ENDOMETRIAL CARCINOMA: PROGNOSTIC INDICATORS

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TRADITIONAL STAGING AND RELATED ISSUES

Table 1: Staging of endometrial carcinoma as per FIGO (2018 update) and AJCC 8th edition

FIGO (2018)	AJCC (2018)	Description
I	T1	Tumor confined to the uterus
1A	T1a	Tumor confined to the endometrium or invades < 50% of the myometrial wall
1B	T1b	Tumor invades > 50% of the myometrial wall
II	T2	Tumor infiltrates cervical stroma
III	T3, N1	Tumor extends outside the uterus
IIIA	T3a	Tumor involves serosa or adnexa (direct extension or metastases)
IIIB	T3b	Tumor involves vagina or parametria (direct extension or metastases)
IIIC	N1	Tumor with pelvic lymph node metastasis
IIIC1	N1 mi	Micrometastases in pelvic lymph nodes (> 0.2 mm or 200 cells but ≤ 2 mm)
	N1a	Macrometastases in pelvic lymph nodes (> 2 mm in size)
IIIC2	N2 mi	Micrometastases in para-aortic lymph nodes (> 0.2 mm or 200 cells but ≤ 2 mm)
	N2a	Macrometastases in para-aortic lymph nodes (> 2 mm in size)
IV	T4, M1	Tumor invades bladder or bowel mucosa or involves distant organs
IVA	T4	Tumor invades bladder mucosa or bowel mucosa
IVB	M1	Distant metastases (including intra-abdominal metastases and inguinal lymph nodes; excluding metastases to vagina, pelvic serosa or adnexa)
	N0i+	Isolated tumor cells in regional lymph nodes*

Table 2: 2023 FIGO staging of cancer of the endometrium

Stage	Description
I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium or nonaggressive histological type (i.e., low grade endometroid, with invasion of < 50% of myometrium with no or focal lymphovascular space involvement [LVSI] or good prognosis disease)
IA1	Nonaggressive histological type limited to an endometrial polyp or confined to the endometrium
IA2	Nonaggressive histological types involving < 50% of the myometrium with no or focal LVSI
IA3	Low grade endometrioid carcinomas limited to the uterus and ovary
IB	Nonaggressive histological types with invasion of ≥ 50% of the myometrium and with no or focal LVSI
IC	Aggressive histological types limited to a polyp or confined to the endometrium
II	Invasion of cervical stroma without extrauterine extension or with substantial LVSI or aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of nonaggressive histological types
IIB	Substantial LVSI of nonaggressive histological types
IIC	Aggressive histological types with any myometrial involvement
III	Local or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa or both by direct extension or metastasis
IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)

“Aggressive histotypes”

- FIGO grade 3 endometrioid
- Serous
- Clear cell
- Mesonephric-like
- Gastrointestinal-type mucinous
- Un/de-differentiated
- Carcinosarcoma
- p53-abnormal

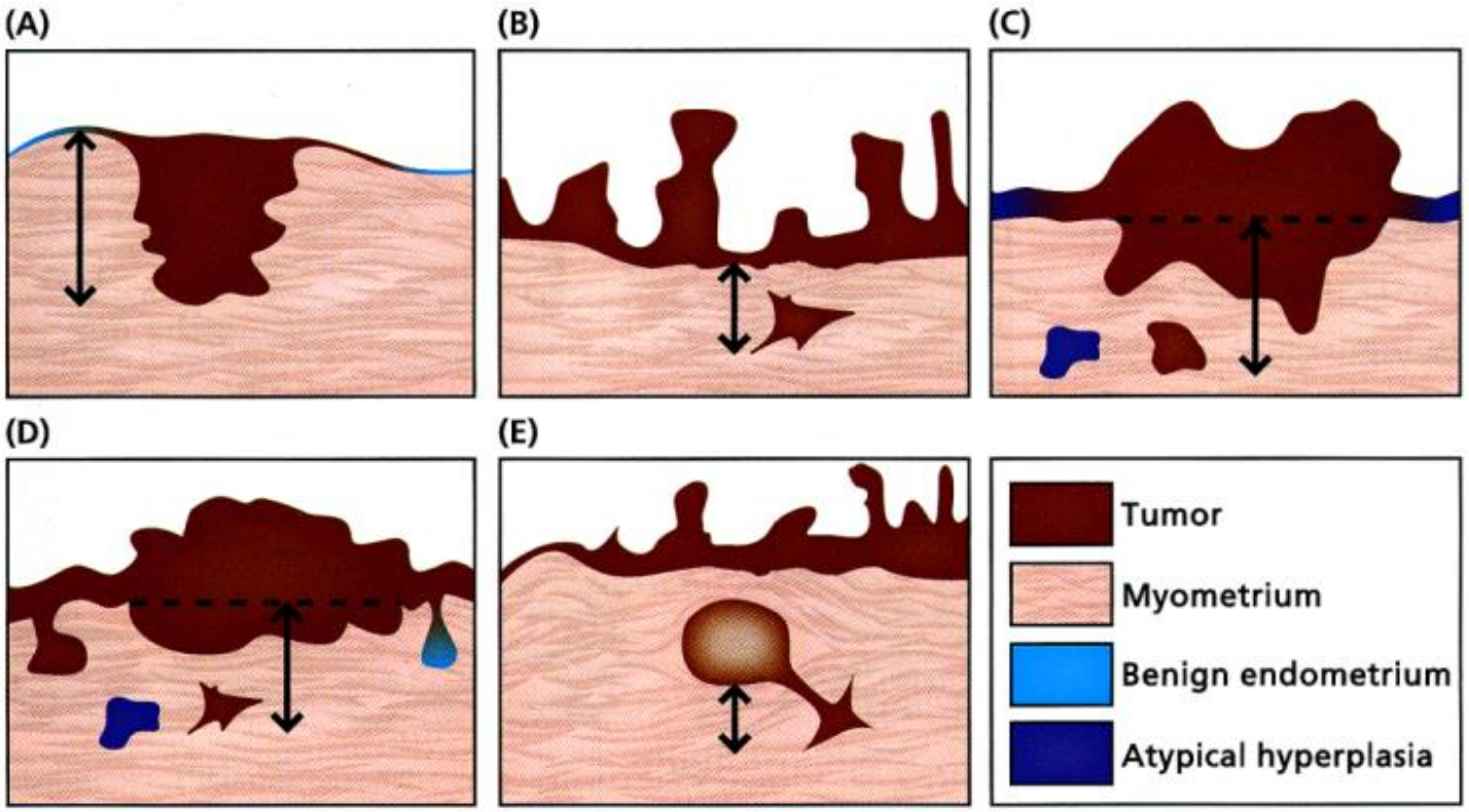
Table 2. EC risk groups

Risk group	Description[a]
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[b] and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers[c]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype[b]

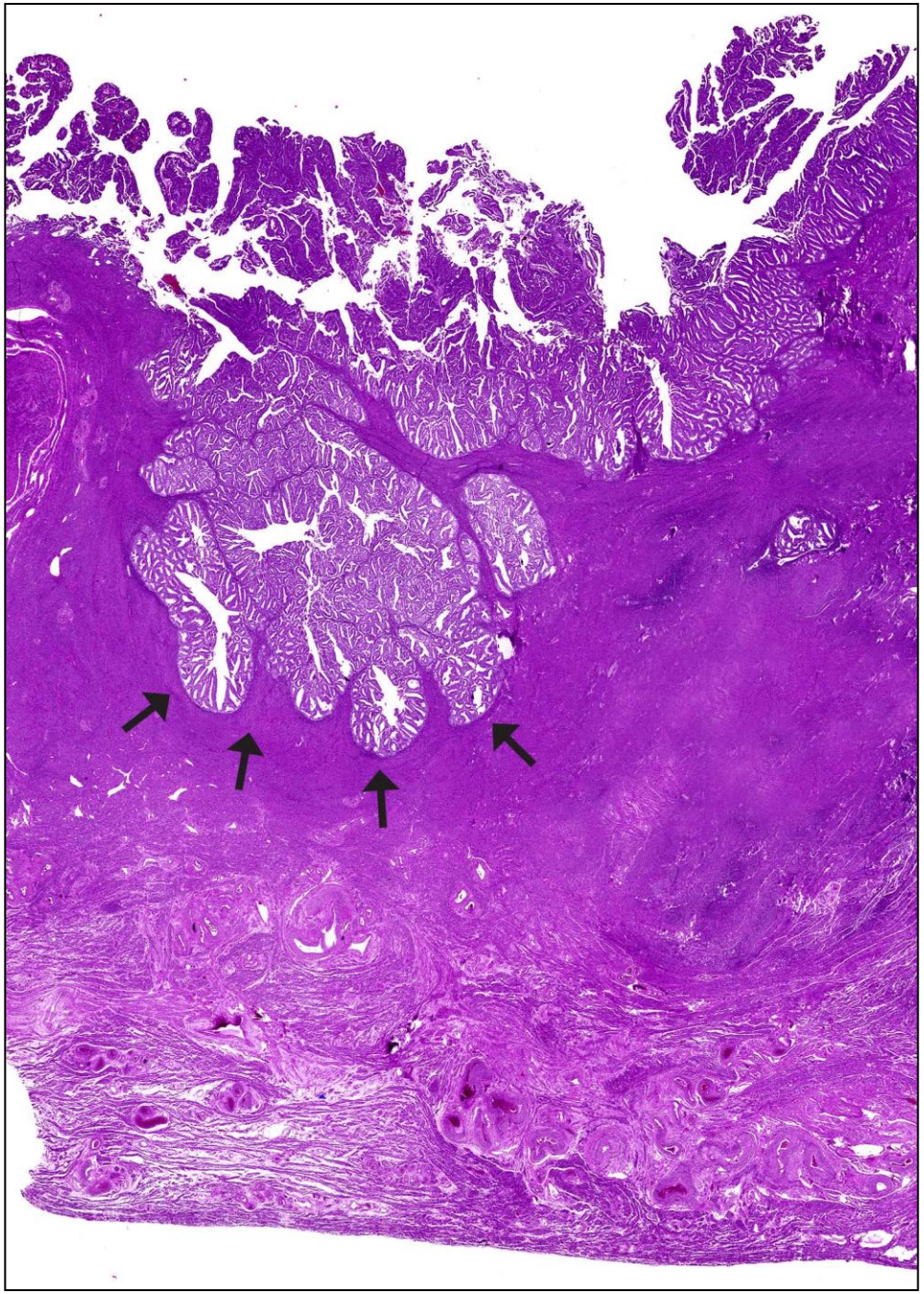
ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up Ann Oncol. 2022

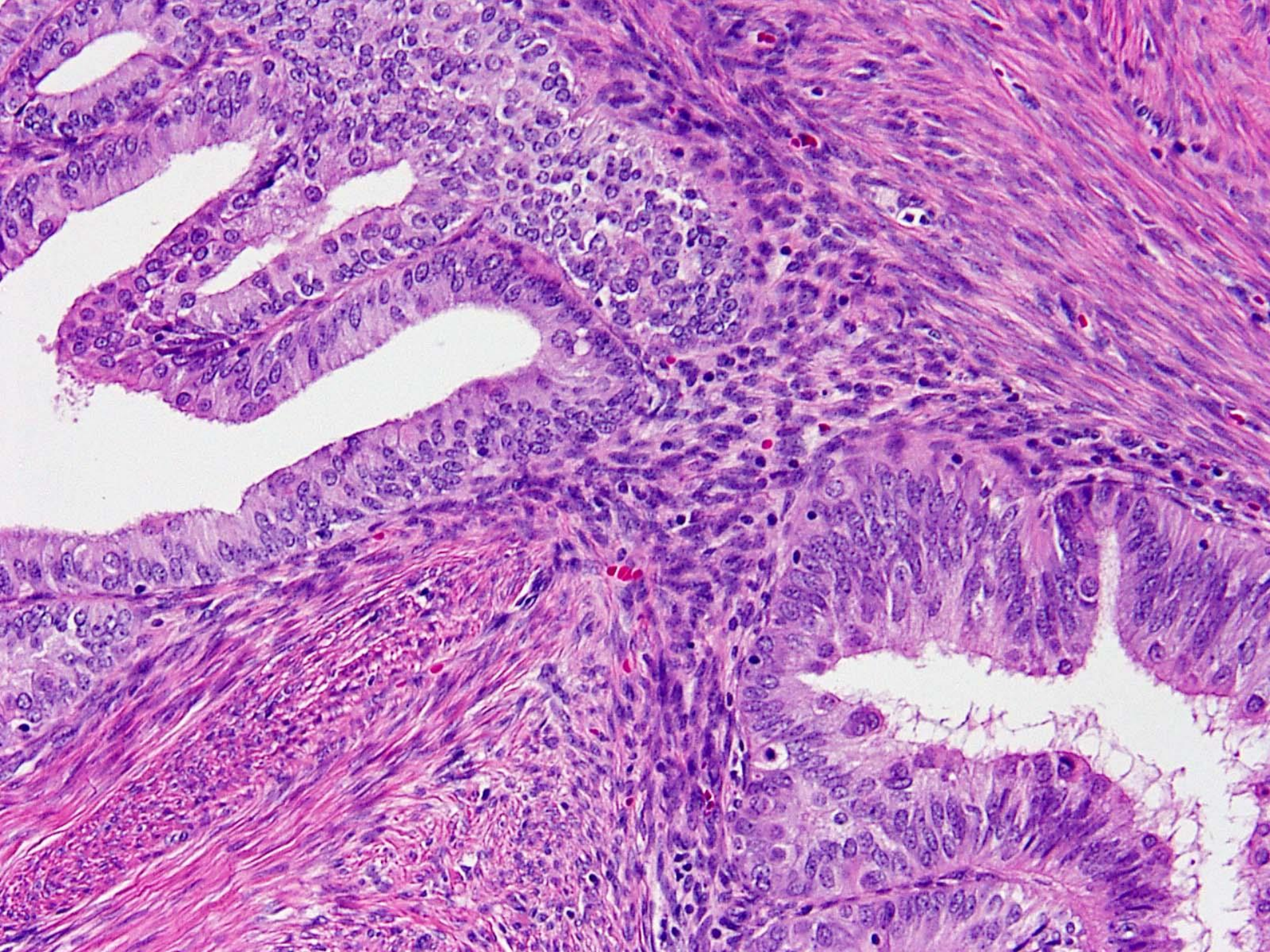
Myometrial invasion

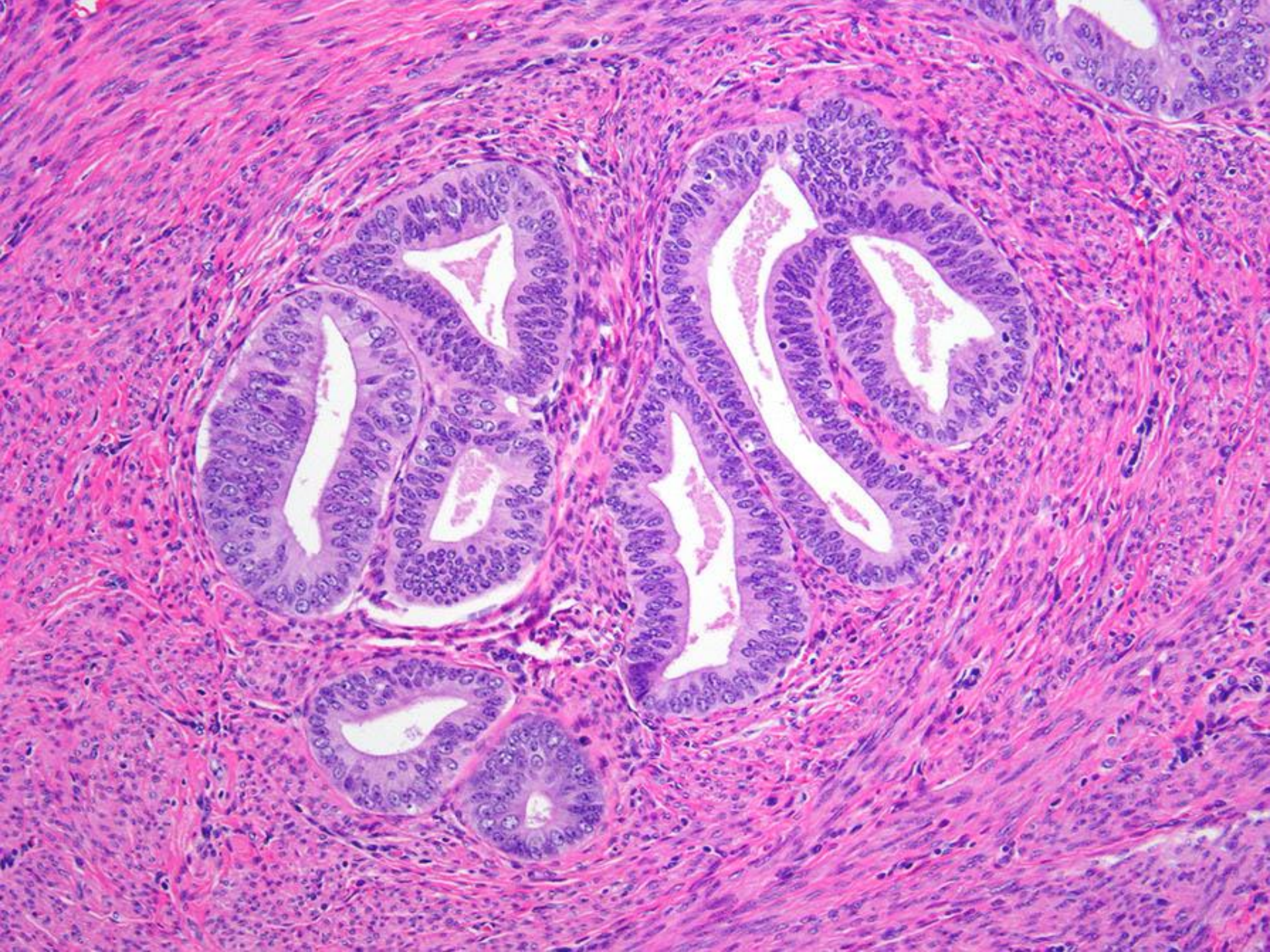
- Frequently overcalled (at least 30%)
- Overcalls related to:
  - Irregular endomyometrial junction
  - Inapparent and metaplastic stroma
  - Measuring thickness rather than depth
- Undercalls related to:
  - Unfamiliarity with microcystic, elongated and fragmented invasion pattern (MELF)

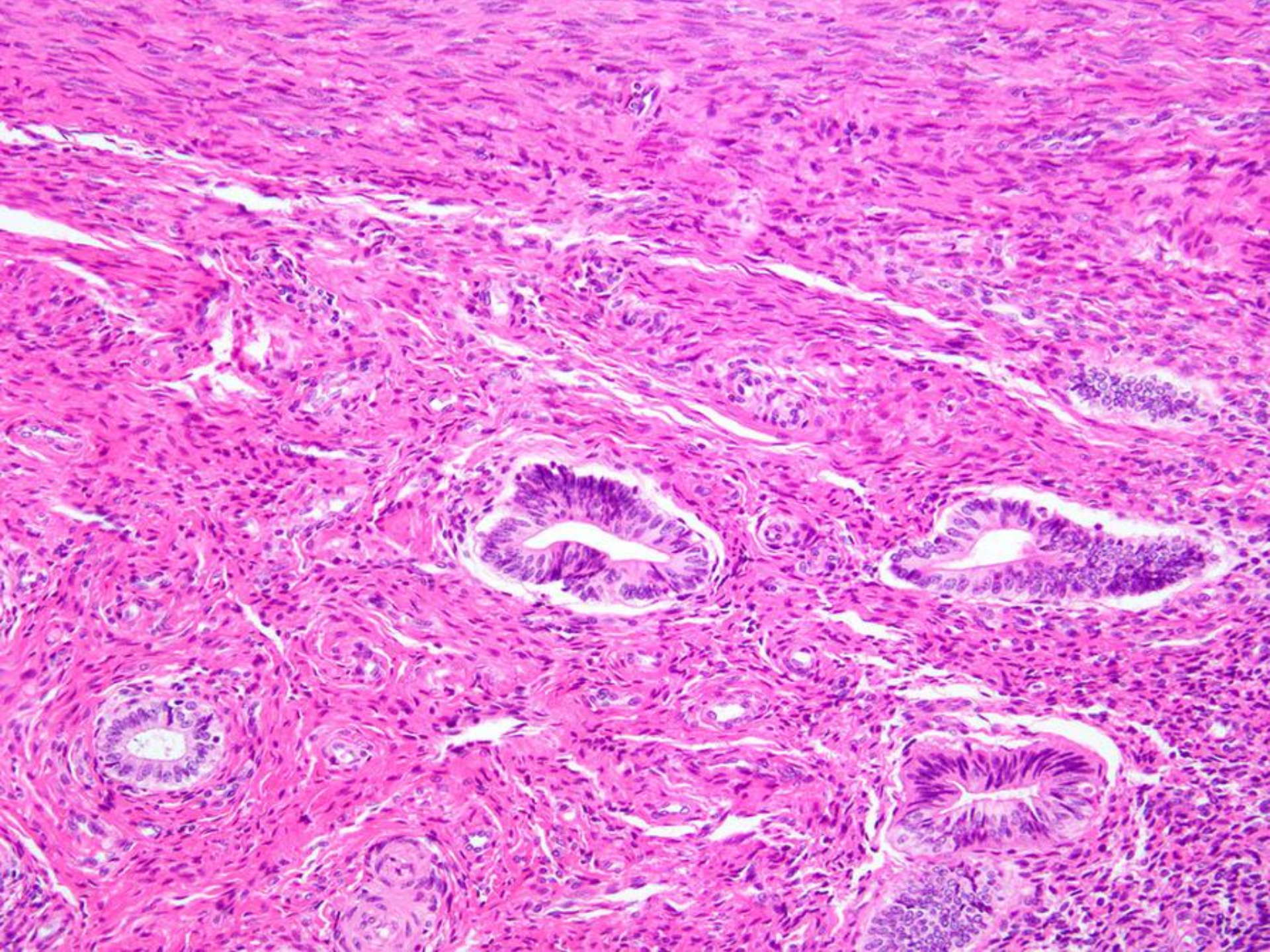


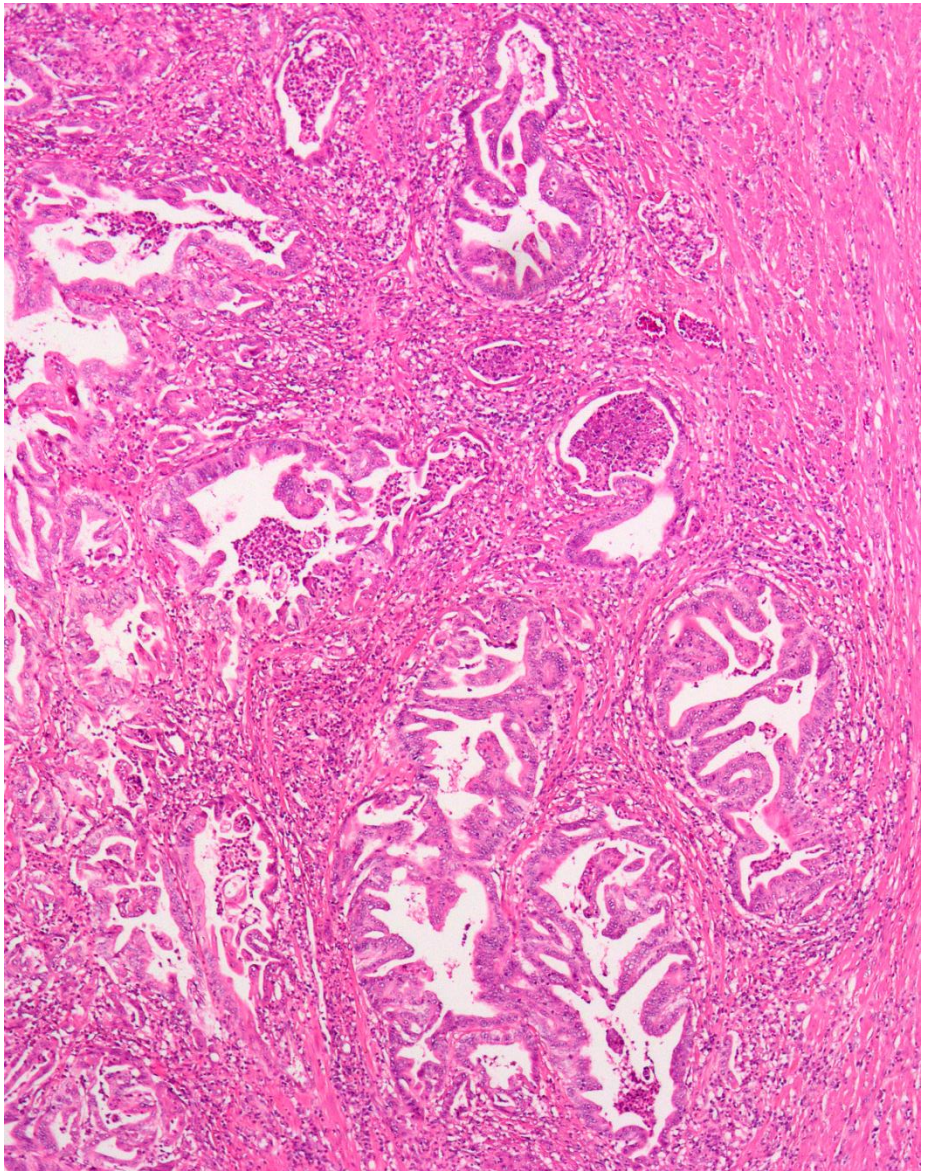
Soslow and Longacre. Uterine Pathology. Cambridge Univ. Press 2012

