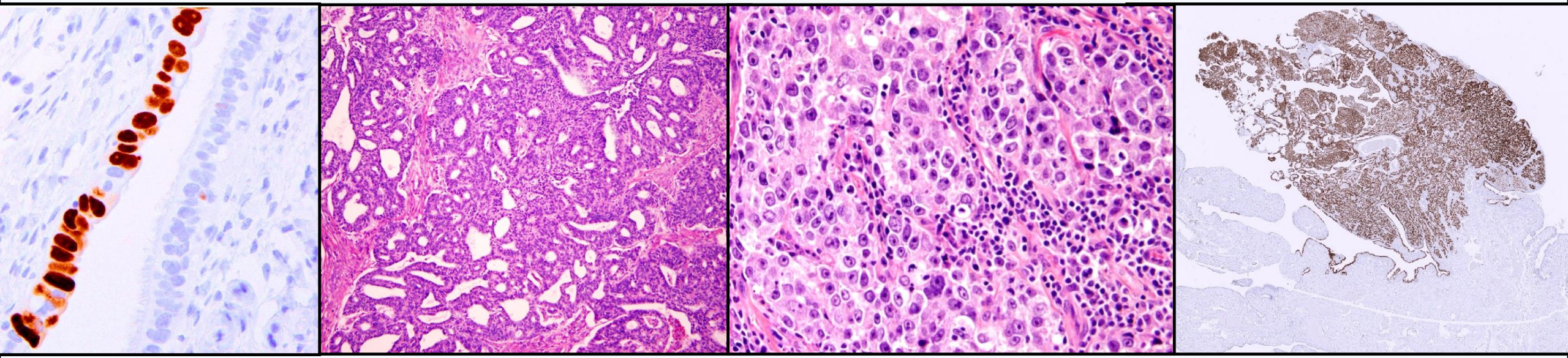
PAP 2022 ANNUAL SCIENTIFIC MEETING

Diagnostic Dilemmas in Extrauterine Pelvic Serous Carcinoma



T. Rinda Soong, MD PhD MPH

Assistant Professor, Department of Pathology

University of Pittsburgh School of Medicine

4/9/2022

Extrauterine serous carcinomas

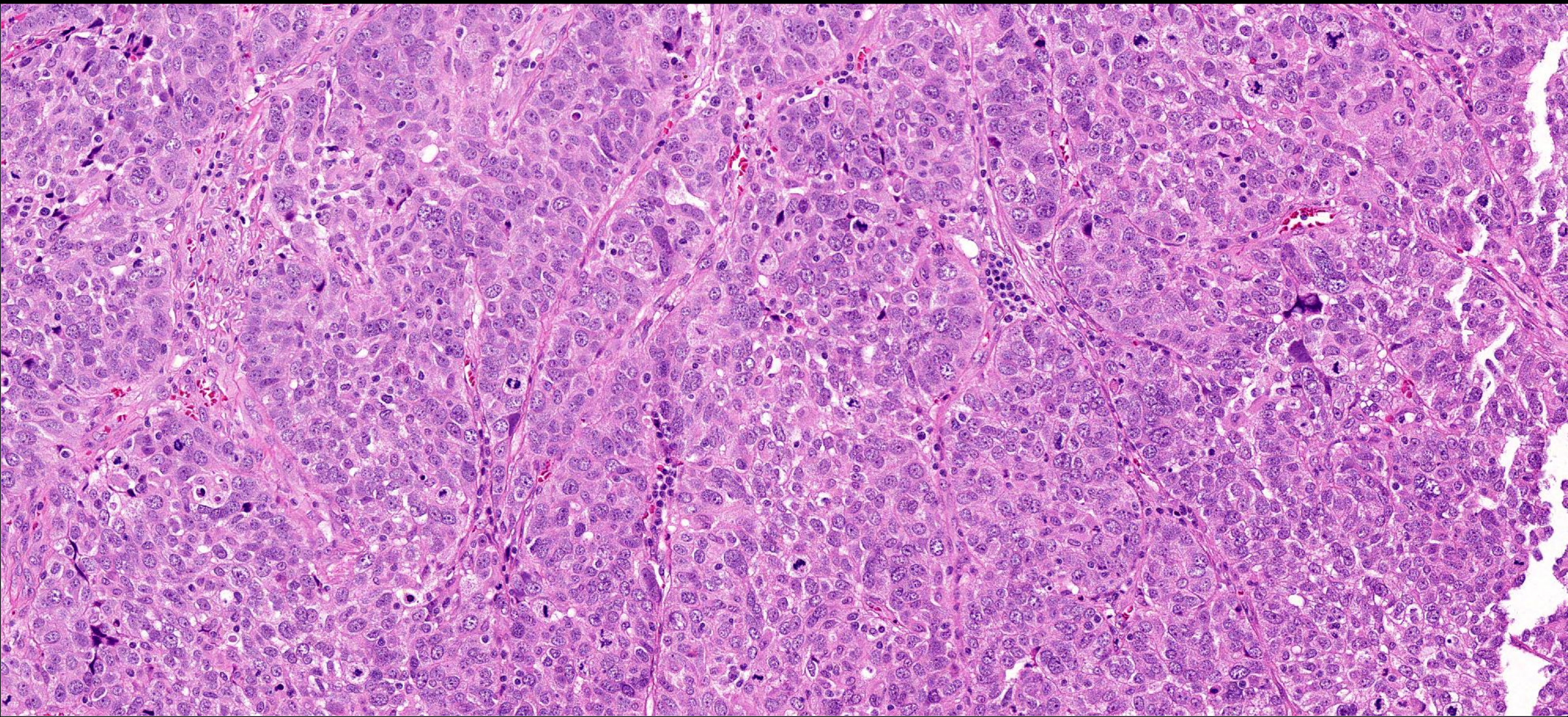
Diagnostic challenges - examples:

1. **Subtypes and classification?**

2. Site(s) of origin – ovary, fallopian tube, peritoneum, endometrium?

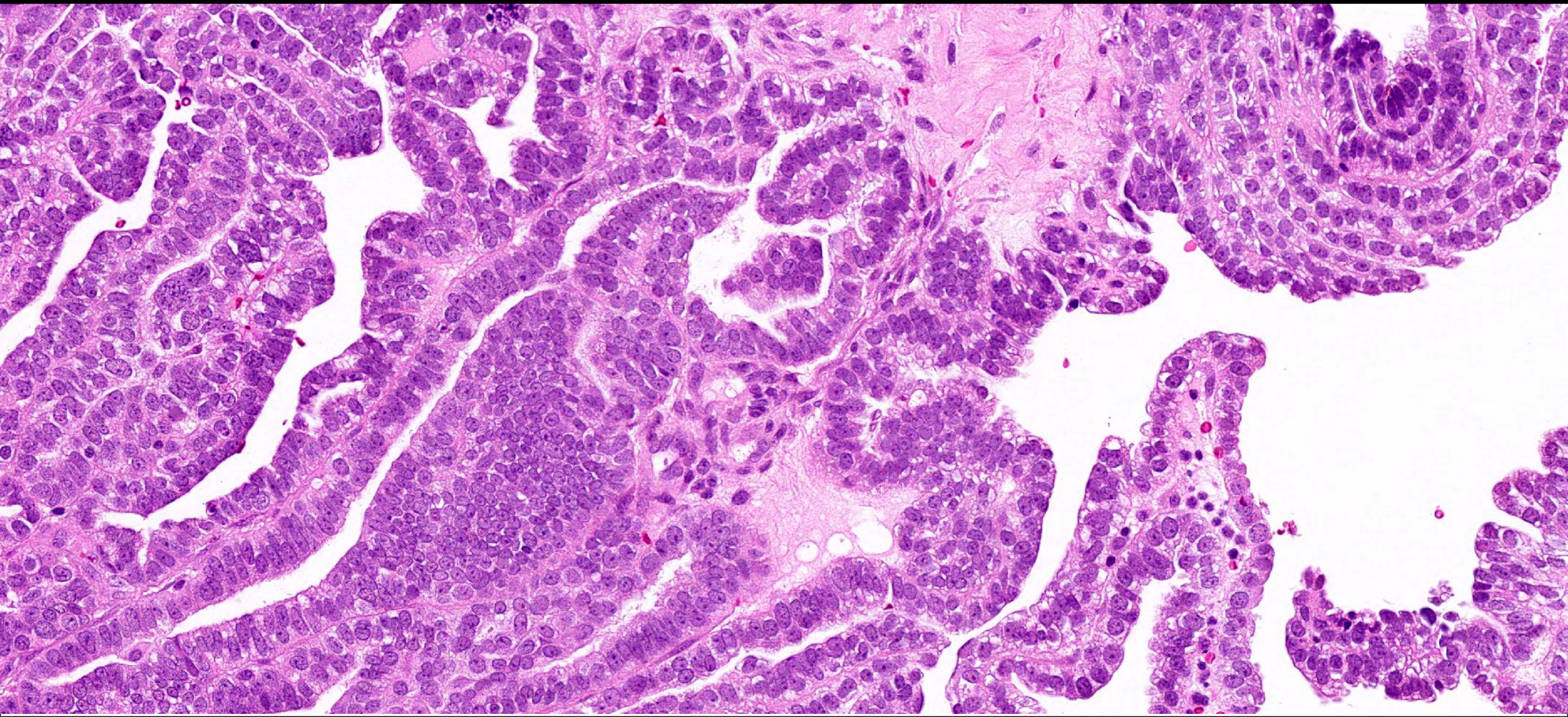
Clinical case #1: 45 year-old woman with ovarian mass

Ovary: one representative area of the tumor

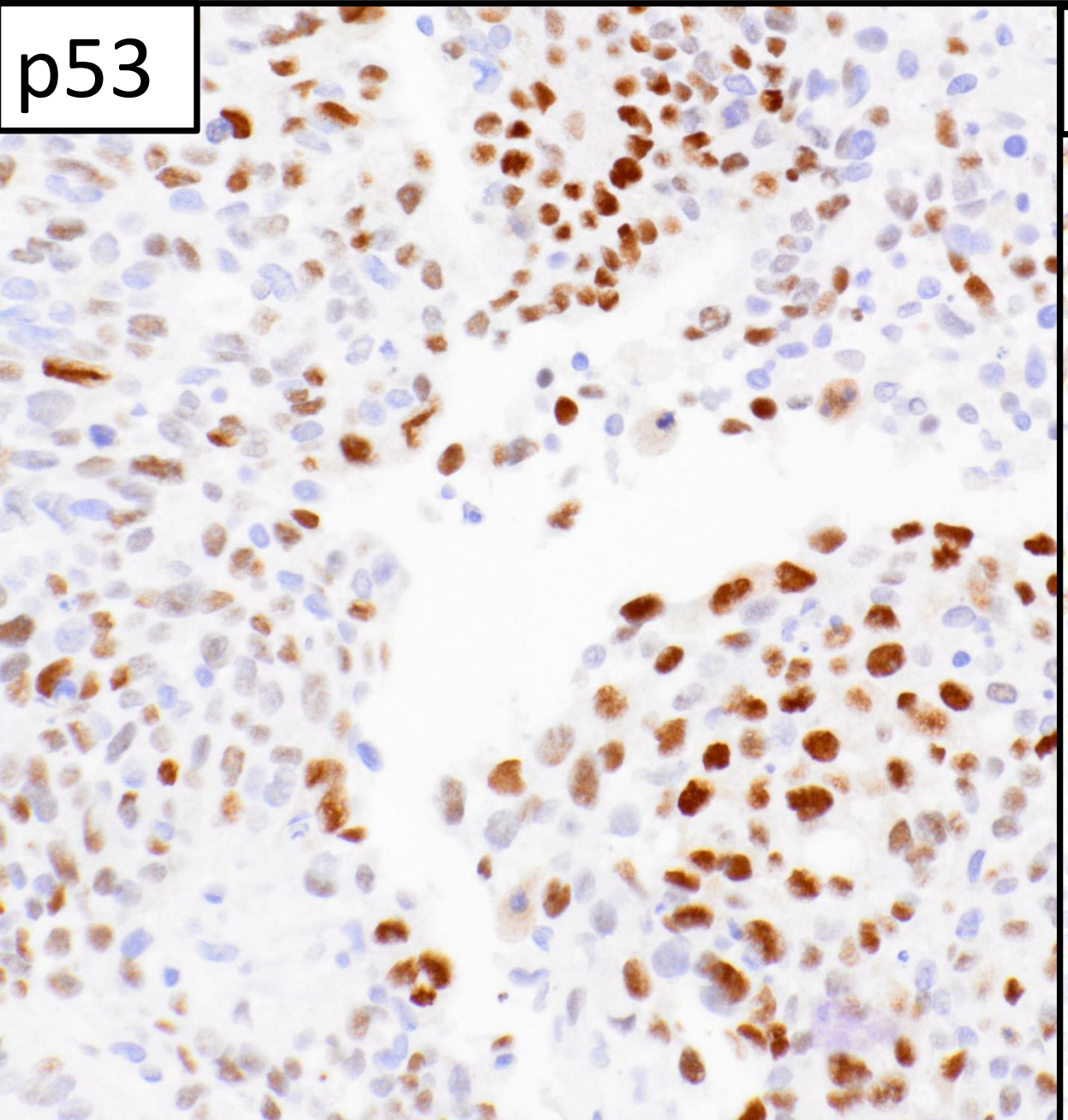


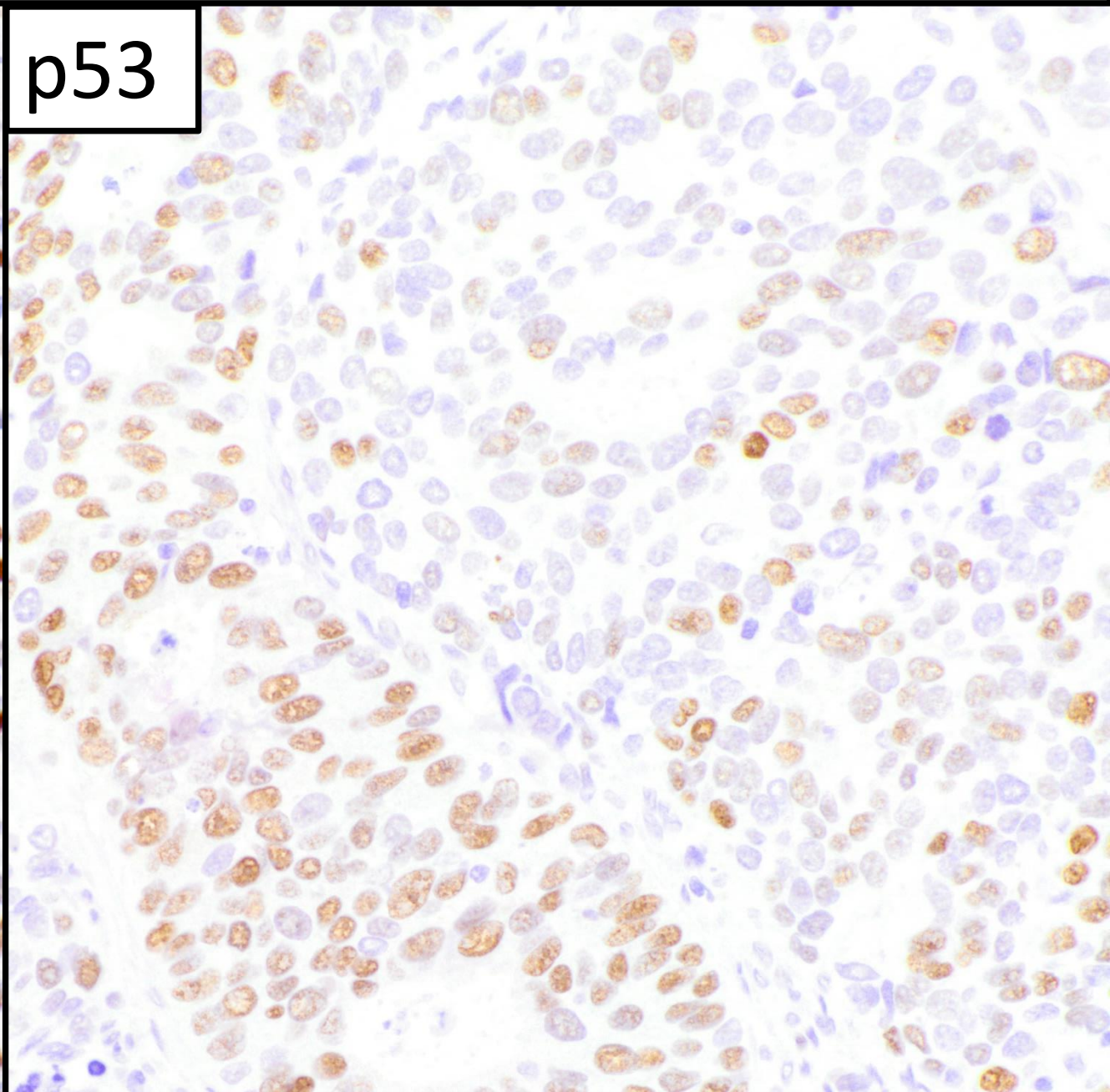
Clinical case #1: 45 year-old woman with ovarian mass

Same ovary: another representative area of the tumor



Clinical case #1: 45 year-old woman with ovarian mass





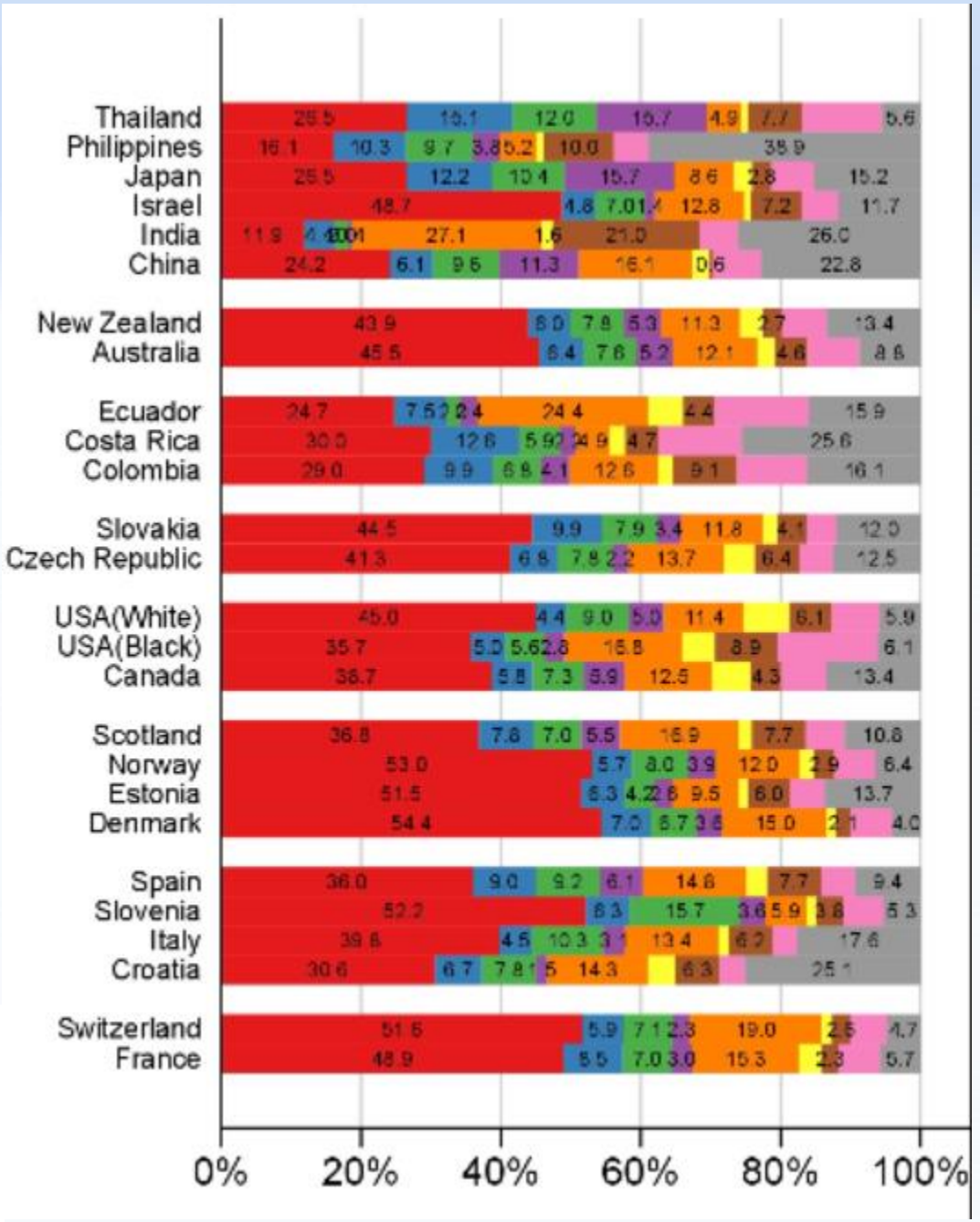
Clinical case #1

- 45 year-old woman with ovarian mass.
- Other IHC markers:
  - PAX8: diffusely positive
  - WT-1: diffusely positive
  - P16: variable and patchy expression
  - ER: patchy expression

How should we classify this tumor?

