Updates in HPV-Associated vs HPV-Independent Adenocarcinomas of the Endocervix

Park City Anatomic Pathology Update
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Disclosures

- I have no conflicts of interest to disclose.

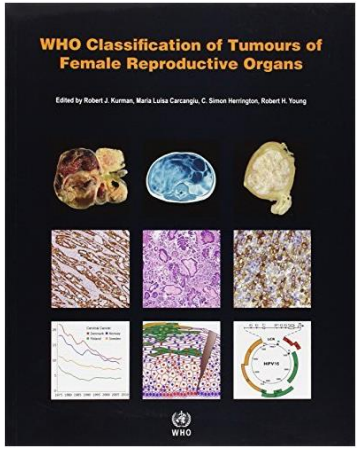
Learning Objectives

- WHO Classification of Tumours-Female Genital Tumours (Uterine Cervix): Updates from the 5th Edition
- Utilizing a case-based approach, the following topics will be discussed:
- HPV-associated adenocarcinomas of the endocervix: Pattern-based assessment of invasive carcinoma (Silva classification)
- HPV-independent adenocarcinomas of the endocervix
  - International Endocervical Adenocarcinoma Criteria and Classification (IECC)
  - Proposed algorithmic workup

WHO Classification Update

WHO Classification of Tumours of Female Reproductive Organs (4th Ed.): Uterine Cervix

- Epithelial tumors
  - Squamous cell tumors and precursors (Squamous intraepithelial lesions (SILs), Squamous cell carcinoma (SCC) NOS, benign squamous lesions)
  - Glandular tumors and precursors (Adenocarcinoma in situ, Adenocarcinoma [usual type and variants])
  - Benign glandular tumors and tumor-like lesions
  - Other epithelial tumors (Adenosquamous carcinoma and other uncommon variants)
  - Neuroendocrine tumors (low-grade neuroendocrine tumor, high-grade neuroendocrine carcinoma)
- Mesenchymal tumors and tumor-like lesions
  - Benign (leiomyoma, rhabdomyoma, etc.)
  - Malignant (Leiomyosarcoma, rhabdomyosarcoma, alveolar soft part sarcoma, etc.)
  - Tumor-like lesions (Postoperative spindle-cell nodule, lymphoma-like lesion)
- Mixed epithelial and mesenchymal tumors
  - Adenomyoma, adenosarcoma, carcinosarcoma
- Melanocytic tumors
- Germ cell tumors
- Lymphoid and myeloid tumors
- Secondary tumors



WHO Classification of Tumors of the Female Reproductive Organs, 4th ed. 2014

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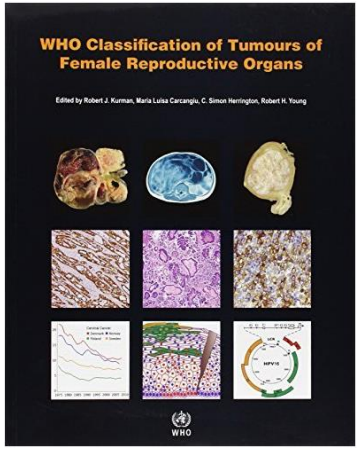

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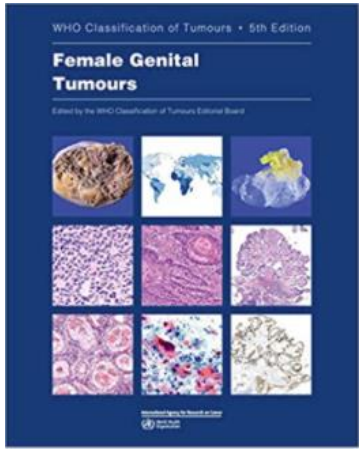
WHO Classification of Tumours-Female Genital Tumours (October 2020)



(5th Ed.): Uterine Cervix

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  - Mimics of squamous precursor lesions
  - Squamous cell tumors and precursors
- Glandular tumors and precursors
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  - Adenocarcinomas
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Differences from prior edition - major highlights

- Recognition of HPV-independent squamous cell carcinomas

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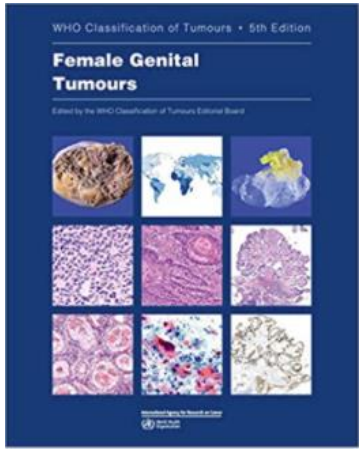

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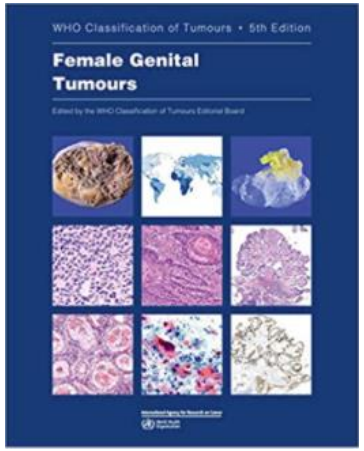

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- Staging updated to FIGO 2018 system

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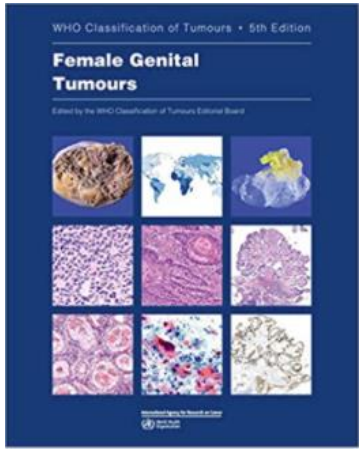

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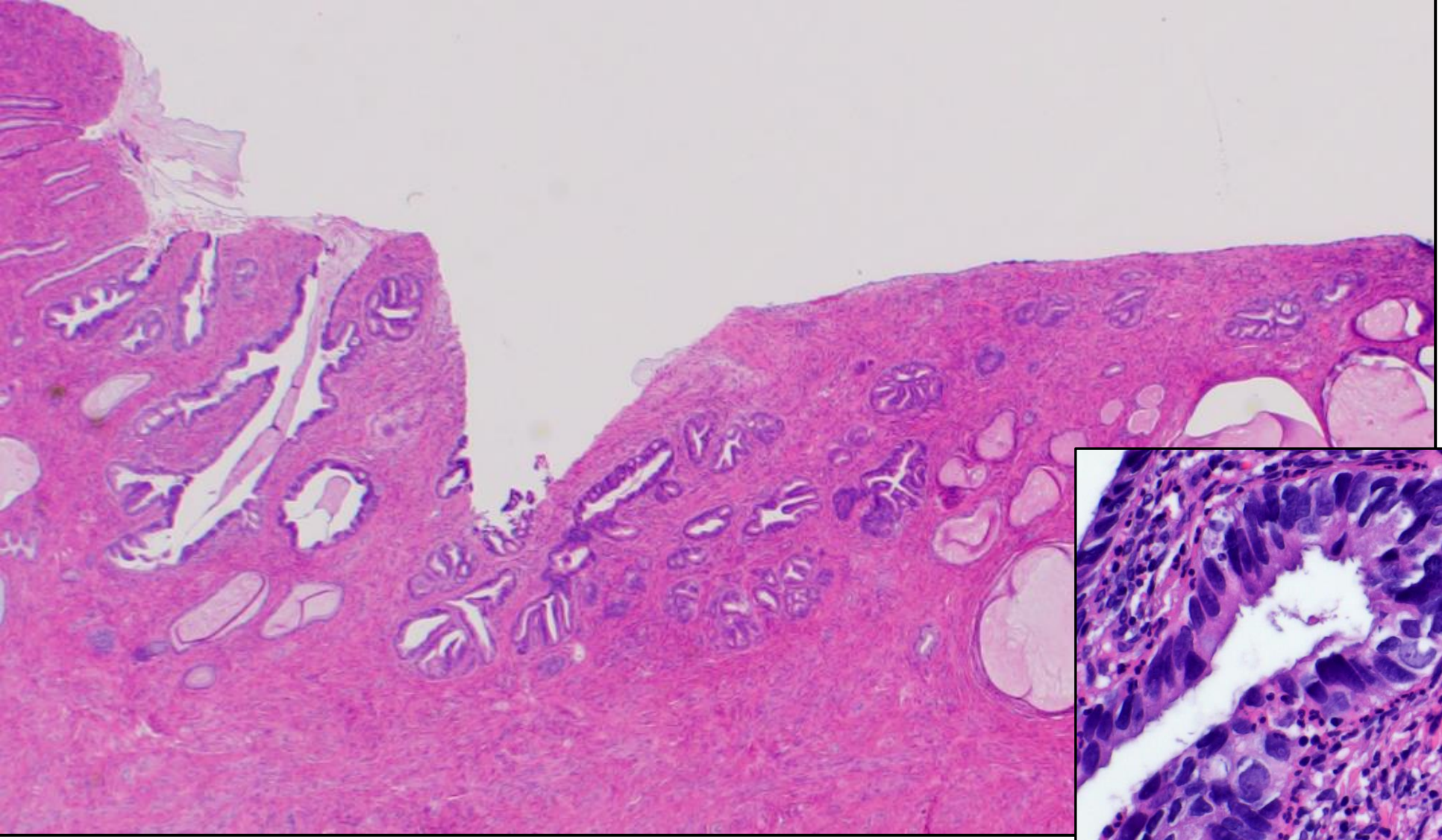
Differences from prior edition - major highlights

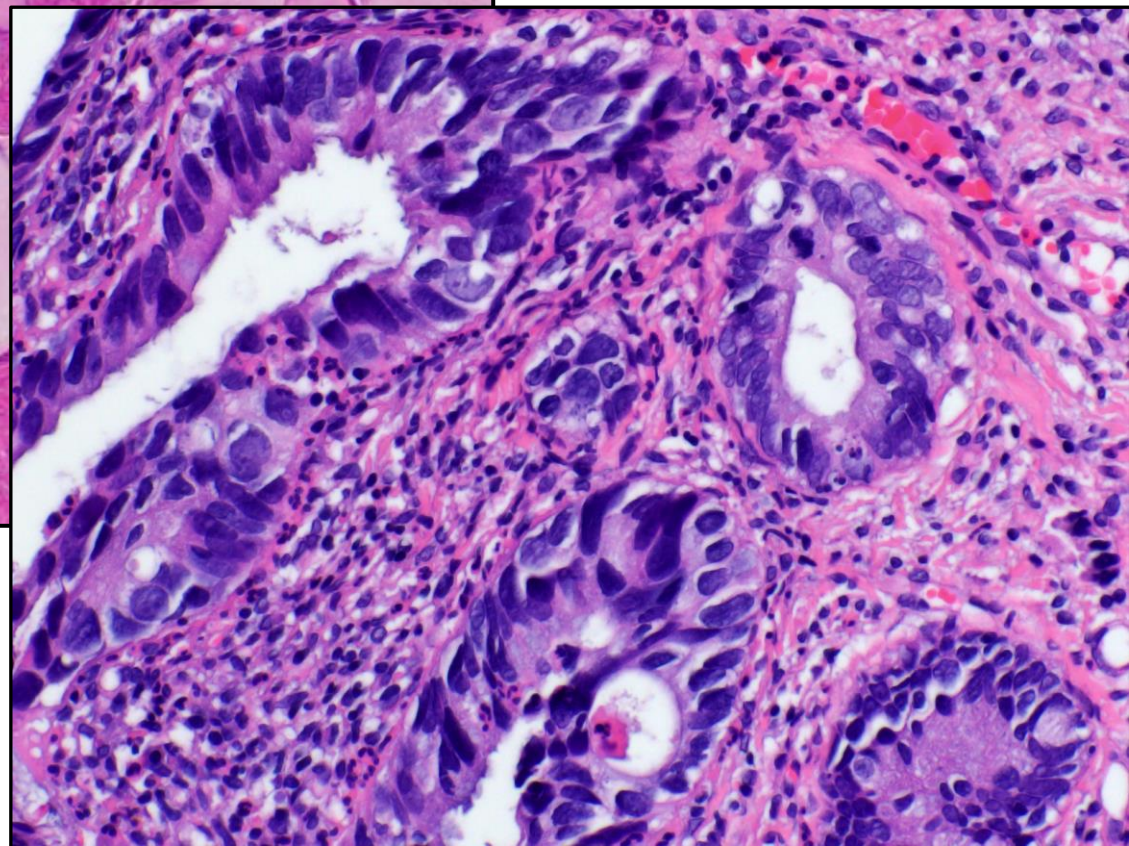
- Recognition of HPV-independent squamous cell carcinomas and adenocarcinomas
- Recognition of HPV-independent adenocarcinomas (clear cell, mesonephric, gastric-type, endometrioid carcinomas)
- Staging updated to FIGO 2018 system
- Neuroendocrine, hematolymphoid, mesenchymal, melanocytic and metastatic tumors are discussed in separate chapters

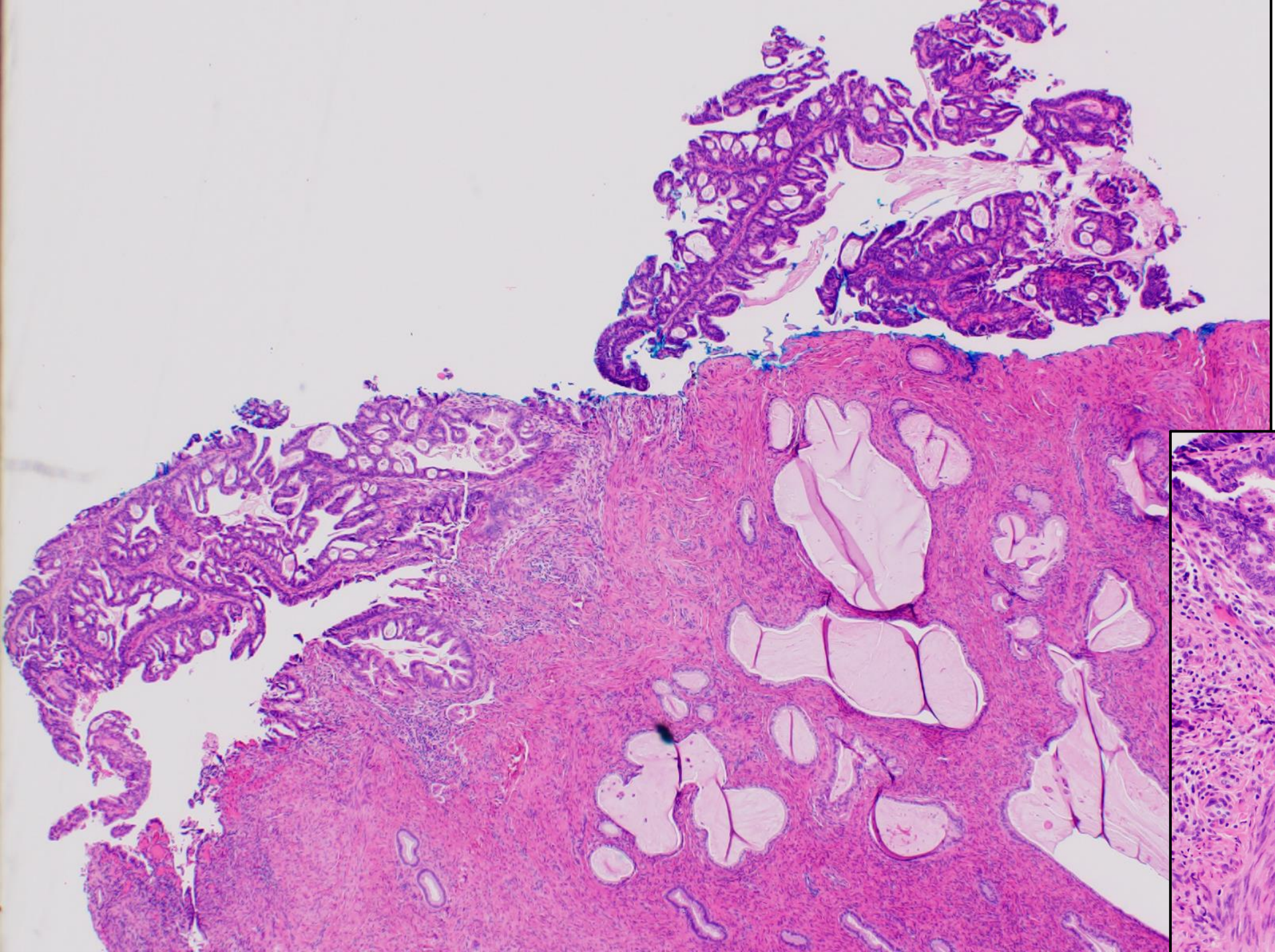
HPV-Associated Endocervical Adenocarcinomas

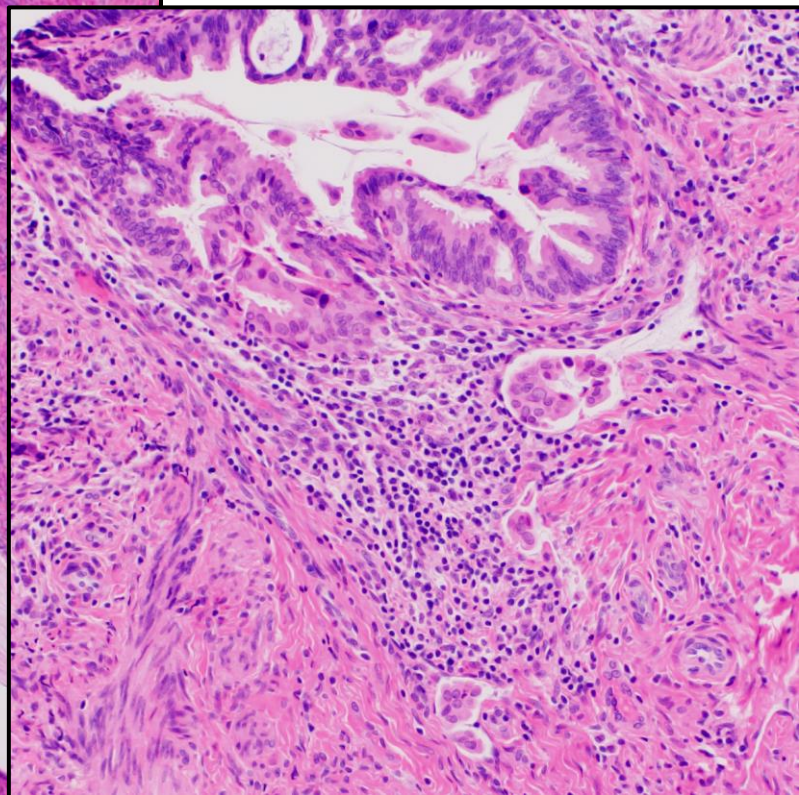
Case 1

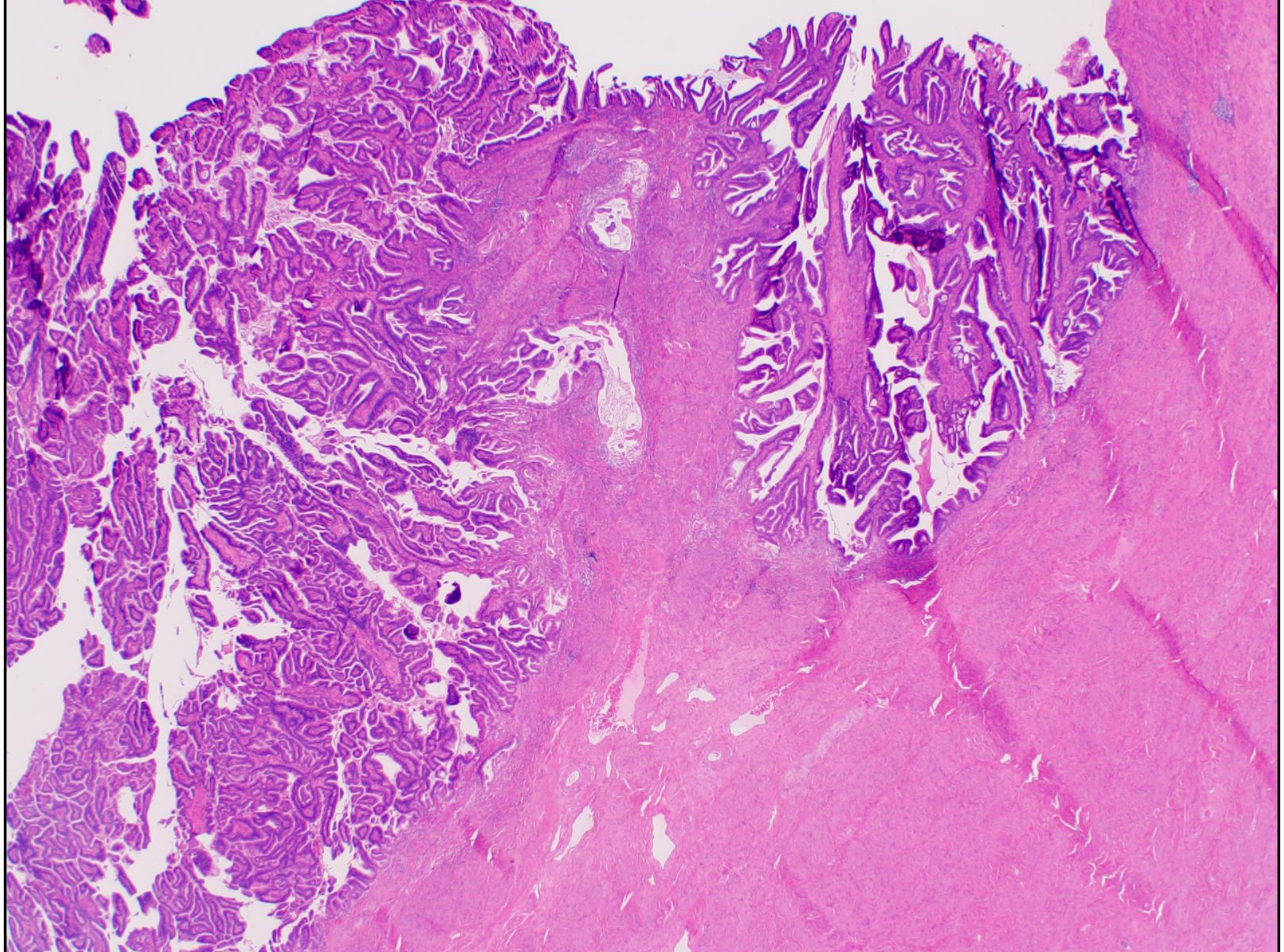
- 63-year-old female initially presented with “Atypical glandular cells” on a screening Pap smear
- HPV status was not provided; a prior endocervical and endometrial biopsy showed “at least adenocarcinoma in situ”
- The patient underwent a cold knife conization











