Carlos Parra-Herran MD, Boston MA US



Title: Adenosquamous and unusual HPV associated cervical cancers

- **Dr. Carlos Parra-Herran is an academic gynecologic pathologist at Brigham and Women's Hospital and Associate Professor of Pathology at Harvard Medical School. He graduated from Universidad Nacional de Colombia and completed his residency at Jackson Memorial Hospital, followed by subspecialty training at Brigham and Women's Hospital and Sunnybrook Health Sciences Centre. His research focuses on the morphologic and molecular characterization of gynecologic tract neoplasia, particularly lower genital tract epithelial lesions, mesenchymal tumors and non-serous ovarian neoplasia. He has authored over 80 peer-reviewed publications and edited one reference textbook in Gynecologic Pathology (Foundations in Diagnostic Pathology series, Elsevier 2020). He has served as teaching faculty for continuing medical education events offered by the United States and Canadian Academy of Pathology (USCAP), the Latin American Pathology Society, the Canadian Association of Pathologists, the European Society of Pathology and the College of American Pathologists. He is also part of the organizing team of the International Society of Gynecological Pathologists (ISGyP) Live Virtual Education program. Dr. Parra-Herran currently serves as a member of the ISGyP board of directors and the USCAP education committee.**

The British Association of Gynaecological Pathologists

17th Annual Meeting

- Title: Adenosquamous and unusual HPV associated cervical cancers
- Speaker: Carlos Parra-Herran
- Affiliation: Brigham and Women's Hospital, Boston MA US
- Date: June 10th 2021, 12:30-13:00

The British Association of Gynaecological Pathologists

Speaker disclosures

Choose one

- ❑ I have no financial conflicts of interest to disclose

ADENOSQUAMOUS AND UNUSUAL HPV ASSOCIATED CERVICAL CANCERS

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OUTLINE

- Adenosquamous carcinoma
- Glassy cell carcinoma
- Adenoid basal and adenoid cystic carcinoma
- Infrequent variants of HPV-associated adenocarcinoma
  - Villoglandular
  - Mucinous
  - Invasive stratified mucin producing

Histopathological classification of endocervical adenocarcinoma

The purpose of this website is to provide training in performing histopathological classification of endocervical adenocarcinoma. This is done by diagnosis of one of the histotypes of endocervical adenocarcinoma, using the criteria below:



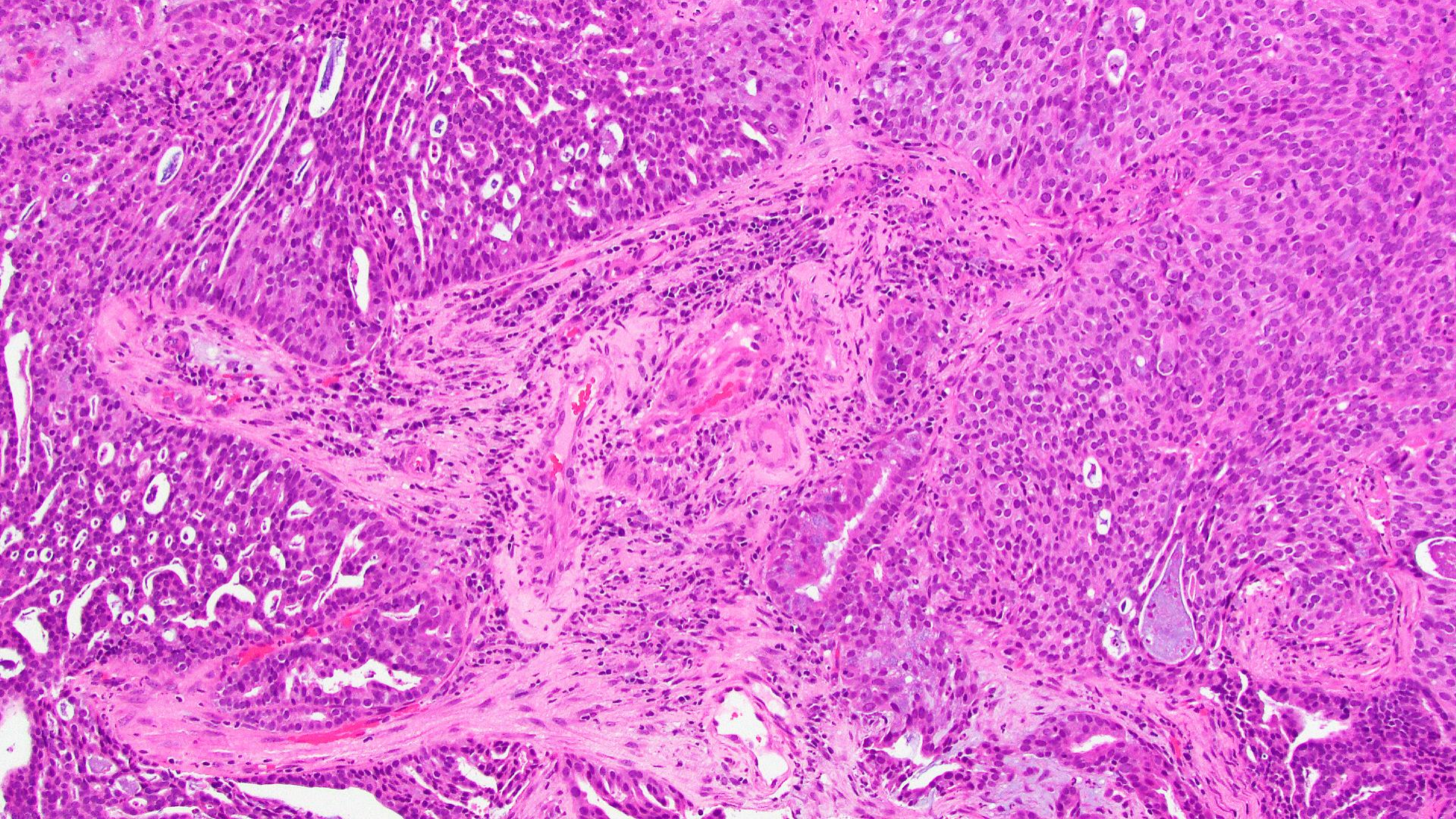
HPV-associated endocervical adenocarcinomas

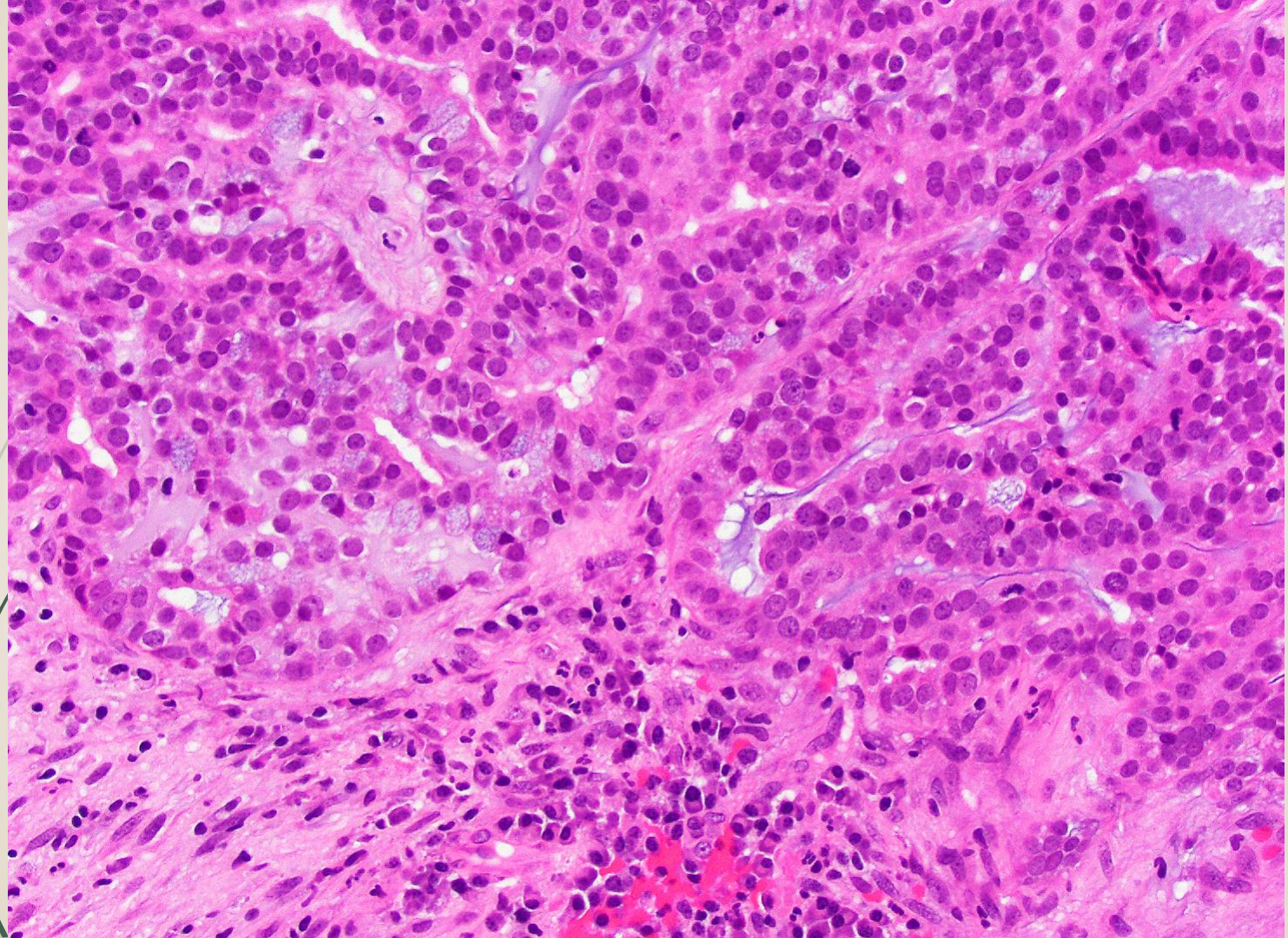
- ~85% of all endocervical adenocarcinomas in an international series
- Easily identified apical mitotic figures and karyorrhexis (apoptotic bodies) at 40X ma
- Confirmation of HPV status is optional; it can be performed with HR-HPVmRNA-ISH, cognizant of its imperfect specificity.
- Subtypes include:
  - **Usual**
    - Glandular, cystic, cribriforming, papillary, microglandular, solid patterns
    - Extravasated mucin may be seen
    - Pseudostratified, enlarged, elongated, and hyperchromatic nuclei
    - Conspicuous apical mitoses and apoptotic bodies at scanning magnification
    - Apical amphophilic to eosinophilic cytoplasm with < 50% of tumor cells containing intracytoplasmic mucin ("mucin depleted")
  - **Papillary (including villoglandular)**
    - Exophytic growth with long, slender papillae
    - One or several layers of tall mucin-poor endocervical or intestinal-type epithelium
    - Mild cytologic atypia and low mitotic activity
    - Fibrovascular cores contain spindle cells and frequent acute and chronic inflammatory cells
  - **Mucinous**
    - **NOS:**
      - ≥ 50% of tumor cells with intracytoplasmic mucin in a background of usual endocervical type adenocarcinoma
      - No specific features of gastric, intestinal, or signet ring cell morphology
    - **Intestinal (with goblet cells, sometimes with neuroendocrine differentiation):**
      - ≥ 50% of cells with goblet morphology in a background of usual endocervical type adenocarcinoma
      - It may have argentaffin and Paneth cells
    - **Signet ring cell:**
      - ≥ 50% of cell with signet ring cell morphology in a background of usual endocervical type adenocarcinoma
      - Diffuse, trabecular, glandular, and cord-like growths
    - **Invasive stratified mucinous carcinoma:**
      - Invasive nests or trabeculae of pseudostratified pale columnar cells with peripheral palisading and variable intracytoplasmic mucin (closely resembling morphologically SMILE-in situ counterpart-)
      - Intracytoplasmic mucin/microlumens but no well-formed lumens or glands
      - Moderate cytologic atypia, brisk mitoses and apoptotic bodies
      - Brisk acute inflammatory infiltrate common
      - Often confused with adenosquamous carcinoma
  - **Mixed**

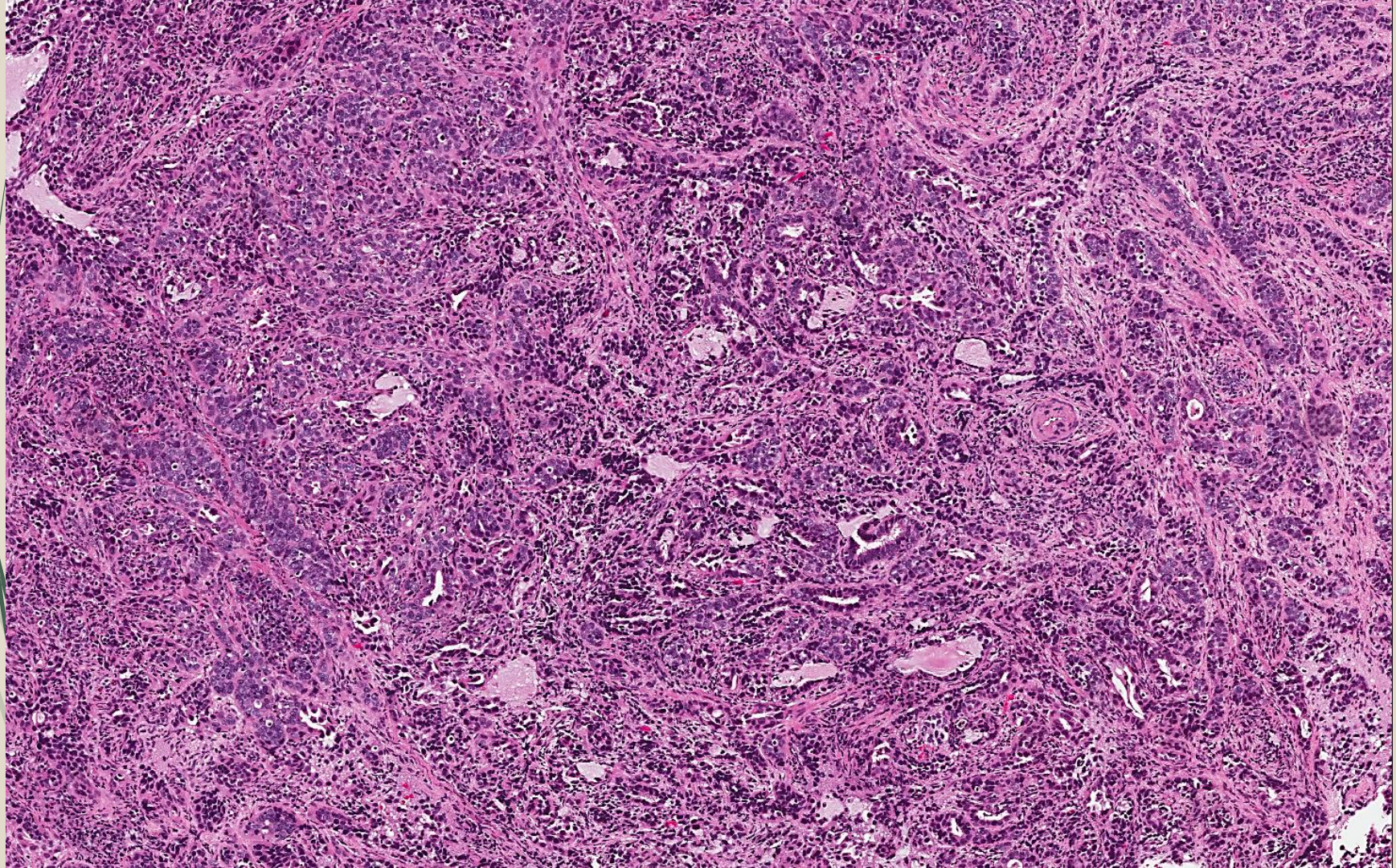
ADENOSQUAMOUS CARCINOMA

- ~5% all cervical malignancies
- Median age = 46 years (SCC = 53 years)
- HPV18 most common
- Closely admixed areas of glandular and squamous differentiation
  - Glandular: Lumen formation, intracellular mucin, columnar shape
  - Squamous: Usually poorly diff; keratinization, intercellular junctions

