Gynaecological Pathology reporting. What really matters - When and Why

Pathology of the Ovary and Fallopian Tube

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Barts Health NHS Trust

What Matters?

- **Benign vs Malignant/Borderline**
- **(If malignant, primary/metastatic)**
- **Histotype**
- **Stage**
- **(A few miscellaneous things at the end …)**

Why?

- **Surgical or non-surgical treatment**
- **If surgical**
  - **Fertility preservation**
  - **Ovary conservation (62)**
  - **Extent of surgery: initial or completion, eg lymphadenectomy**
- **Adjuvant therapy (including targeted)**
- **Hereditary cancer screening**
- **Entry into clinical trials**
- **Duration of follow-up**

Dataset for Reporting: ICCR

Ovary, Fallopian Tube and Primary Peritoneal Carcinoma
Histopathology Reporting Guide

Clinical:

- (Indication)

- **Genetic status: BRCA, Lynch, unknown**

- **Specimen type: cystectomy vs oophorectomy vs salpingo-oophorectomy**
  - Can be difficult to work out later; contact clinician if specimen does not correspond

Macroscopic Description:
Specimen integrity

Ovary:

- Ovarian capsule intact
- Ovarian capsule ruptured
- Tumour on surface (?ink)
- Fragmented specimen
- Other (specify)

Fallopian tube:

- Serosa intact
- Serosa ruptured
- Tumour on serosal surface
- Fragmented specimen
- Other (specify)

STATE IF TUBE IS INSEPARABLE FROM OVARY
IMPORTANT FOR STAGING AND SUB STAGING
MAY DETERMINE ADJUVANT Rx

Measurements

- (No need to weigh)
- Ovary size
- Fallopian tube size
- Tumour size; size of solid component
- Omentum size
- Presence and size of omental deposits (Stage III sub staging)

All measurements in THREE dimensions (mm)

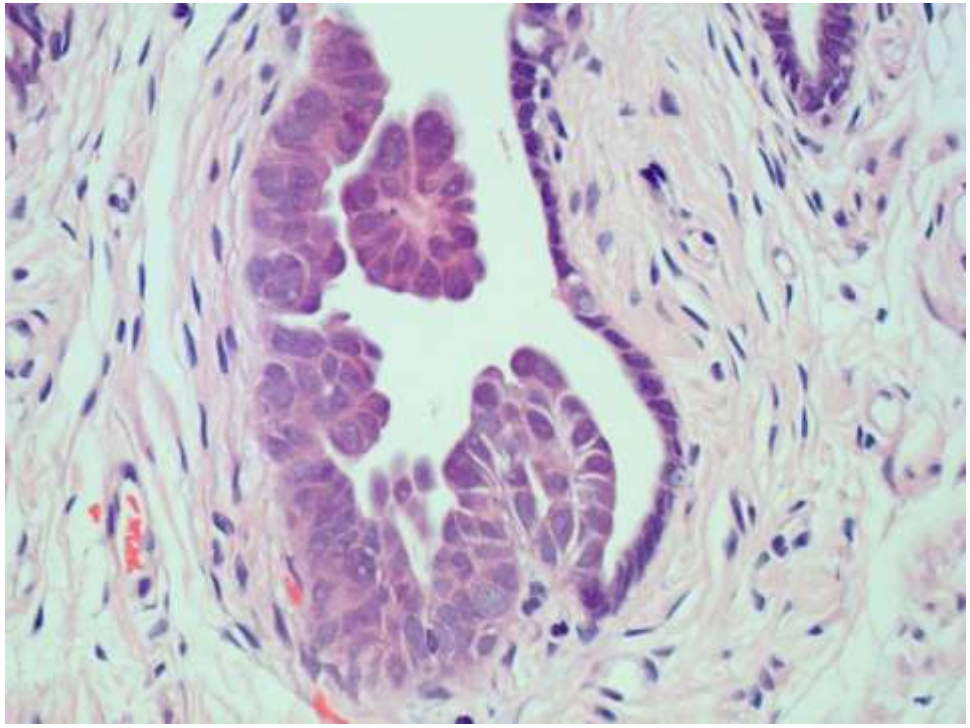
Macroscopic tumour site

- Indeterminate;
- Ovary L/R ;
- Fallopian tube L/R
  - Fimbrial/Non fimbrial;
- Peritoneum;
- Other (specify)

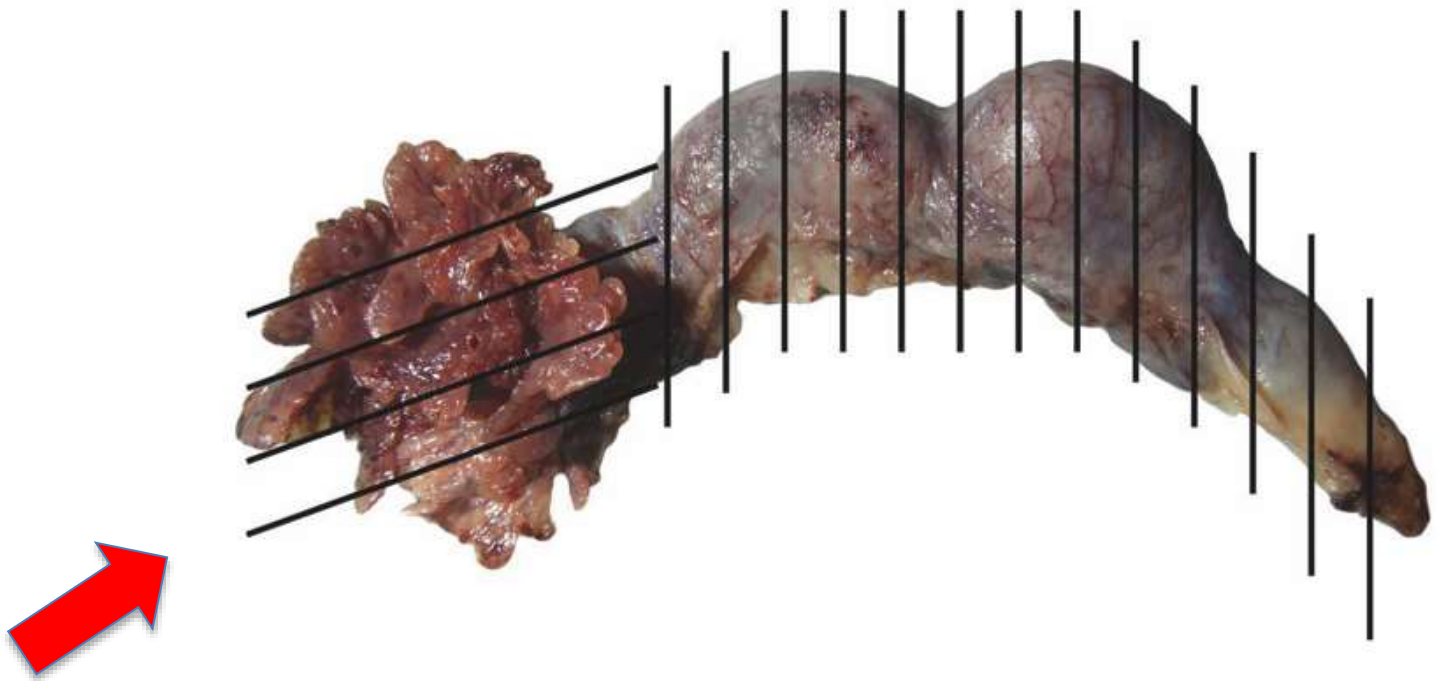
Block selection

- Ovary: 1 per cm of max dimension
  - Solid: one block per cm
  - Cystic: >one strip per cassette
- Fallopian tube
  - State how/what is sampled

Serous Tubal Intraepithelial Carcinoma, STIC



SEE-FIM (Sectioning and Extensively Examining the FIMbriated end of the Fallopian tube



Tubal sampling: what and when

- SEE-FIM:
  - All RRSO/high risk of ovarian cancer
  - All apparent normal tubes in HGSC
  - (USC)

- Single fimbrial block in all other cases

- **Careful visual examination of all cases**

How many levels of fimbrial sections? NS: Just one

Block selection

- Omentum
  - 4 if abnormal;
  - more extensive in SBT;
  - 10 if normal (sensitivity 95% - grossly normal omentum when other staging is negative; based on mathematical modelling) (Int J Gynecol Pathol. 2015 May;34(3):281-7)
- Other sites
  - representative blocks if obvious abnormality economical)
  - More extensive if normal

Block selection

- Spleen, liver
  - Parenchymal abnormality needs to be confirmed /excluded
- Diaphragm (sample in strips)
  - If full thickness state whether one or both surfaces are involved; presence of skeletal muscle infiltration
- Lymph nodes
  - Size of metastasis matters (IIIA1 vs IIIA2 depends on </= 10mm vs >10mm)

Block Key

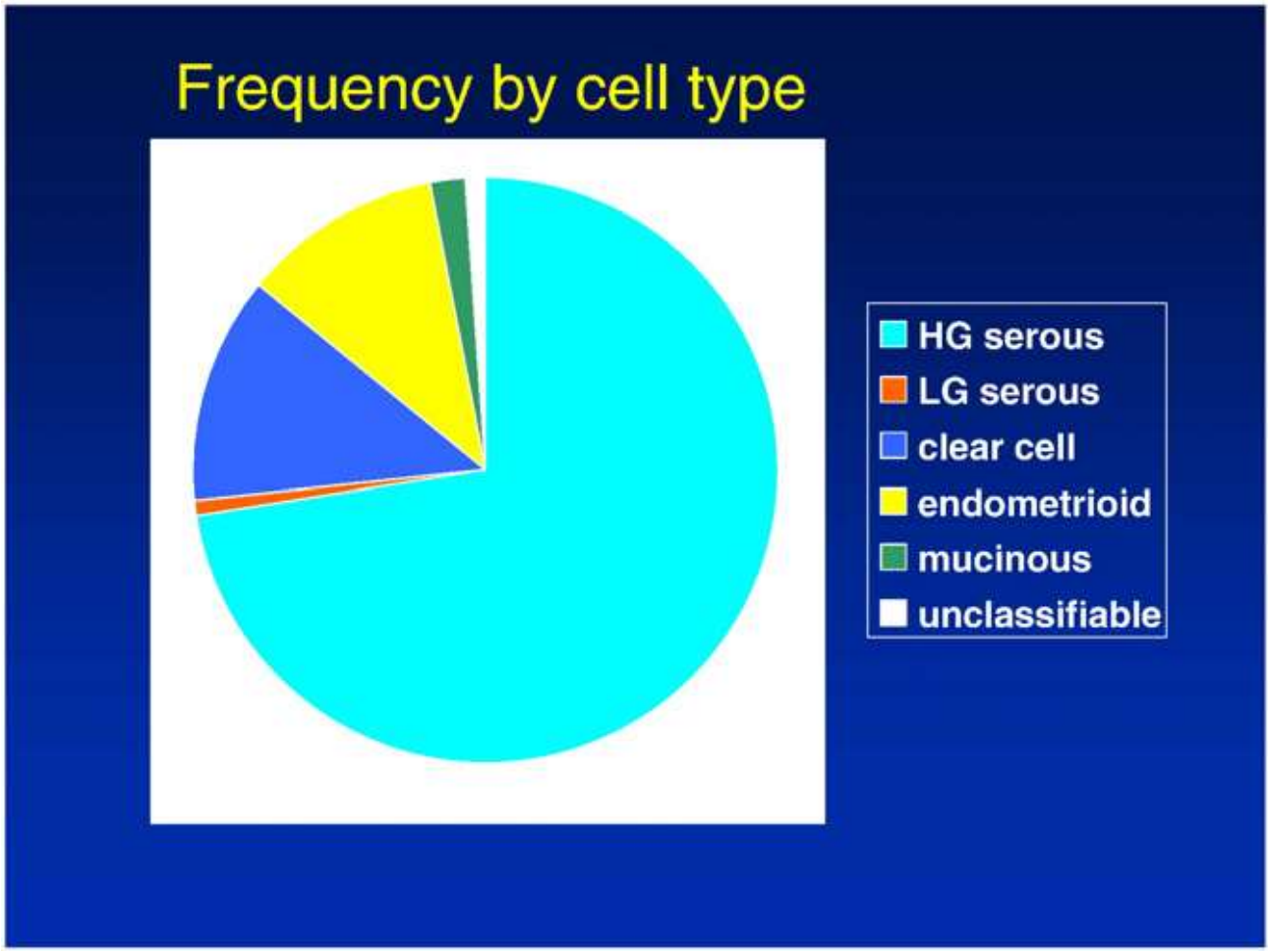
- Crucial!
- Ovary: which sections include the external surface; sample rupture site
- Fallopian tube: state if SEE-FIM/SEE-FIM-like

Microscopy: What matters?

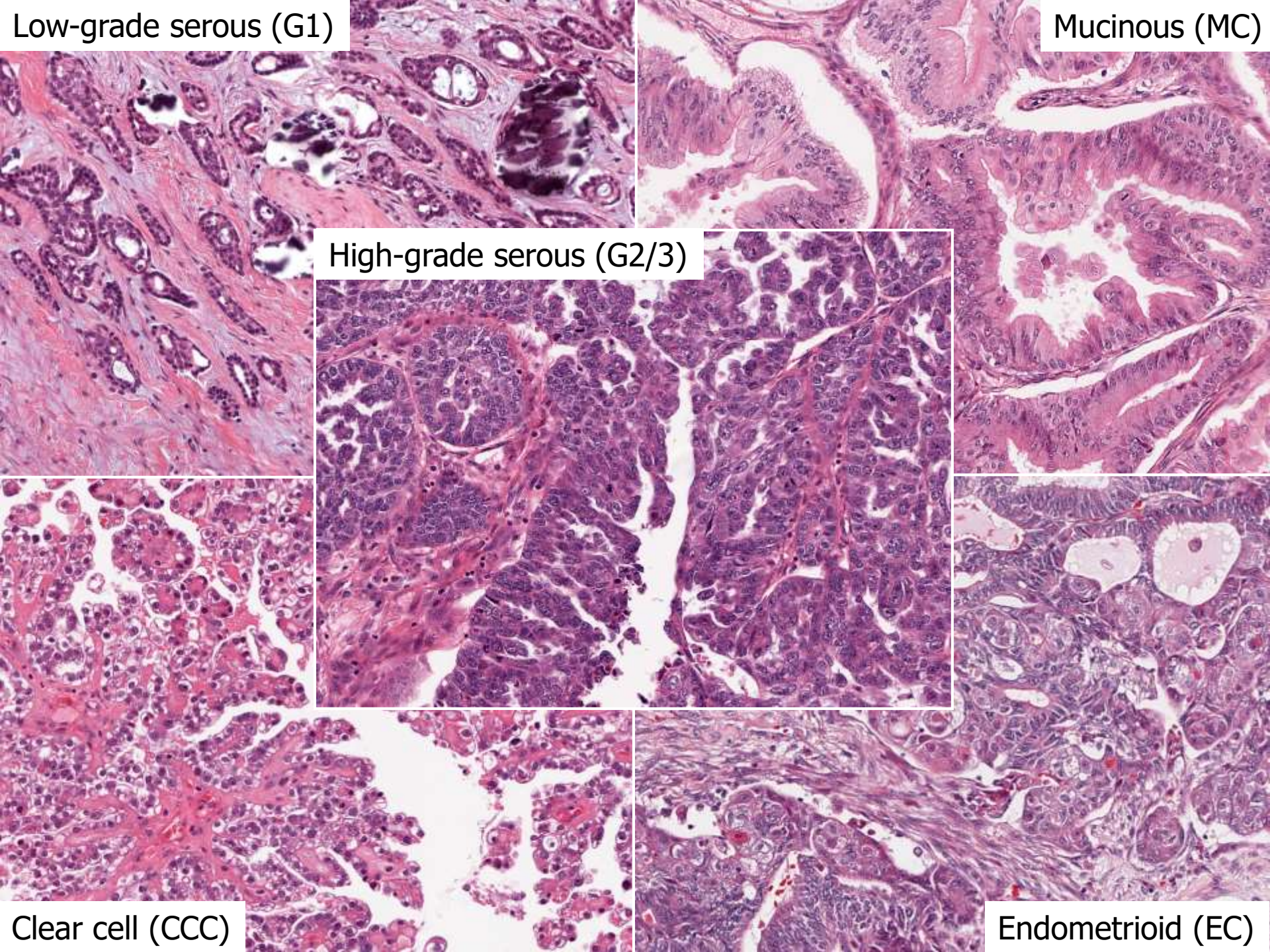
FIGO 2013 ovarian cancer staging: Additional requirements

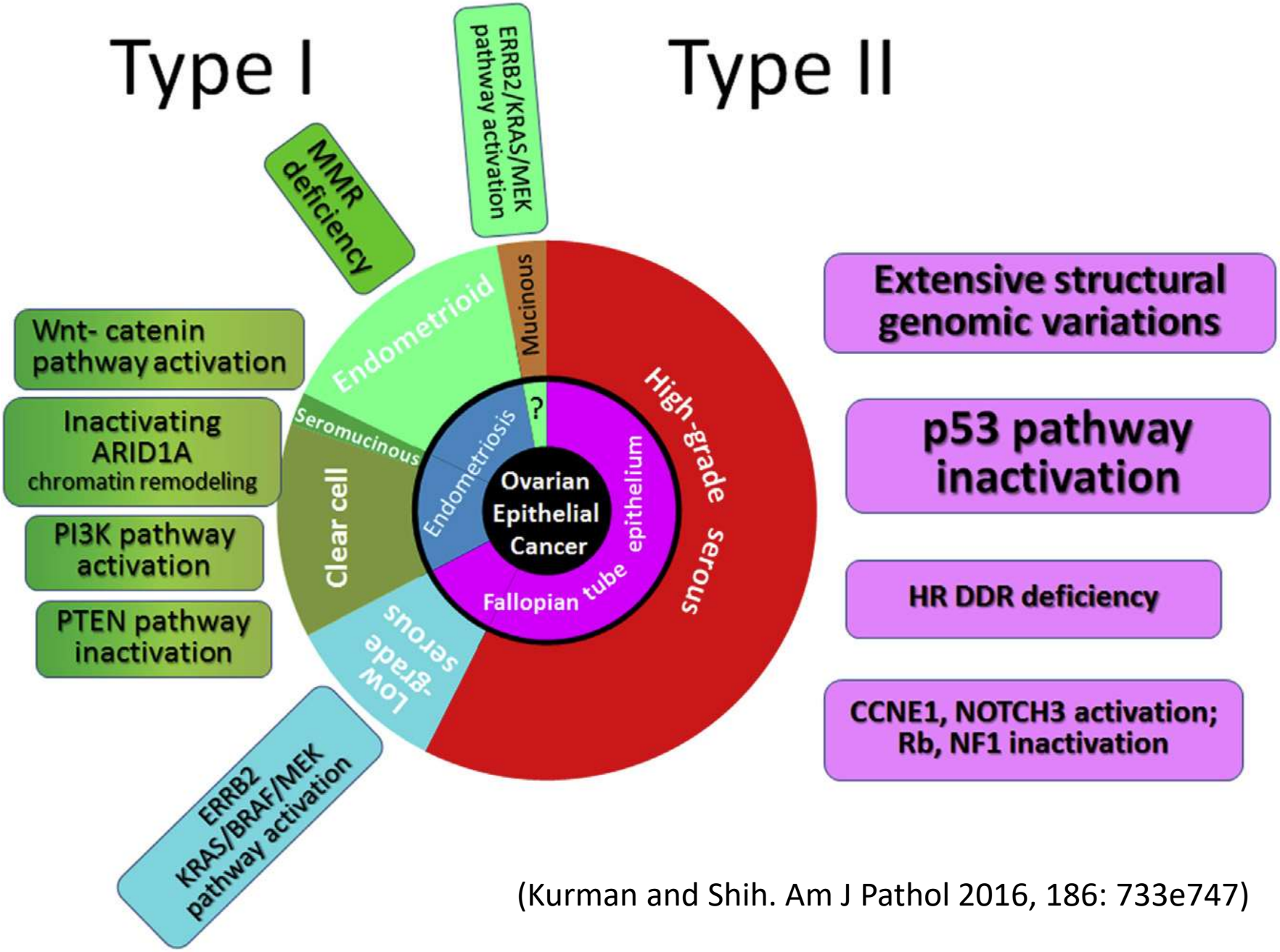
- Designate histotype

- Designate primary site (O, T, P, U)



Gilks and Prat. Human Pathology (2009) 40, 1213–1223


Low-grade serous (G1)
Mucinous (MC)
High-grade serous (G2/3)
Clear cell (CCC)
Endometrioid (EC)



(Kurman and Shih. Am J Pathol 2016, 186: 733e747)