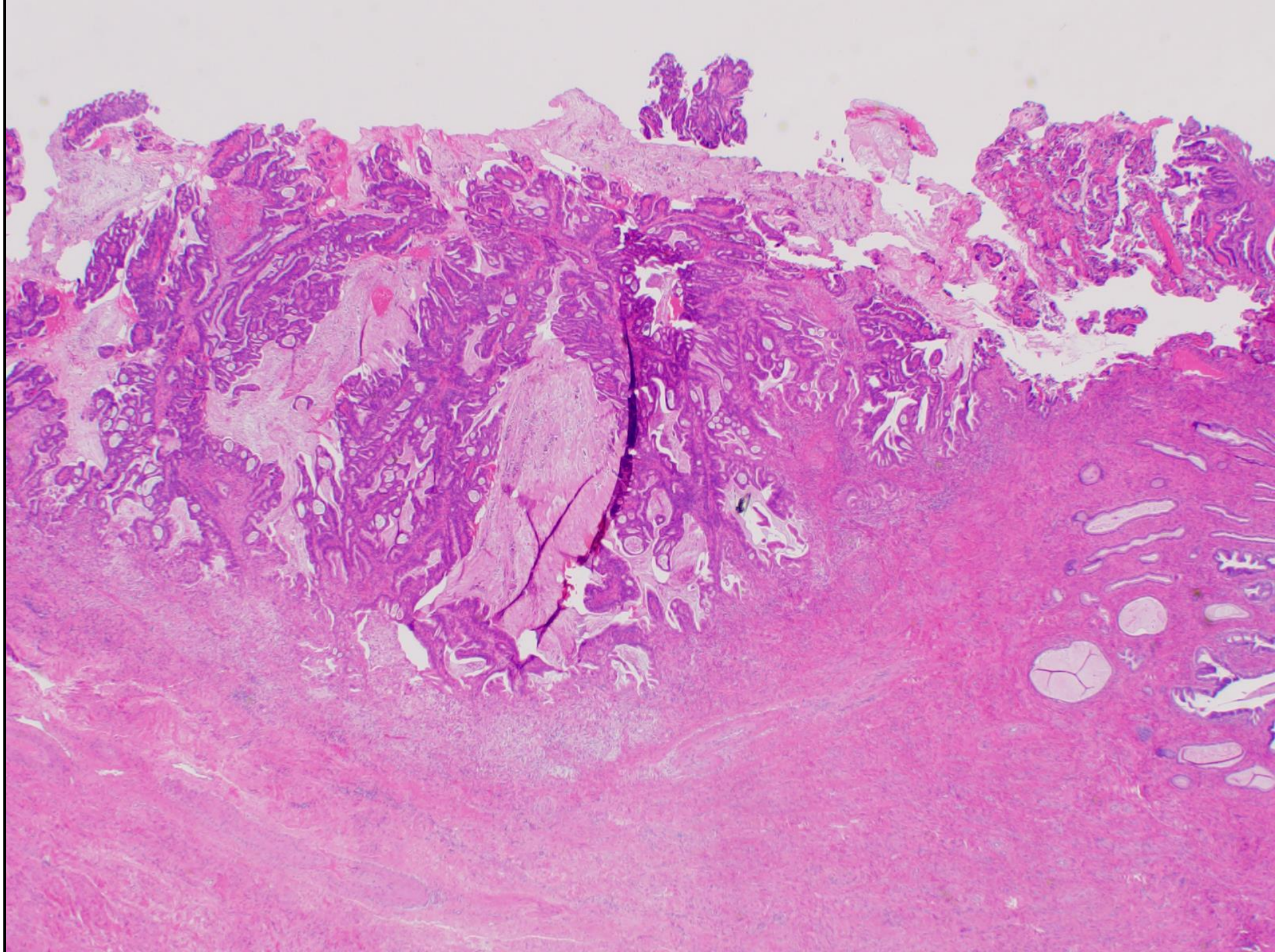
Case 1

- The sections showed invasive adenocarcinoma, 0.8 cm greatest dimension, with one focus of conventional stromal invasion measuring up to 0.35 cm depth of invasion, transected at the endocervical margin

- The patient subsequently underwent a radical hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection; gross findings included a 2.4 cm mass centered in the cervix

Radical hysterectomy:

- Invasive endocervical adenocarcinoma, usual type (HPV-associated)
- 2.4 cm in greatest dimension
- 0.4 cm depth of invasion
- Lymphovascular invasion present
- Negative margins, negative lymph nodes
- Stage pT1b2 (FIGO IB2)



Cervical Invasive Carcinoma: Revised FIGO Staging (2018):

1. Stage IA: lateral extension measurement removed
2. Stage IB divided into 3 subgroups
   - IB1: stromal invasion > 5 mm and ≤ 2 cm greatest dimension
   - IB2: invasive carcinoma > 2 cm and ≤ 4 cm greatest dimension
   - IB3: size > 4 cm greatest dimension
3. Imaging or pathology acceptable for evaluating retroperitoneal lymph nodes; if positive:
   - IIIC1: Positive pelvic lymph nodes
   - IIIC2: Positive paraaortic lymph nodes

Bhatla N et al. Int J Gynecol Obstet 2019

Cervical Invasive Carcinoma- Revised FIGO Staging (2018), Fertility-Sparing Considerations:

1. Stage IA: lateral extension measurement removed
   - IA1: stromal invasion ≤ 3 mm in depth (CKC, LEEP)
   - IA2: stromal invasion > 3 mm and ≤ 5 mm in depth

Trachelectomy, cone biopsy

2. Stage IB divided into 3 subgroups
   - IB1: stromal invasion > 5 mm and ≤ 2 cm in greatest dimension
   - IB2: invasive carcinoma > 2 and ≤ 4 cm in greatest dimension
   - IB3: invasive carcinoma > 4 cm

*For stage IB tumors treated with hysterectomy, additional factors such as size, LVI and stromal invasion may influence decision for additional adjuvant treatment

Bhatla N et al. Int J Gynecol Obstet 2019
NCCN Guidelines Version 1.2021

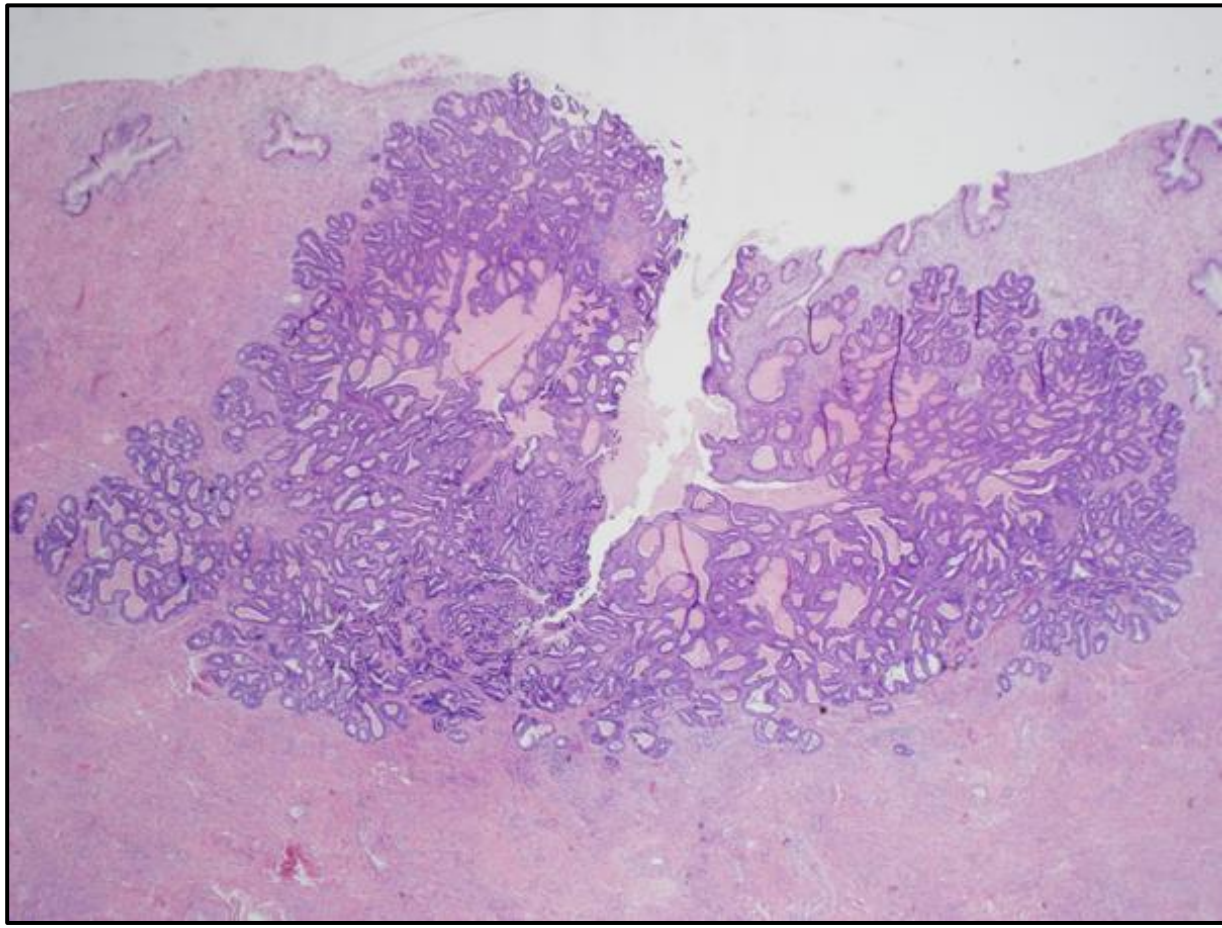
Problematic Growth Patterns in Assessment of Invasion

- Exophytic tumors (measure tumor thickness)
- Extensive adenocarcinoma in situ (AIS)
- Multifocal dispersed foci of superficial invasion in extensive AIS

Pattern-Based Classification of HPV-Associated Endocervical Adenocarcinoma: The Silva Classification

Pattern A: Non-destructive invasion

- Well demarcated glands with rounded contours
- Complex intraglandular growth permissible
- Relationship to large cervical vessels or depth of extension irrelevant
- No lymphovascular invasion
- Lack of solid growth, single cell infiltration or destructive stromal invasion
- Architecturally well to moderately differentiated, no high-grade cytology

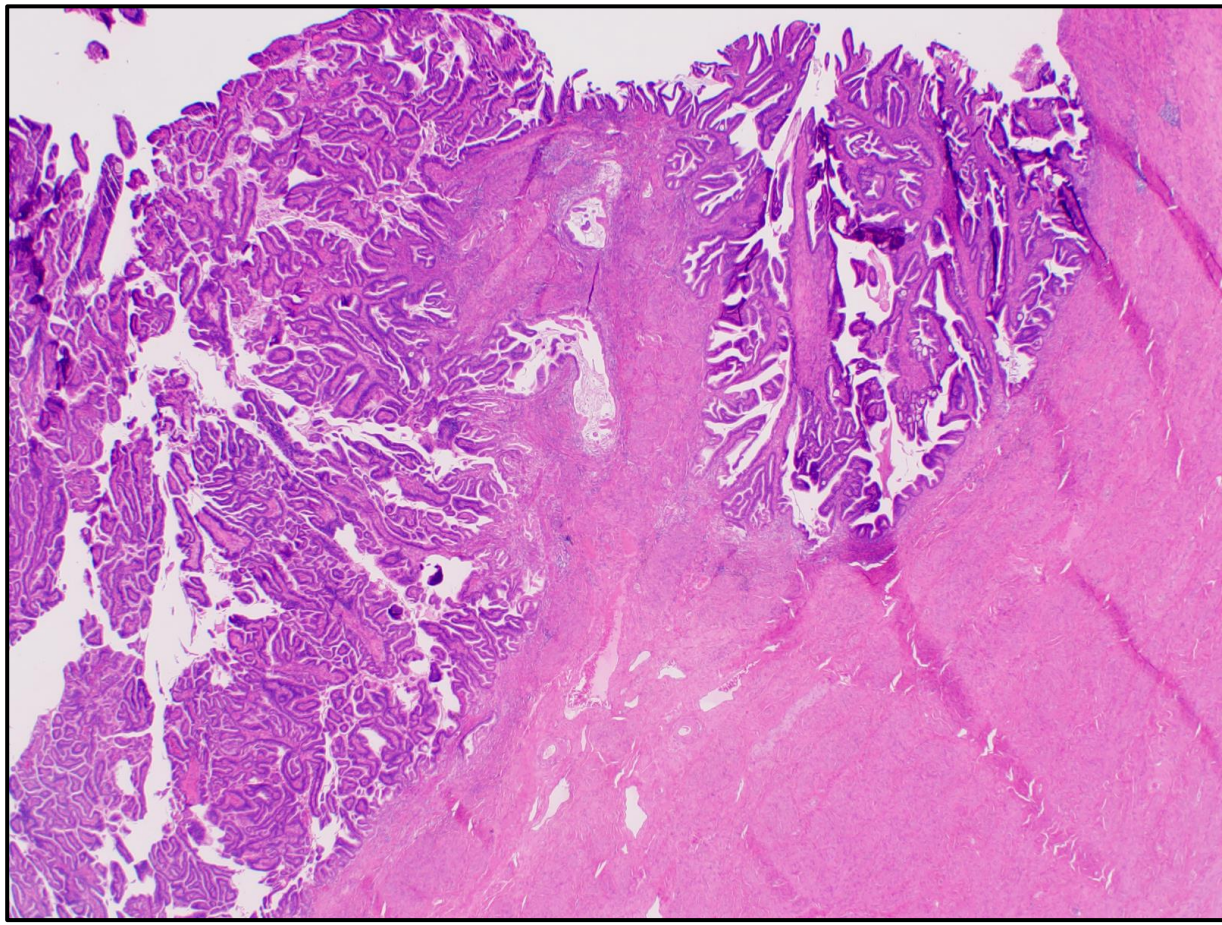


WHO Classification of Tumors, Female Genital Tract, 5th ed., 2020; Diaz De Vivar et al., 2013

Pattern-Based Classification of HPV-Associated Endocervical Adenocarcinoma: The Silva Classification

Pattern B: Early/focally destructive invasion

- Single cell or small group stromal invasion arising from well-demarcated glands
- Foci may be single, multiple or linear at base of tumor
- With or without lymphovascular invasion
- No solid growth (architecturally well to moderately differentiated)



