are automatically considered high-grade
- HPVA endocervical adenocarcinomas with ≤10% solid growth are Grade 1, 11-50% solid growth Grade 2 and >50% solid growth Grade 3. Tumours can be upgraded in the presence of marked nuclear atypia involving >50% of the tumour.
- **HPVI adenocarcinomas should not be graded; in particular, gastric-type adenocarcinomas should not be graded but considered high-grade regardless of morphology.**
- Endocervical adenocarcinoma admixed with neuroendocrine carcinoma should not be graded but considered high-grade regardless of morphology.


Grade 1, <10% solid

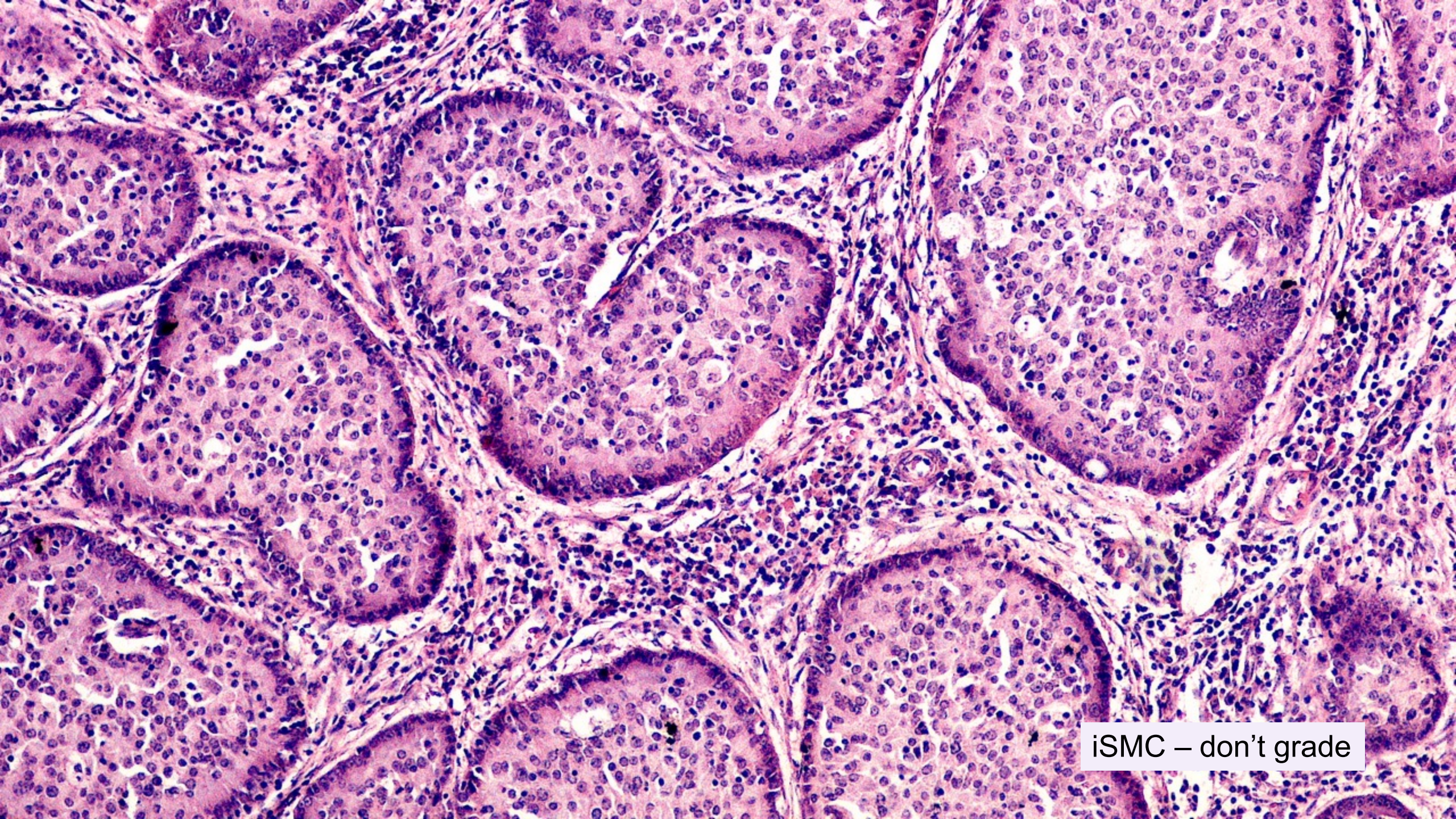

Grade 1, <10% solid

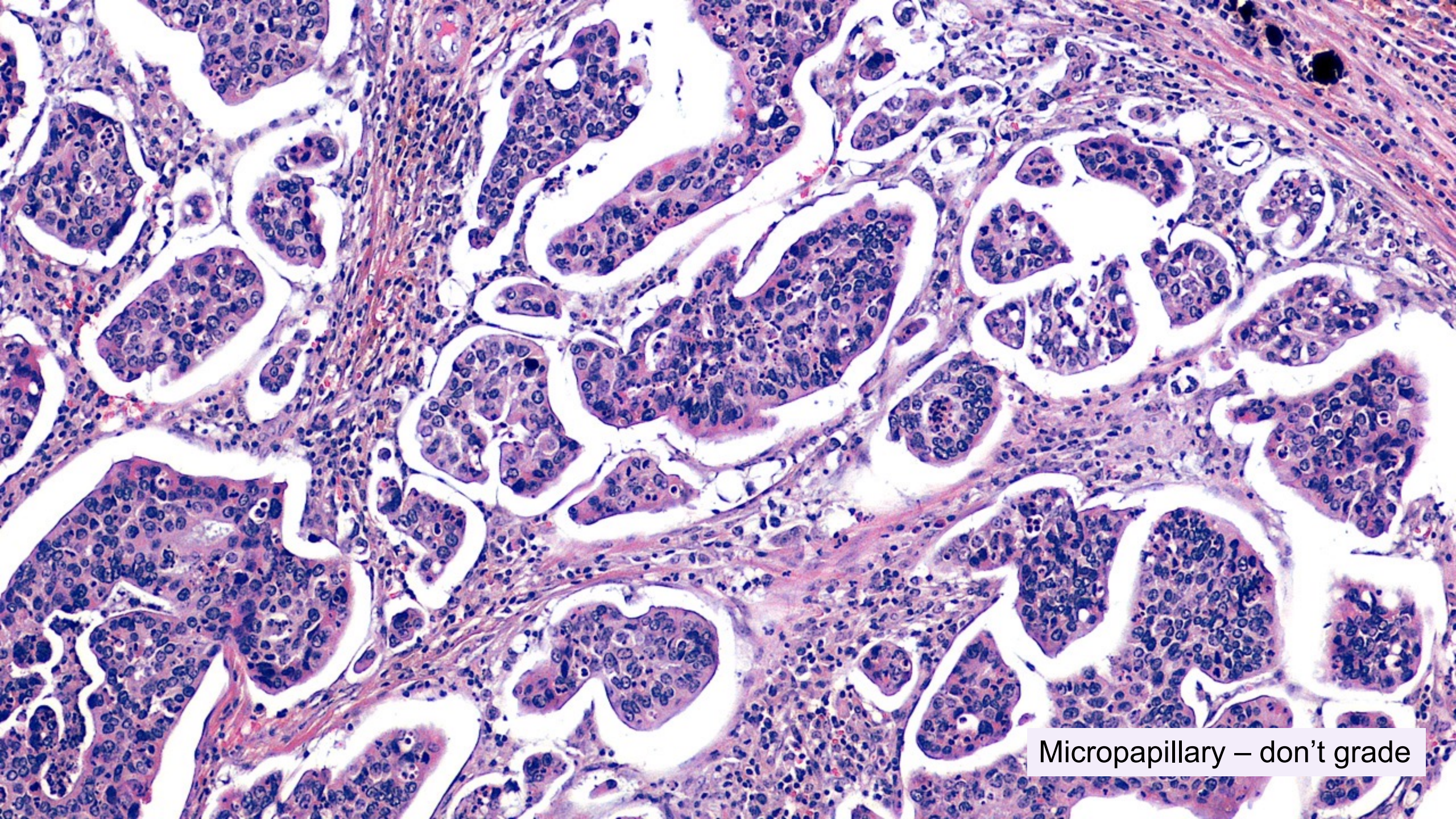

Grade 2, 11-50% solid

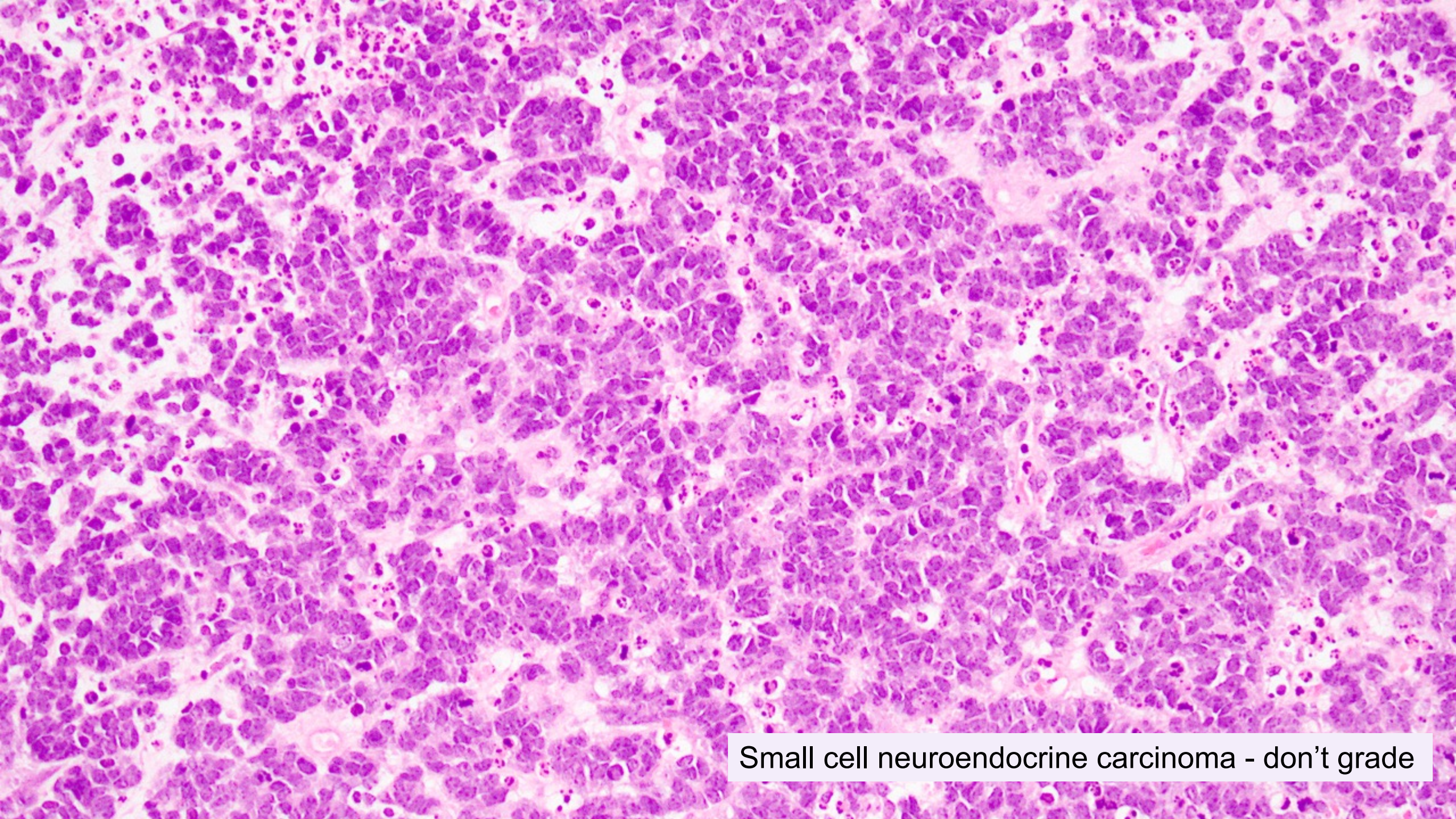

Microacinar pattern