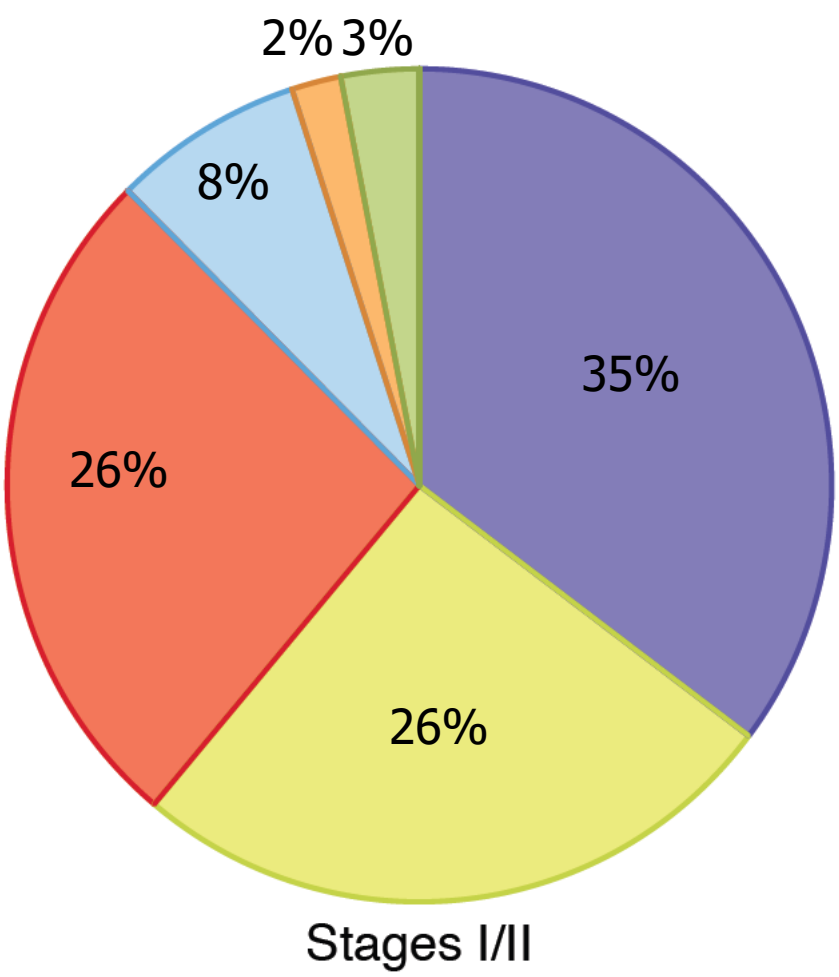
Morphologic and Molecular Characteristics of Mixed Epithelial Ovarian Cancers

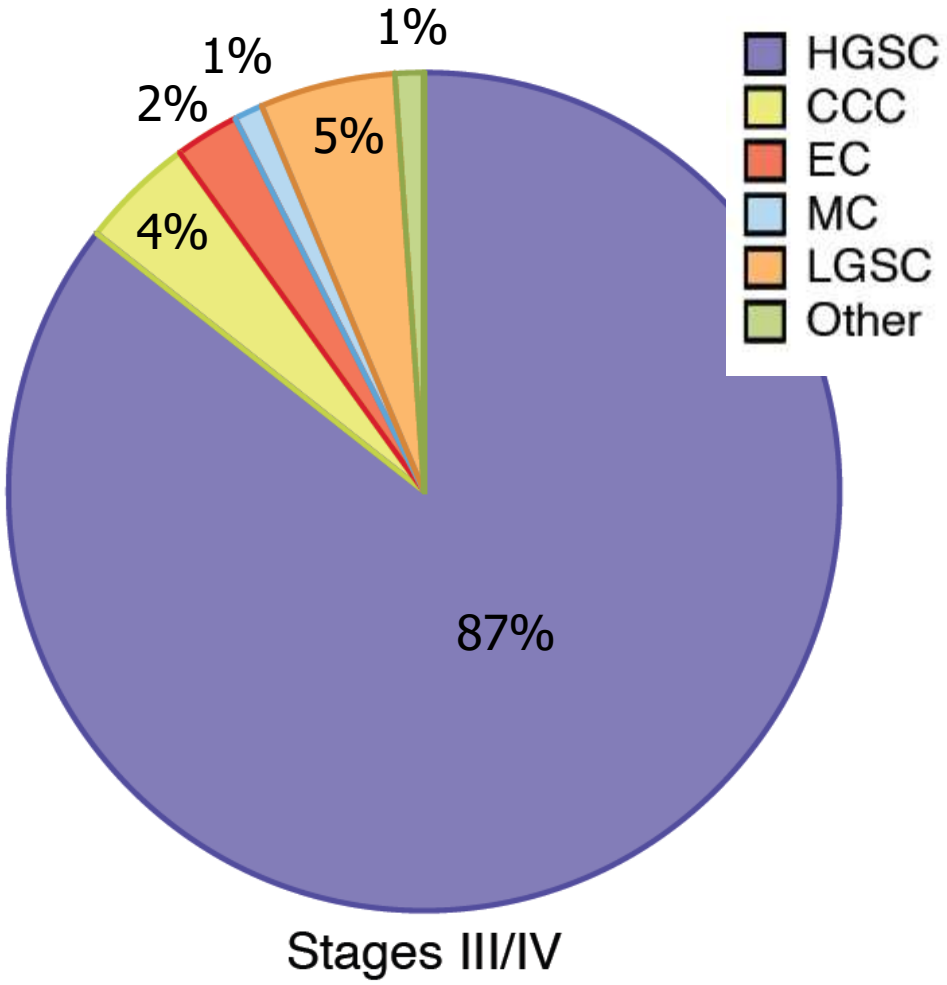
Robertson Mackenzie, BSc, Aline Talhouk, PhD,† Sima Eshragh, MD,‡ Sherman Lau, BSc,‡ Daphne Cheung, BMLSc,‡ Christine Chow, BMLSc,‡ Nhu Le, PhD,§ Linda S. Cook, PhD,‖ Nafisa Wilkinson, MD,¶ Jacqueline McDermott, MD,# Naveena Singh, MD,# Friedrich Kommoss, MD,** Jacobus Pfisterer, MD,†† David G. Huntsman, MD,*†‡‡ Martin Köbel, MD,§§ Stefan Kommoss, MD,‖‖ C. Blake Gilks, MD,†‡ and Michael S. Anglesio, PhD†‡‡*

Am J Surg Pathol 2015

- <1% truly mixed
- Usually endometriosis-related histotypes
- Mixed [ECa + CCC] and [ECa + LGSC] accounted for most cases

Five major types - stage





Int J Gyn Pathol, 2010, 29: 203-11

Reasons for Accurate Subtyping: Treatment

- Platinum sensitivity
- Surgery vs NACT
- ?RT in CCC
- Other treatment: entry to clinical trials; personalised medicine

Reasons for Accurate Subtyping: Genetics assessment

Genetic Testing and Cancer Prevention

- HGSC: BRCA1, BRCA2, hereditary breast-ovarian cancer syndromes
- Non-Serous Ca (CCC and EC): Lynch Syndrome
- SCCHT: 40% hereditary
- Sertoli-Leydig cell tm (mod-poorly diff): DICER1
- SCTAT: Peutz-Jeghers

High grade serous carcinoma, HGSC what matters?

- Primary site
  - Correct sampling of tubes
  - Correct identification of STIC
- Stage in low-stage disease
- Terminology: Tubo-ovarian or tubal/ovarian; NOT ovarian/tubal/PERITONEAL
- IHC; p53 IHC patterns
- Chemotherapy response reporting
- Eligible for hereditary ca assessment (direct to testing)
- (Node dissection not indicated - will receive adjuvant treatment irrespective of nodal status)

Site Assignment in HGSC

- **TUBAL**, in the presence of:
  - STIC
  - Invasive *mucosal* carcinoma
  - Part or all of tube is incorporated into tubo-ovarian mass
- **OVARIAN**, in the absence of tubal involvement as above
- **PERITONEAL**, in the absence of gross or microscopic involvement of tubes (mucosal) and ovaries (WHO 2014)
- **TUBO-OVARIAN** if diagnosis based on small samples/post chemo/post-BSO when tubes were not fully examined
- **UNDESIGNATED:** USE SPARINGLY! (genuine uncertainty between uterine vs tubo-ovarian)

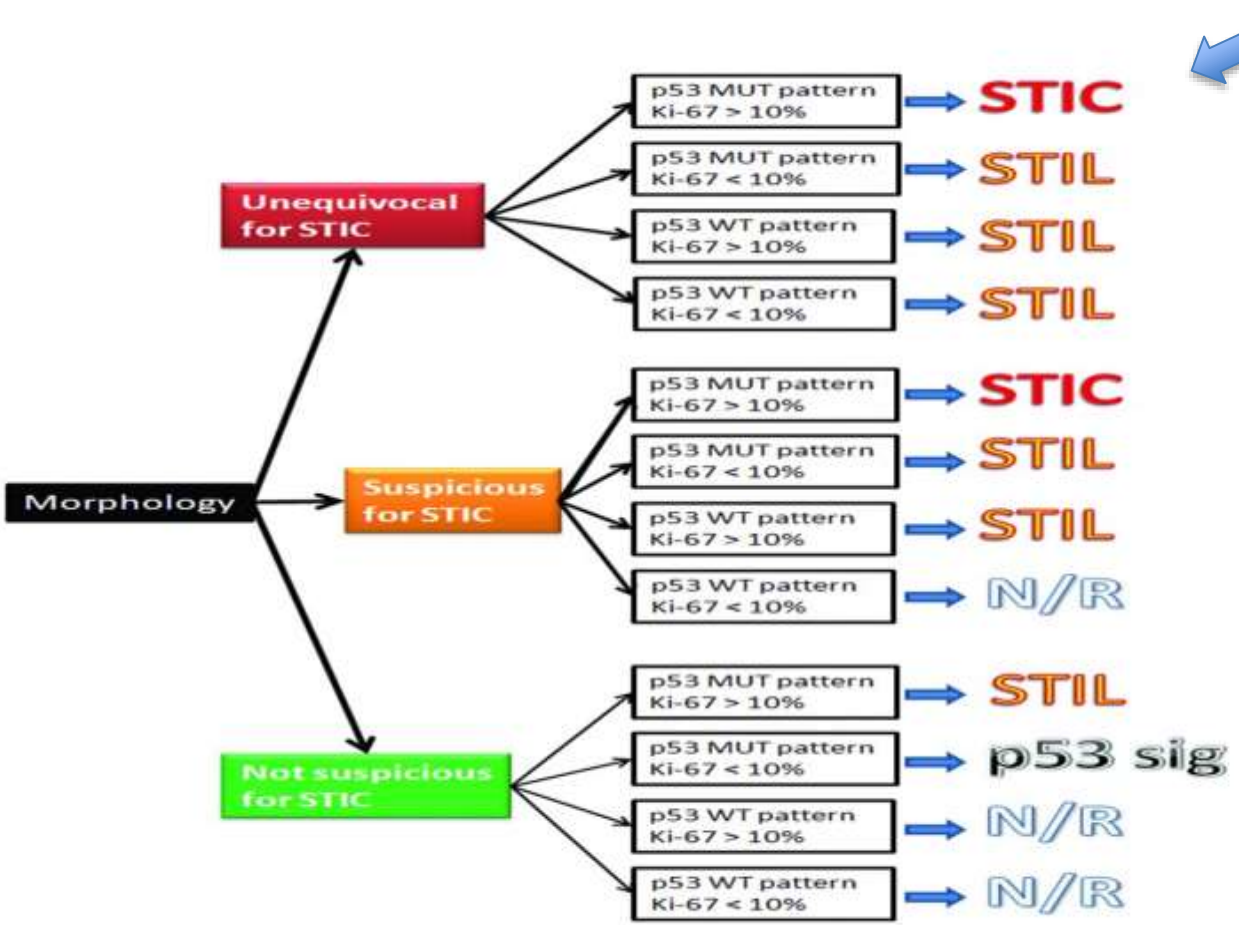
If not happy with this at least say TUBO-OVARIAN!

Gynecol Oncol 2016; 141:195.
CAP checklist 2016.

Does site assignment matter?

- Not for patient management
- Paradigm shift, pathologist-led
- Impacts on stage assignment

STIC detection – Diagnostic criteria



(IHC probably not necessary in morphologically clearcut lesion)

Lesions other than STIC

- (STIC = morphology atypical PLUS p53 mutant PLUS Ki67 >10%)
- STIL = morphology atypical but only one out of p53 mutant and Ki67>10%
- p53 signature = morphology NORMAL but p53 mutant

Lesions other than STIC, should we report?

- STIC → clinical implications: site assignment, stage, mandates surgical staging, ???chemo
- STIL → report but state significance uncertain
- p53 signature → no clinical implications; do NOT report OR state its biological implications are unclear

FIGO stage in low-stage disease – controversial areas

- Does STIC constitute ‘involvement’?
  - “STIC capable of metastasising therefore cannot be considered as *in-situ*”
  - Recommend stage as IA
  - ***But*** stage as IIa “only when there is ‘direct evidence’ of spread”
  - Lesions identical to STIC may represent metastases
- Does bilateral adnexal involvement represent independent primary or metastasis
  - Stage IB represent 1-5% of stage I carcinomas

Reasons to adopt uniform protocol

Uniformity in primary site assignment

Results of international survey (173 pathologists from different countries):

Fallopian tube STIC + ovary HGSC (no other disease site)

- Ovary primary: 40%
- FT primary: 60%

McCluggage et al, 2016

Reasons to adopt uniform protocol

Uniformity in staging FIGO I and II

Results of international survey (173 pathologists from different countries):

Fallopian tube STIC + ovary HGSC (no other disease site)

- Stage I: 42%
- Stage II: 58%

McCluggage et al, 2016

Reasons to adopt uniform protocol

Uniformity in staging FIGO I and II

- Stage I/II constitute <10% of all cases in historic data
- Likely to change with
  - ↑Opportunistic salpingectomy **(careful macroscopic examination and representative sampling)**
  - Earlier detection
- Consistent staging →whether staging provides valid prognostic grouping

Bilateral HGSC is clonal based on *TP53* sequencing

No	Site 1, nature and size	Site 2, nature and size	Common TP53 alteration			COSMIC
			CDS	AA	Genomic Start	
1	RO, 130mm HGSC	LO, 100mm HGSC	c.613_614A>CC	p.Y205fs	Chr17:7578234	No*
2	LFT, 40mm, HGSC	RFT, 22mm HGSC	c.746G>T	p.R249M	Chr17:7577535	COSM43871
3	LO, 130mm HGSC	RO, 3mm HGSC	c.451C>T	p.P151S	Chr17:7578479	COSM10905
4	RO, 150mm HGSC	LFT, STIC and 12mm HGSC	c.701A>G	p.Y234C	Chr17:7577580	COSM10725
5	RFT, 7mm HGSC	LO, 4mm HGSC	c.524G>A	p.R175H	Chr17:7578406	COSM10648
6	RO, 90mm HGSC	LFT, STIC	c.672+1G>A	(intronic/ splice)	Chr17:7578176	COSM6906
7	LO, 220mm	RFT, HGSC 0.5mm and STIC	c.742C>T	p.W248R	Chr17:7674221	COSM10656

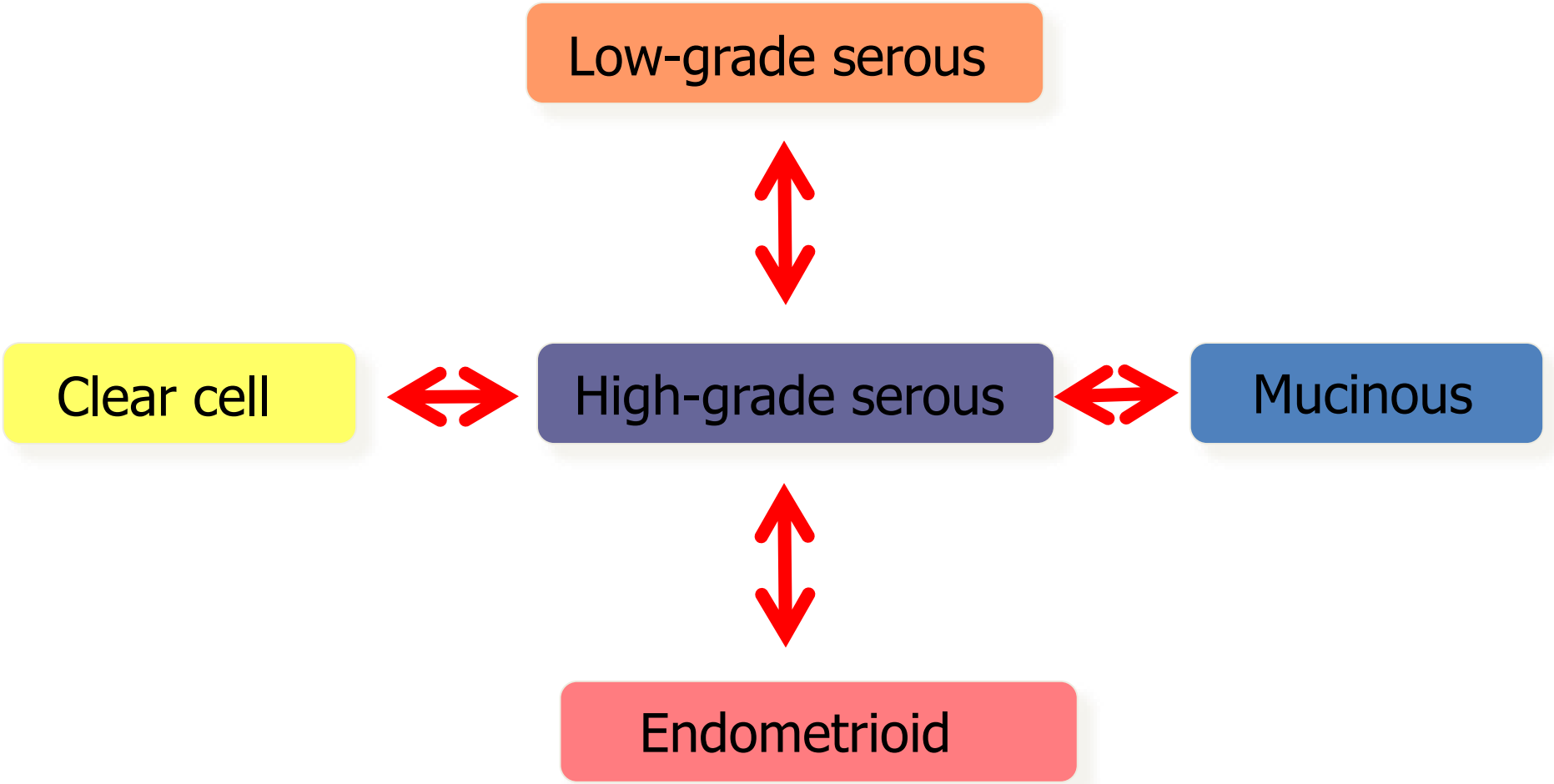
Singh et al, Mod Pathol, accepted

FIGO stage in low-stage disease – controversial areas

- STIC should be included in staging as a disease site as it represents either the primary OR a metastatic site

- ?Bilateral involvement in HGSC should be considered stage II (very rare)

Diagnosis of HGSC: role of IHC



IHC marker expression

	HGSC	LGSC	EC	CCC	MC
PAX8 present	98%	100%	85%	98%	35-60%
WT1 present	97%	98%	10%	1%	0.5%
TP53 abnormal	94%	0	14%	12%	61%
P16 block	65%	3%	8%	17%	10%
Napsin A present	2%	0	8%	92%	3%
PR present	37%	58%	85%	7%	4%
ER present	93%	96%	90%	15%	9%

Int J Gynecol Pathol 2016; 35:430-441

Immunostains for histotype differential diagnosis:

- **Too many stains are not necessary!**

- HGSC vs LGSC: p53
- Serous vs Endometrioid: WT1, p53
  - LGEEC can be WT1 positive; consider reporting as mixed LGSC-EEC; try MMR; other EC-related morphology
  - HGEEC can be p53 mutant; but not WT1 positive
- Clear Cell vs Serous: WT1, ER, Napsin A
- Mucinous vs Endometrioid: ER

- **Co-expression of WT1 and p53 has very high specificity for HGSC**

HGSTOC vs USC

- Different entities biologically and clinically
- Distinction has implications for management and genetic counseliing

- Disease distribution
- Status of tube: FT involved in 20% of USC, fimbrial in 50% of these (Kommoss et al 2017)
- WT1: but some USC can be WT1 positive
- Discuss difficulties at MDT

p53 IHC in HGSC

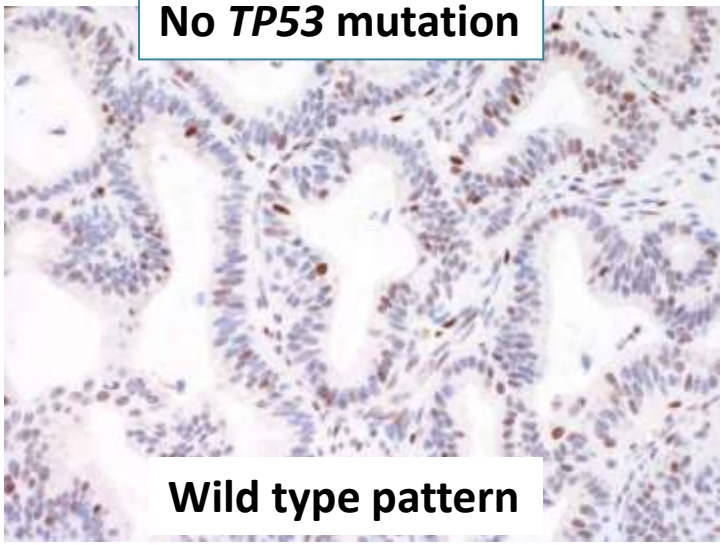
- (p53 IHC interpretation is tumour-specific)