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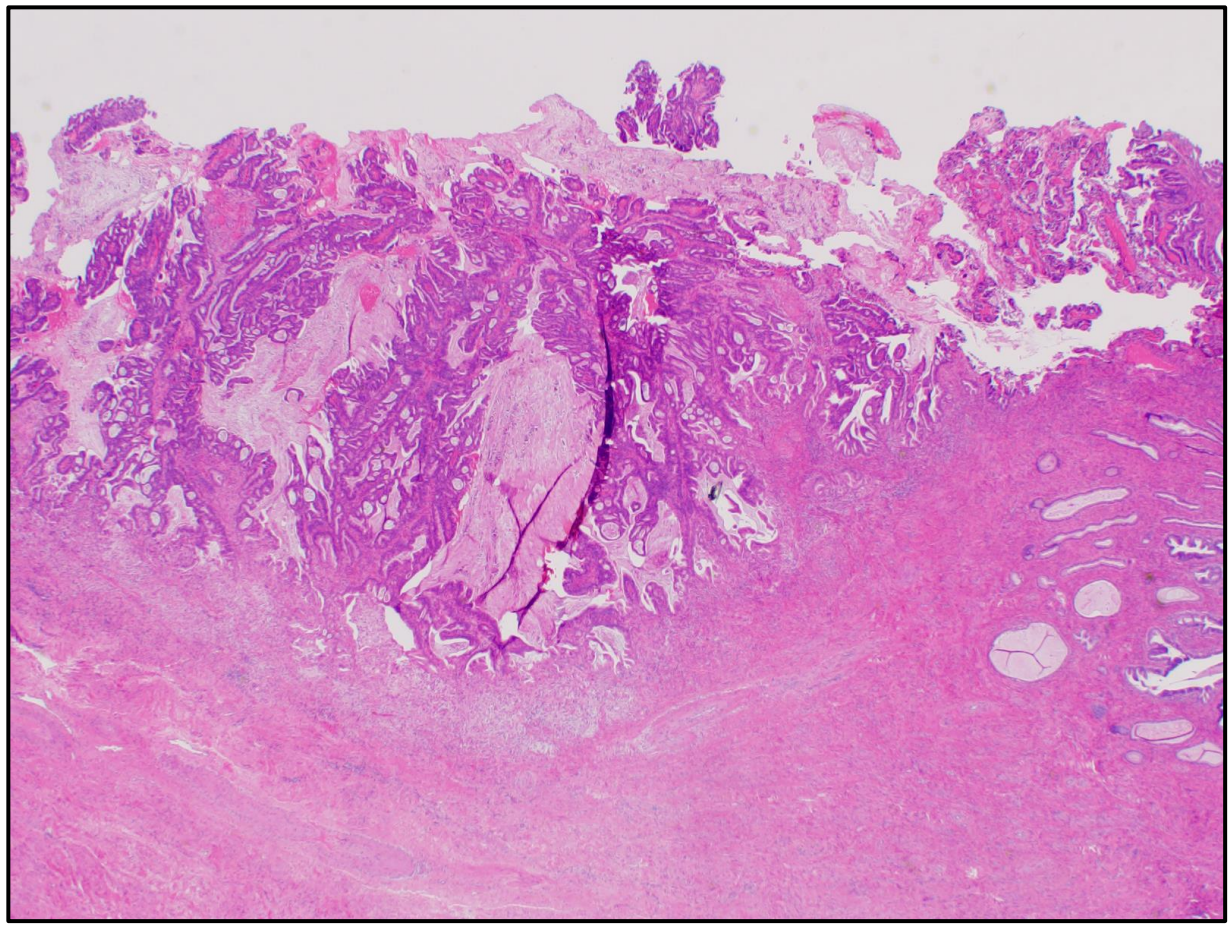
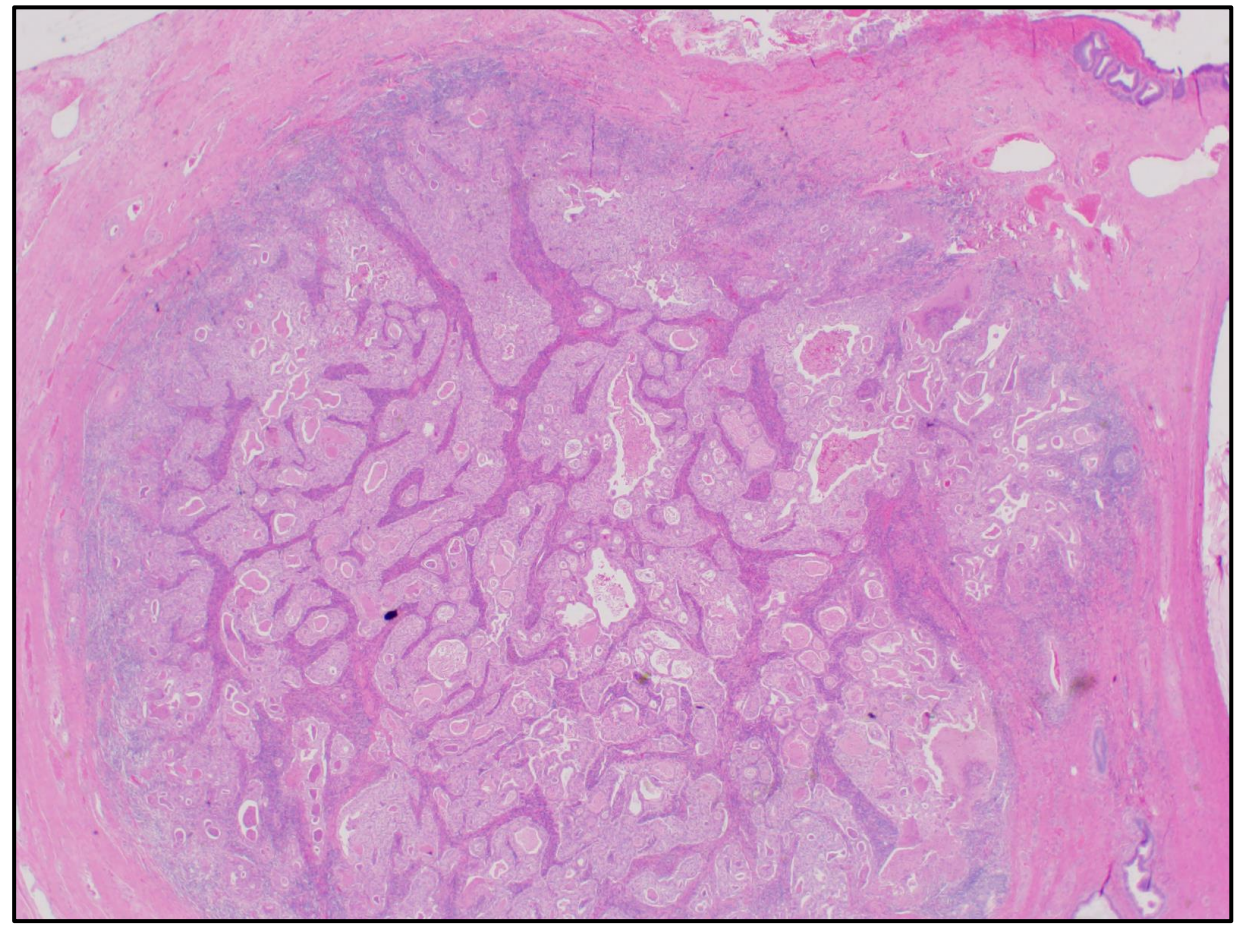
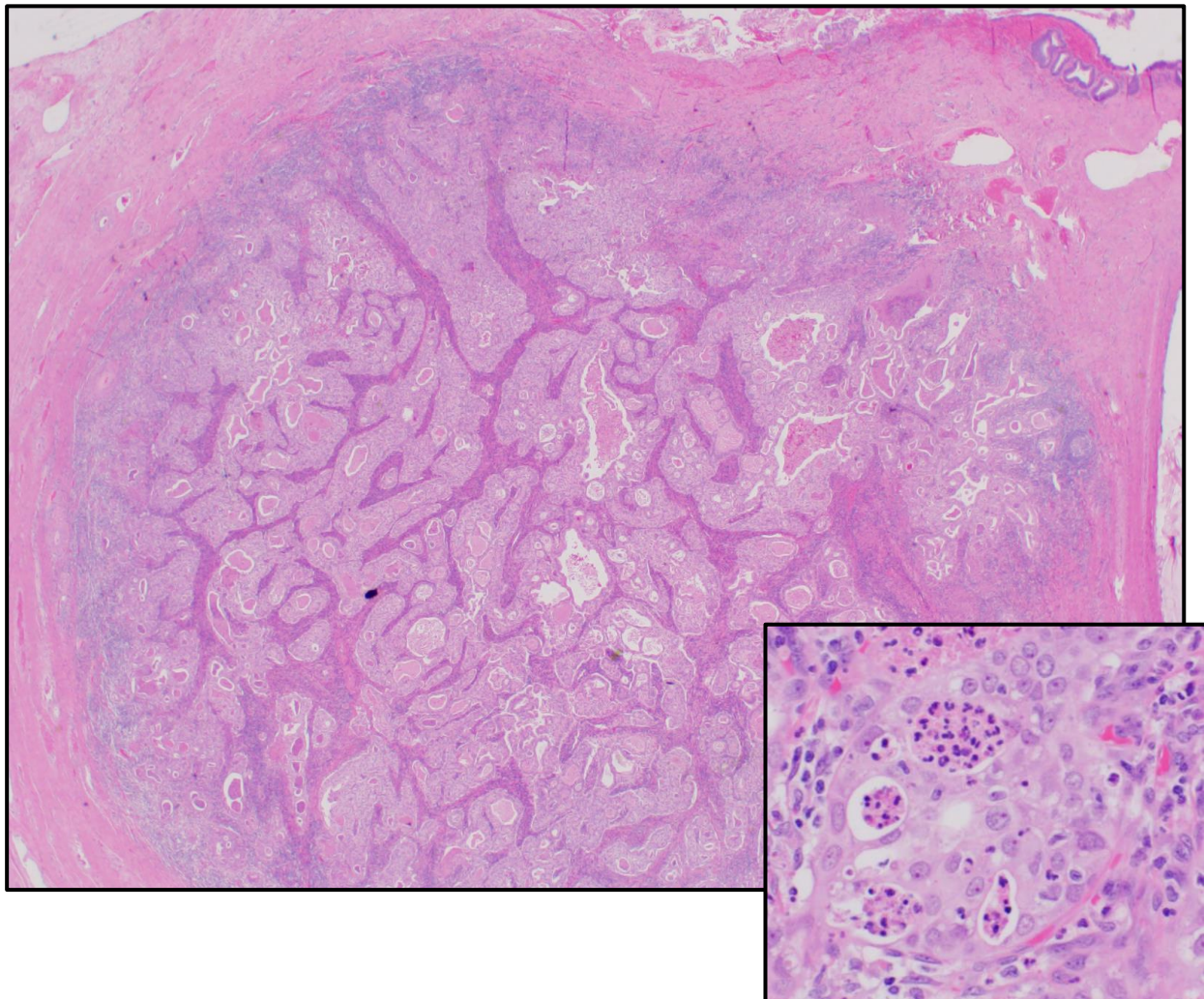




Pattern-Based Classification of HPV-Associated Endocervical Adenocarcinoma: The Silva Classification

Pattern C: Diffuse destructive invasion

- Diffusely infiltrative glands and/or extensive destructive invasion
- Associated desmoplastic response
- Confluent growth filling a 4x field (5 mm): glands, papillae or mucin lakes
- Solid growth pattern (architecturally poorly differentiated)
- With or without lymphovascular invasion



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Utility of the Pattern-Based Classification of Invasive Endocervical Adenocarcinoma

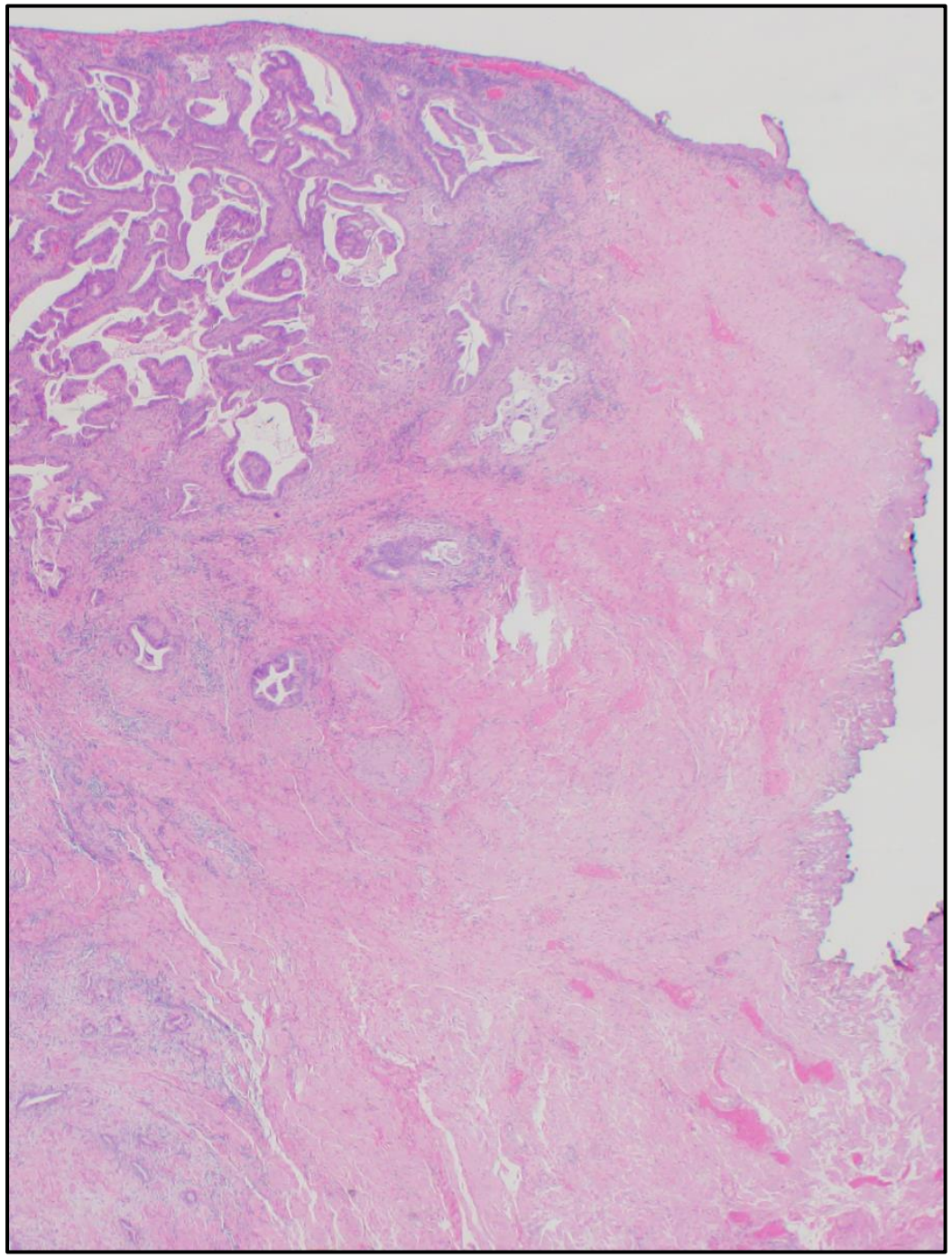
In a multi-institutional study of > 350 cases of HPV-associated invasive endocervical adenocarcinoma treated with excision and lymphadenectomy (at least 1 node excised), mean follow-up time of 52.8 months:

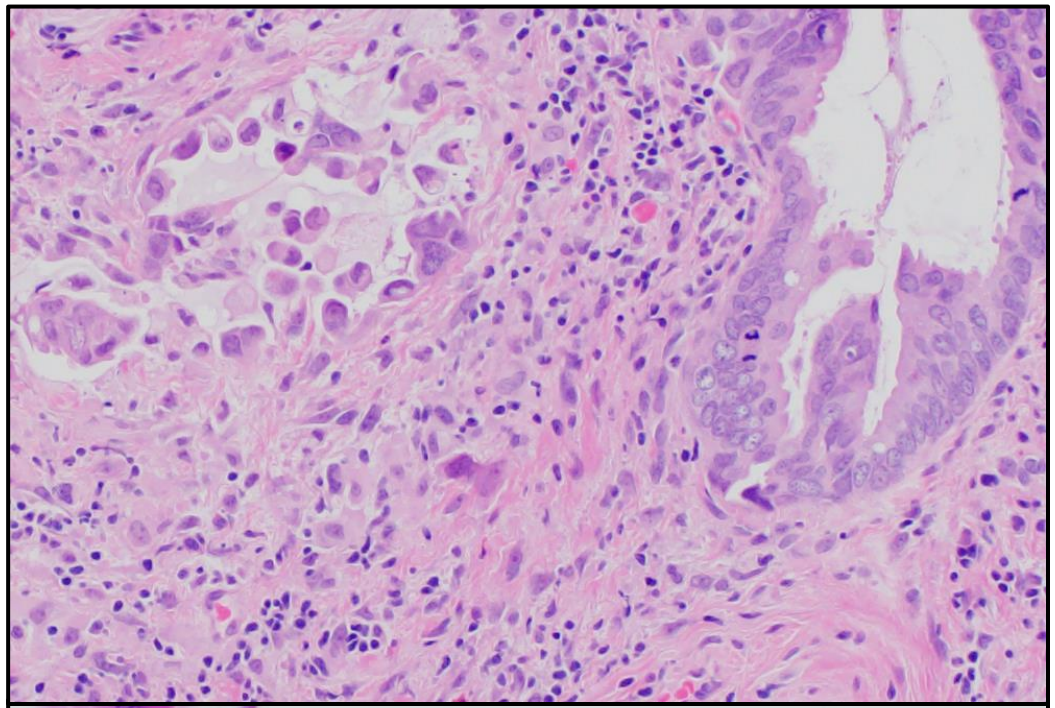
Pattern	N	DOI (x mm)	DOI > 5 mm	LVI	Pts with LN met	Recurrences	DOD	Stage I	Stage II-IV
Standard	352 (100%)	6.7			49 (13.9%)	39 (11.4%)	16 (4.6%)	311 (88.3%)	41 (11.7%)
A	73 (20.7%)	3.8	20 (27.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	73 (100%)	0 (0%)
B	90 (25.6%)	4.0	21 (23.3%)	24 (26.6%)	4 (4.4%)	1 (1.2%)	0 (0%)	86 (95.6%)	4 (4.4%)
C	189 (53.7%)	9.2	140 (74.1%)	117 (61.9%)	45 (23.8%)	38 (22.1%)	16 (8.8%)	152 (80.4%)	37 (19.6%)

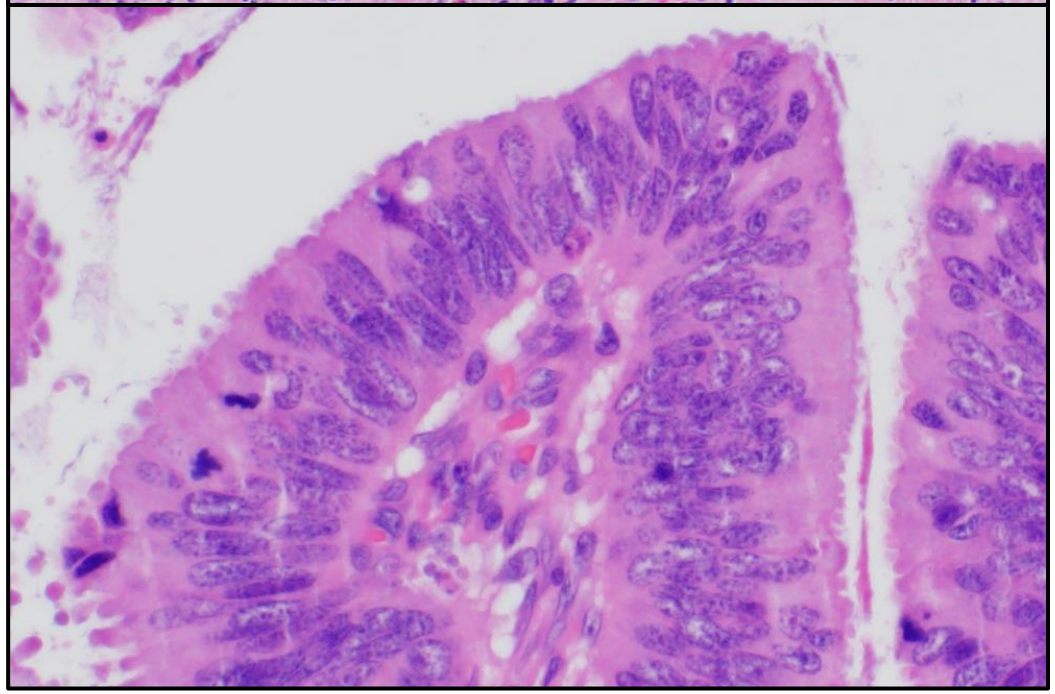
Diaz De Vivar et al., Int J Gynecol Pathol 2013;
Roma et al. AJSP 2015

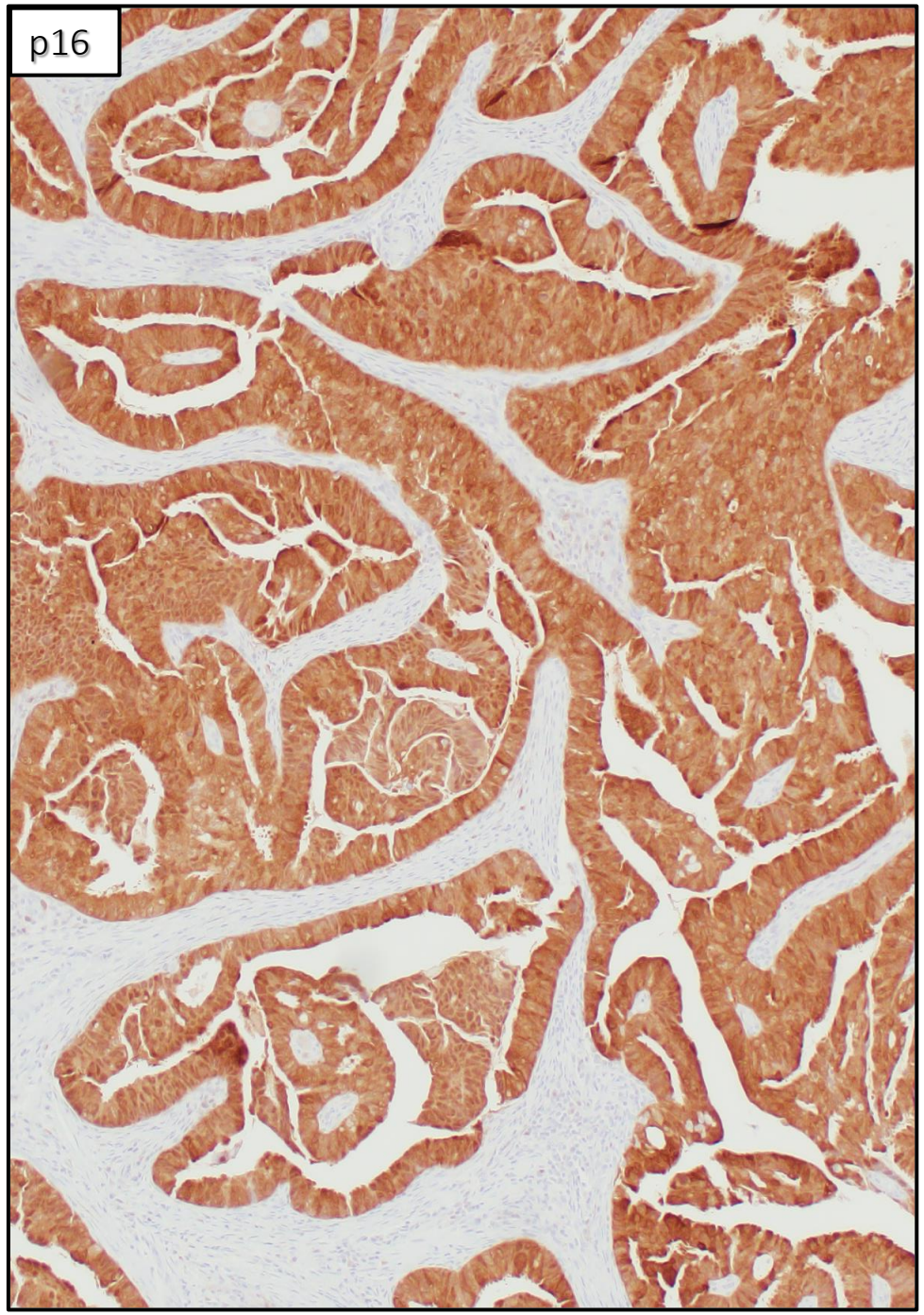
Case 2

- 56-year-old female initially presented with “Atypical glandular cells, favor neoplastic” on a screening Pap smear and abnormal pelvic exam
- HPV status was not provided and no prior biopsy was available for review
- A radical hysterectomy specimen was received which grossly showed a 3.3 cm mass in the endocervical canal extending to the lower uterine segment





