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Pathologie

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Problems in the Histological Grading and Typing of Endometrial Carcinoma

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The Gyn Oncologists' Need for Therapy

- Type
- Grade
- Stage (FIGO/TNM)

Curettage

Postoperative Report

Endometrial Carcinoma (WHO 2014)

- Endometrioid carcinoma, usual type
- Endometrioid carcinom, variants
  - Variant with squamous differentiation
  - Secretory variant
  - Villoglandular variant
- Serous carcinoma
- Clear cell carcinoma
- Neuroendocrine carcinoma
  - Carcinoid/ well differentiated neuroendocrine tumor
  - Small cell neuroendocrine carcinoma
  - Large cell neuroendocrine carcinoma
- Mixed carcinomas, specify type
- Undifferentiated carcinoma, including dedifferentiated carcinoma

The correct histological type matters

	Stage > I at diagnosis (%)	5 year survival (%)
Endometrioid low grade	10	>90
Endometrioid high grade	40-50	60
Serous	50-70	40
Clear cell	50	40
Secretory endometrioid	10	>90

It influences prognosis and treatment

2 Biological Types of Endometrial Carcinoma

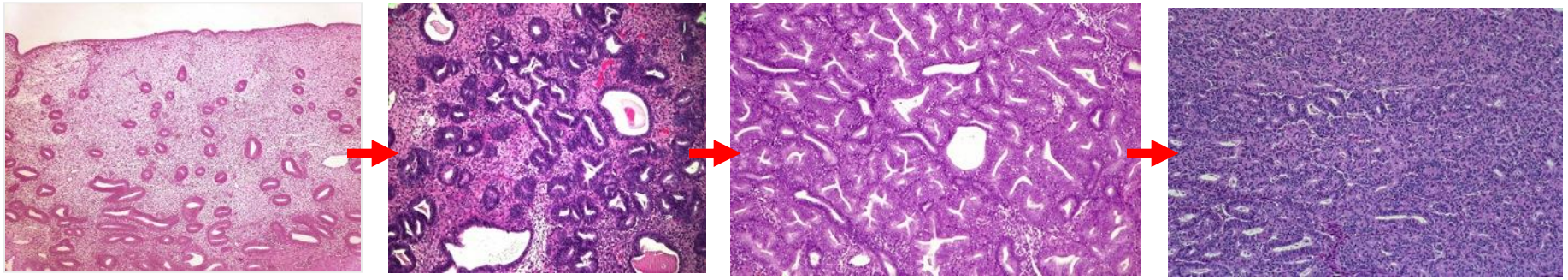
- 


Pathogenetic Model for endometrioid Carcinoma: "Adenoma-Carcinoma Sequence"

Driven by estrogens

PTEN **K-ras**

Gatekeeper Pathway ß-catenin **PIK3C** **p53**



Normal endometrium → **Hyperplasia** → **Atypical Hyperplasia** → **Endometrioid carcinoma**