Serous carcinoma

- Most common histologic subtypes of ovarian cancer and cancers in the extrauterine genital tract.



Adapted from WHO 2020

Current classification system

Two-tier system:

- High-grade serous carcinoma
- Low-grade serous carcinoma (≤5% of ovarian carcinomas)

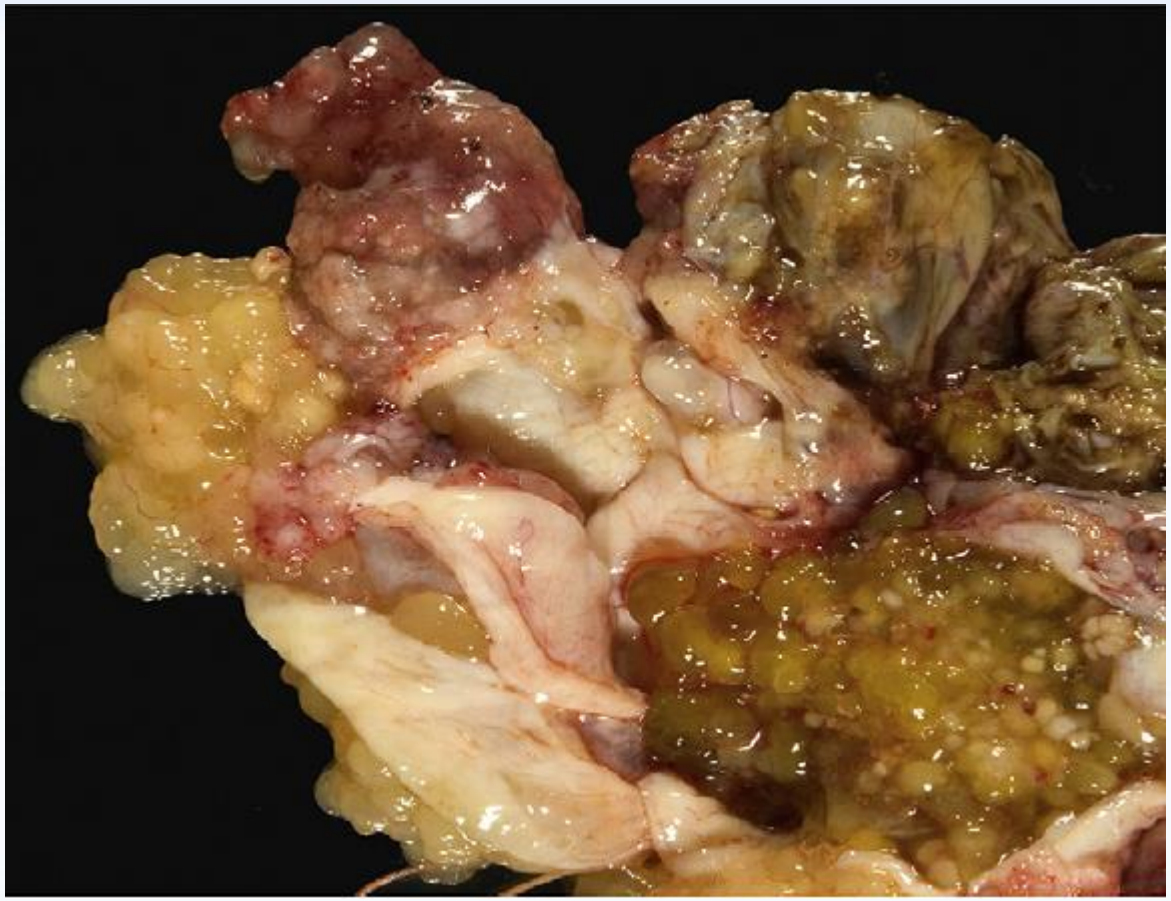
Distinguished by nuclear pleomorphism and mitotic activity

Two distinct diseases with differences in:

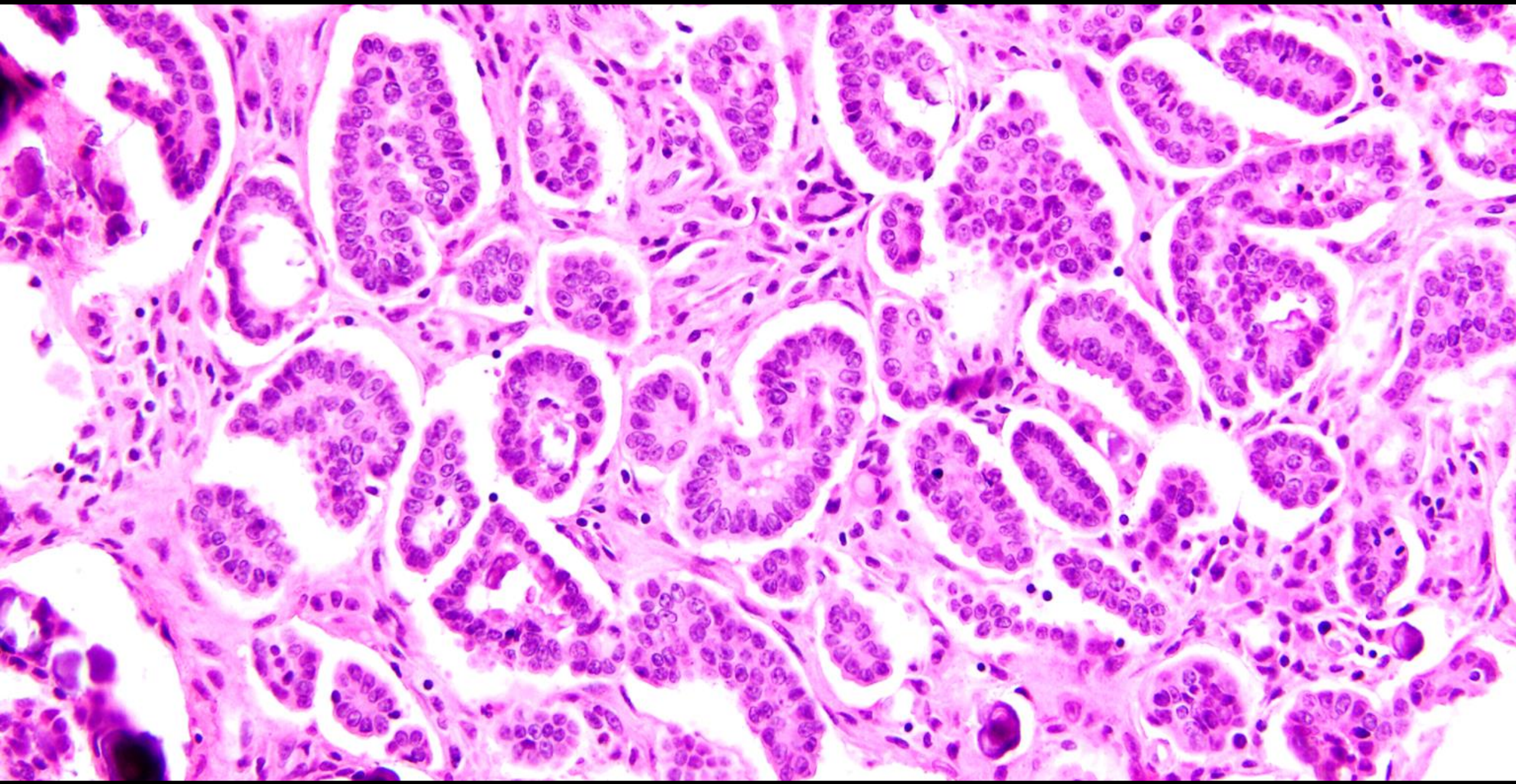
- Morphology
- Prognosis
- Pathogenesis

Low-grade serous carcinomas (LGSCs)

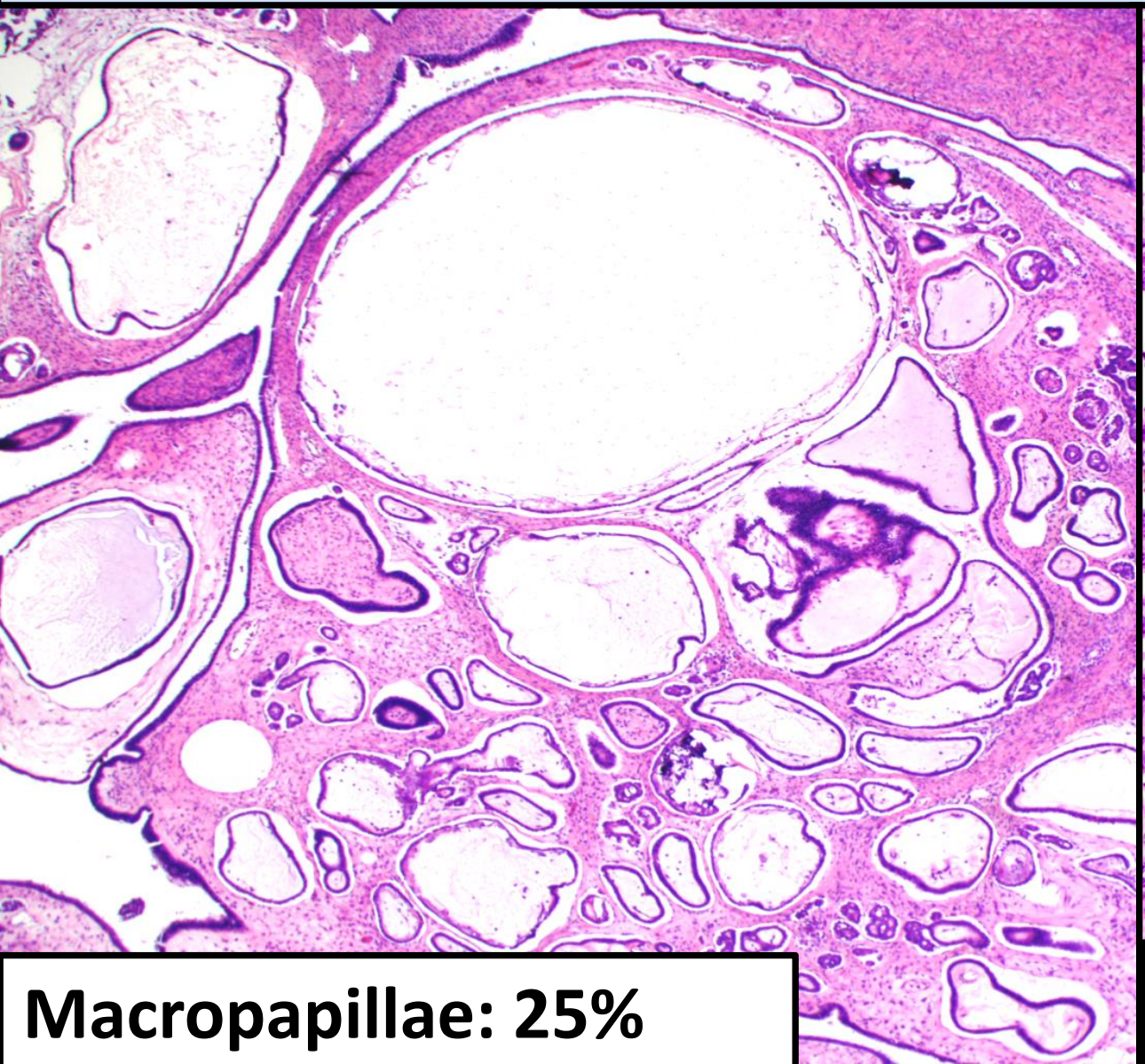
- Predominantly stage 3 at presentation.
- Indolent clinical course but long term prognosis for stage 3-4 disease is poor.
- Relatively resistant to conventional chemotherapy.
- Subset with *KRAS* (~15-20%), *BRAF* (~2-5%), *NRAS, ERBB2,USP9X* mutations.
- Subset with loss of 9p and homozygous deletions of *CDKN2A/2B.*
- Little genetic instability. Those with more CNVs are associated with recurrence (Soong et al 2017).



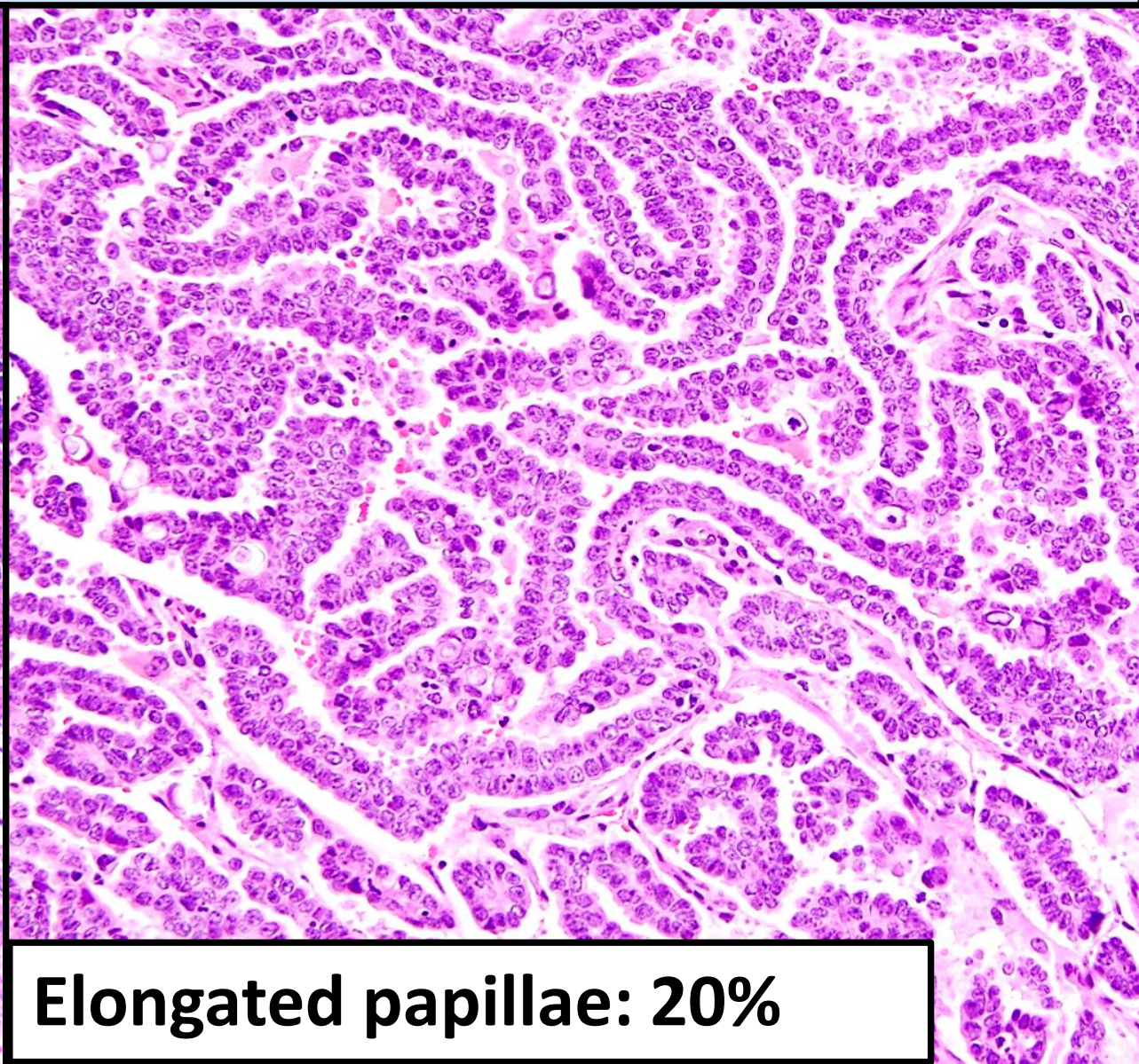
LGSCs with classic micropapillary morphology