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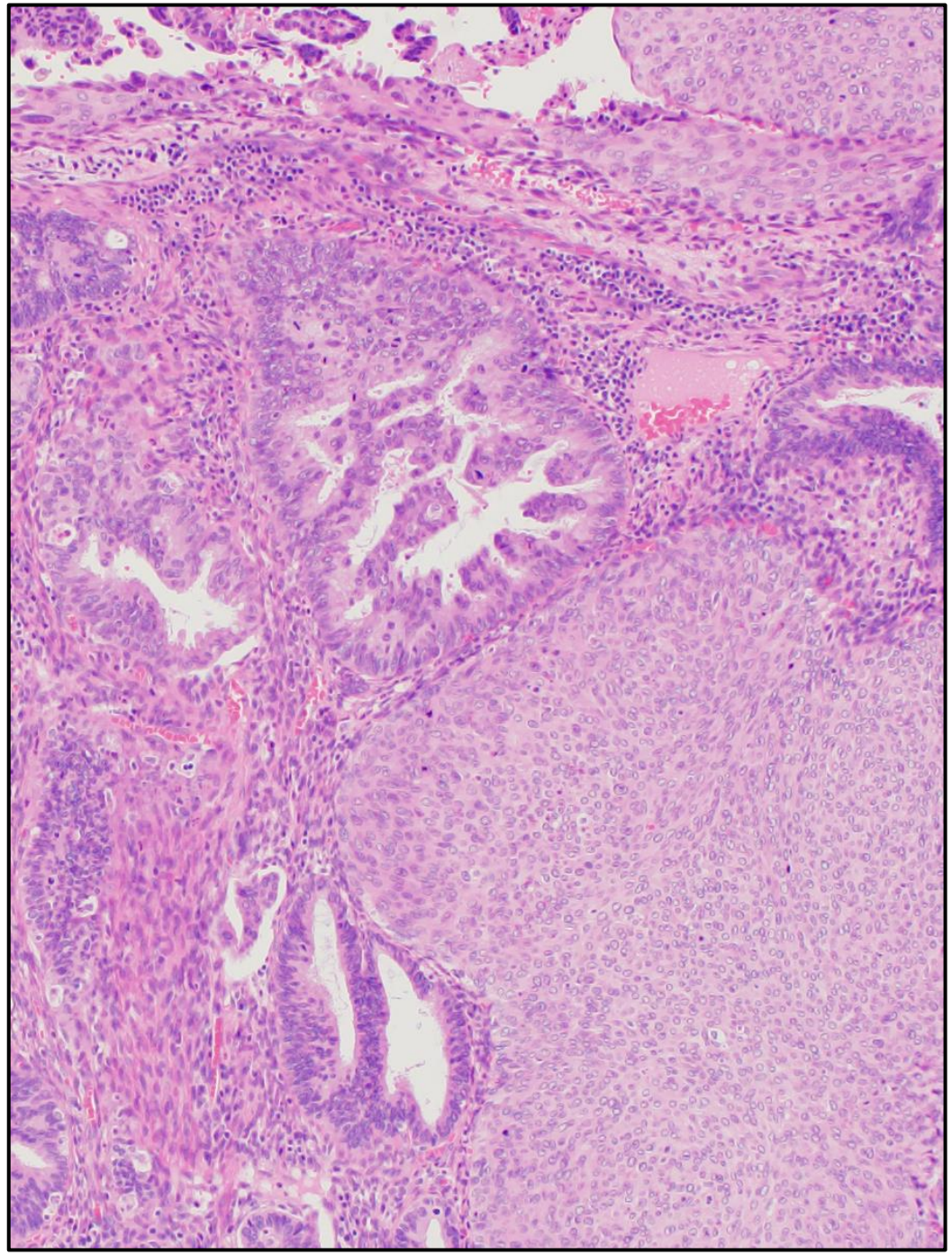
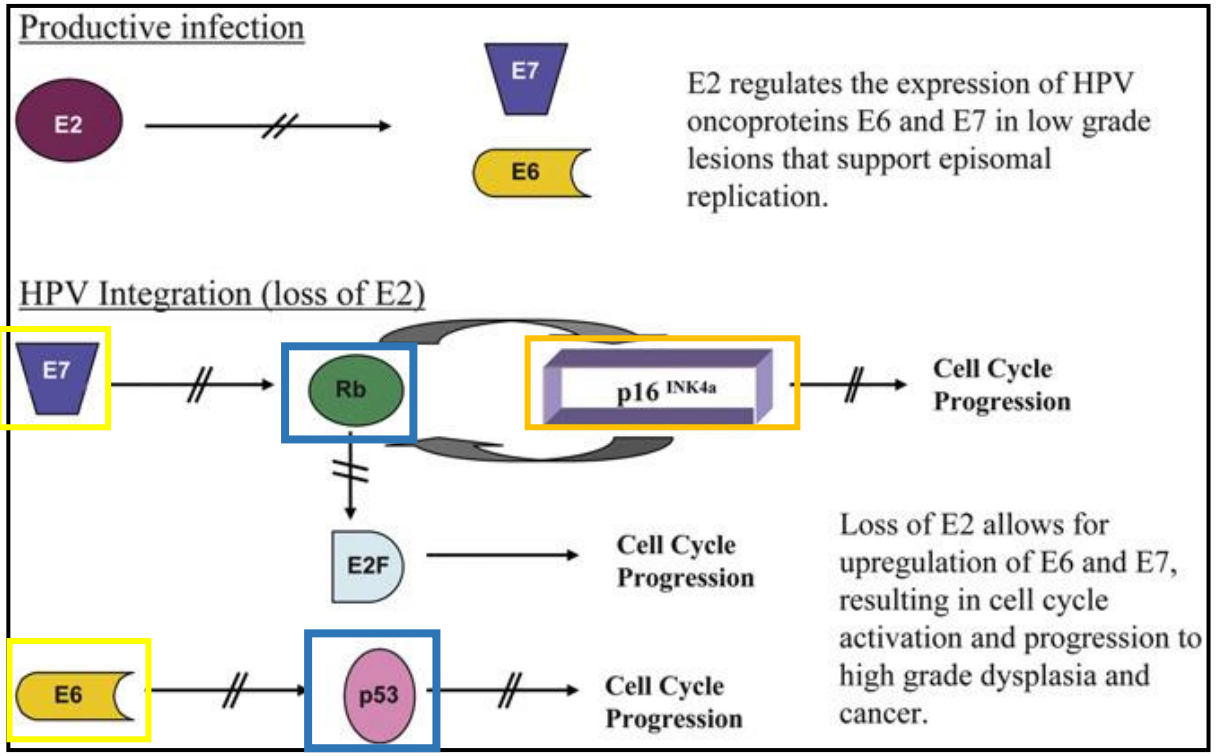
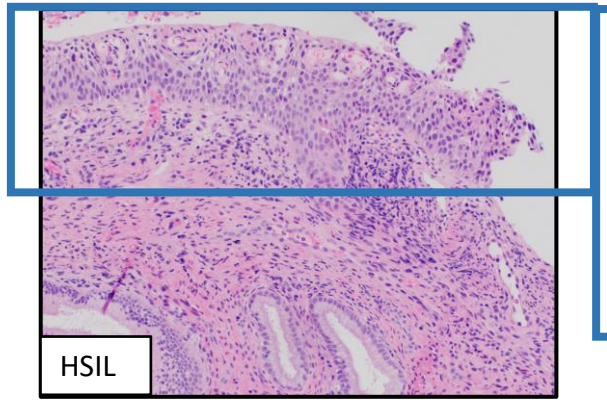
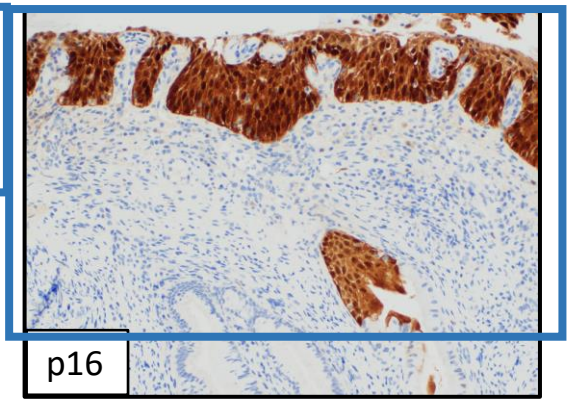


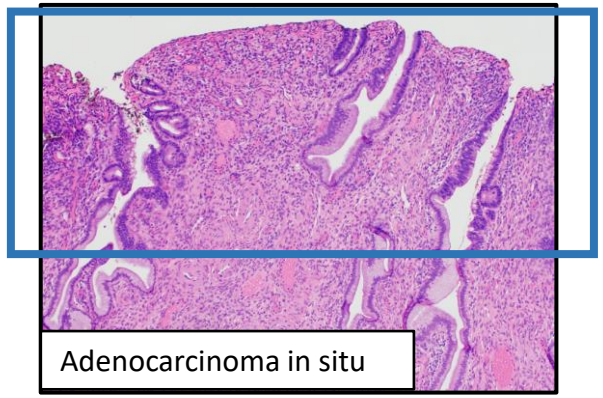
Etiology of HPV Infection and p16 Immunohistochemistry

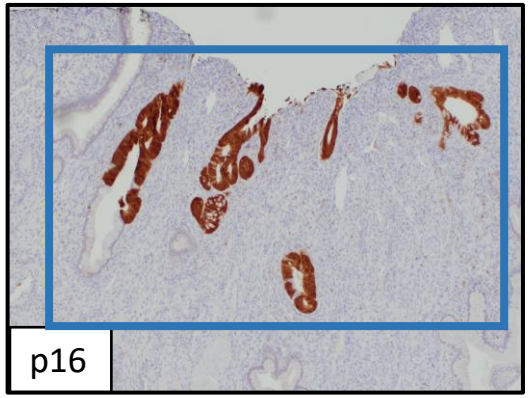


Thomison et al., Hum Pathol 2008

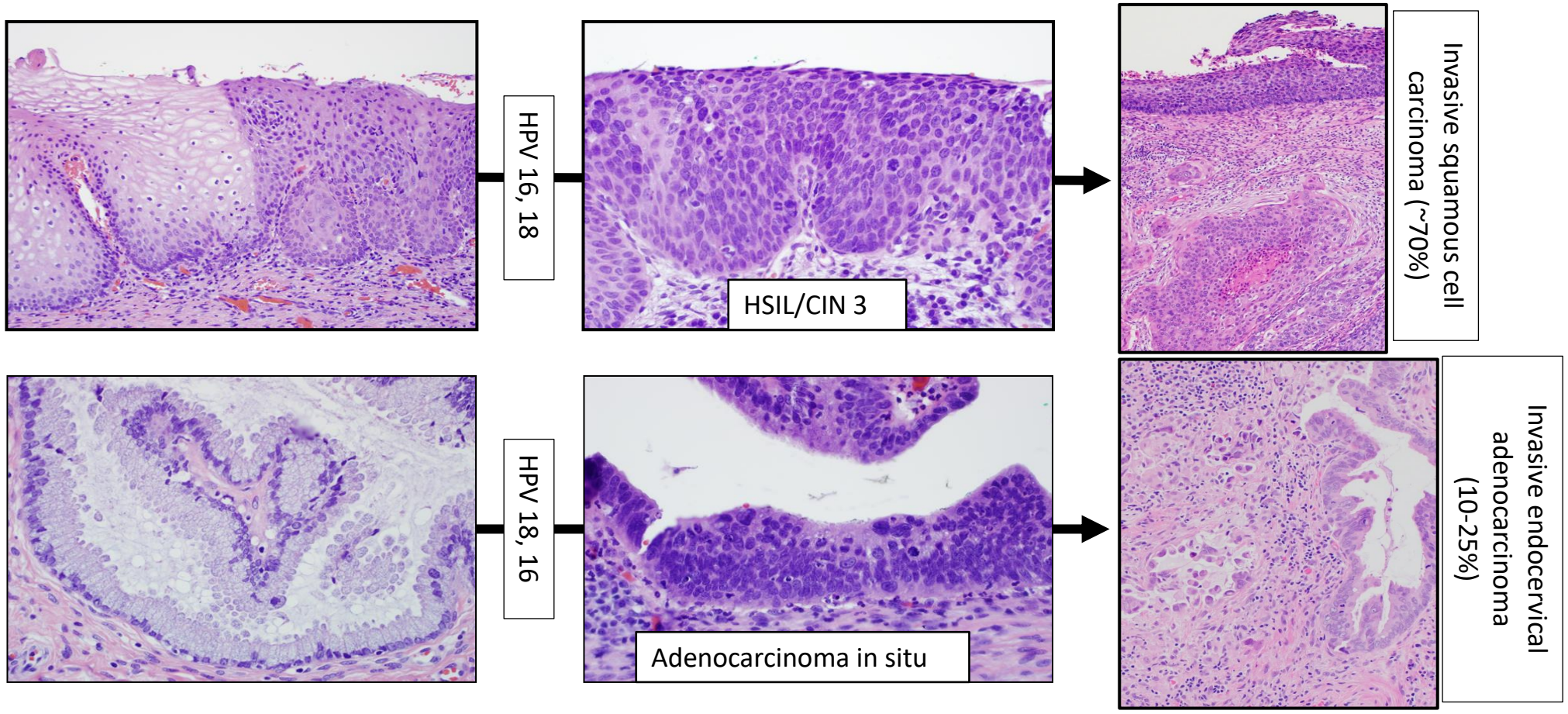








Histologic Features of HPV-Associated Lesions

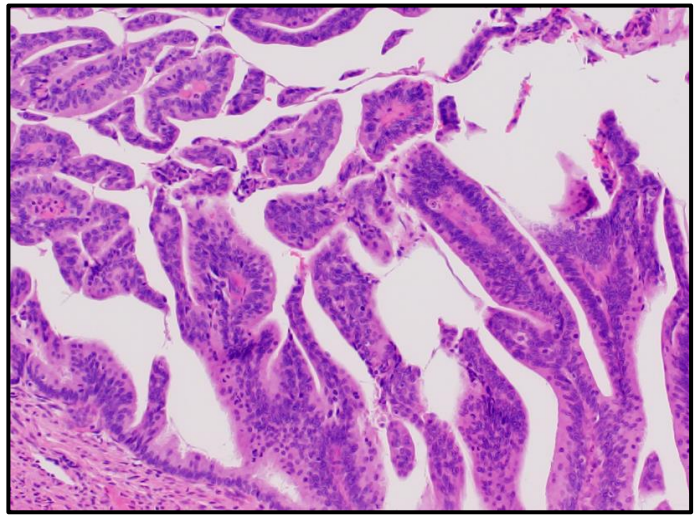


Cytohistologic features of HPV-associated epithelial atypia in cervical lesions

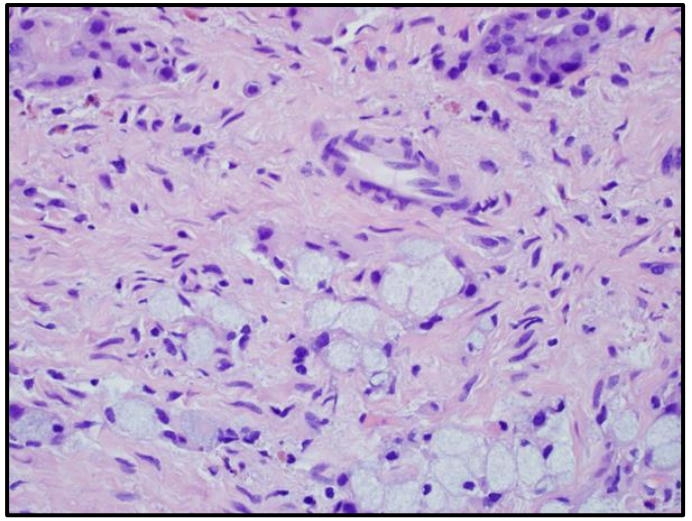
Histologic Subtypes of HPV-Associated Endocervical Adenocarcinoma

- Usual type (70%), including villoglandular variant
- Mucinous type (10%; intracytoplasmic mucin in >50% of tumor)
  - Mucinous adenocarcinoma NOS
  - Intestinal
  - Signet-ring cell
  - Stratified mucin-producing carcinoma

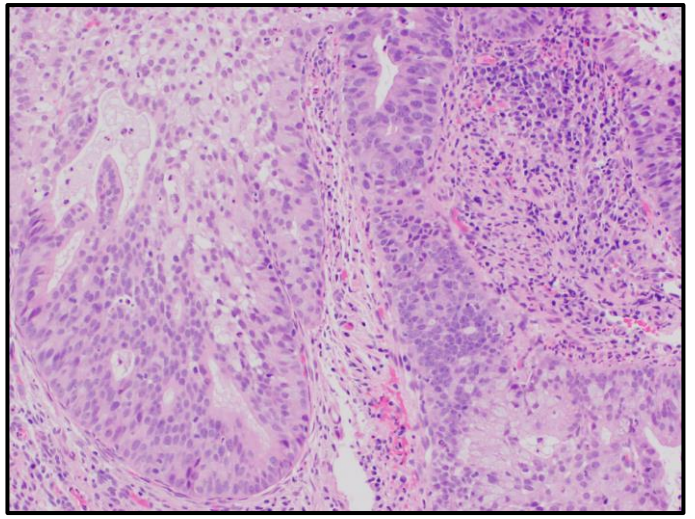
WHO Classification of Tumors, Female Genital Tract, 5th ed., 2020



Villoglandular

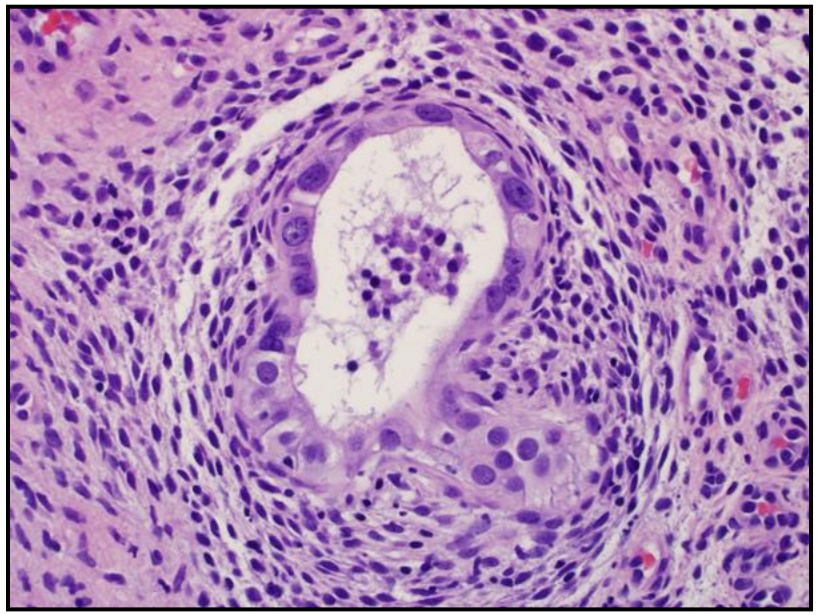


Signet-ring cell

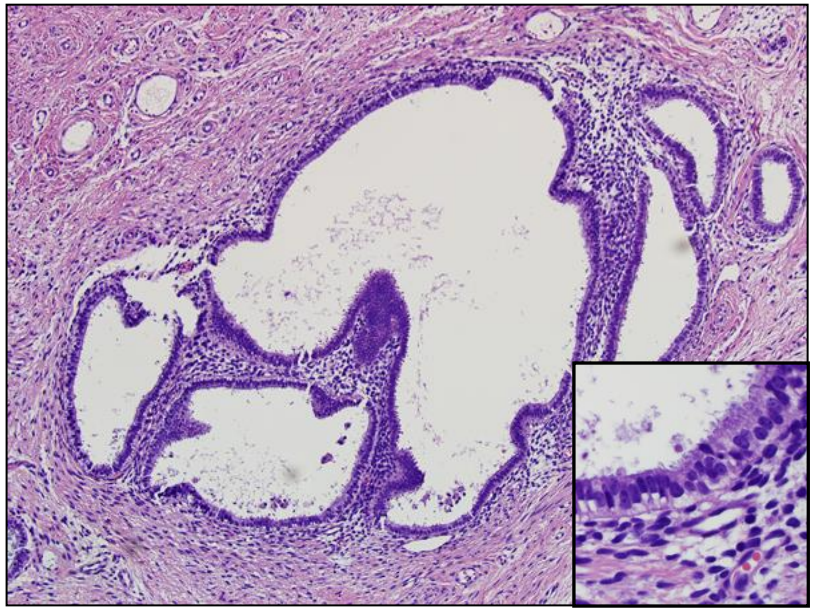


Stratified mucin-producing

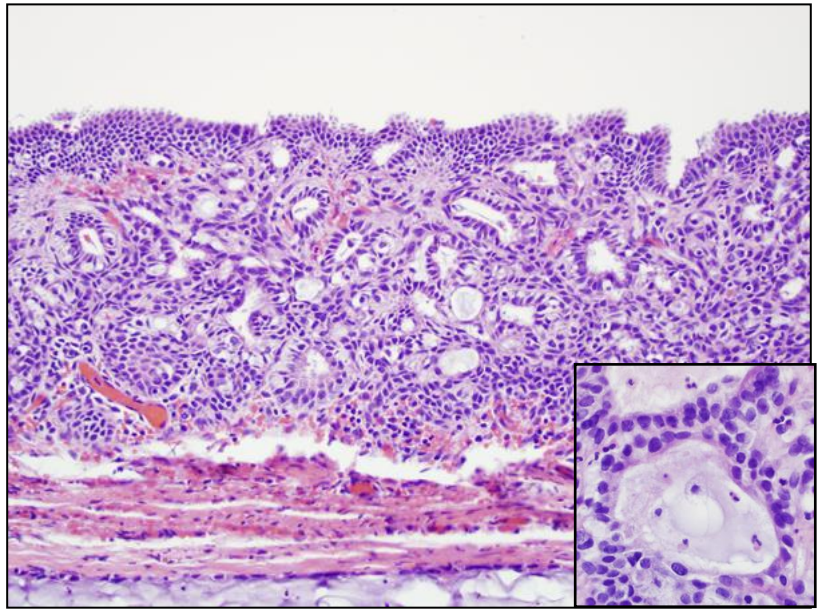
Typical Differential Diagnosis of Atypical Glandular Proliferations: Benign Mimics (mucin-poor)