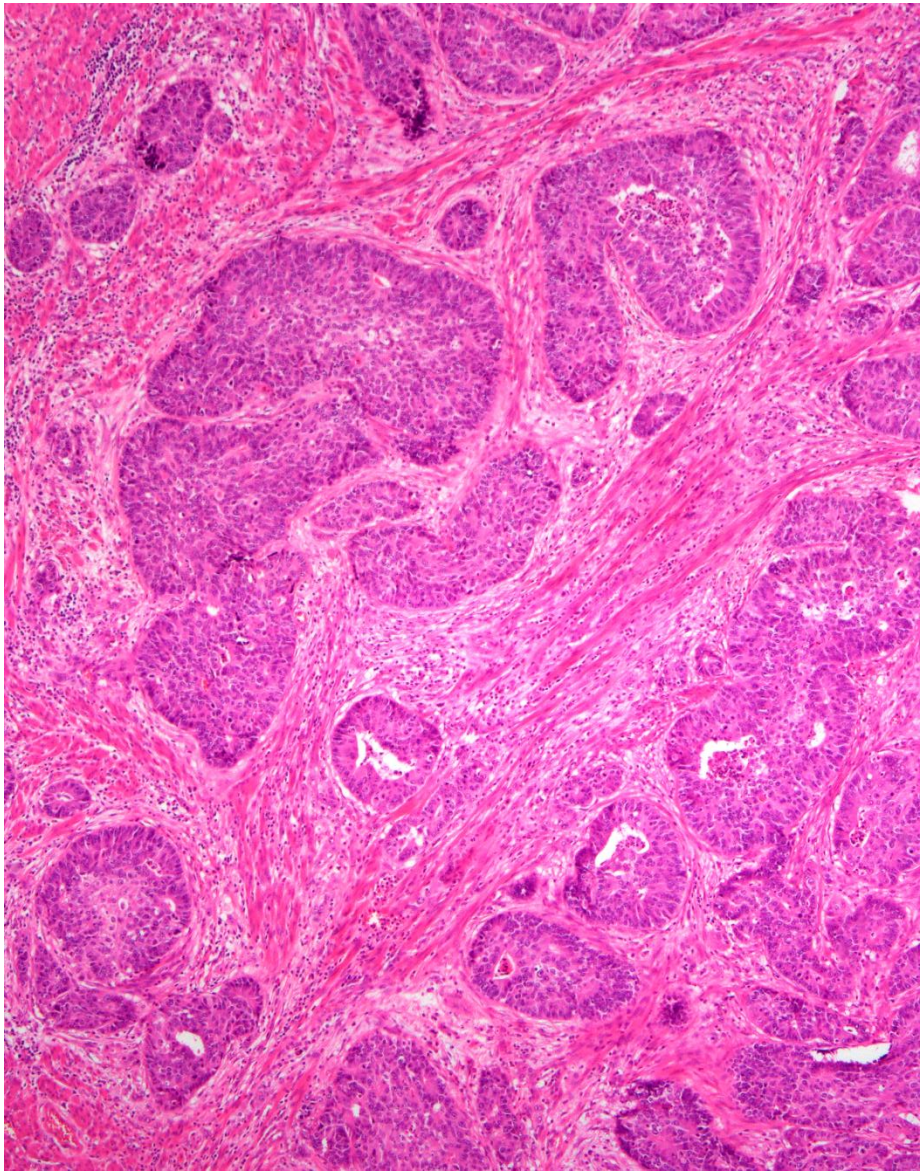




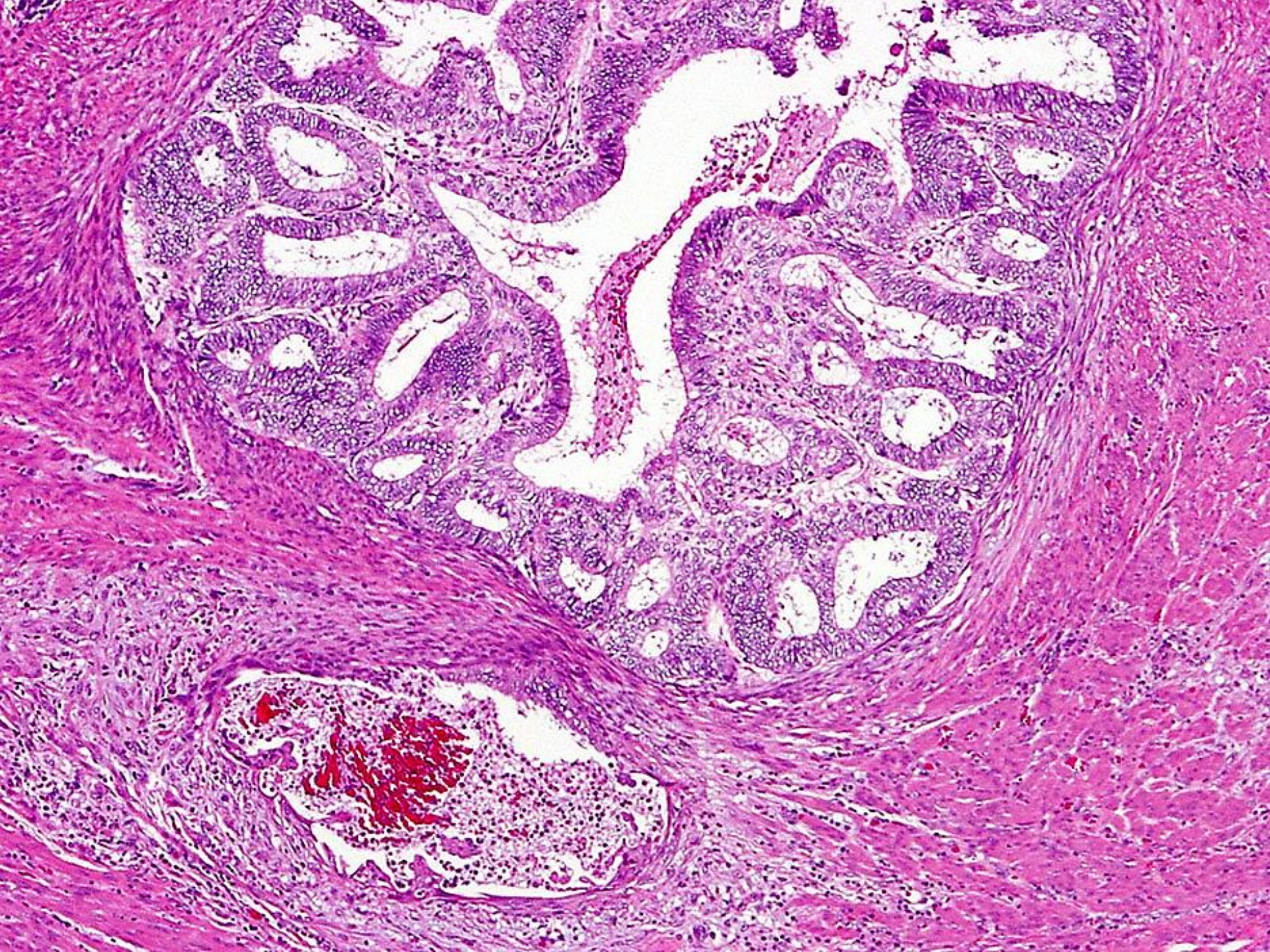


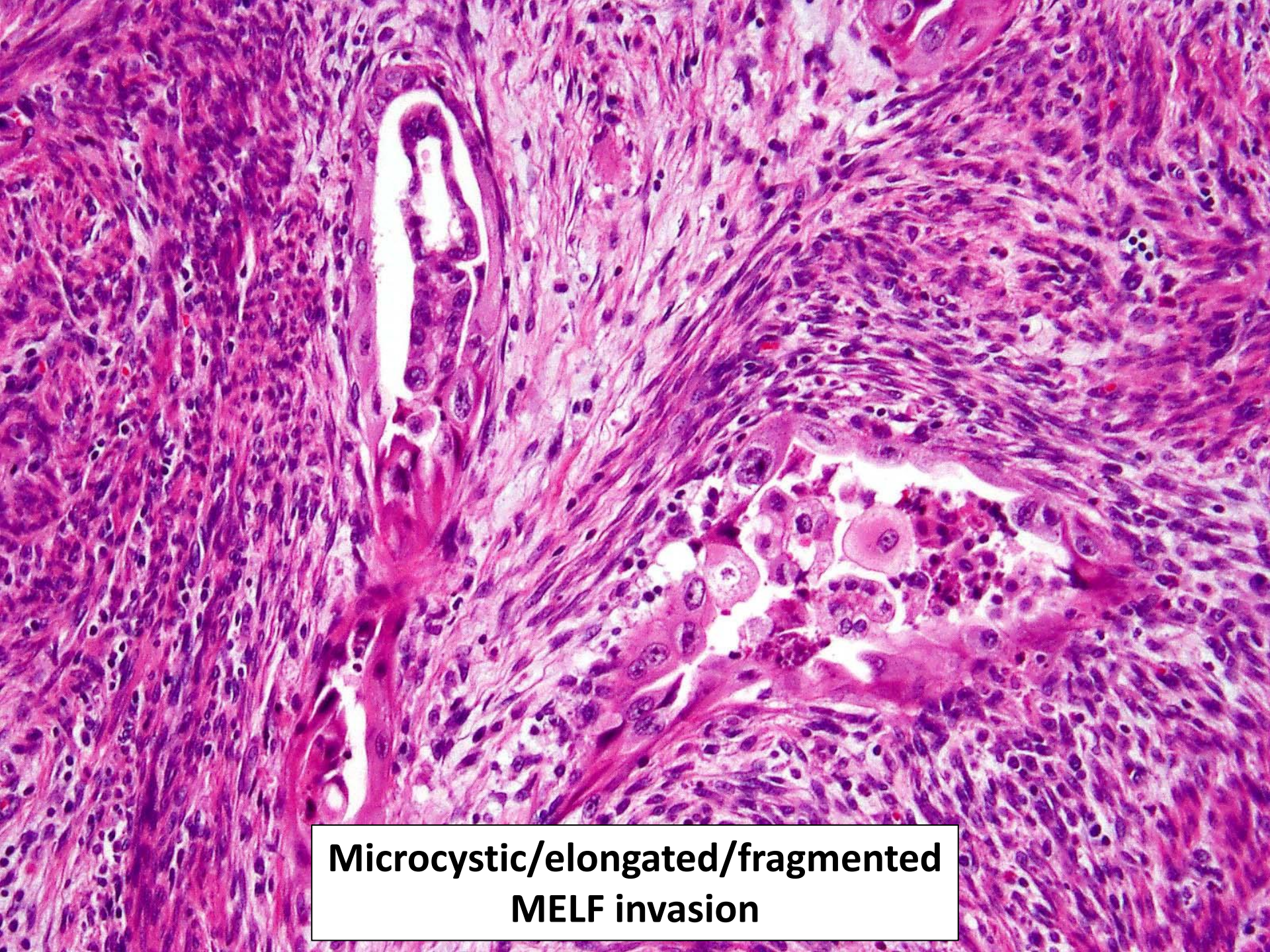






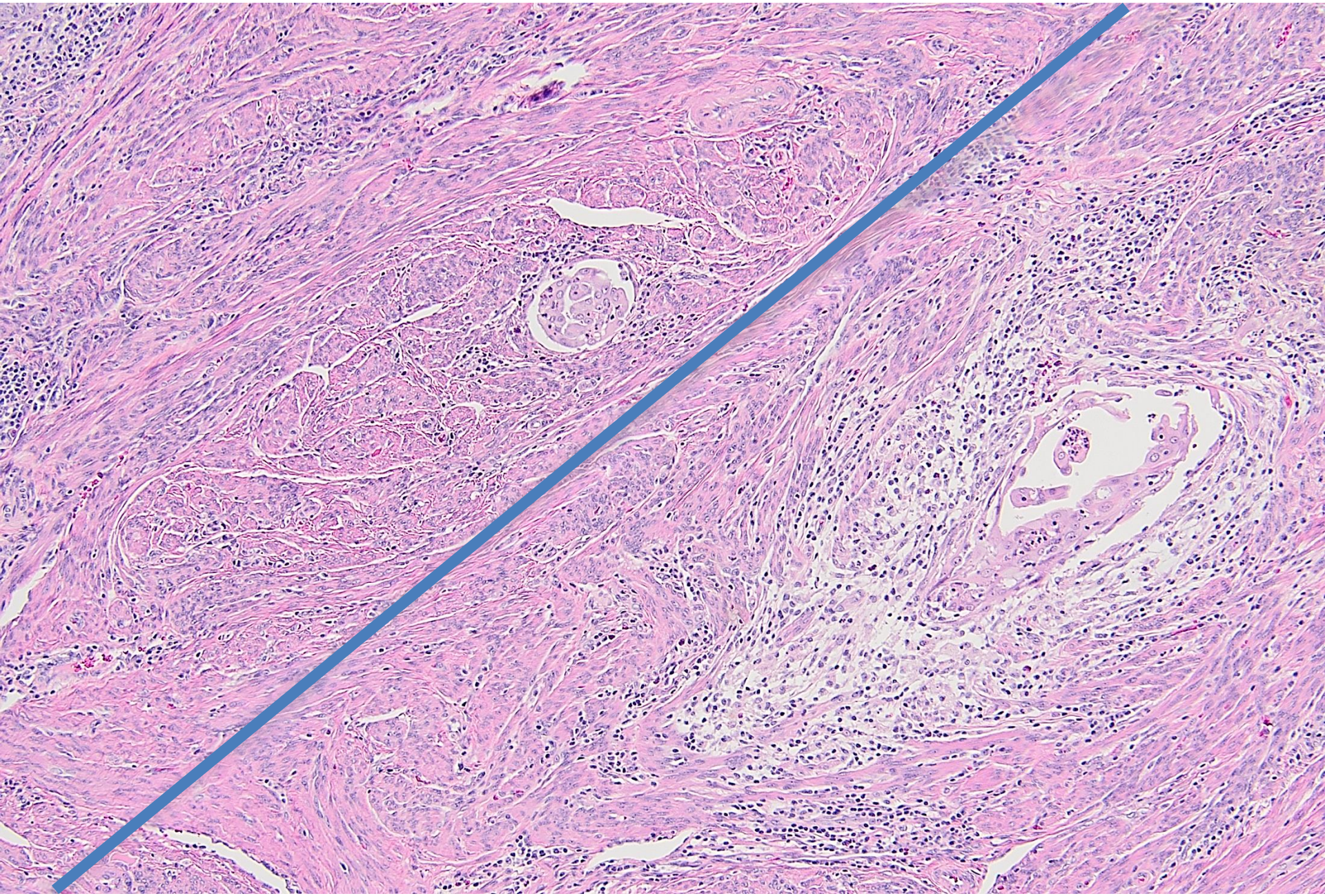
Conventional myometrial invasion

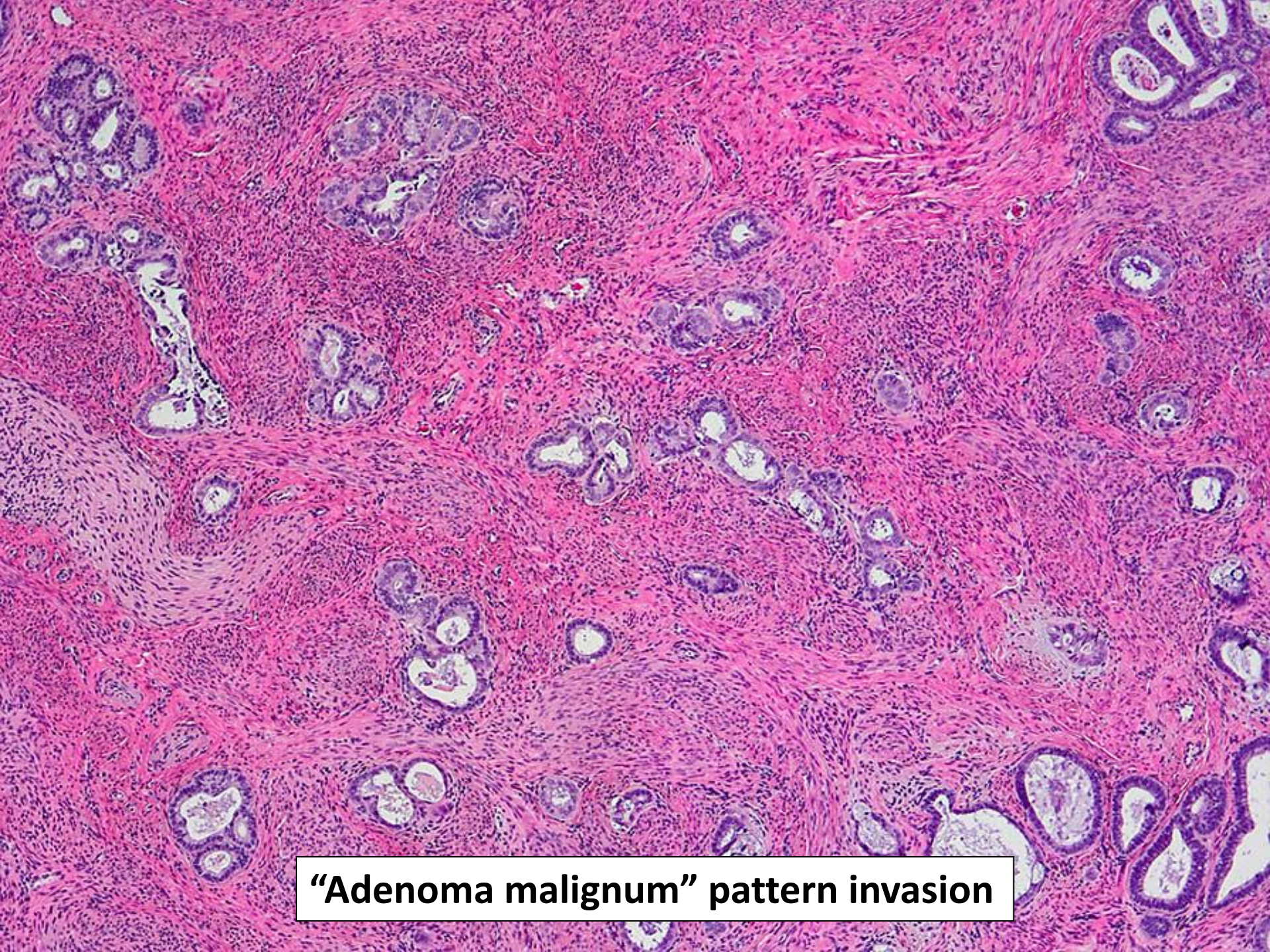


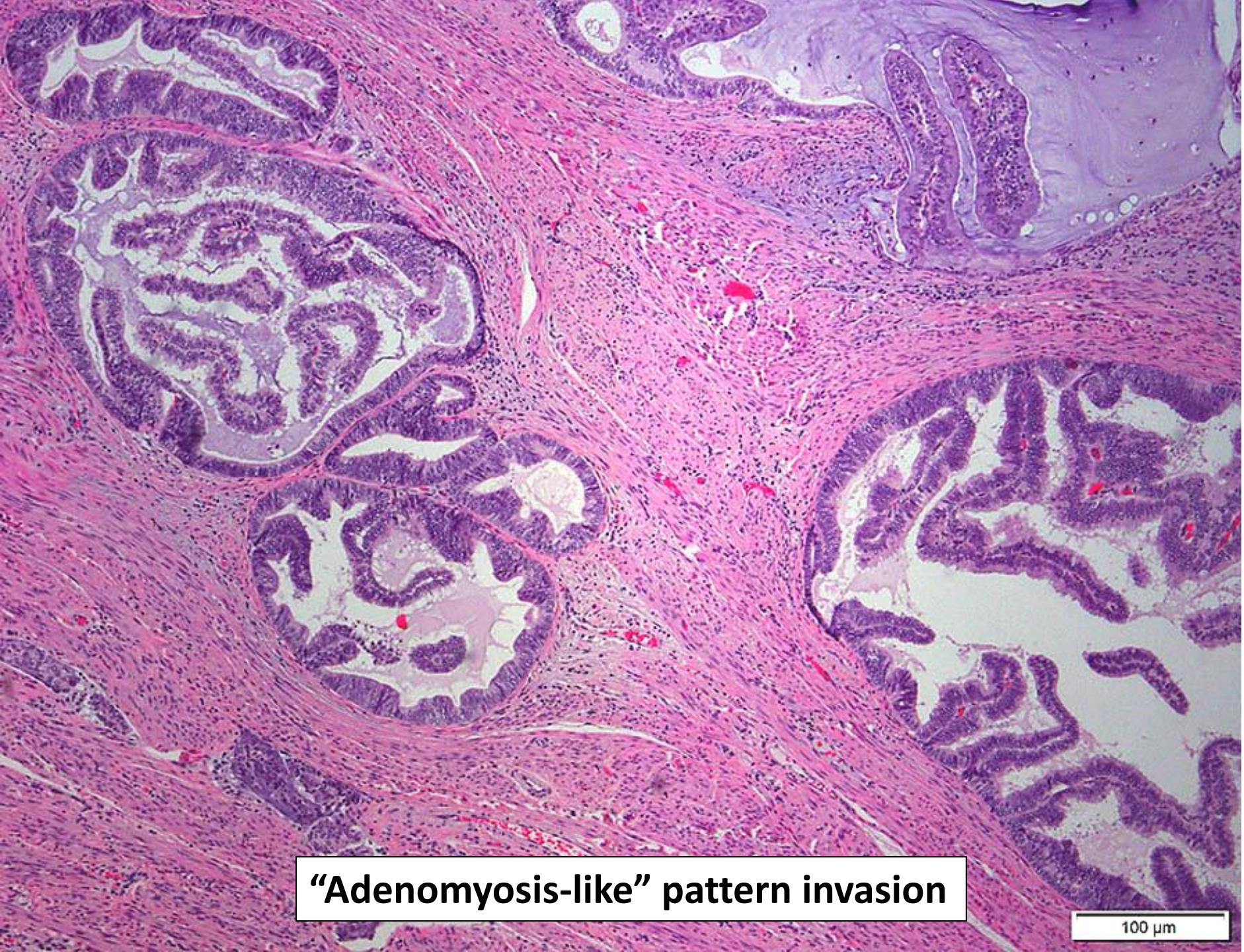

Microcystic/elongated/fragmented
MELF invasion

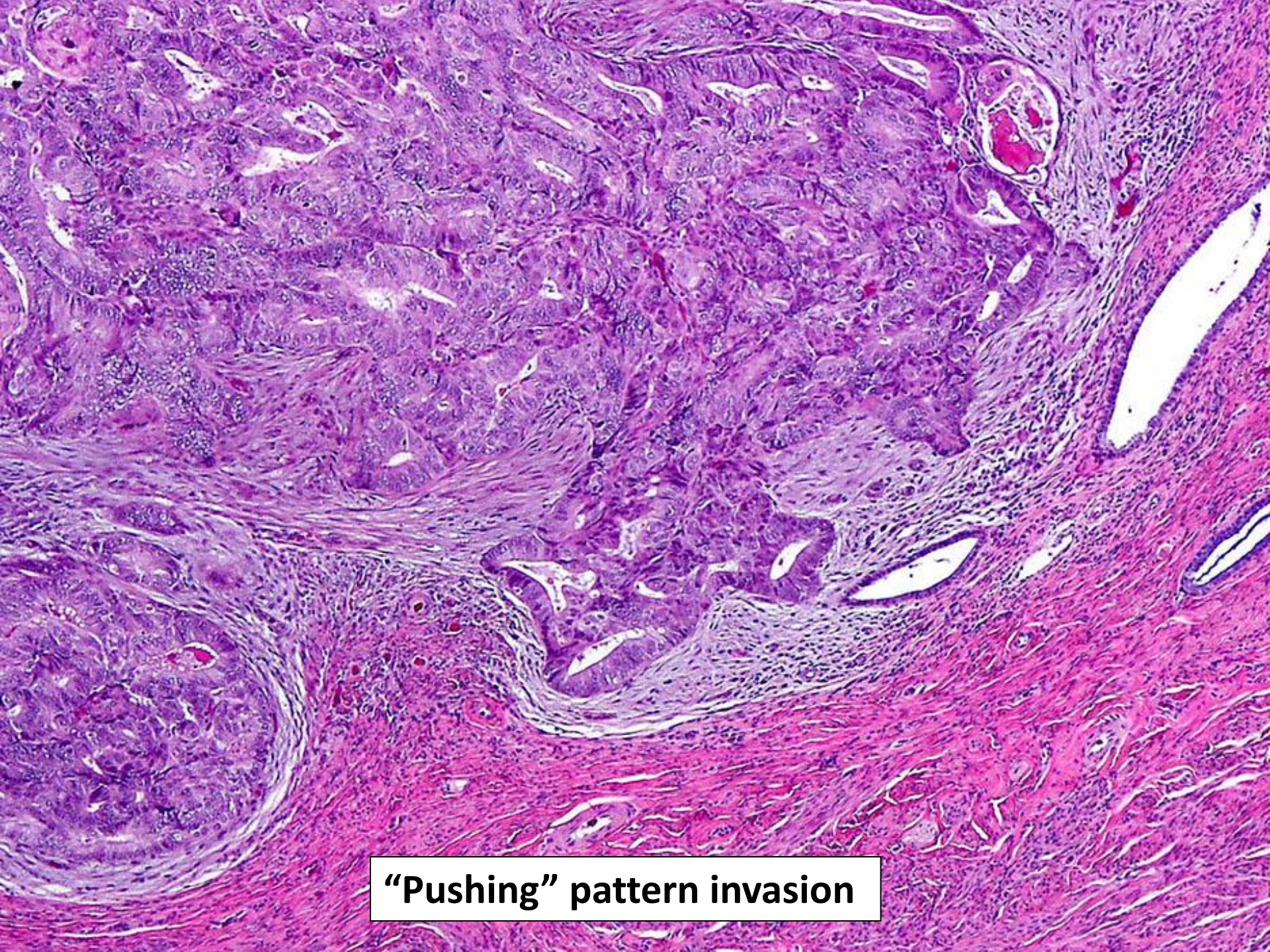
MELF

- Prevalent in FIGO G1 carcinoma and adenomyosis
- May be discontinuous with endomyometrial junction and deep
- Associated with lymphovascular invasion and may resemble lymphovascular invasion
- Associated with deceptive pattern of lymph node involvement
- May not have prognostic signficance