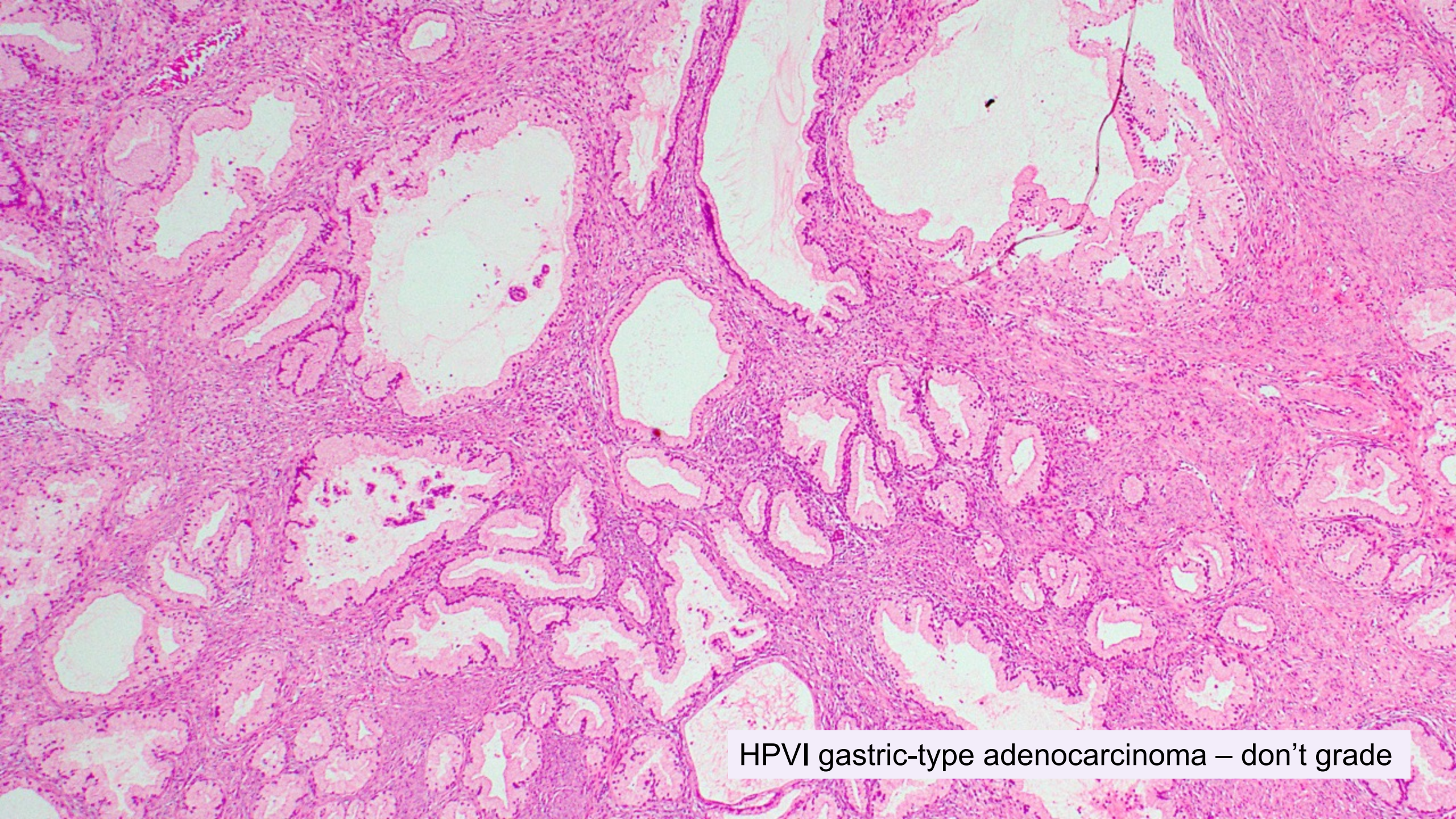

Grade 3, > 50% solid

Upgrade if significant atypia > 50% of cells


iSMC – don’t grade


Micropapillary – don’t grade


Small cell neuroendocrine carcinoma - don’t grade


HPVI gastric-type adenocarcinoma – don’t grade

THANK-YOU FOR LISTENING!