Tubal/tuboendometrioid metaplasia

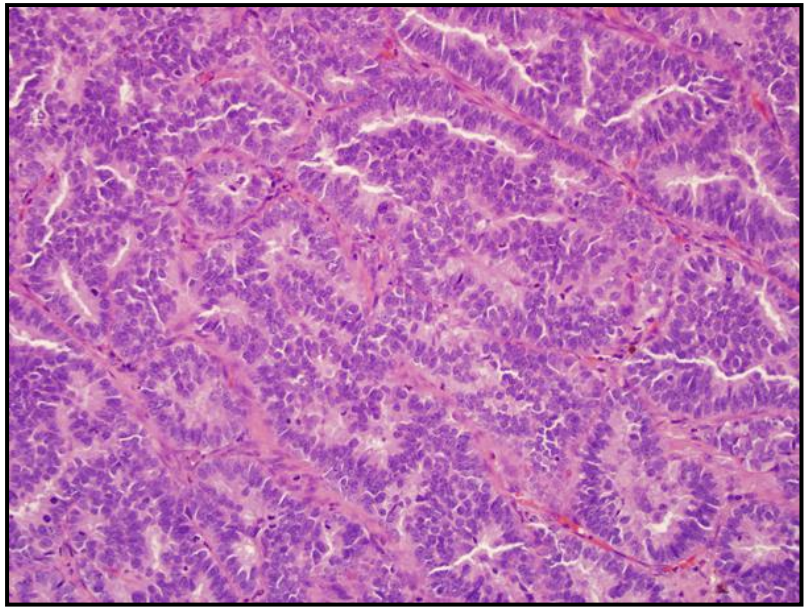


Endometriosis

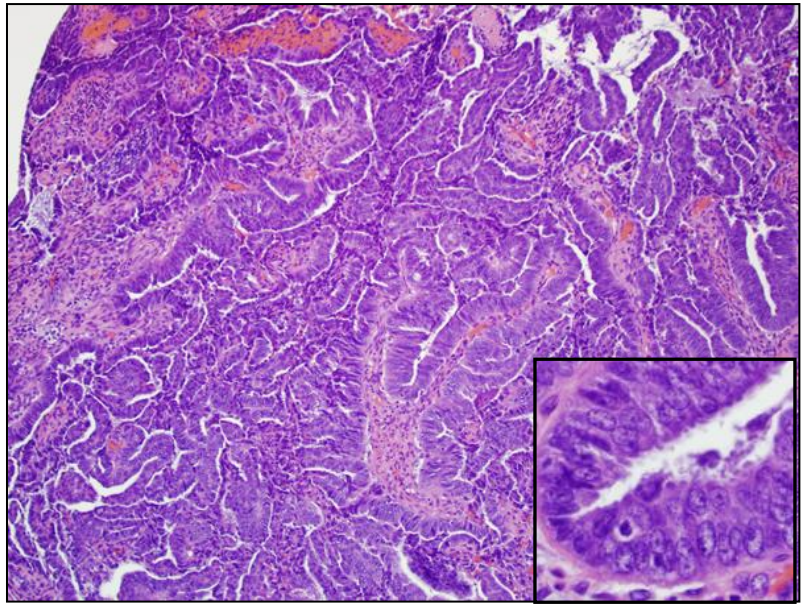


Microglandular hyperplasia

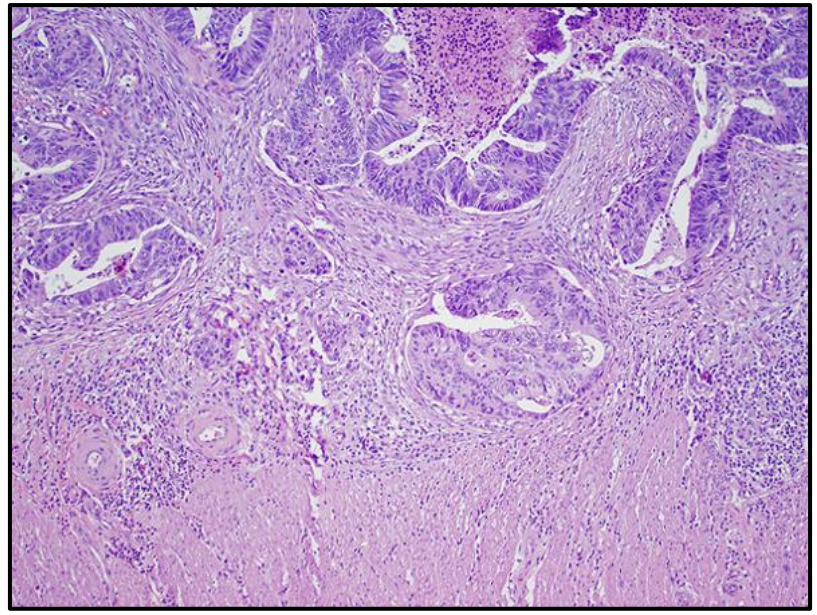
Typical Differential Diagnosis of Atypical Glandular Proliferations: Secondary Malignancies



Metastatic endometrioid carcinoma

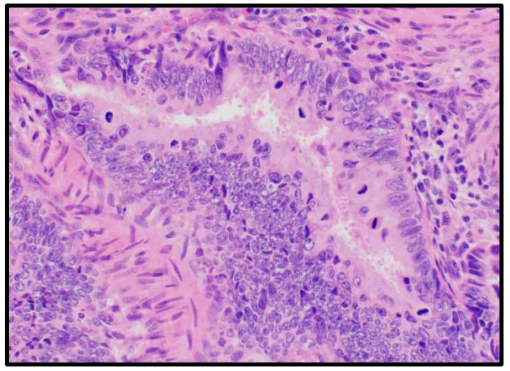


Metastatic serous carcinoma

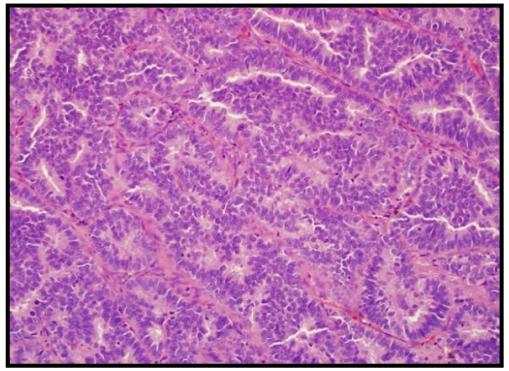


Metastatic colorectal carcinoma

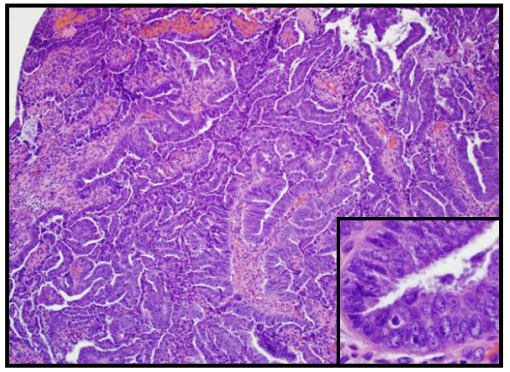
Typical Differential Diagnosis of Atypical Glandular Proliferations: Secondary Malignancies



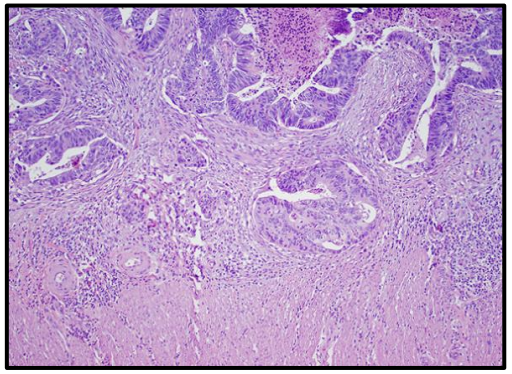
Primary endocervical adenocarcinoma



Metastatic endometrioid carcinoma



Metastatic serous carcinoma



Metastatic colorectal carcinoma

Stains				
p16	Positive (strong, diffuse)	Negative or patchy positive	Positive (strong, diffuse***)	Negative
CEA	Positive	Negative	Typically negative	Positive
Estrogen receptor	Typically negative	Positive or negative (grade dependent)	Positive or negative	Negative
Vimentin	Negative	Positive	Negative	Negative
Other studies	HR HPV ISH positive	p53: wild type expression pattern (grade dependent)	p53: completely negative (null) or strongly positive	CK20, CDX2, positive (strong, diffuse), PAX8, ER negative

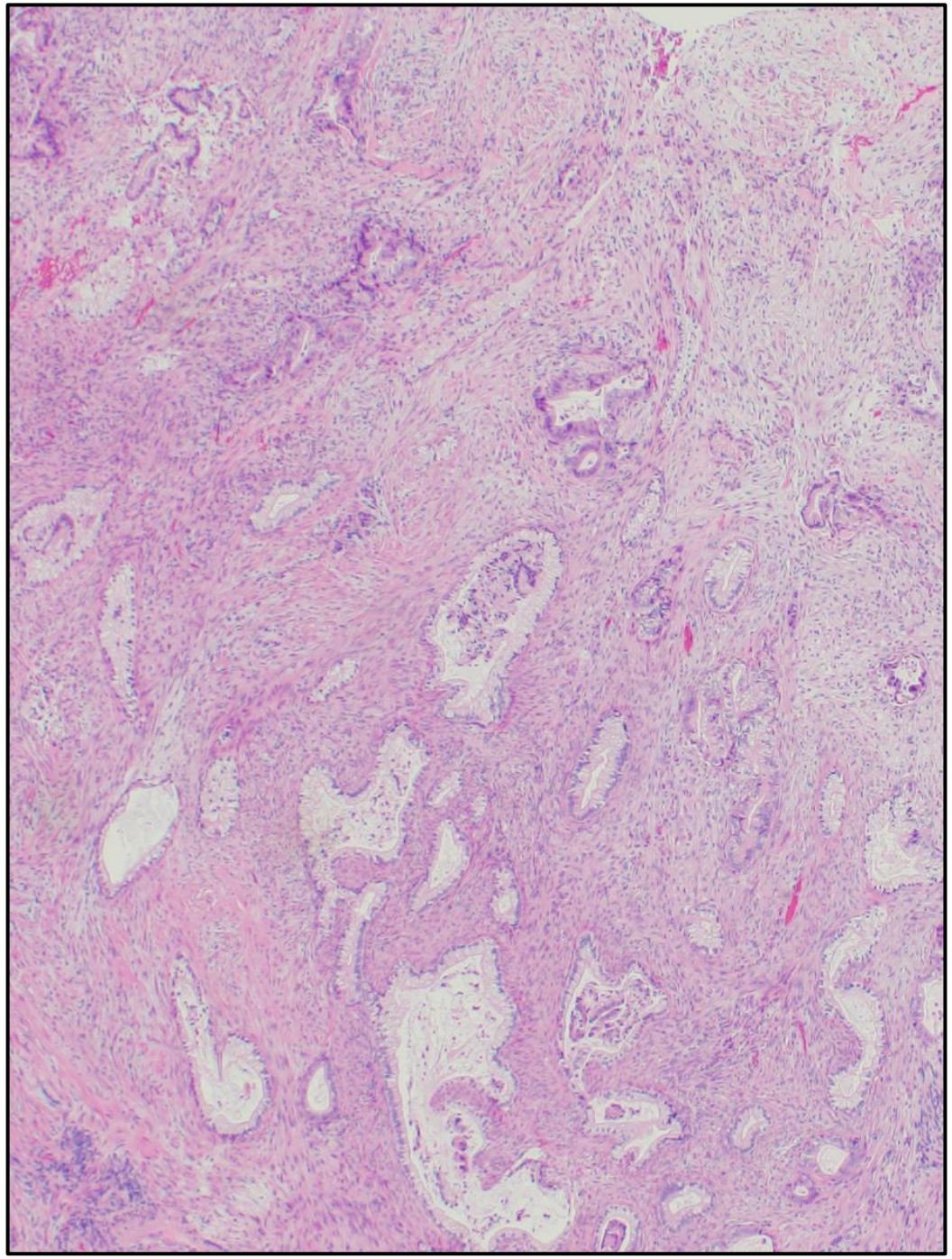
*****Beware strong diffuse p16 positivity in a high grade carcinoma, could represent metastatic serous carcinoma (non-HPV-associated pathway)**

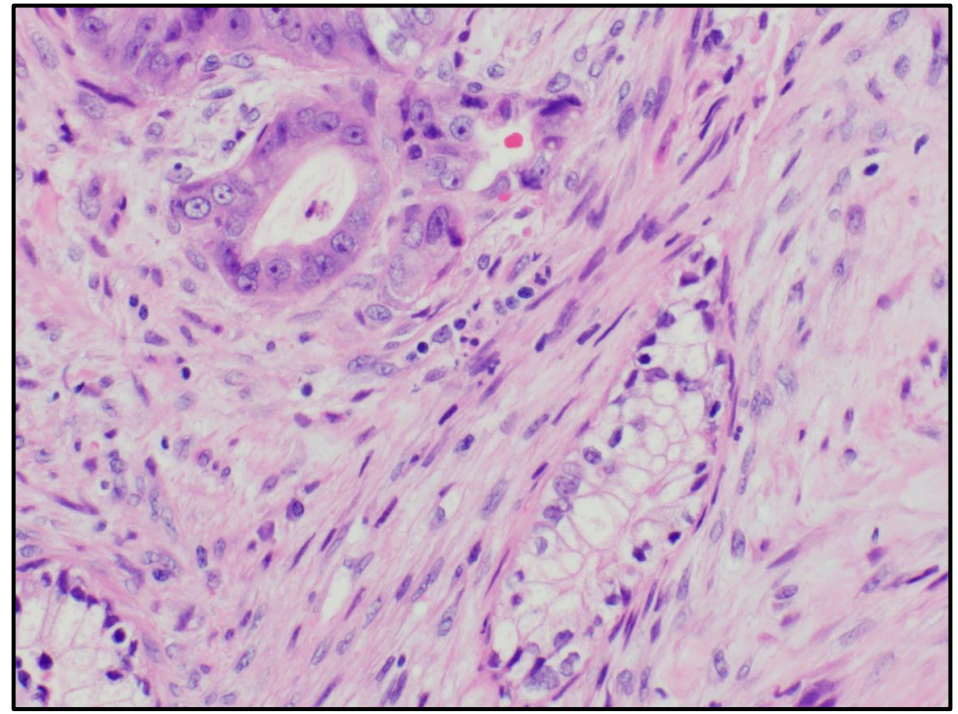
Case 1&2 - HPV-Associated Endocervical Adenocarcinoma: Take Home Points

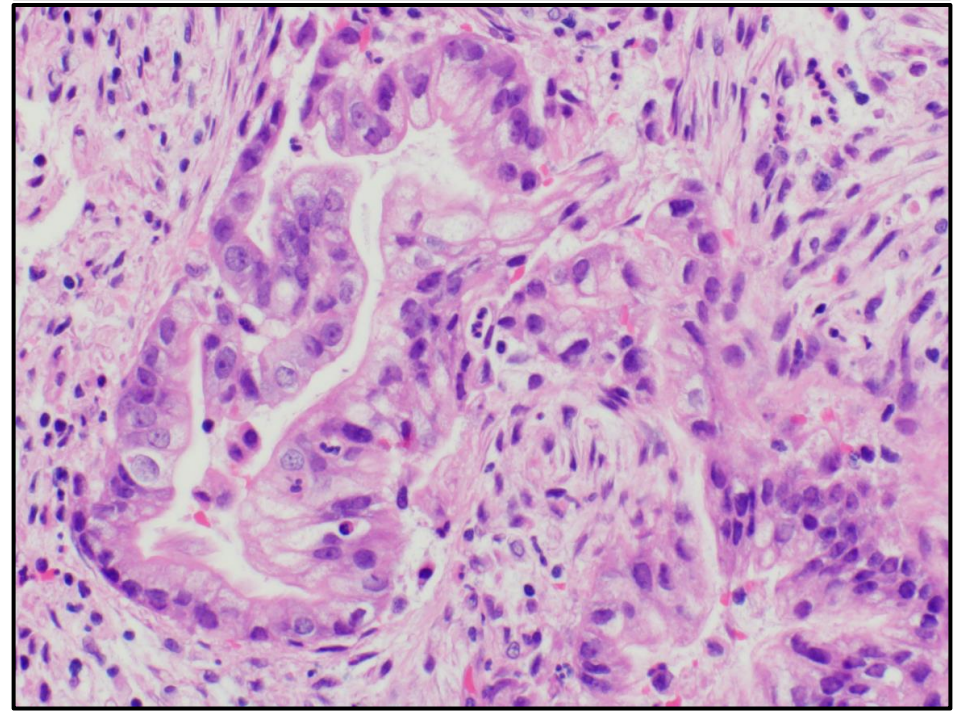
- The pattern-based classification of HPV-associated invasive endocervical adenocarcinoma is prognostically relevant
- HPV-associated lesions are associated with characteristic cytomorphologic features
- The differential diagnosis of atypical glandular proliferations of the endocervix includes both benign and malignant (primary and secondary gynecologic and extra-gynecologic) entities
- Ancillary testing is helpful in the appropriate morphological context

Case 3

- 47-year-old female presented with copious mucoid vaginal discharge and abdominal pain
- Imaging workup disclosed a cervical mass, ascites and peritoneal nodules
- The patient underwent an exam under anesthesia with hysteroscopy and diagnostic laparoscopy
- Clinical findings included a cervical mass, pelvic sidewall and peritoneal nodularity
- Cervical and peritoneal biopsies were obtained