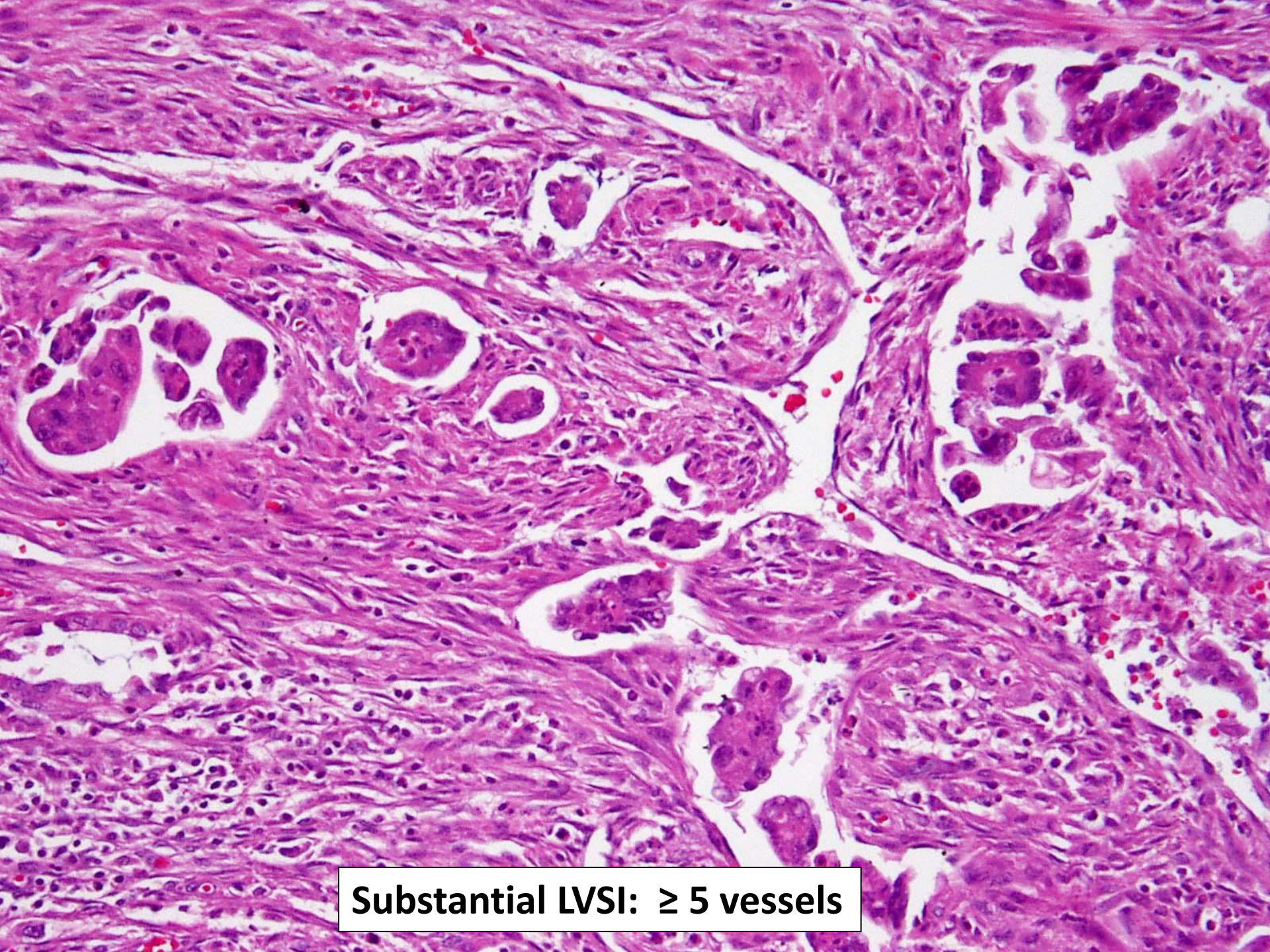


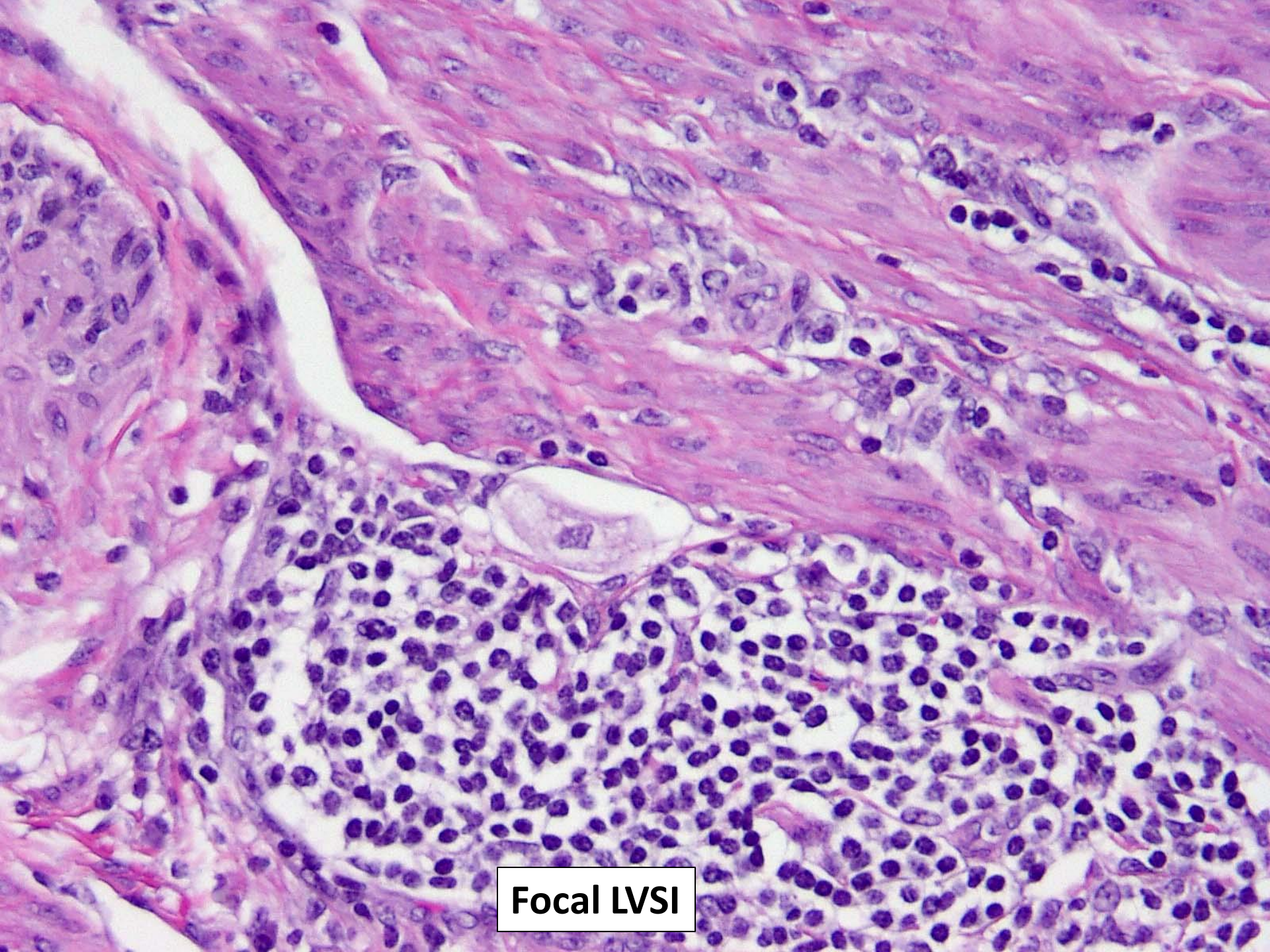

“Adenoma malignum” pattern invasion

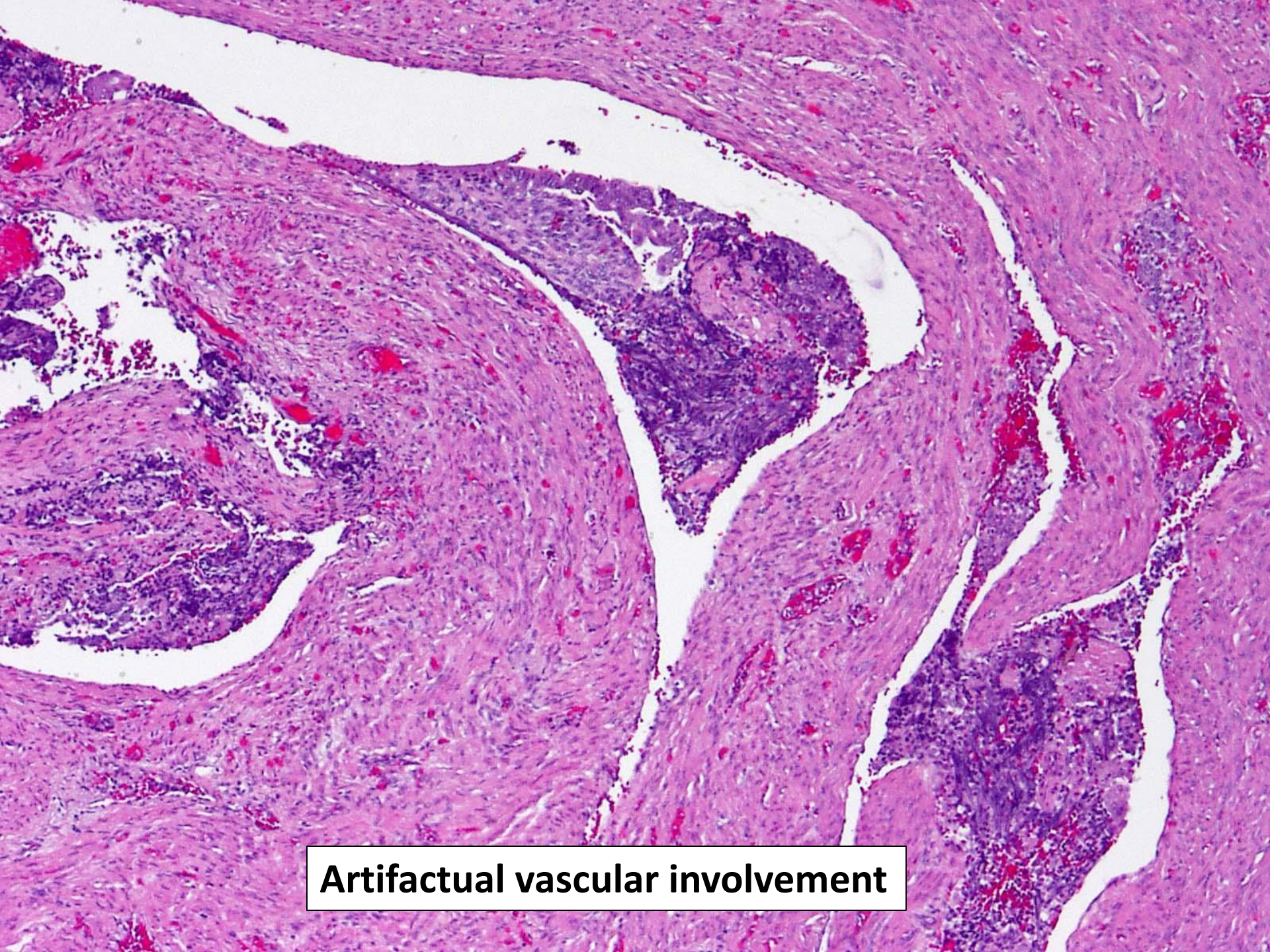

“Adenomyosis-like” pattern invasion
100 µm


“Pushing” pattern invasion

Lymphovascular invasion


Substantial LVSI: ≥ 5 vessels

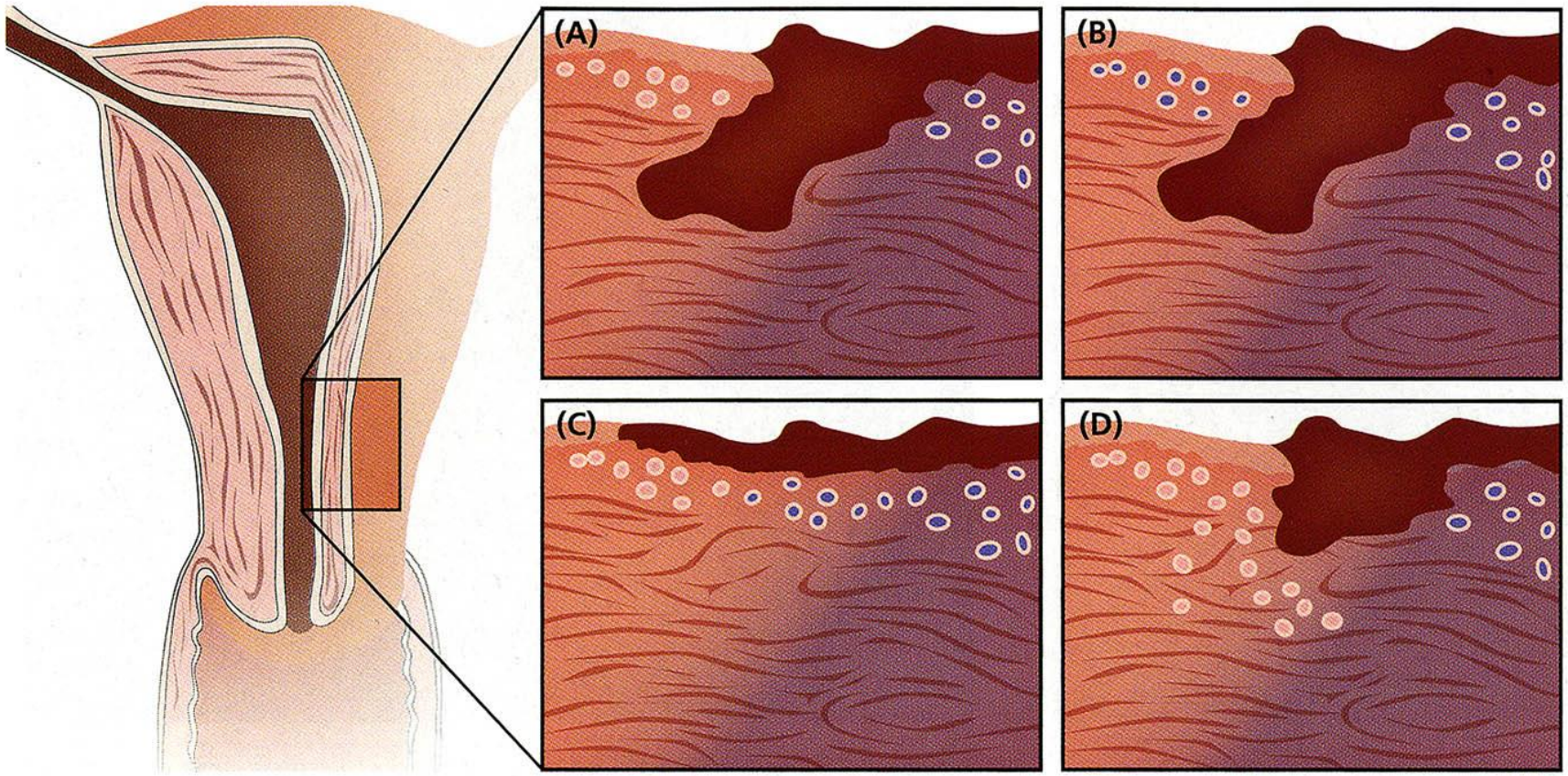

Focal LVSI


Artifactual vascular involvement

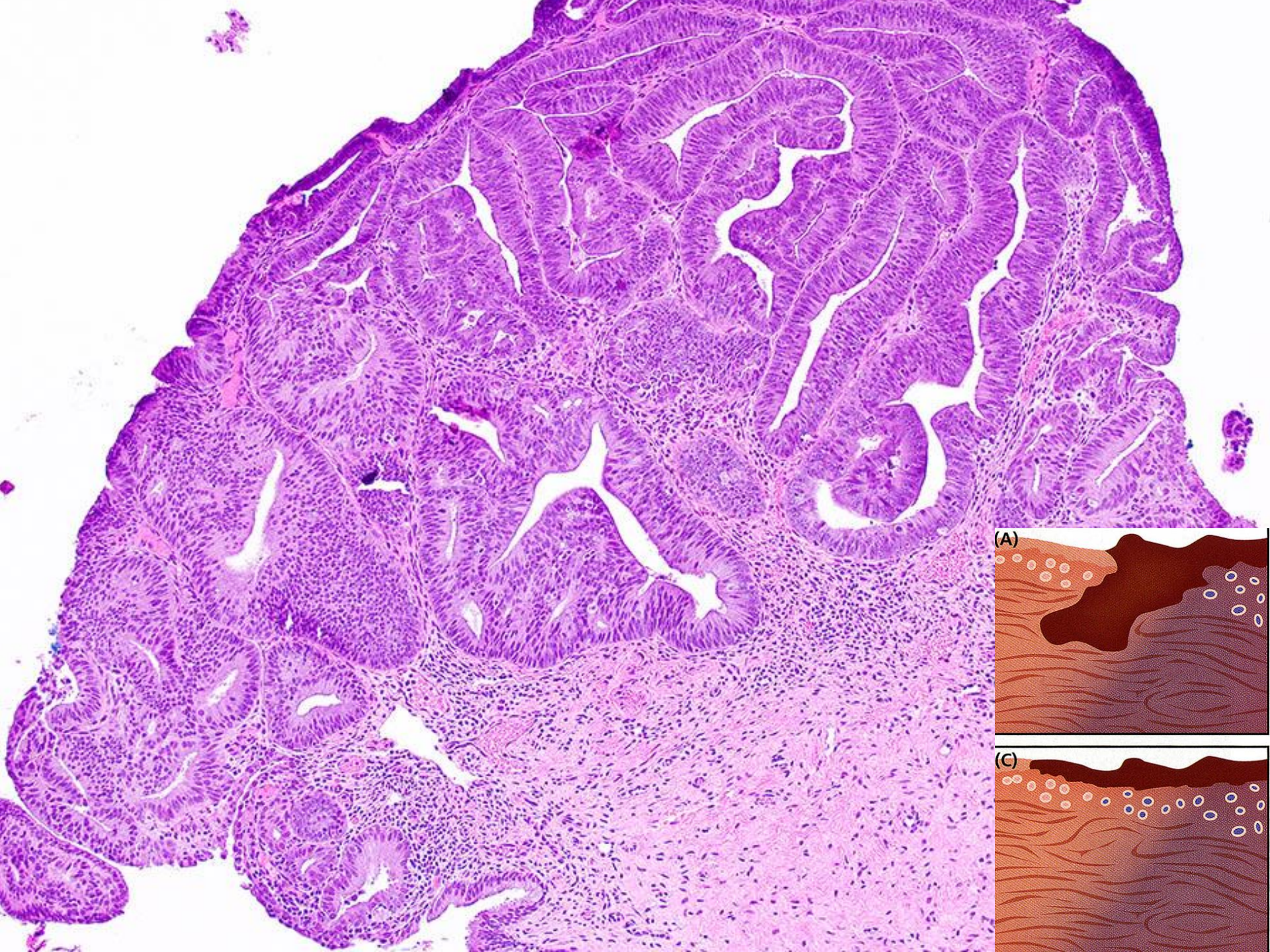
Cervical involvement

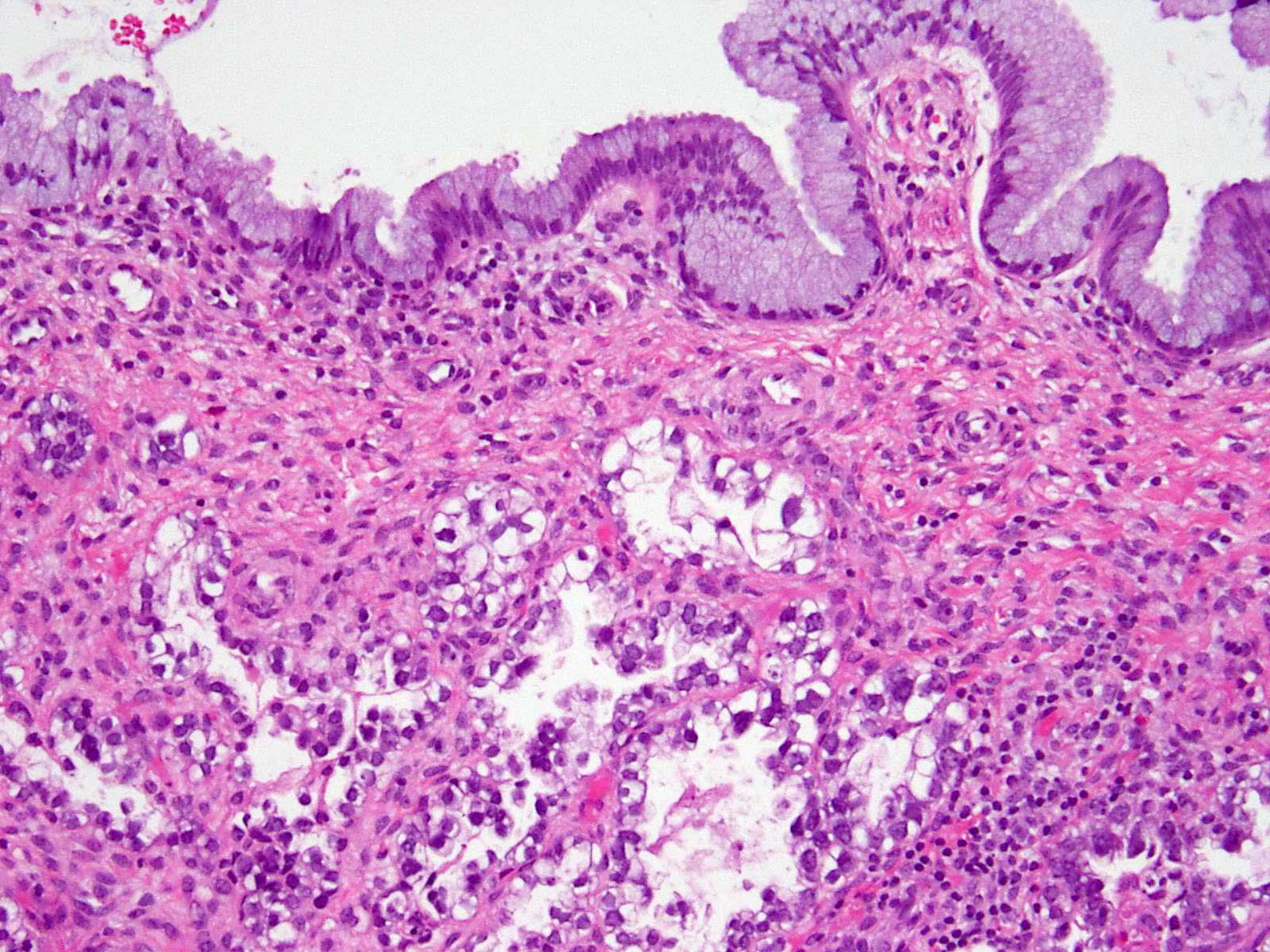
Cervical stromal involvement

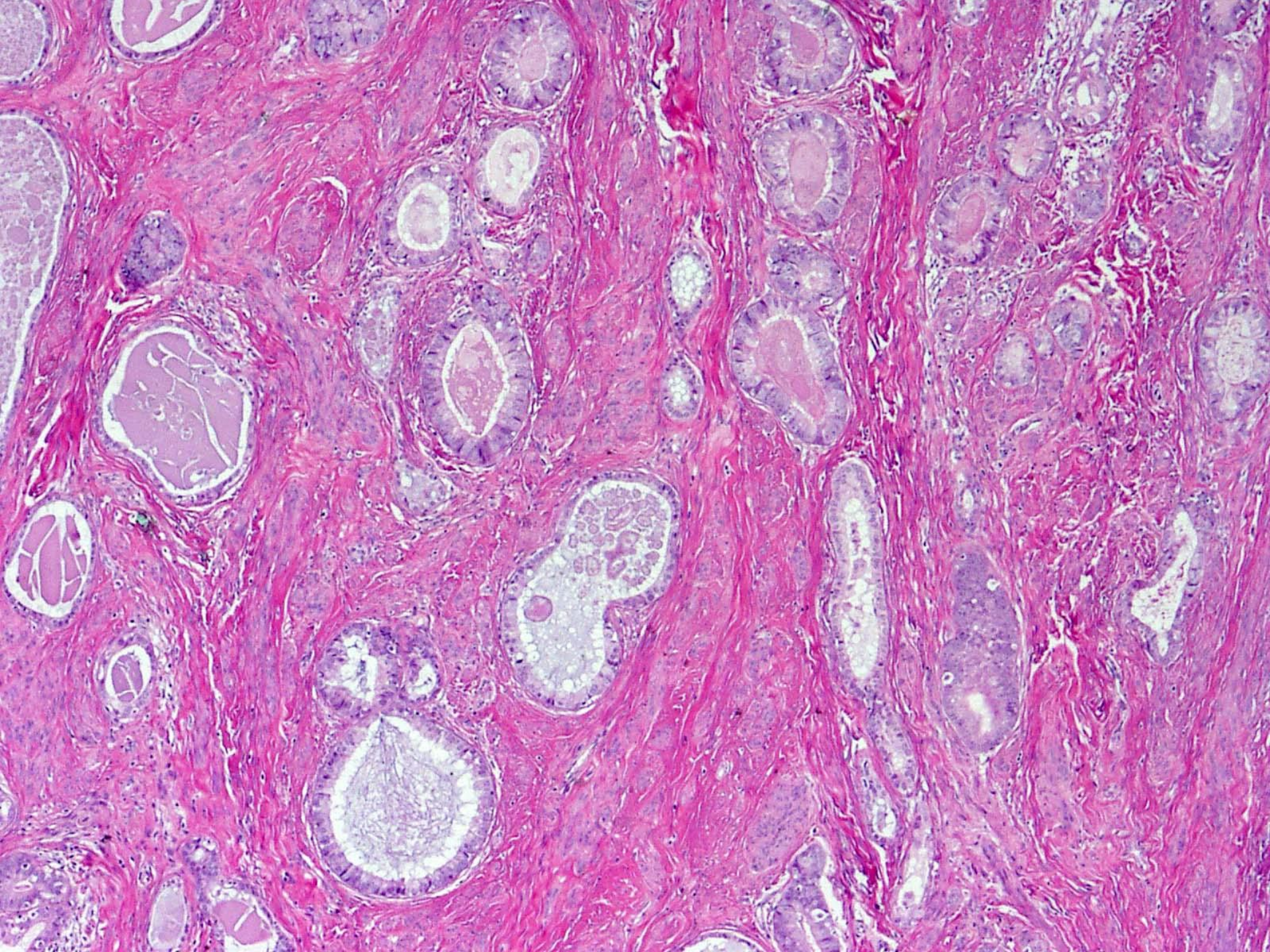
- Undercalls
  - Unfamiliarity with adenoma-malignum pattern invasion
  - Morphologic overlap with benign mimics
- Overcalls
  - Detached tumor
  - Tumor in lower uterine segment
  - Non-invasive tumor



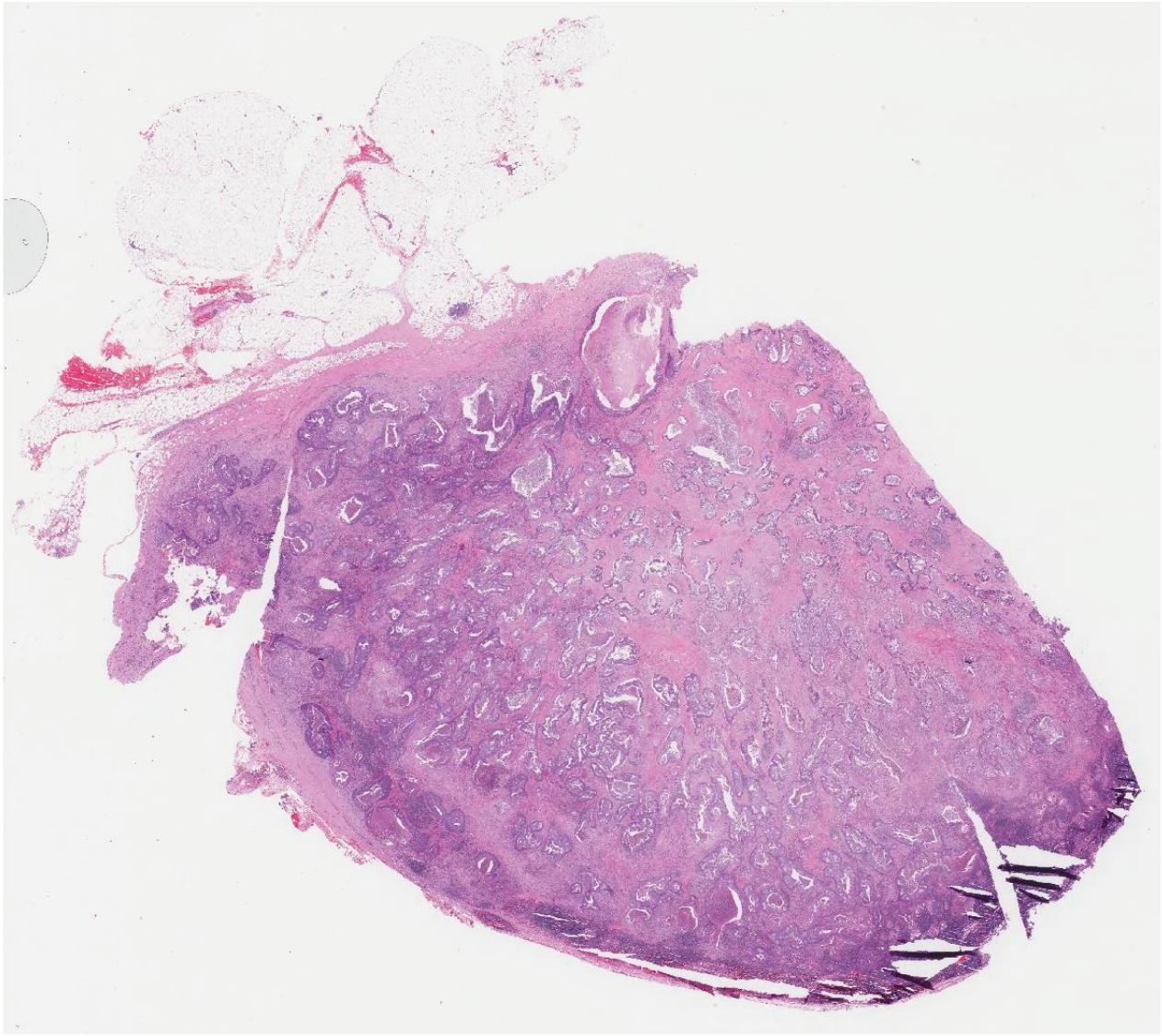
Soslow and Longacre. Uterine Pathology. Cambridge Univ. Press 2012


(A)
(C)