- Optimised p53 IHC is good surrogate for *TP53* mutation

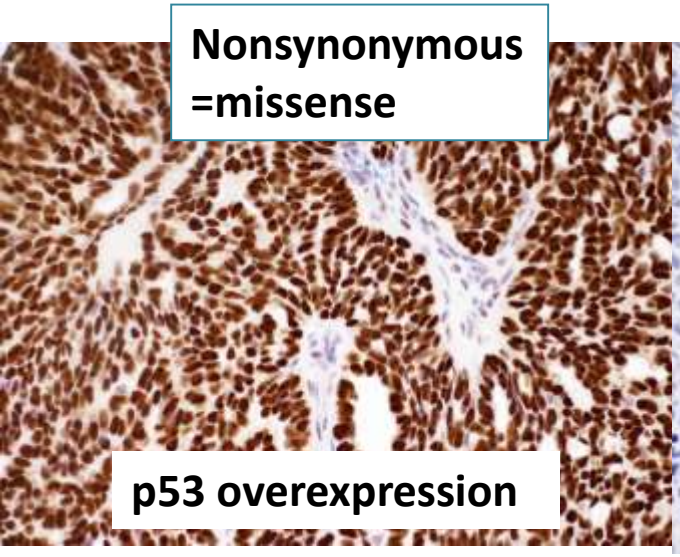
- **Optimisation of protocol is essential**
- **Correct interpretation is essential**

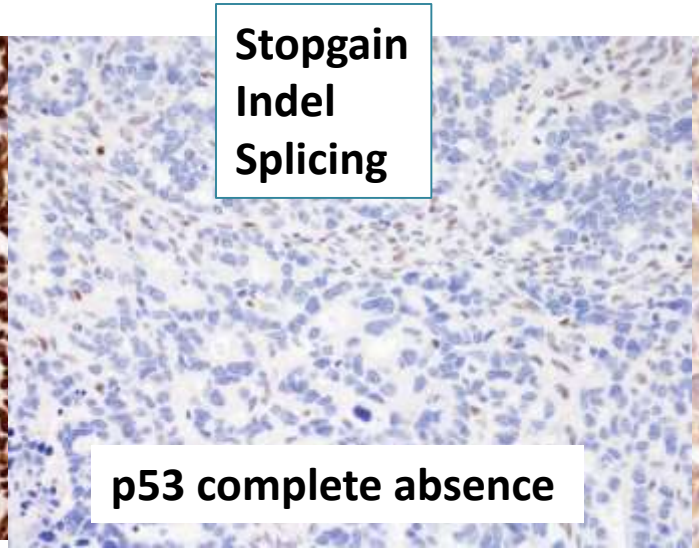
- Classically “all or none”
- Recent identification of further patterns

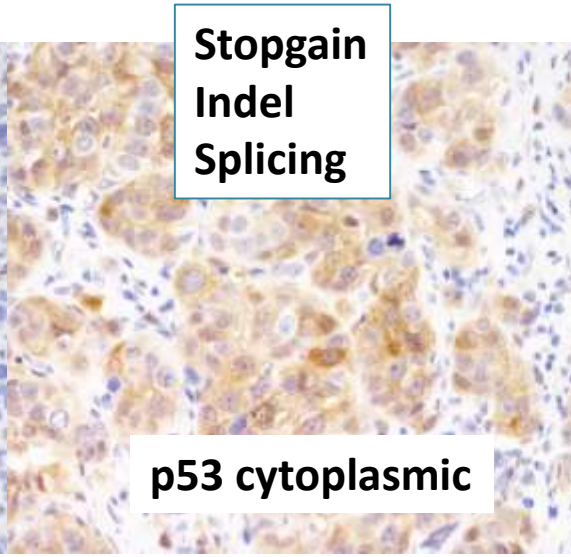
Interpretation of p53 immunohistochemistry



Normal







Abnormal

J Pathol Clin Res 2016;2:247

p53 IHC Interpretation

(www.thebagp/resources)

Pattern	p53 IHC interpretation	*TP53* mutation type	Frequency in HGSC
		***TP53* MUTATION ABSENT**	
Wild type	Normal	No mutation	<1%
		***TP53* MUTATION PRESENT**	
Overexpression	Abnormal	Non-synonymous (missense); also in-frame deletion, splicing	66%
Complete absence/ null	Abnormal	Indels, stopgains, splicing mutations	25%
Cytoplasmic	Abnormal	Indels and stopgains with disruption of the nuclear localization domain	2%
Wild type	Normal	Truncating mutation	4%

p53 IHC In Clinical Practice, results of a BAGP project: Interpretation Summary

		Review result				
Participant Result		OE	CA	WT	NA	TOTAL
	oe	**385**	2	9	11	407
	ca	4	**474**	102	320	900
	cy	3	0	28	5	36
	wt	36	73	**1858**	139	2106
	na	7	12	47	139	205
	total	435	561	2044	614	3654

Overall concordance (excluding NA): 2717/3040 (89.4%)

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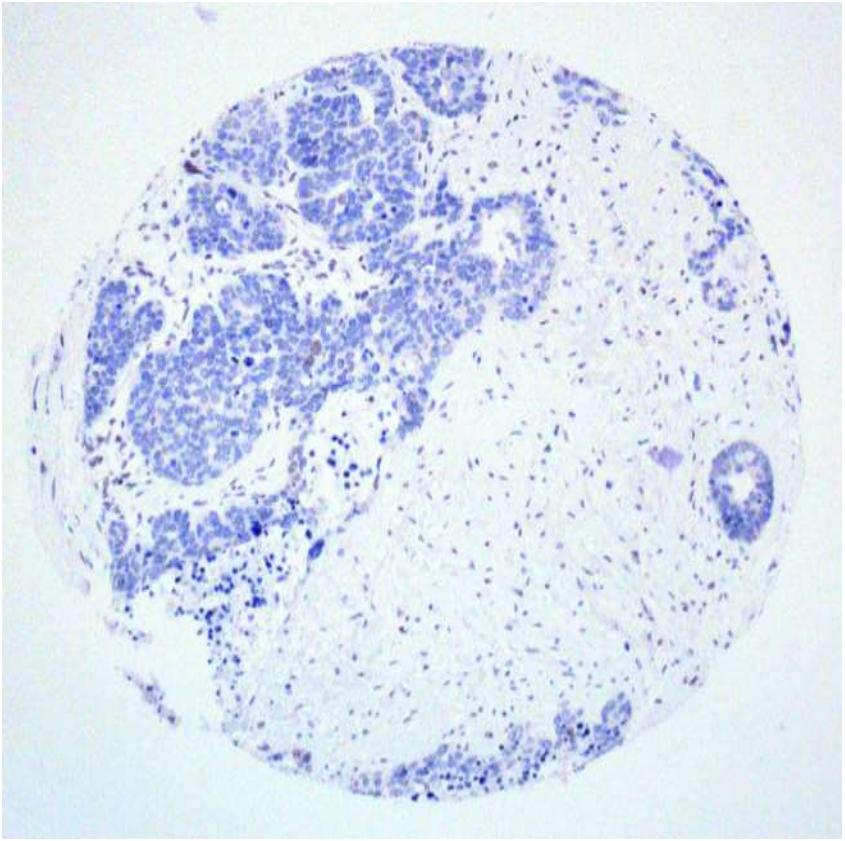
	total	435	561	2044	**614**	3654

614/3654 (16.8%) cores deemed not assessable (NA) on central review

Absent staining in internal control



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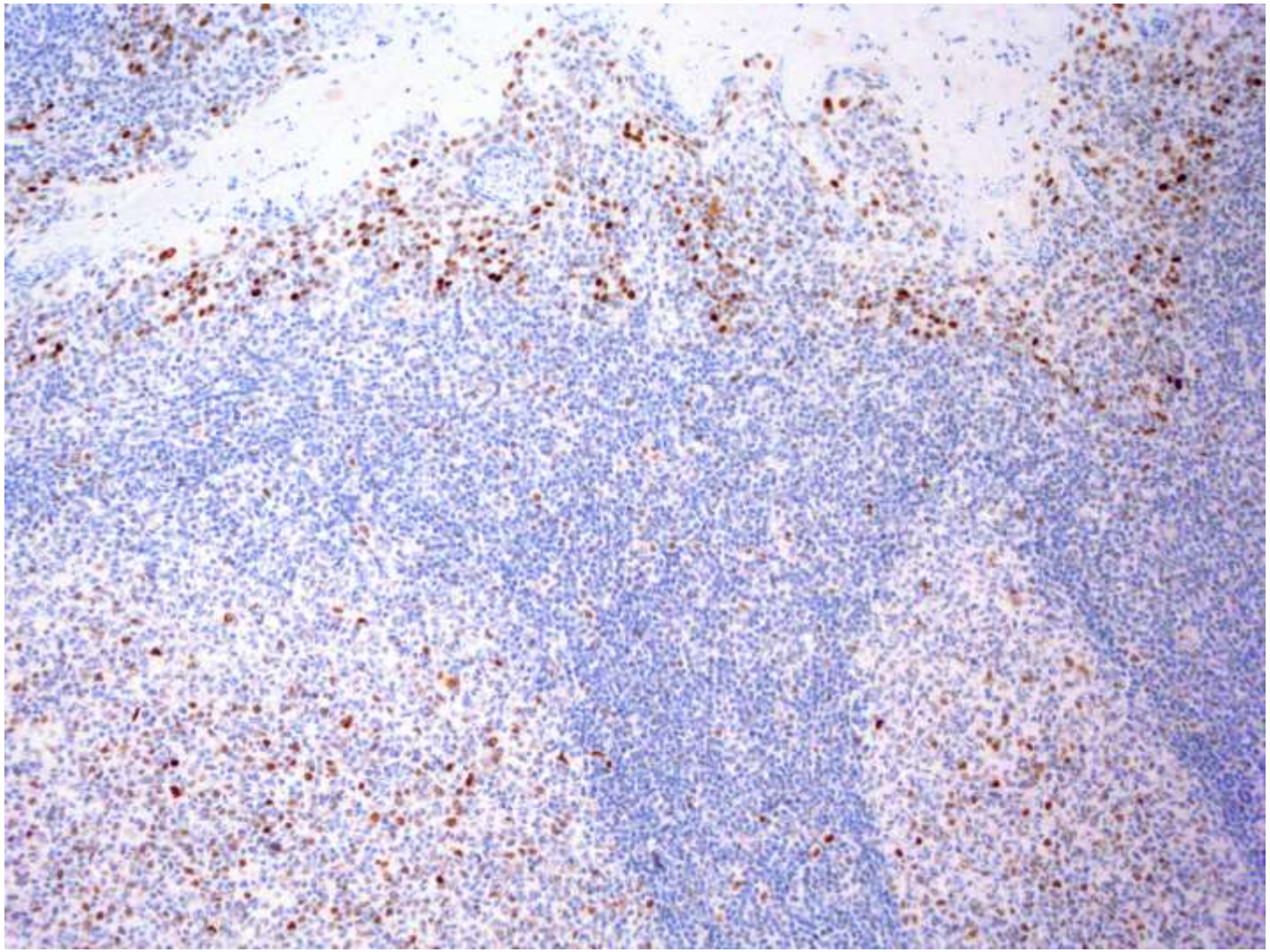
Single commonest reason for discrepancy: WEAK staining

Optimal On-slide Control for p53: TONSIL



p16 in HGSC

- Often equated with p53 in significance
- About 60% show diffuse positive (block) staining
- Heterogeneous, and therefore of no diagnostic value in the remainder in distinguishing from other OC histotypes
- Prognostic value reported; needs further study

Chemotherapy Response Score: included in ICCR and CAP datasets

CRS 1: No or minimal tumour response

(mainly viable tumour with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci)

CRS 2: Appreciable tumour response with residual tumour, both readily identified

(ranging from multifocal or diffuse fibro-inflammatory regressive changes, with tumour in sheets, streaks or nodules, to extensive regression associated fibro-inflammatory changes with multifocal residual tumour which is **regularly** distributed and easily identifiable)

CRS 3: Complete or near-complete response

(mainly regression associated fibro-inflammatory changes with minimal (very few **irregularly** scattered individual tumour cells or cell groups) or nodules up to 2mm OR no residual tumour identified)

Only **omental** sections are scored

CRS summary

- CRS allows for uniform reporting to NACT in IDS
- Worst omental section scored (4-6 routine sections)
- Simple, reproducible, irrespective of experience
- Predicts PFS and OS
- CA125 response does not predict CRS
- ?Independent of debulking status
- Predicts platinum response (CRS 3 94% NPV for Pt resistance)
- Clear separation of CRS 3 vs CRS 1-2
- Online teaching tool: http://www.gpecimage.ubc.ca/aperio/images/crs

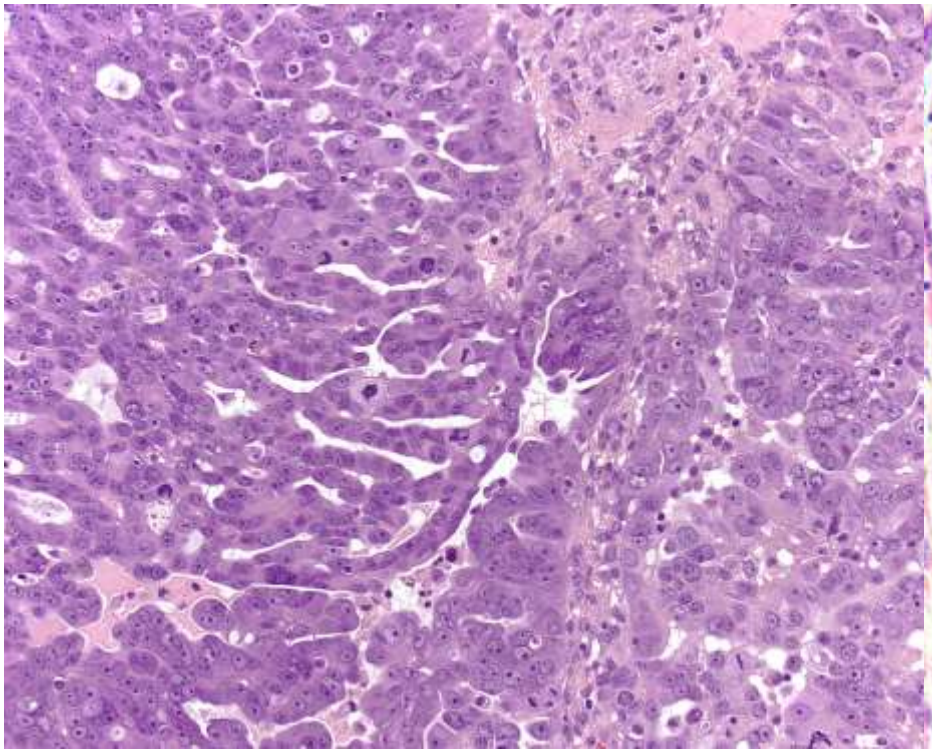
CCC, EC, LGSC: What matters?

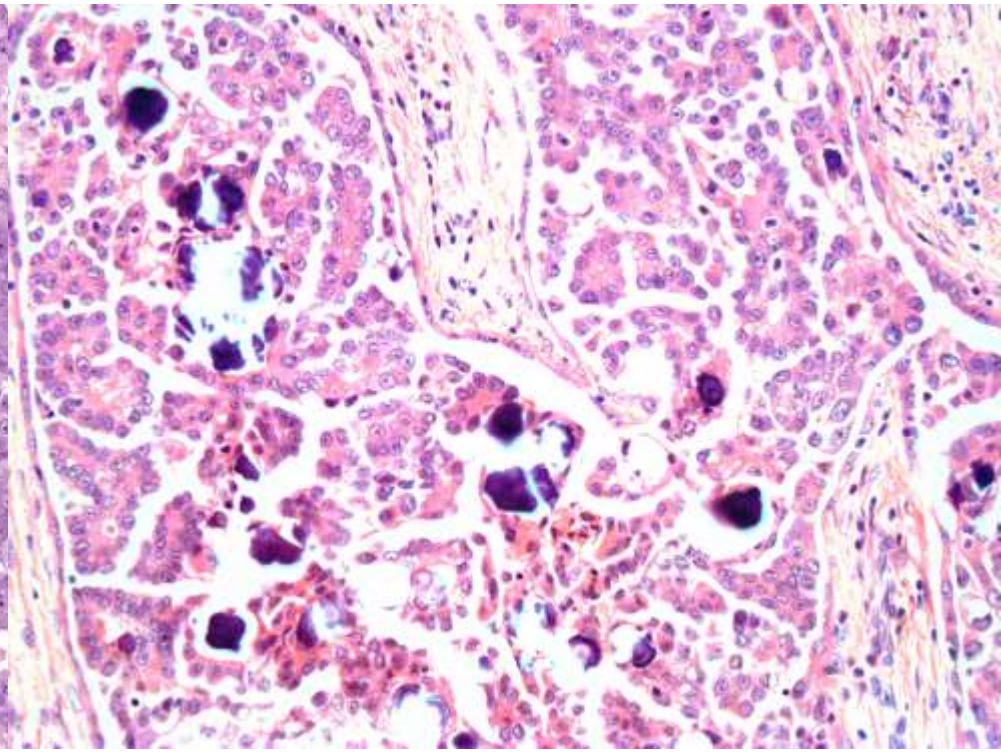
- Correct distinction from HGSC: rare patterns; IHC
- Correct distinction from each other: LGSC with glandular pattern; EC resembling SBT/LGSC; CCC resembling EC/SBT
- Can co-exist
- MMR IHC; LS screening
- Refractory to platinum-based chemo
- Entry into clinical trials

Low Grade Serous Carcinoma, LGSC

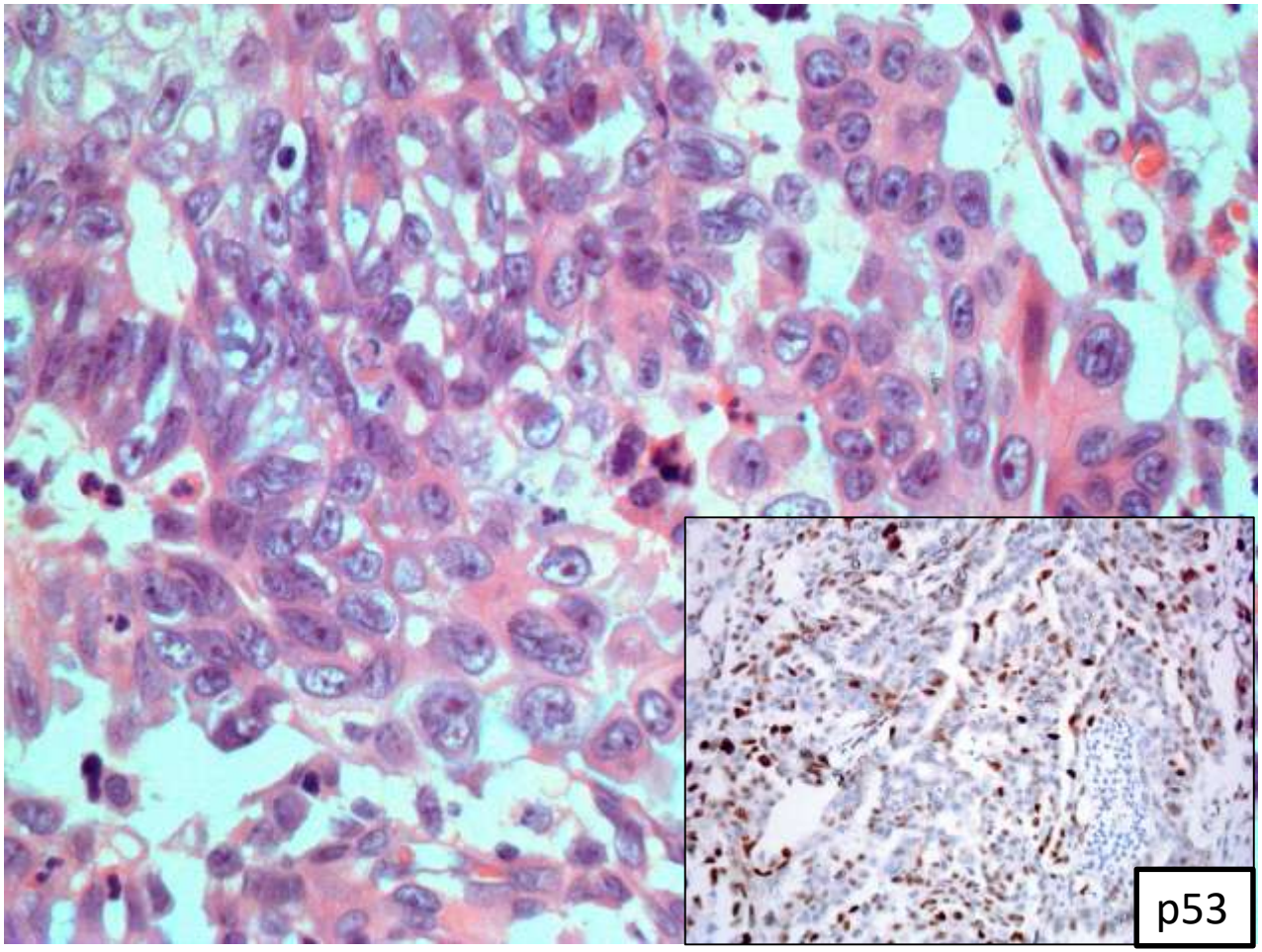
- New WHO terminology: invasion at ANY site = LGSC
- May show SBT, non-invasive implants (include in stage; qualify in comment)
- Distinguish from HGSC
  - Distinction is morphological (Malpica 2004)
  - mutant pattern p53 IHC
  - wild type expression may NOT distinguish, use other markers, eg p16

HGSC vs LGSC





HGSC vs LGSC



HGSC vs LGSC

- Do NOT occur as mixed tumours
- Transformation to high grade carcinoma is reported rarely
- RARE and DIFFICULT: focal nuclear enlargement and high mitotic activity can occur in LGSC
- Do not represent transformation to HGSC; p53 normal

Serous Borderline Tumour

“There are no borderline tumours, only borderline pathologists.”