LGSCs with other morphologies

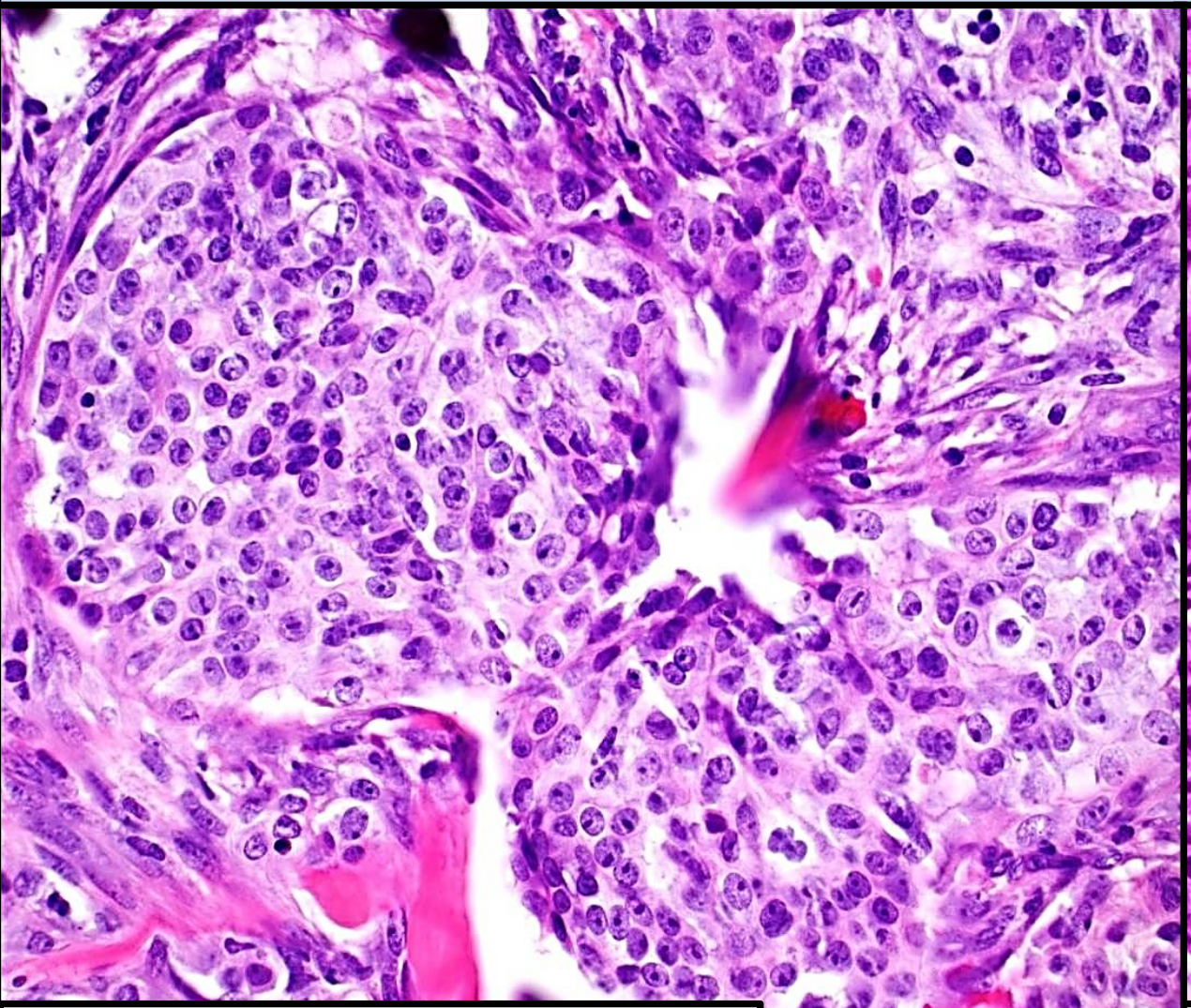


Macropapillae: 25%

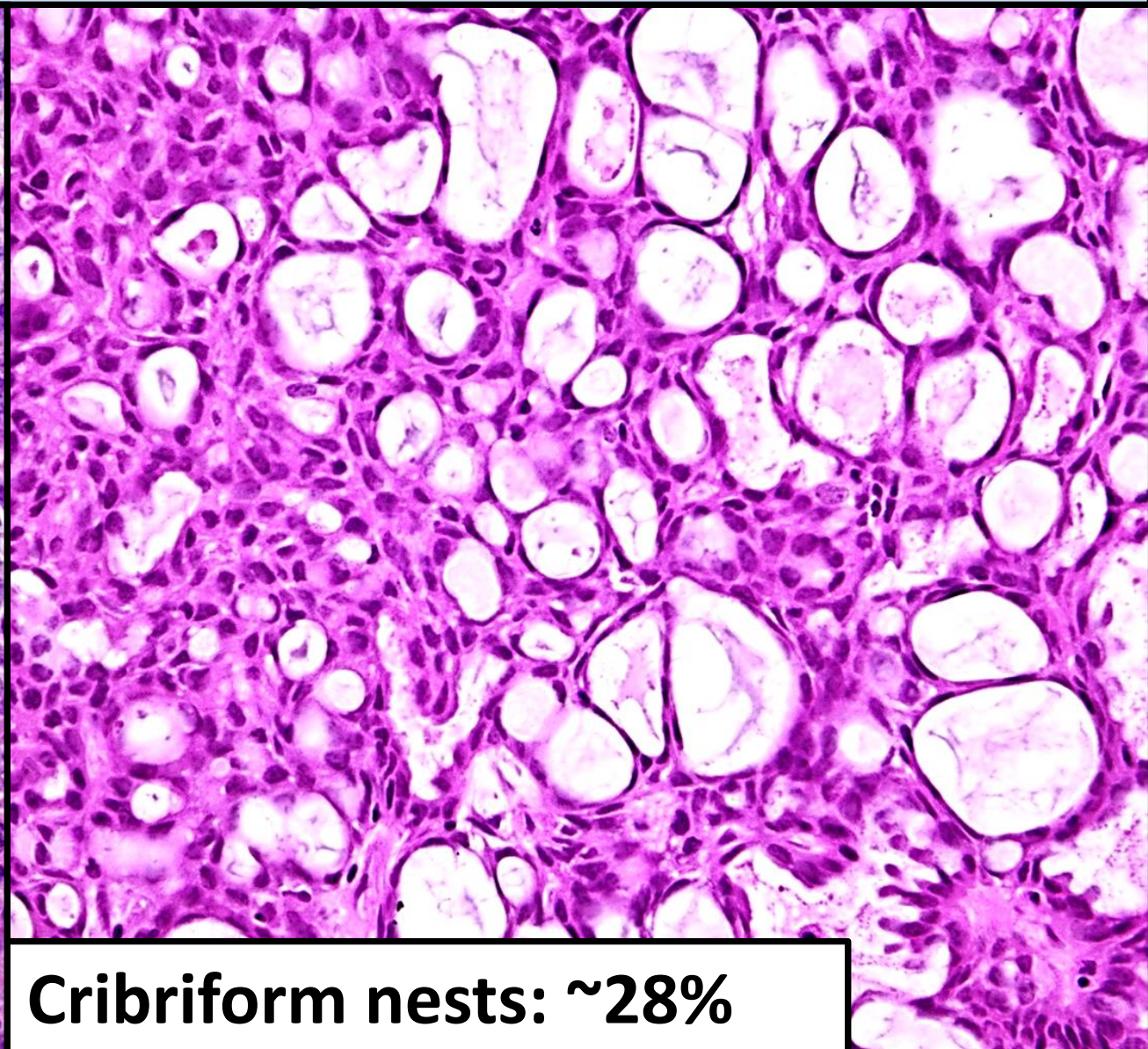


Elongated papillae: 20%

LGSCs with other morphologies

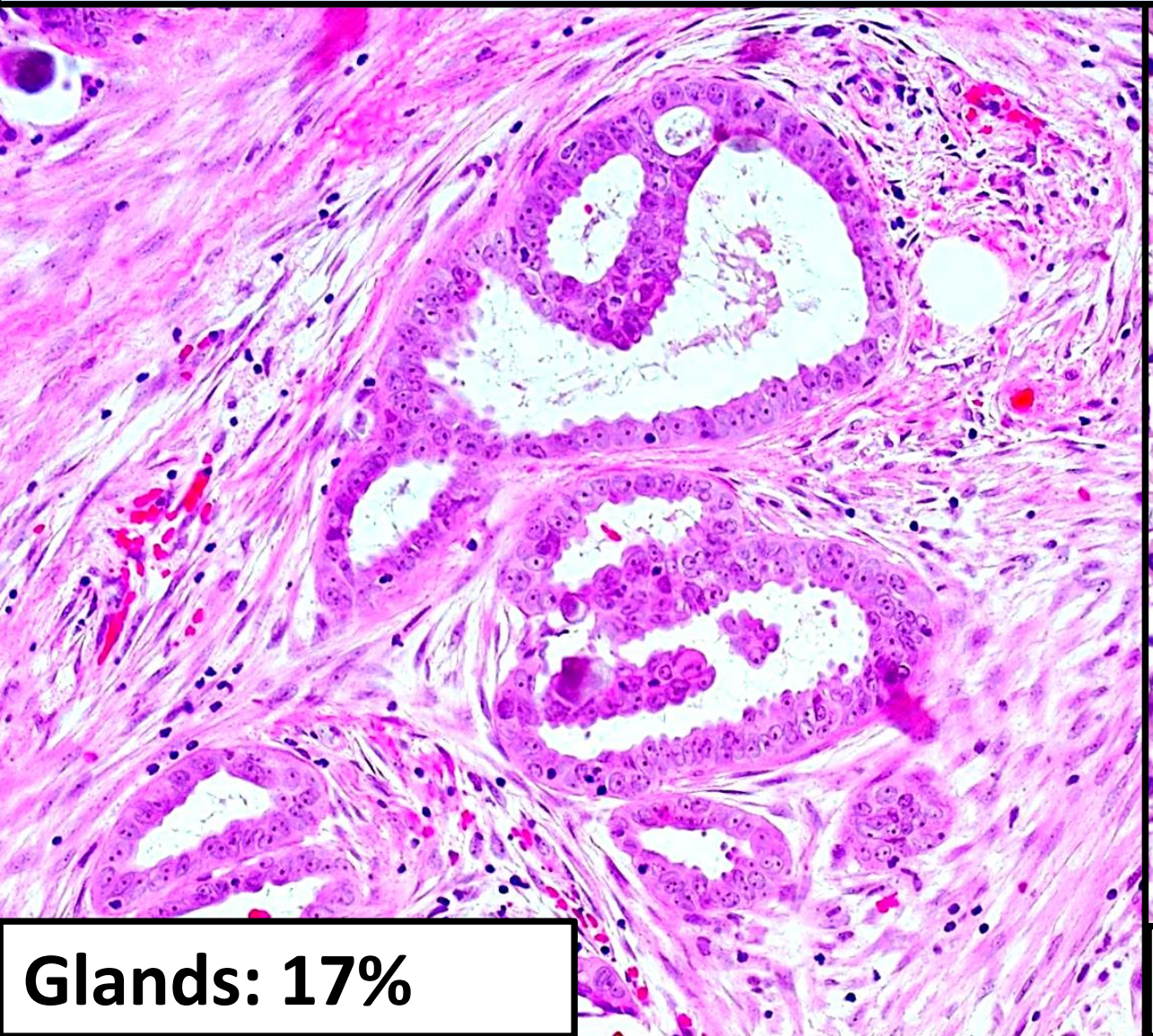


Solid nests: ~29%

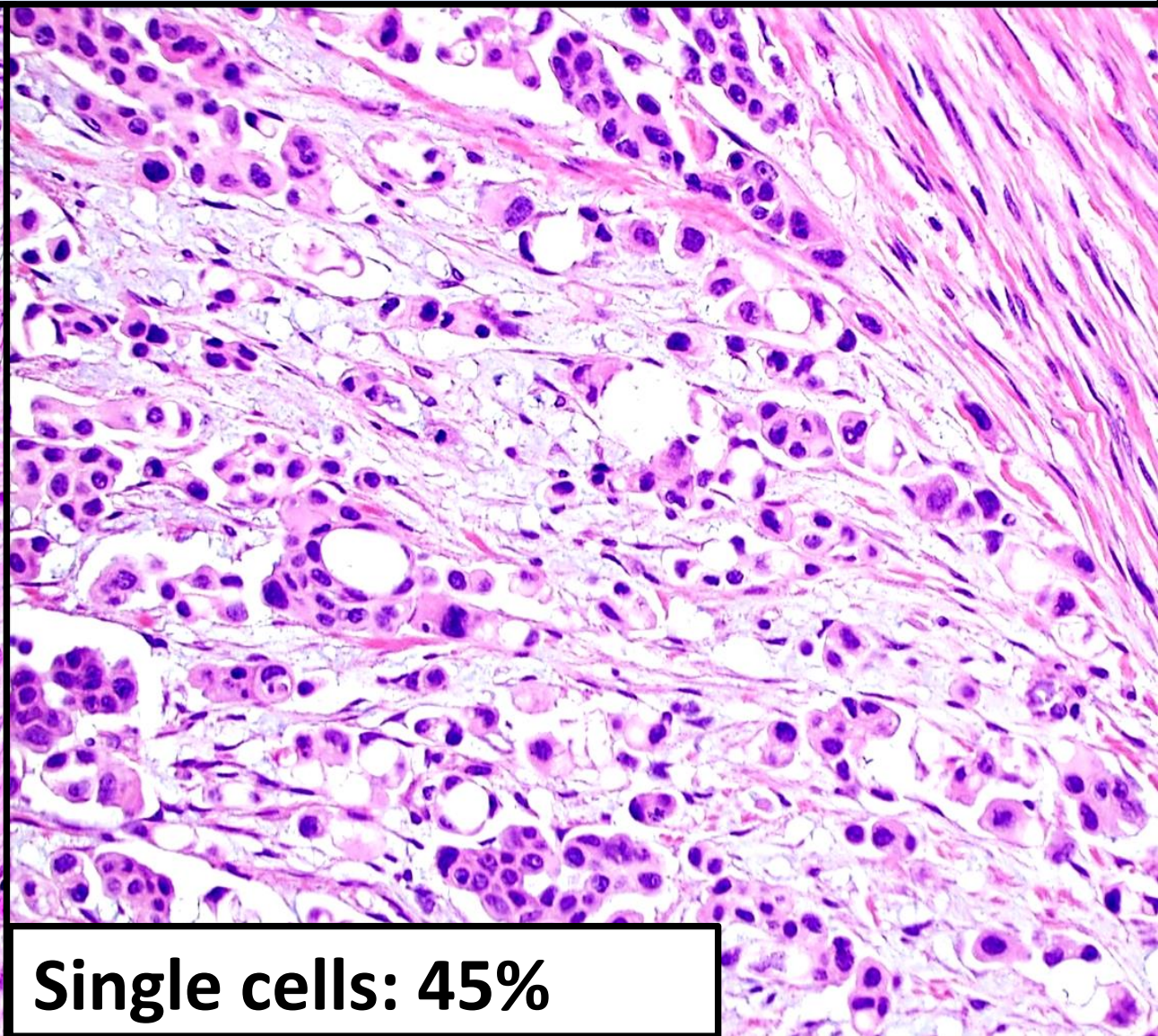


Cribriform nests: ~28%

LGSCs with other morphologies

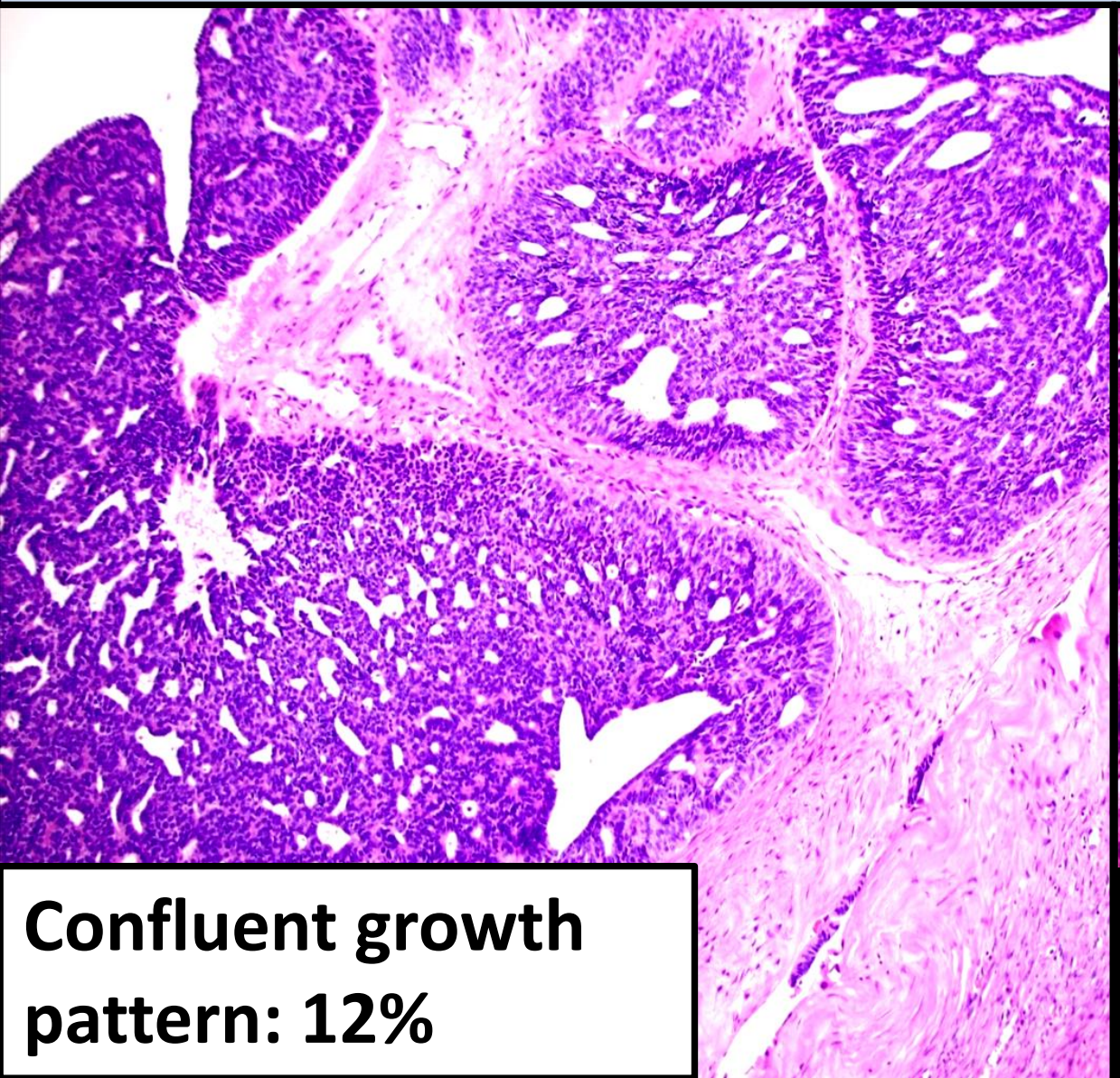


Glands: 17%

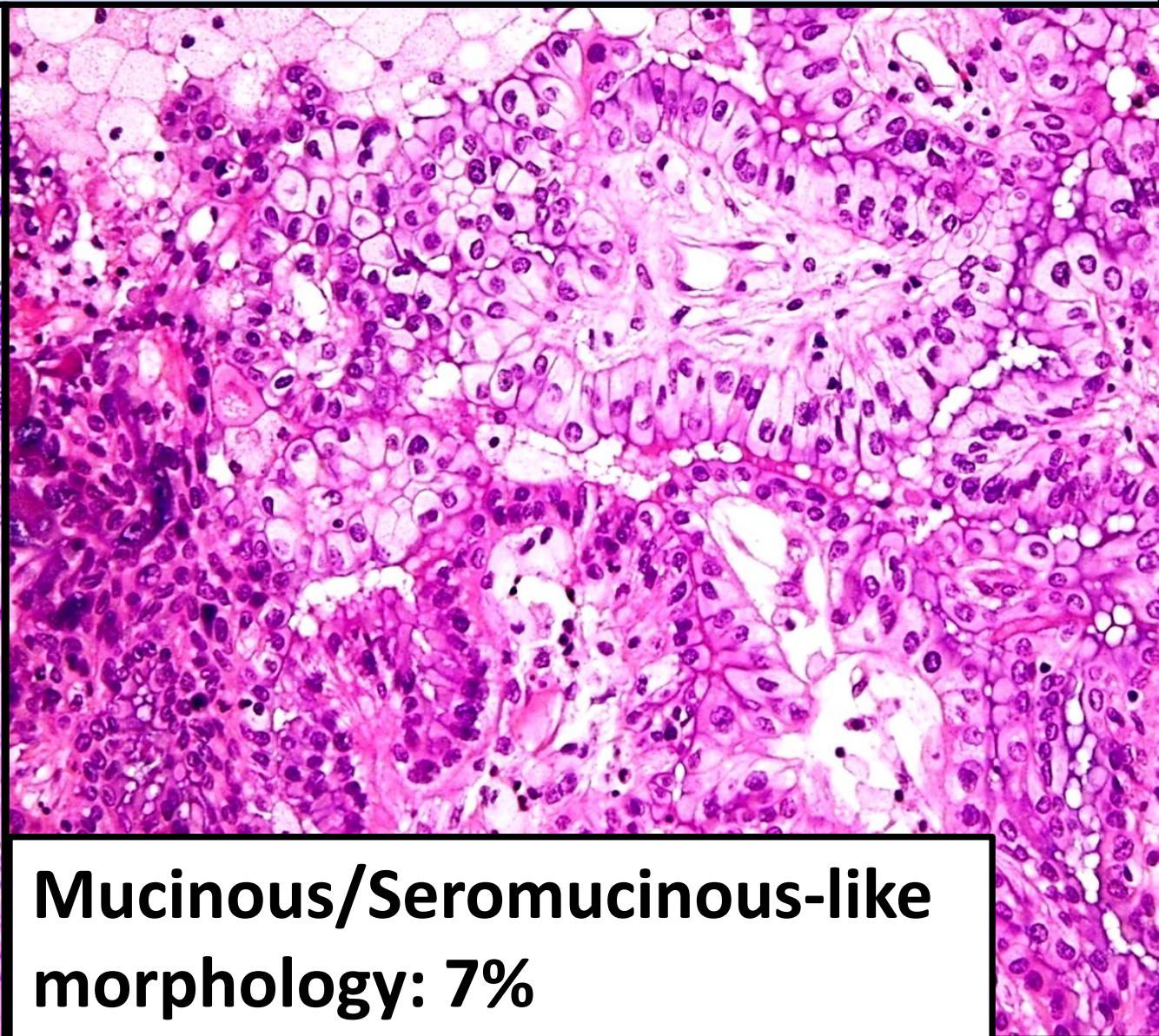


Single cells: 45%

LGSCs with other morphologies



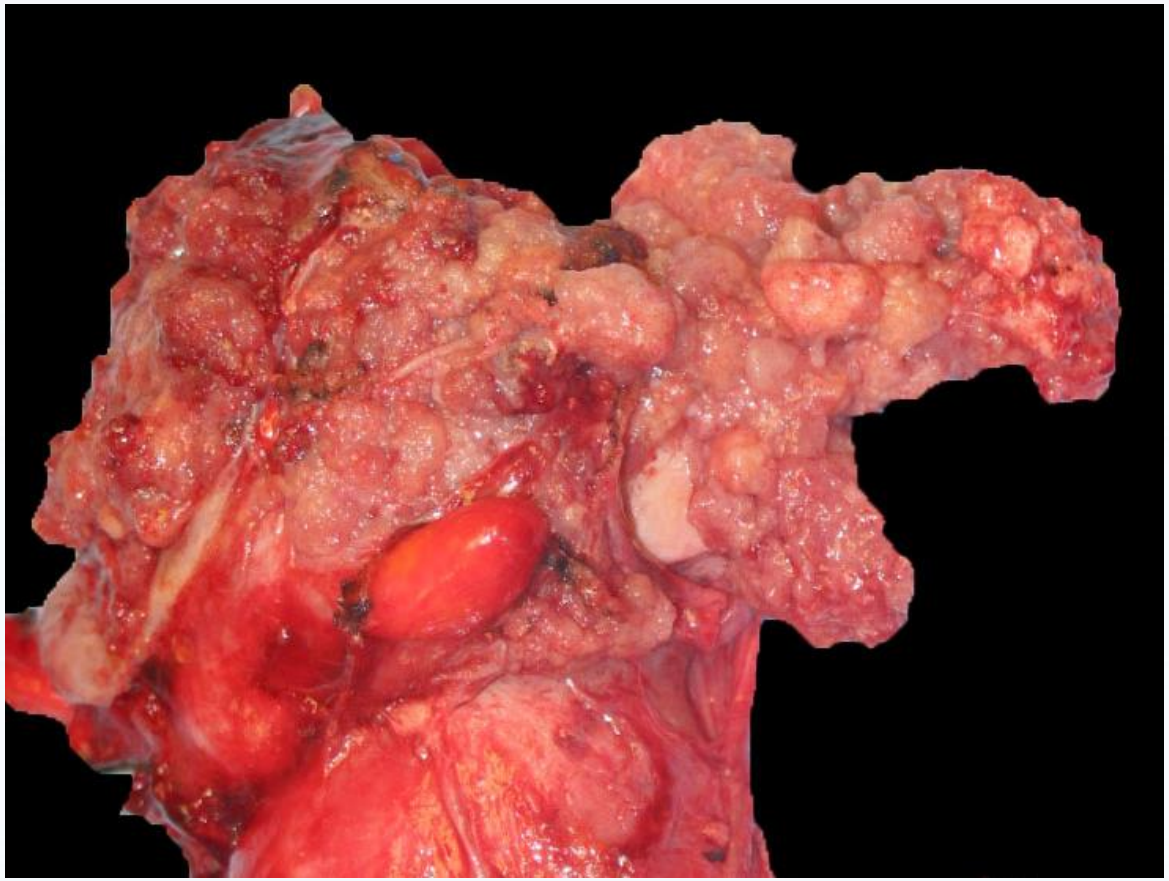