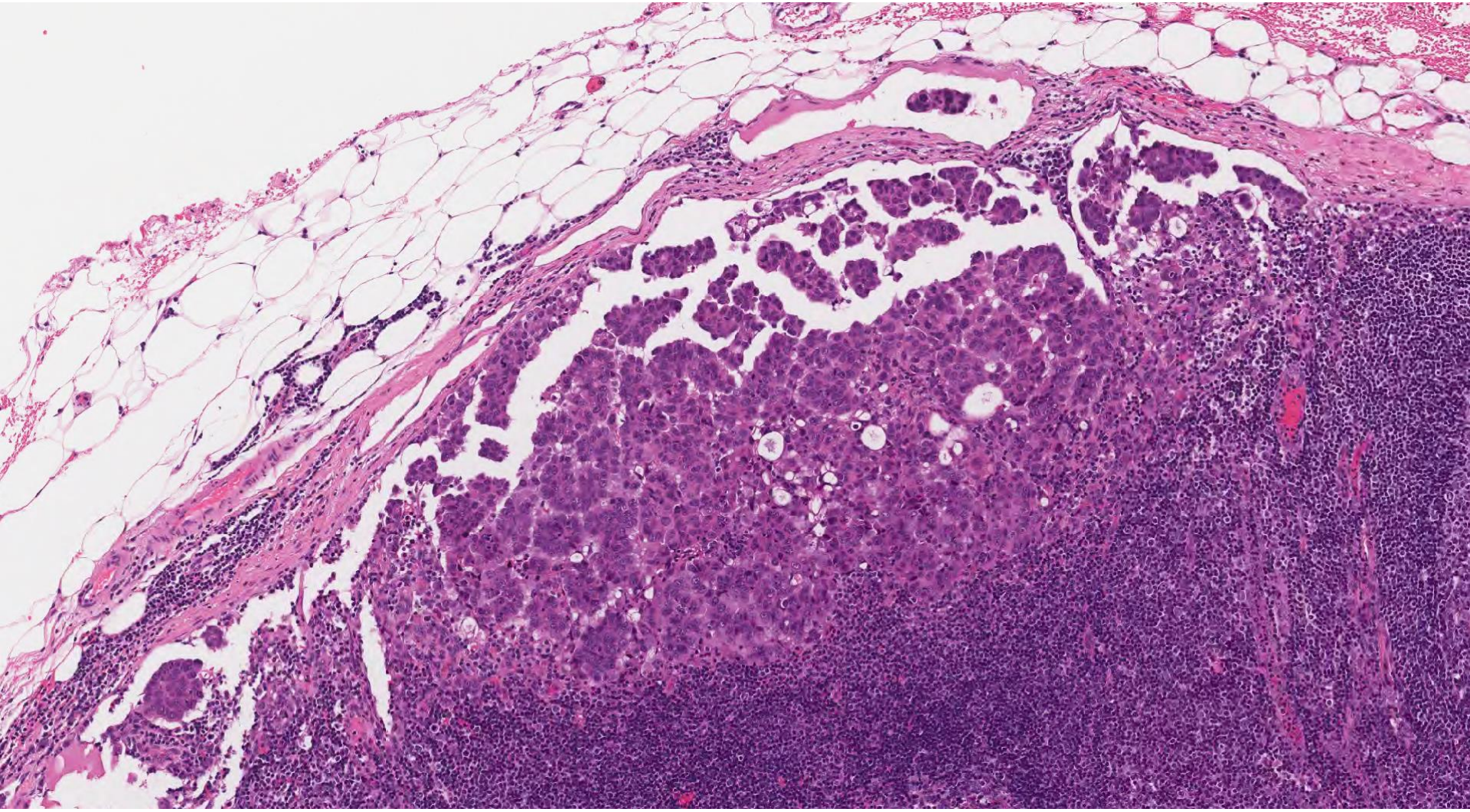


Lymph node metastasis



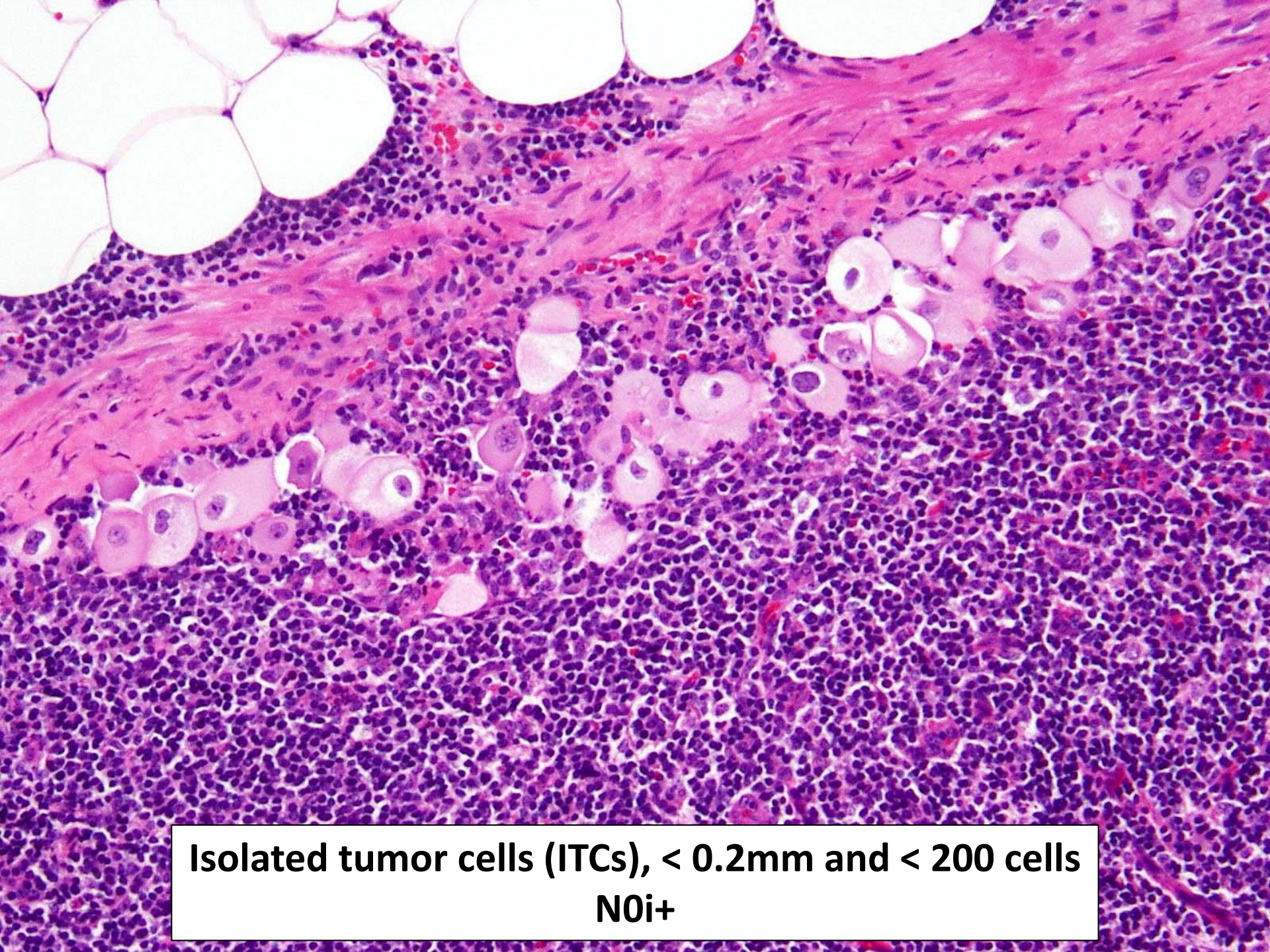
Macrometastasis, > 2mm

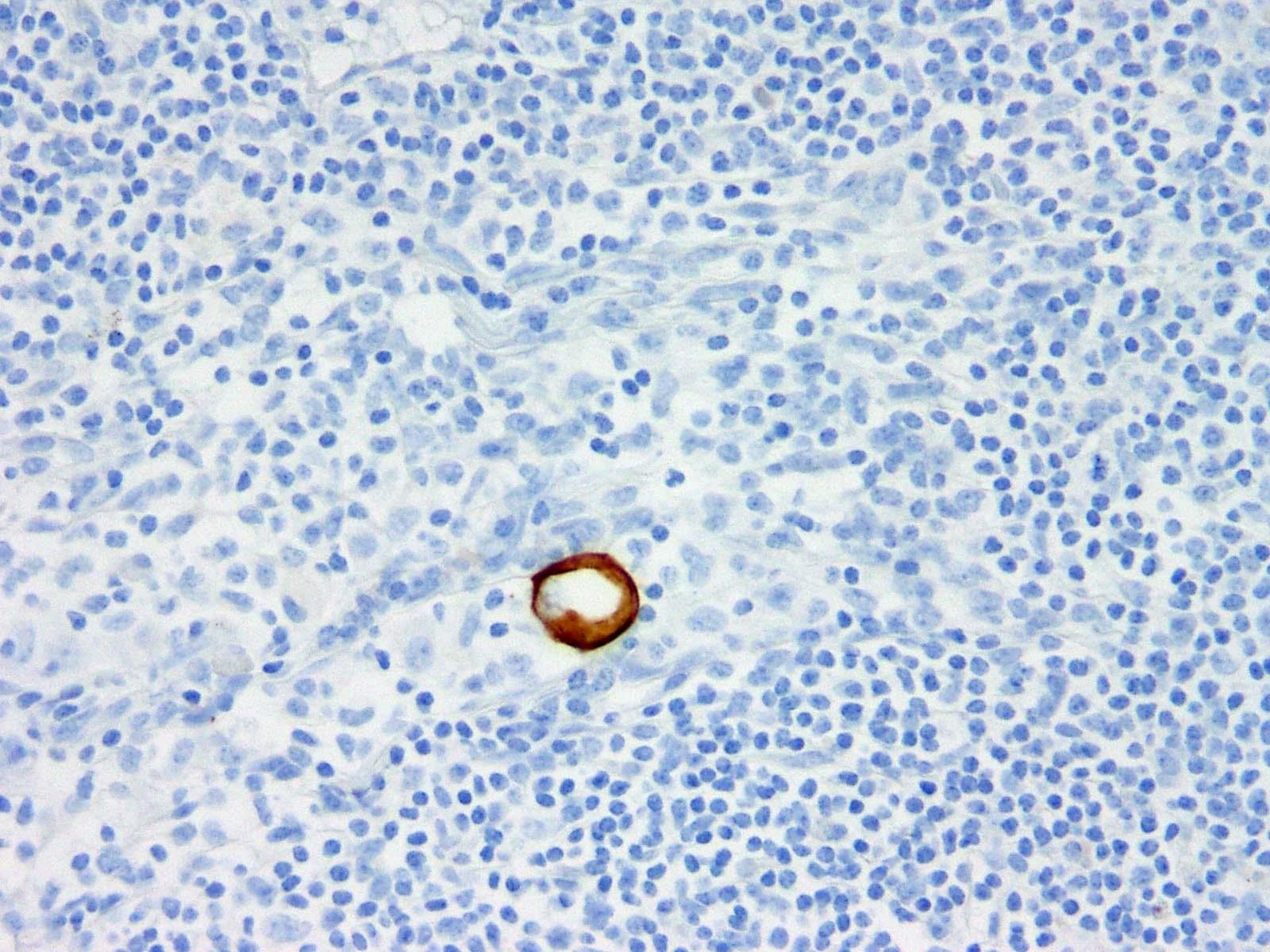
Courtesy of Amy Joehlin-Price



Micrometastasis, 0.2-2mm

Courtesy of Amy Joehlin-Price


Isolated tumor cells (ITCs), < 0.2mm and < 200 cells
N0i+

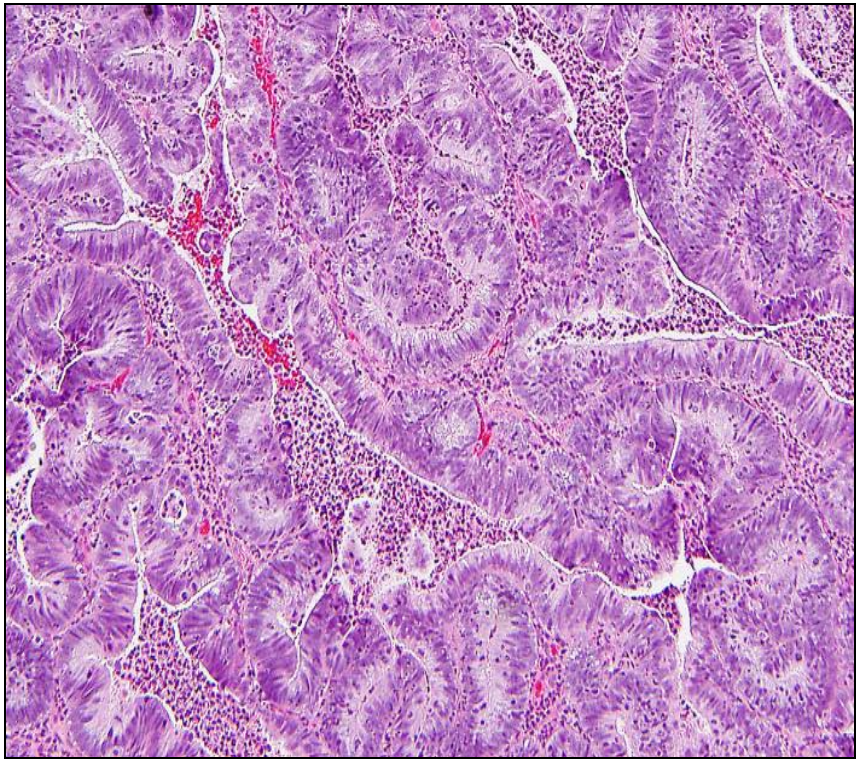


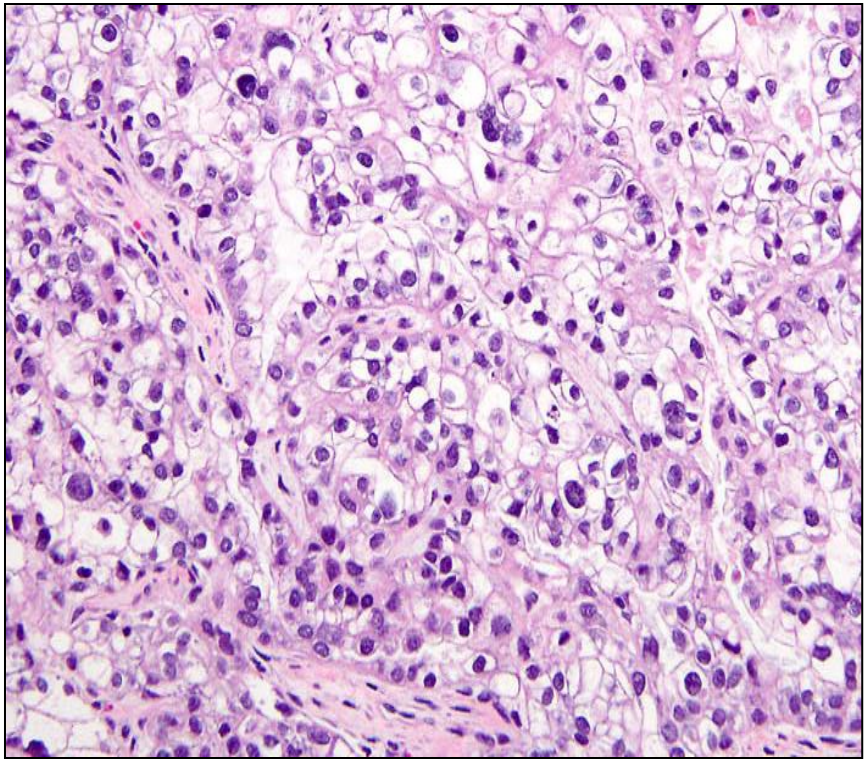
ITCs

- MELF myometrial invasion is associated with single cell and histiocyte-like lymph node metastasis
- Clinical significance is unknown

Adnexal involvement and synchronous tumors (“independent primary tumors”)

Classical synchronous tumors (Tumors of different types, stage each site separately)





Classical synchronous tumors (endometrioid in both sites)

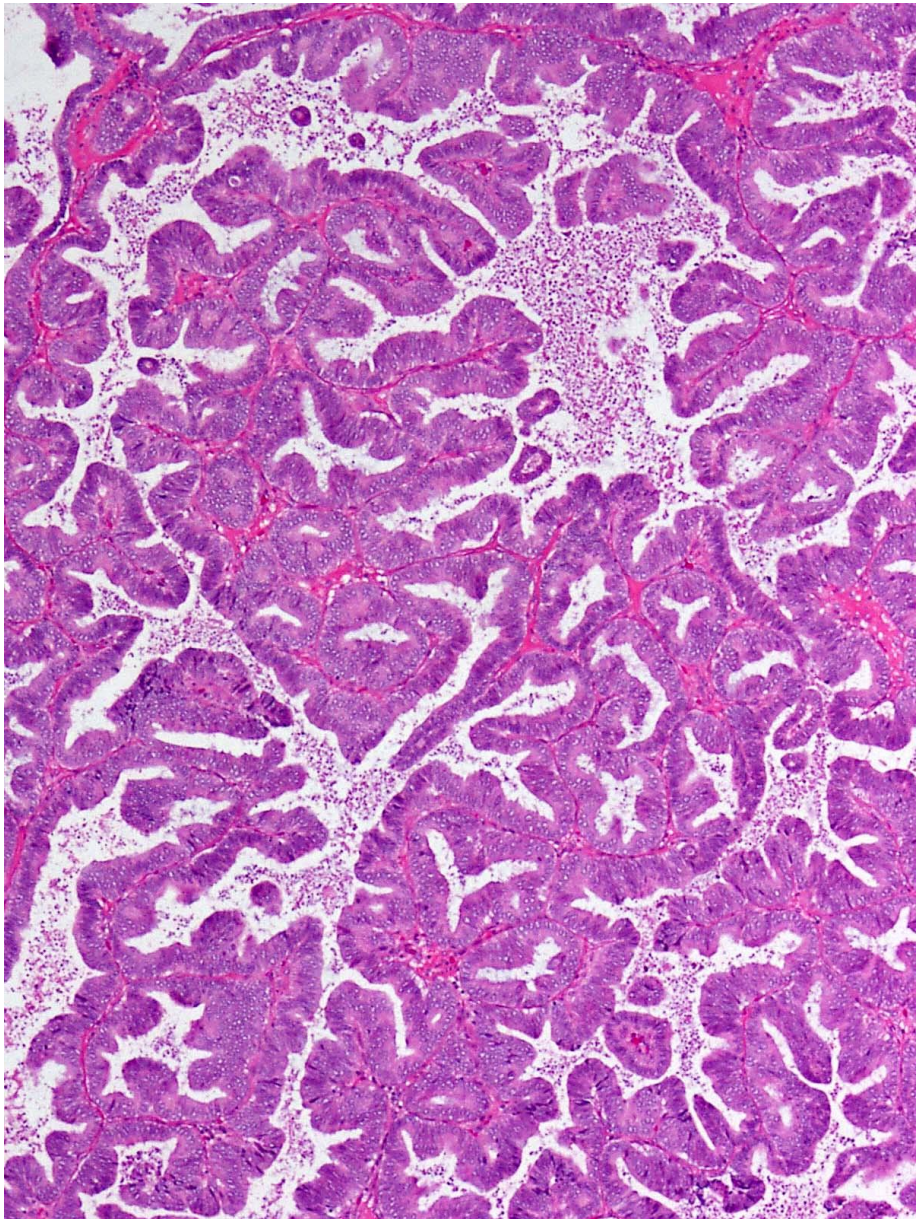
- Endometrium
  - ***Low-grade endometrioid***, no or superficial myometrial invasion, no extensive LVSI
- Ovary
  - ***Low-grade endometrioid***
  - Ovarian capsule uninvolved
  - No pelvic or abdominal metastasis
  - Large, unilateral tumor
  - Expansile invasion
  - Associated endometriosis, Mullerian borderline tumor
  - Patient < 50 yrs

Classical synchronous tumors (endometrioid in both sites)

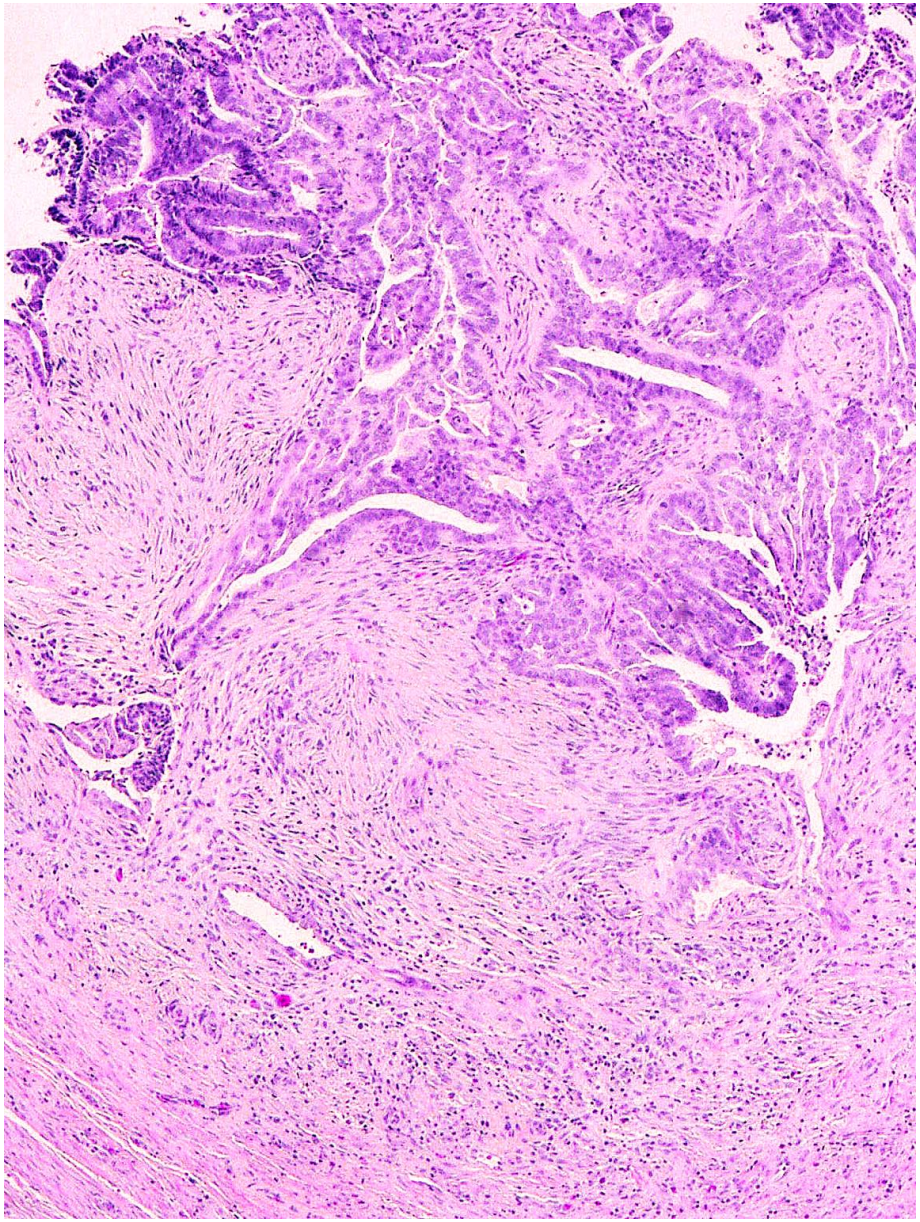
- FIGO 2023 staging considers this low-stage endometrial carcinoma (low risk)

Metastatic endometrioid carcinoma to ovary FIGO 2023 at least IIIA1

- Extraovarian disease
- Bilateral ovarian involvement
- Multinodular configuration, small ovaries
- Ovarian surface involvement
- Destructive ovarian stromal invasion
- No associated endometriosis or Mullerian borderline tumor



Synchronous carcinoma



Metastatic carcinoma

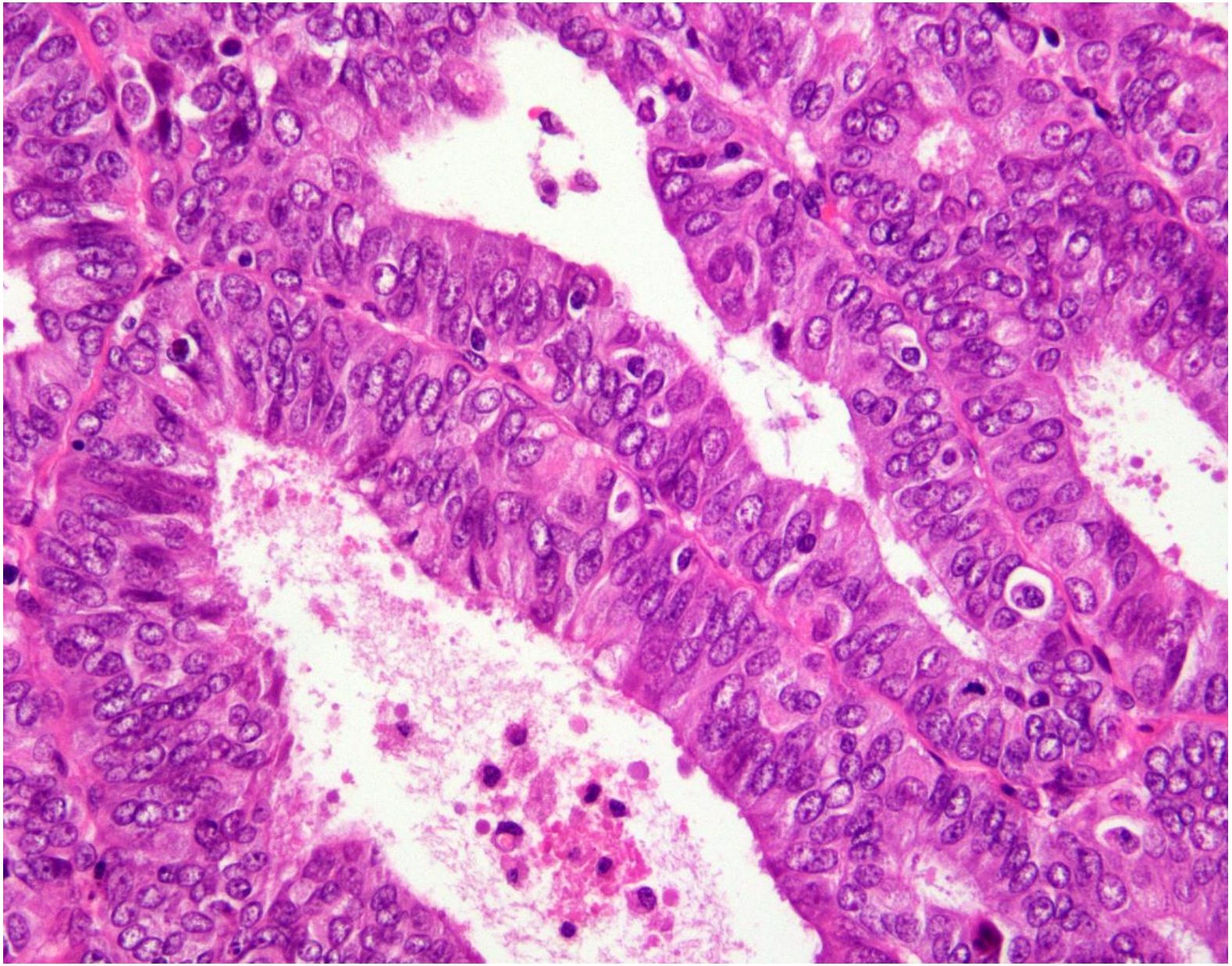
Grading endometrioid carcinoma

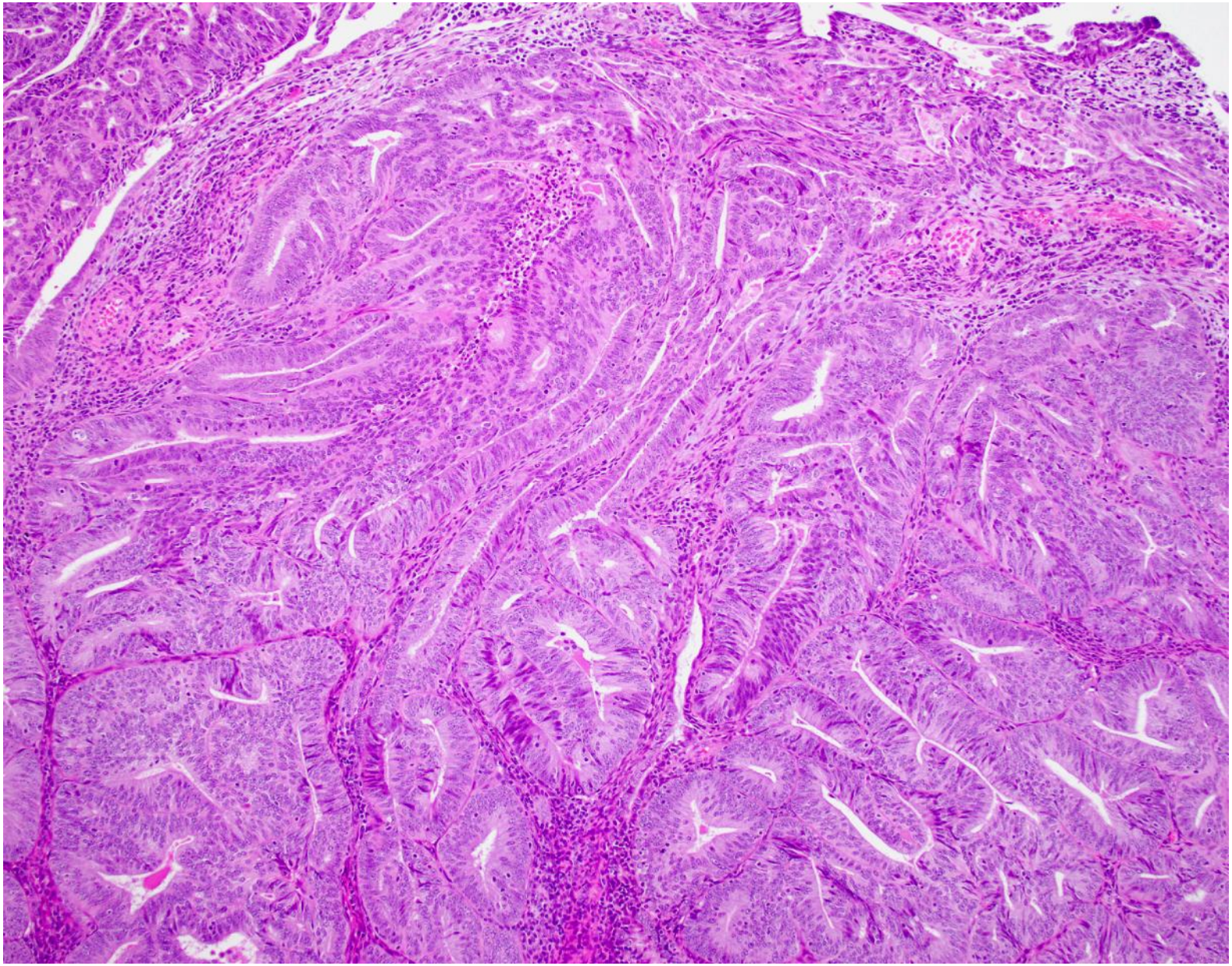
FIGO grading

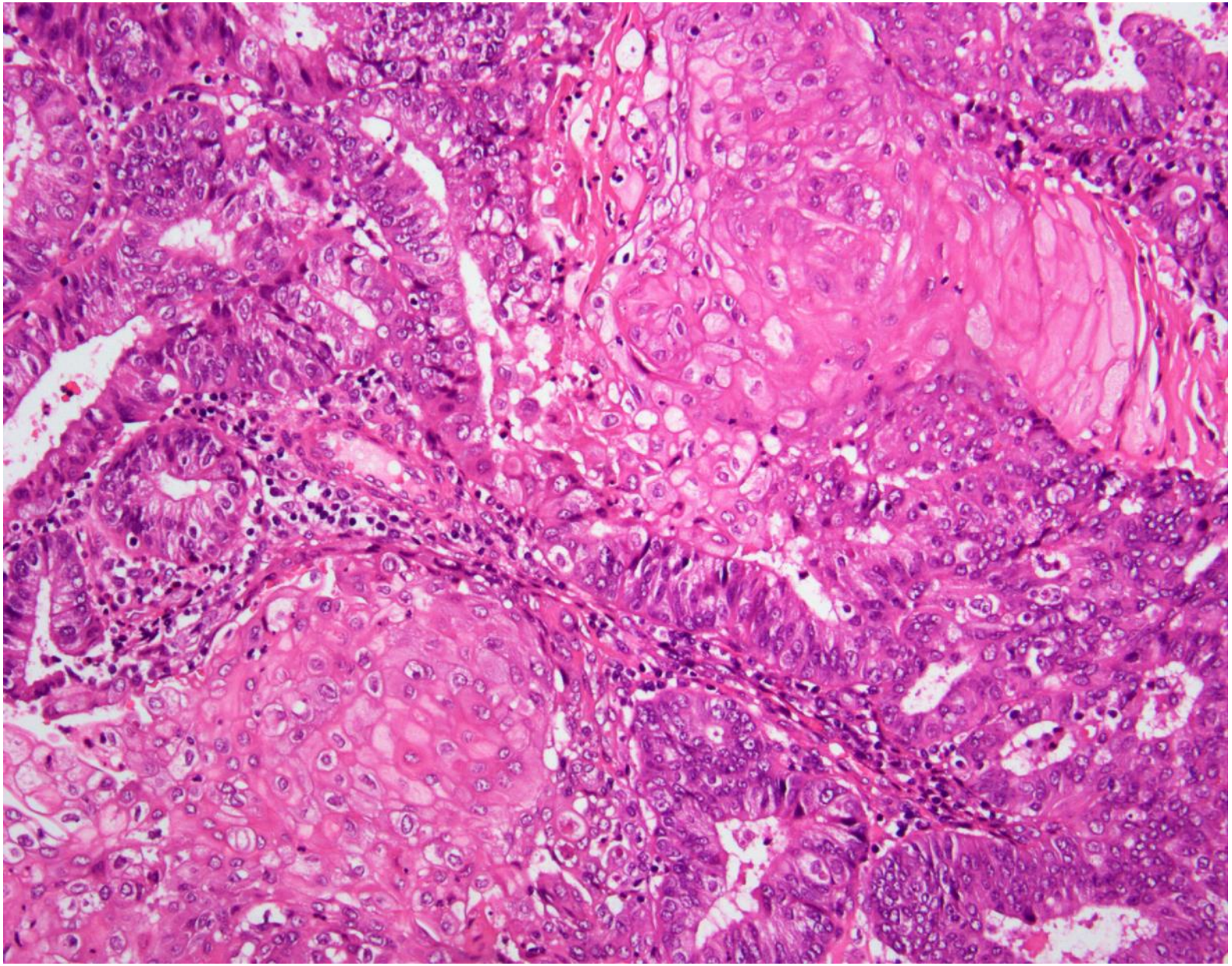
- Applied only to endometrioid carcinomas
- Primarily based on % solid non-squamous architecture
- Not used:
  - Clear cell
  - Serous
  - Mixed epithelial
  - Undifferentiated
  - Carcinosarcoma
  - Morphologically ambiguous tumors

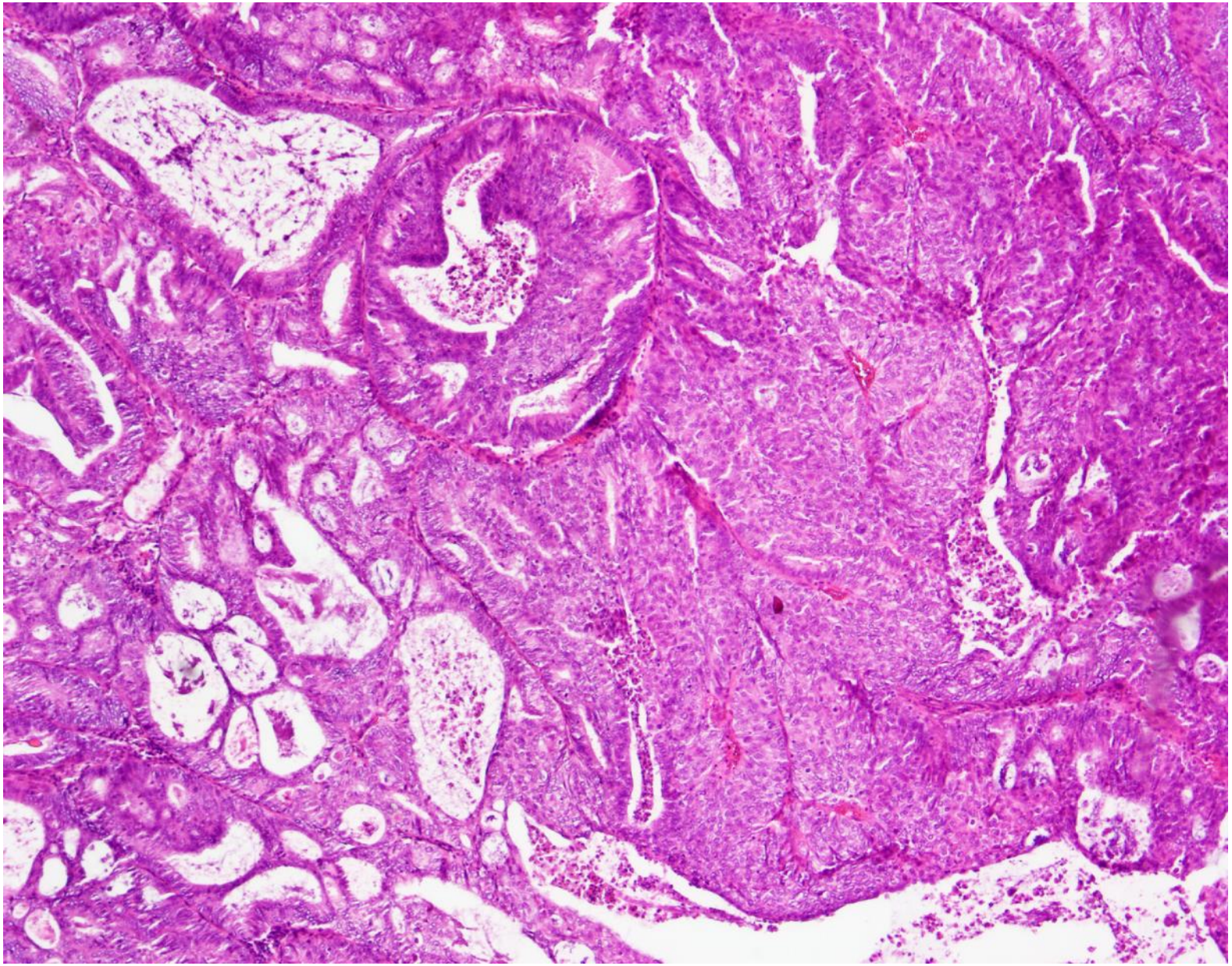
FIGO grade

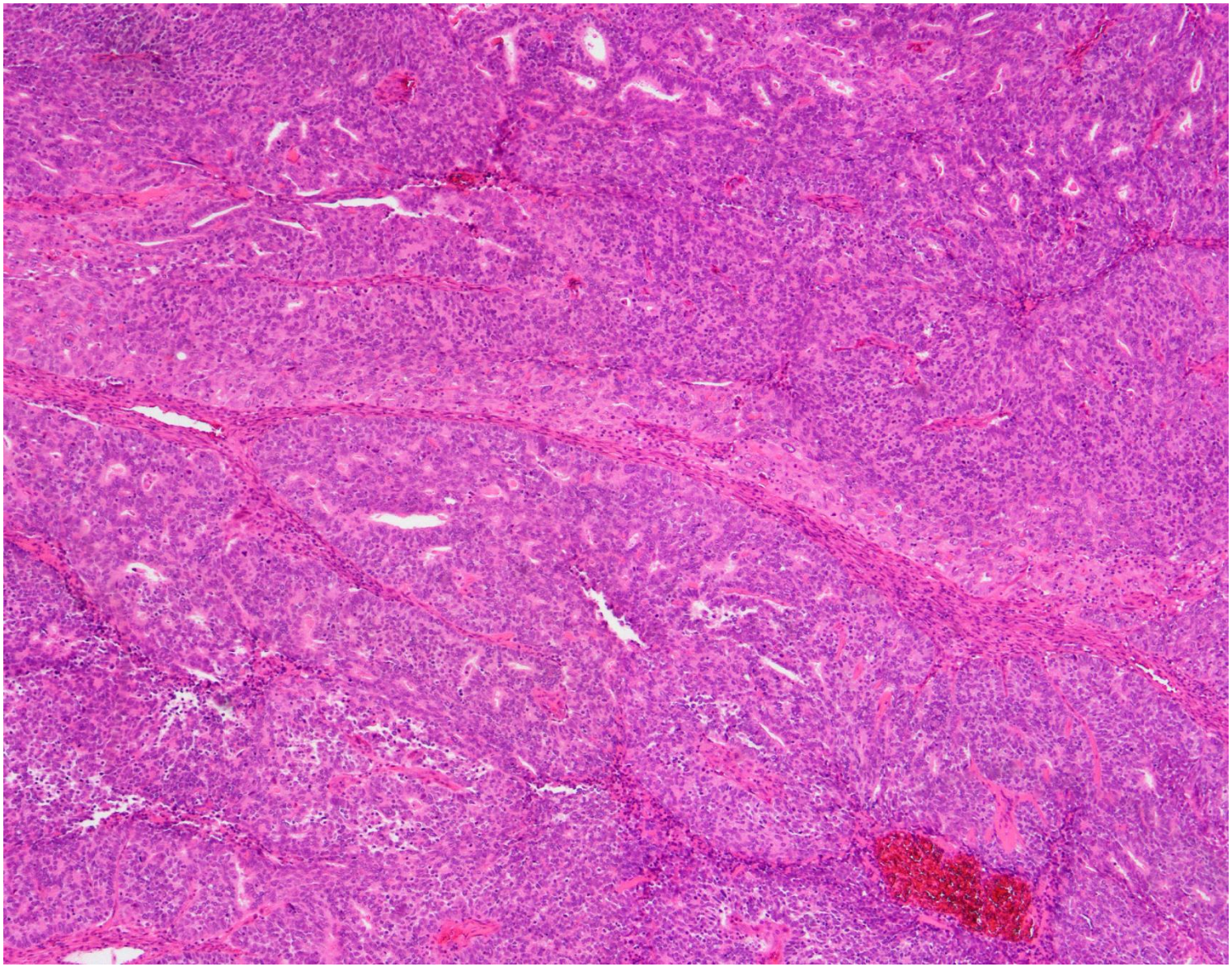
- Associated with
  - Depth of myometrial invasion
  - Lymph node metastasis
  - Clinical outcomes (usually, but not always!)