Mod Pathol 2019;32:269-279







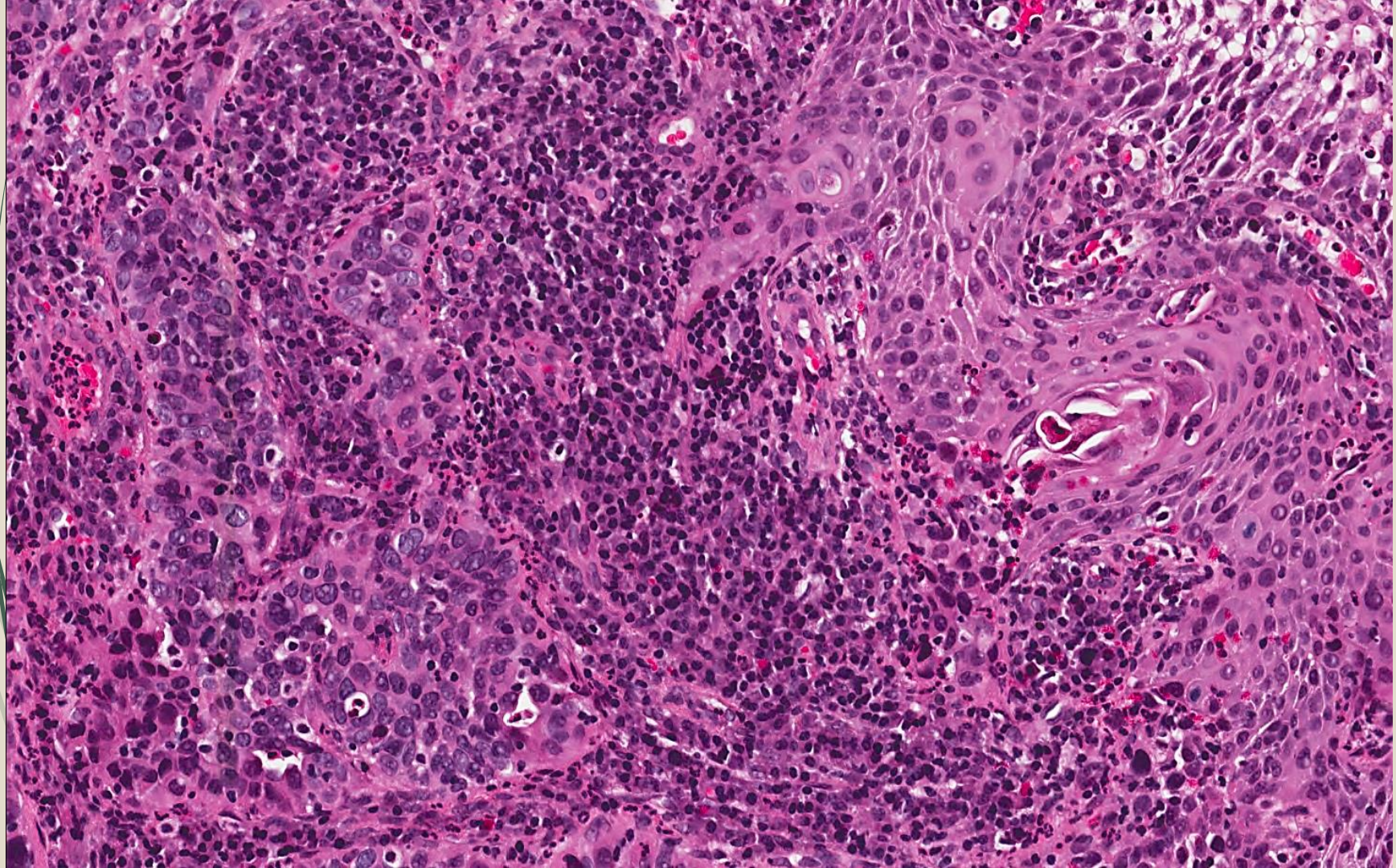


Table 2 The immunohistochemical profile of pure invasive stratified mucin-producing carcinomas in comparison with adenosquamous carcinomas

Marker	Pure invasive stratified mucin-producing carcinomas *n* (%)	Adenosquamous carcinomas *n* (%)	*p*
HPV*	8/8 (100)	19/23 (82.6)	<0.0001
P16	5/8 (62.5)	18/25 (72)	0.1757
PAX8*	2/7 (28.5)	10/23 (43.4)	0.0382
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PR	2/8 (25)	6/25 (24)	1.0000
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CAIX	4/7 (57.1)	16/23 (69.5)	0.4022
MUC6*	4/7 (57.1)	5/23 (21.7)	<0.0001
HIK1086	0/8 (0)	1/23 (4.3)	0.1212
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GATA3	1/7 (14.2)	2/23 (8.7)	0.2747
Vimentin*	1/8 (12.5)	0/25 (0)	0.0003
HER2	1/8 (12.5)	1/25 (4)	0.0652
SATB2	0/8 (0)	0/23 (0)	1.0000
CDX2	0/8 (0)	0/23 (0)	1.0000
p53*	2/7 (28.5)	2/25 (8)	0.0004
CK7*	8/8 (100)	20/23 (86.9)	0.0002

*Statistically significant differences

Mod Pathol 2019;32:269-279

ADENOSQUAMOUS CARCINOMA

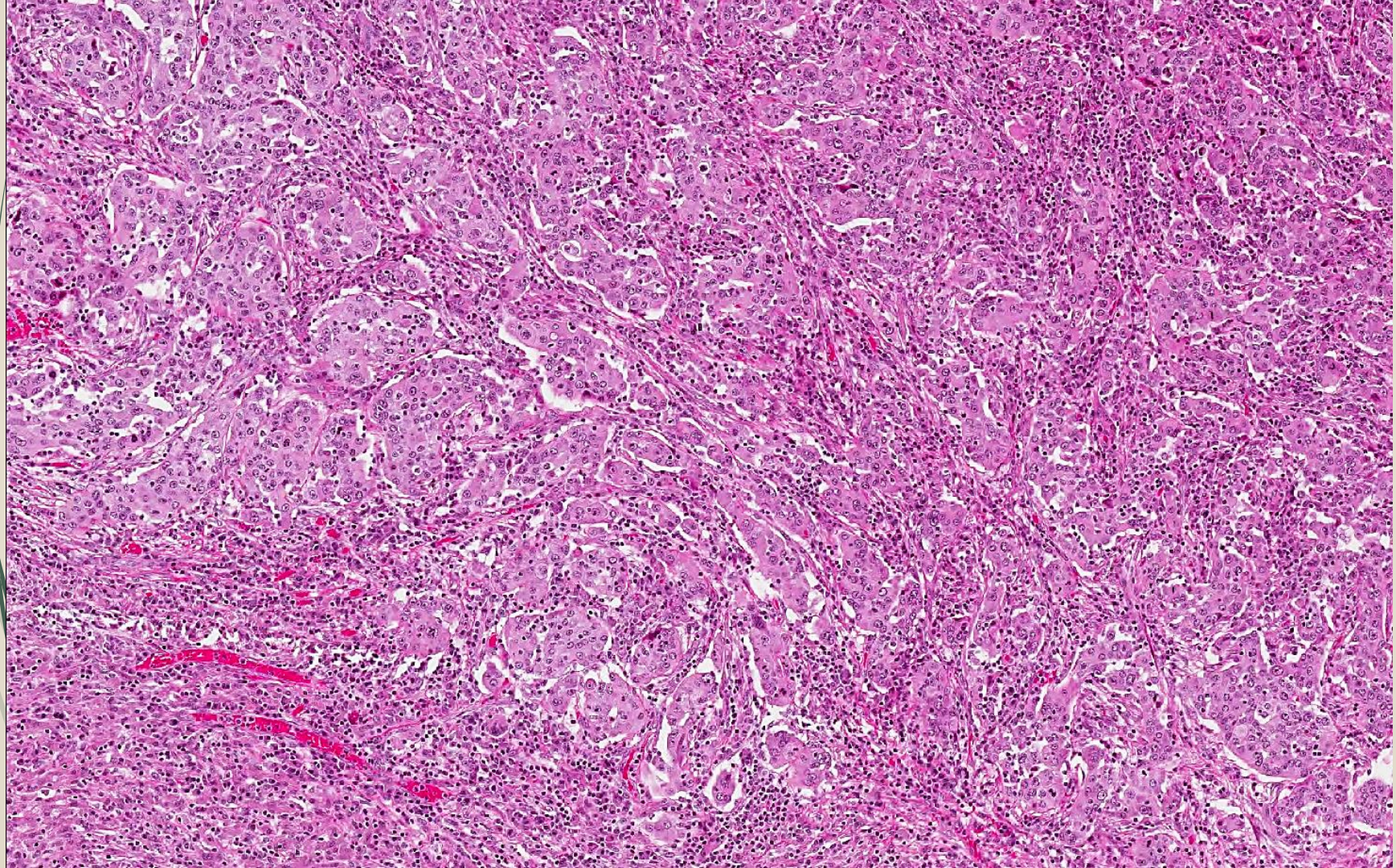
- P16 overexpression – hr-HPV positivity
- Mucins, CK5, p63, p409: variable expression
- DDx: glassy cell carcinoma, ISMC, SCC
- Prognosis worse than SCC regardless of stage
- Prognosis worse than adenoCA in advanced stage

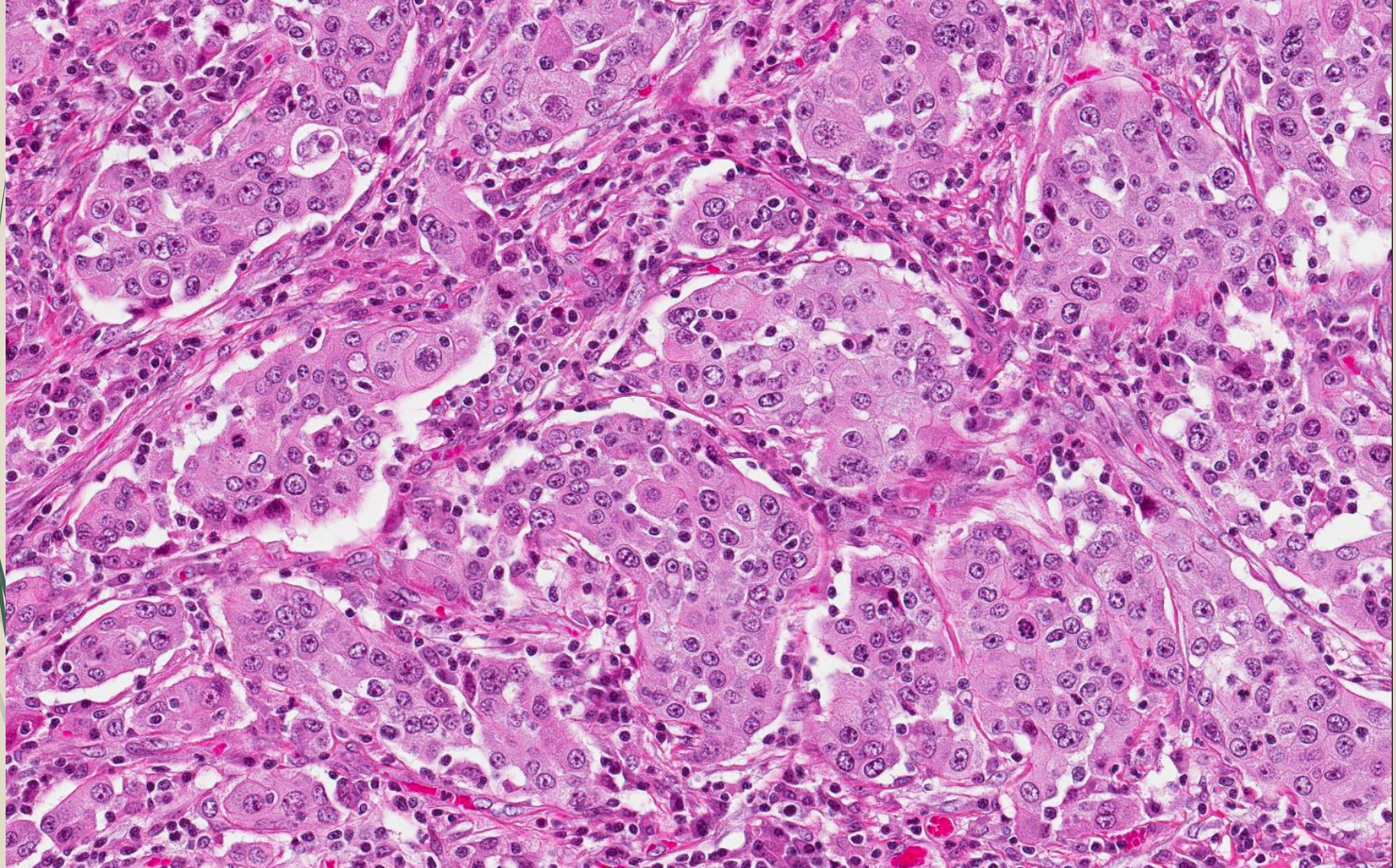
Gynecol Oncol 2014;135:208-12
J Cancer Res Clin Oncol 2017;143:115-22
J Clin Oncol 2017;28(2):e19
Mod Pathol 2019;32:269-279
Int J Gynecol Cancer 2014;24:289-94
Cancer 2003;97:2196-2202