This comment only illustrates the lack of understanding about this disease

Serous Borderline Tumour

➔ 3-10% risk of recurrence; higher in incompletely staged

➔ 4% risk of malignant transformation

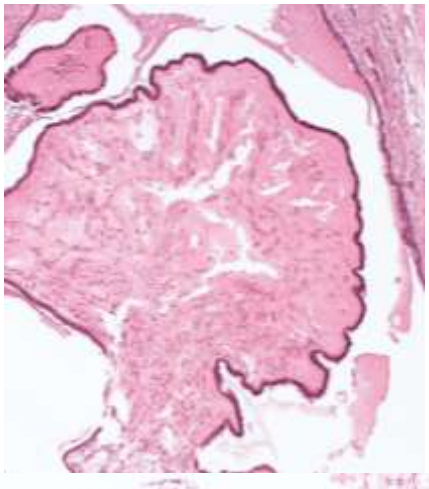
➔ Higher all-cause mortality

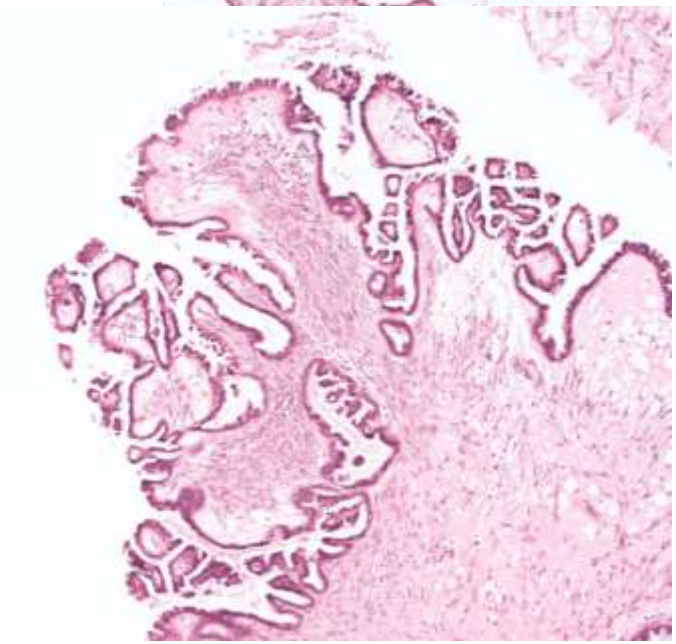
- ALL above occur irrespective of tumour morphology/stage
- All above can occur after long intervals
- At diagnosis there are few morphological and no molecular parameters to predict poor outcome

Serous Borderline Tumour (SBT)

- Diagnosis and why it matters
- Micropapillary pattern/niLGSC
- Implant morphology
- Nodal involvement: upstage but do not imply adverse outcome
- Stage
- Extent of surgery
  - Fertility sparing an option but strong consideration to completion surgery after childbearing done, if > stage Ia
  - Node dissection not indicated (unless clinically involved, then “plucked”)

SBT diagnosis: how and why

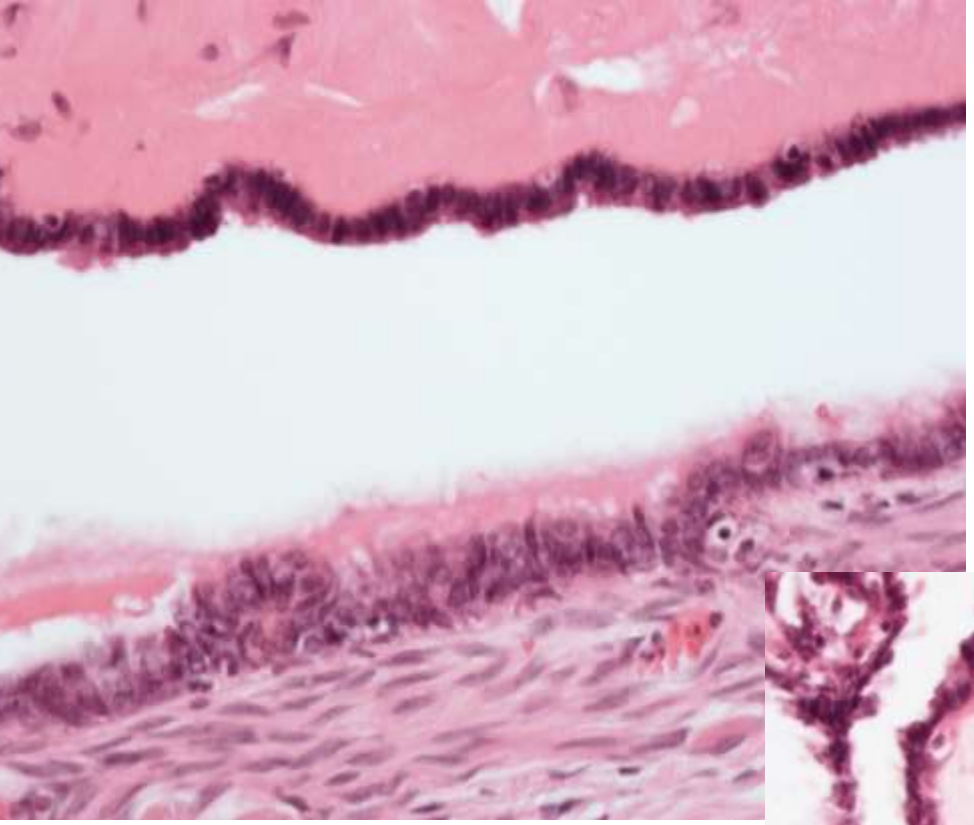


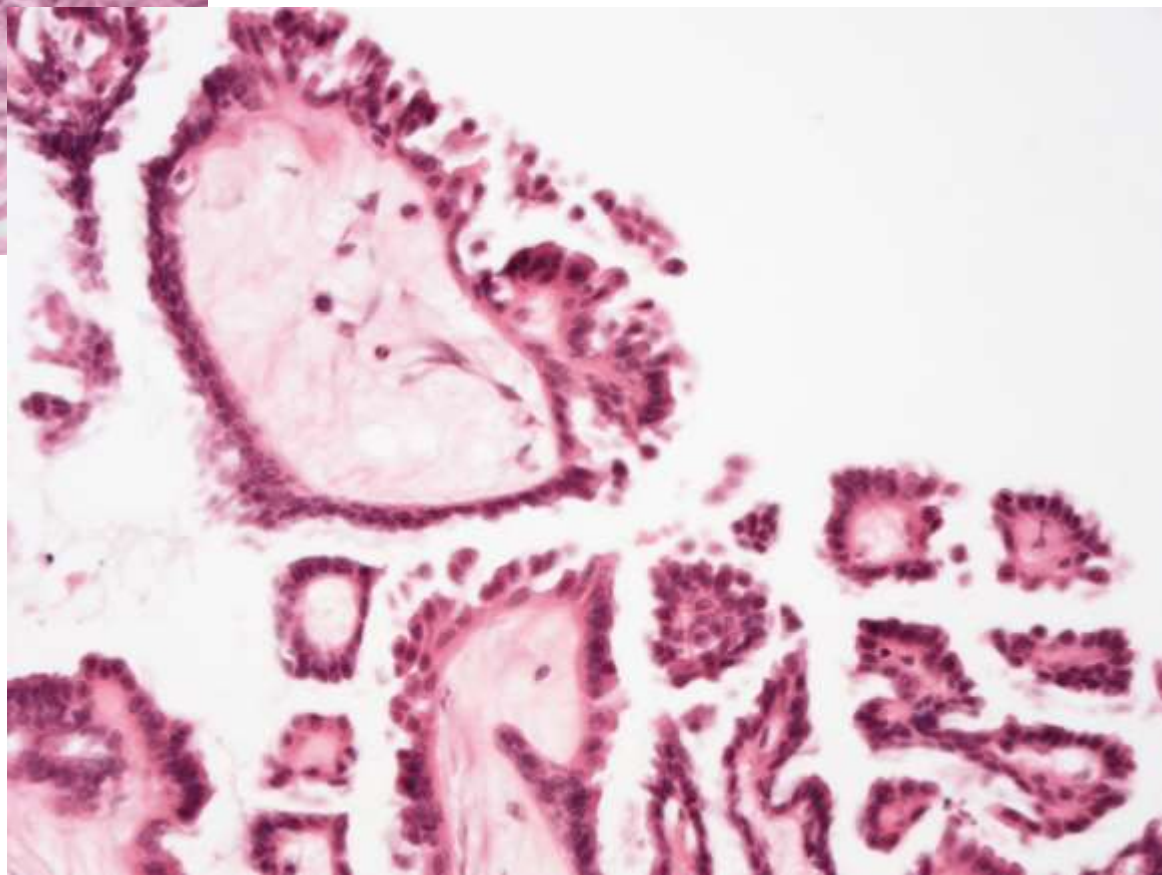


- ARCHITECTURAL features: tufts, detachment of cell groups
- >10% of epithelium

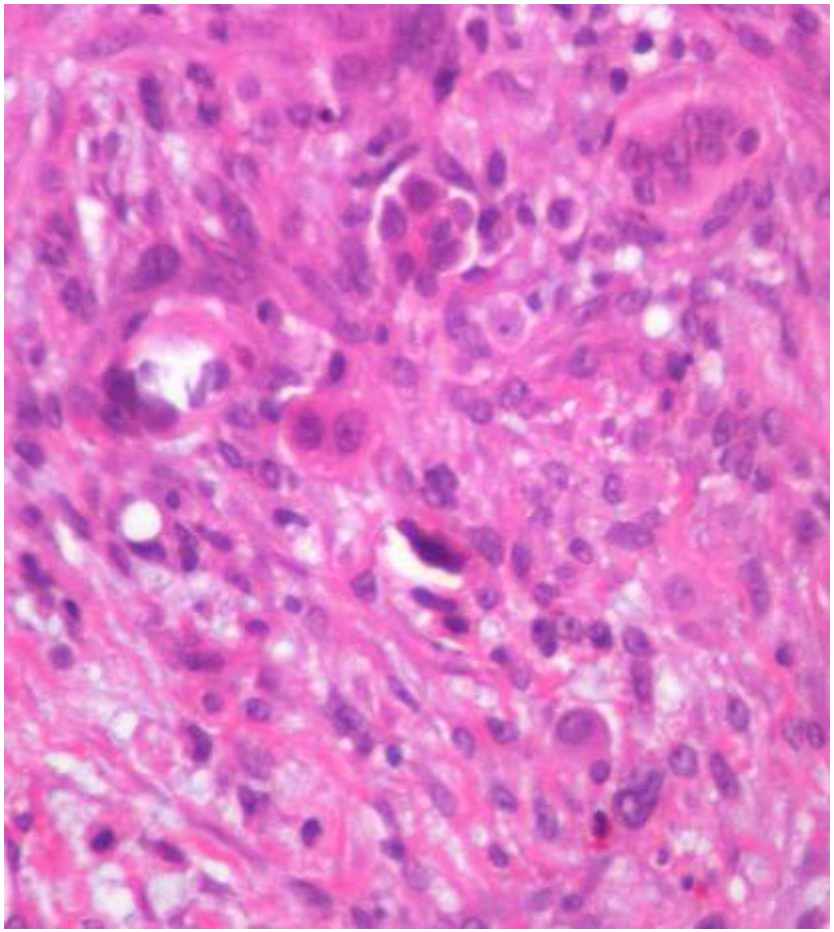
CAREFUL in presence of

- Surface involvement
- Necrosis/infarction



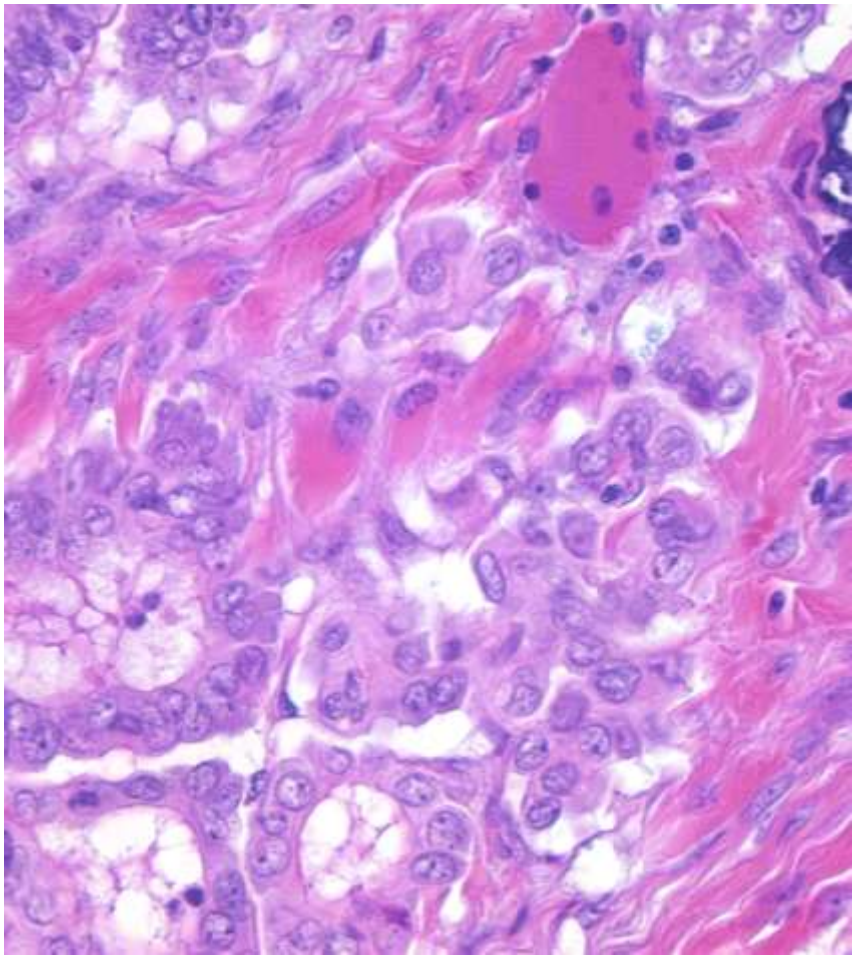


SBT: Microinvasion



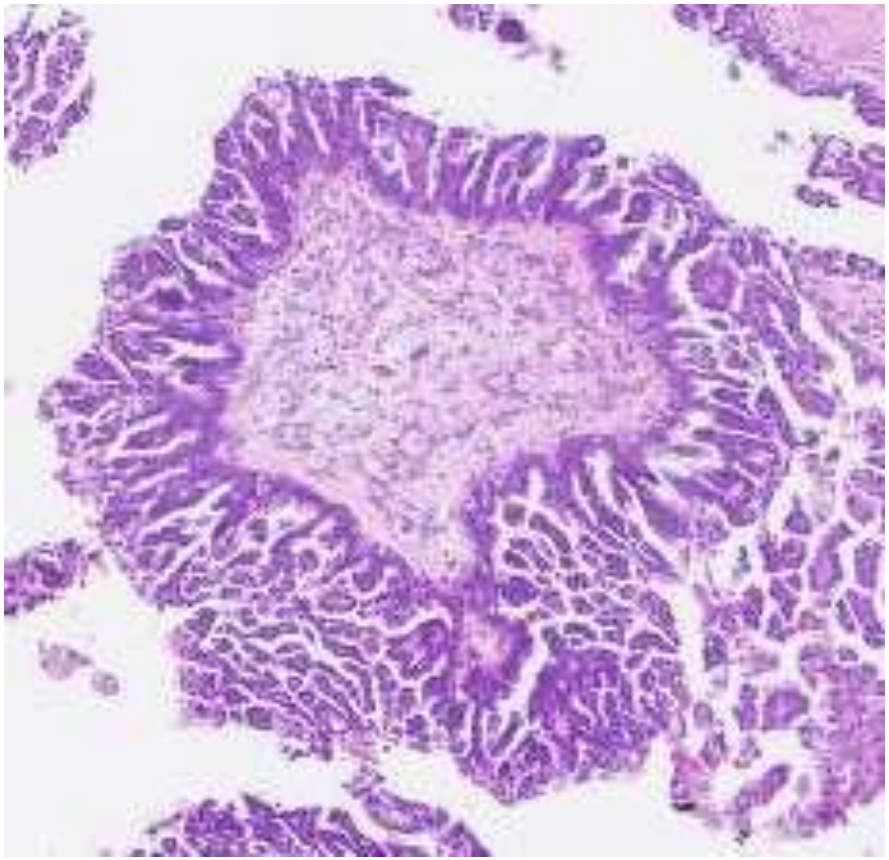
- Single cells or small papillae surrounded by cleft
- <5mm in longest dimension
- <10mm^2 in area
- No adverse impact on prognosis
- Terminally diff, senescent, low Ki67

SBT: Microinvasive Ca



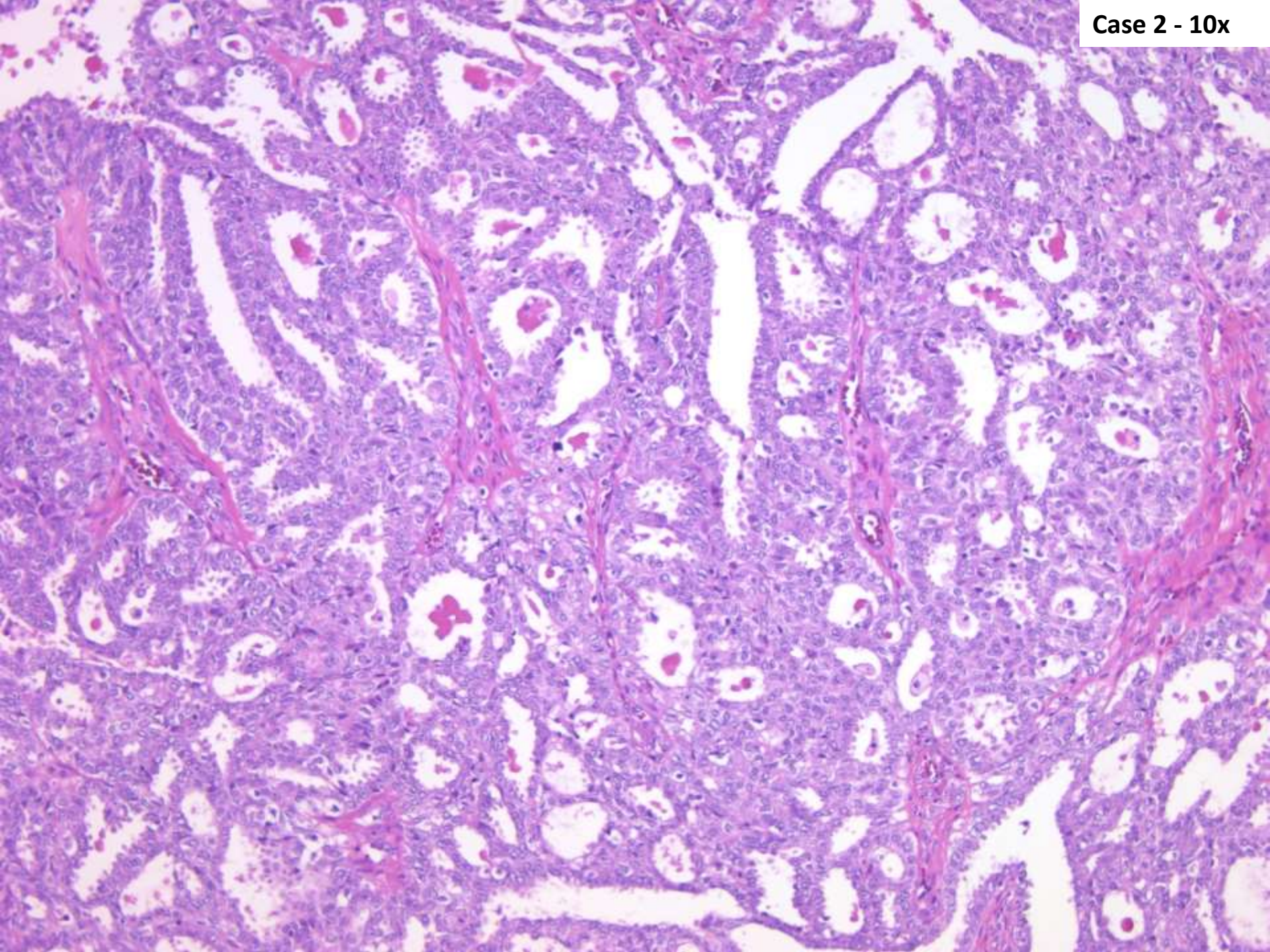
- Small foci of LGSC
- Should prompt extensive sampling
- Insufficient data to determine outcome

SBT micropapillary pattern/non invasive LGSC (8% of SBT)