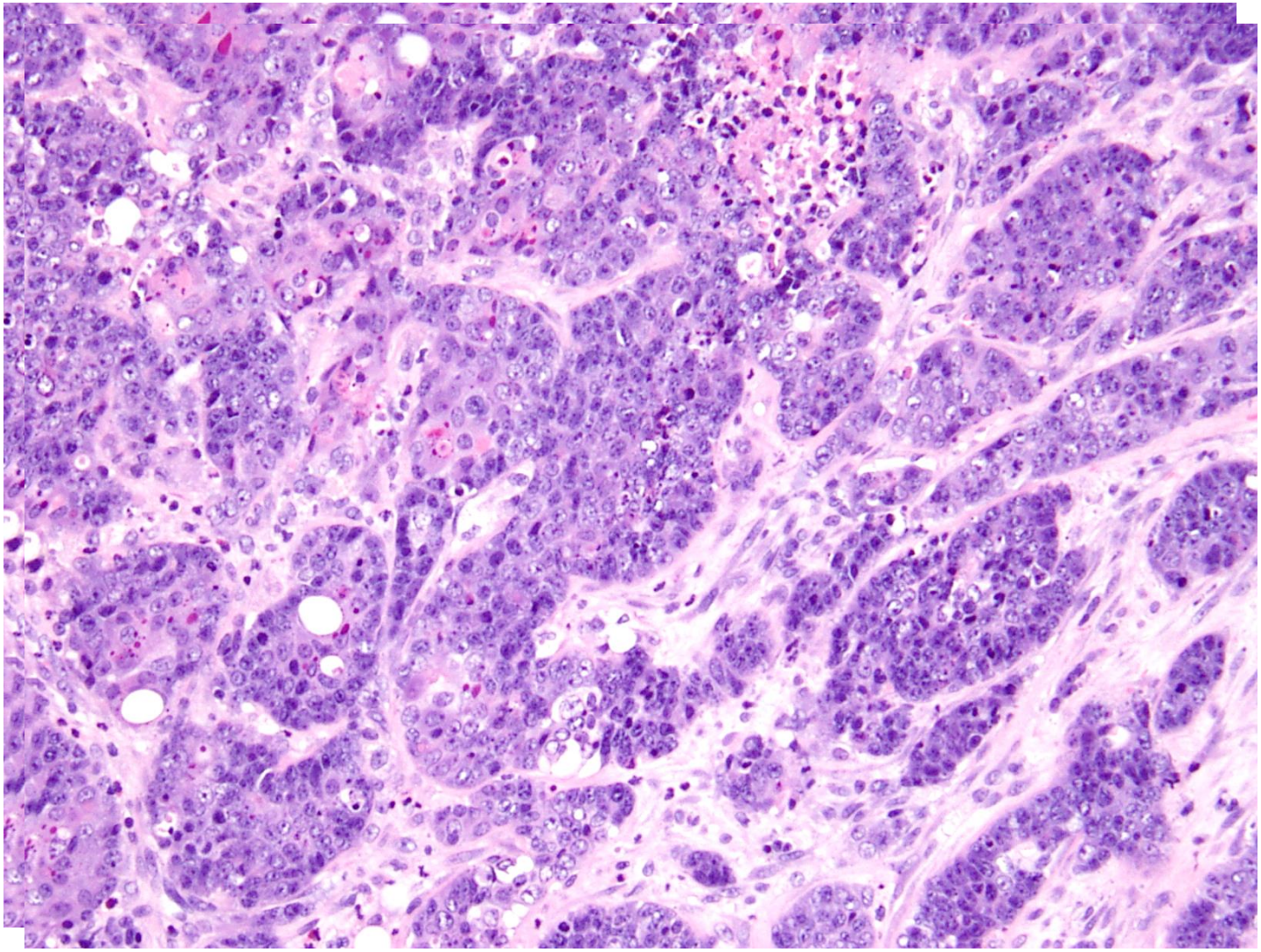






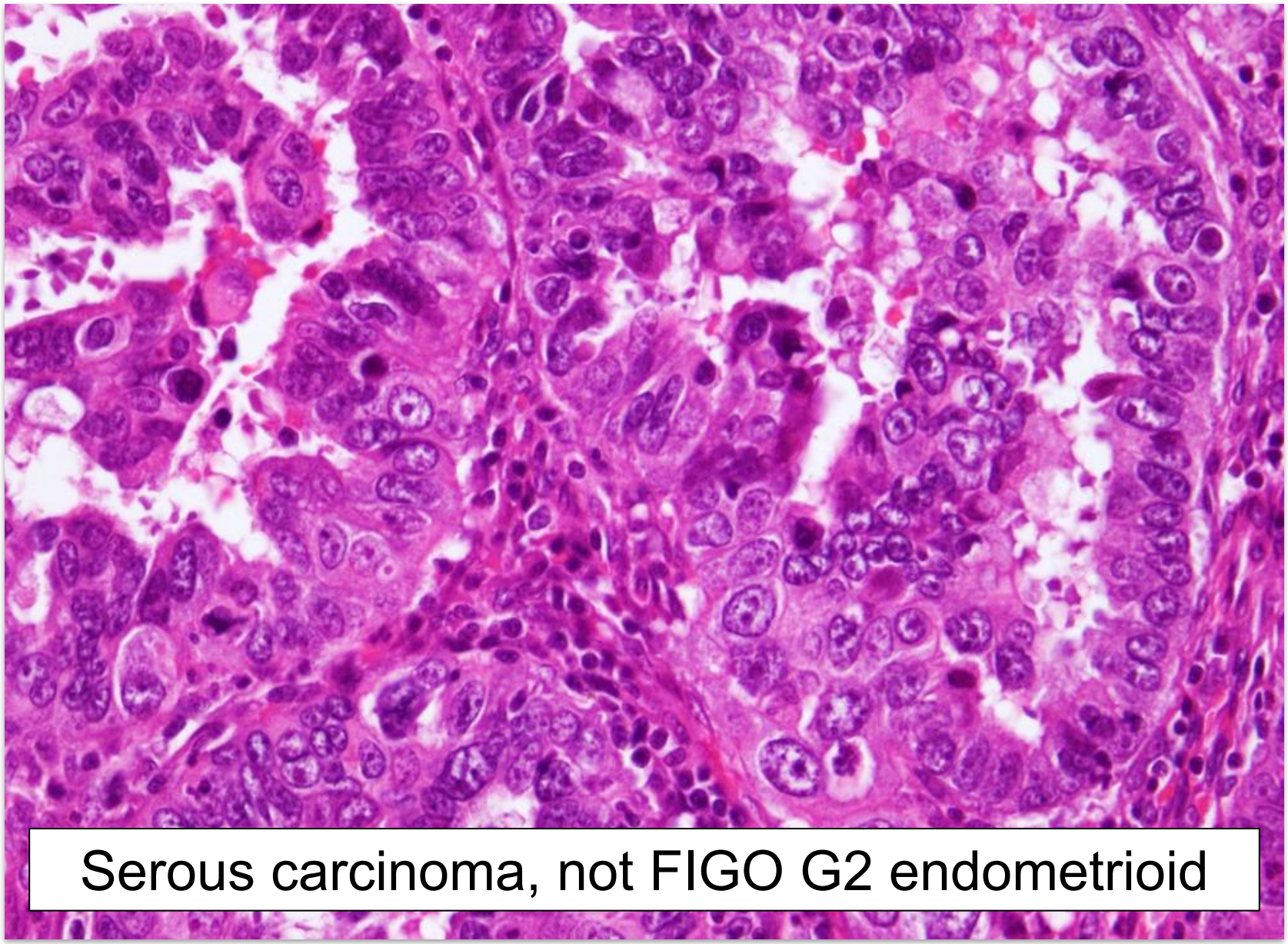


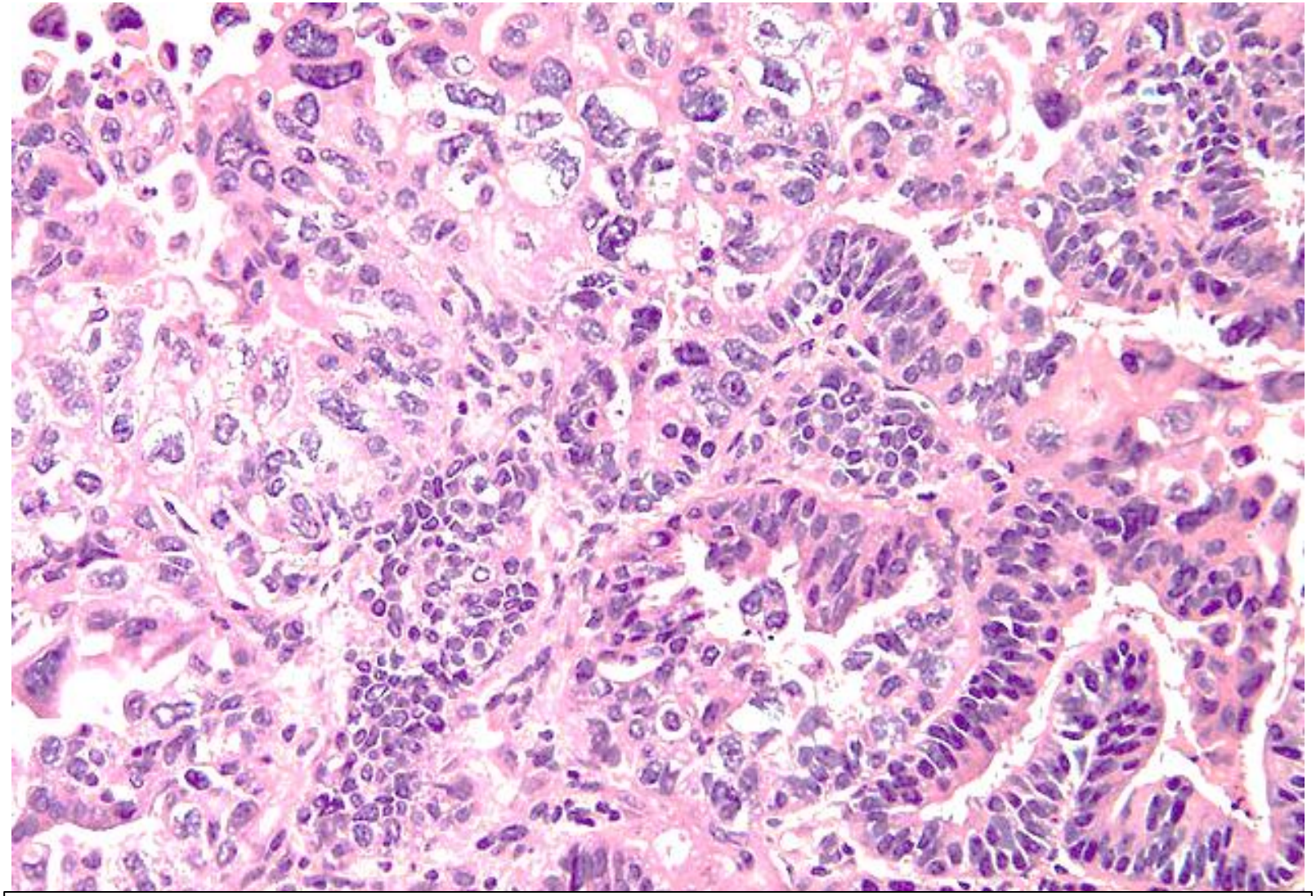




FIGO grade provisos

- High nuclear grade can advance the architectural grade ***but***
  - Carcinoma must be endometrioid (serous and clear cell excluded)
  - High nuclear grade must be present in large portions of the tumor and be easily recognizable


Serous carcinoma, not FIGO G2 endometrioid

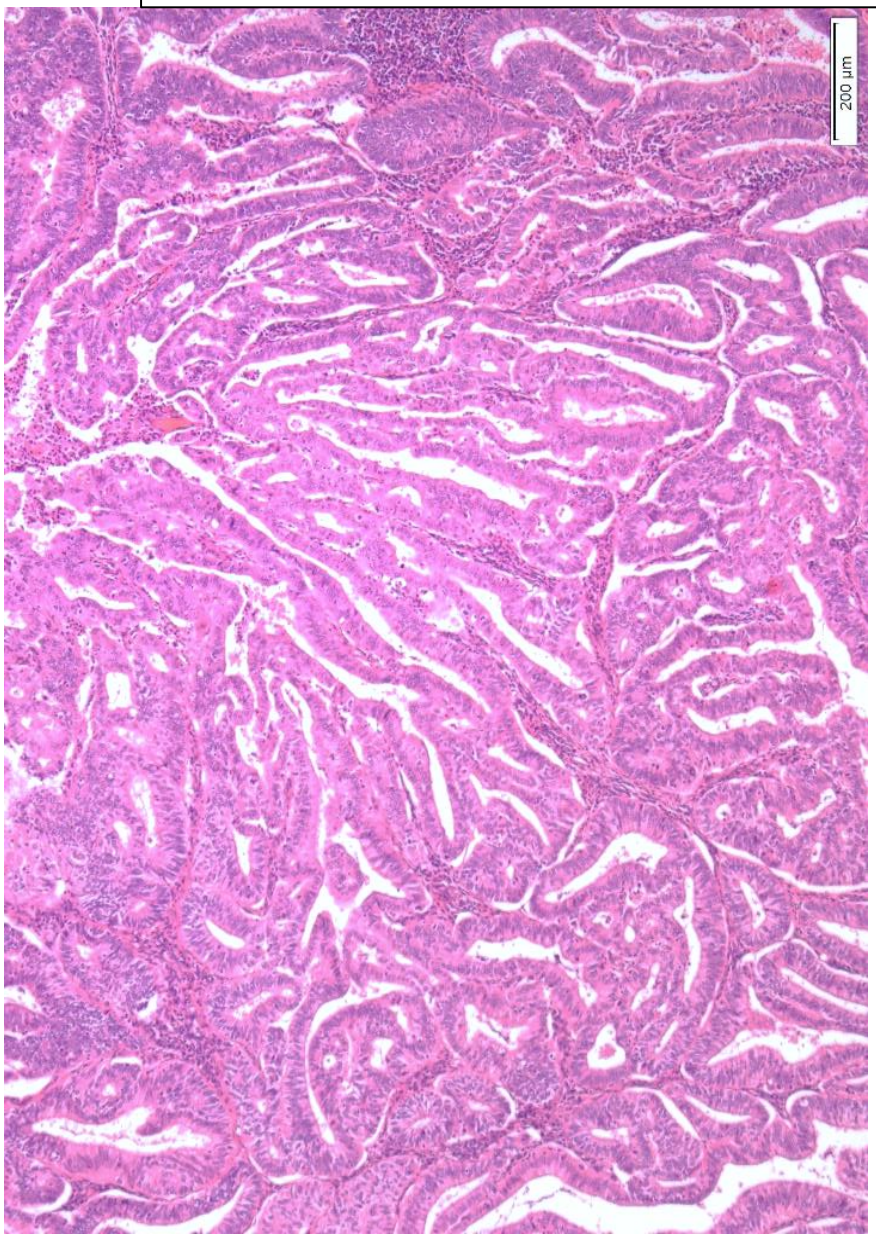


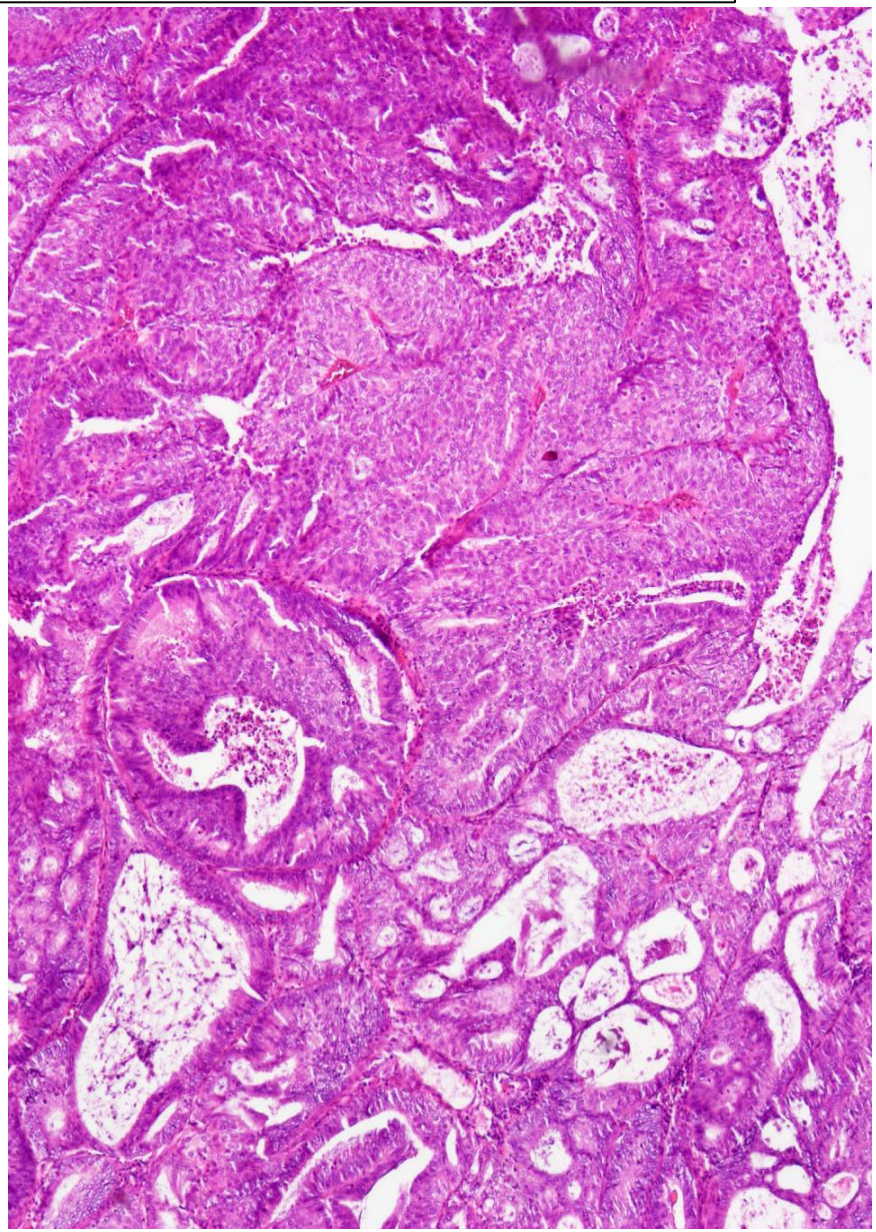
Endometrioid carcinoma, *POLE* mut

Other grading schemes

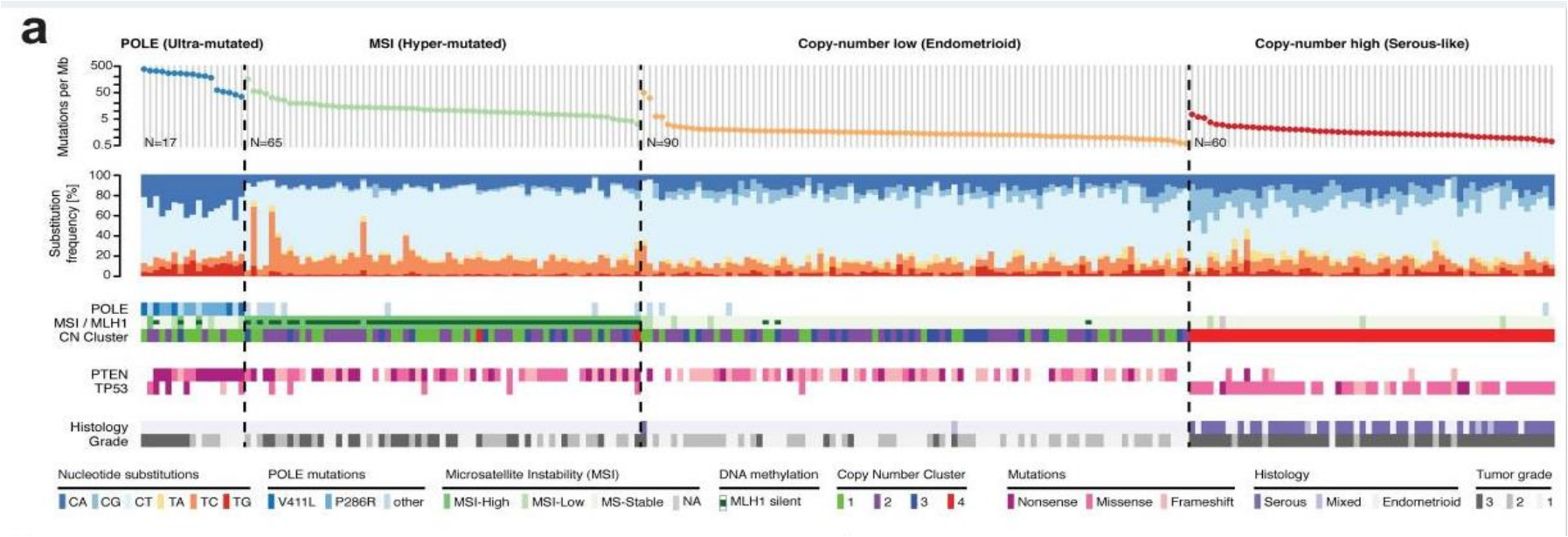
- Endometrioid carcinoma divides into two main low- and high-risk prognostic groups
  - Lax/Kurman
    - Solid architecture; myometrial invasion pattern; necrosis
  - Gilks
    - Solid or papillary architecture; nuclear atypia; mitotic index
  - **Binary FIGO**
    - FIGO 1+2= low-grade
    - FIGO 3= high-grade