Confluent growth pattern: 12%



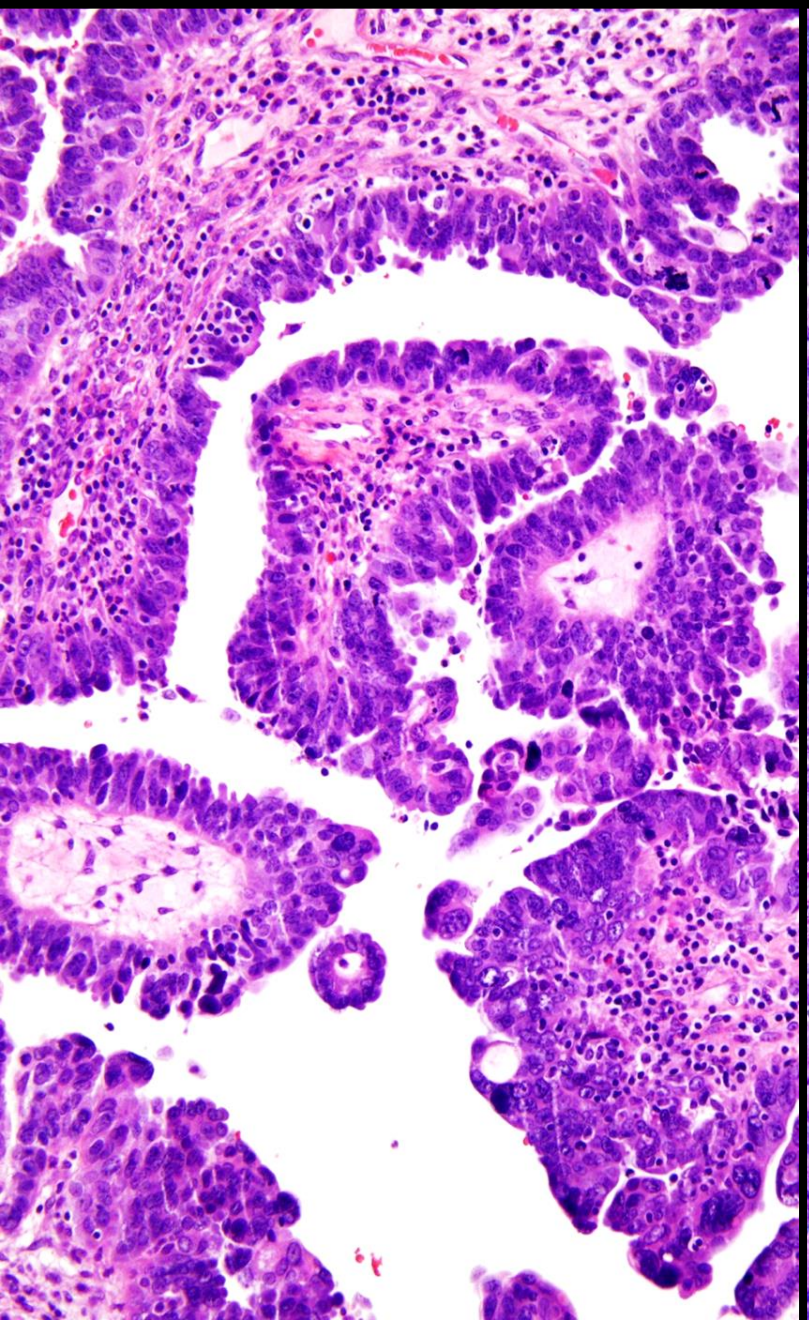
Mucinous/Seromucinous-like morphology: 7%

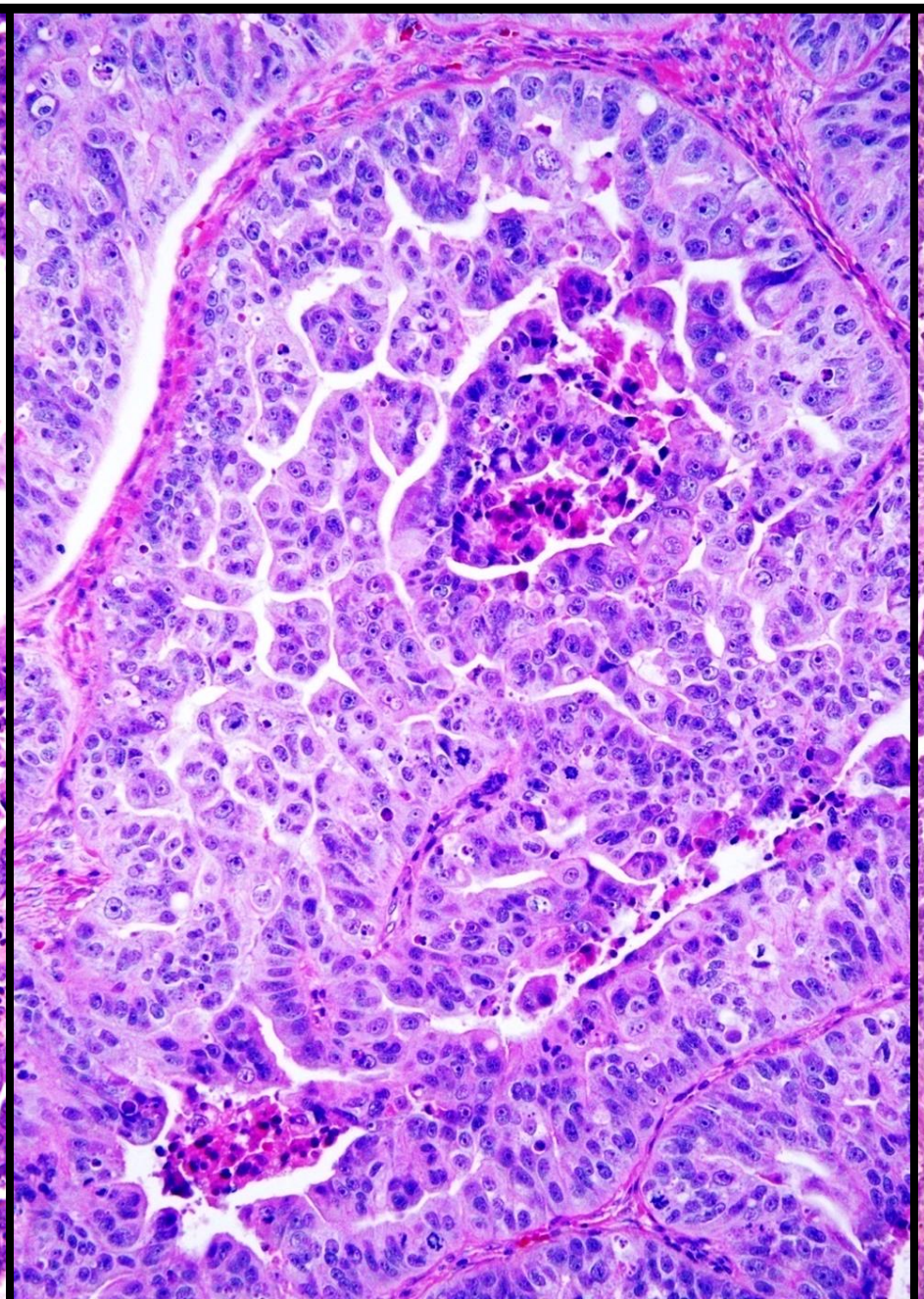
High-grade serous carcinomas (HGSCs)

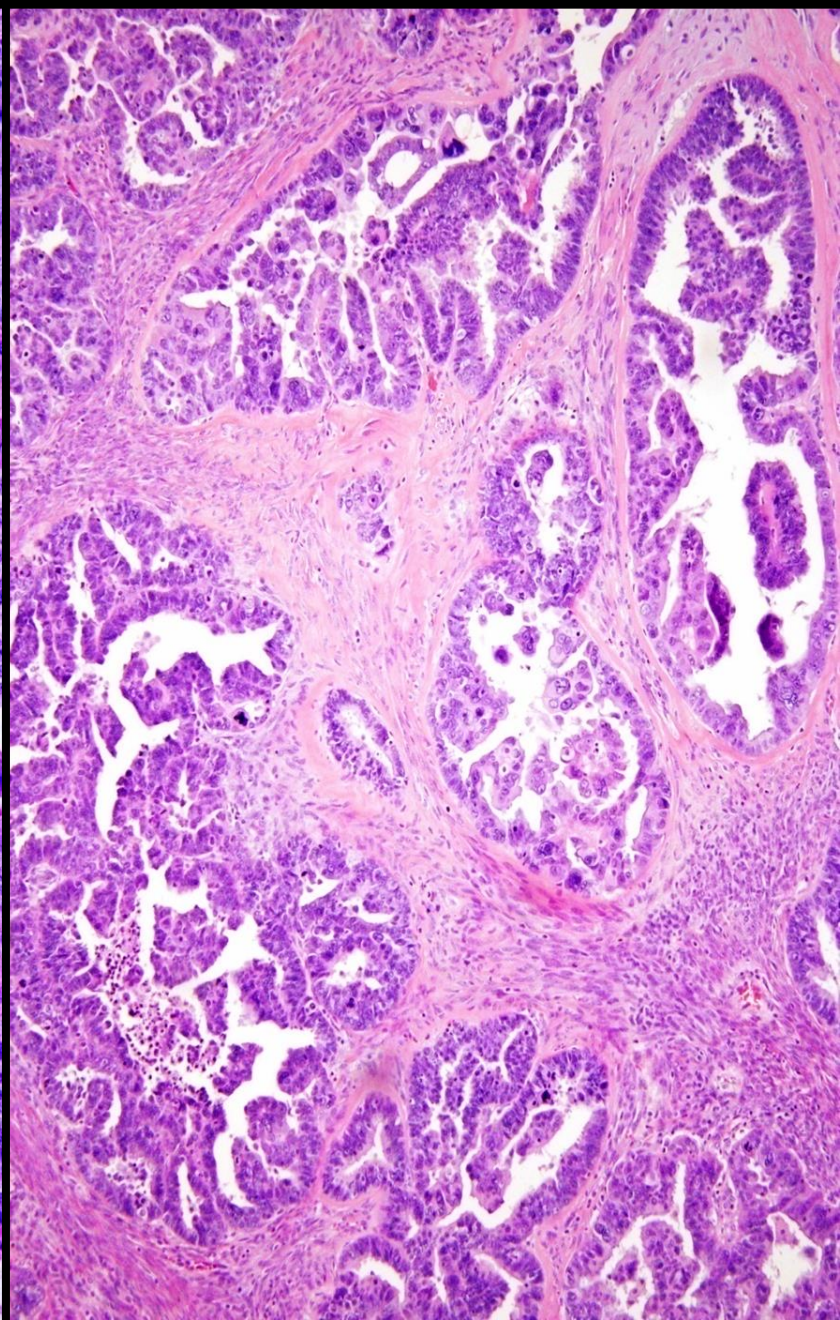
- 80% are stage 3 or 4 when diagnosed.
- Mortality: 70-80% in 10 years.
- >95% contain loss of p53 function via mutation/LOH.
- Complex high-level CNVs.
- 10-40% of women with *BRCA1/2* germline mutations develop ovarian cancer.
- ~1% associated with germline mutations in genes with moderate penetrance, e.g. *RAD51C/D, BRIP1.*