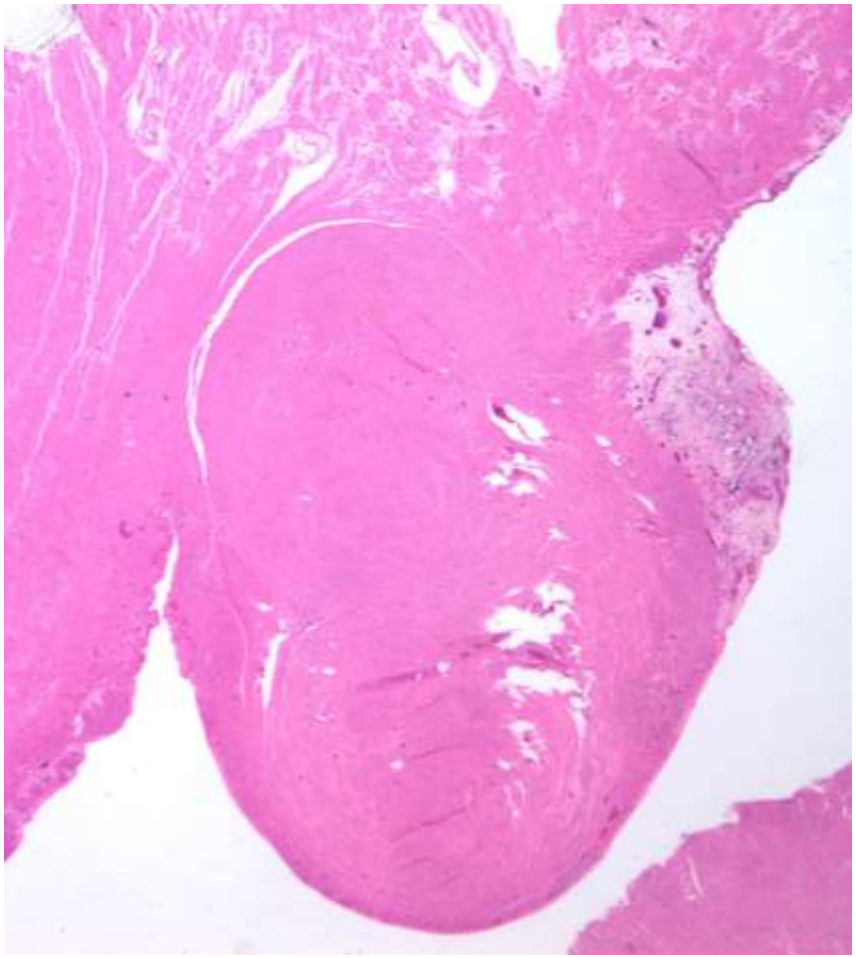


- Micropapillae 5x as tall as wide; >5mm in any one section
- May be cribriform
- ↑ Invasive implants (LGSC)
- Also ↑ LGSC with stage I disease (v few outcomes)
- → important to distinguish apart from association with invasive implants

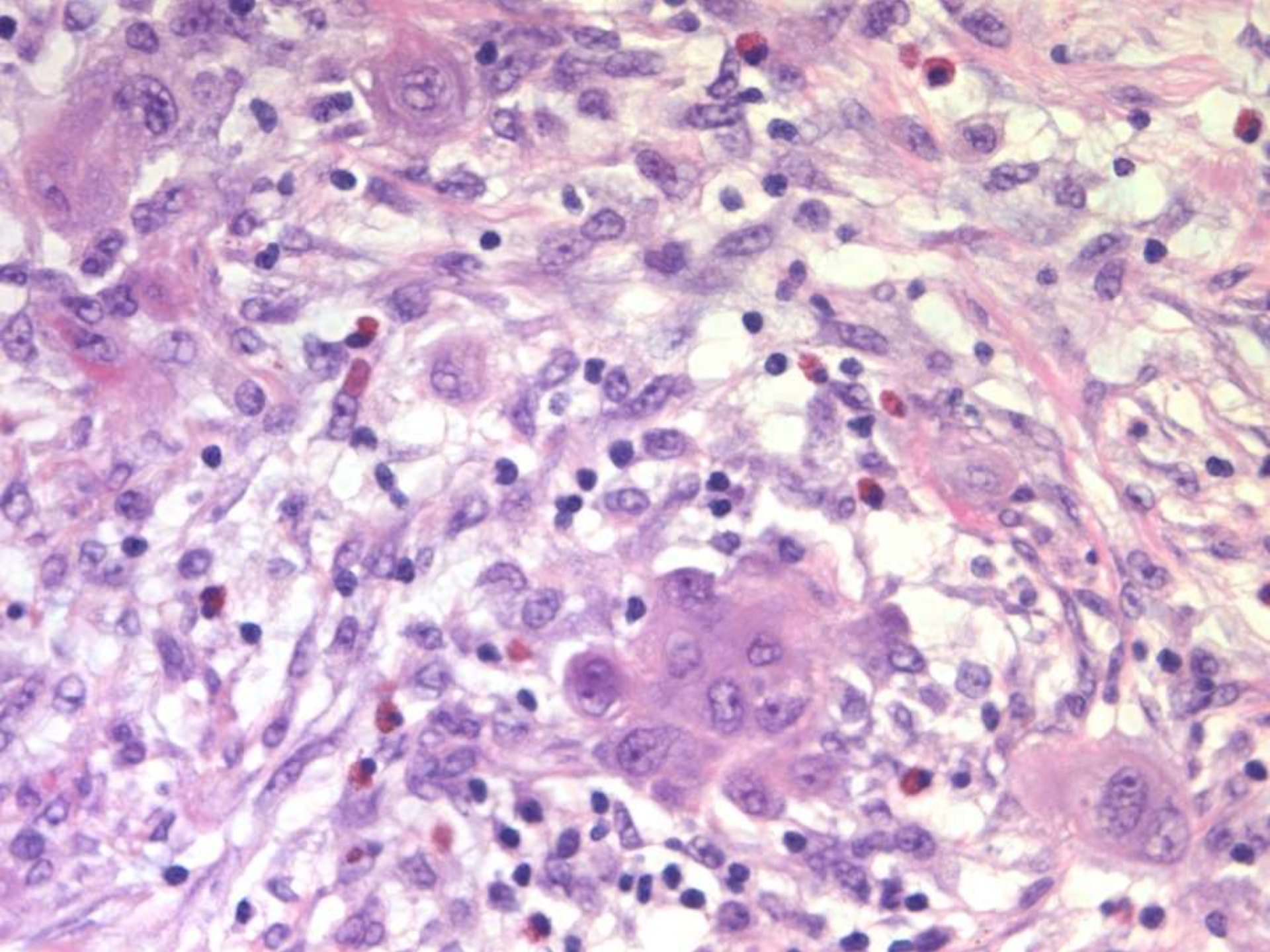
Am J Surg Pathol. 2017 Jun;41(6):725-737

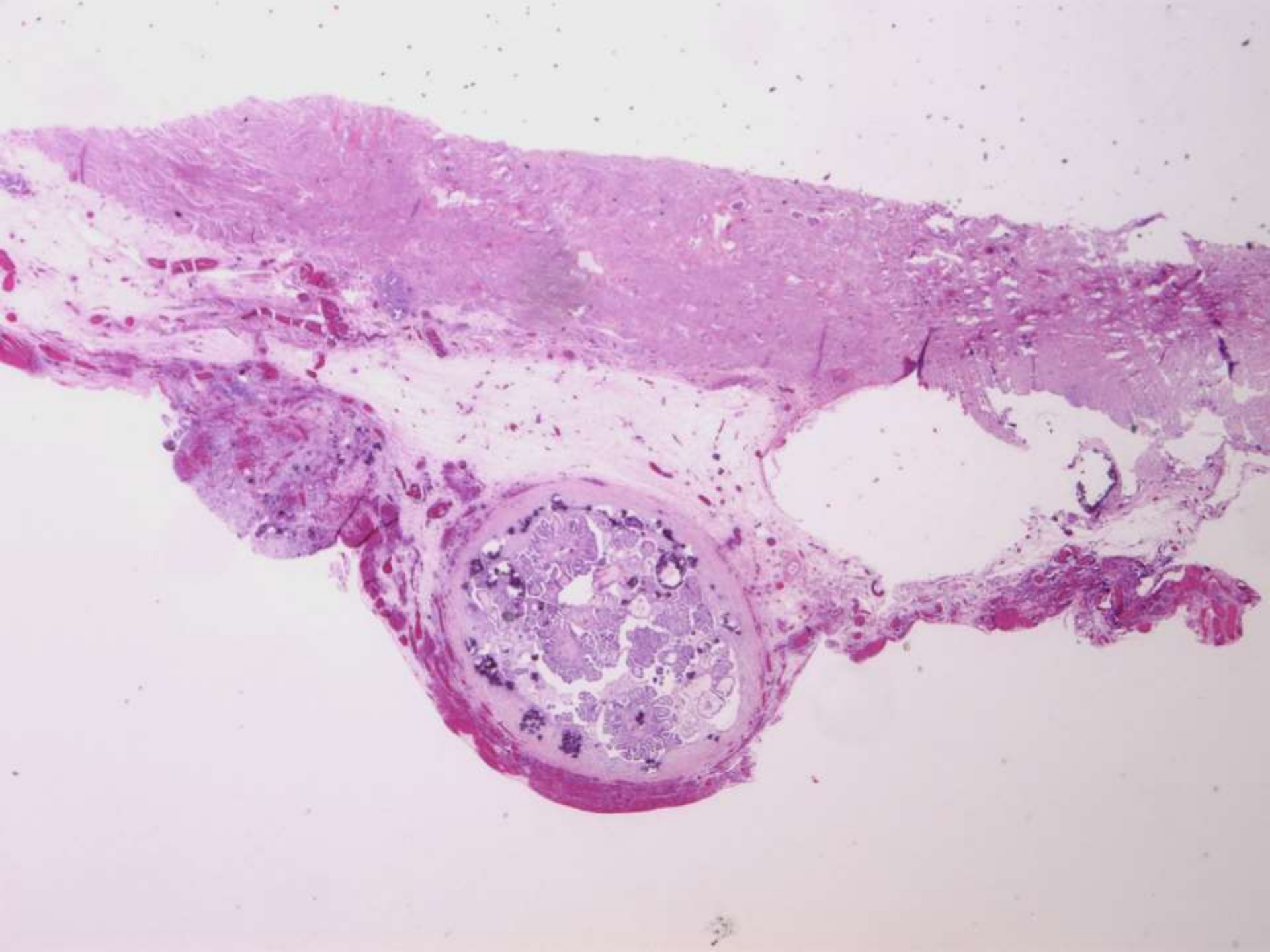

Case 2 - 10x

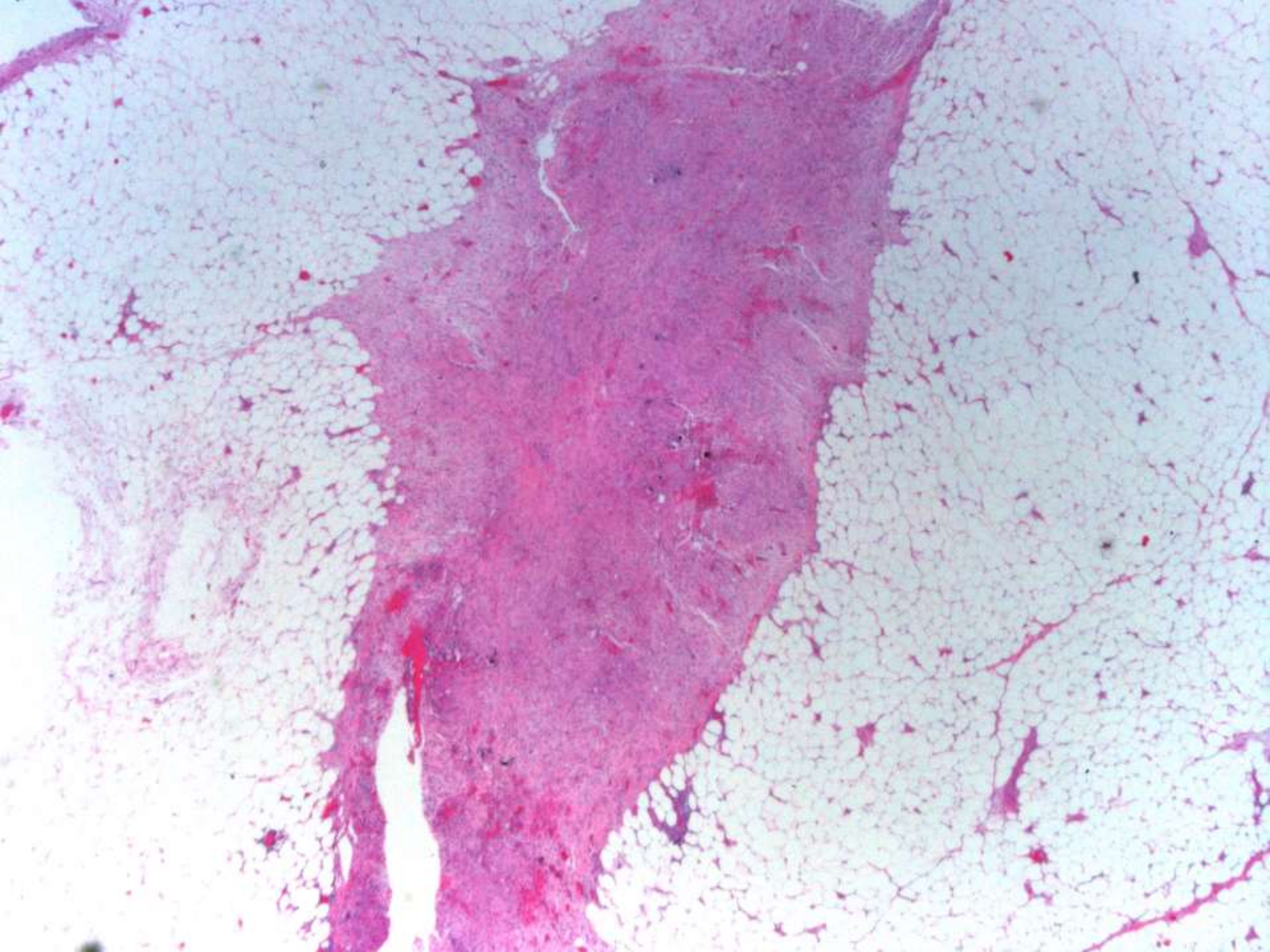
SBT: (Non-invasive) Implants

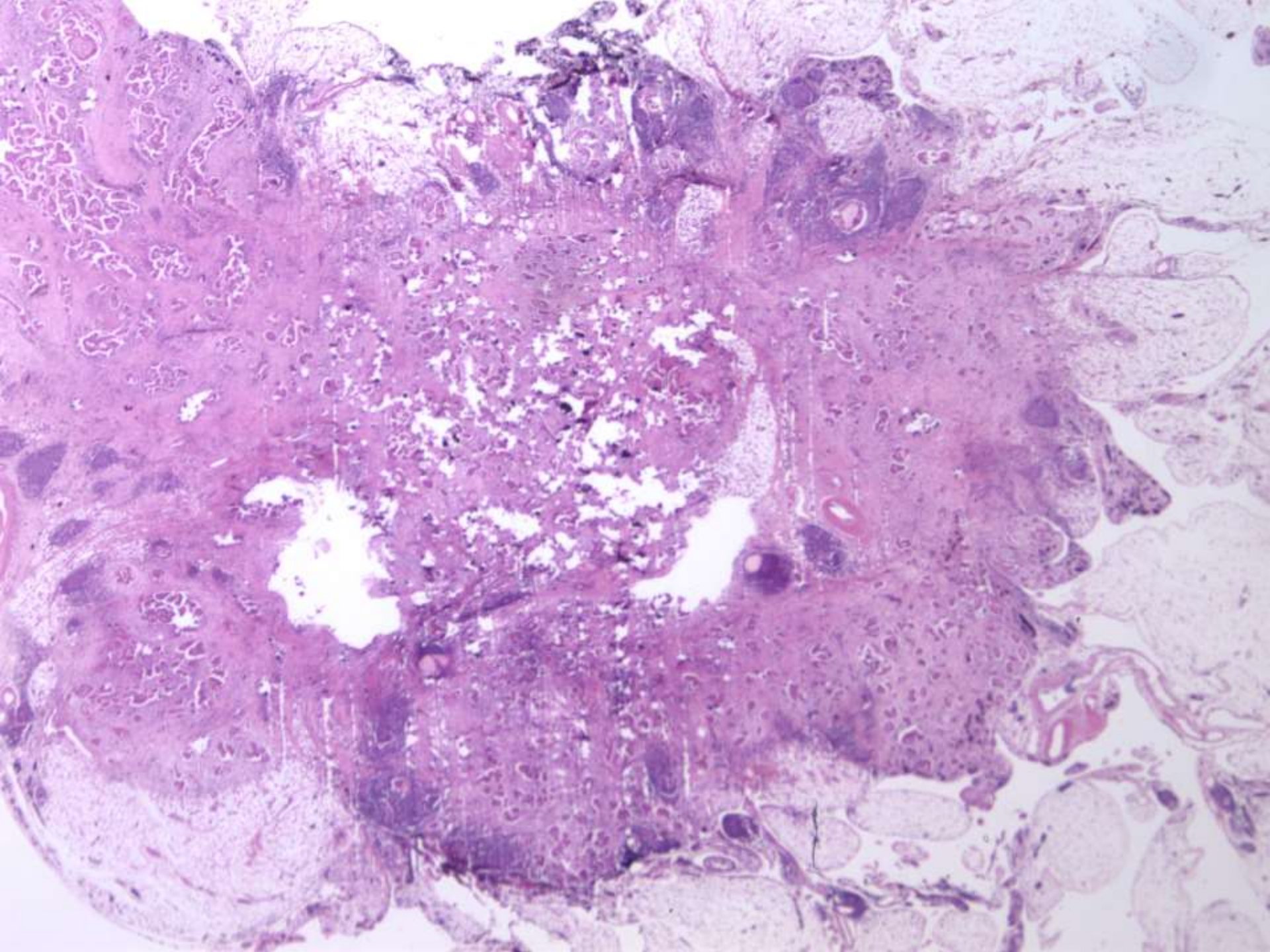


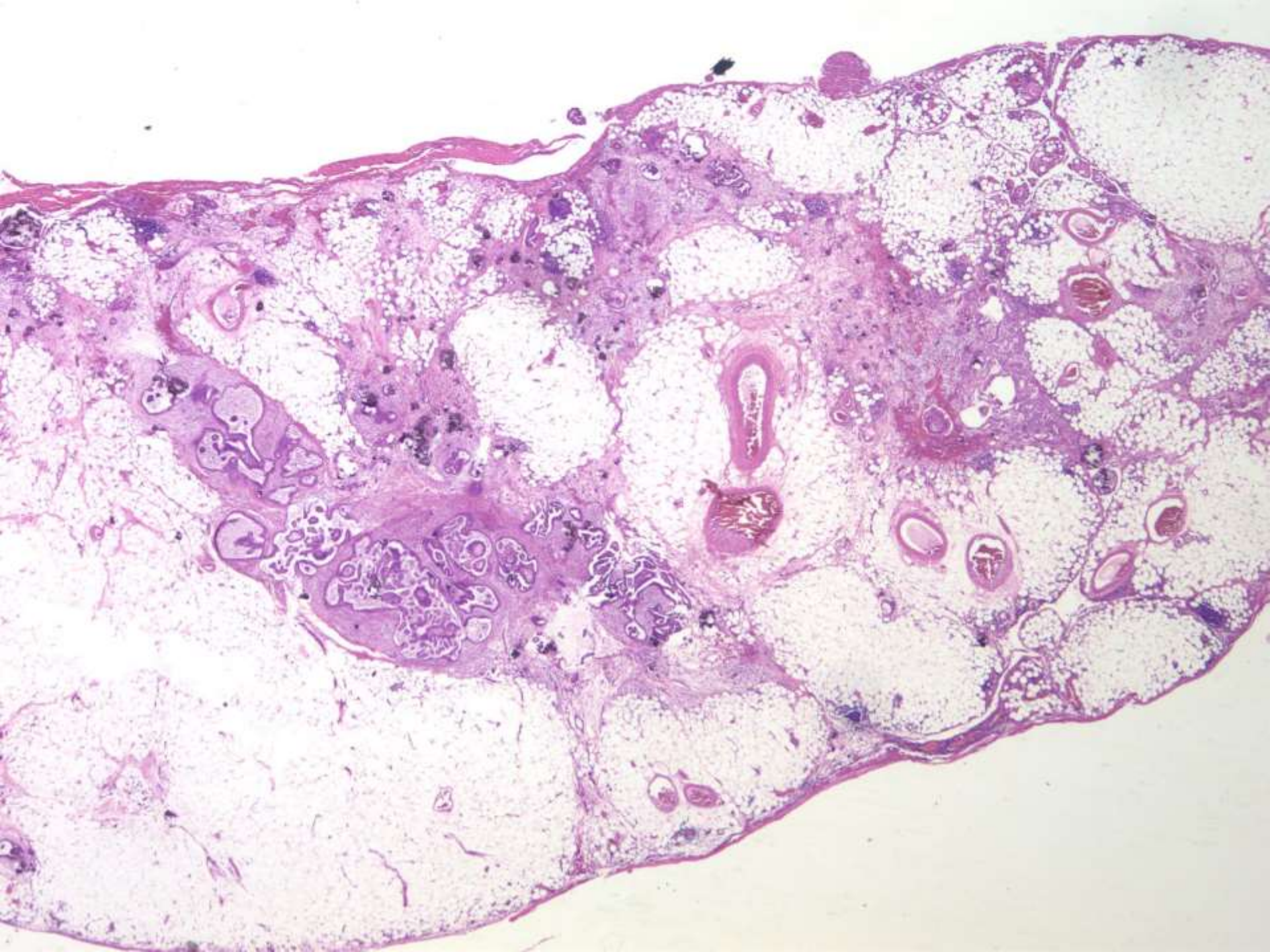
- 86% extra-ovarian disease in advanced stage SBT are non-invasive implants
- 92% in usual SBT
- 50% in niLGSC/micropapillary
- **Non-invasive implants also have risk of subsequent Ca**
- **Include in staging**