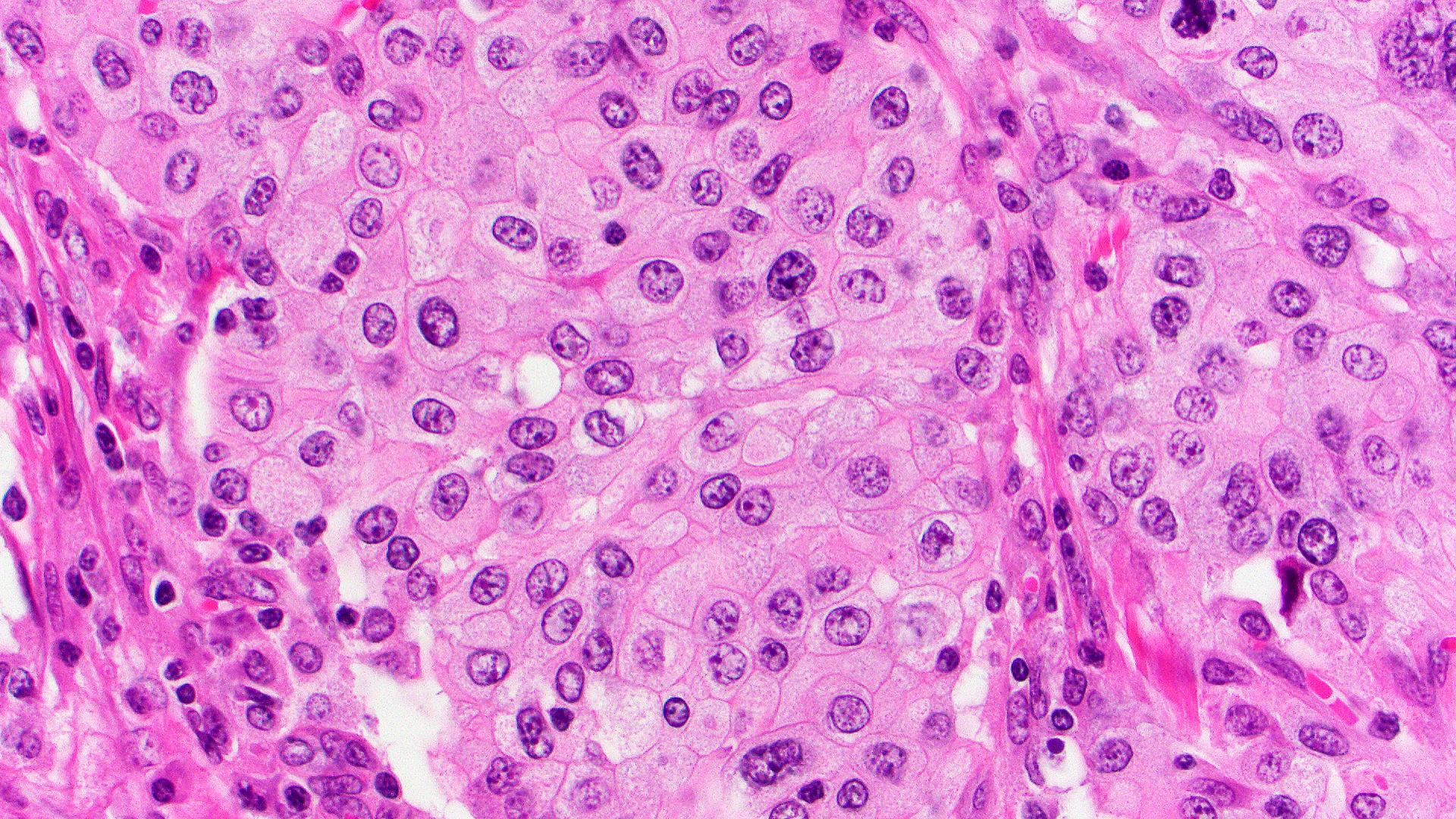
GLASSY CELL CARCINOMA

- Young patients (~4th decade)
- Poorly differentiated
- Cells with sharp borders (PAS positive)
- Eosinophilic "ground glass" cytoplasm
- No evident squamous or glandular differentiation
- Glassy cell morphology can be focal
  - Adenosquamous carcinoma
  - Non-keratinizing SCC

Gynecol Oncol 2014;133:186–191
Eur J Obstet Gynecol Reprod Biol 2014;179:232–235







GLASSY CELL CARCINOMA

- P16 overexpression (HPV 18 and 16 most common)
- ER/PR negative
- Variable squamous / glandular marker expression
- GATA3 negative
- Aggressive clinical course (55% 5-year OS)

Gynecol Oncol 2014;133:186–191
Int J Gynecol Pathol 2002;21:134–140
Obstet Gynecol 1998;91:136–138
Am J Clin Pathol 1992;98:180–187

ADENOID BASAL CARCINOMA

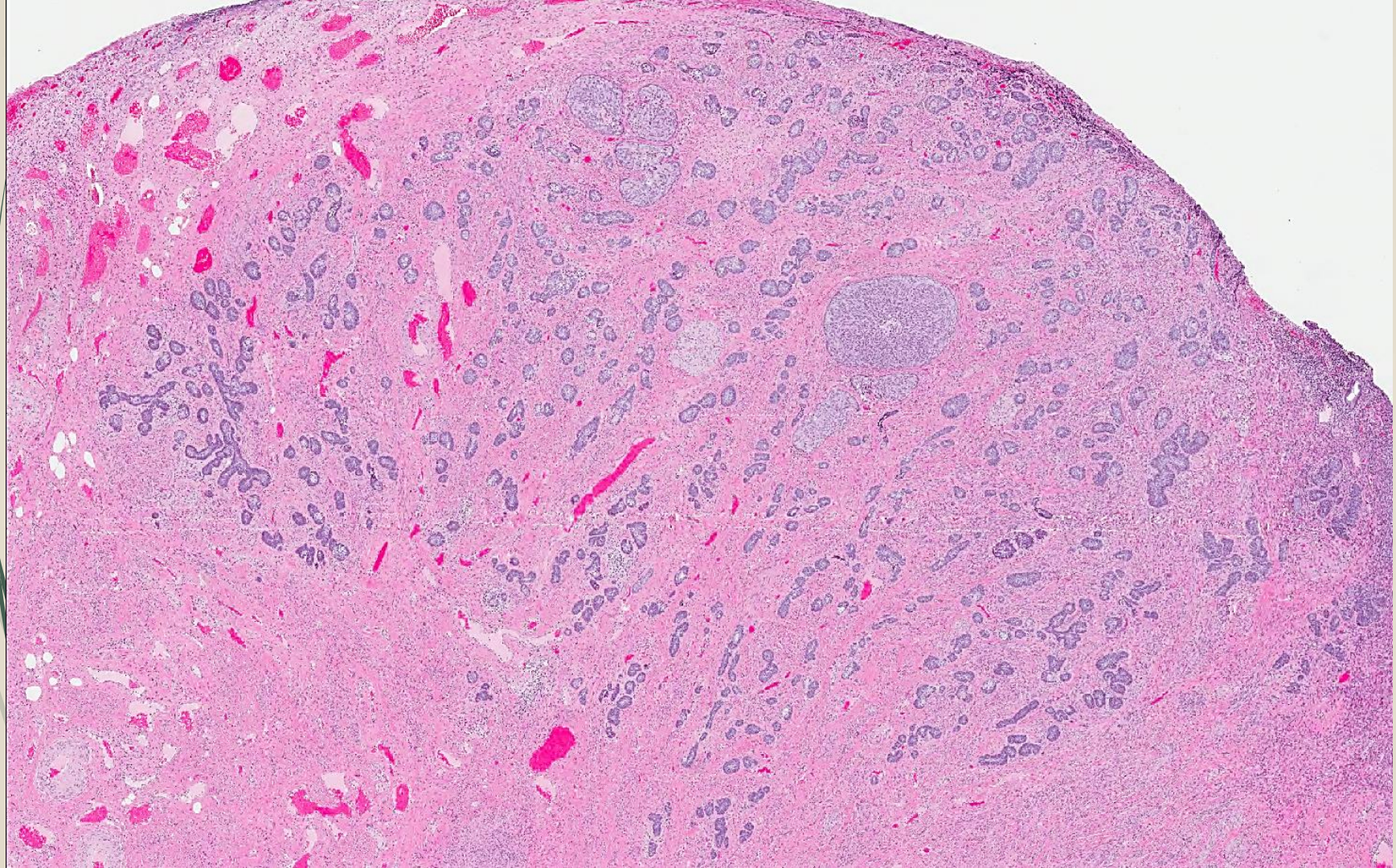
- <1% all cervical cancers
- Typically post-menopausal women
- Frequently associated with HSIL
- Pure or admixed with conventional SCC or adenoCA
- When pure, indolent behavior
  - Adenoid basal epithelioma
- Mixed lesions also behave well
- Complete excision is necessary

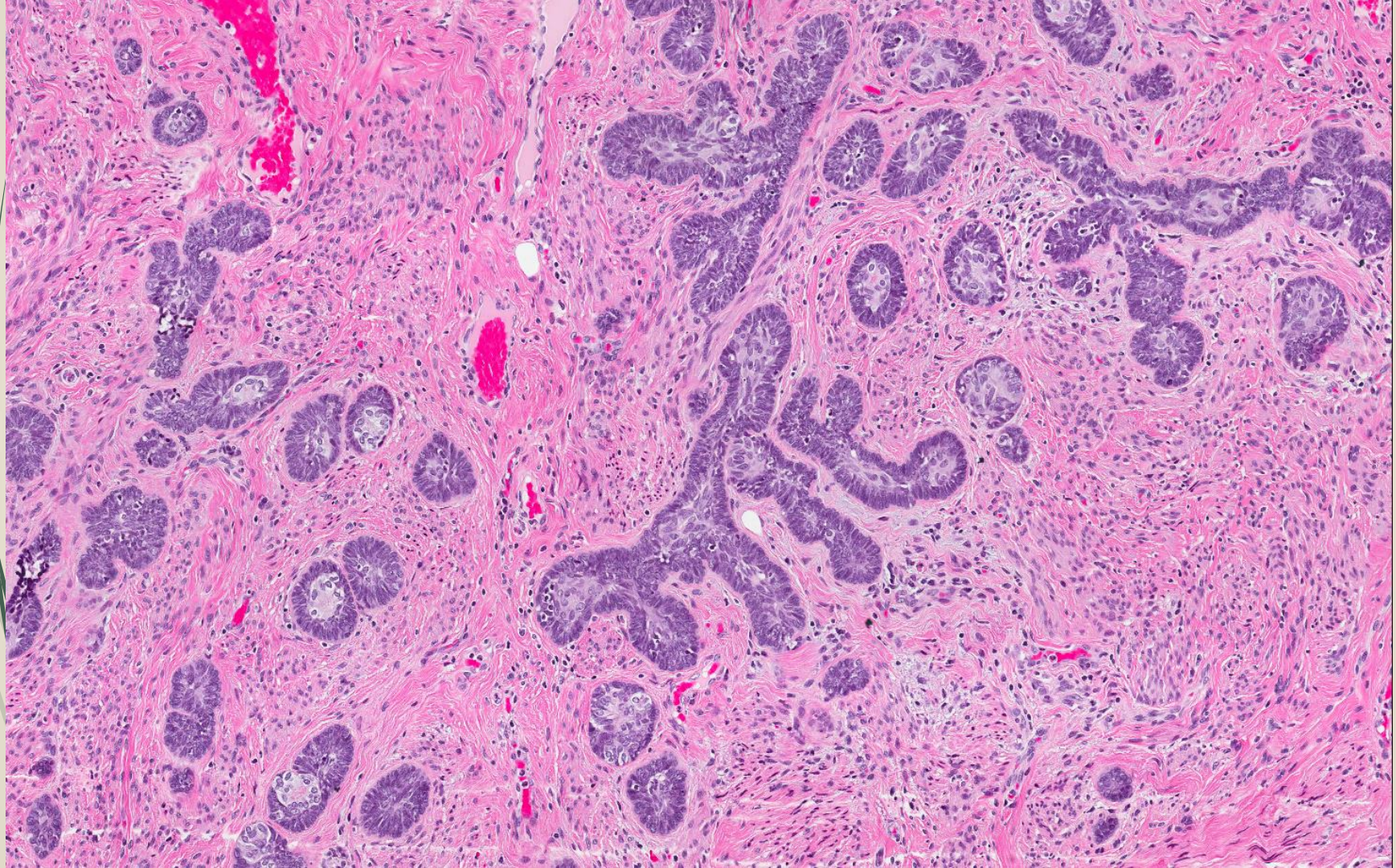
Diagn Pathol 2006;1:18
Hum Pathol 2005;36:82–90
Am J Surg Pathol 1998;22:965–975