“Low grade” endometrioid carcinoma





Molecular classification of endometrioid and serous carcinomas

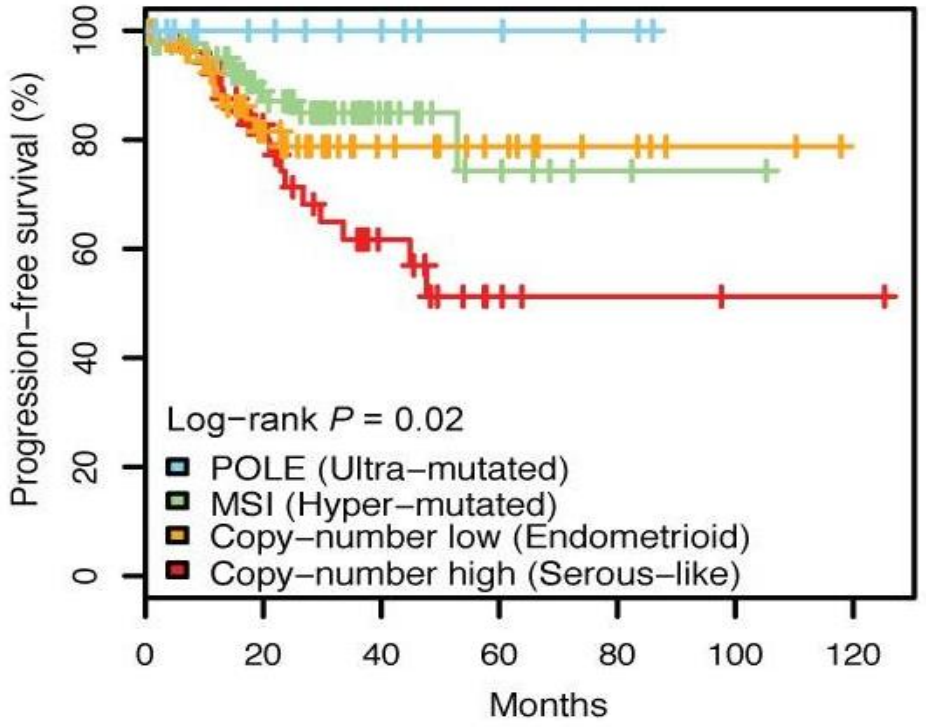


TCGA study: Integrated Genomic Characterization of Endometrial Carcinoma

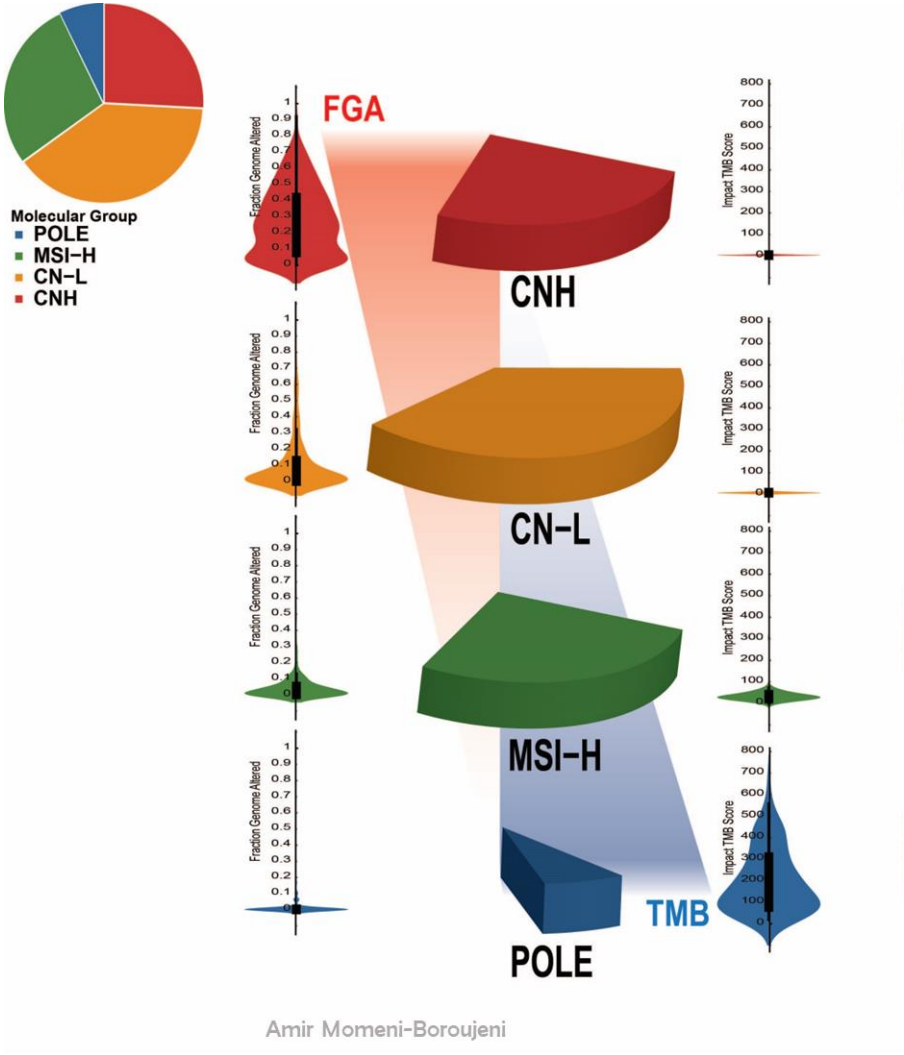
Nature. 2013 May 2;497(7447):67-73

Advantages of molecular classification

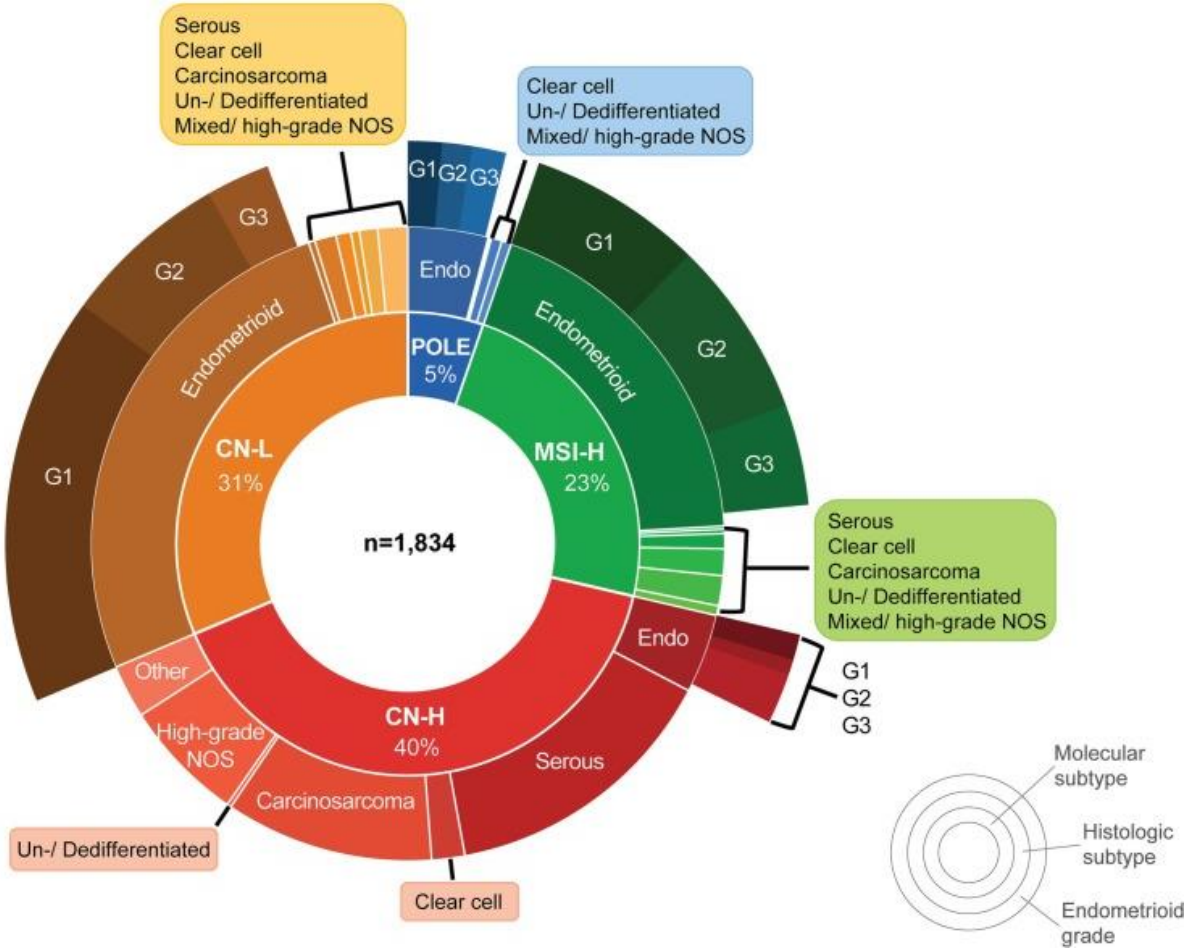
- **More precise prognosis**



Nature 2013 May 2;497(7447):67-73

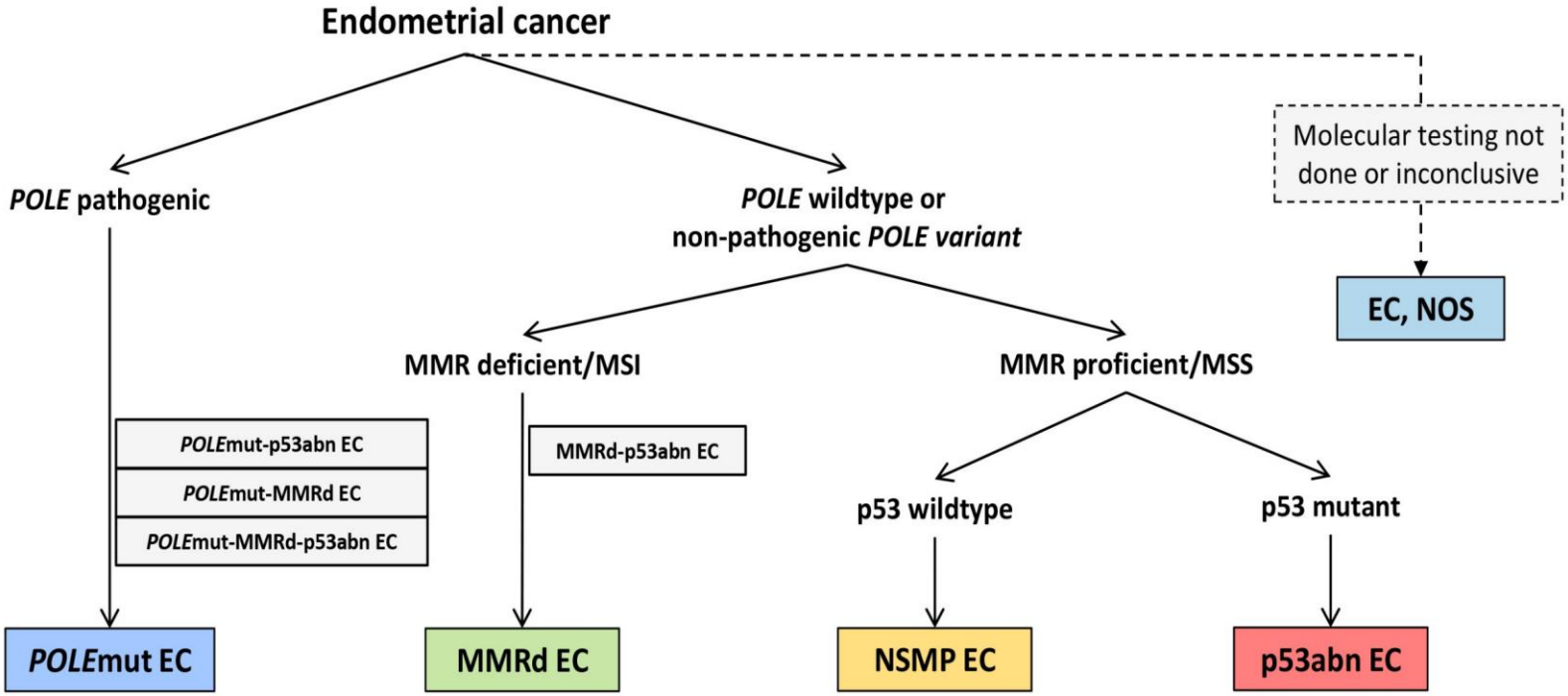


- **<u>POLE</u>:**
  - *POLE* exonuclease hotspot mutation
- **<u>MSI/MMRd</u>:**
  - Defective MMR or MSI-H, no *POLE* mutation
- **<u>CN-L/NSMP</u>:**
  - No *POLE* mutation or defective MMR or aberrant p53
- **<u>CN-H/p53 abnormal/ serous-like</u>:**
  - Abnormal p53 expression without *POLE* mutation or defective MMR



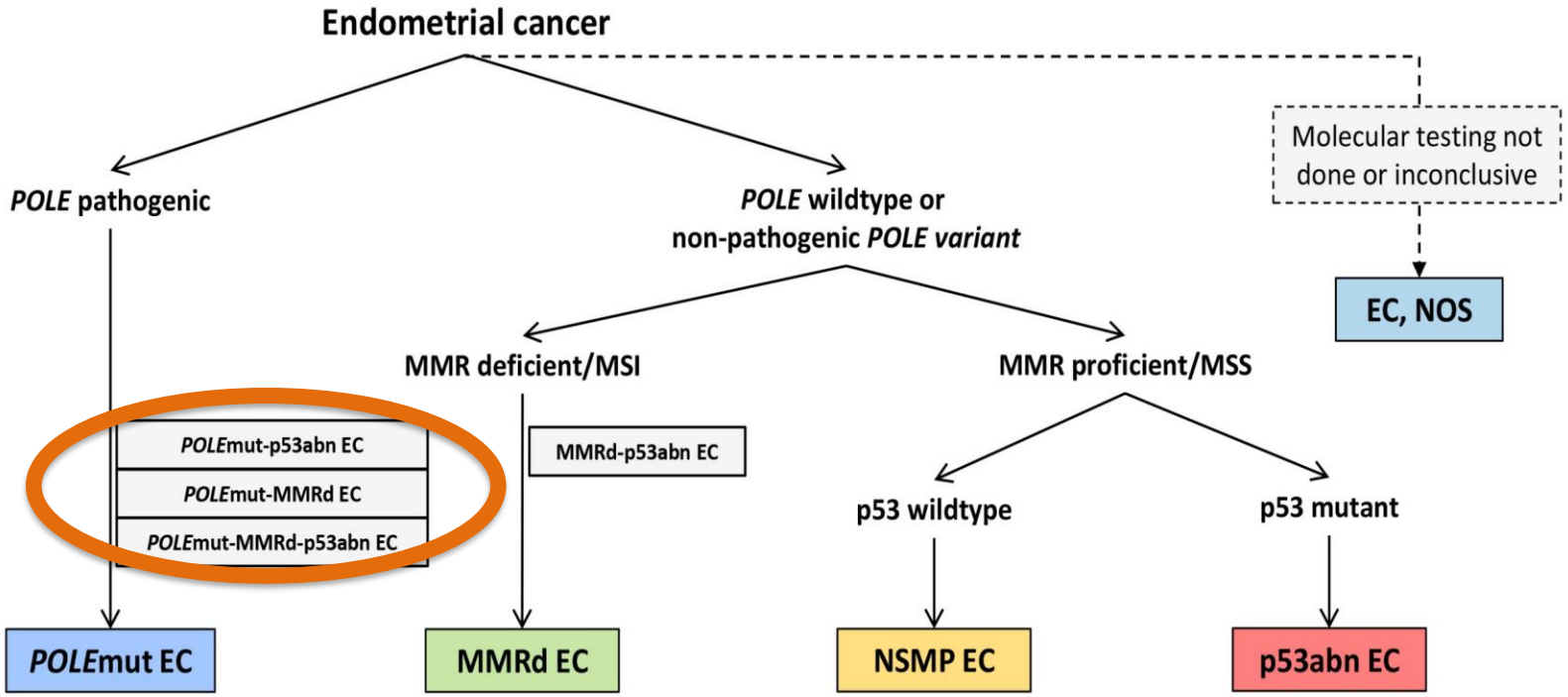
Gynecol Oncol. 2023 Jul;174:262-272

Harnessing genomic data for diagnosis, prognostication, therapeutic prediction



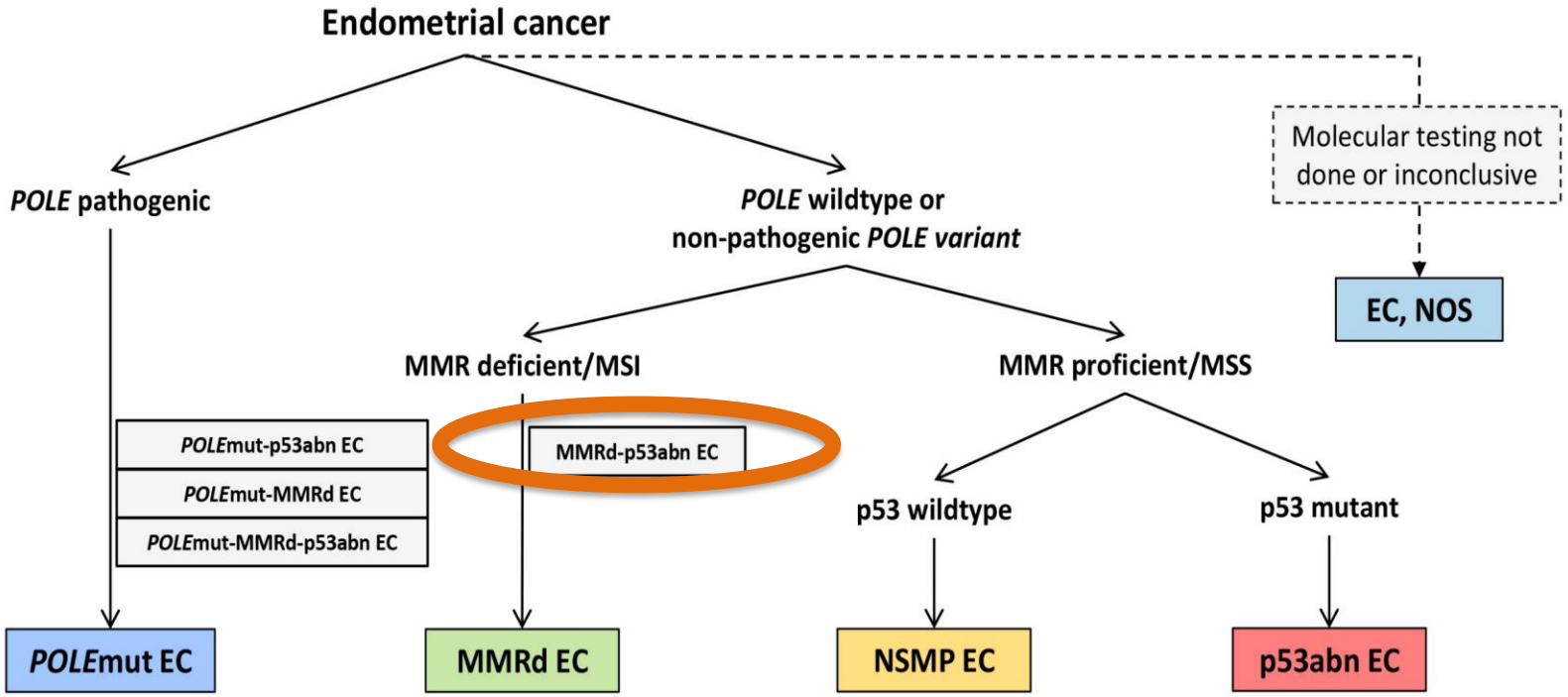
Courtesy of Tjalling Bosse MD

Harnessing genomic data for diagnosis, prognostication, therapeutic prediction

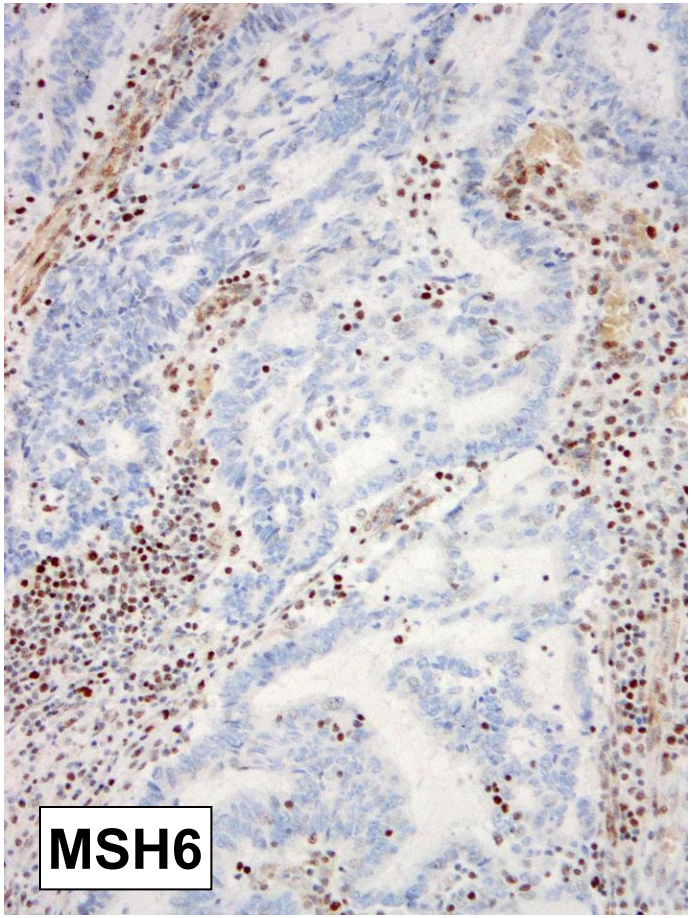


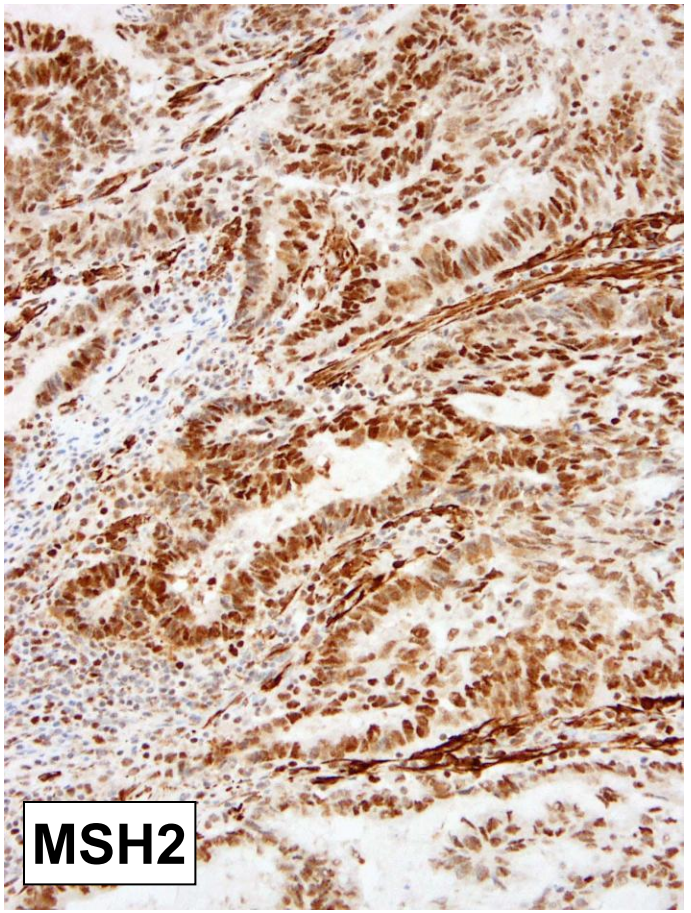
Courtesy of Tjalling Bosse MD

Harnessing genomic data for diagnosis, prognostication, therapeutic prediction

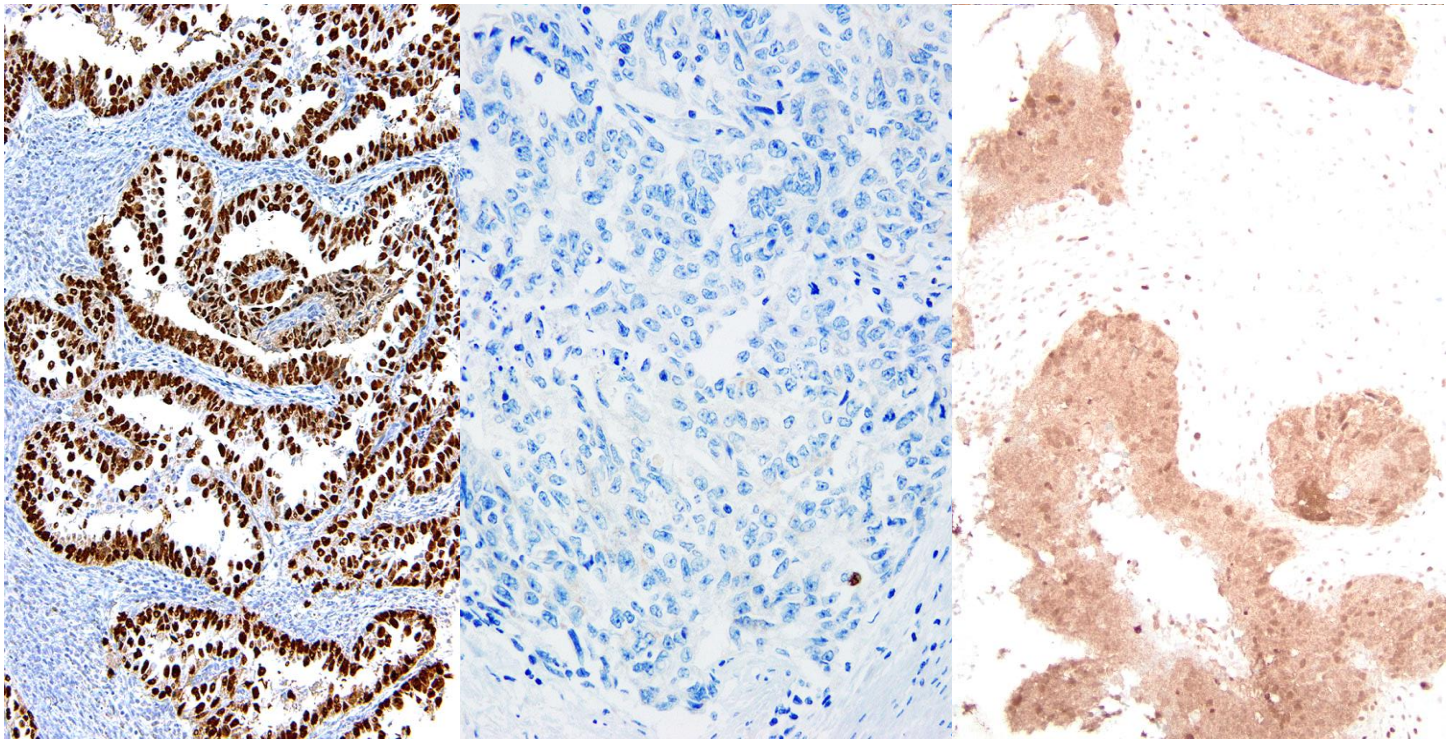


Courtesy of Tjalling Bosse MD

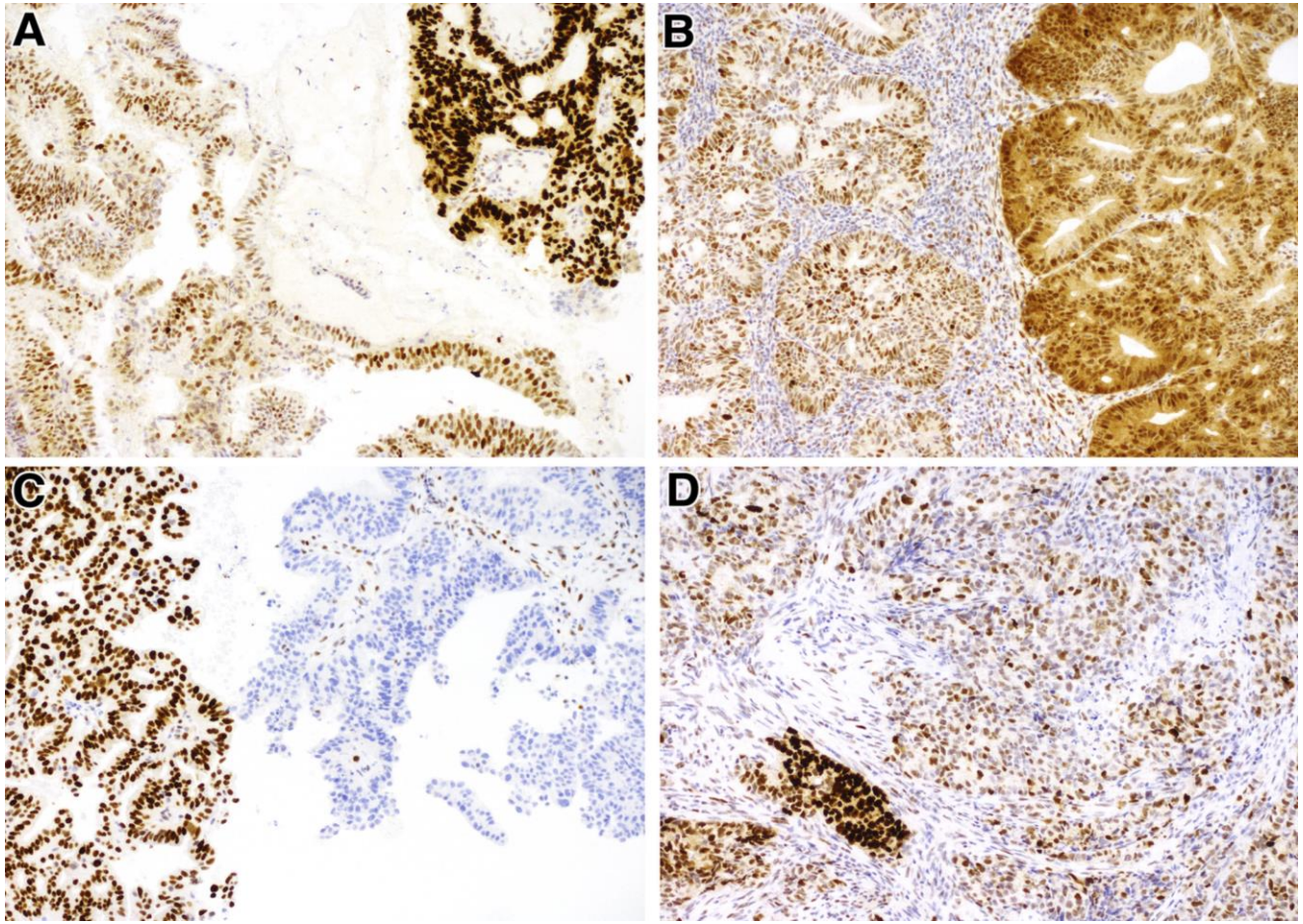

MSH6


MSH2

Aberrant p53 staining



Subclonal staining



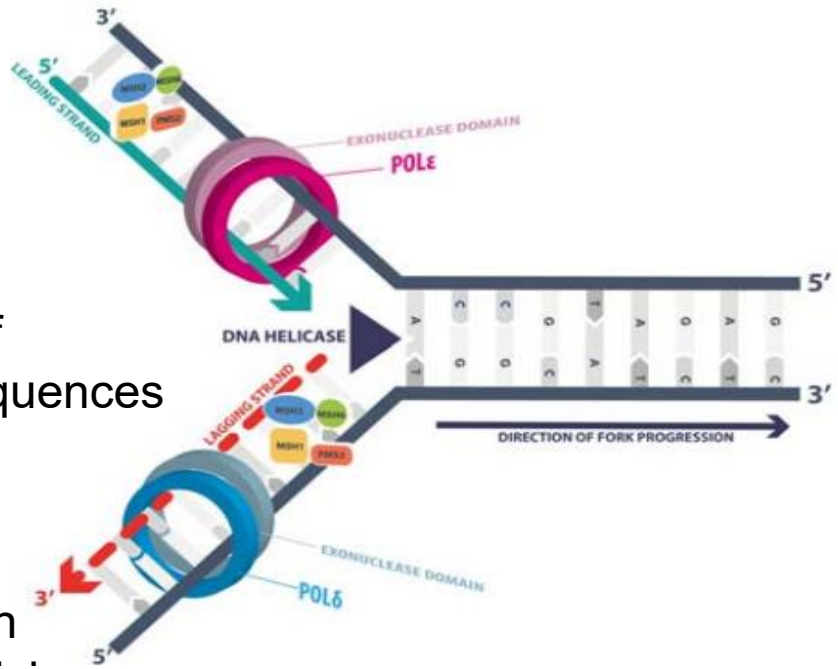
J Pathol: 3, 336-345

POLE AND MSI-H CARCINOMAS

POLE and MMR functions

MMR:
Mismatch repair
- Correct replication errors
- Prevent recombination of
  non-identical DNA sequences