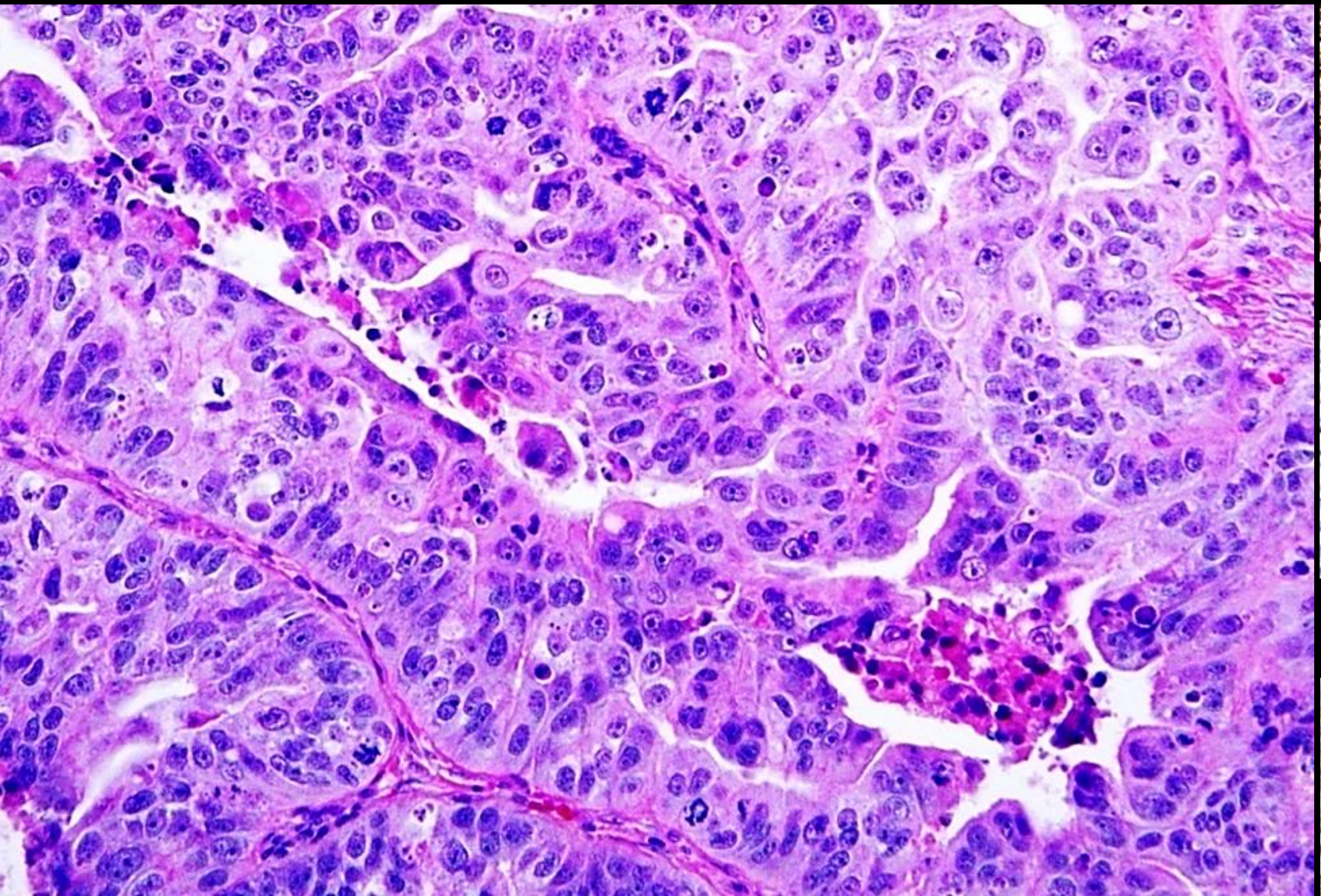
HGSCs with classic morphology



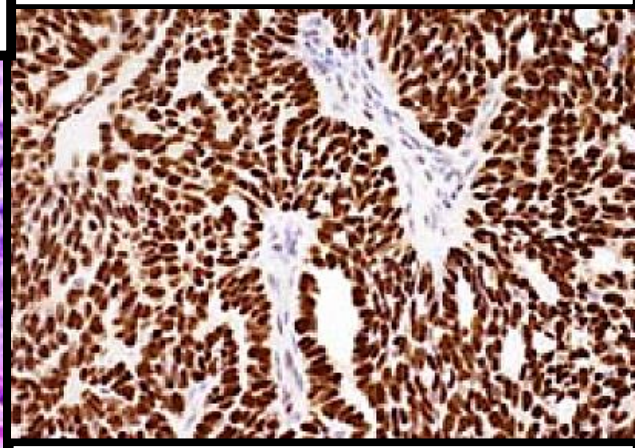




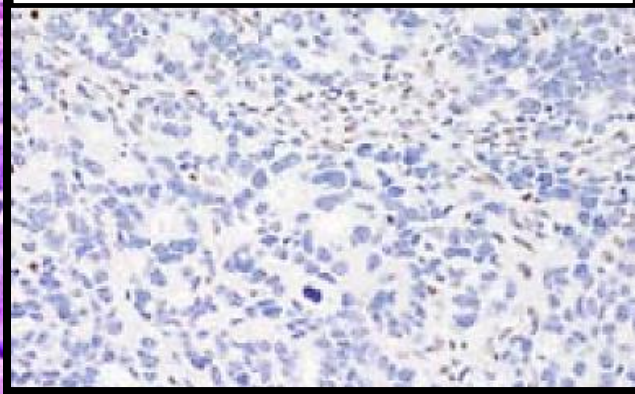
HGSCs and classic p53 IHC profiles



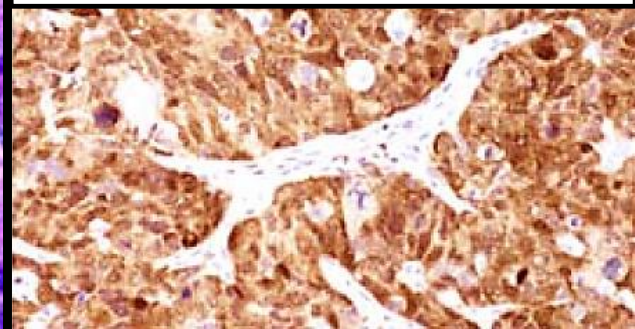
P53 over-expression



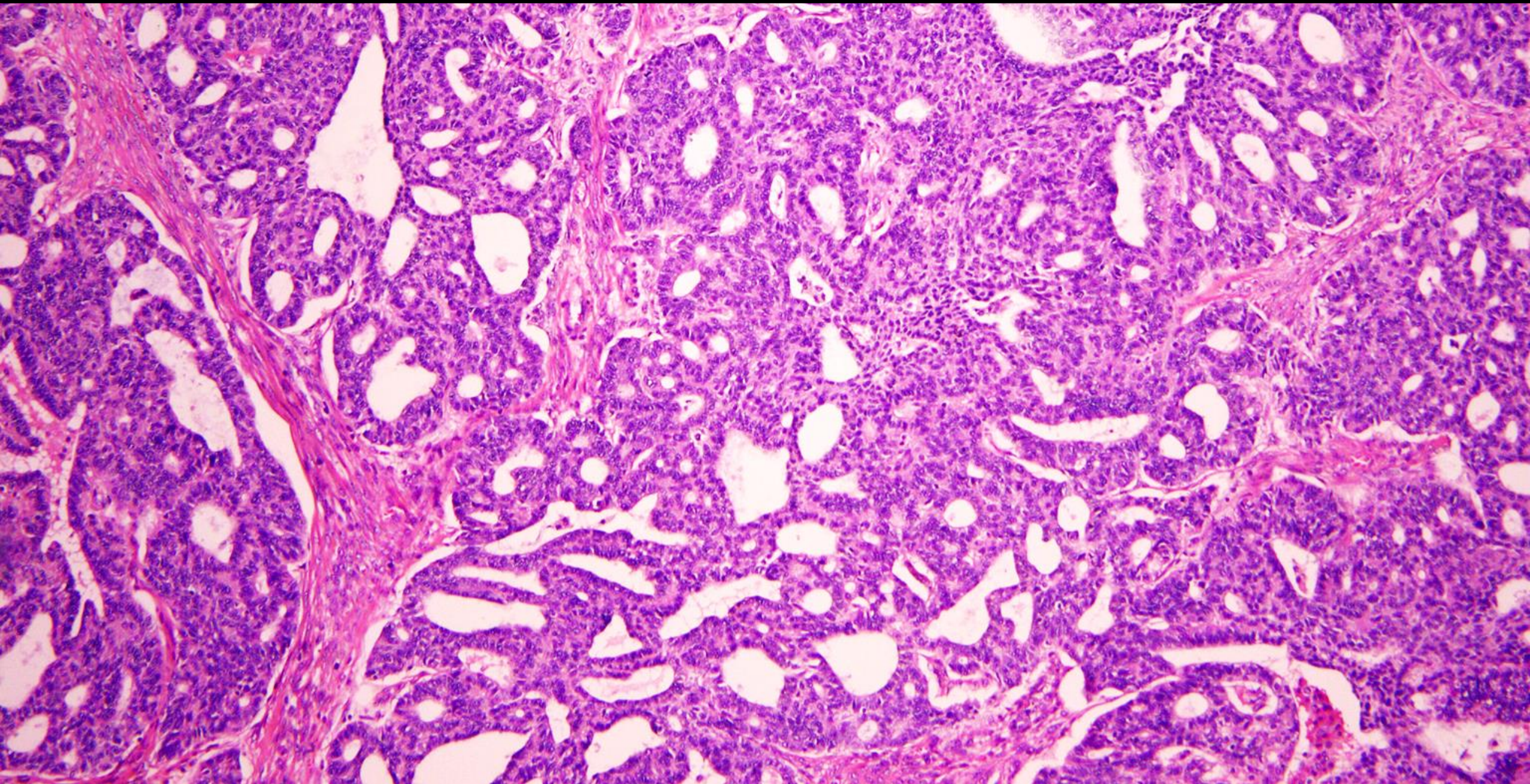
P53 null expression



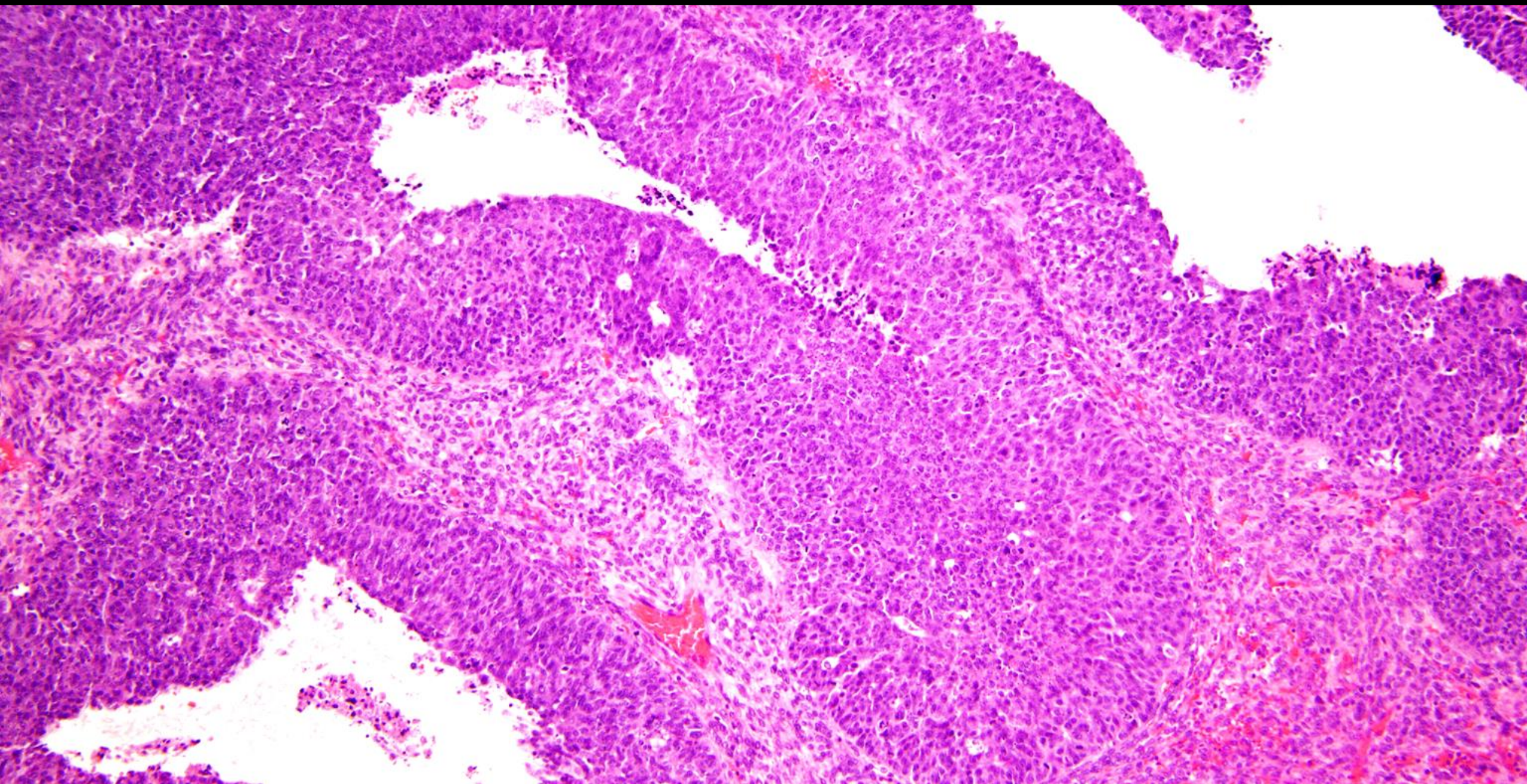
P53 diffuse cytoplasmic expression



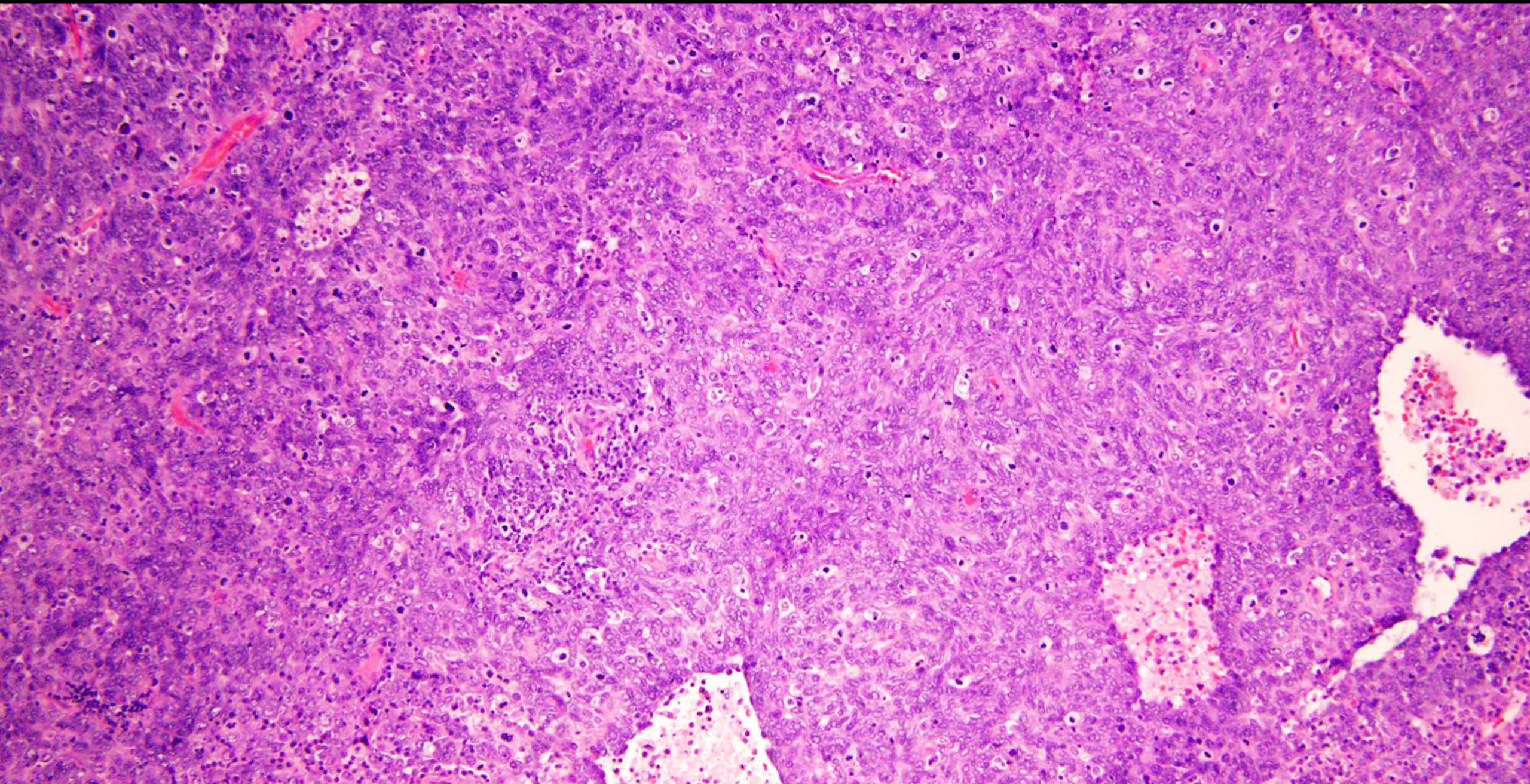
HGSCs with pseudo-endometrioid morphology



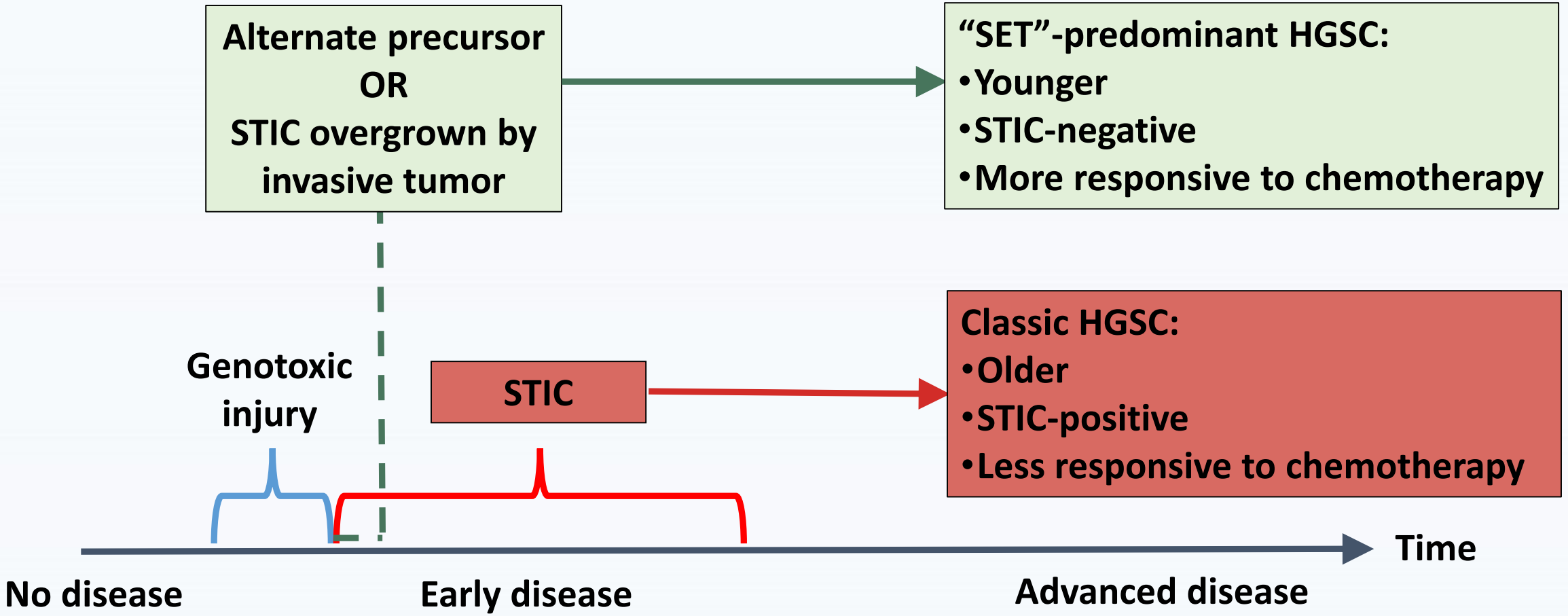
HGSCs with transitional-like morphology



HGSCs with solid morphology



Are HGSCs enriched with SET (Solid, pseudo-Endometrioid and Transitional) morphology biologically different from classic HGSCs?



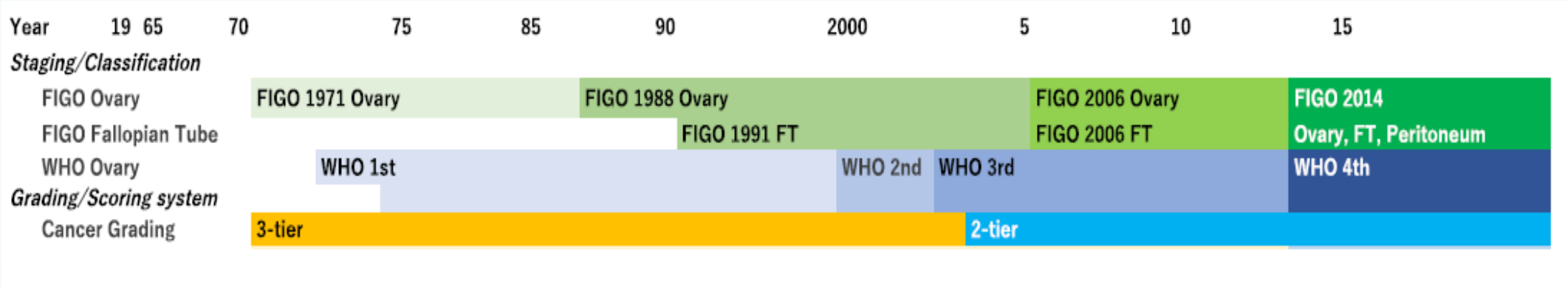
Howitt, Meserve and Crum et al 2015

IHC profiles of HGSC vs LGSC vs others

	PAX8+	WT1+	Aberrant p53	NapsinA+	PR+
HGSC	95%	97%	≥95%	1%	37-42%
LGSC	85-100%	98-100%	0%	0	59-60%
Endometrioid carcinoma	82%	10-14%	14-15%	3-8%	81-85%
Clear cell carcinoma	95%	1%	11-12%	92%	5-7%
Mucinous carcinoma	39-47%	0-1%	61-66%	0-3%	0-4%

Adapted from WHO 2020

Evolution in classification and grading of serous carcinomas



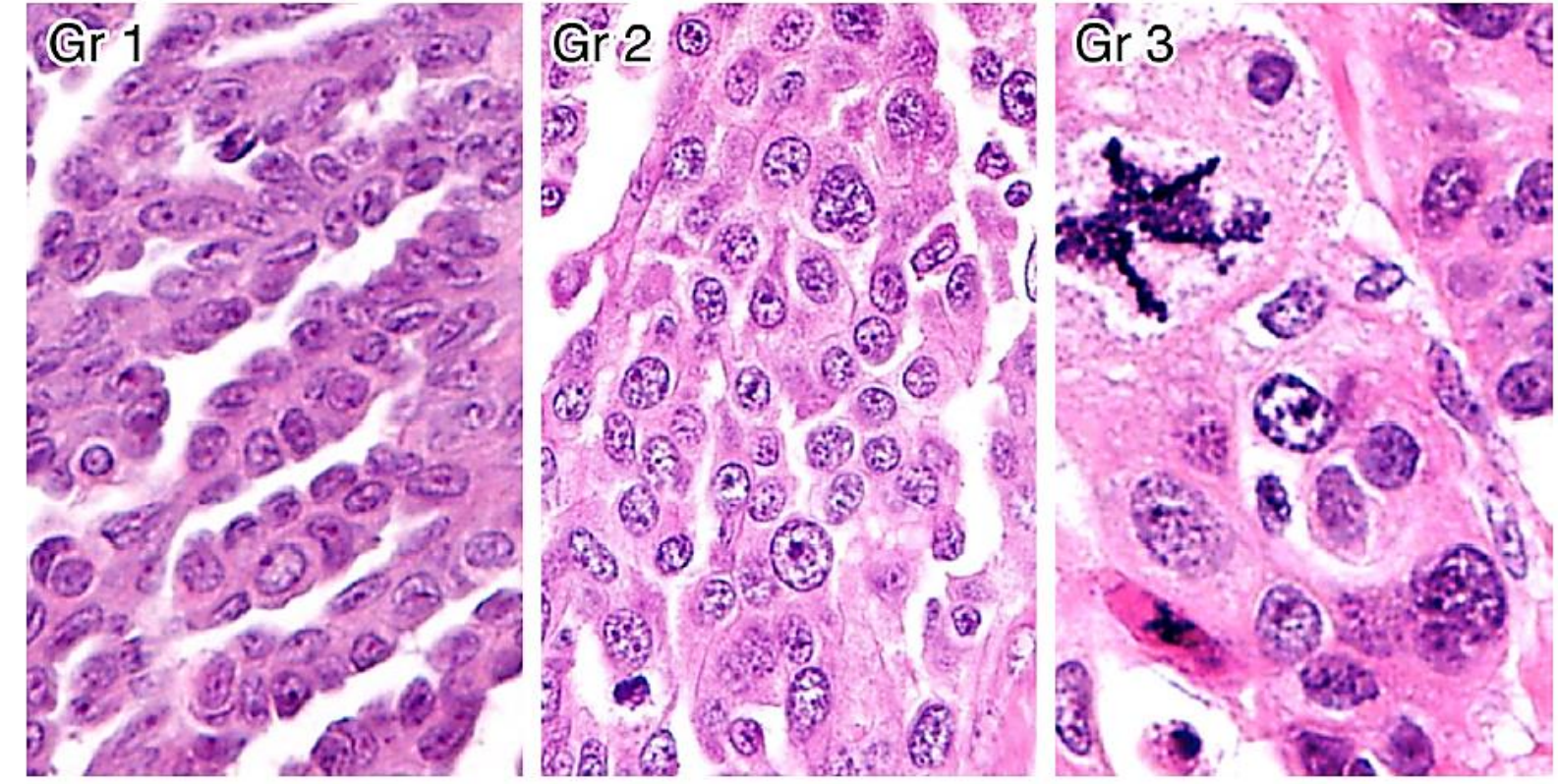
2021

FIGO 2018
Ovary, FT, Peritoneum
WHO 5th

2-tier grading system

- The previous 3-tier system was based on assessment of architectural pattern, cytologic atypia, and mitotic counts.
- The current 2-tier system was introduced by Malpica et al 2004, and then officially incorporated in WHO afterwards.

Grading of serous carcinomas in previous 3-tier system



Bodurka & Gershenson et al 2012

Comparison of estimates of progression-free survival (PFS) and overall survival (OS) according to the 2-tier and 3-tier (old FIGO) grading systems

Grade	No. of Patients	PFS			OS		
		3 Year, %	Median, mo	*P*	3 Year, %	Median, mo	*P*
MDACC							
Low	21	55.9	45.0	.01	90.5	126.2	.002
High	220	27.7	19.8		67.6	53.8	
FIGO							
1	16	50.0	37.5	.07	87.5	113.8	.02
2	102	23.1	19.8		66.1	52.7	
3	123	33.3	20.1		69.9	58.2	

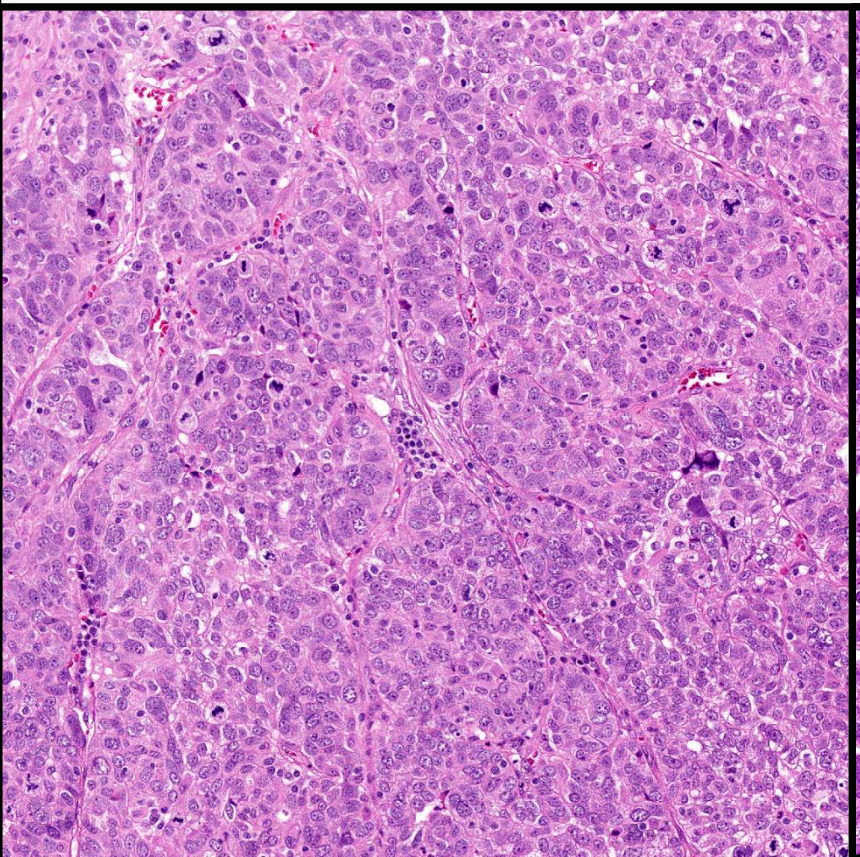
Abbreviations: FIGO, Federation of Gynecology and Obstetrics; MDACC, The University of Texas MD Anderson Cancer Center; OS, overall survival; PFS, progression-free survival.