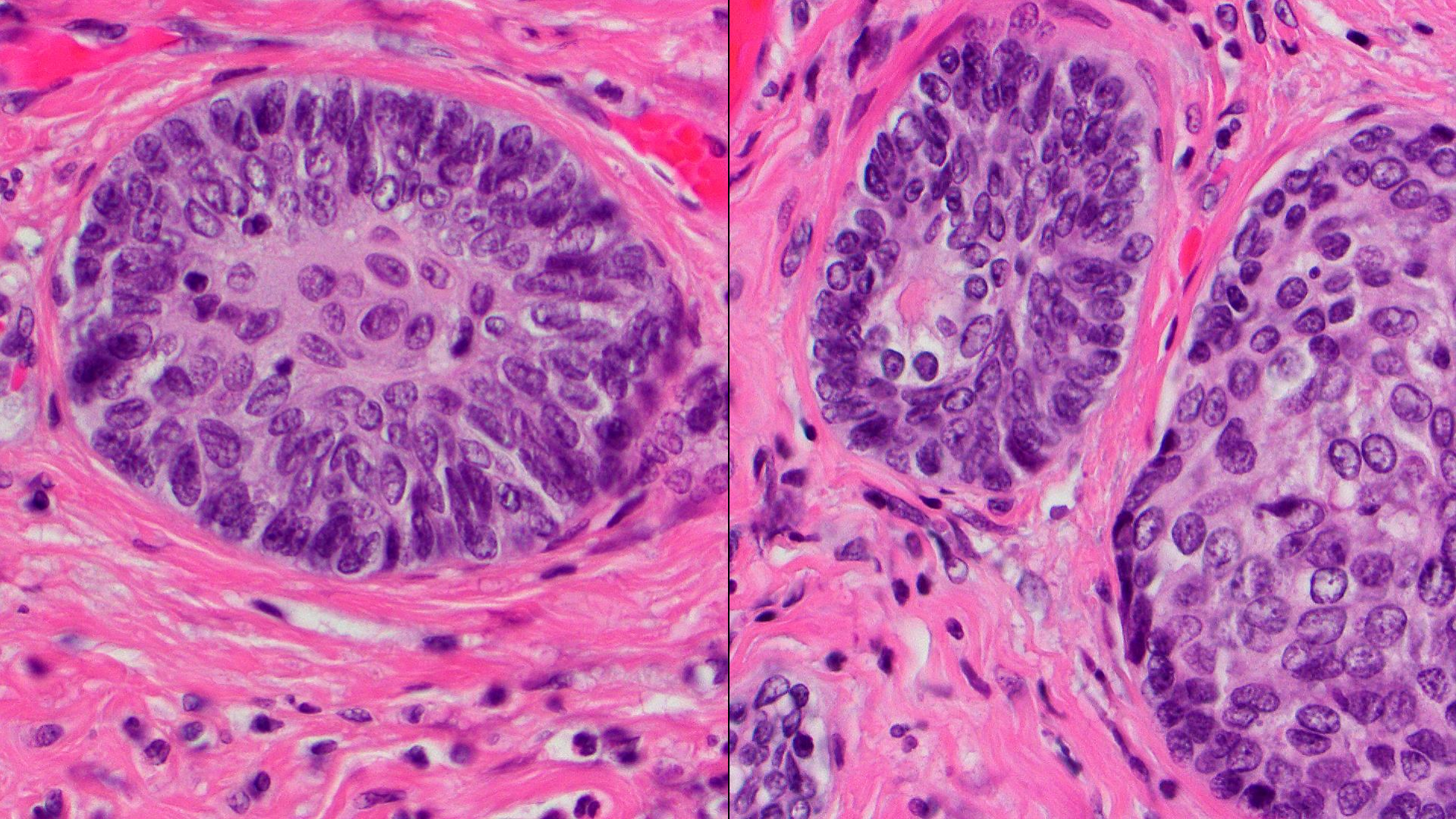
ADENOID BASAL CARCINOMA

- Haphazard nest distribution
- Basaloid organization at the periphery
- Central squamous and/or glandular differentiation
- Absence of desmoplasia
- No LVI or PNI
- P16 overexpressed / hrHPV +

Diagn Pathol 2006;1:18
Hum Pathol 2005;36:82–90
Am J Surg Pathol 1998;22:965–975







DDx: ADENOID CYSTIC CARCINOMA

- Tumors with adenoid cystic differentiation
  - Vulva > vagina > cervix

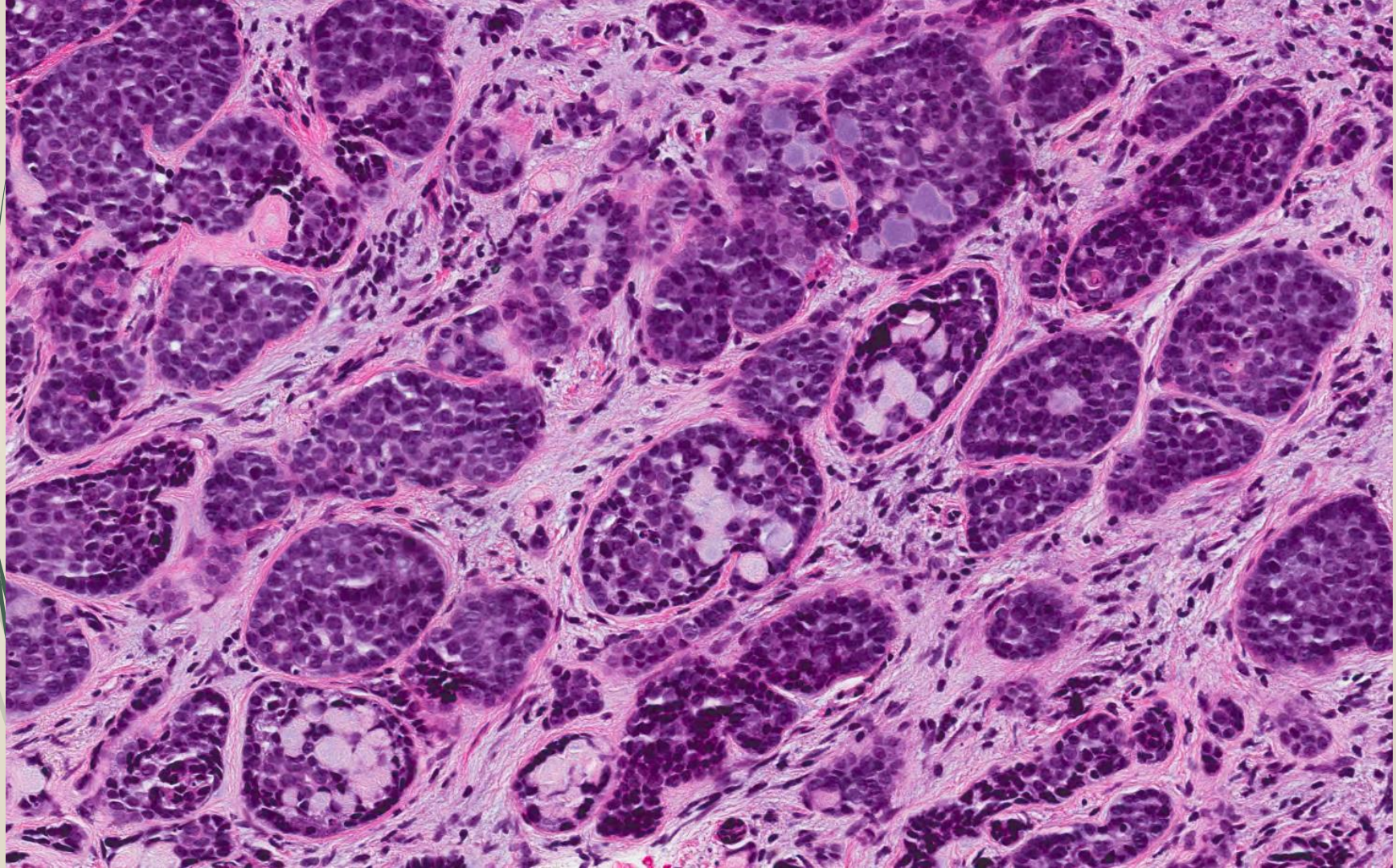
	Pure adenoid cystic carcinoma	**Mixed carcinoma with adenoid cystic differentiation**
Patient age	Median 48 years (27-74)	Median 76 years (50-86)
Adenoid cystic component	100%	Usually <25%
High-risk HPV	Not detected	Detected (usually HPV16)
p16 IHC	Non-diffuse	Diffuse and strong
Perineural invasion	~50%	Absent

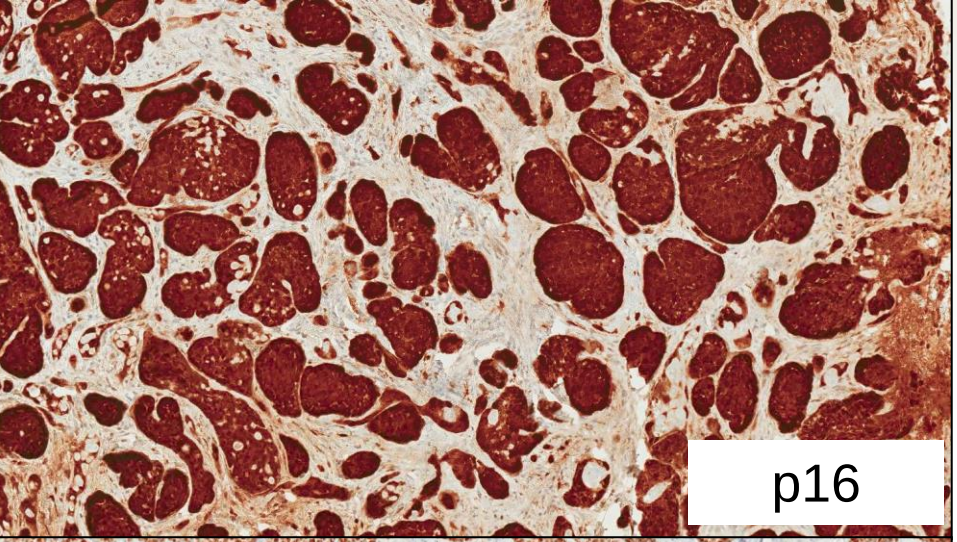
Am J Surg Pathol 2016;40:529–536

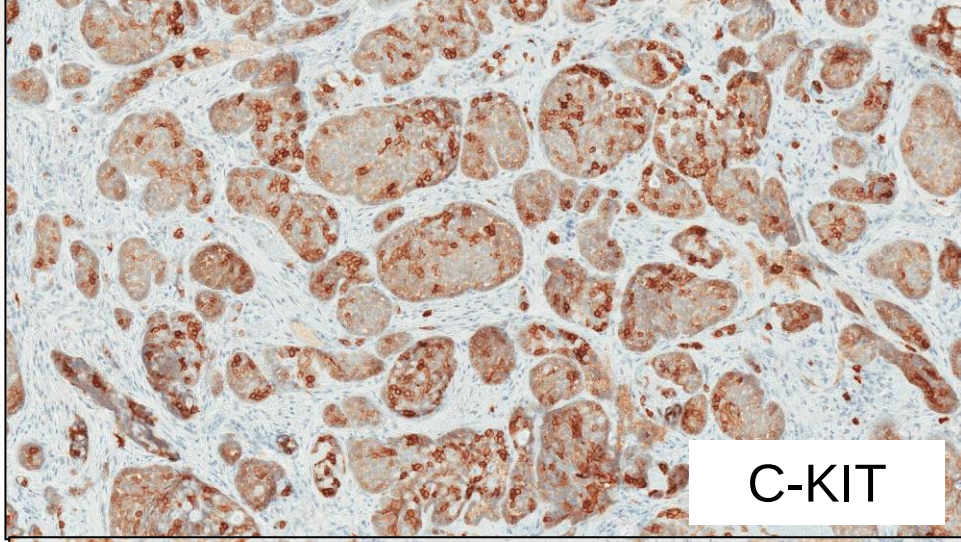
DDx: ADENOID CYSTIC CARCINOMA

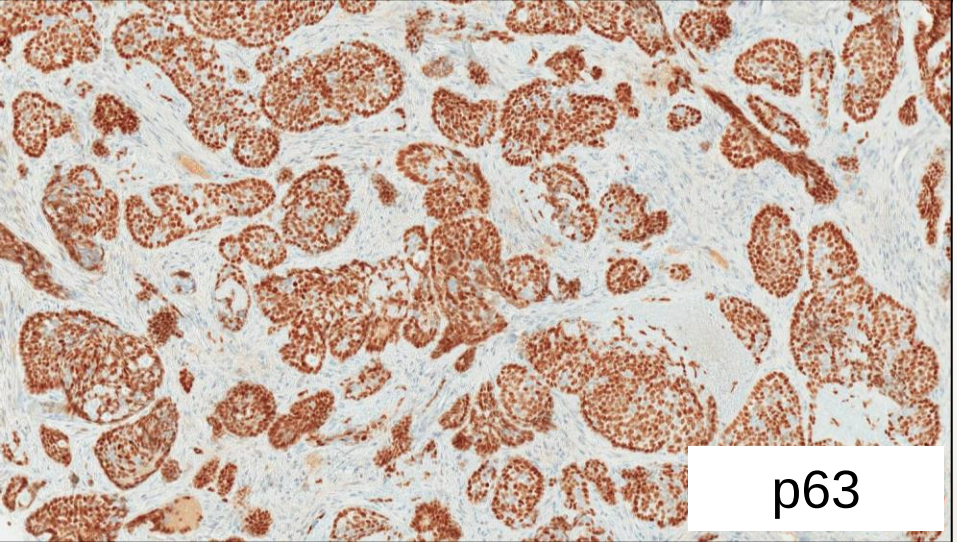
- Similar morphology to H&E, lung and breast ADCCs
- Cribriform, tubular and solid growth patterns
- Cysts containing mucinous / eosinophilic secretions
- Pseudocysts containing basement membrane-like material
- ER / PR negative
- C-KIT and MYB expression
  - Adenoid basal CA is negative