POLE:
- Leading strand replication
- Nucleotide and base excision repair

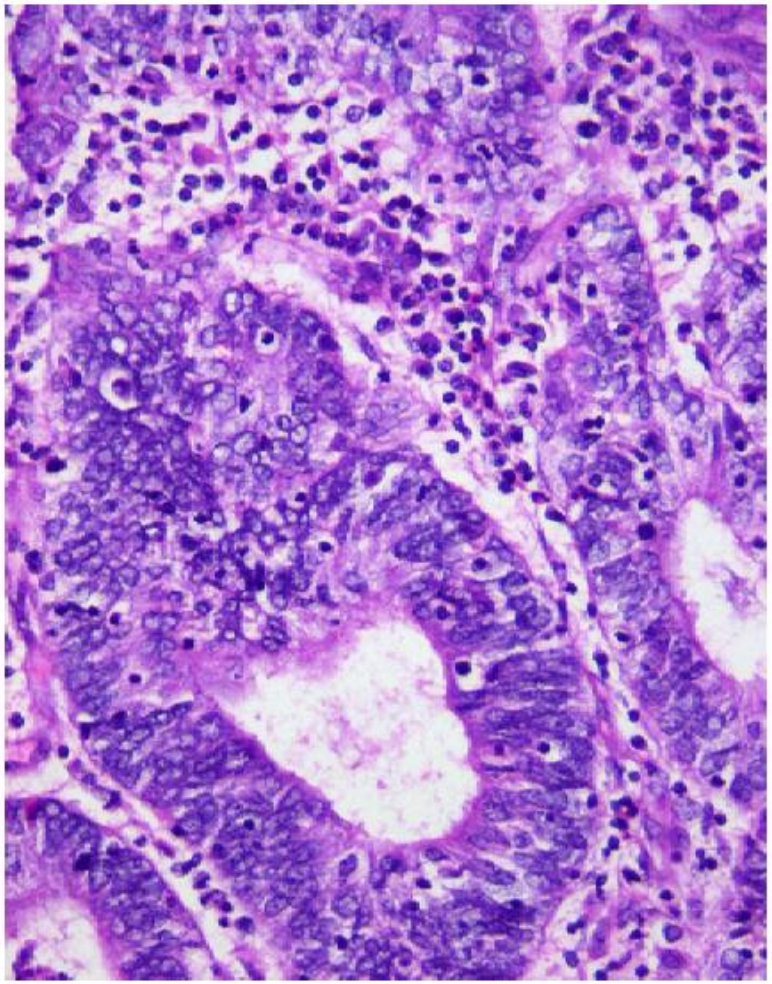


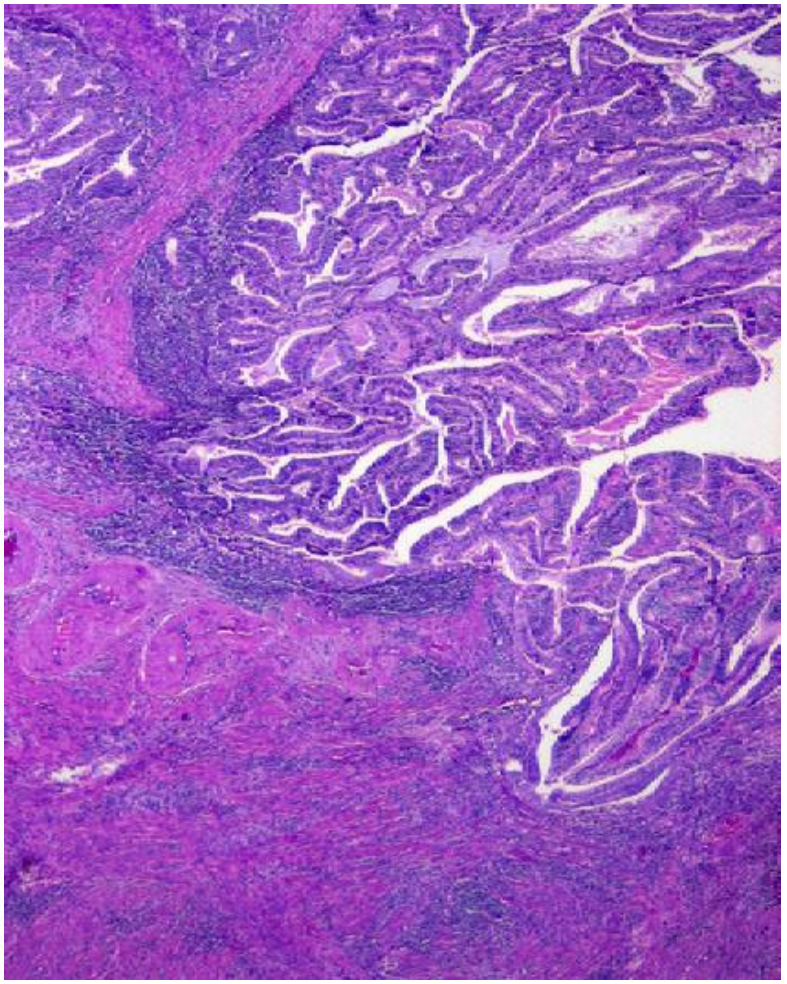
Casey L, Singh N, Int J Gynecol Pathol. 2021 Jan;40(1):5-16

MSI-H/POLE histotypes and grades

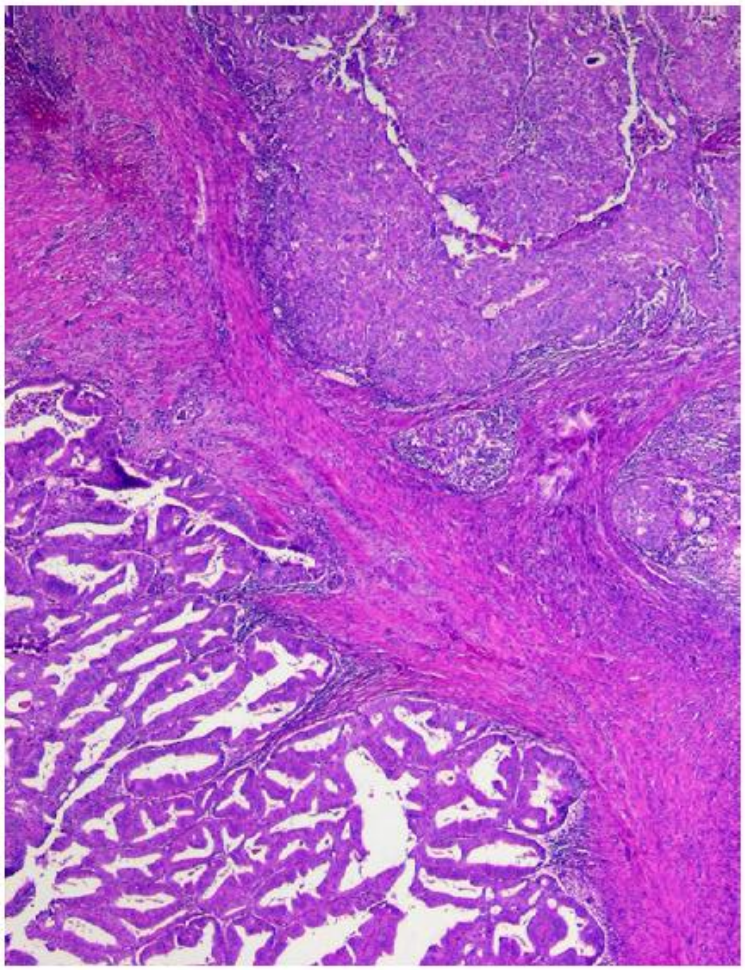
- Any endometrial carcinoma ***except serous carcinoma***
- Disproportionately histologically high-grade
- Morphologic heterogeneity and immunohistochemical heterogeneity (subclonal staining patterns)
- ***Surprise: Neither FIGO grade nor histotype is clinically relevant***

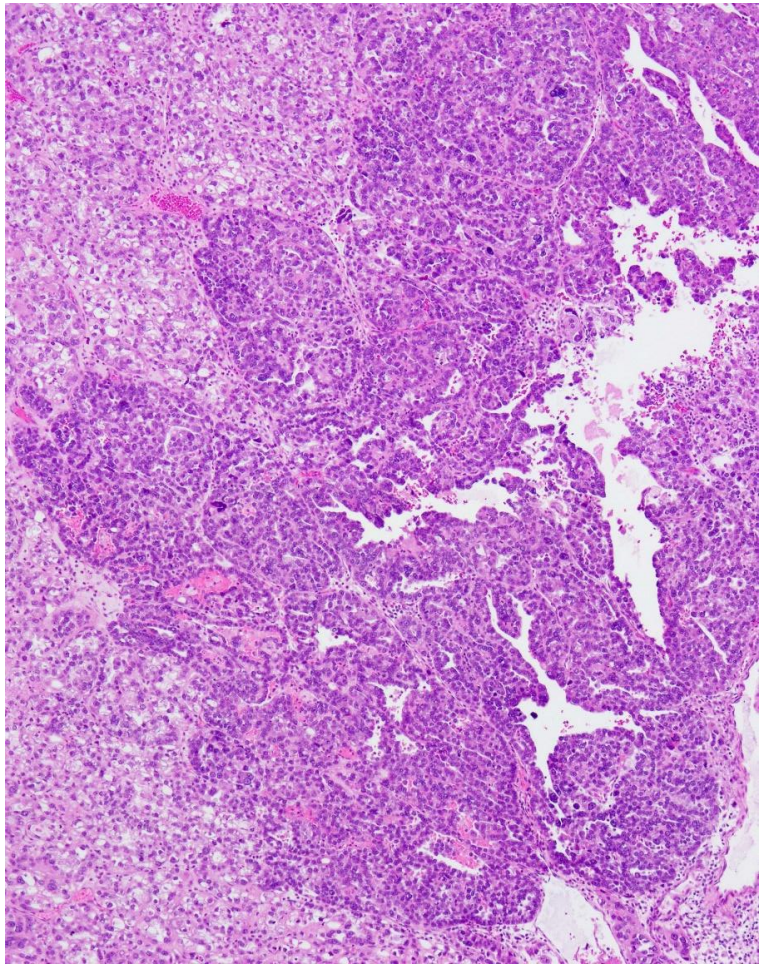
MSI-H/POLE morphology: frequent TILs and PTLs

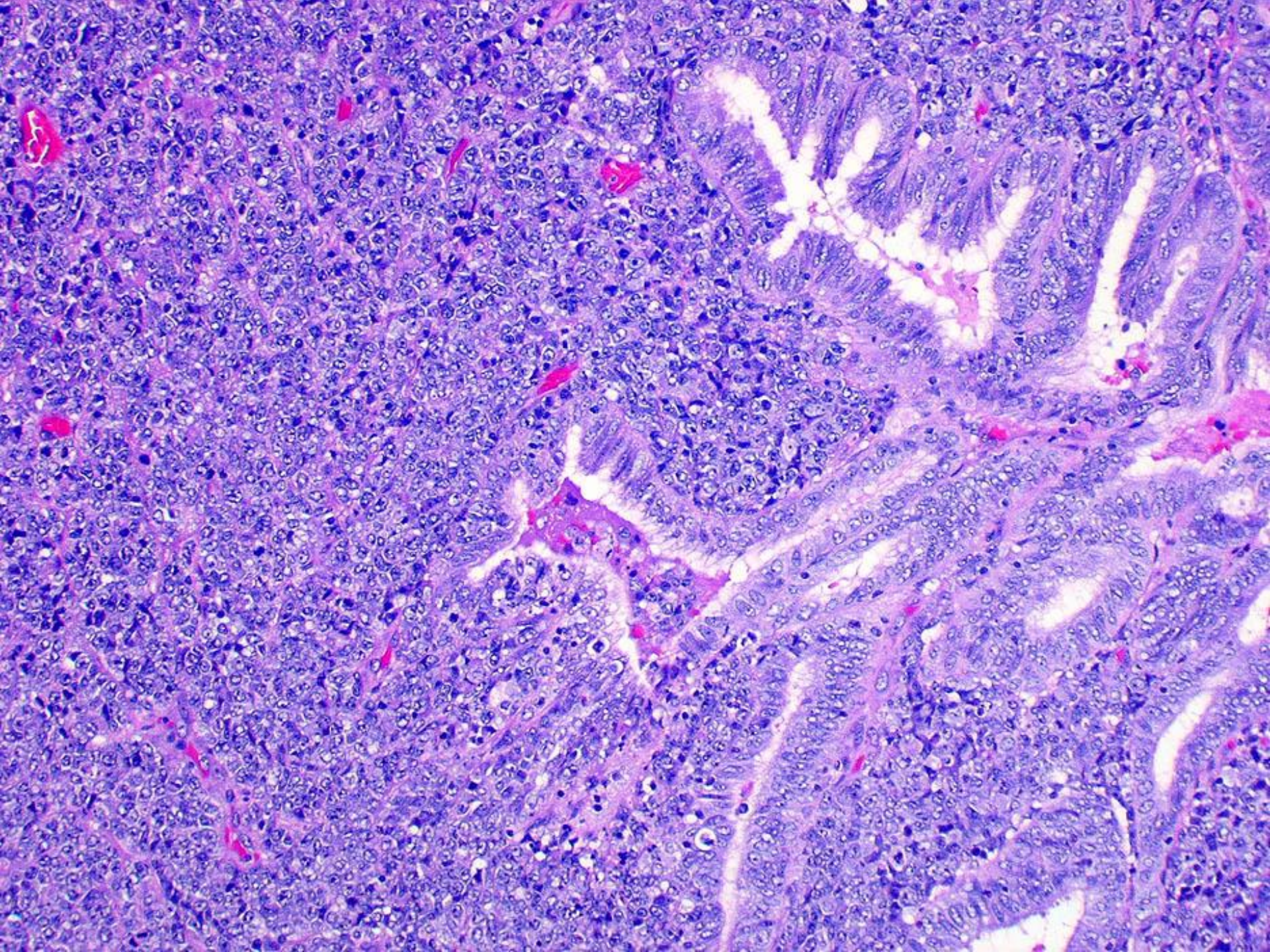




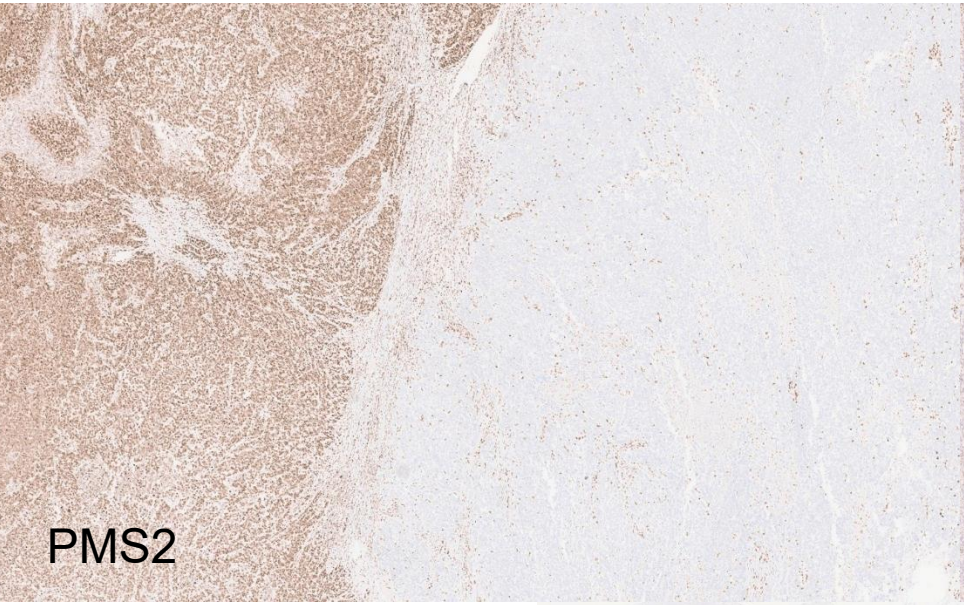
MSI-H/POLE morphology: frequent tumoral heterogeneity

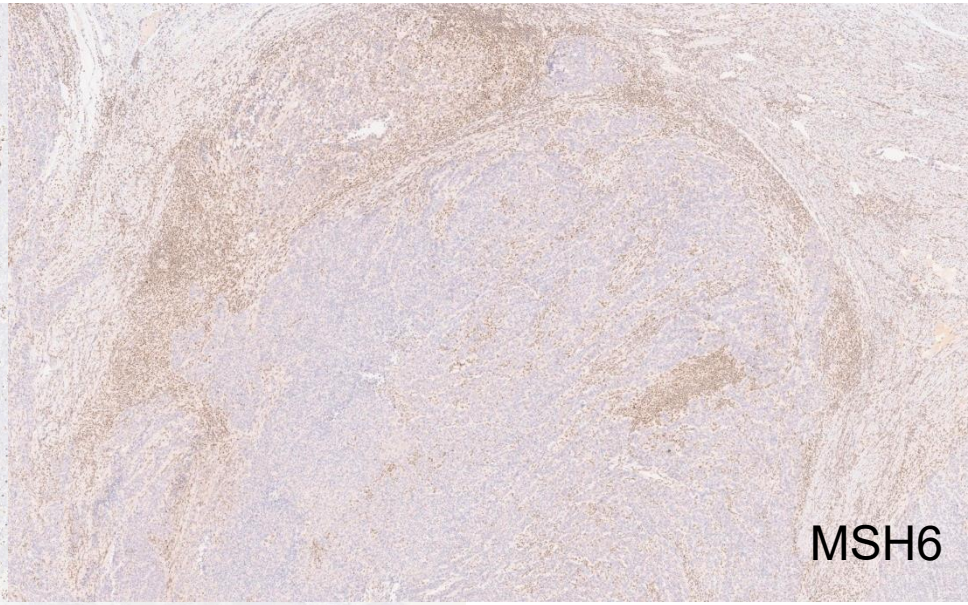


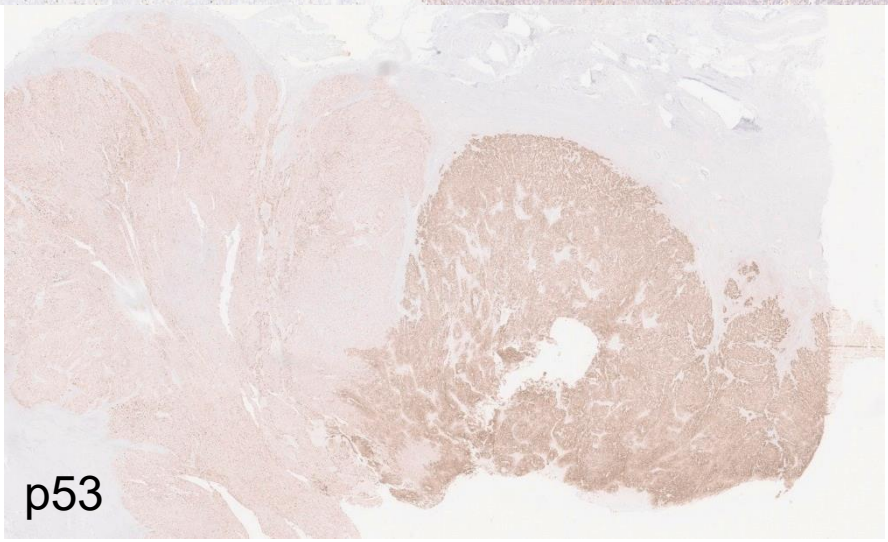




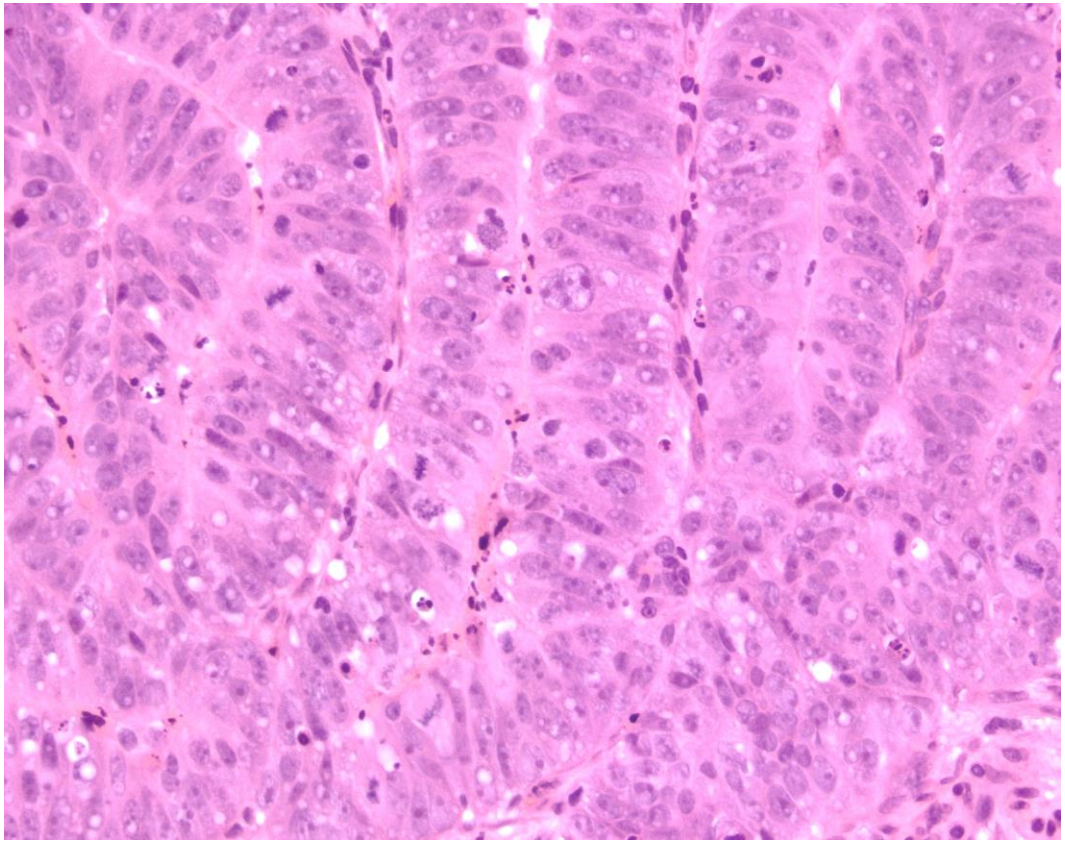
Subclonal staining

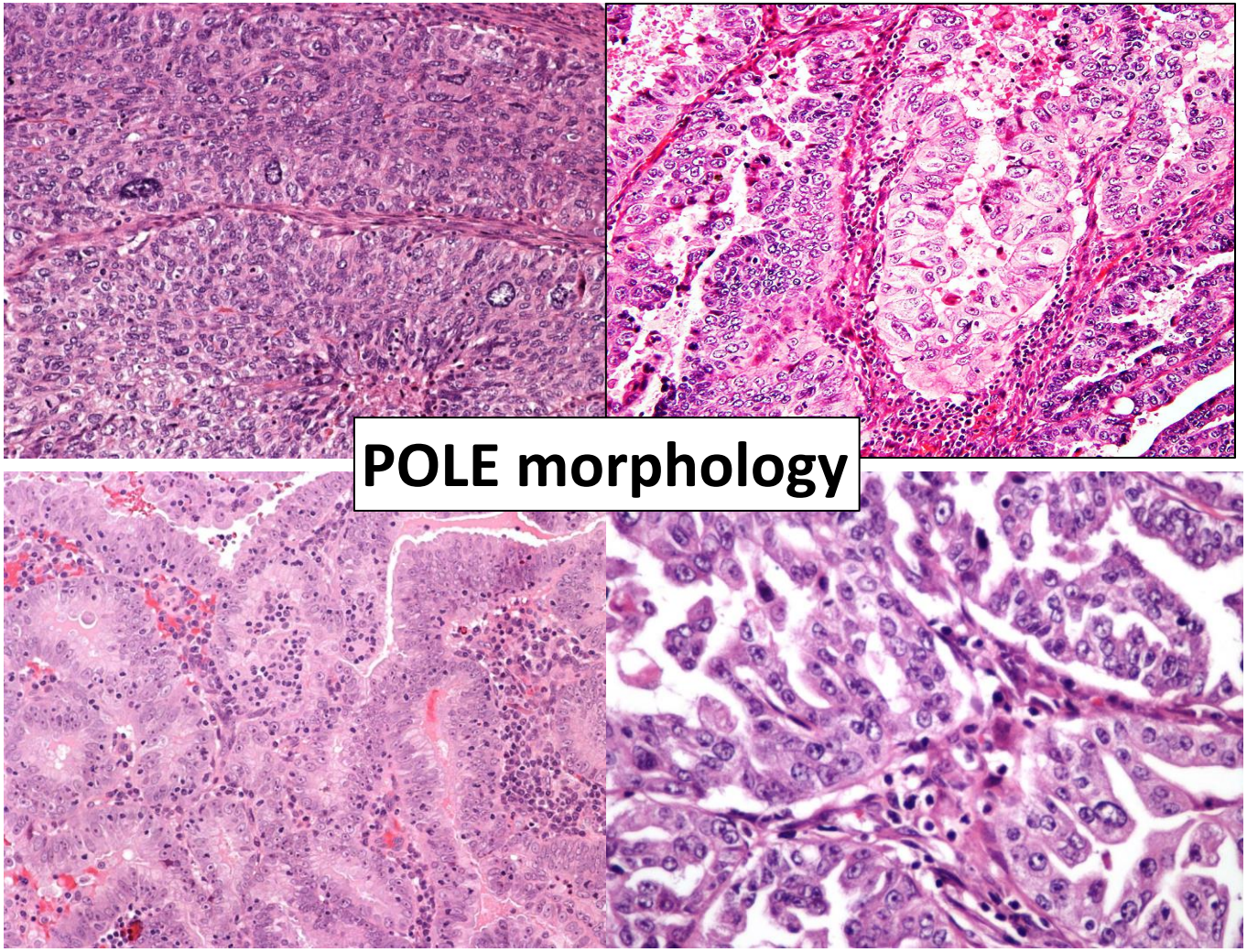




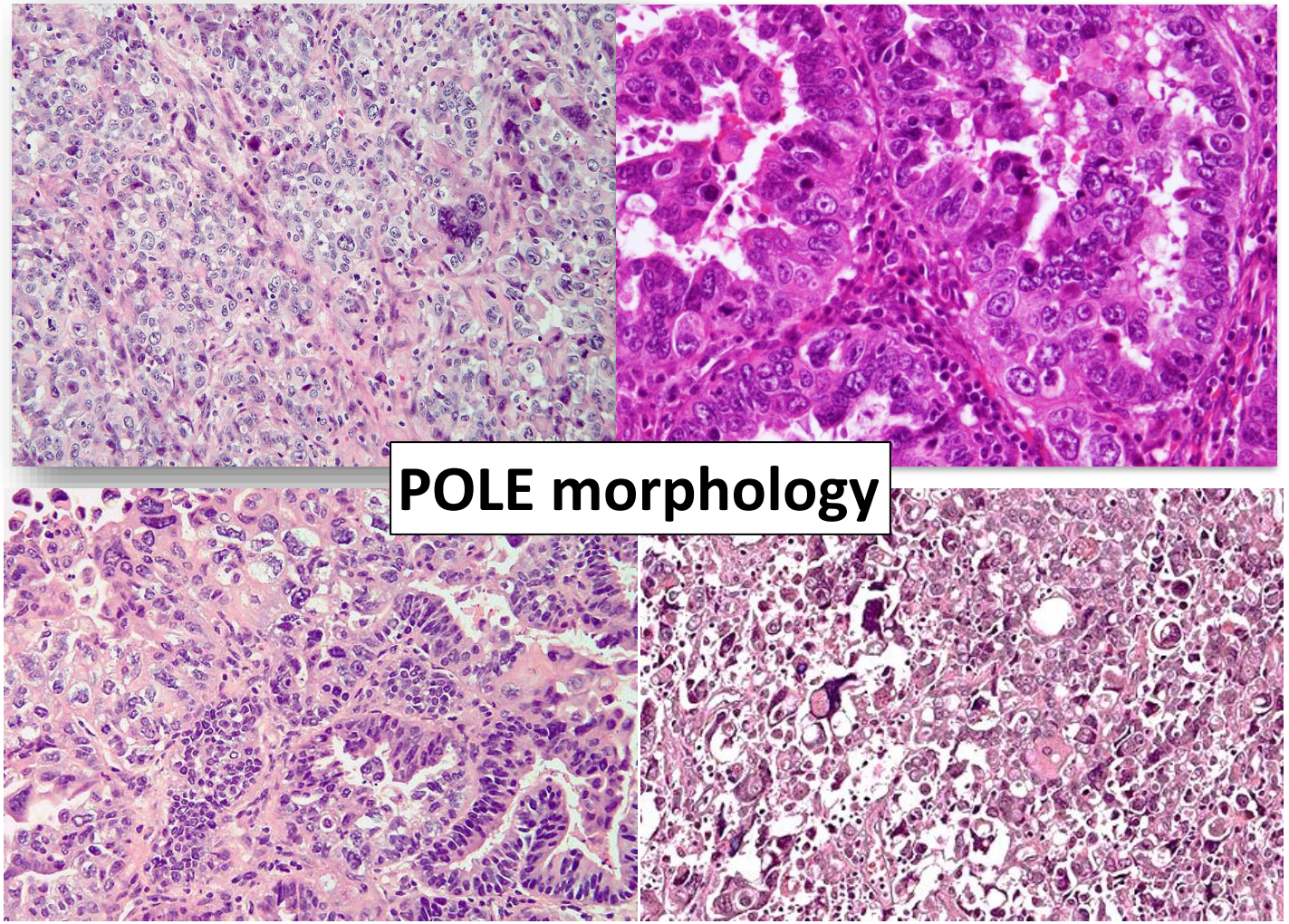


MSI-H/POLE morphology: frequent histologic ambiguity





Hussein, Y, et al. *Mod Pathol.* 2015 Apr;28(4):505-14



Hussein, Y, et al. *Mod Pathol.* 2015 Apr;28(4):505-14

What makes *POLE* "POLE"?

Table 3. Pathogenic *POLE* EDM based on POLE-score

Protein change	Nucleotide substitution
P286R	c.857C>G
V411L	c.1231G>T/C
S297F	c.890C>T
S459F	c.1376C>T
A456P	c.1366G>C
F367S	c.1100T>C
L424I	c.1270C>A
M295R	c.884T>G
P436R	c.1307C>G
M444K	c.1331T>A
D368Y	c.1102G>T

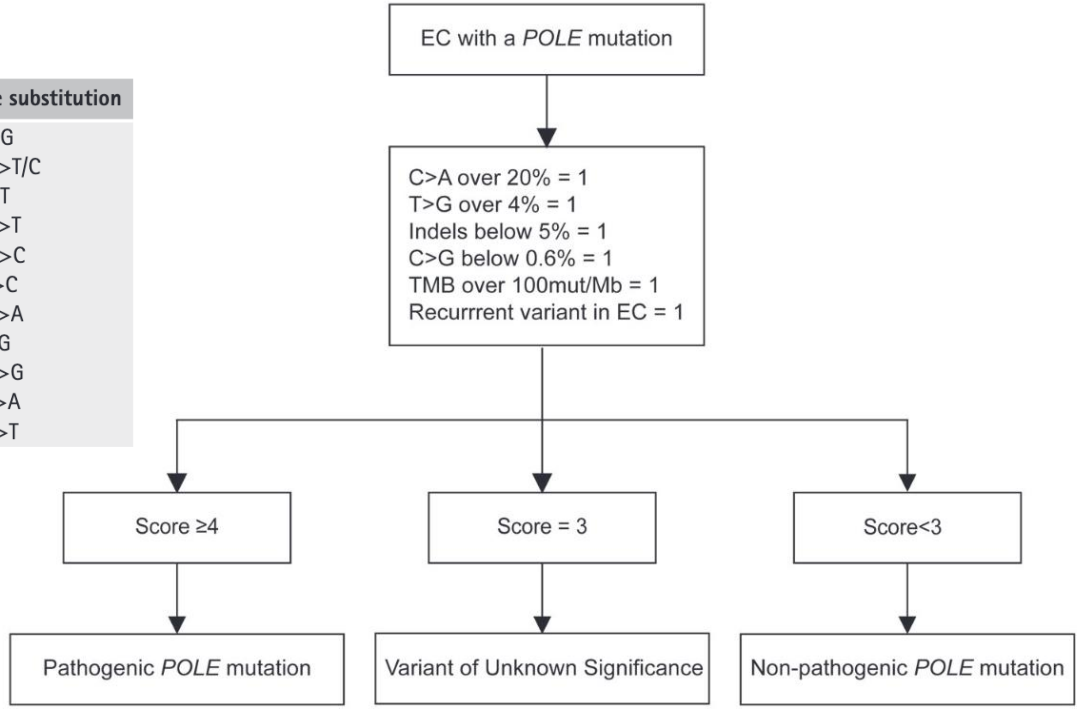


Figure 2. *POLE* genomic alteration score (POLE-score). Diagnostic scoring system based on mutation type proportion and TMB of the five hotspot *POLE* mutations, as well as the variant recurrence.