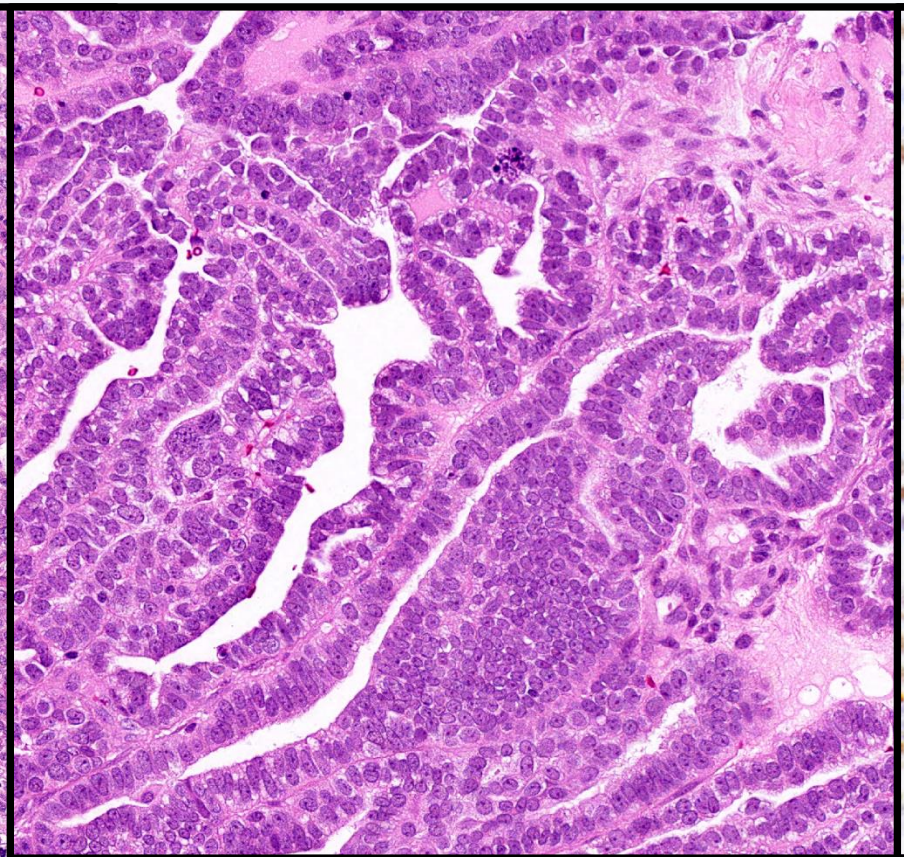
[a] Survival was estimated by Kaplan-Meier procedure, and survival functions were compared using log-rank test.

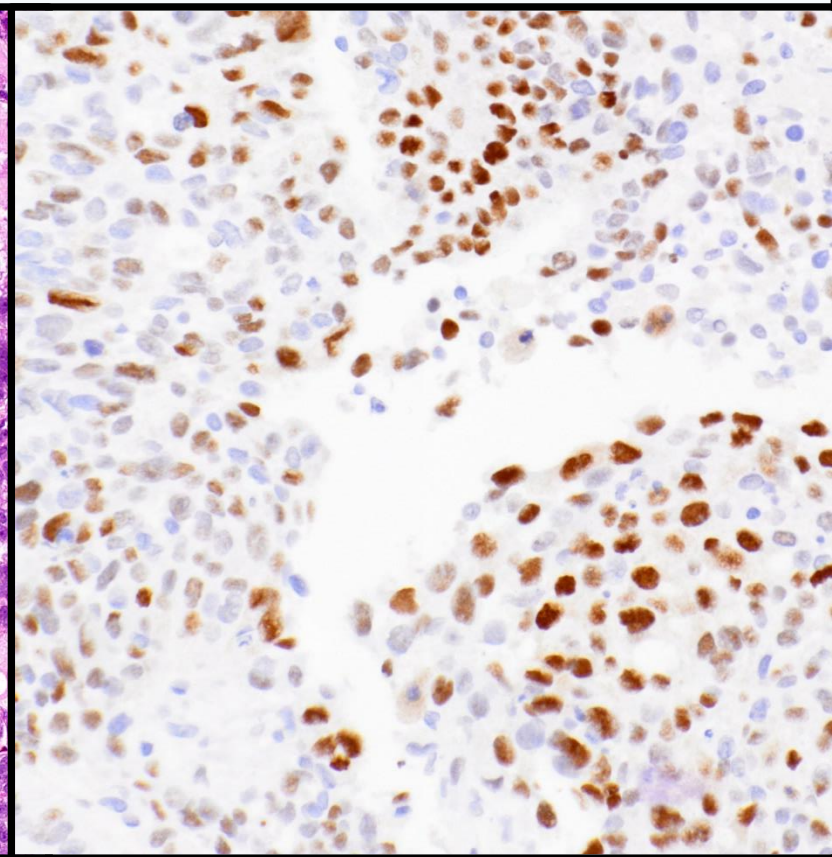
Bodurka & Gershenson et al 2012

Back to clinical case #1

- What to do with cases showing “mixed” low-grade and high-grade, or intermediate grade features (IGSCs)?



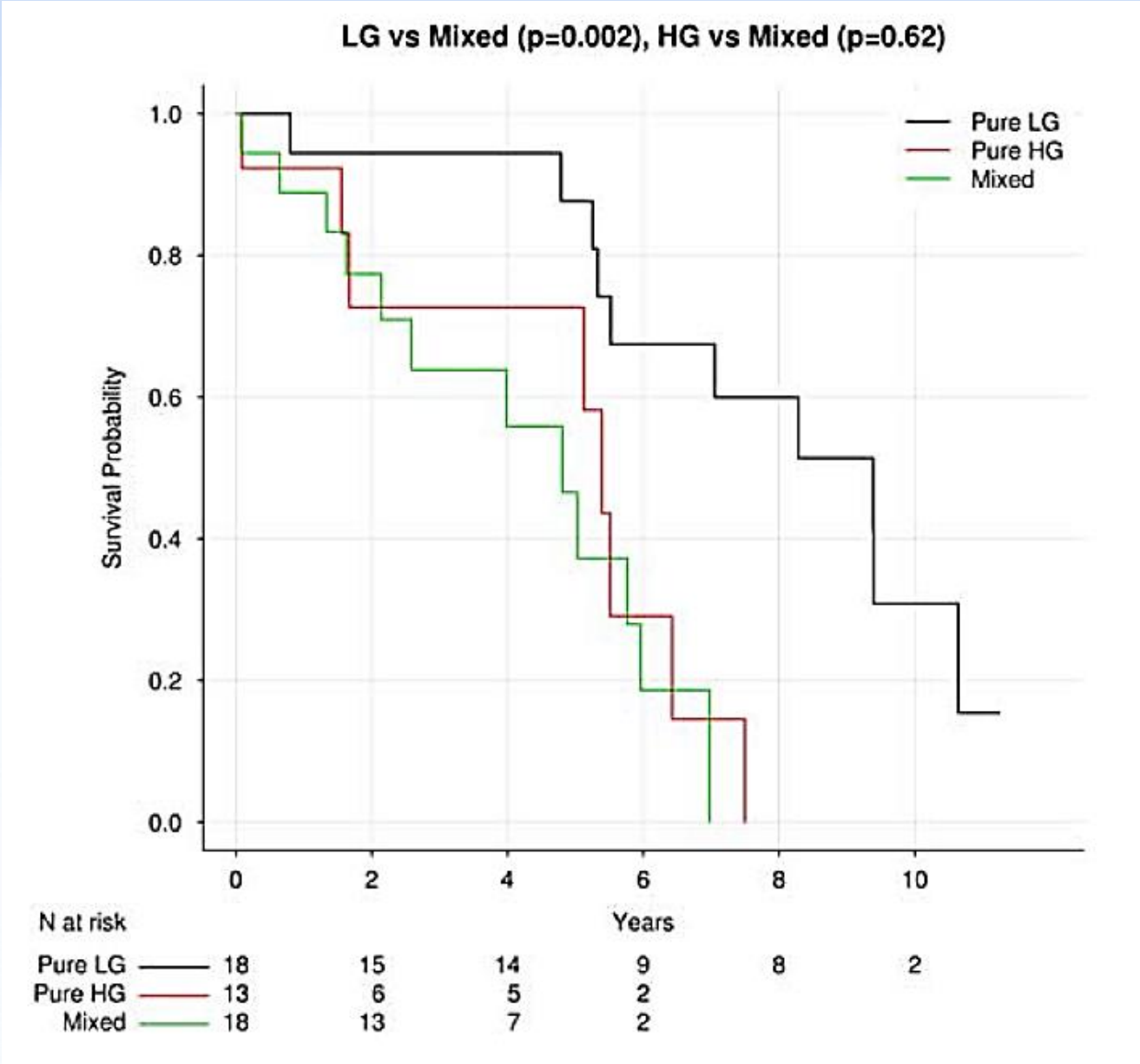




Difference in clinical behavior?

Outcome analyses on:

- Classic HGSCs (n=19)
- Classic LGSCs (n=19)
- Serous carcinomas with mixed/intermediate features (n=13)



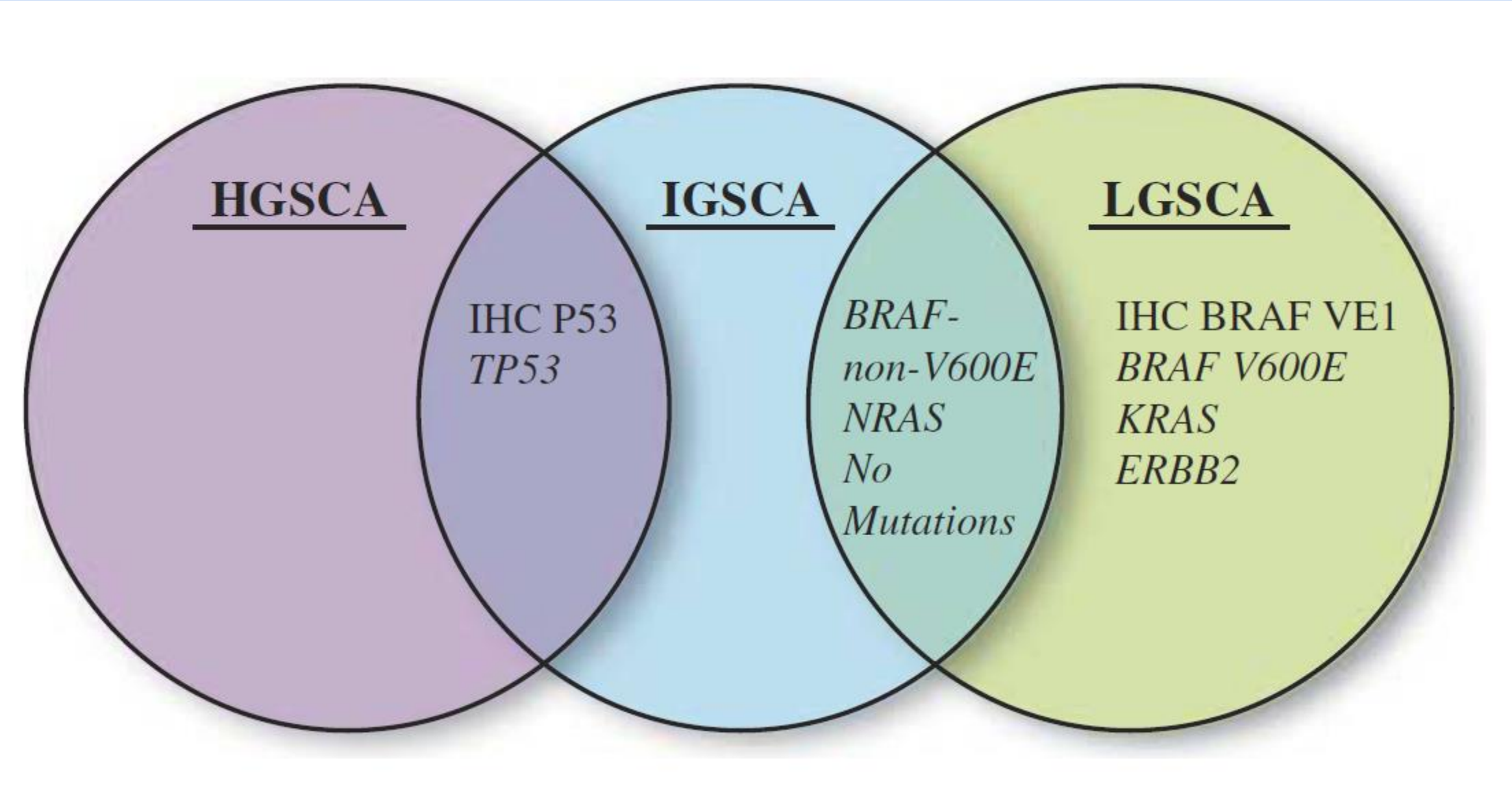
Shabnam & Bell et al. 2020

IHC profiles of classic HGSCs, LGSCs, and SCs with mixed features (IGSCA)

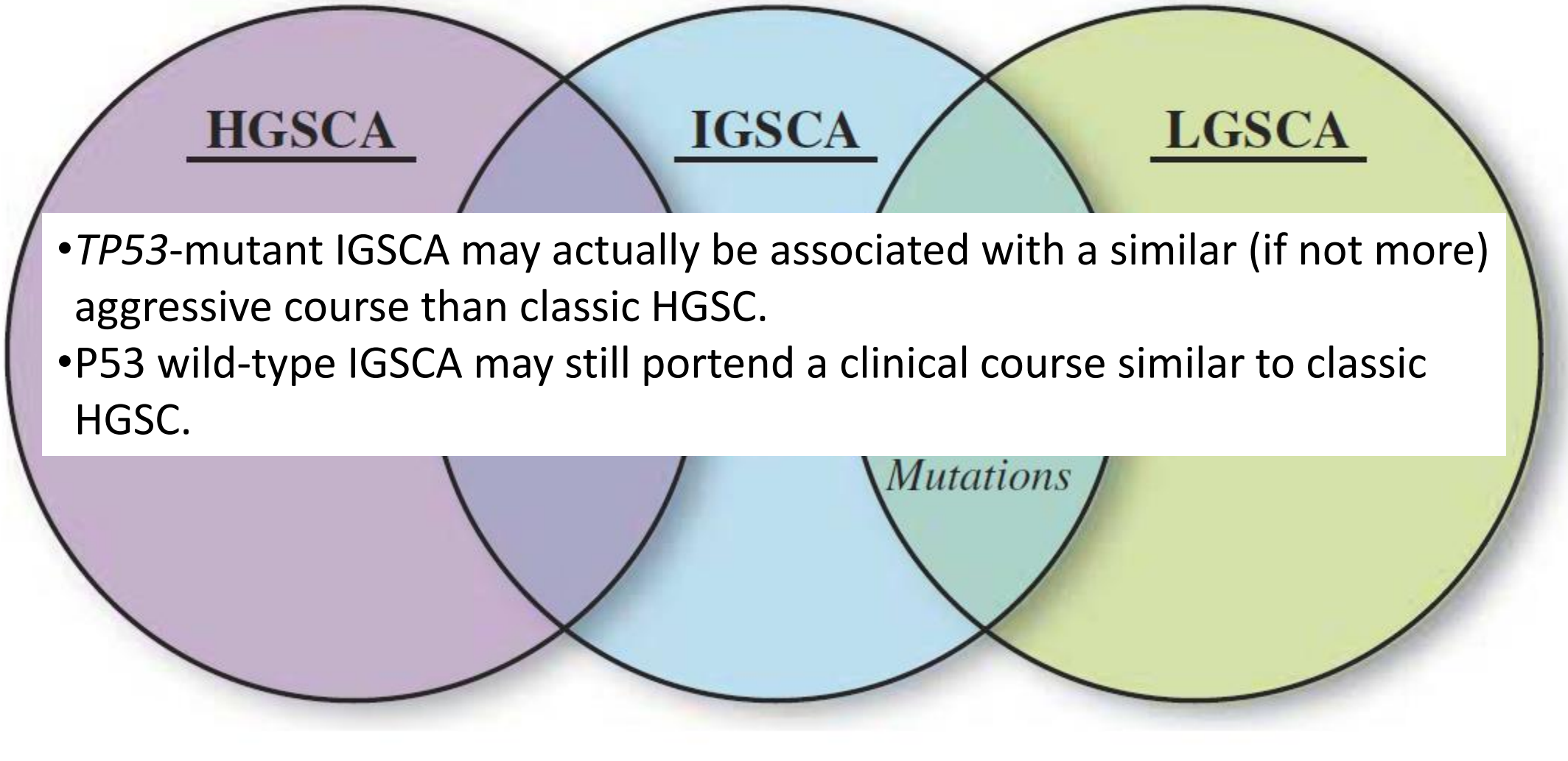
			p53 IHC			BRAF V600E IHC
Groups		**Type**	**# of Patients**		**Type**	**# of Patients**
Classic LGSC		Mutant	0		Mutant	1
		Wild	19		Wild	18
Classic HGSC		Mutant	12		Mutant	0
		Wild	1		Wild	13
	LG area	HG area	# of Patients	LG area	HG area	# of Patients
IGSCA	NA	Mutant	1	NA	Wild	2
	NA	Wild	1	Wild	Wild	17
	Equivocal	Mutant	1			
	Mutant	Mutant	1			
	Wild	Equivocal	1			
	Wild	Mutant	1			
	Wild	Wild	13			

NA indicates not available.

Shabnam & Bell et al. 2020



Shabnam & Bell et al. 2020



- *TP53*-mutant IGSCA may actually be associated with a similar (if not more) aggressive course than classic HGSC.
- P53 wild-type IGSCA may still portend a clinical course similar to classic HGSC.

Shabnam & Bell et al. 2020

Extrauterine serous carcinomas

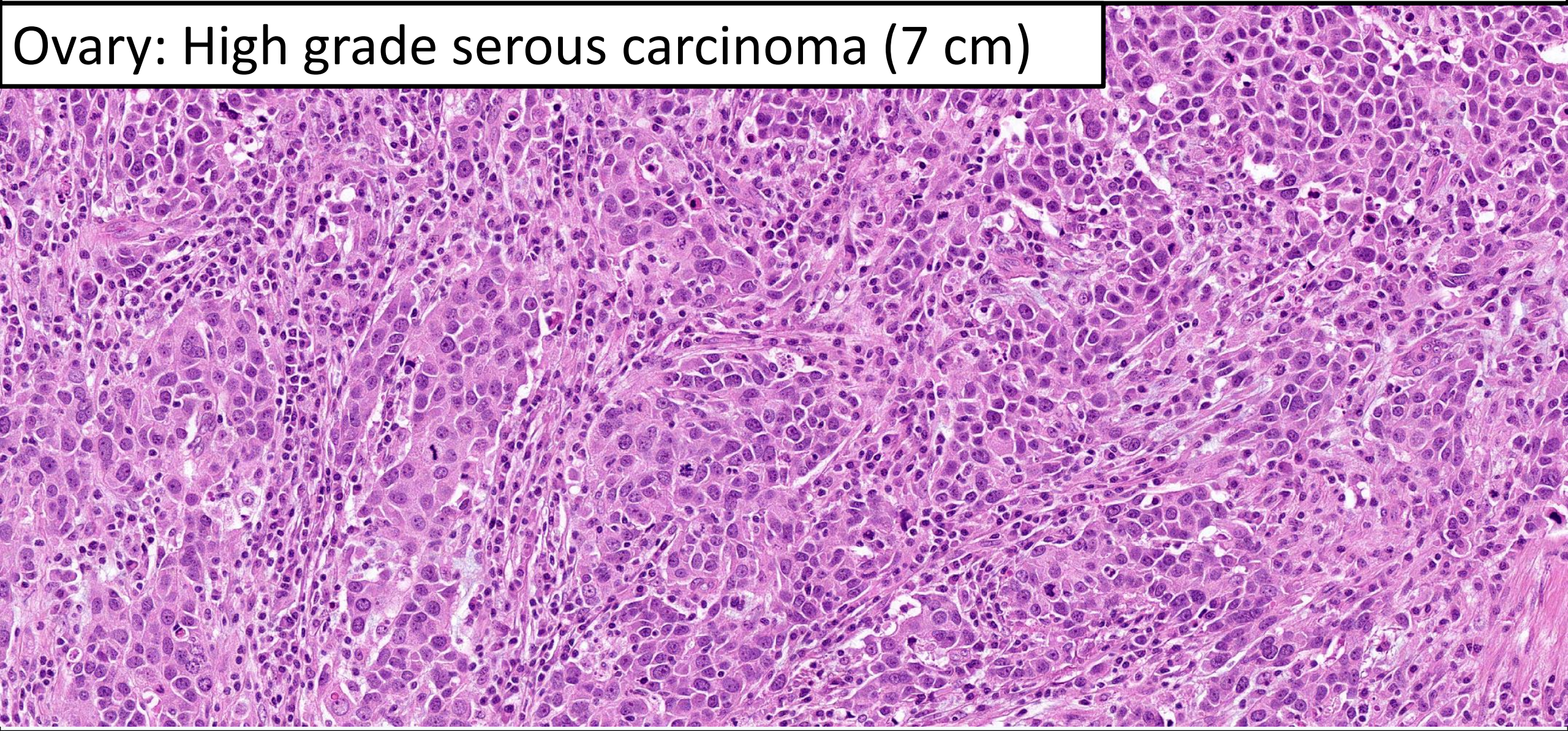
Diagnostic challenges:

1. Subtypes and classification?

2. **Site(s) of origin – ovary, fallopian tube, peritoneum, or endometrium?**

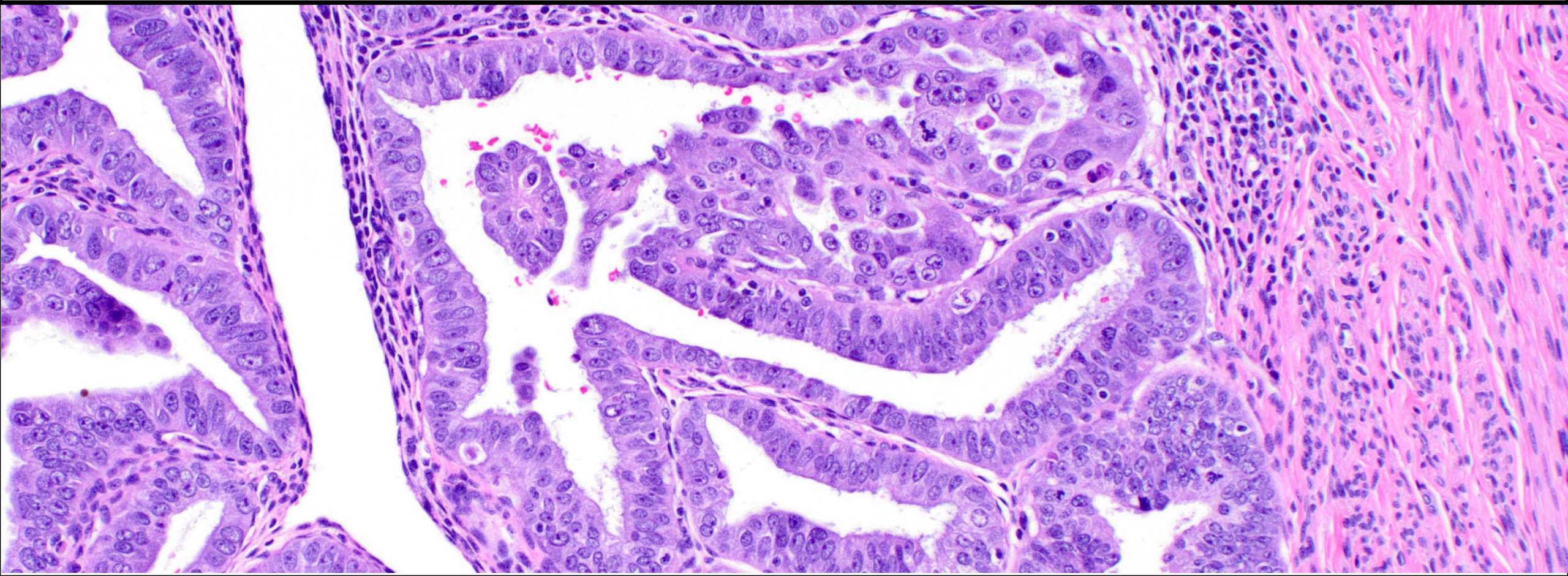
Clinical case #2: 79 year-old woman with pelvic mass and peritoneal carcinomatosis

Ovary: High grade serous carcinoma (7 cm)



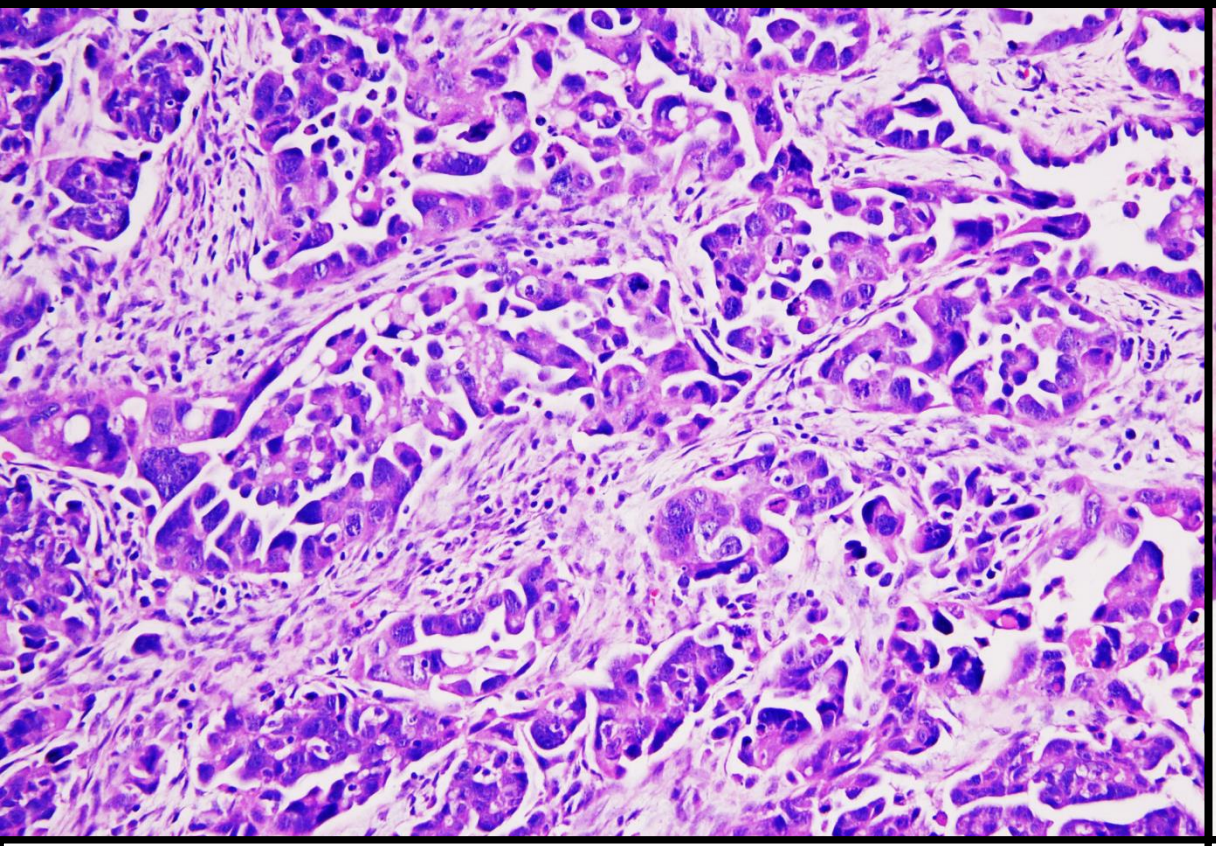
Clinical case #2

Endometrium: Focal serous carcinoma (2 cm) with superficial (<5%) myometrial invasion, similar high-grade cytomorphology and same IHC profile as carcinoma in ovary

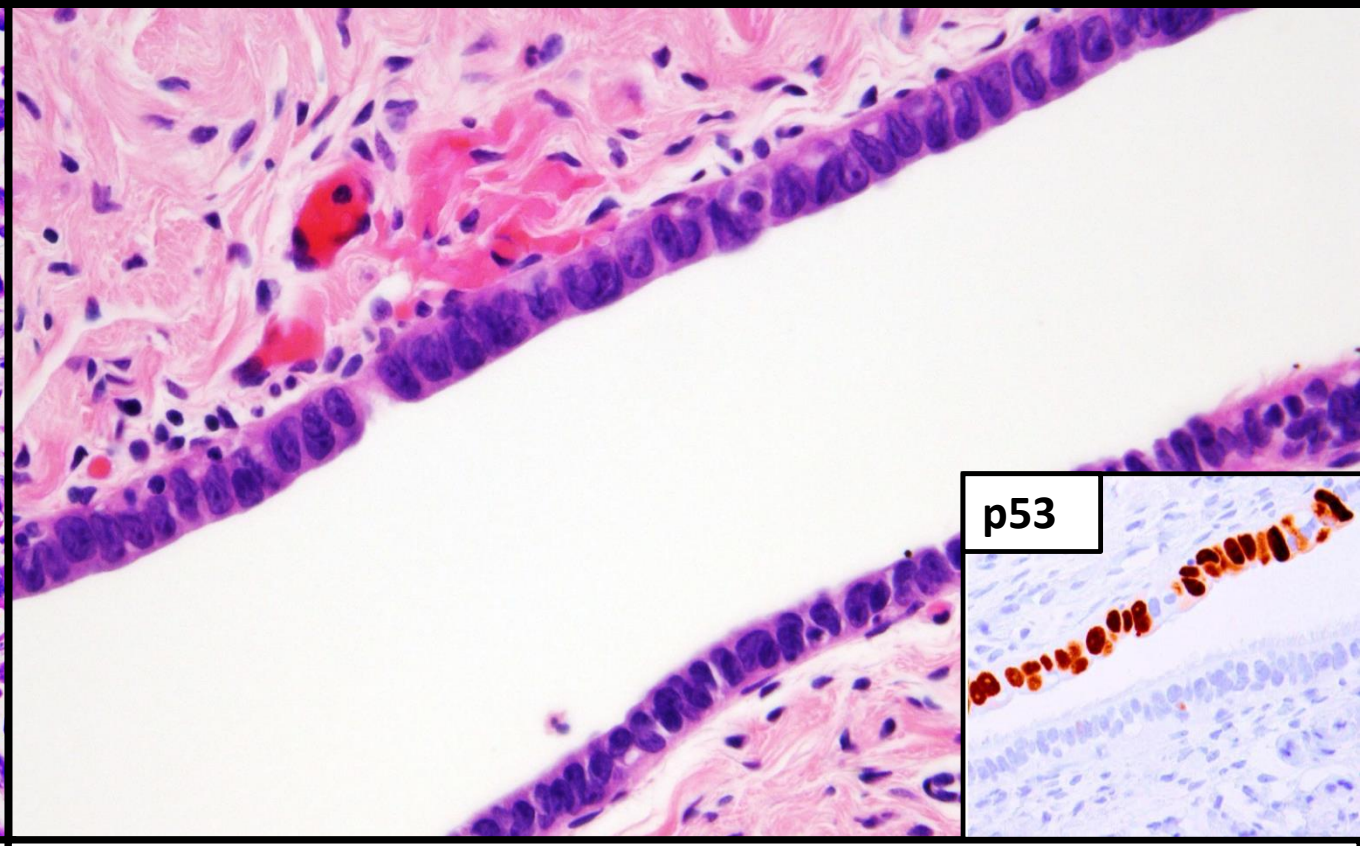


Clinical case #2

- 79 year-old woman with carcinoma in ovary, endometrium, peritoneum.



High-grade serous carcinoma diffusely involving the peritoneum and omentum (10 cm)

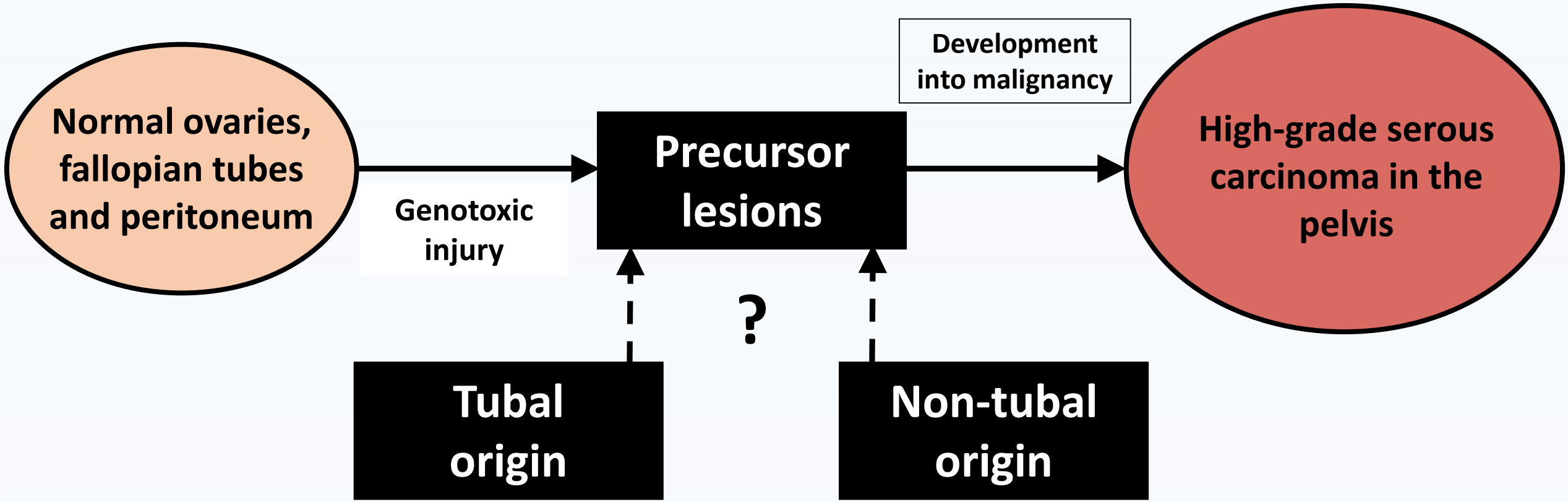


Serous tubal intraepithelial lesion (STIL) of uncertain significance in otherwise benign fallopian tubes

Clinical case #2

- 79 year-old female with carcinoma in ovary, endometrium, and diffuse peritoneal carcinomatosis.
- Site(s) of origin:
  - Ovary?
  - Fallopian tube?
  - Peritoneum?
  - Endometrium?
  - Synchronous primaries?
- Sequencing of carcinoma at the different sites show the same *TP53* mutational profile, supporting one neoplastic process.

The challenge in identifying the origin for HGSCs



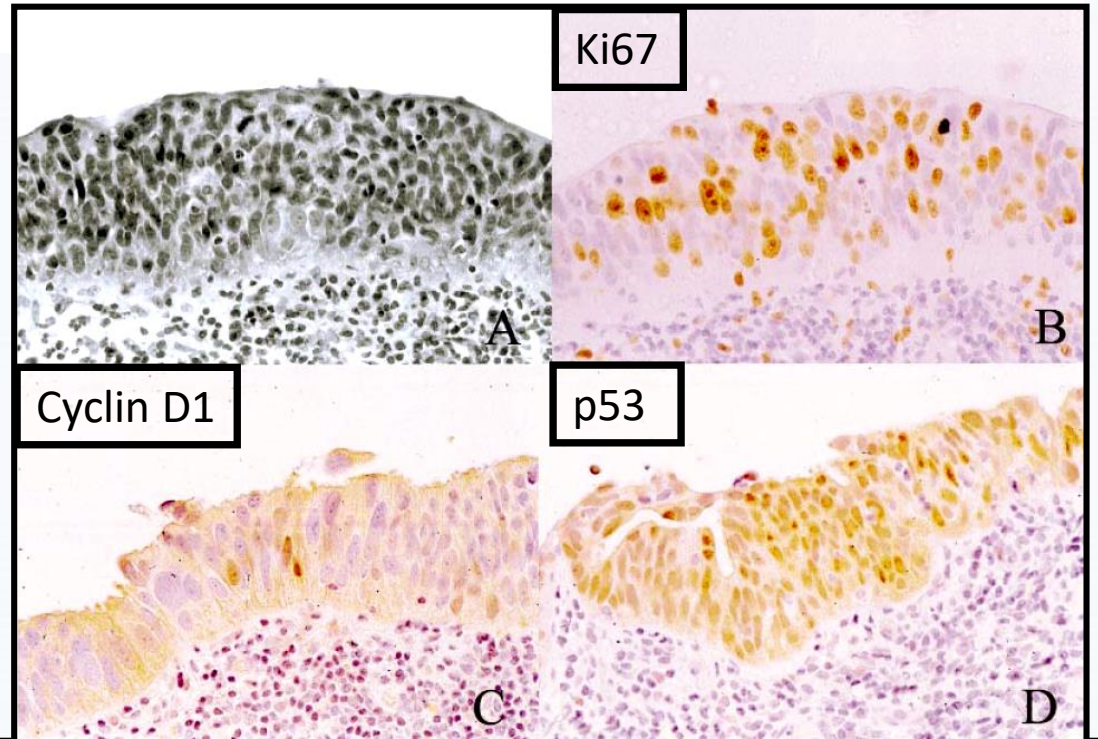
The quest for tubal precursors

2000
2001

Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer

Jurgen M. J. Piek[1], Paul J. van Diest[2]*, Ronald P. Zweemer[1], Jan W. Jansen[3], Ria J. J. Poort-Keesom[1], Fred H. Menko[4], Johan J. P. Gille[4], Ans P. M. Jongsma[1], Gerard Pals[4], Peter Kenemans[1] and René H. M. Verheijen[1]

Journal of Pathology
J Pathol 2001; **195**: 451–456.



The quest for tubal precursors

2000

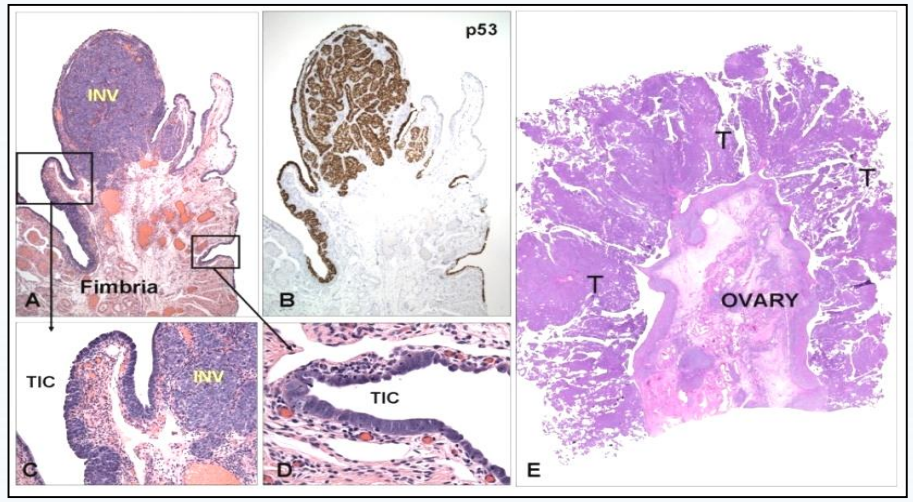
2001

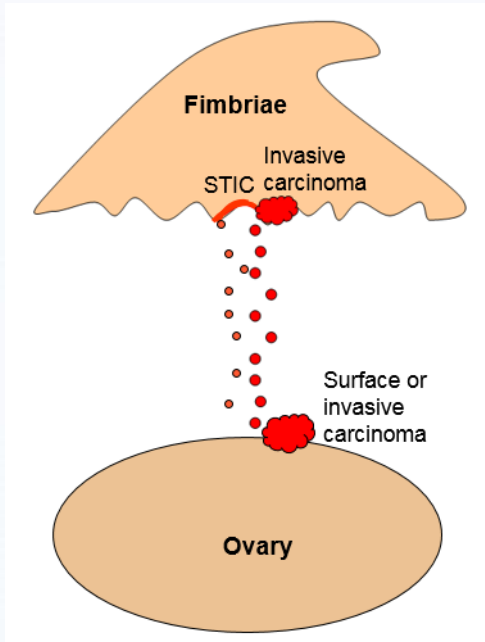
2005-2007

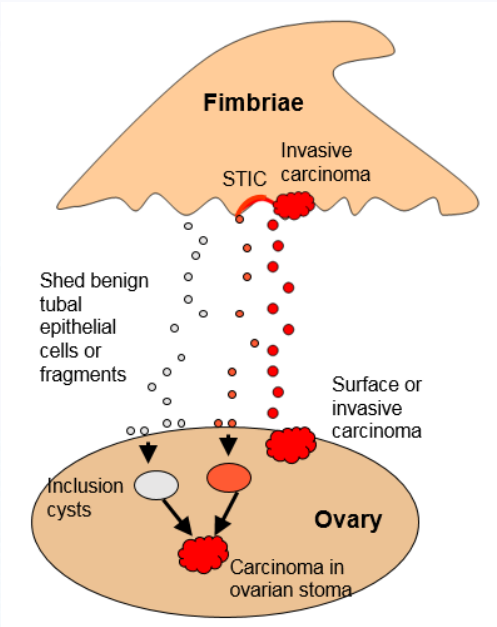
Intraepithelial Carcinoma of the Fimbria and Pelvic Serous Carcinoma: Evidence for a Causal Relationship

David W. Kindelberger, MD, Yonghee Lee, MD,* Alexander Miron, PhD,† Michelle S. Hirsch, MD, PhD,* Colleen Feltmate, MD,‡ Fabiola Medeiros, MD,* Michael J. Callahan, MD,‡ Elizabeth O. Garner, MD, MPH,‡ Robert W. Gordon,† Chandler Birch,* Ross S. Berkowitz, MD,‡ Michael G. Muto, MD,‡ and Christopher P. Crum, MD**

(*Am J Surg Pathol* 2007;31:161–169)