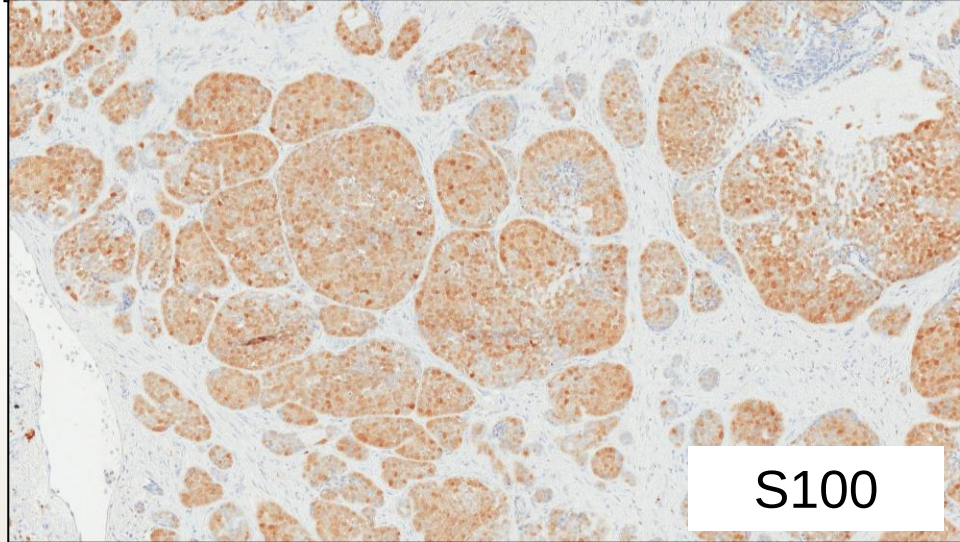
Am J Surg Pathol 1999;23:448–458
Int J Gynecol Pathol 1992;11:2–10
Int J Gynecol Pathol 2012;31:25–32




p16


C-KIT

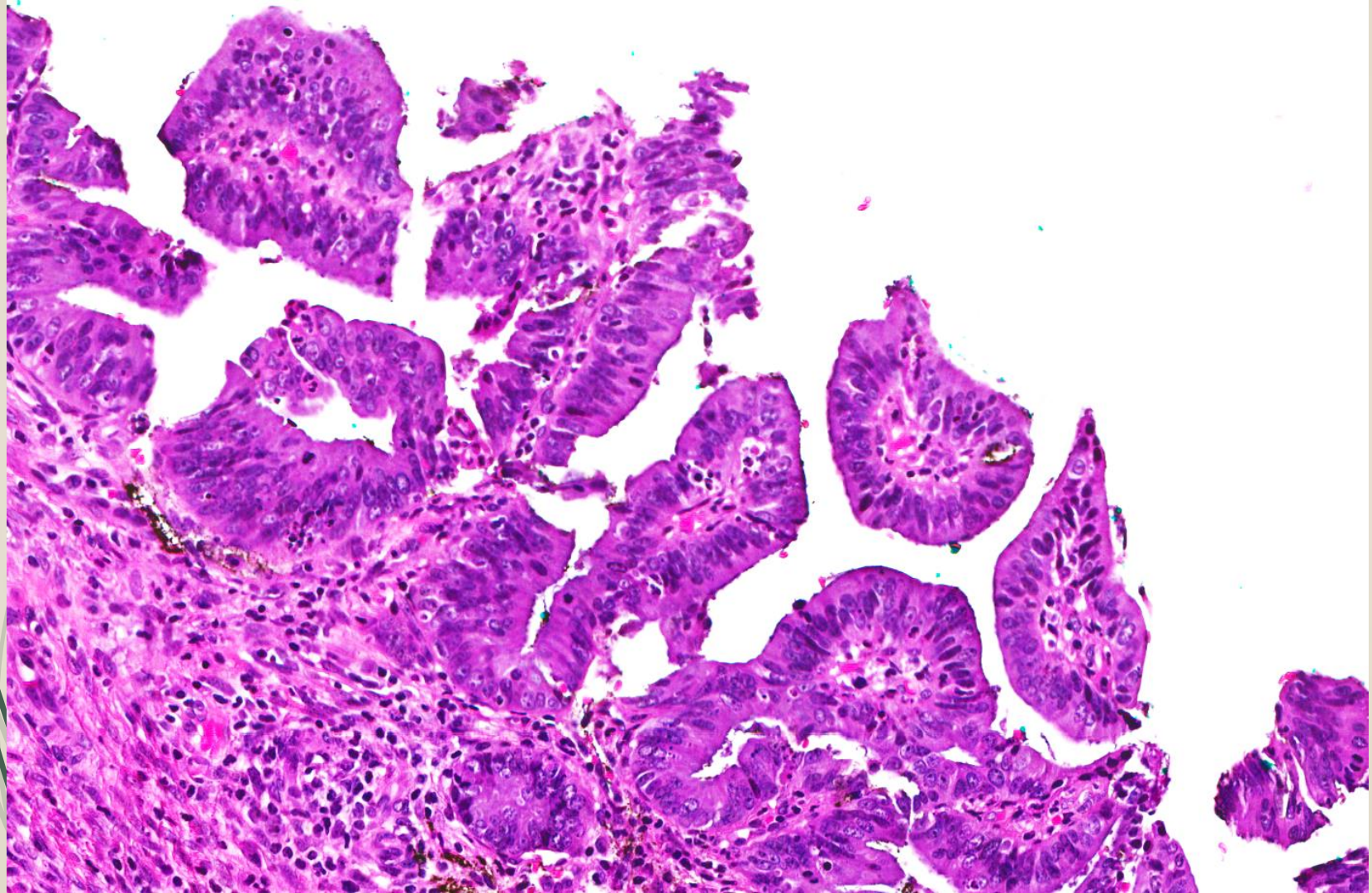

p63

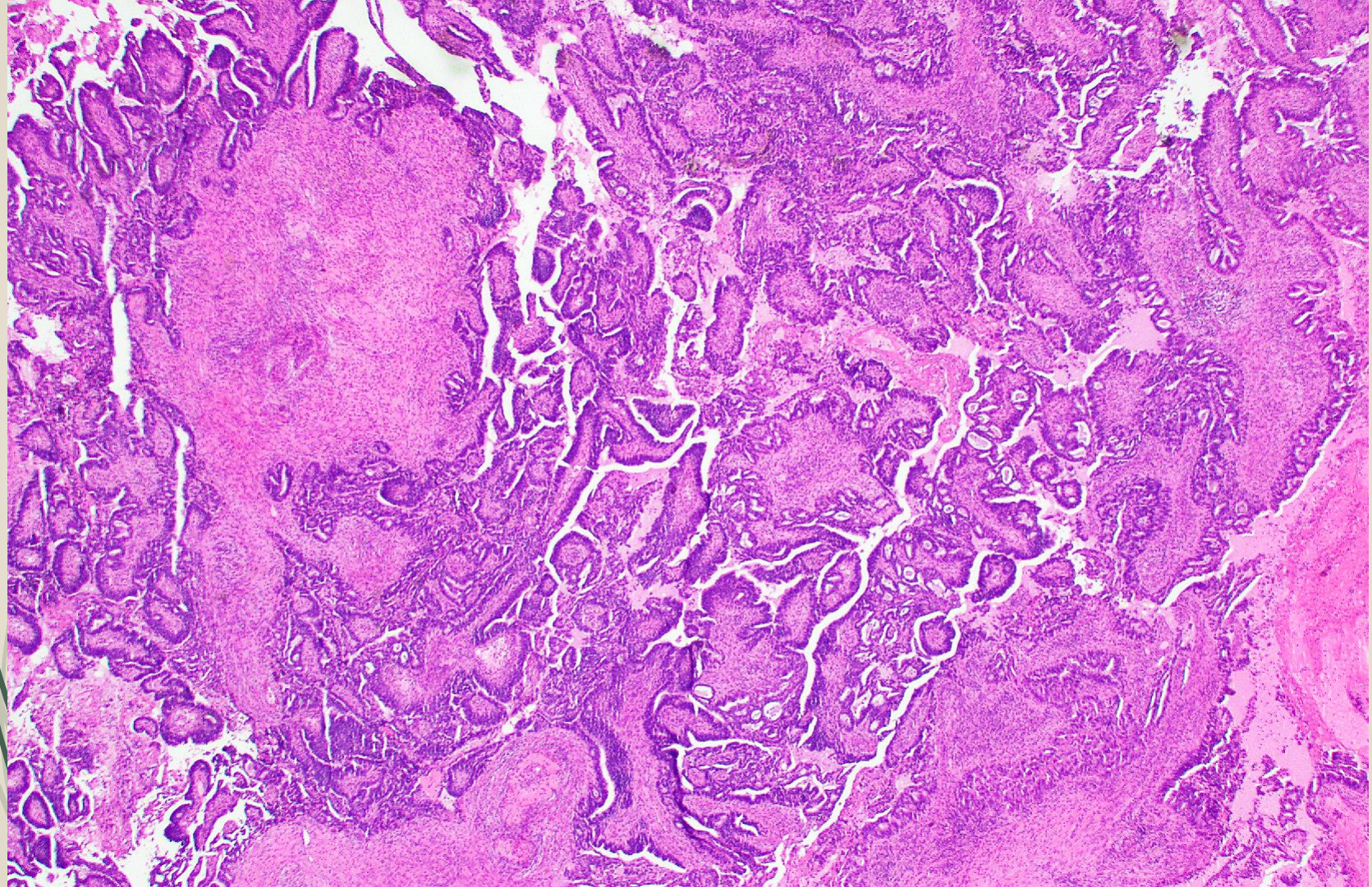

S100

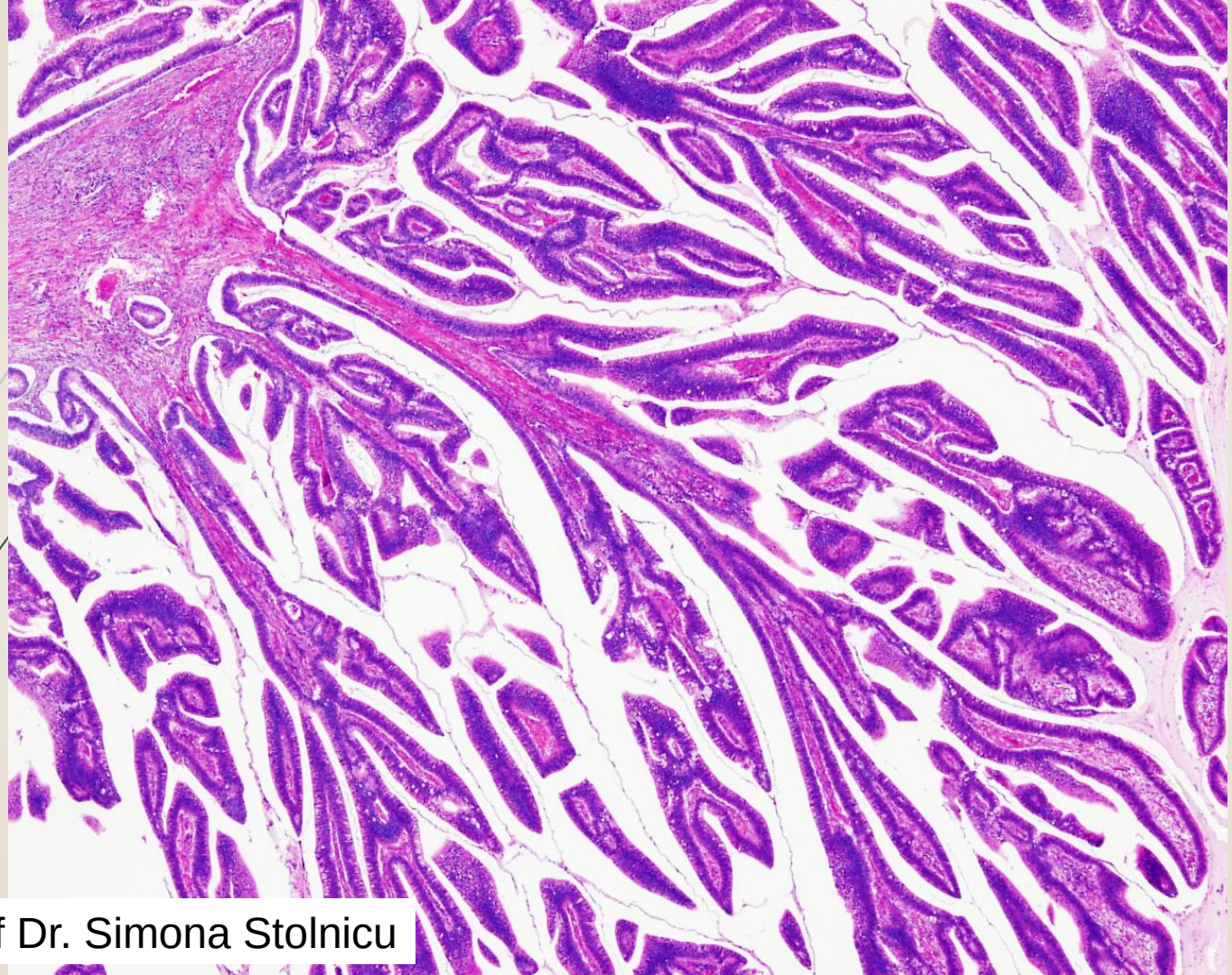
VILLOGLANDULAR ADENOCARCINOMA

- Exophytic form of usual type HPVA
- Mucinous forms can also exist
- Most are purely or predominantly exophytic
  - 71% had less than 50% wall invasion*
- Well to moderately differentiated (97%)*
- LVI 3%*

Cancer. 1989;63:1773–9
Int J Gynecol Pathol. 1993;12:1–7
* Int J Gynecol Cancer 2021;31:512-517







Courtesy of Dr. Simona Stolnicu

VILLOGLANDULAR ADENOCARCINOMA

- Historically, indolent outcome
  - 100% 5-year OS and DFS (n=47)*
  - 82% 5-year OS and 75% DFS (n=28)**
  - 96% indolent outcome (n=88 >1 year f/u)***
- But… ~60% are stage IB1
  - 71% are >2 cm (41% 2-4 cm; 30% are >4 cm)*

* Int J Gynecol Cancer 2021;31:512-517
** Int J Gynecol Cancer 2013;23:900-5
*** Histopathology 2007;51(2):268-9