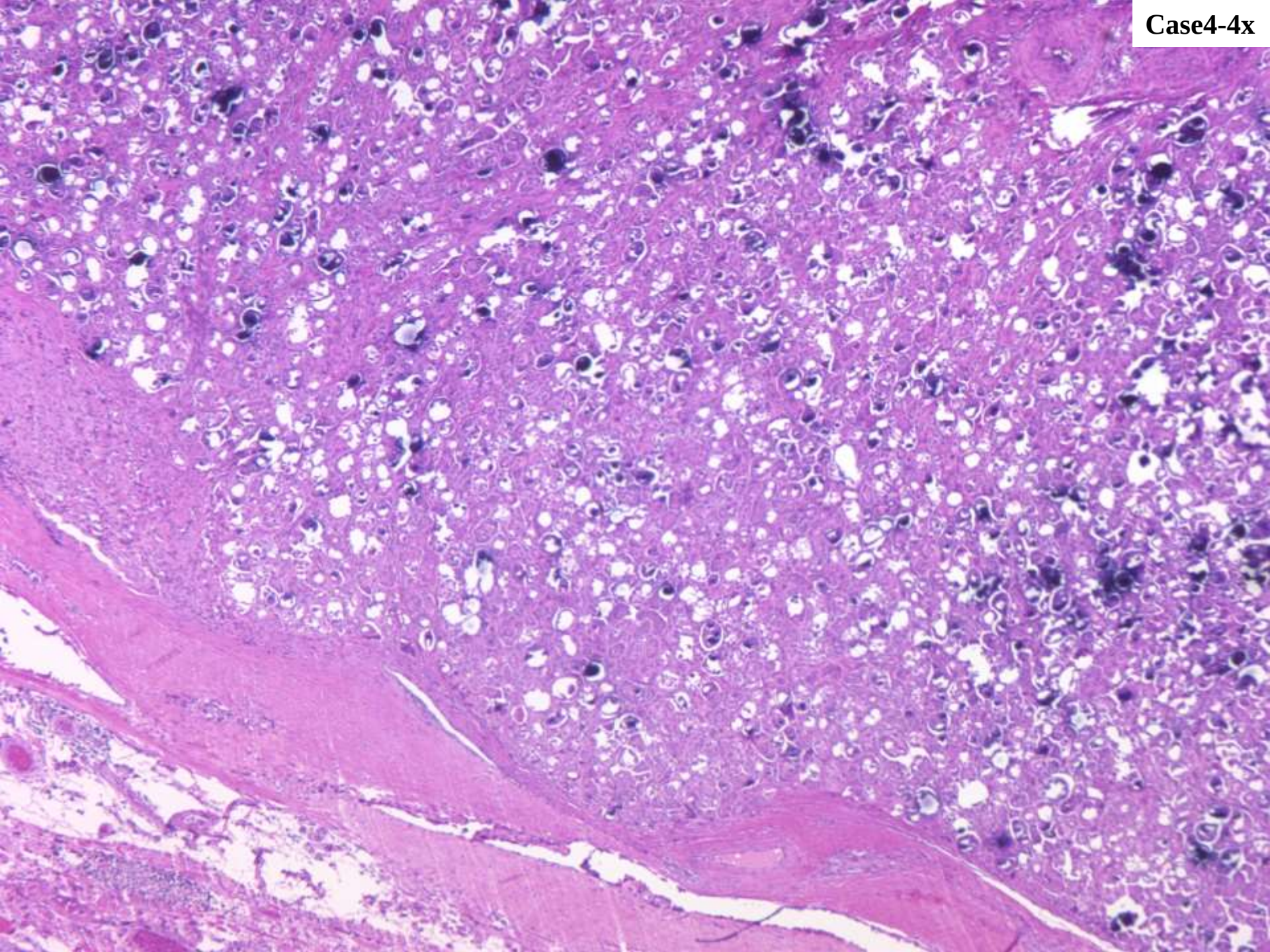











Case4-4x

Extra-ovarian LGSC (previously “invasive implant”)

- Destructive invasion: irregular, aggressive-appearing infiltration of normal tissue with tumor replacing or destroying it
- Obliteration of omental tissue

- Presence of small papillae or single tumor cells within abundant desmoplastic stroma is not interpreted as stromal invasion
- Small superficial biopsy specimens of desmoplastic implants with underlying tissue absent = noninvasive; assumption that easily stripped away from underlying tissue

Staging of SBT

- Staged as carcinoma

- Non-invasive implants and nodal involvement are included in staging of SBT and LGSC (include comment if all extra-ovarian disease is non-invasive)

Mucinous neoplasms

- Sampling – treacherously heterogeneous (1.5-2/cm in difficult cases)
- Exclusion of metastasis: when necessary
- (Limited) role of IHC
- (No) need for appendicectomy.
- Patterns of invasion in MC
- Fertility sparing an option for stage Ia (do not need comprehensive staging)
- If primary MC do HER2 IHC (interpret as for breast) for cases > stage Ia or at recurrence

WHO (2014) classification of mucinous tumors

Malignant
- -Adenocarcinoma

Borderline
- -Borderline with intra-epithelial carcinoma
- -Borderline with microinvasion/microinvasive ca

Benign
- -Cystadenoma
- -Adenofibroma

Mucinous tumor with mural nodule

Mucinous tumor associated with benign cystic teratoma

Mucinous carcinoma and metastasis

EXCLUDE METASTASIS IF:

- Signet ring morphology
- Colloid carcinoma morphology
- Pseudomyxoma peritonei
- Ruptured
- Bilateral involvement
- Extensive abdominal disease
- Borderine with microinvasion/microivasive Ca

Patient can be denied the correct Rx and inclusion into trials if misdiagnosed or stated to be CUP

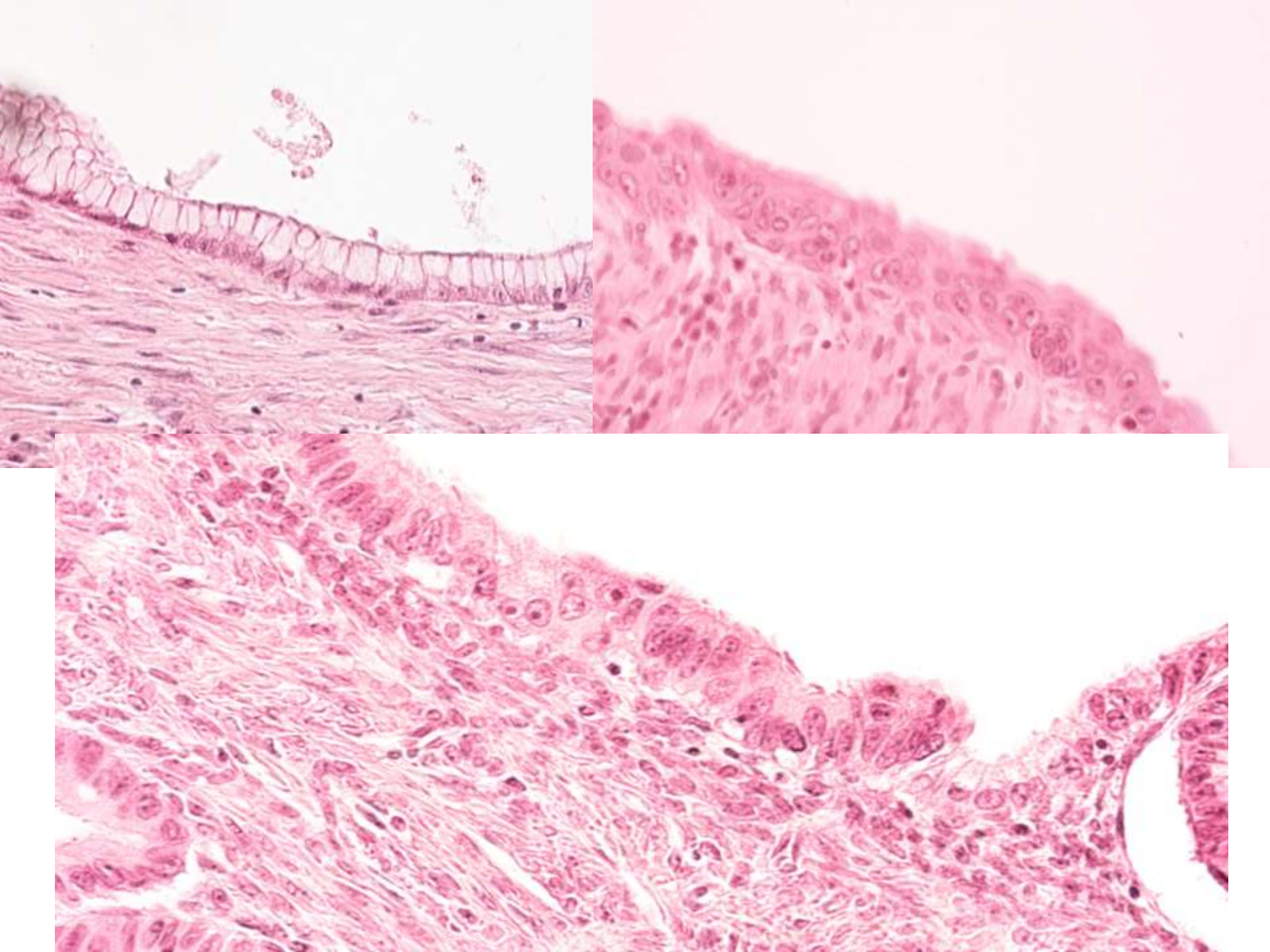
In absence of the above, DO NOT worry about metastasis in each and every MBT/MC!

Differential diagnosis of primary vs metastatic mucinous carcinoma of ovary (Modified from Lee and Young) – no single feature is diagnostic

	Primary %	Metastatic %	p-value
Bilateral	0	75	<0.001
Surface involvement (microscopic)	0	79	<0.001
Nodular growth	0	42	<0.001
Infiltrative invasion pattern	16	91	<0.001
Small glands/tubules	12	94	<0.001
Single cells	8	42	0.005
Signet ring cells	0	27	0.032
Size greater than 10cm	88	48	0.007
Borderline appearing areas	76	36	0.008
Expansile invasion pattern	88	18	<0.001
Microscopic cysts	84	40	0.002
Complex papillae	60	8	<0.001
Necrotic luminal debris	44	14	0.019

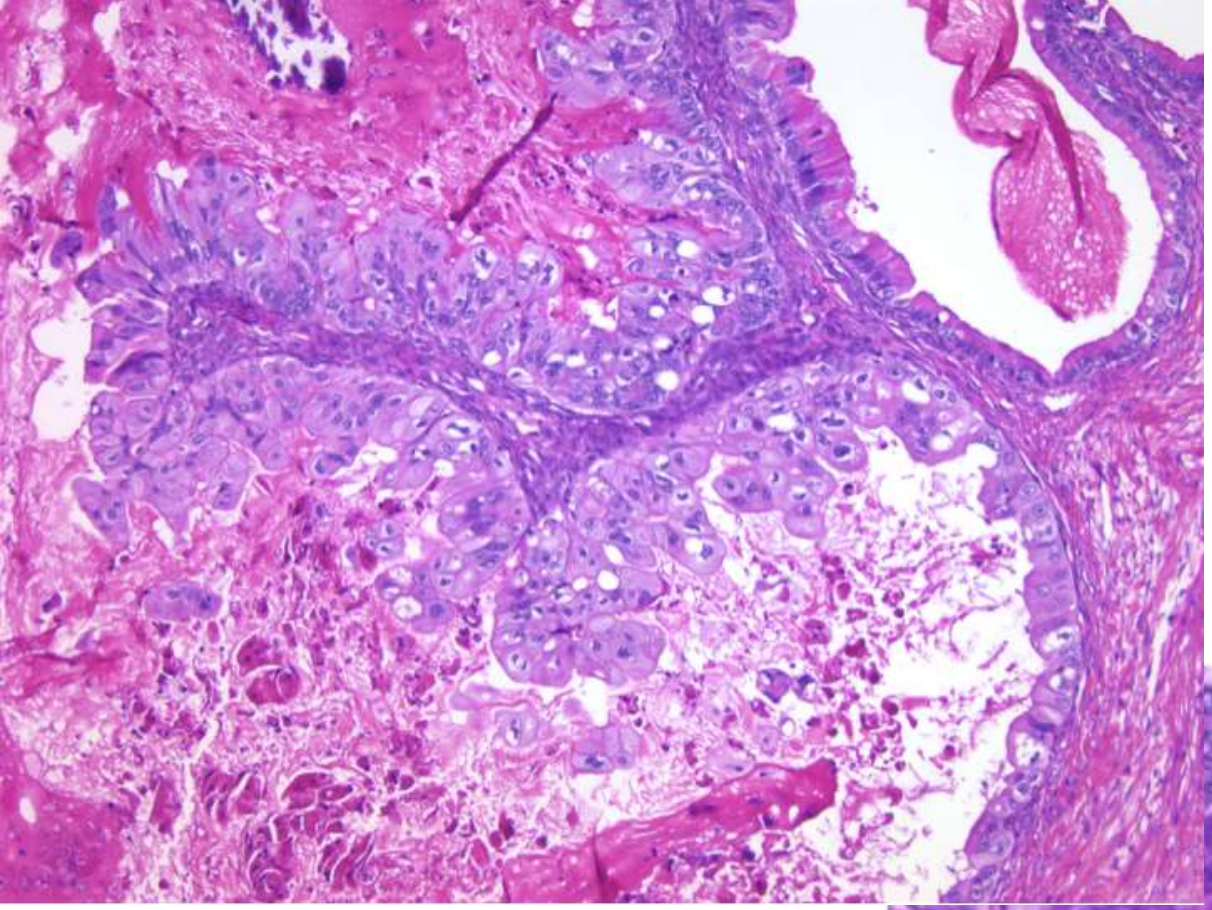
Benign vs Borderline

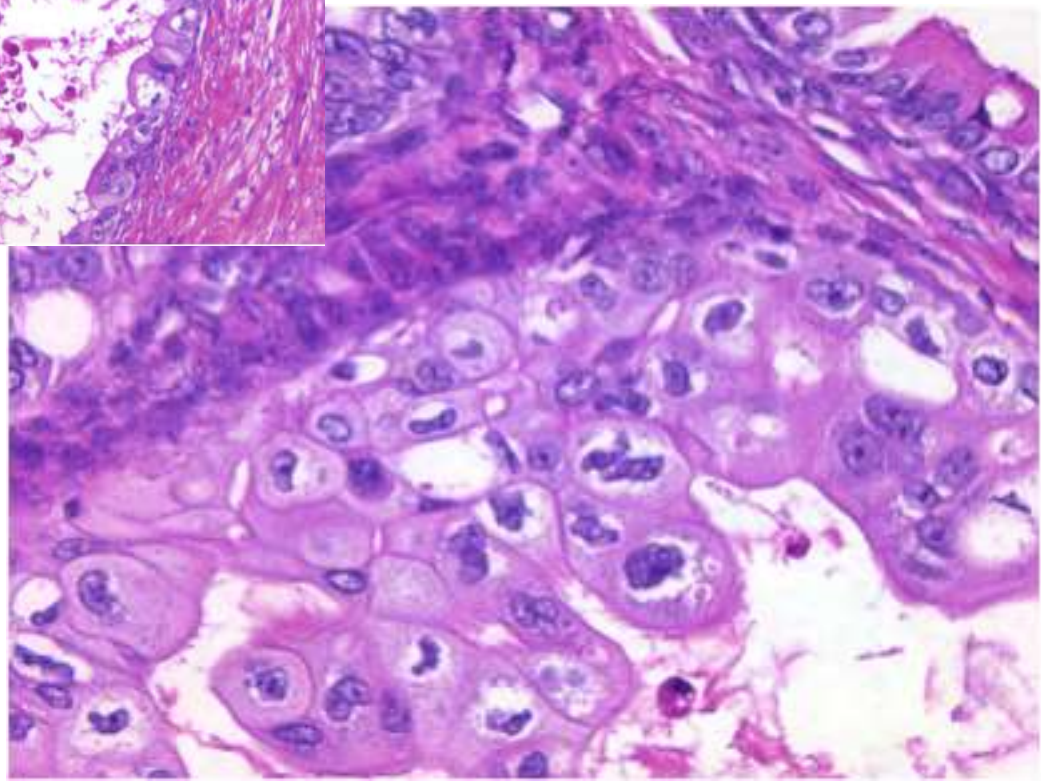
- Stratification
- Atypia
- Mitoses
- >10%
- No Invasion!



Mucinous borderline tumor with intraepithelial carcinoma

- Epithelial lining shows malignant cytological features: nuclear pleomorphism, prominent nucleoli, numerous mitotic figures, loss of mucin production
- Usually appreciable architectural proliferation
- Architectural change without severe atypia is insufficient for IEC
- NO invasion





MBT vs MBT-IEC, what matters?

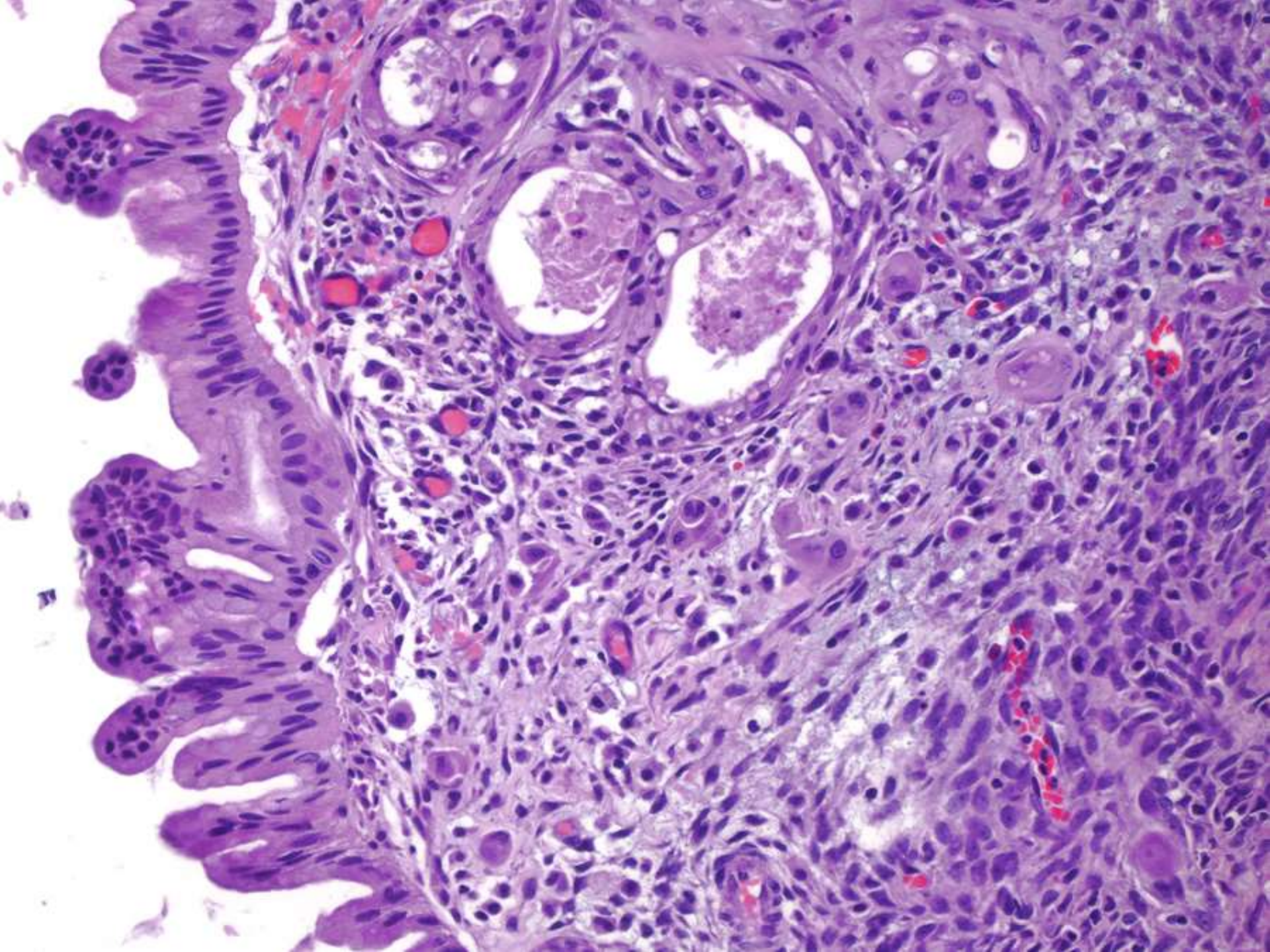
- NO!: outcome entirely uneventful in vast majority of cases, BUT
  - Uneventful after oophorectomy
  - Risk of recurrence after cystectomy
  - MBT/MBT-IEC have NO (non-malignant) EXTRA-OVARIAN MANIFESTATIONS (implants); if present this is CARCINOMA
  - SAMPLING is crucial, especially with IEC