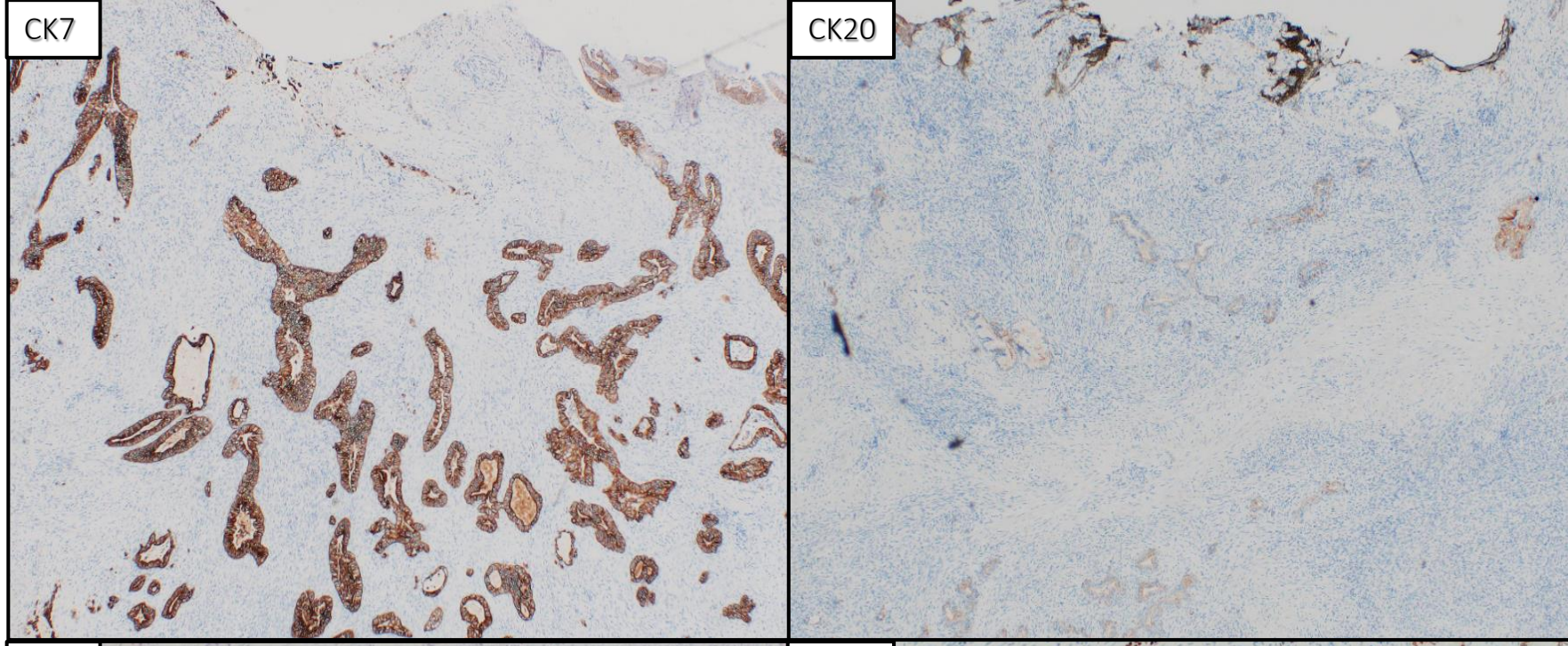


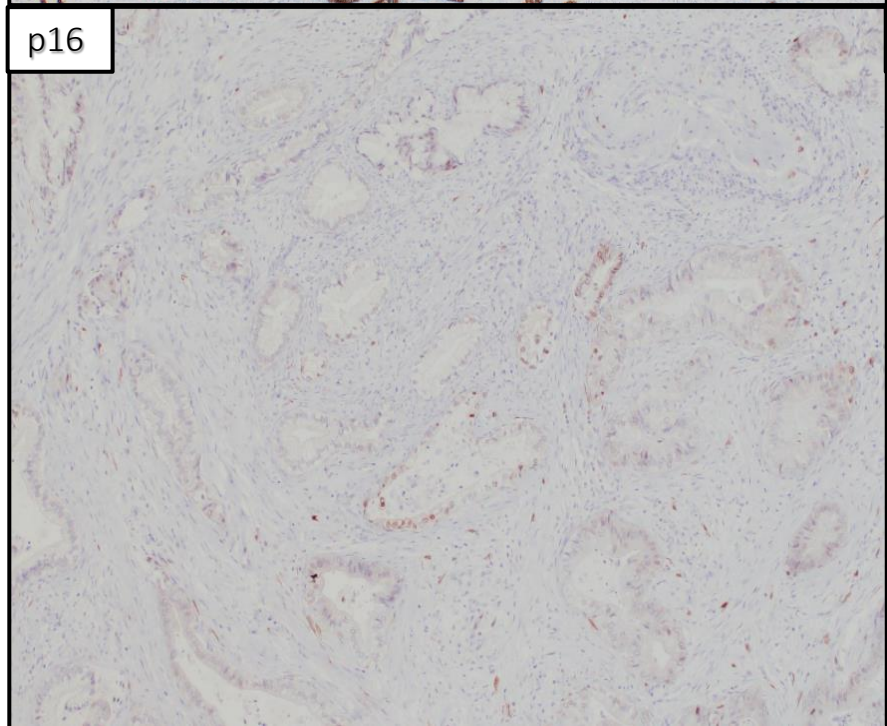


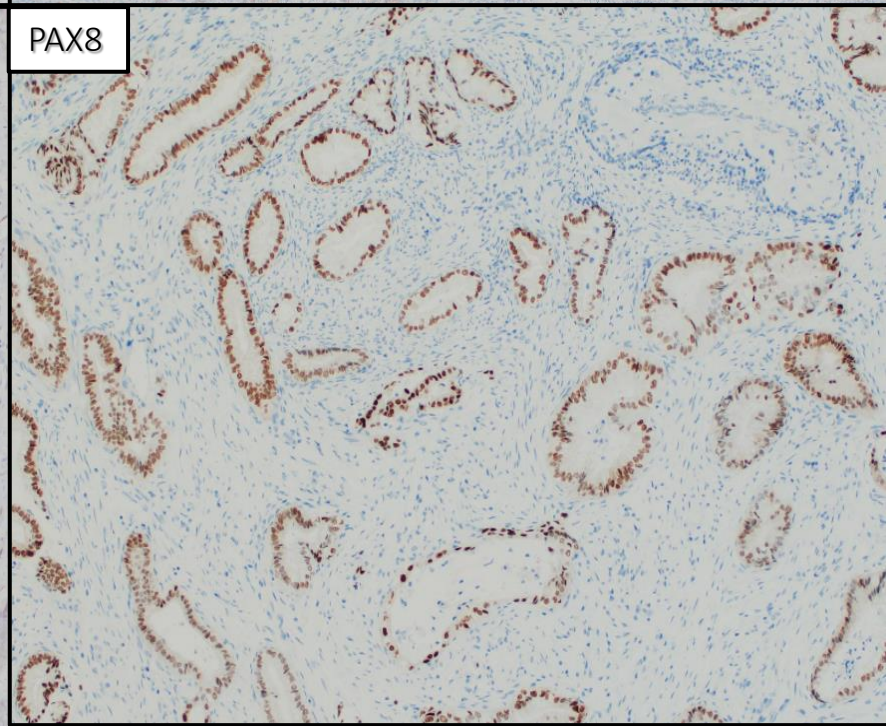


Case 3

- IHC panel applied:
  - ❖ CK7, PAX8: positive (strong, diffuse)
  - ❖ CK20, p16: positive (focal, weak)
  - ❖ ER, PR: negative
  - ❖ p53: positive, patchy (wild-type pattern)
  - ❖ HR HPV ISH: negative
- Additional studies: radiologically, no gastrointestinal mass or other dominant primary site identified





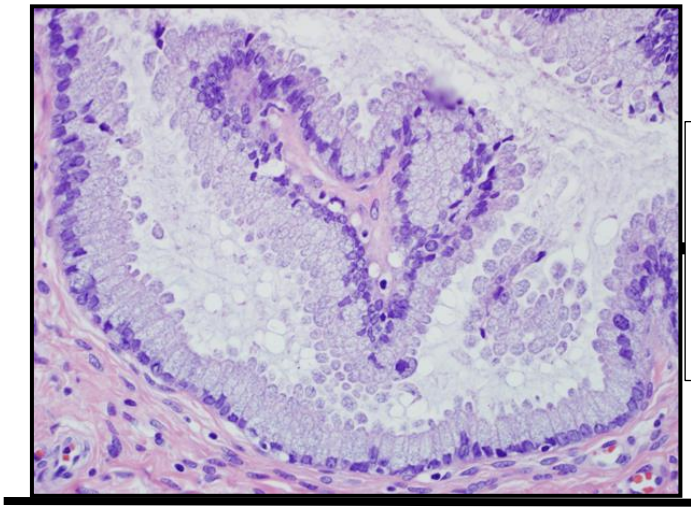


Gastric-type Primary Endocervical Adenocarcinoma

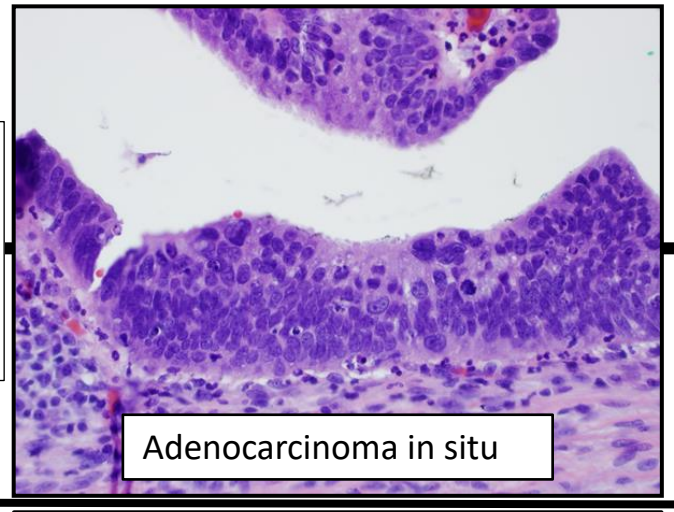
- HPV-independent
- Can be seen in Peutz-Jeghers syndrome
- Postulated to arise from atypical lobular endocervical glandular hyperplasia and gastric-type adenocarcinoma in situ
- Intracellular neutral mucin with absence of HPV-associated cytologic features
- Morphology varies from bland, very well-differentiated features (formerly adenoma malignum or minimal deviation adenocarcinoma) to cytoarchitecturally conventional high-grade adenocarcinoma
- Typically positive for PAX8, CK7, and CEA and negative for ER, PR and p16
- Aggressive tumors with higher propensity for destructive invasion, advanced stage at presentation compared with HPV-associated tumors

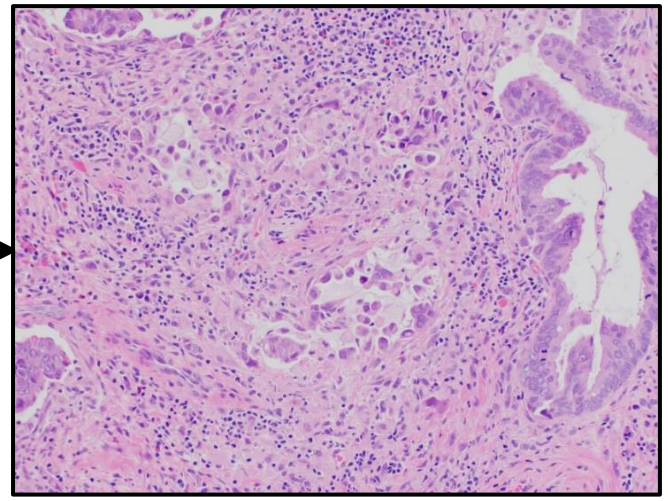
HPV-Independent Endocervical Adenocarcinomas

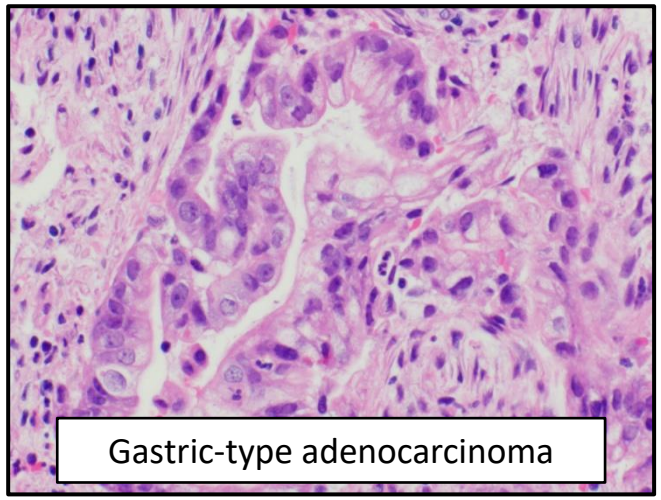
Primary Endocervical Adenocarcinomas

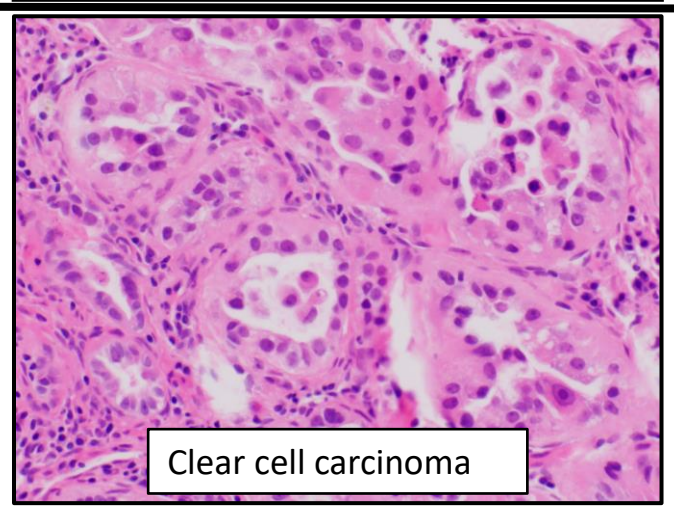


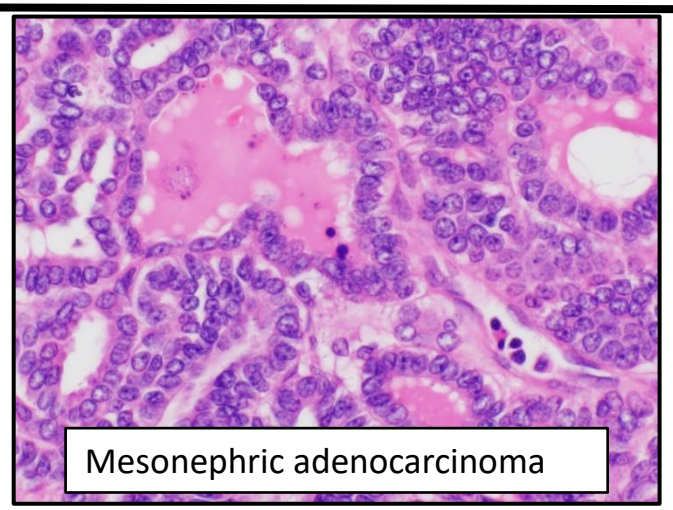
HPV 18, 16











International Endocervical Adenocarcinoma and Criteria System

HPVA
(HPV Associated)

Apical mitotic figures and apoptotic bodies at scanning magnification

If features not seen at scanning, cursory exam at 200x to detect additional cases

NHPVA
(Non-HPV Associated)

No easily identifiable mitotic activity and apoptotic bodies at scanning mag

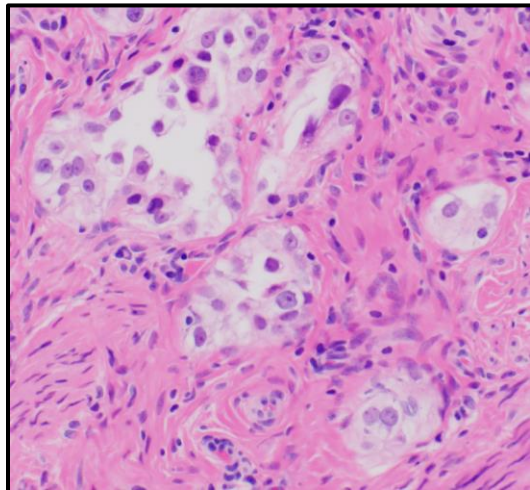
Focal or equivocal HPVA features at 200x – limited HPVA, tentatively classified as NHPVA

Park, KJ. Histopathol 2020

Gastric-type adenocarcinoma	Clear cell carcinoma	Mesonephric adenocarcinoma
No HPV associated atypia	Tubulocystic, papillary, solid patterns	Lateral wall location when small
PAX8 positive, ER negative	HNF1-beta, Napsin-A positive	GATA-3 positive

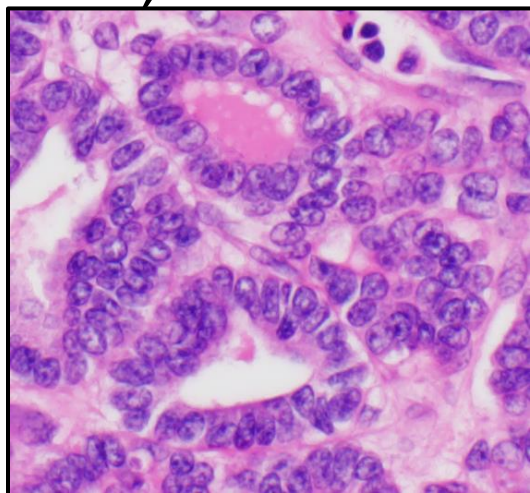
Primary Endocervical Clear Cell Carcinoma

- HPV-independent
- Two presentations: DES-associated (ectocervical); sporadic (endocervical)
- Tubulocystic, papillary, solid growth patterns
- Typically positive for HNF-1β and Napsin A (sensitive but not specific), and negative for ER and GATA3
- Likely better overall survival and lower recurrence rate in lower stage disease; lymph node status is important predictor of overall survival and recurrence

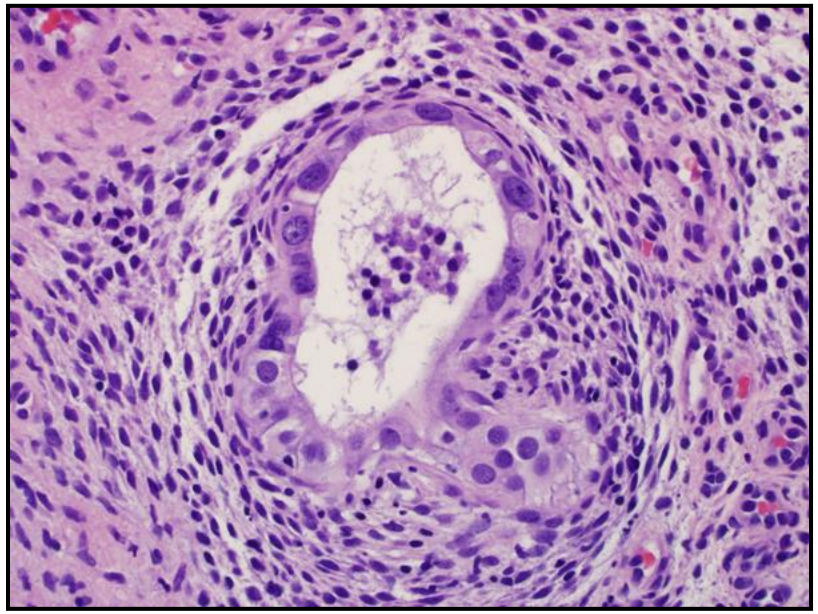


Mesonephric Adenocarcinoma

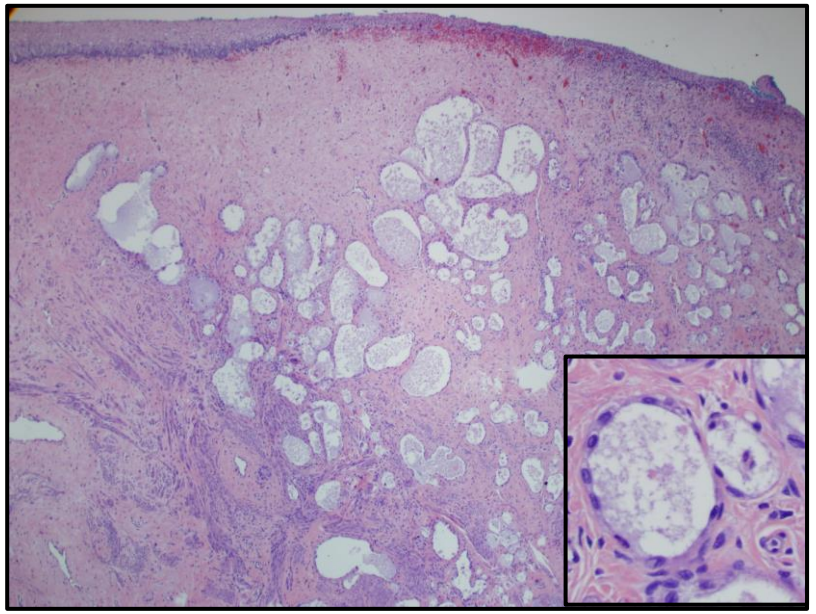
- HPV-independent
- Arise from mesonephric remnants in the lateral cervical wall
- Tubular growth pattern with PAS- and mucicarmine-positive eosinophilic luminal secretions
- Typically positive for PAX8 and GATA3, and negative for ER and Napsin A
- Very rare entity; about 1/3 of cases have been reported to recur, often after extended periods



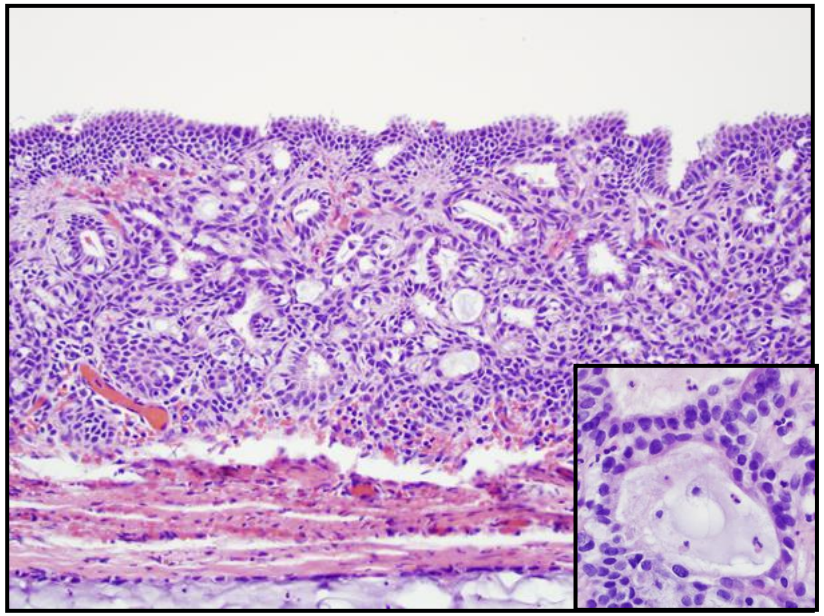
Typical Differential Diagnosis of Atypical Glandular Proliferations: Benign Mimics (Non-mucinous)