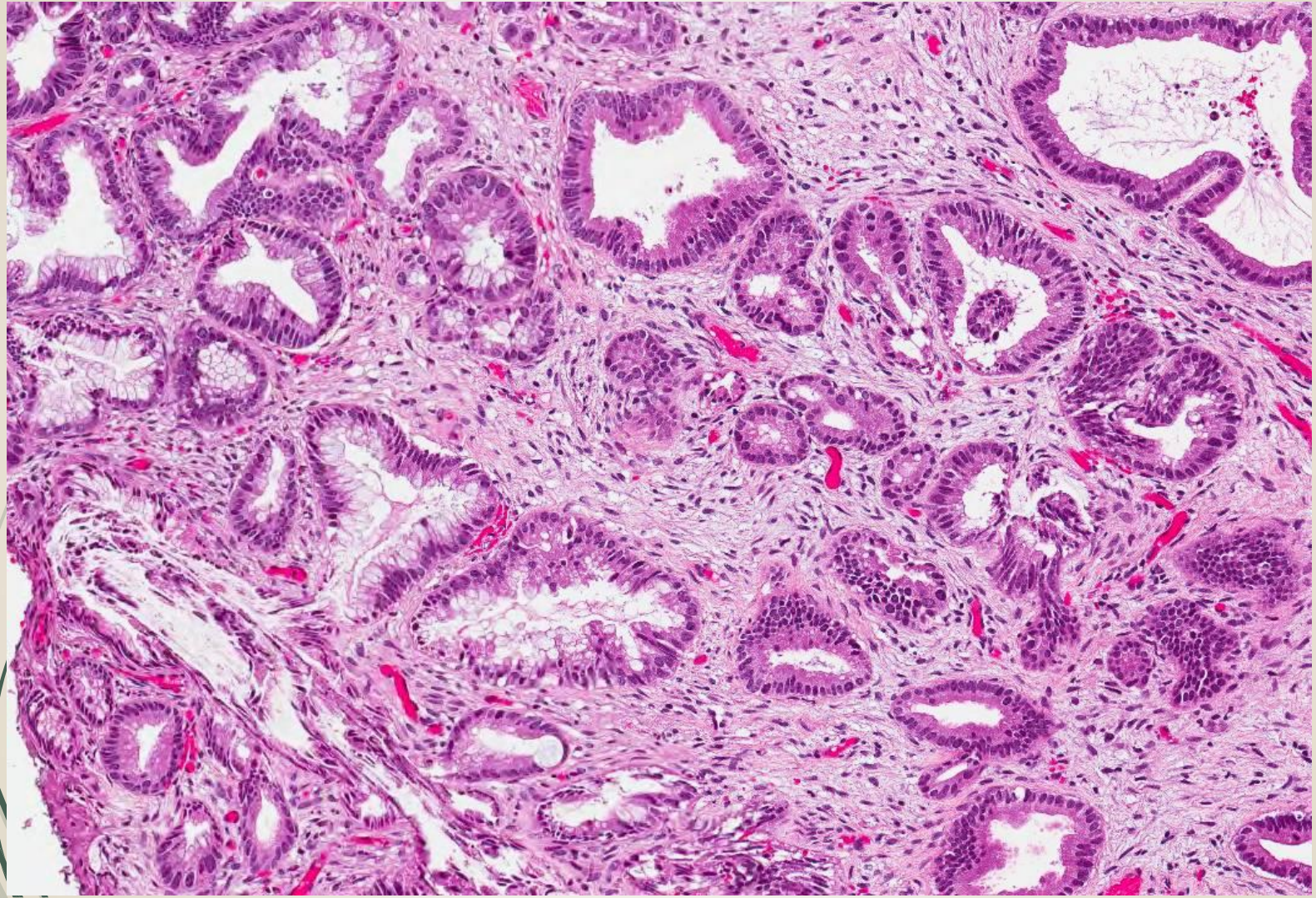
VILLOGLANDULAR ADENOCARCINOMA

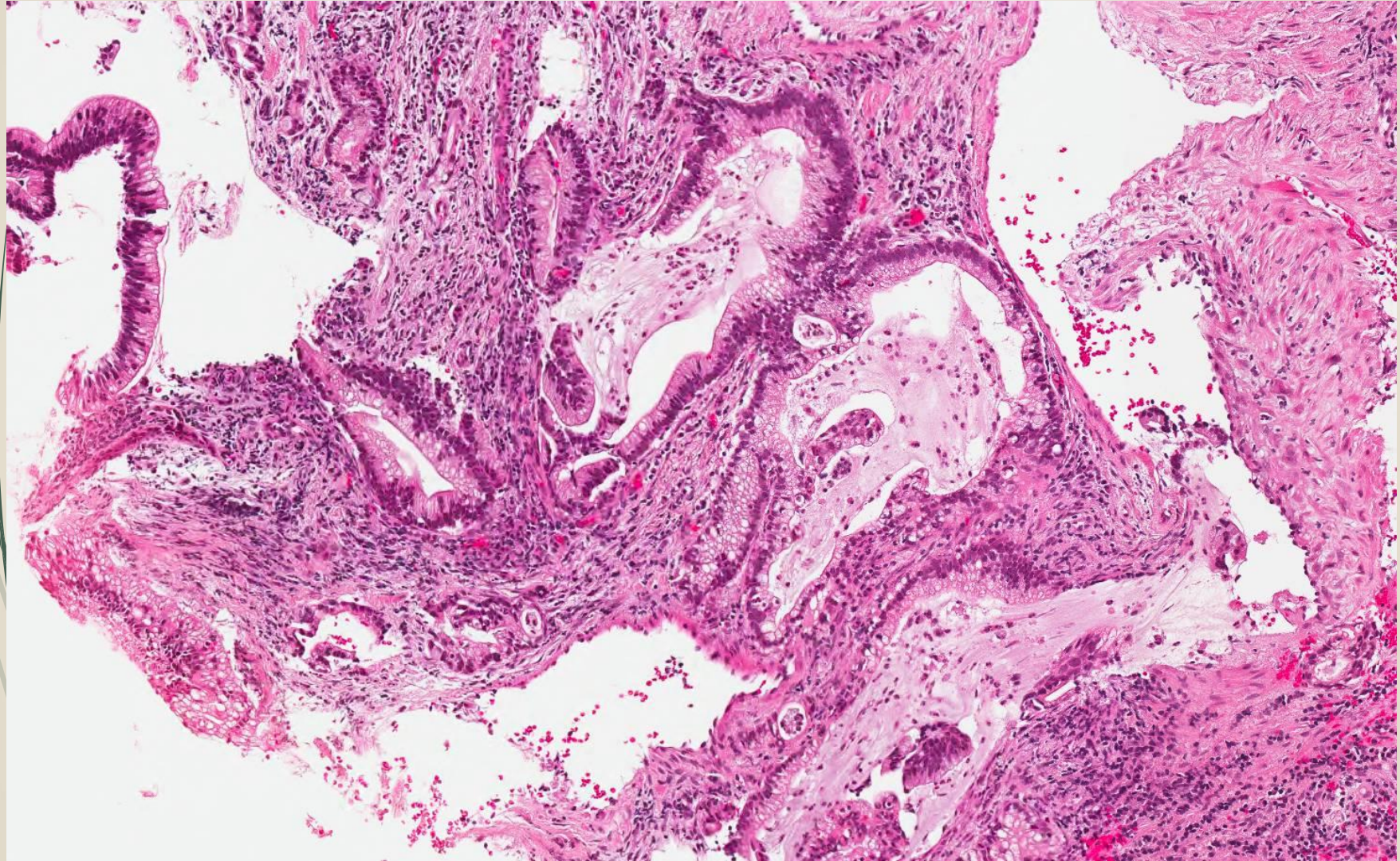
- Also…… some present at stage II-IV
- ~5% had lymph node metastases
- Subset associated with poorly diff component
- Poor reproducibility
- Recommend at least complete excisional sampling
  - Ensure complete removal
  - Exclude adverse features (LVI, deep invasion, second components, etc)

Int J Gynecol Cancer 2021;31:512-517
Cancer 2001;92(9):2471-83
Histopathology 2007;51(2):268-9
Gynecol Oncol 2003;90;282–289

MUCINOUS HPV-ASSOCIATED ADENOCARCINOMA

- Mucinous HPVA, no otherwise specified
  - Cells with endocervical-type mucin
  - Comprise most of the tumor (≥50%)