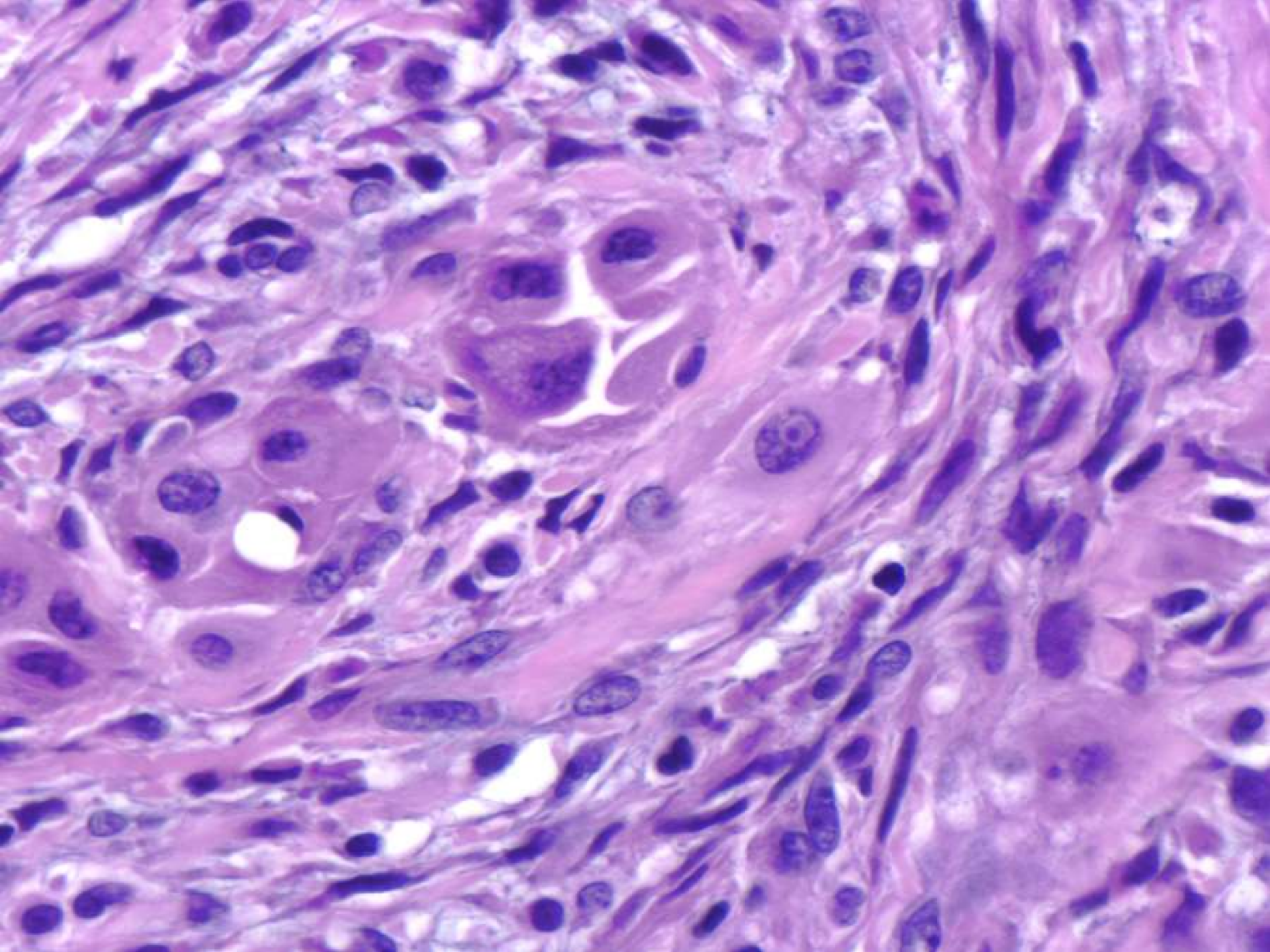
MBT with Microinvasion

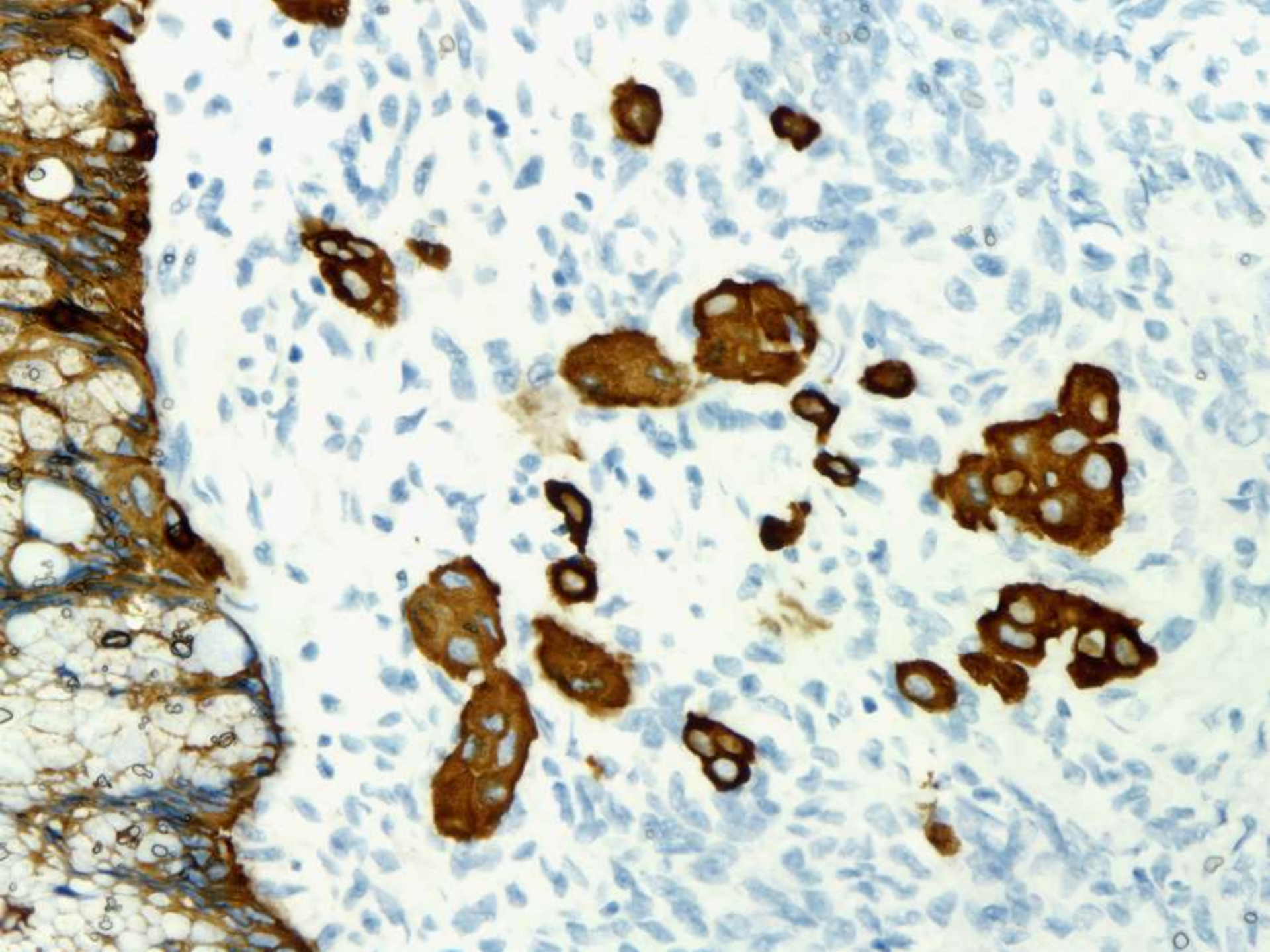
- -<3mm, <5mm, <10mm^2
- Expansile/destructive
- Most studies have shown uniformly good outcome
- But these are very rare!
- SAMPLING is crucial; most are frank carcinoma

Mucinous carcinoma

- Destructive invasion
- Expansile invasion

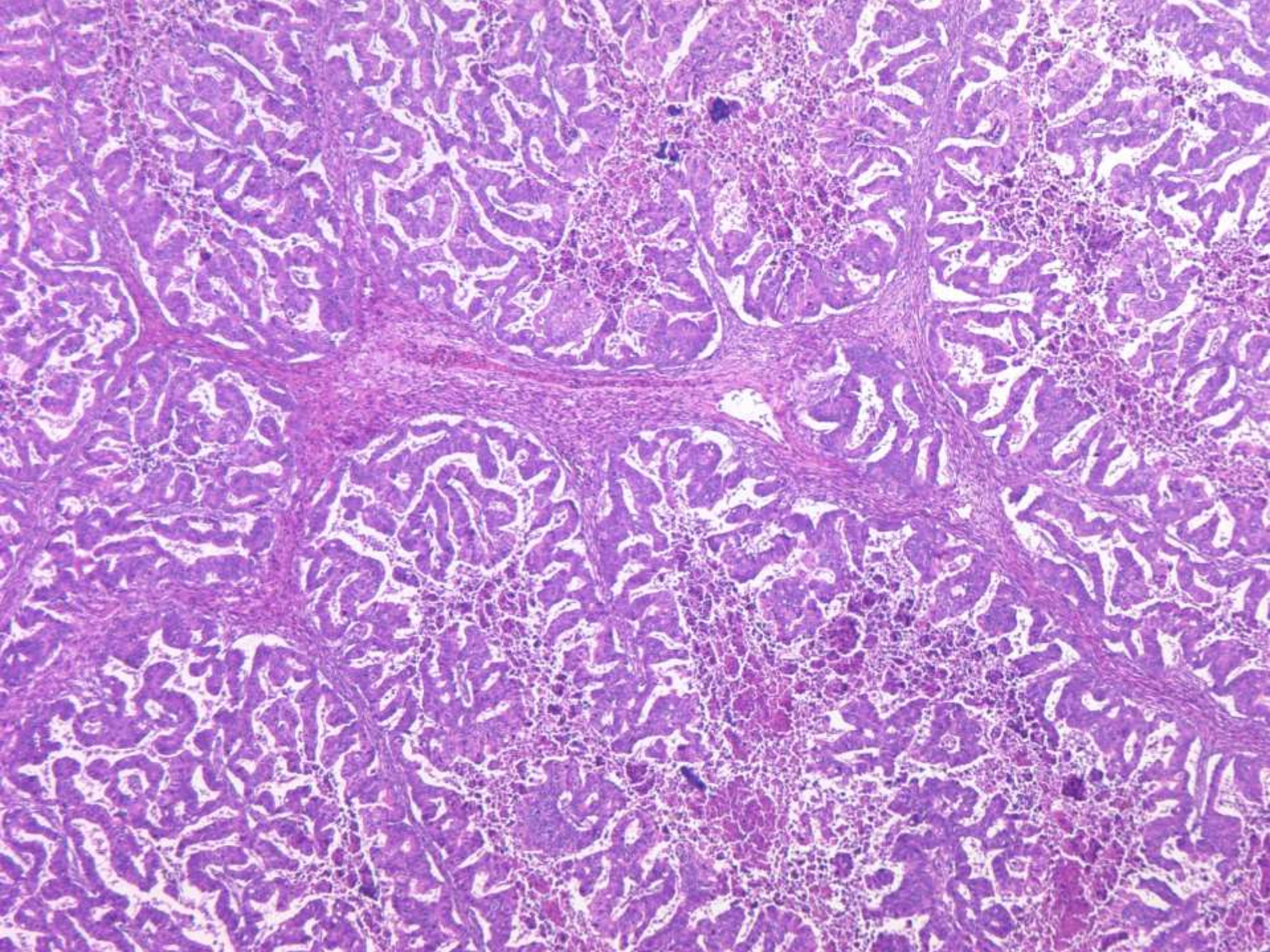


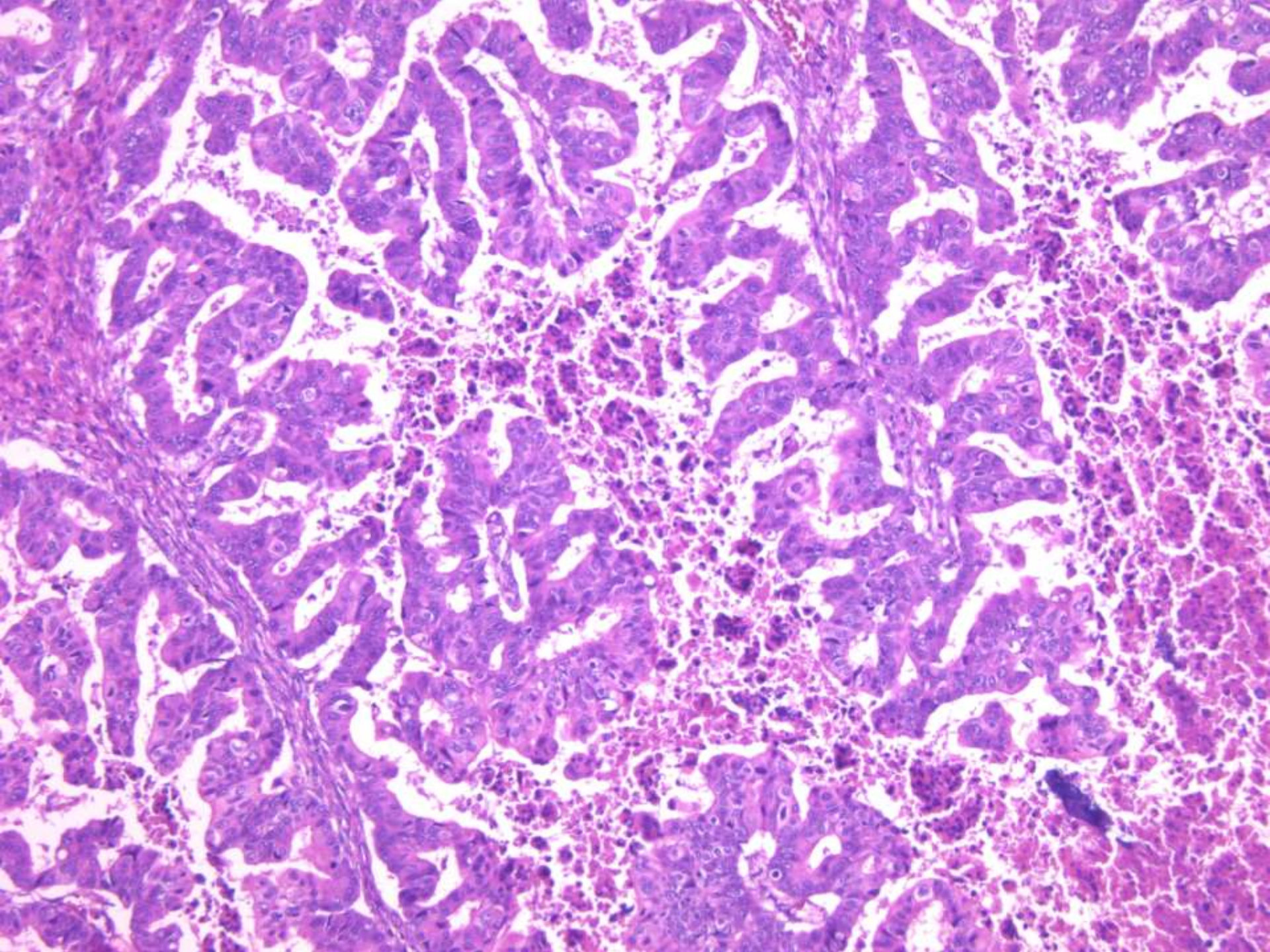


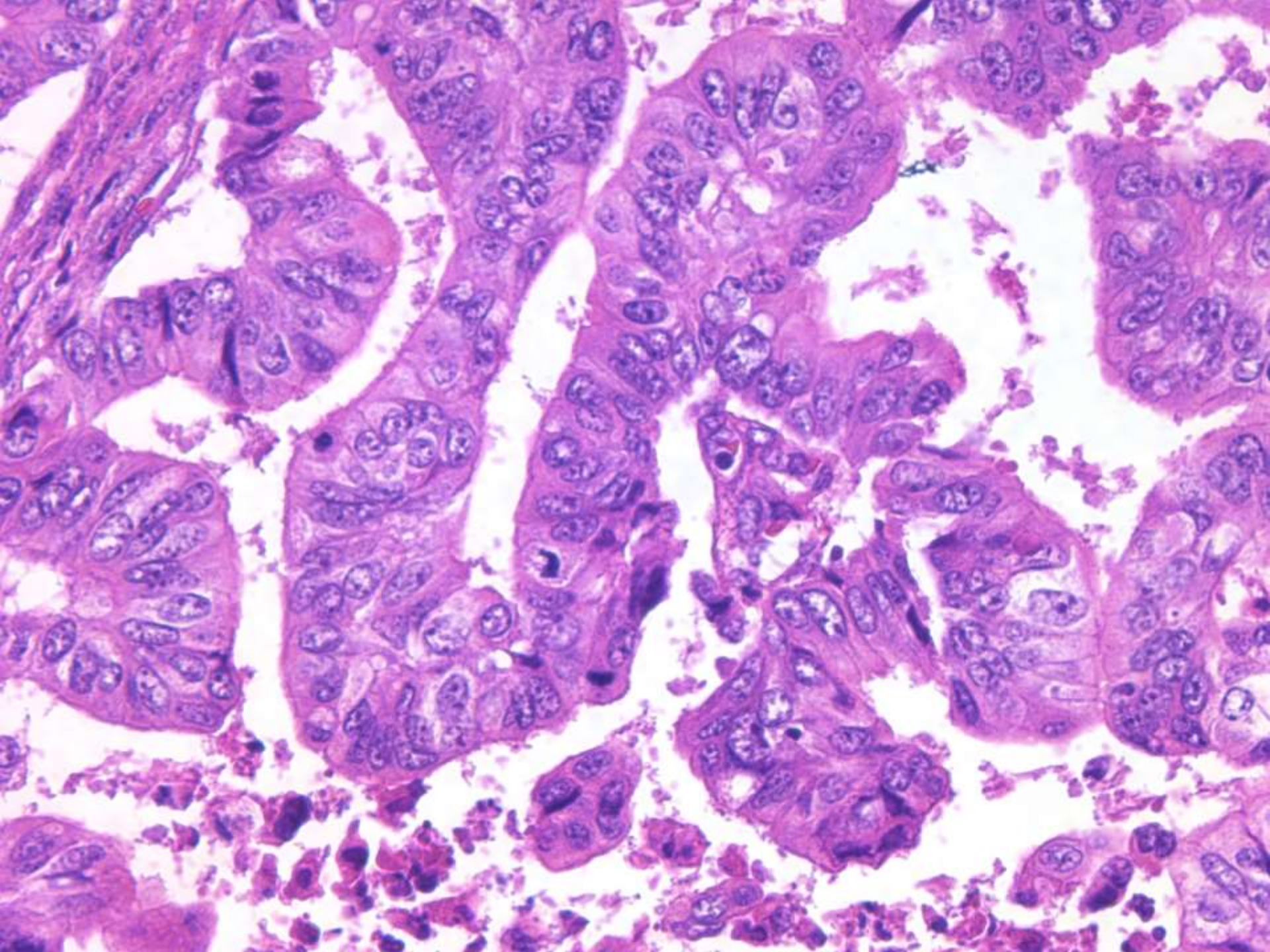


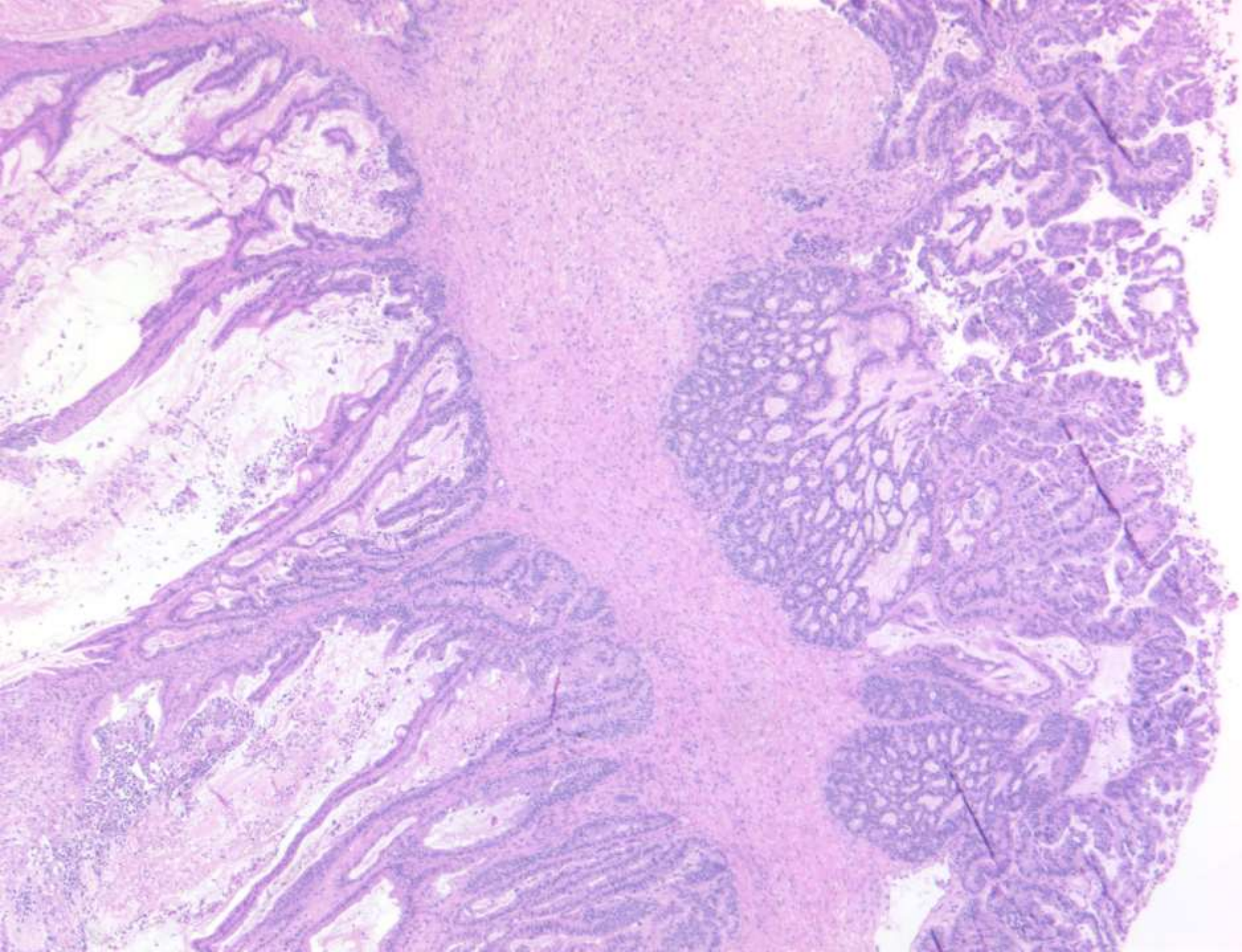
Mucinous carcinoma with expansile invasion