Tubal/tuboendometrioid metaplasia

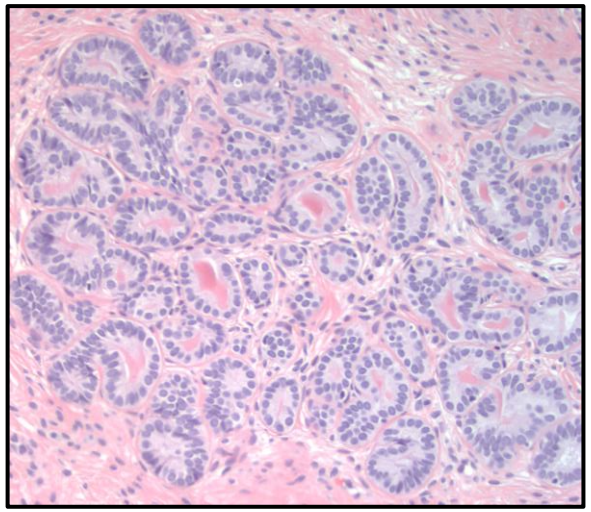


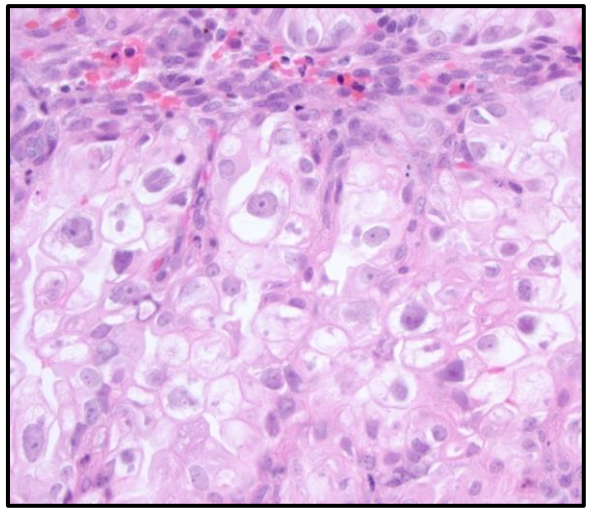
Tunnel clusters



Microglandular hyperplasia

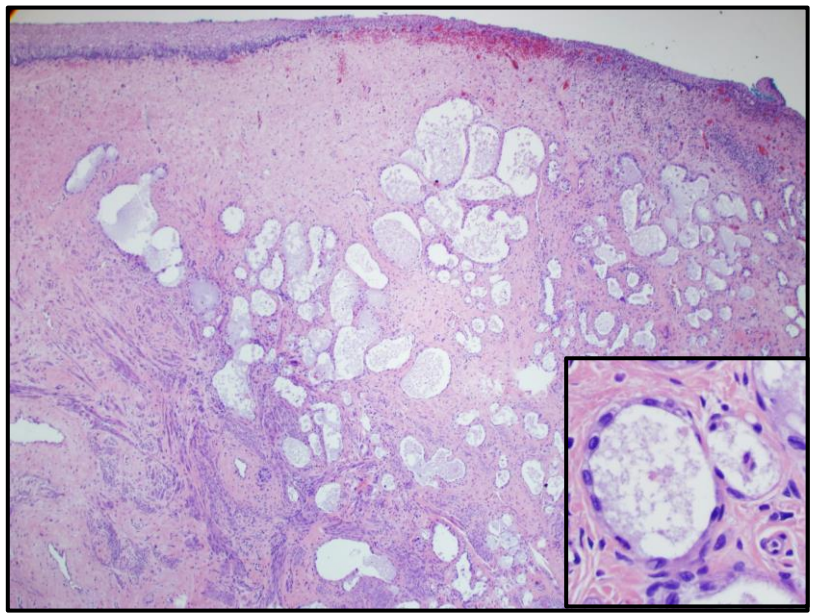
Mesonephric remnants/hyperplasia



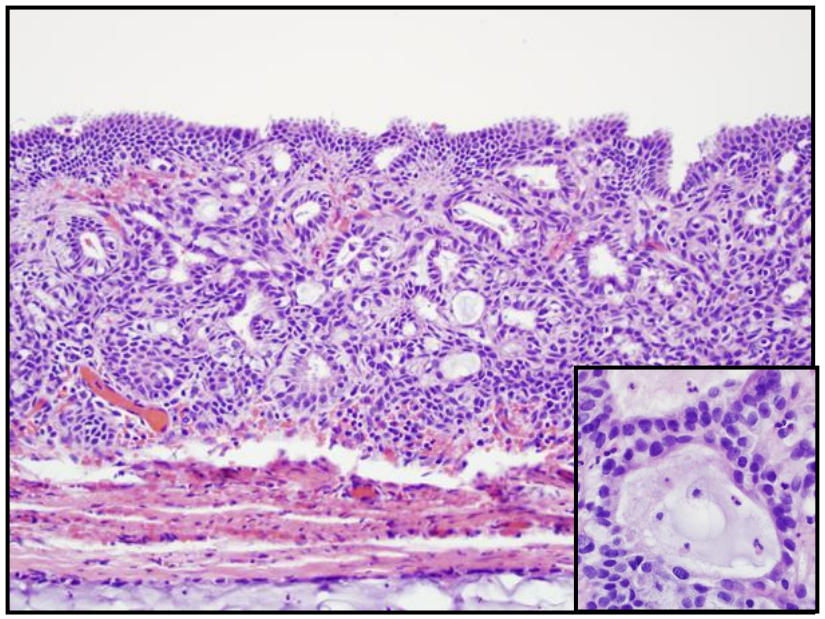


Arias-Stella Reaction

Typical Differential Diagnosis of Atypical Glandular Proliferations: Benign Mimics (Mucinous)



Tunnel clusters



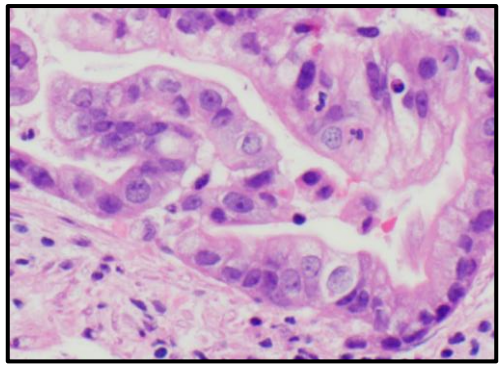
Microglandular hyperplasia

Also:

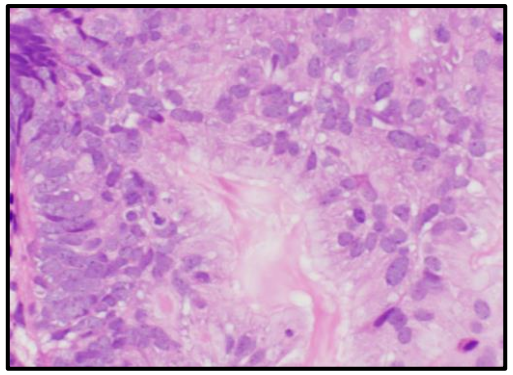
- Lobular endocervical glandular hyperplasia

- Diffuse laminar endocervical hyperplasia

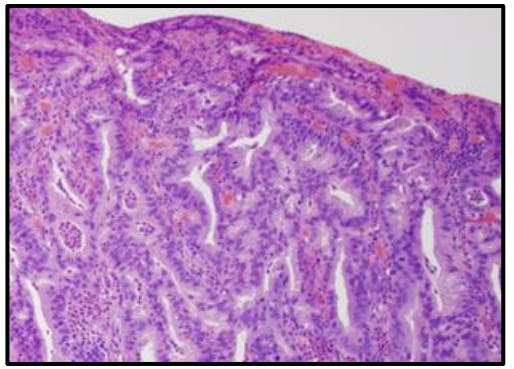
Typical Differential Diagnosis of Atypical Glandular Proliferations: Secondary Malignancies (Mucinous)



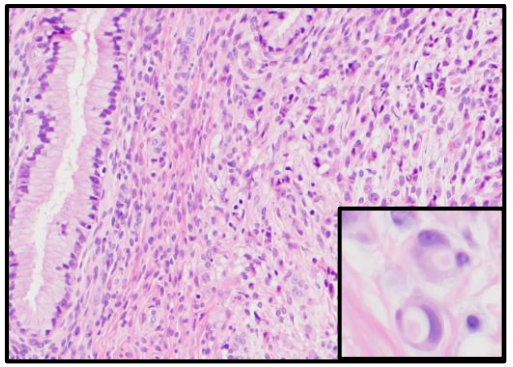
Primary endocervical adenocarcinoma, gastric-type



Metastatic endometrial endometrioid carcinoma with mucinous features



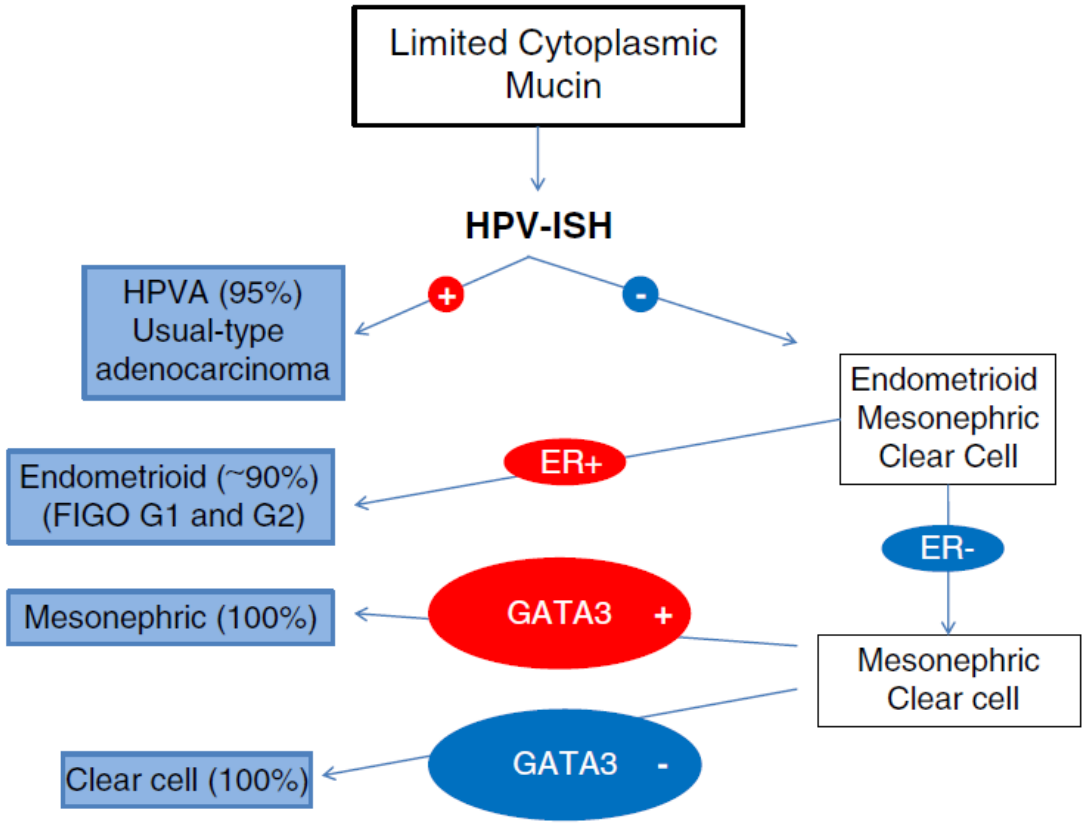
Metastatic gastric (or other GI) adenocarcinoma

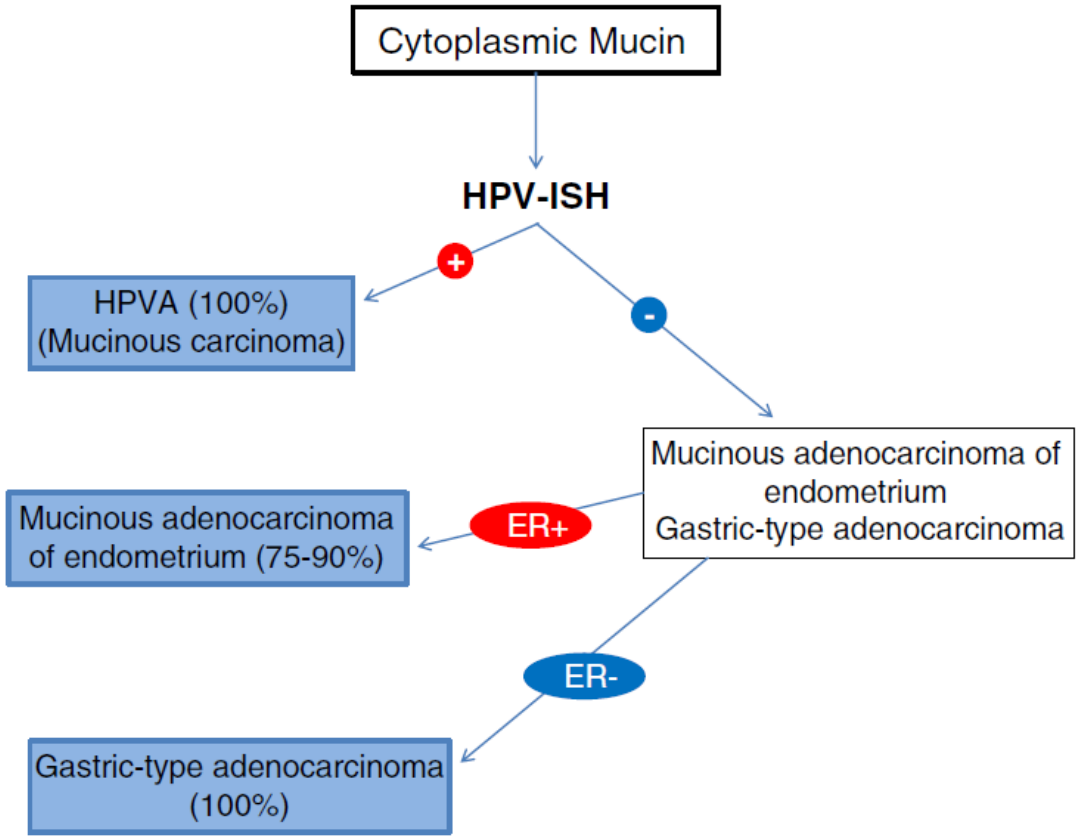


Metastatic mammary lobular carcinoma

Stains				
PAX8	Positive	Positive	Negative	Negative
ER	Negative	Positive (grade dependent)	Negative	Positive
CK7, CK20	Positive/negative	Positive/negative	Positive/positive or negative	Positive/negative
GATA3	Negative	Negative	Negative	Positive
Other helpful findings	No uterine mass; no other known primary	Dominant uterine mass	Known primary	Known primary; targetoid inclusions

Proposed Diagnostic Algorithm for Primary HPV-Independent Endocervical Adenocarcinoma





Stolnicu et al. AJSP 2018 42:989-1000

Case 3 –HPV-Independent Endocervical Adenocarcinoma: Take Home Points

- Non-HPV-associated endocervical adenocarcinomas include gastric-type, clear cell and mesonephric adenocarcinomas
- Distinction between gastric-type adenocarcinomas of the endocervix and metastatic adenocarcinomas of gastrointestinal origin can be challenging
- Judicious use of ancillary testing including HR HPV ISH will often assist in clarifying the diagnosis

Case 4

- Cervical biopsy in a 64-year-old female presenting with postmenopausal bleeding.

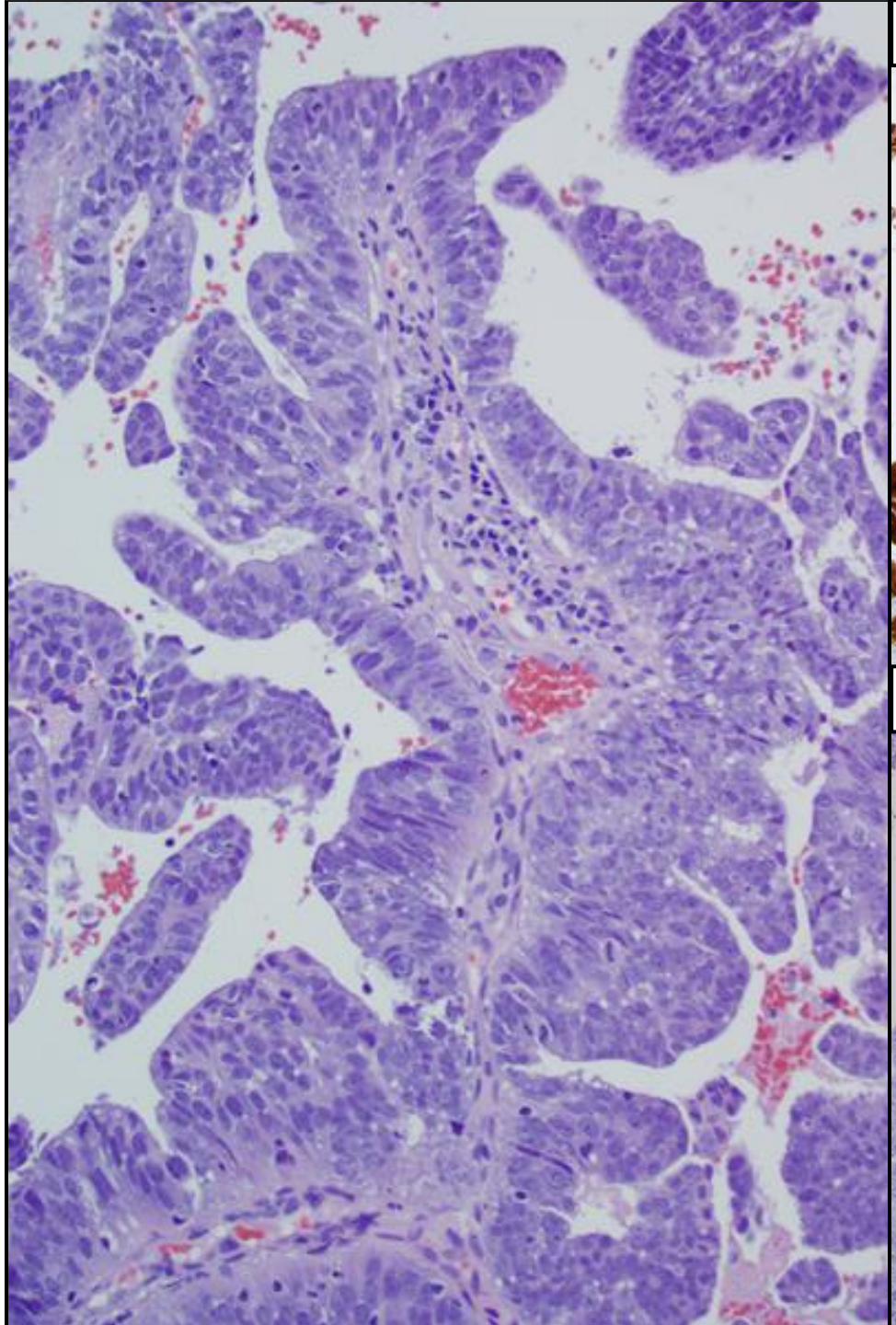
- IHC panel applied:

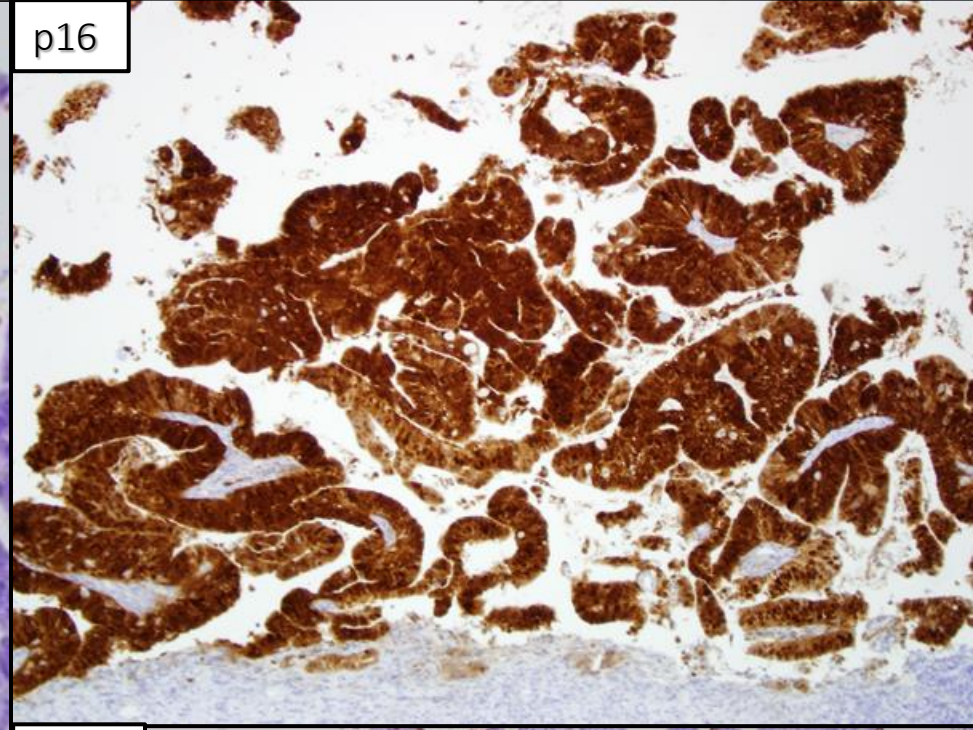
❖ p16: positive (strong, diffuse)

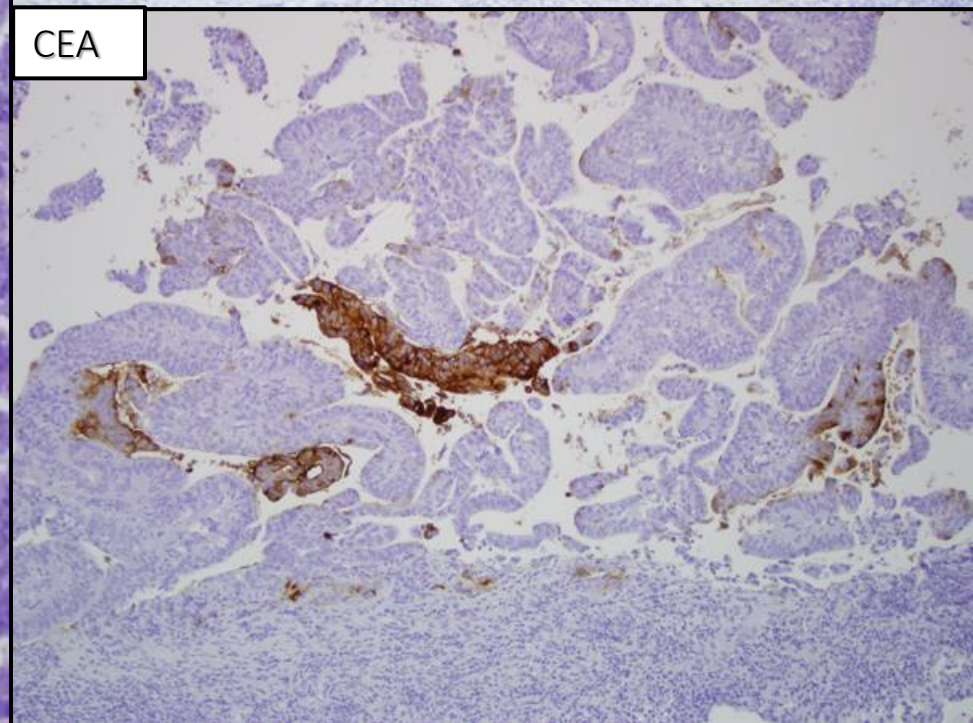
❖ CEA: positive (focal)

❖ Estrogen: negative

❖ Vimentin: negative







Case 4

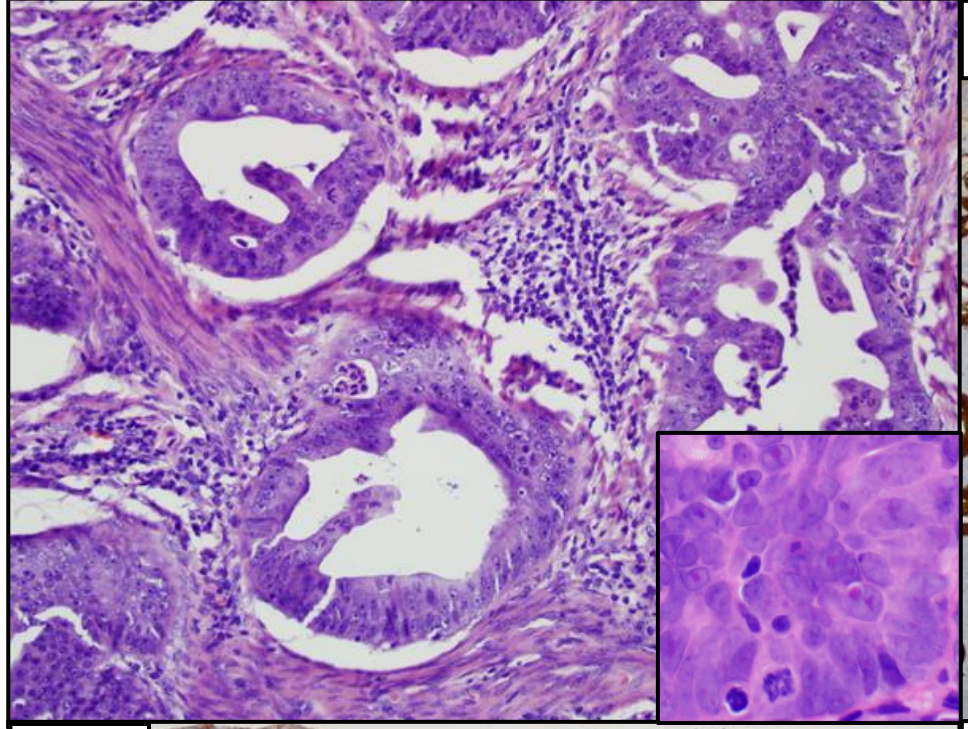
- The patient was lost to follow-up and returned with marked anemia due to severe vaginal bleeding.
- She underwent a radical hysterectomy showing a deeply invasive dominant uterine mass extending into the cervix.
- IHC panel applied:

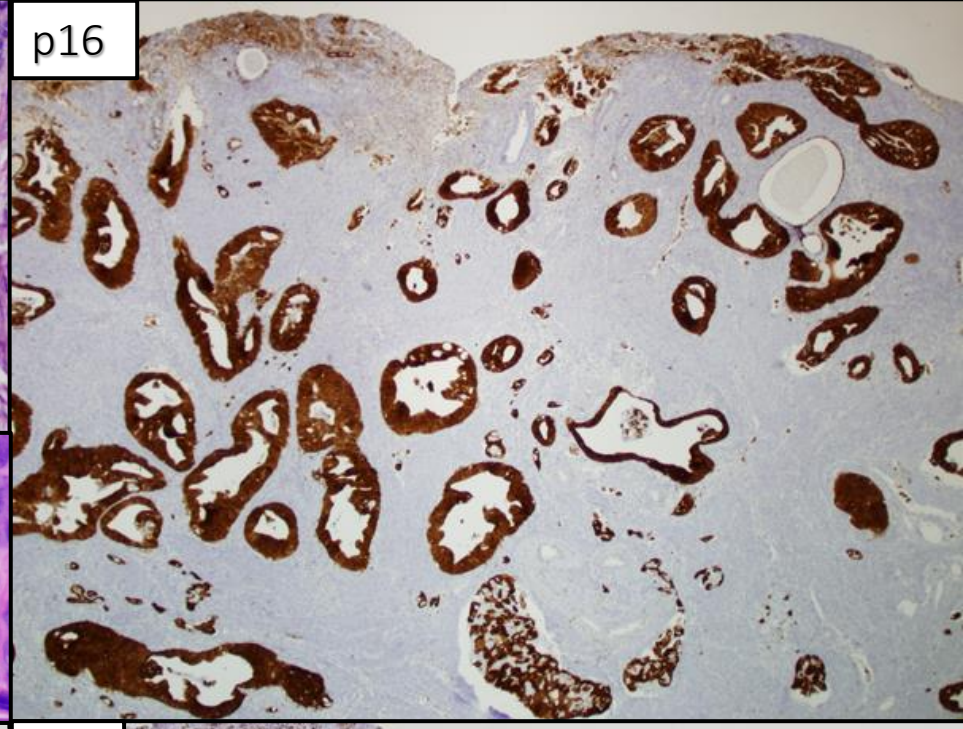
❖ P16: positive (strong, diffuse)

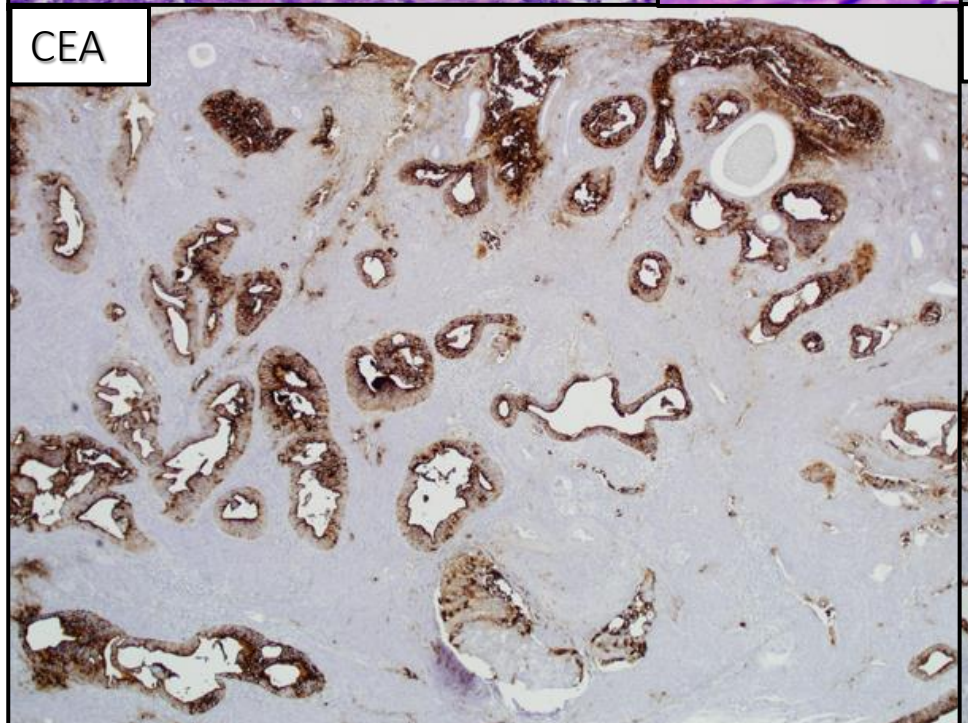
❖ CEA: positive (strong, diffuse)

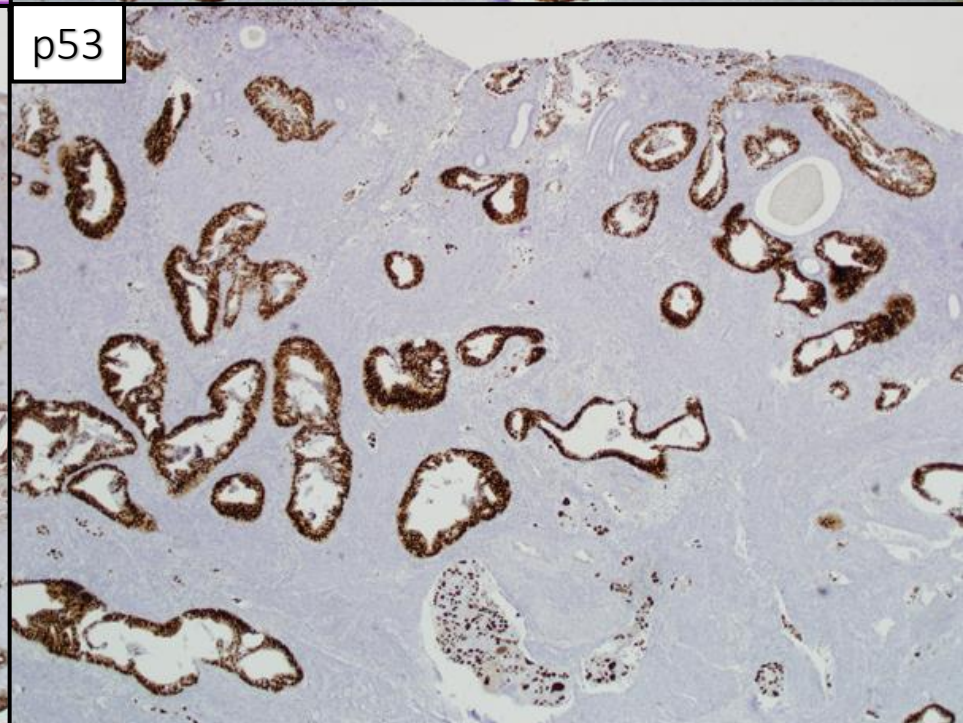
❖ P53: aberrant (strong, diffuse)

❖ HR HPV ISH: Negative







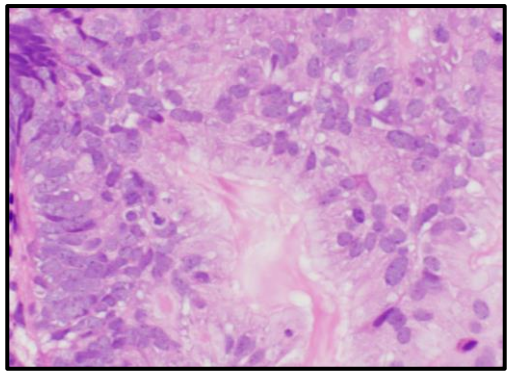


Endometrial Adenocarcinoma

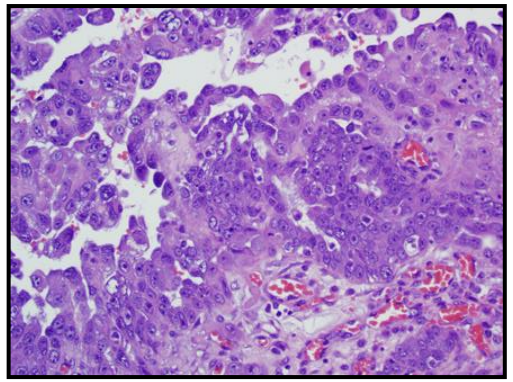
Characteristics	Type I	Type II
Age	55-65 years	65-75 years
Clinical setting	Unopposed estrogen, obesity	Atrophy
Background endometrium	Hyperplastic	Atrophic
Tumor characteristics		
• Histology	Endometrioid	Serous, clear cell, others
• Grade	1,2>3	3
• Depth of myometrial invasion	Often superficial	Deep
• Nodal involvement	Dependent on extent of invasion	Frequent
Stage	Typically early	Frequently advanced
Precursor lesion	Endometrial intraepithelial neoplasia/atypical hyperplasia	Serous endometrial intraepithelial carcinoma
Genetic basis	*PTEN, ARID1A, PIK3CA,* etc.	*TP53, PIK3CA, PPP2R1A,* etc.
Prognosis	Favorable	Unfavorable

Adapted from Robbins and Cotran, 10th ed.

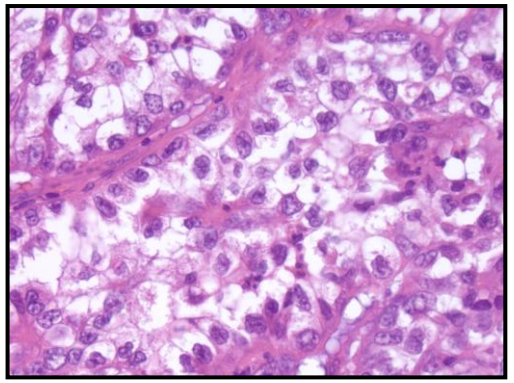
Endometrial Adenocarcinoma



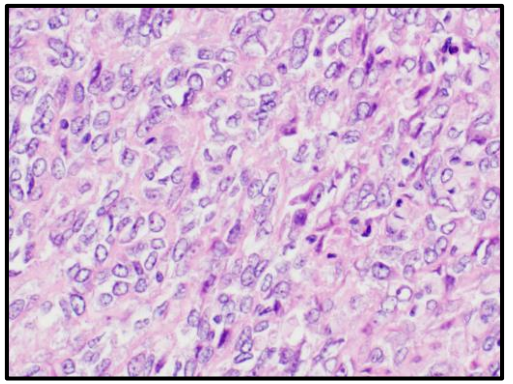
Endometrial endometrioid adenocarcinoma



Endometrial serous carcinoma



Endometrial clear cell carcinoma

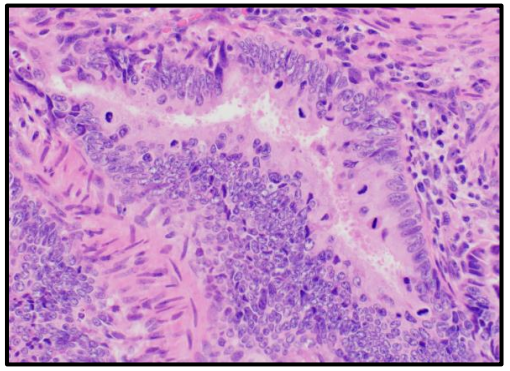


Endometrial dedifferentiated or undifferentiated carcinoma

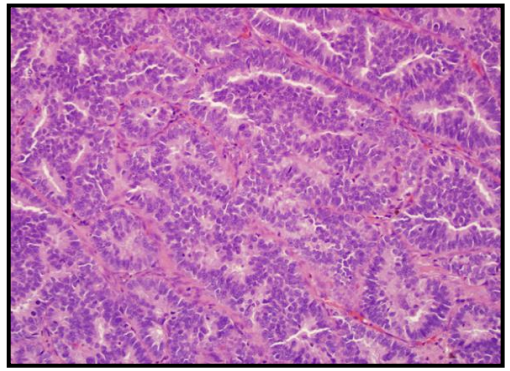
Markers				
p53	Wild-type (can be aberrant in subset of grade 3 tumors)	Null or strongly positive	Typically wild-type	Wild-type
ER	Positive	Positive or negative	Typically negative	Negative
p16	Positive (focal)	Positive (diffuse and strong)	Positive (focal)	
Genetic markers	*PTEN, ARID1A, PIK3CA, CTNNB1, TP53* (subset), *POLE* ultramutation	*TP53, PIK3CA, PPP2R1A, FBXW7, ERRB2 (HER2)* amplification (30%)	*TP53, PPP2R1A, PIK3CA, PIK3R1, KRAS, ARID1A, SPOP*	
Other helpful findings	Often associated with EIN/AEH, metaplasias (mucinous, squamous)	Can be superficial or involve an endometrial polyp, typically WT-1 negative	Napsin-A, HNF1-beta positive	Dedifferentiated carcinoma: grade 1 or 2 endometrioid component; both keratin positive

Adapted from Goebel EA, et al. Virchows Archiv 2018 472:885-896, WHO Classification, 5th ed., 2020

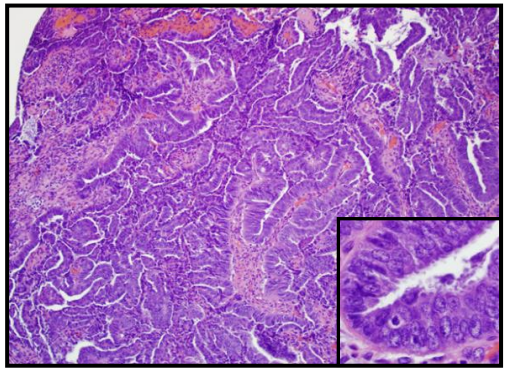
Endocervical vs. endometrial adenocarcinoma: Classification in biopsies matters!



Endocervical adenocarcinoma



Endometrial endometrioid carcinoma (type I)



Endometrial serous carcinoma (type II)

Studies			
Surgery	Cold knife cone, trachelectomy, radical hysterectomy	Total hysterectomy with potential intraoperative frozen section evaluation	Total hysterectomy
Lymph node sampling	Dependent on tumor stage	Dependent on depth of myoinvasion or sentinel lymph node biopsy if gr 1-2	Regional lymph node sampling
Systemic/ radiation therapy	Dependent on tumor stage	Dependent on stage and presence/extent of LVSI	Dependent on stage; platinum-based regimens

Case 4 – Endometrial Adenocarcinoma: Take Home Points

- Distinction between primary endocervical and endometrial carcinomas is crucial from a clinical perspective and histologic assessment can be challenging
- While p16 is a surrogate marker of HPV infection, it can be strongly expressed in high grade endometrial carcinomas via a non-HPV-associated pathway
- Ancillary testing such as HR HPV ISH is definitive but not always available
- Ultimately the decision to apply ancillary testing must be anchored in histomorphology (HPV-associated cellular features, high grade vs. low grade cytology)
- Use of panels is strongly recommended