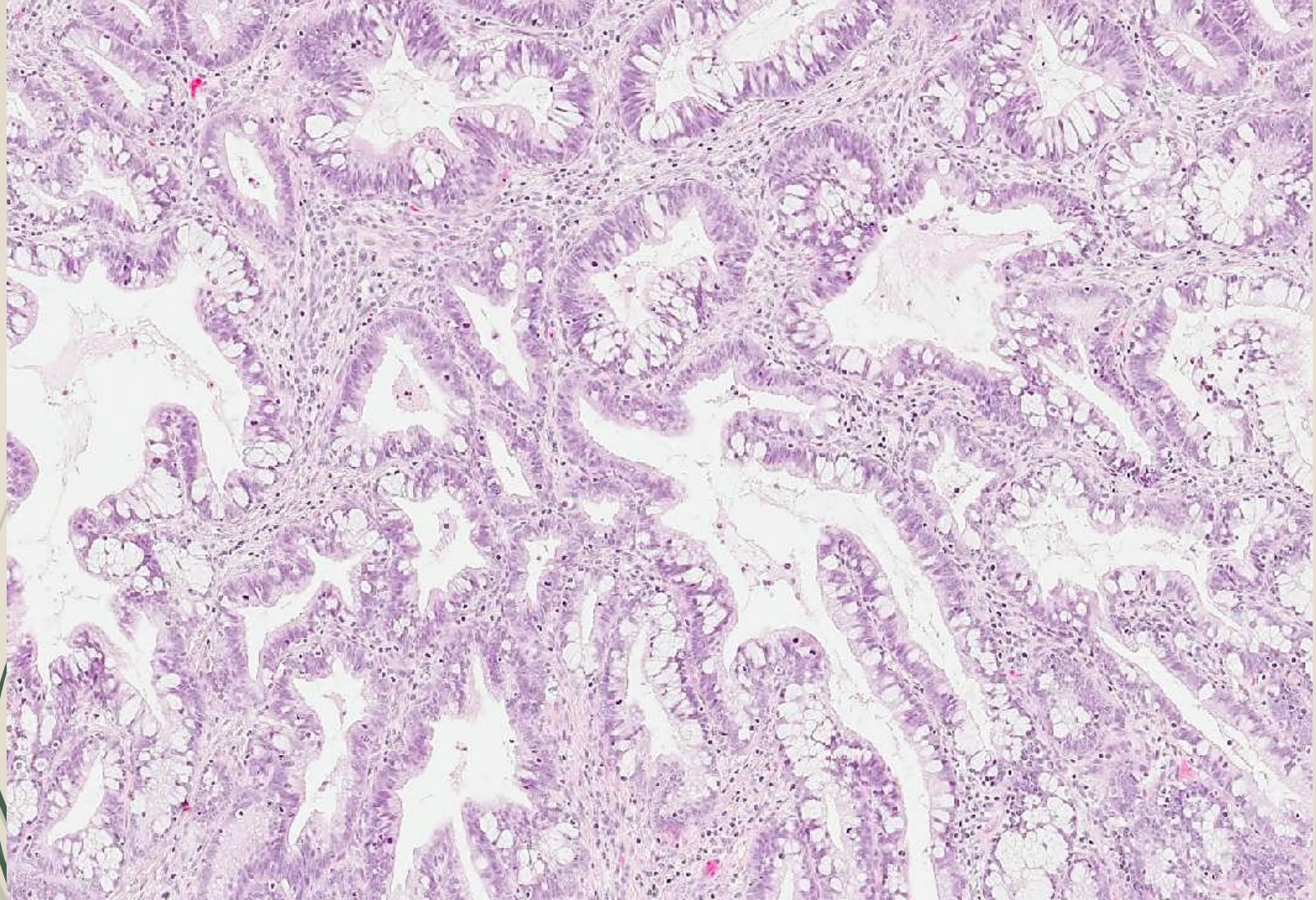


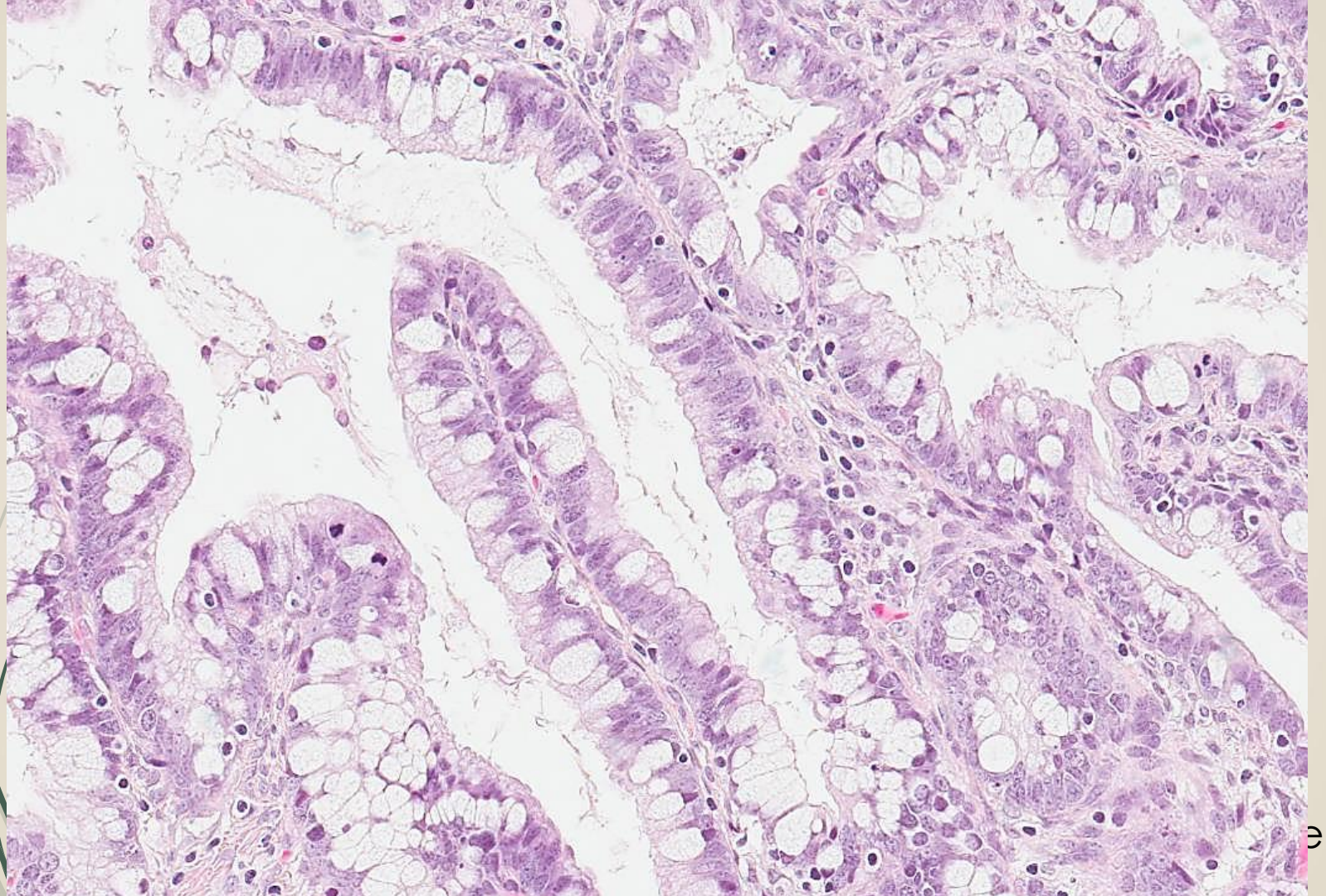


HPV-RELATED ADENOCARCINOMA

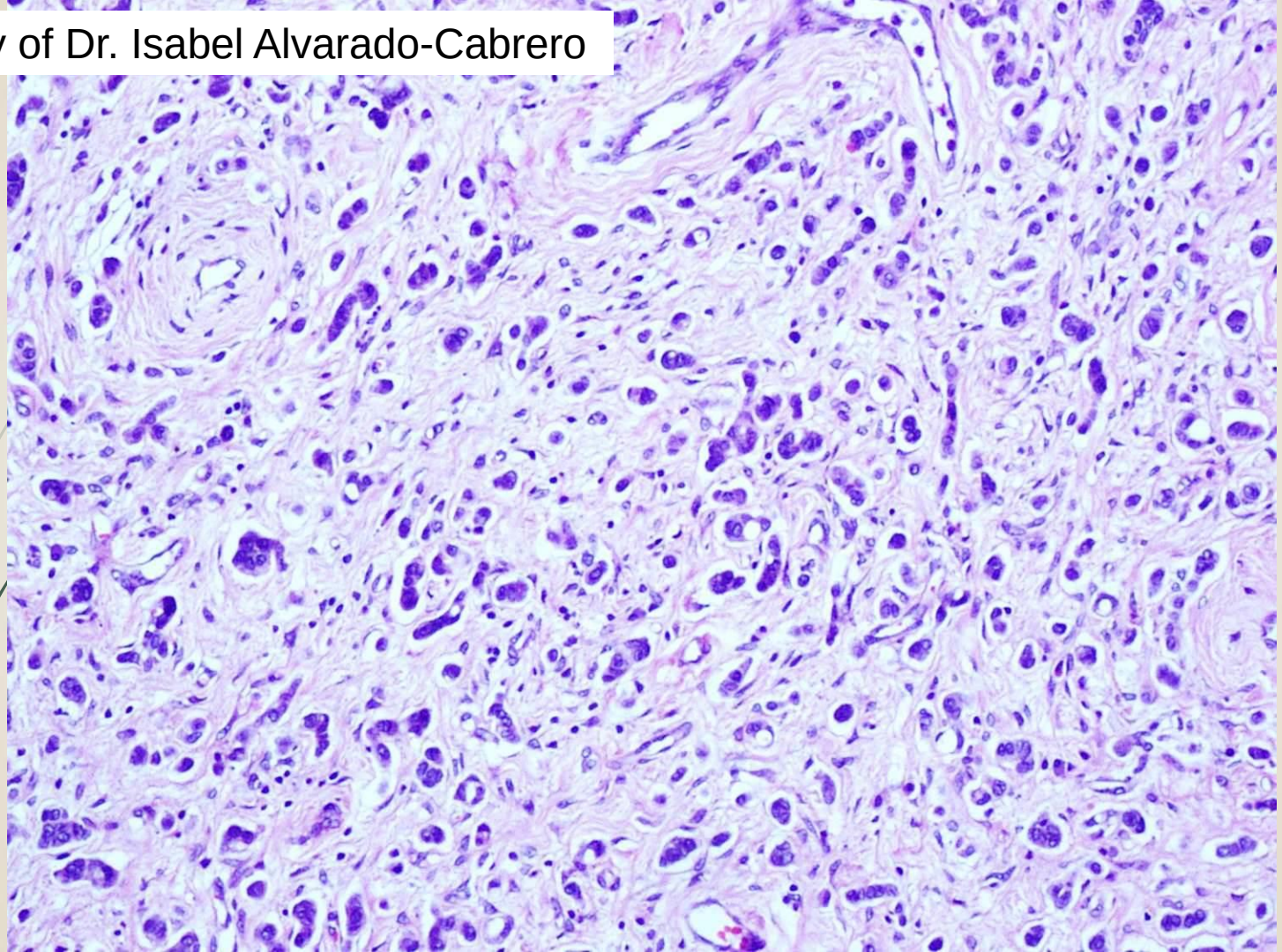
- MUCINOUS
- Intestinal-type HPVA
  - Goblet cells
  - Enteroendocrine cells (Paneth cells)
- Signet-ring cell HPVA
  - Rare

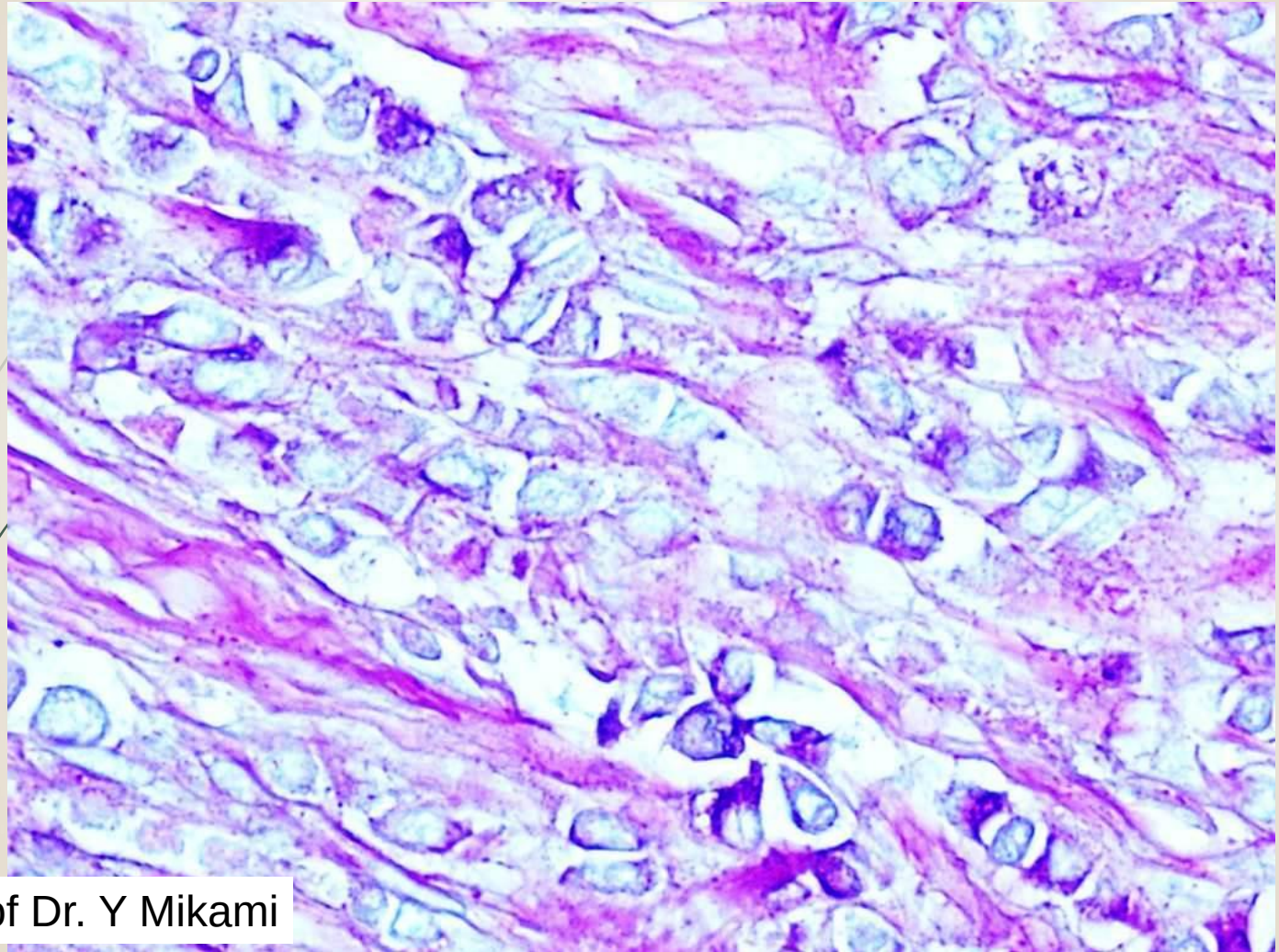
FIRST EXCLUDE:
- Gastric-type Cx adenoCA
- Metastases from GI tract to Cx