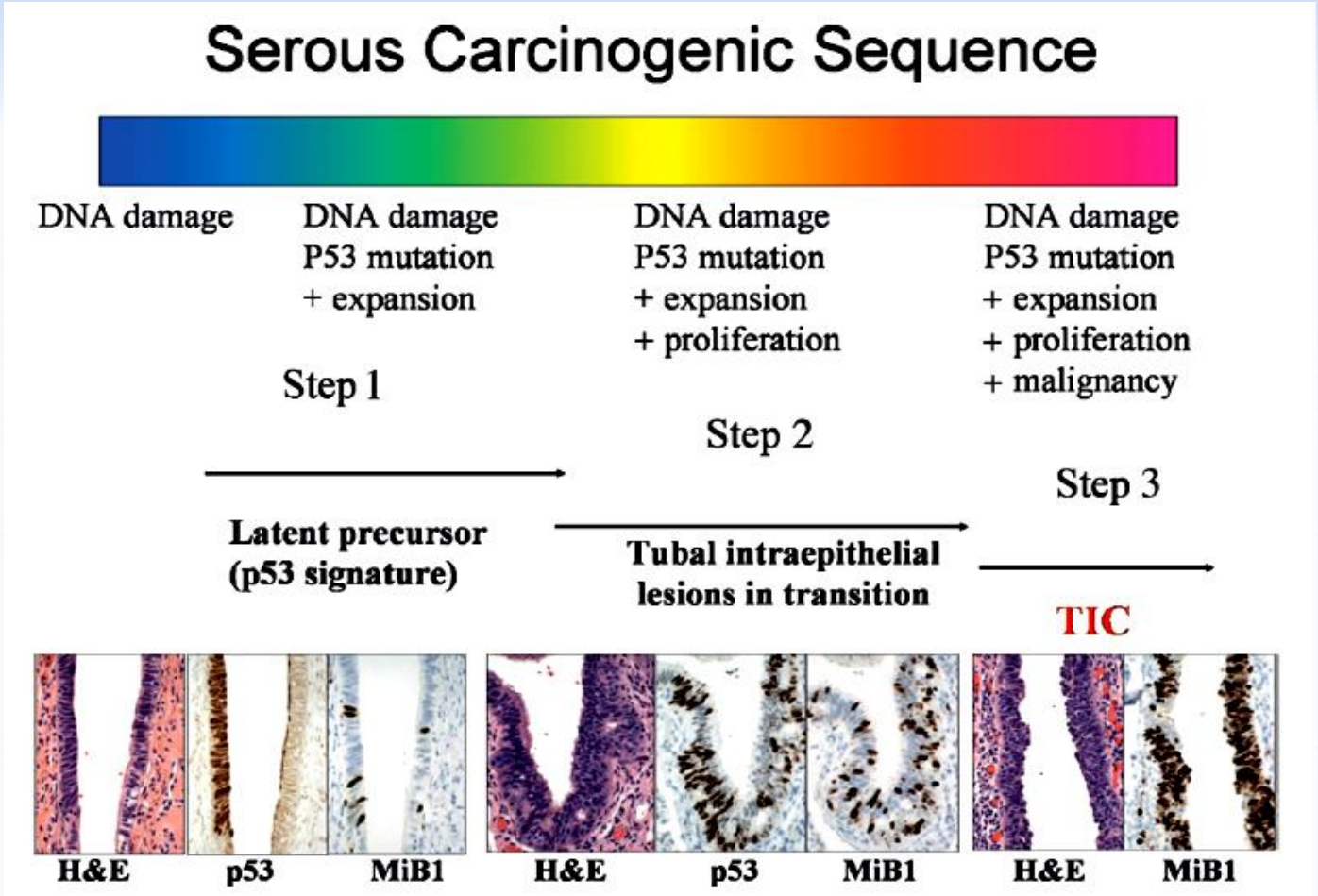






The quest for tubal precursors

2000
2001
2006
2007
2009
2010
2017



P53 signature

STIL (serous tubal intraepithelial lesion)

STIC (serous tubal intraepithelial carcinoma)

Reviewed in Jarboe et al 2015

Controversy on tubal origin of high grade serous carcinomas (HGSCs)

Pros	Cons
• STIC is associated with from 19–60% of advanced HGSCs. • Large number of STICs in *BRCA* mutation carriers; increased number of STICS in women with HGSCs. • Identical *TP53* mutations in coexisting STICs and HGSCs in a significant number of cases suggests monoclonal origin. • A spectrum of accumulated genomic disturbances link p53 signatures, STICs and carcinomas.	• About 40-60% of HGSCs are not associated with STICs. • HGSCs could spread to the tubal mucosa, mimicking STIC. • Molecular profiles suggest non-tubal origin in a subset of HGSC.

Questions:

- Are there “hidden” precursors of HGSCs that should be recognized?
- Are there HGSCs developing via a different pathway not involving STICs?

TP53 sequencing of occult intraepithelial lesions in the fallopian tubes

Objectives:

- To exhaustively serially section a cohort of fallopian tubes initially diagnosed as STIC-negative:
  - To identify previously occult STICs or ESPs*.

    *Early serous proliferations (ESPs): p53 signatures or serous tubal intraepithelial lesions (STILs) that do not meet the diagnostic threshold of STICs
  - To characterize the genetic link between ESPs and synchronous HGSCs by comparing their *TP53* mutation profiles.

Serial sectioning of the fallopian tubes: Case selection

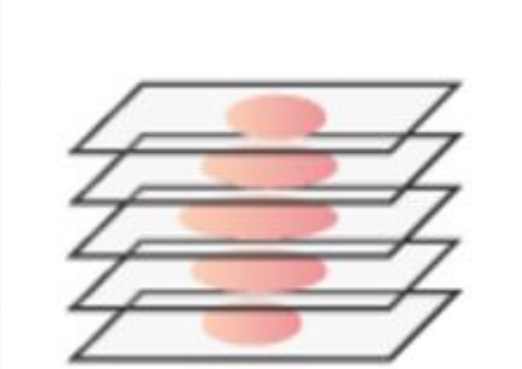
Total pelvic HGSC resections in 2009-2015 N=683

No STIC/carcinoma in tubes N=353 (52%)

STIC/carcinoma in tubes N=330 (48%)

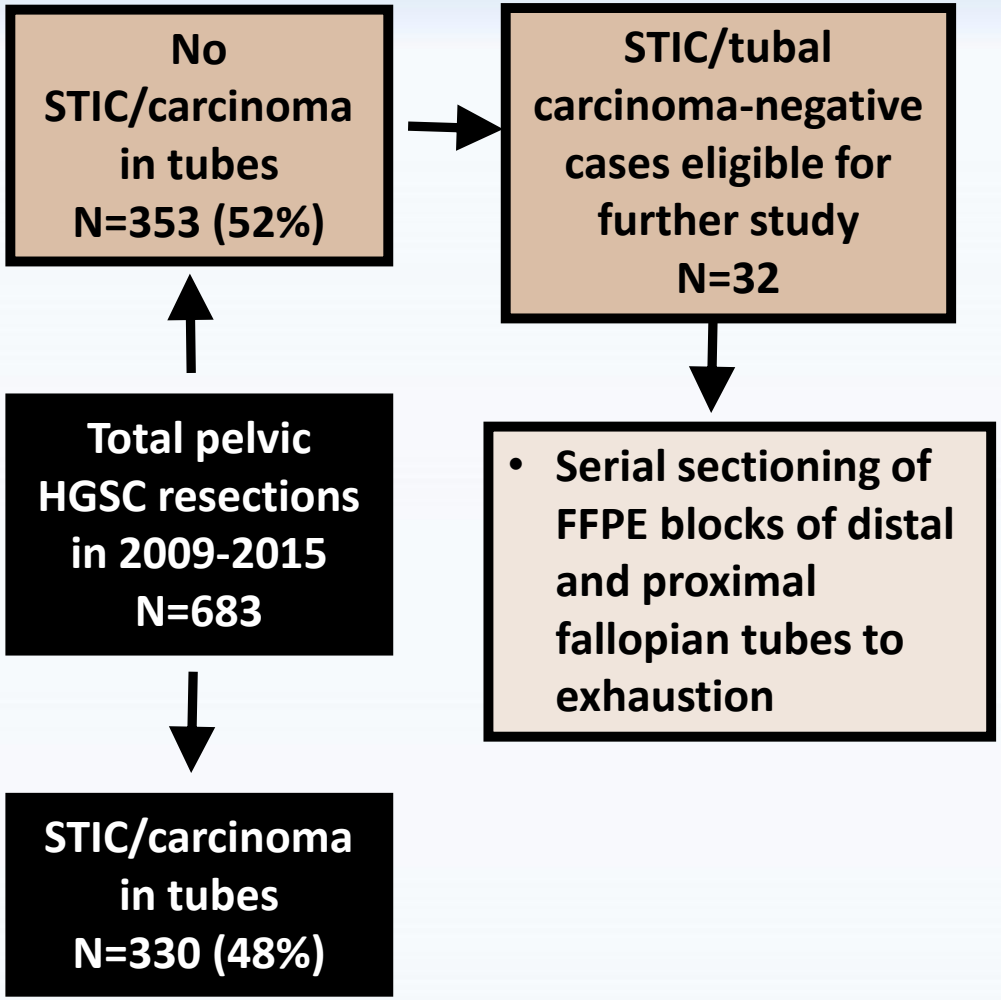
STIC/tubal carcinoma-negative cases eligible for further study N=32

- Serial sectioning of FFPE blocks of distal and proximal fallopian tubes to exhaustion
- H&Es and unstains prepared on every other level to examine for tubal abnormalities



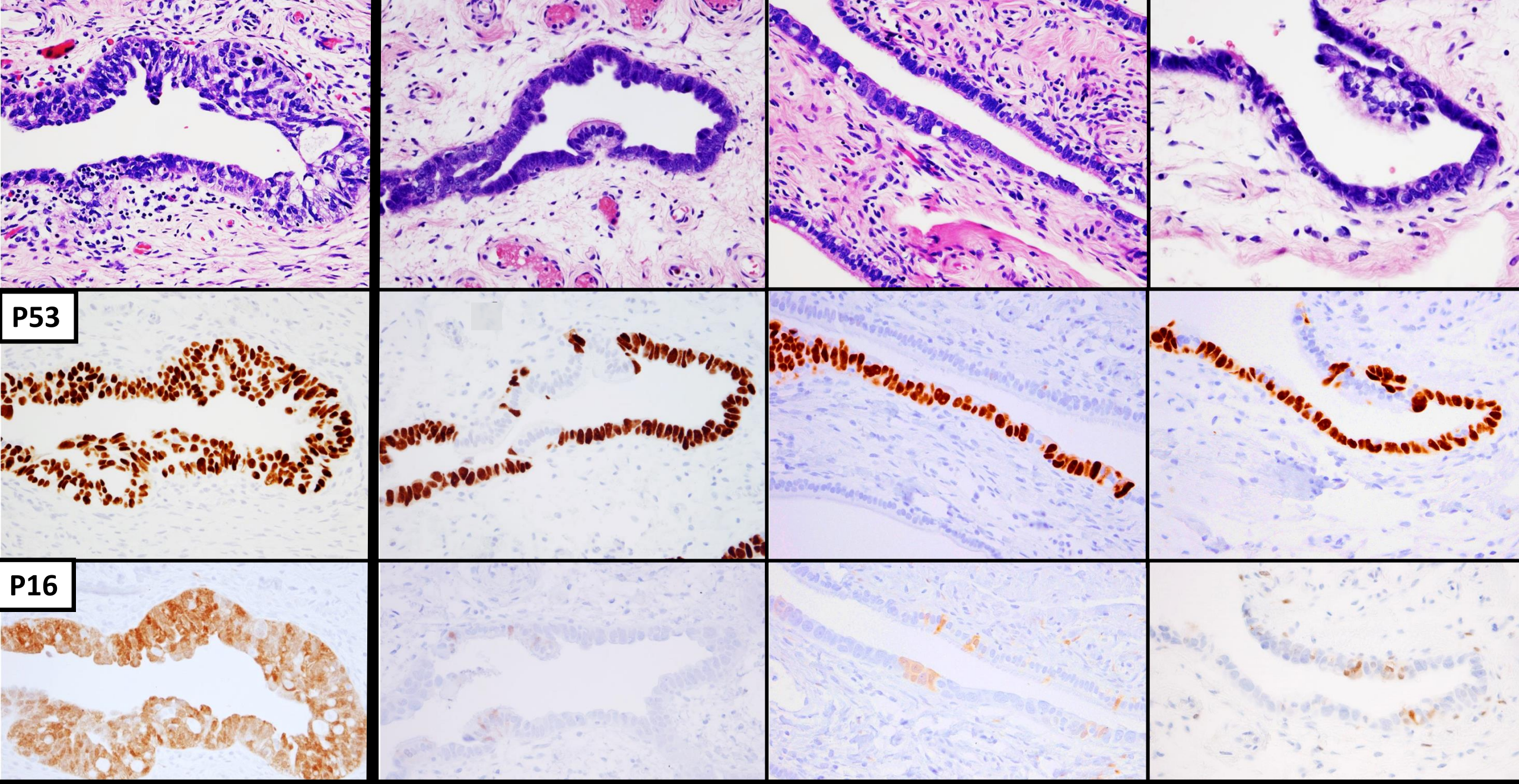
200-300 H&Es of serial sections per tube for examination with unstains on alternate level for further study

Serial sectioning of the fallopian tubes: Case selection



	Total cases (N=32)	
Occult tubal epithelial lesions revealed in serial sections	**Distal fallopian tube**	**Proximal fallopian tube**
None	18	30
Carcinoma or STIC	3*	2*
Mucosal carcinoma	2	1
STIC	2	2
ESPs	12	0

* 2/3 cases showed occults lesions in both distal and proximal tubes. **A total of 3/32 (9%) cases revealed occult STIC or carcinoma in fallopian tubes in serial sections.**



STIC

Early serous proliferations (ESPs)

Up to 75% of ESPs with identical *TP53* mutations as concurrent HGSCs

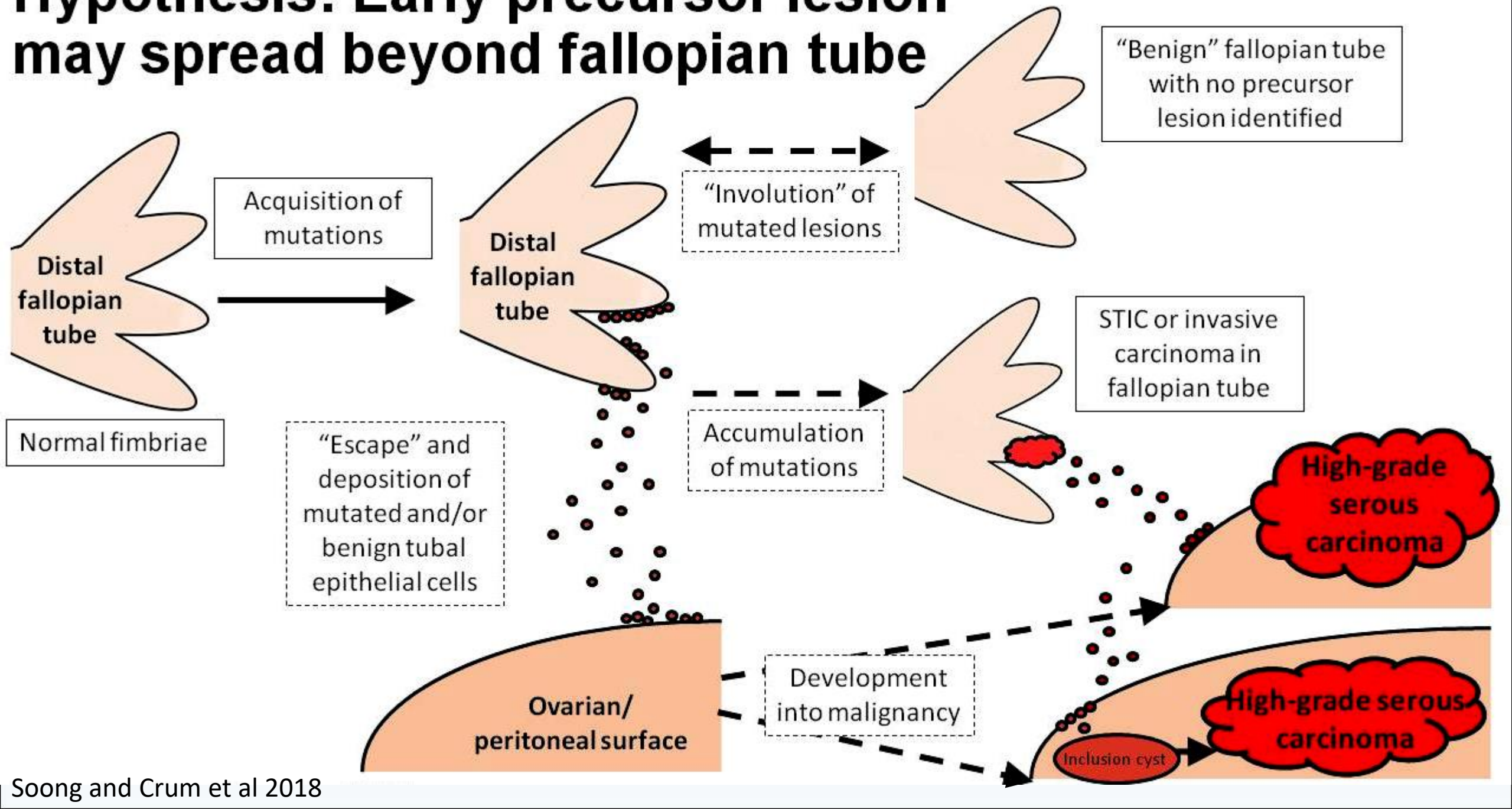
	ESPs						Synchronous HGSCs						
Case	Multiple foci	P53 IHC	*TP53* mutation	Average coverage	Average allele frequency (%)	Identical mutation at multiple foci	Sample site	P53 IHC	*TP53* mutation	Average coverage	Mutation	Average allele frequency (%)	Identical *TP53* mutation in ESPs and synchronous HGSCs
1[b]	Yes	+	c.743G>A	131	20	Yes	Primary	+	c.743G>A	1181	Missense	38	Yes
2	No	EQ	c.279delG	2706	12	NA	Primary	-	c.279delG	4437	Indel	39	Yes
3	No	-	c.112C>T	3612	10	NA	Primary	-	c.112C>T	4818	Nonsense	6	Yes
4	No	EQ	c.919+1G>T	366	5	NA	Primary	-	c.919+1G>T	39193	Indel	50	Yes
5	No	+	c.578A>G	18708	7	NA	Primary	+	c.754_762delCTCACCATC	1435	indel	67	No
6	Yes	+ + +	c.452C>G c.643A>G c.394A>G	4027 2074 8544	21 18 1	No	Primary	+	c.394A>G	5251	Missense	70	No No Yes
7	No	ID	c.273_279delGCCCCTG	13	15	NA	Primary	-	c.273_279delGCCCCTG	8365	Indel	76	Yes
8	No	-	c.916C>T	2097	19	NA	Primary	+	c.455C>G	4718	Missense	33	No
9	No	ID	c.452C>G	7535	2	NA	Primary	+	c.452C>G	7417	Missense	30	Yes
10	No	EQ	c.586C>T	1146	2	NA	Primary	-	c.586C>T	7891	Nonsense	72	Yes
11	No	+	c.476C>T	7301	0.7	NA	Primary	+	c.476C>T	6109	Missense	30	Yes
12	No	ID	c.216delC	2870	0.7	NA	Primary	+	c.818G>A	915	Missense	98	No

+: Positive; -: Null; ID: Indeterminate; EQ: Equivocal due to small extent of lesion.

[b] Case 1 revealed occult contralateral STIC and ESP in serial sections, which share identical *TP53* mutation as synchronous HGSC.

Soong and Crum et al 2018

Hypothesis: Early precursor lesion may spread beyond fallopian tube



Soong and Crum et al 2018

Current criteria for assigning primary site in extrauterine HGSC

Primary Site	Criteria for Diagnosis
Fallopian tube	Presence of: STIC or invasive HGSC in fallopian tube or Part or entire length of tube inseparable from adnexal mass
Ovary	Both fallopian tubes separate from ovarian mass and No STIC or mucosal HGSC in either tube
Tubo-ovarian	Fallopian tubes and ovaries not available for complete examination and Pathological findings consistent with extrauterine HGSC
Peritoneal	Both tubes and both ovaries fully examined and No gross or microscopic evidence of STIC or HGSC in tubes or ovaries

ESMO–ESGO Ovarian Cancer Consensus Conference Working Group. *Int J Gynecol Cancer* 2019;0:1–33.

Summary

1. **<u>Subtypes and classification</u>:**

- Two-tiered classification: high-grade and low-grade serous carcinoma with distinct morphologies, different pathogenic pathways and clinical behaviors.
- Cases with mixed or intermediate grade may portend similar prognosis as classic HGSC.

2. **<u>Site(s) of origin – ovary, fallopian tube, peritoneum</u>:**

- Set criteria are proposed to assign site of primaries for evaluation of surgical resection specimens.
- While fallopian tubes are believed to the origin of HGSCs, it remains unclear whether they represent the sole origin of HGSCs. The question has implications on optimizing preventive strategies of HGSC.