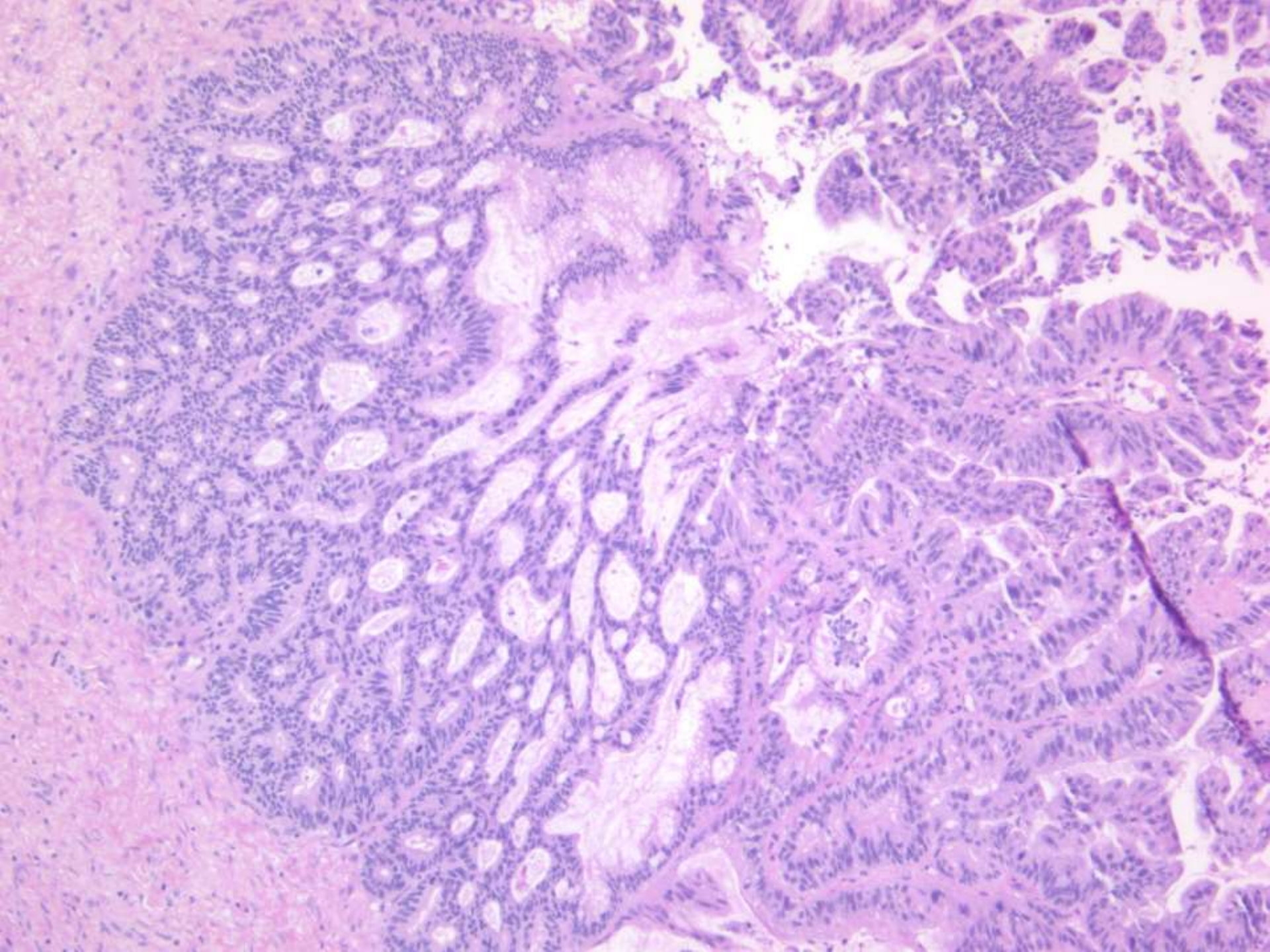
- Complex, often labyrinthine arrangement of glands, cysts or papillae lined by malignant epithelium with minimal or no intervening stroma

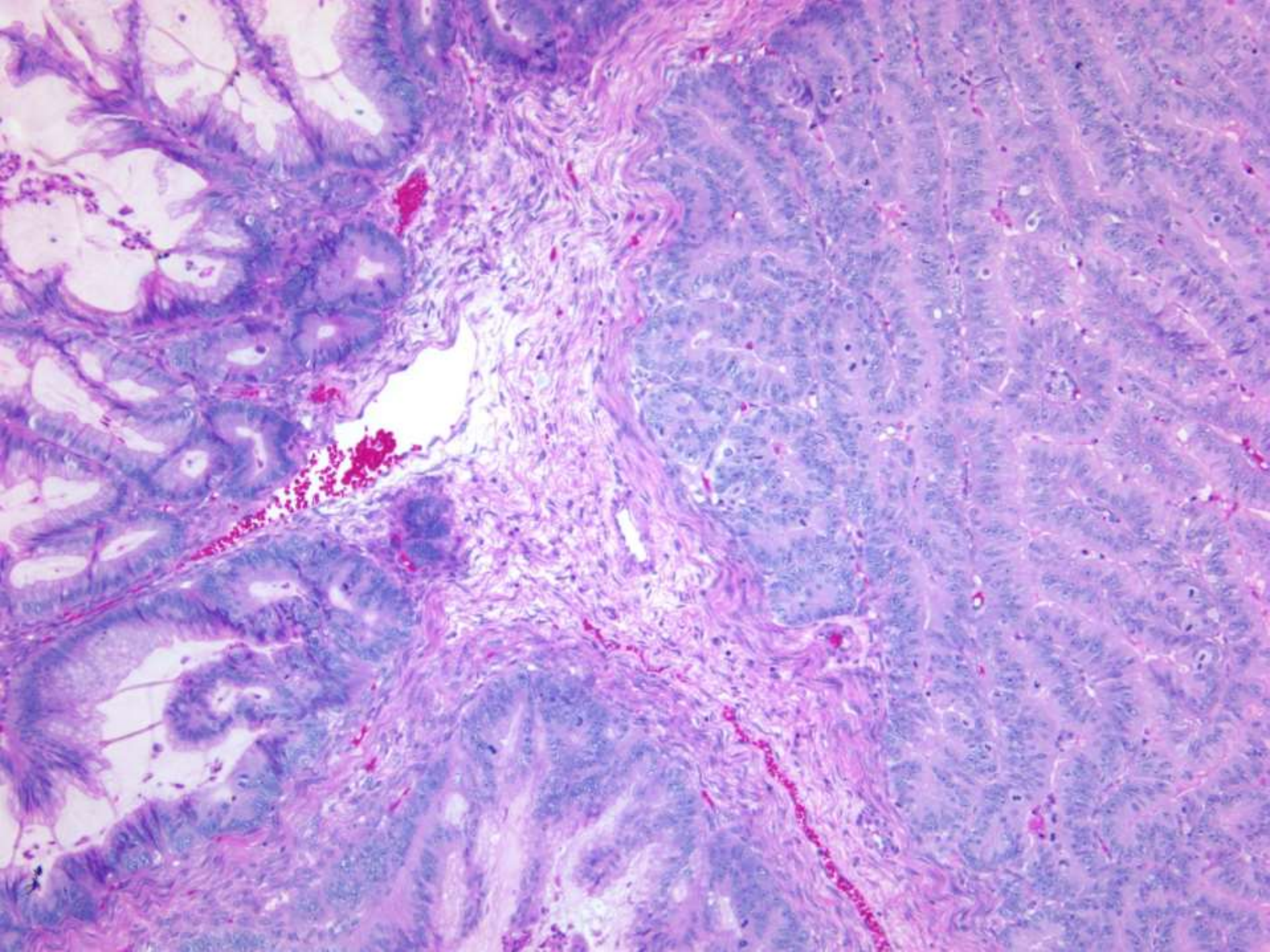


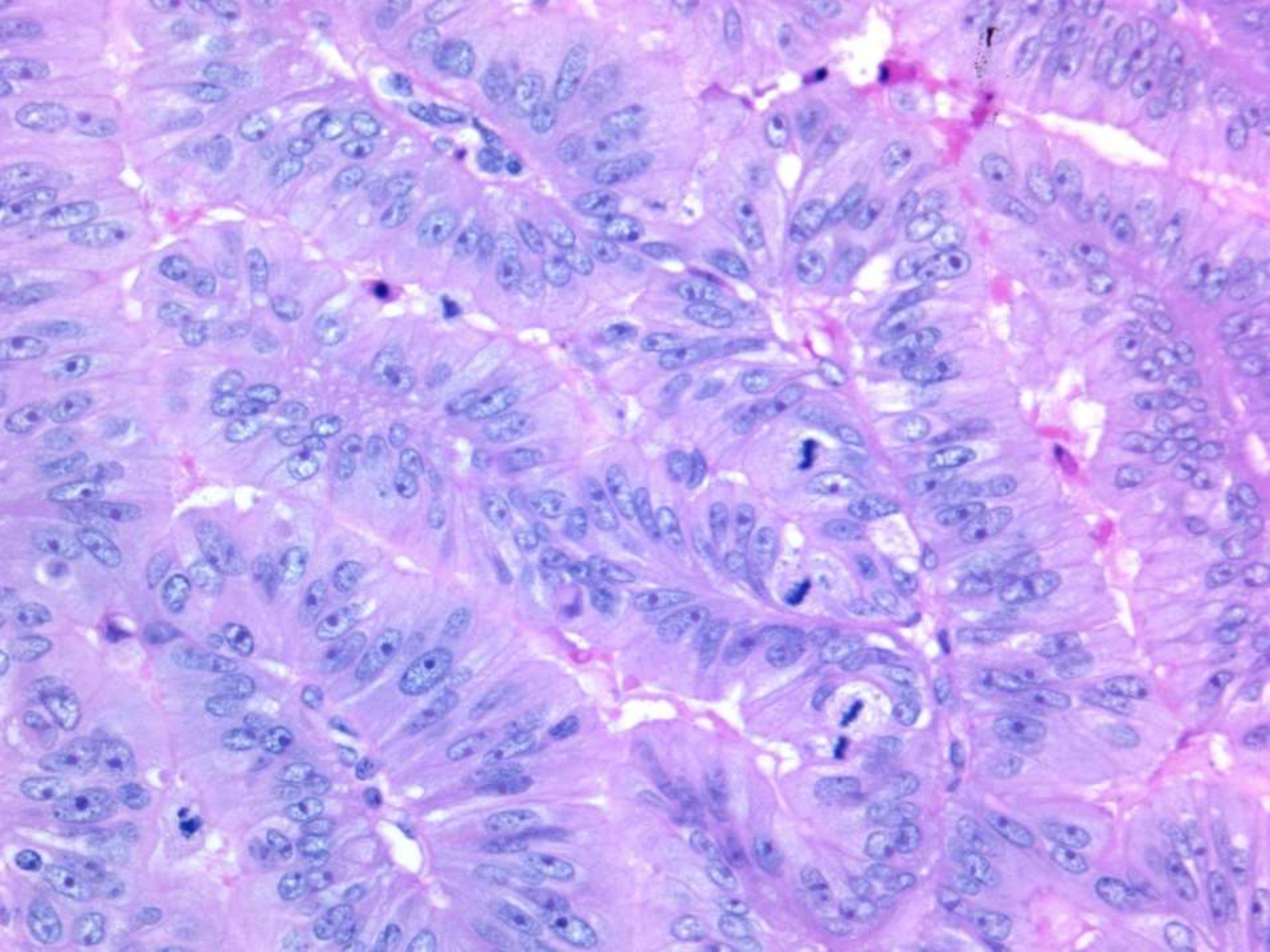












MBT/MC, what matters

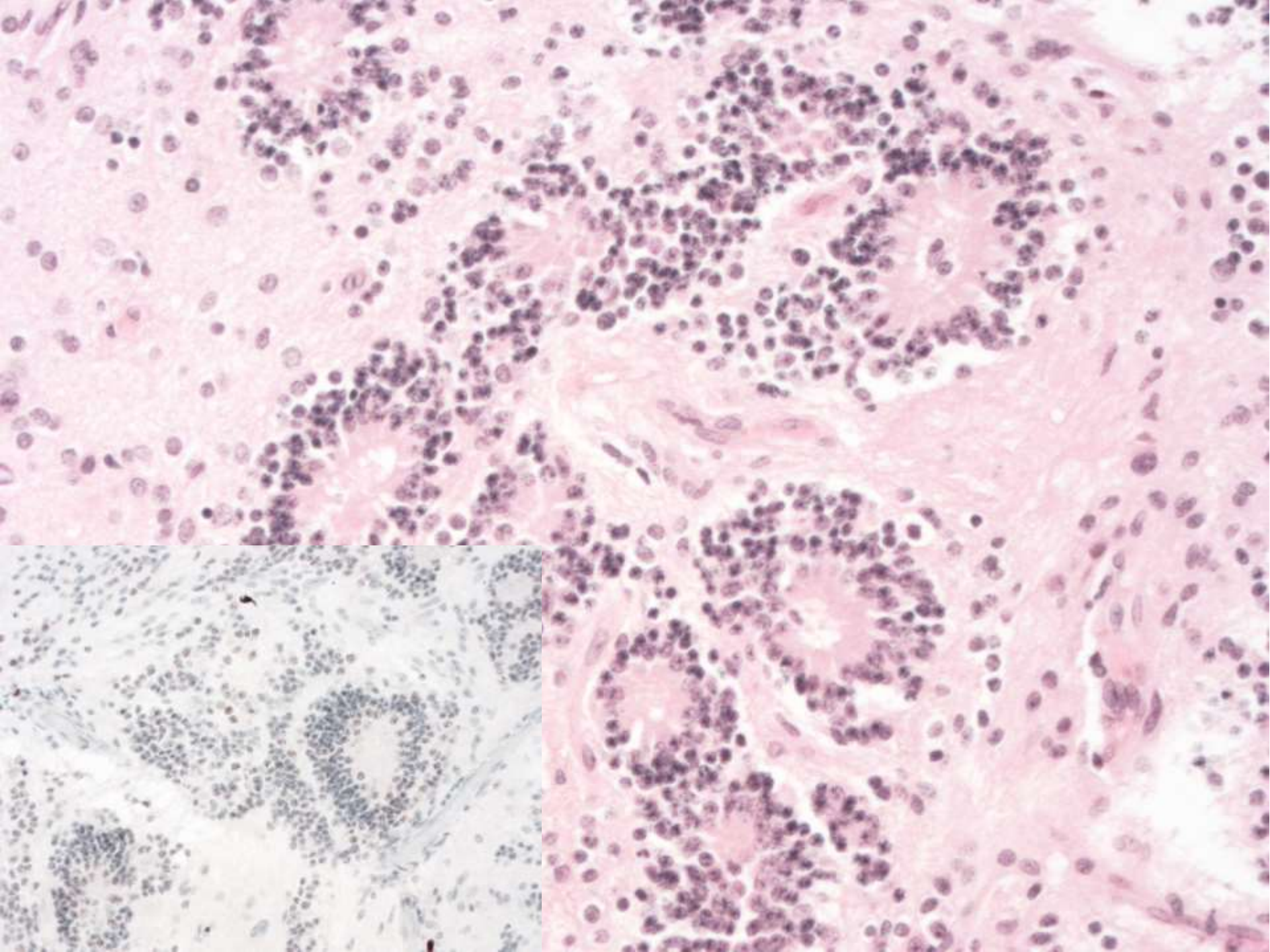
- Exclude metastasis when indicated
- Adequate sampling
- Distinction between MBT/MC (expansile) is subjective, hence variation in incidence
- Majority MC low stage
- Recurrences (25% in one study), even when low stage/expansile pattern
- Recurrences are not ‘typical’ of OC: lung/bone mets
- Low response to OC chemo

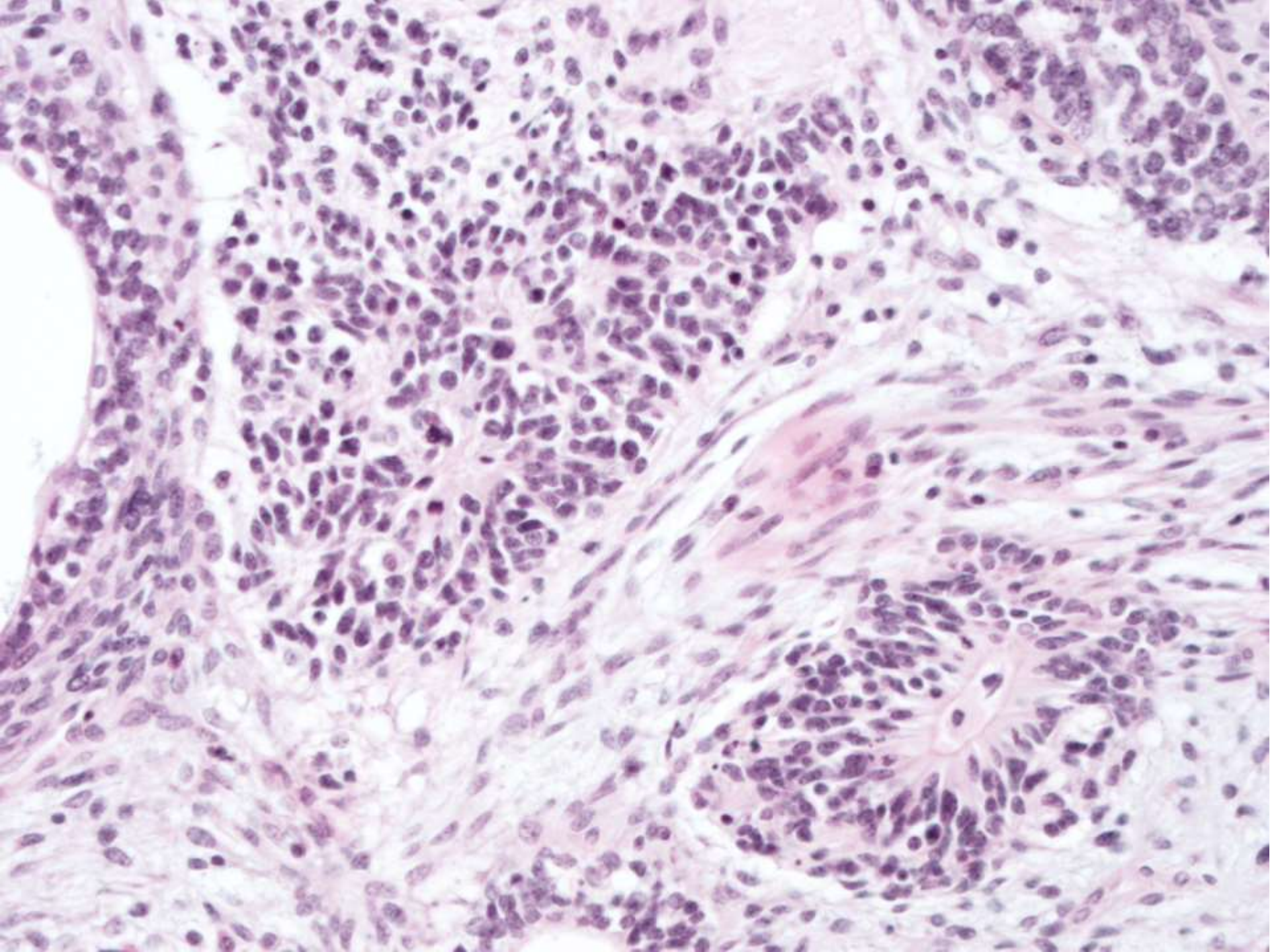
Sex Cord Stromal Tumours, what matters?

- AGCT vs mimics, FOXL2 mutation analysis
  - Fibroma/thecoma with minor sex cord elements
  - Diffuse AGCT vs cellular Fibroma/thecoma
  - SCCHT!!! (AGGRESSIVELY MALIGNANT/often familial)
- DICER1 relationship –Sertoli-Leydig cell tumor (esp grade 2-3, with heterologous or retiform differentiation, young age)
- SCTAT – PJS relationship

Immature teratoma

- Correct identification of immature components
  - Exclude mimics: ependymal, cerebellar, retinal; Ki67 stain useful
- Consider binary grading; chemo considered for HG
- Gliomatosis/peritoneal imvovlement also graded the same way; does not respond to chemo





Primitive Germ Cell Tumours

- Do not misdiagnose!

A few other things …

- Never forget METASTASIS
- Do not overcall gestational trophoblastic disease in ectopic
- Endometriosis-related pathology; diverse

Thank you