Courtesy of Dr. Isabel Alvarado-Cabrero



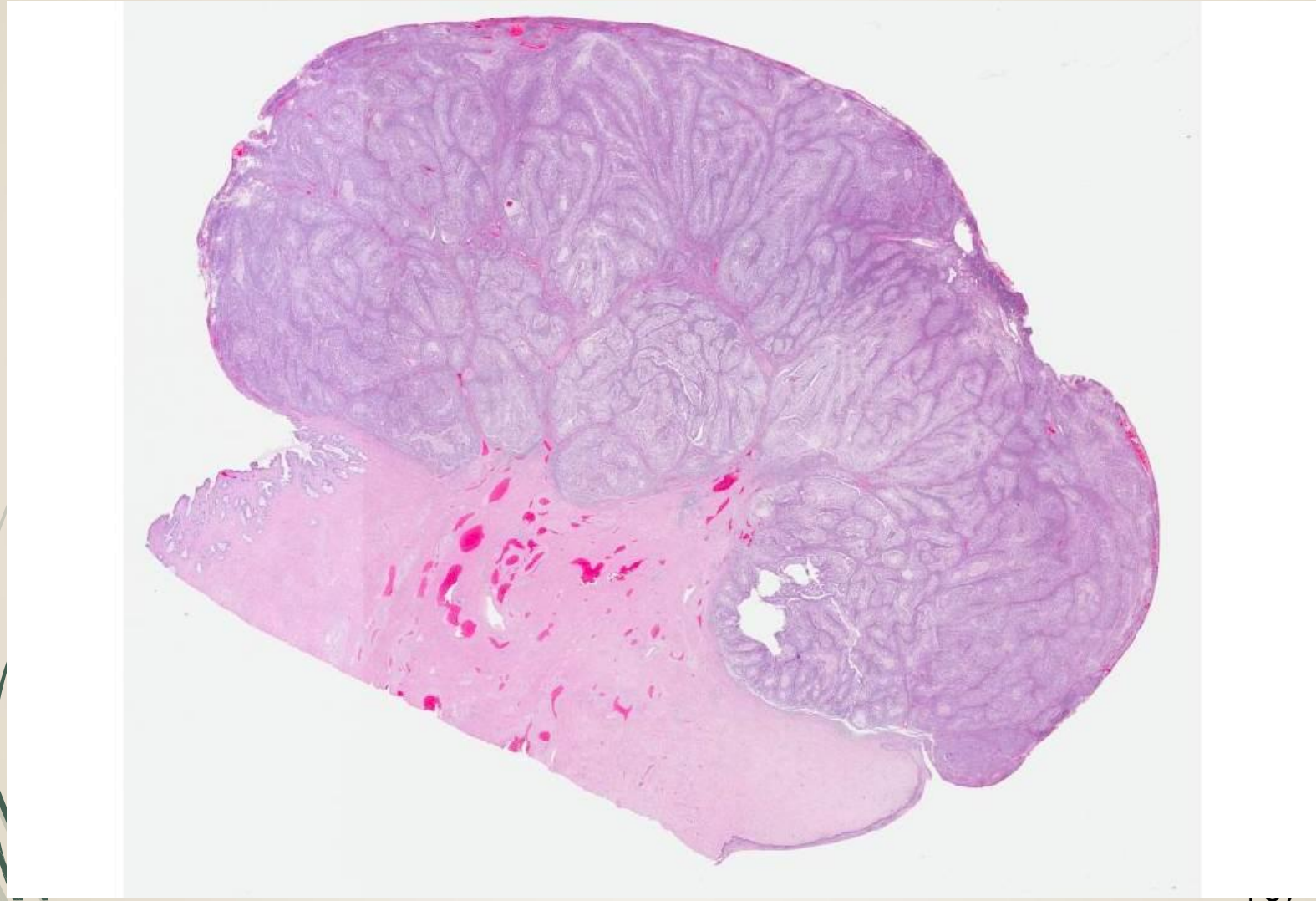


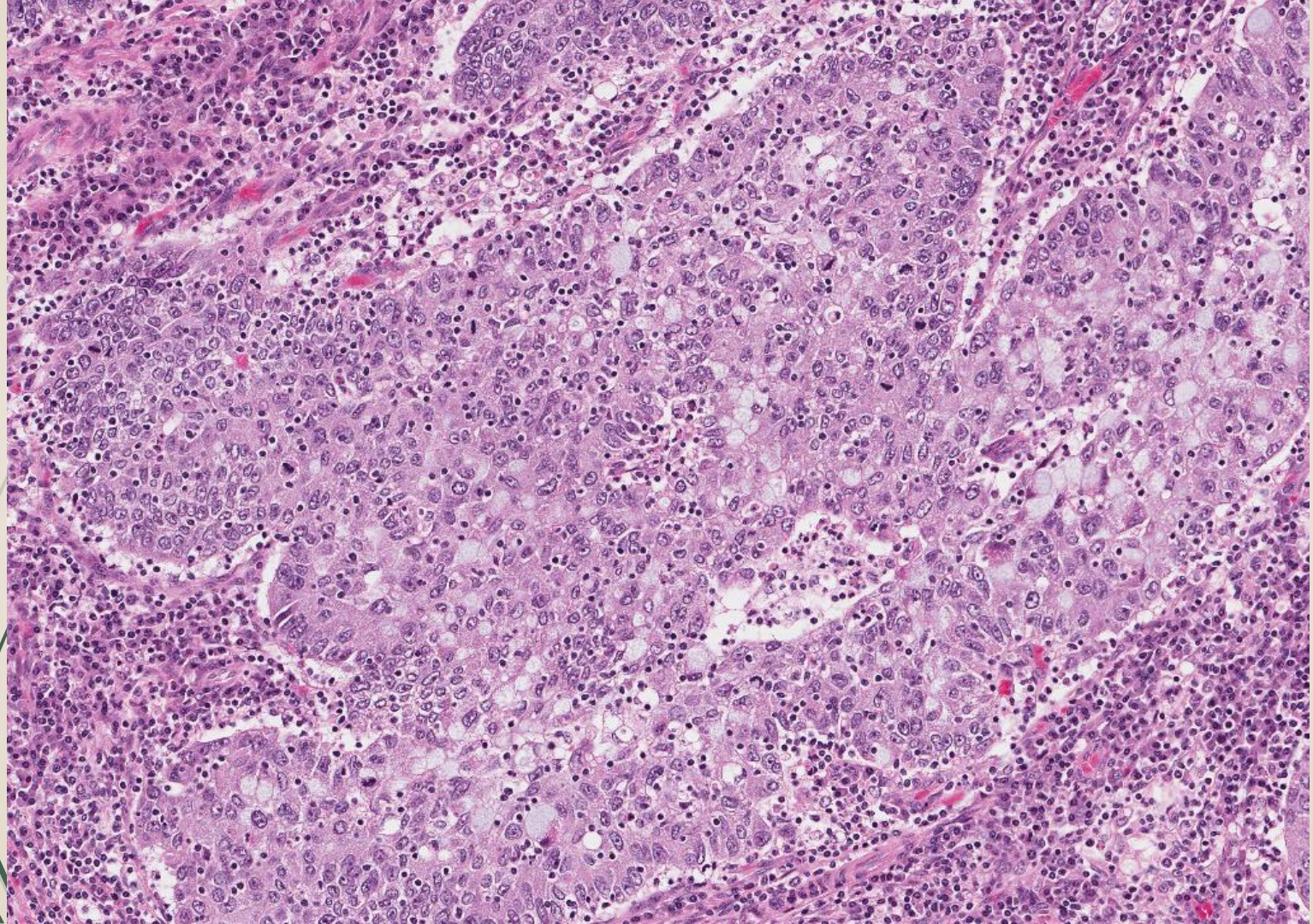
Courtesy of Dr. Y Mikami

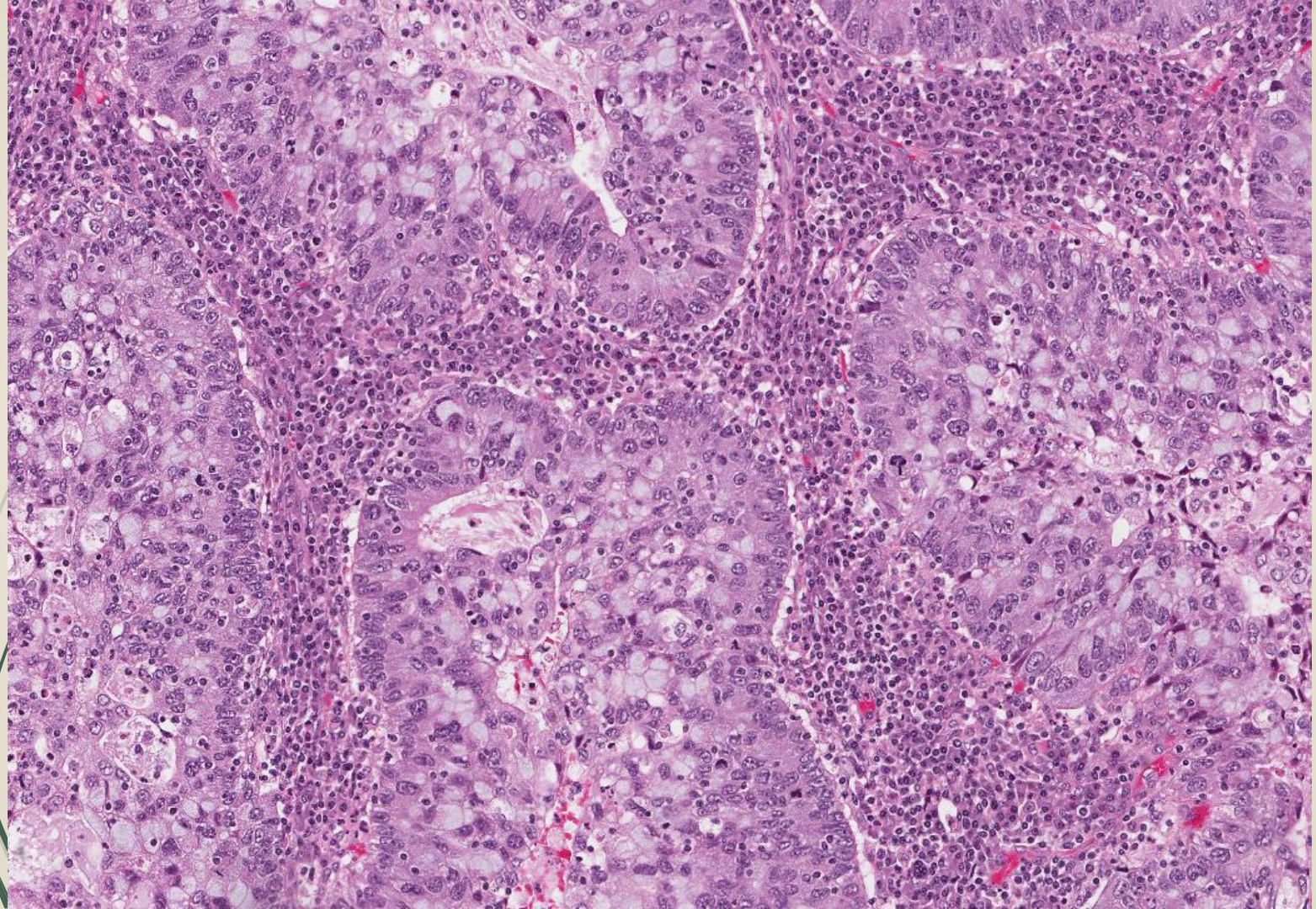
ISMC

- Invasive stratified mucin-producing carcinoma
  - Invasive counterpart of SMILE
  - Insular, solid, trabecular, papillary growth
  - Composed of cells with distinct mucinous cytoplasm
  - *Full-thickness* distribution

Am J Surg Pathol 2016;40:262–9
Am J Surg Pathol 2020;44:873–880



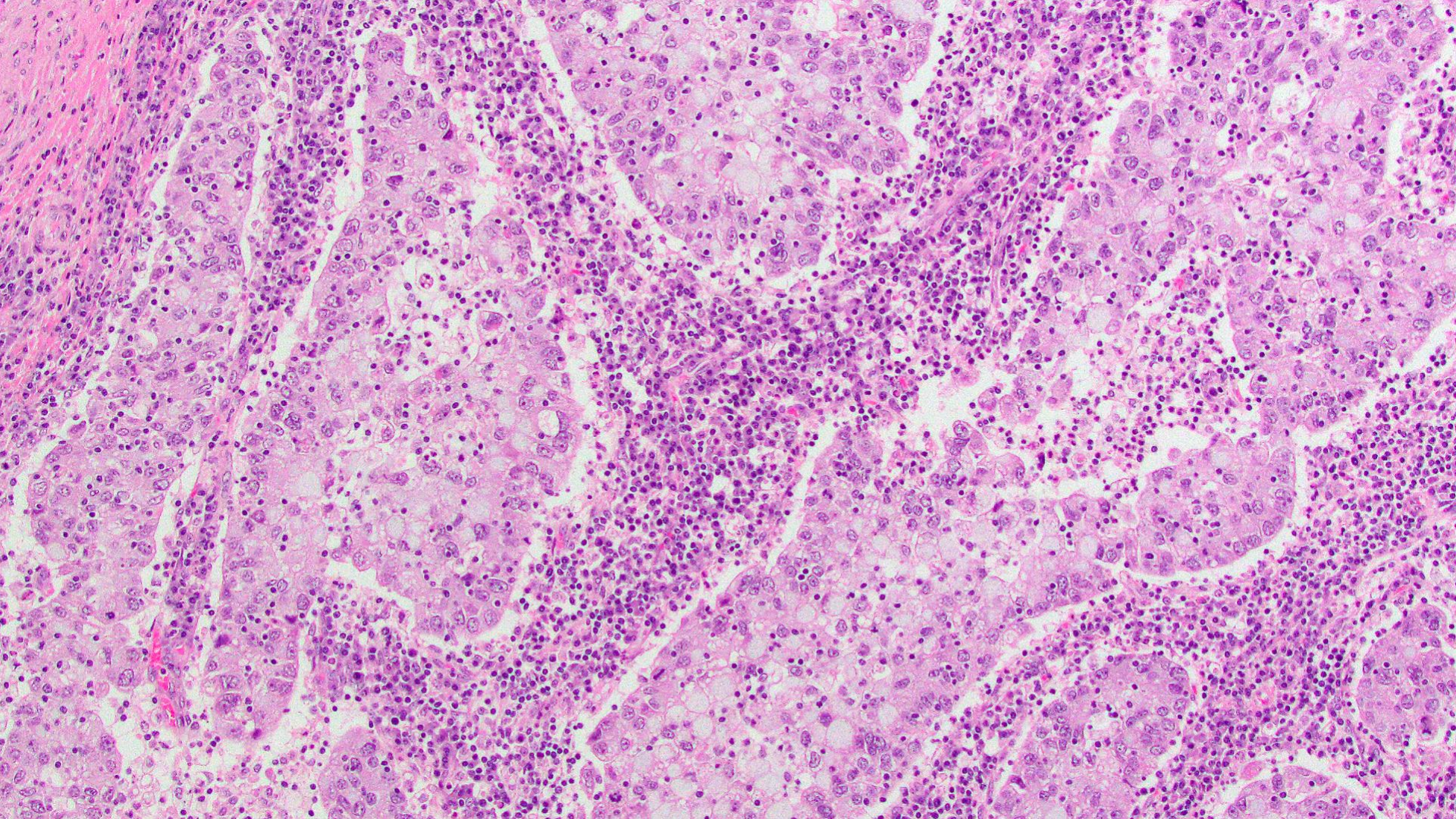




ISMC

- Can be pure (56%) or mixed (44%)
  - Usual, mucinous, neuroendocrine or adenosquamous 2nd component

Am J Surg Pathol 2020;44:873–880



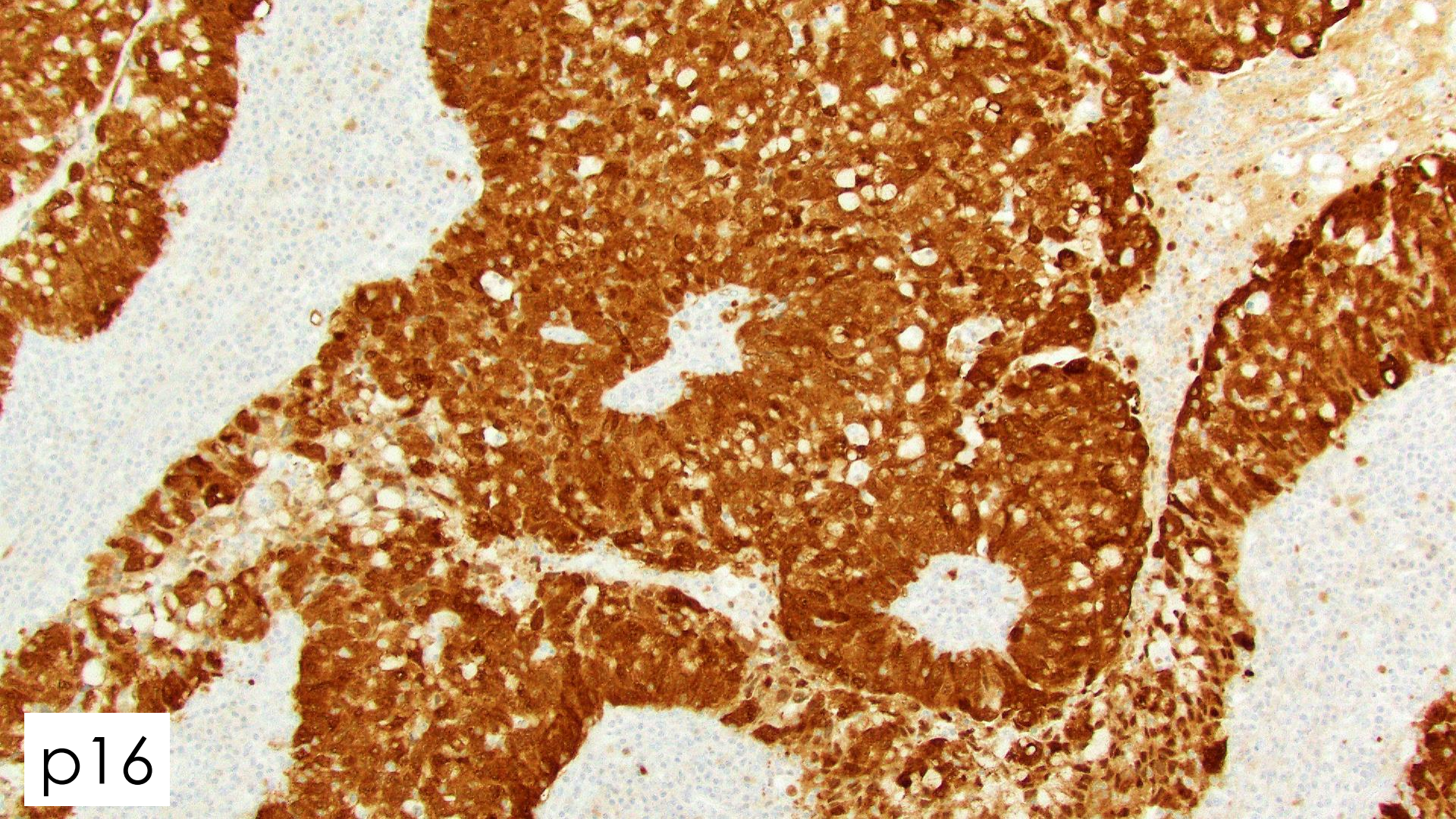

p16

Table 2 The immunohistochemical profile of pure invasive stratified mucin-producing carcinomas in comparison with adenosquamous carcinomas

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*Statistically significant differences

Mod Pathol 2019;32:269-279

Table 3 Recurrence and cancer-related mortality in patients with endocervical adenocarcinoma

		Recurrences	Deaths
HPVA (n=62 with follow-up)	Usual	3/43 (7%)	0/51 (0%)
	Mucinous NOS	1/9 (11%)	0/9 (0%)
	Mucinous intestinal	1/2 (50%)	0/2 (0%)
	ISMC	4/8 (50%)	2/8 (25%)

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

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

ISMC

- Adverse features are frequent
- Worse outcome compared to other HPV-associated adenocarcinomas
- Stage & tumor size are major determinants of outcome

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THANK YOU!!

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