J Pathol. 2020 Mar;250(3):323-335. PMID: 31829442

POLE assays

- Next generation multi-gene panel mutational testing for EDM hotspots

- QPOLE: *POLE* sequencing by multiplex genotyping qPCR

JCO Glob Oncol. 2023 May;9:e2200384.PMID: 37229628

- SNaPshot Assay for POLE exonuclease domain mutations

Int J Gynecol Pathol. 2022 Nov 1;41(6):541-551. PMID: 34907997

POLE testing may not always be necessary

- Low-grade endometrioid carcinoma
- MMR-proficient
- *p53* wild-type
- stage IA
- No lymphovascular space invasion

38% of hysterectomies

Int J Gynecol Pathol. 2023 Jul 1;42(4):353-363 PMID: 36731023
Mod Pathol. 2023 Apr;36(4):100085 PMID: 36788084

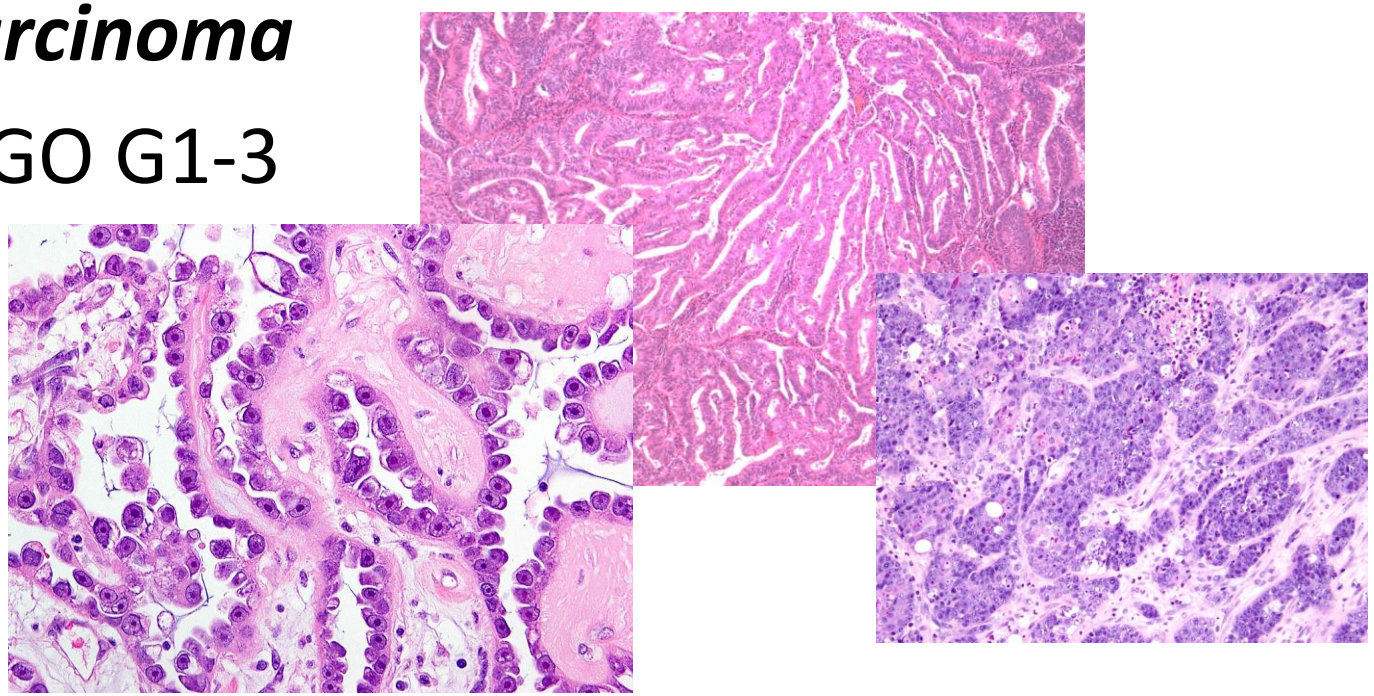
POLE testing strongly recommended

- Stage I ***and***
- “Aggressive histotype”
- Oncologists will to consider treatment de-escalation

NSMP/CN-L CARCINOMAS

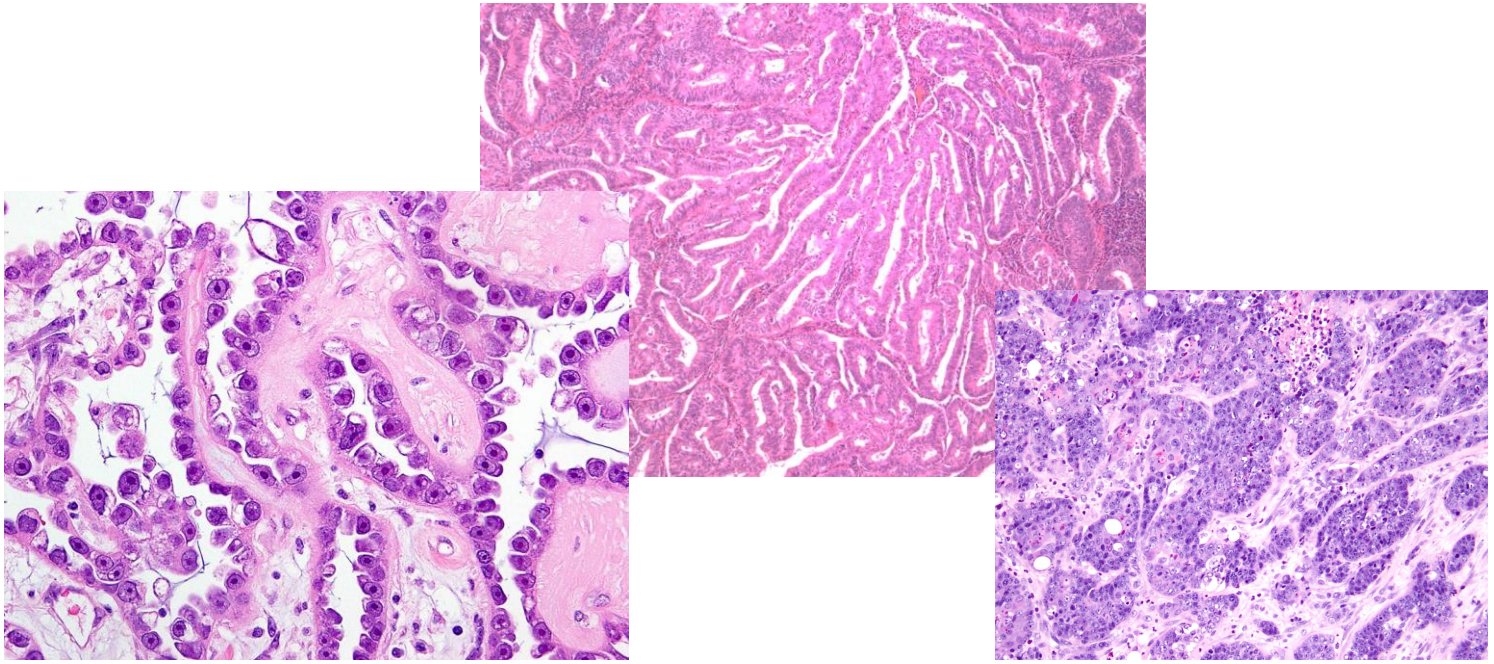
NSMP histotypes and grades

- Any endometrial carcinoma ***except serous carcinoma***
- FIGO G1-3

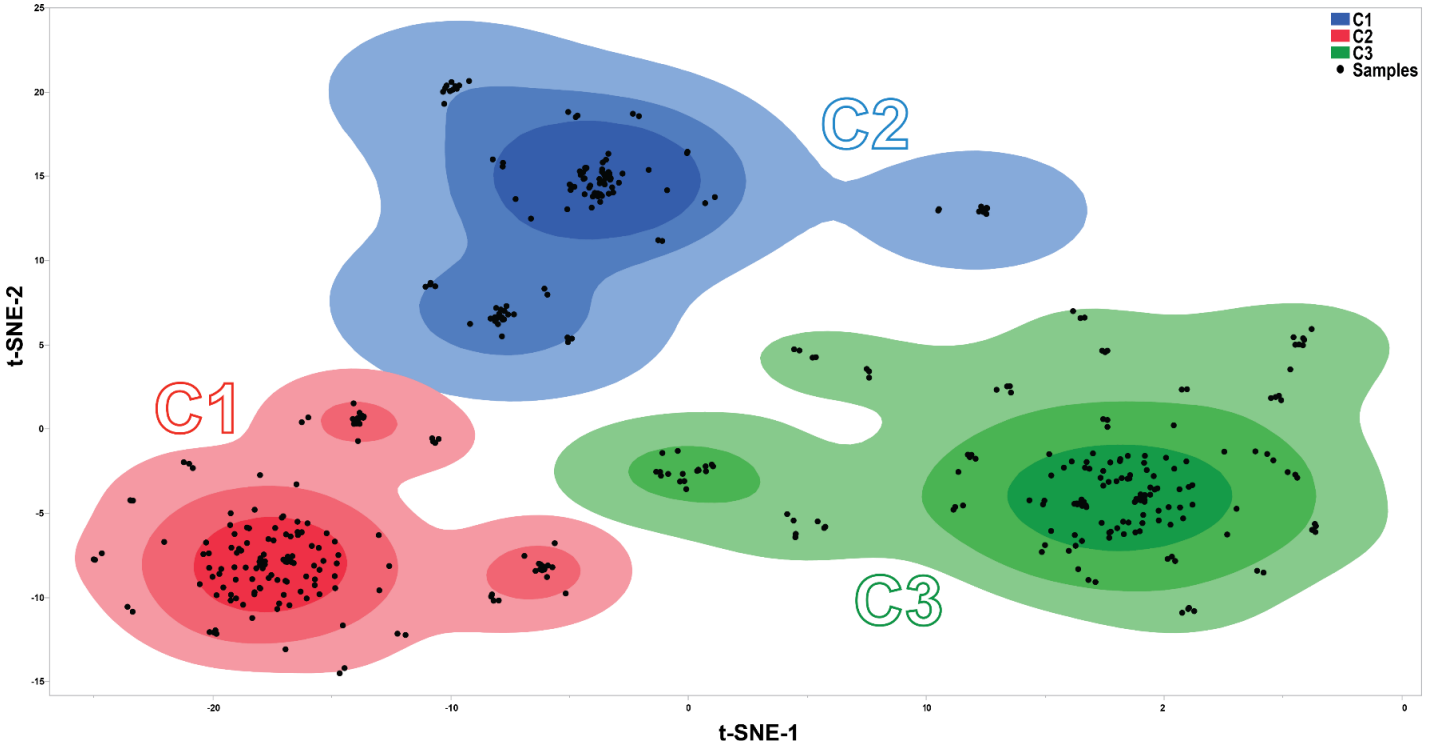


NSMP histotypes and grades

- NSMP is the only molecular group in which **grade** and **histotype** are clinically important



Prognostically relevant info



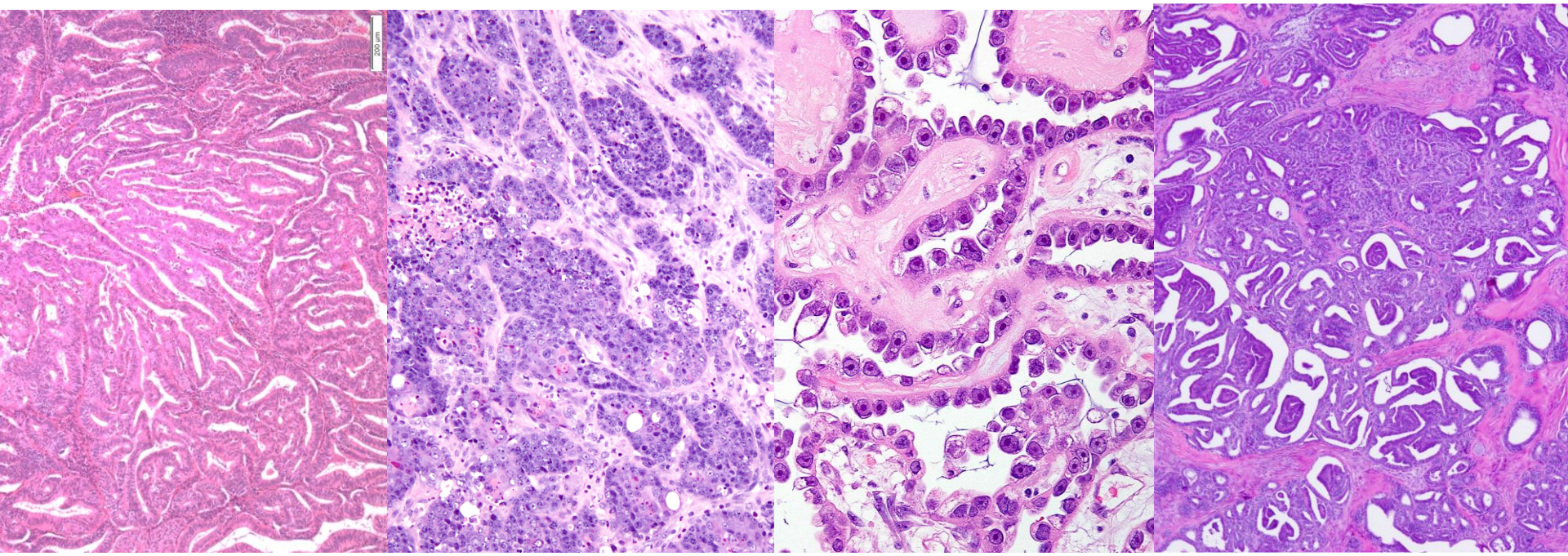
Mod Pathol 2022 Sep;35(9):1269-1278

Prognostically relevant info

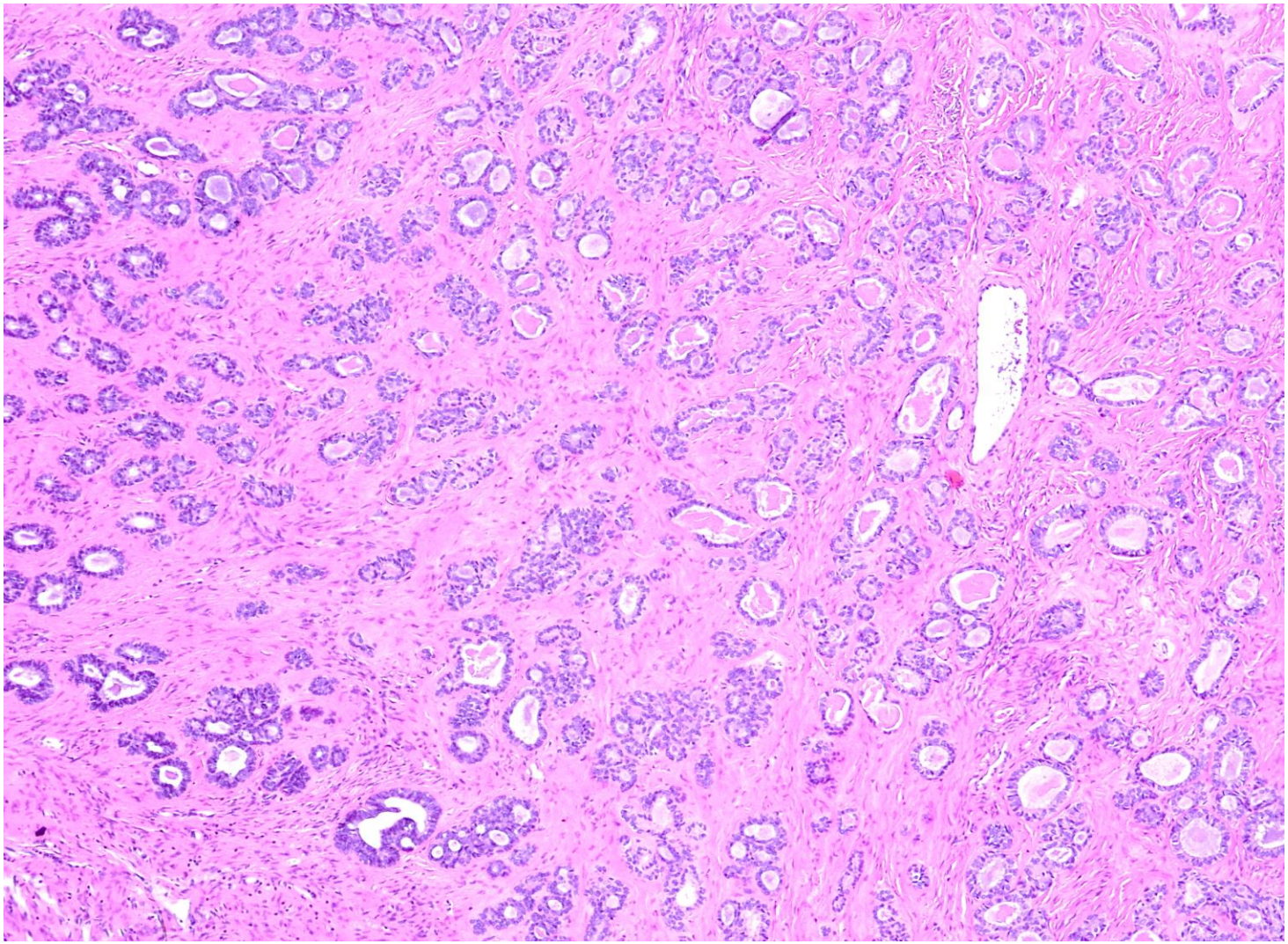
- Aggressive subsets of NSMP tumors:
  - Histologically high-grade
  - Non-endometrioid morphology
  - ER/PR negative
  - 1q gains/amplification
  - *PTEN* wt
  - *SMARCA4, SMARCB1, ARID1B* mut (particularly in un/de-diff)

Mod Pathol 2022 Sep;35(9):1269-1278
Mod Pathol. 2023 Apr;36(4):100085 PMID: 36788084
Lee C-H and Tessier-Cloutier B, et al.

Heterogeneity in CN-L tumors
Aggressive subtypes



Mesonephric-like carcinoma



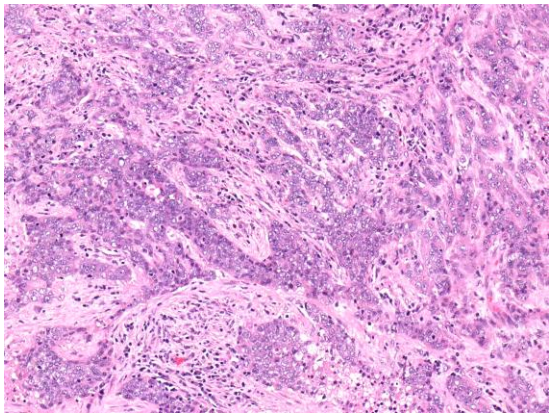
Summary—NSMP/CN-L

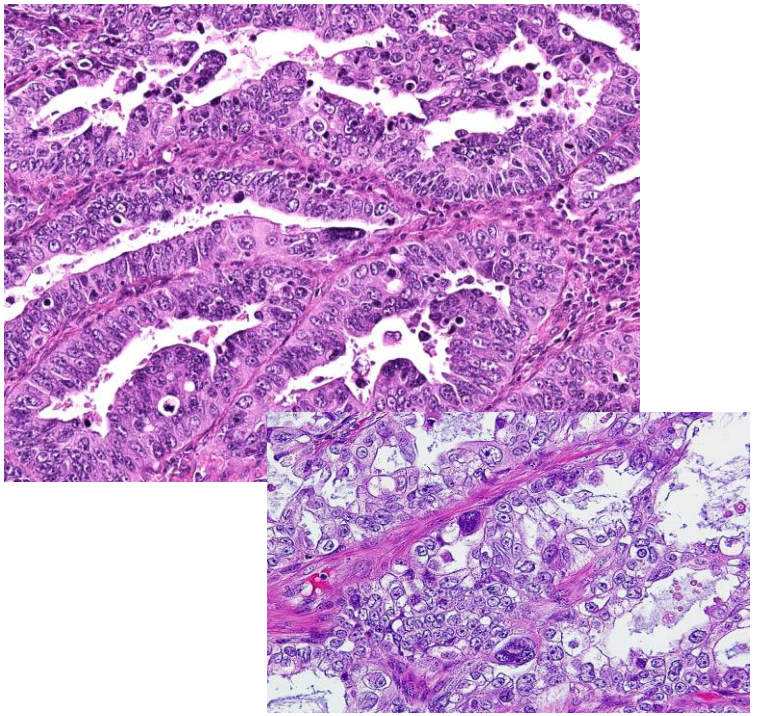
Clinical outcomes are dependent on histotype, grade, hormone receptor expression and genotype

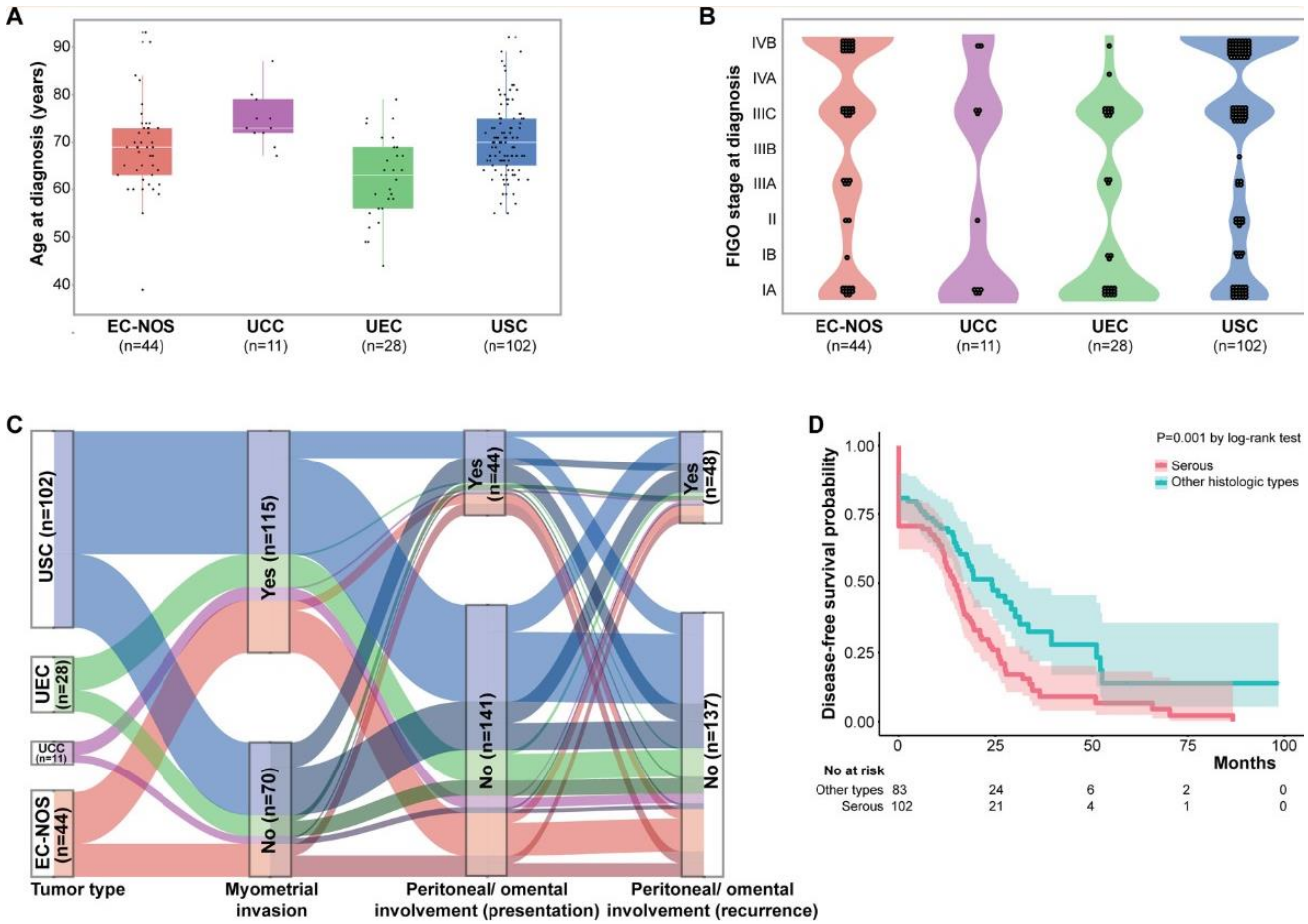
CN-H CARCINOMAS

CN-H histotypes and grades

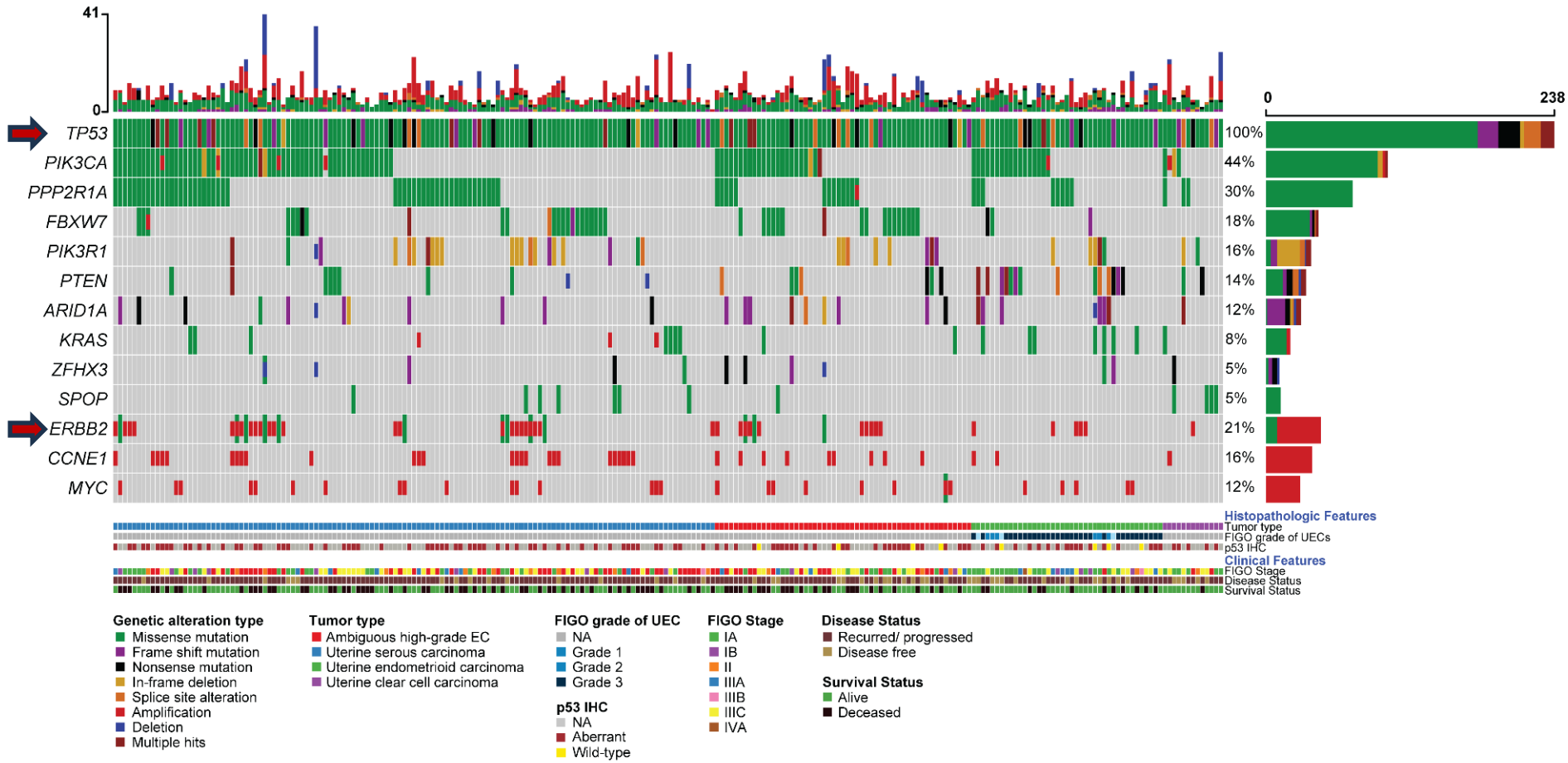
- Any endometrial carcinoma with driver *p53* mutation
- High-grade (>95%)







Clin Cancer Res 2021 May 1;27(9):2613-2623


41
0
0
238
TP53
PIK3CA
PPP2R1A
FBXW7
PIK3R1
PTEN
ARID1A
KRAS
ZFHX3
SPOP
ERBB2
CCNE1
MYC
100%
44%
30%
18%
16%
14%
12%
8%
5%
5%
21%
16%
12%
Histopathologic Features
Tumor type
FIGO grade of UECs
p53 IHC
Clinical Features
FIGO Stage
Disease Status
Survival Status
Genetic alteration type
Missense mutation
Frame shift mutation
Nonsense mutation
In-frame deletion
Splice site alteration
Amplification
Deletion
Multiple hits
Tumor type
Ambiguous high-grade EC
Uterine serous carcinoma
Uterine endometrioid carcinoma
Uterine clear cell carcinoma
FIGO grade of UEC
NA
Grade 1
Grade 2
Grade 3
p53 IHC
NA
Aberrant
Wild-type
FIGO Stage
IA
IB
II
IIIA
IIIB
IIIC
IVA
Disease Status
Recurred/ progressed
Disease free
Survival Status
Alive
Deceased

Summary: Adverse features

- Extrauterine disease
- Cervical stromal invasion
- Deep myoinvasion
- Substantial lymphovascular invasion
- CN-H (*Tp53*)
- FIGO grade 3, ER/PR negative or non-endometrioid if NSMP
- *SMARCA4, SMARCB1, ARID1B* mut
- Sarcomatous and divergent differentiation

Thank you for your interest!!