Caretaker Pathway **MMR Deficiency/MSI**

Pathogenetic Model for Serous Carcinoma: de novo tumorigenesis

Unrelated to estrogens

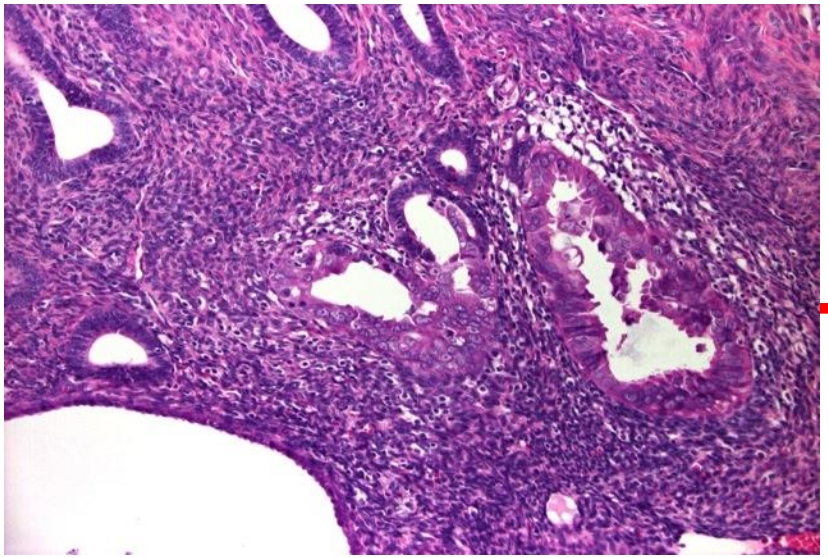
Cyclin E IMP-3 p16

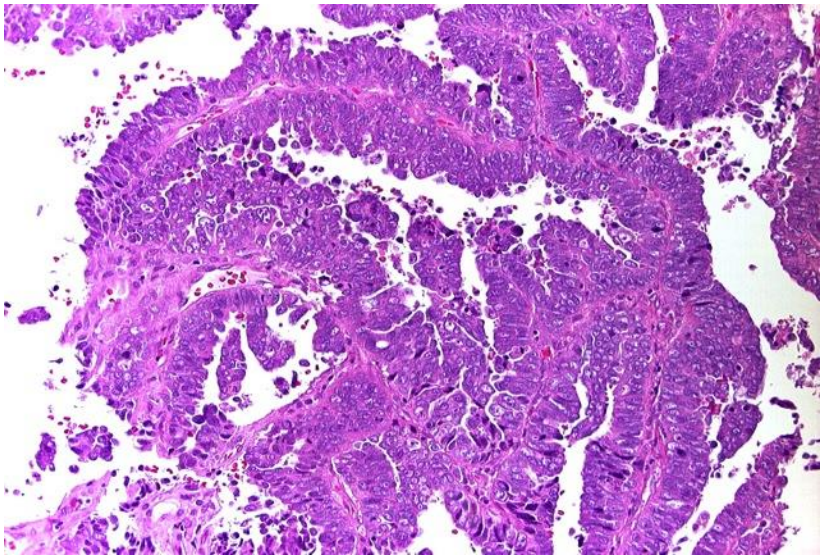
p53 E-cadherin

IMP-3 p16

Cyclin E

p53



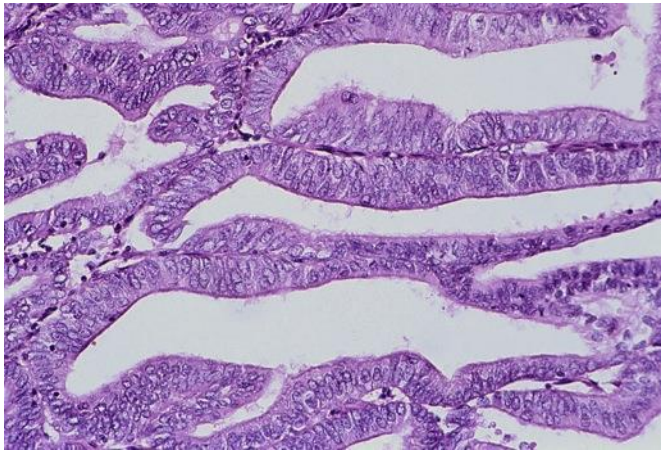


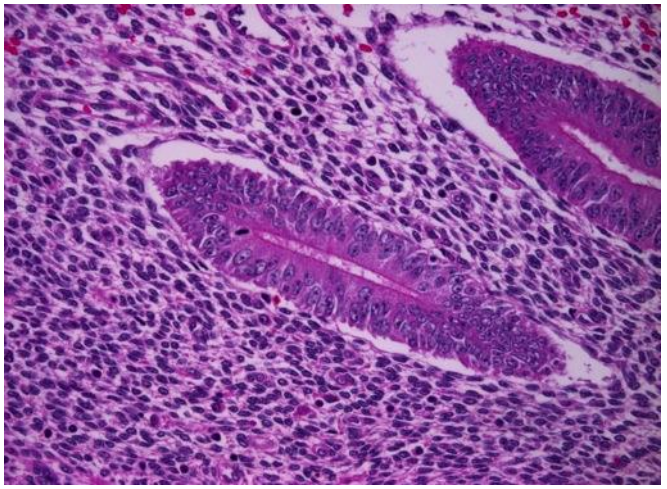
Serous intraepithelial Carcinoma

Serous Carcinoma

Endometrioid histological features

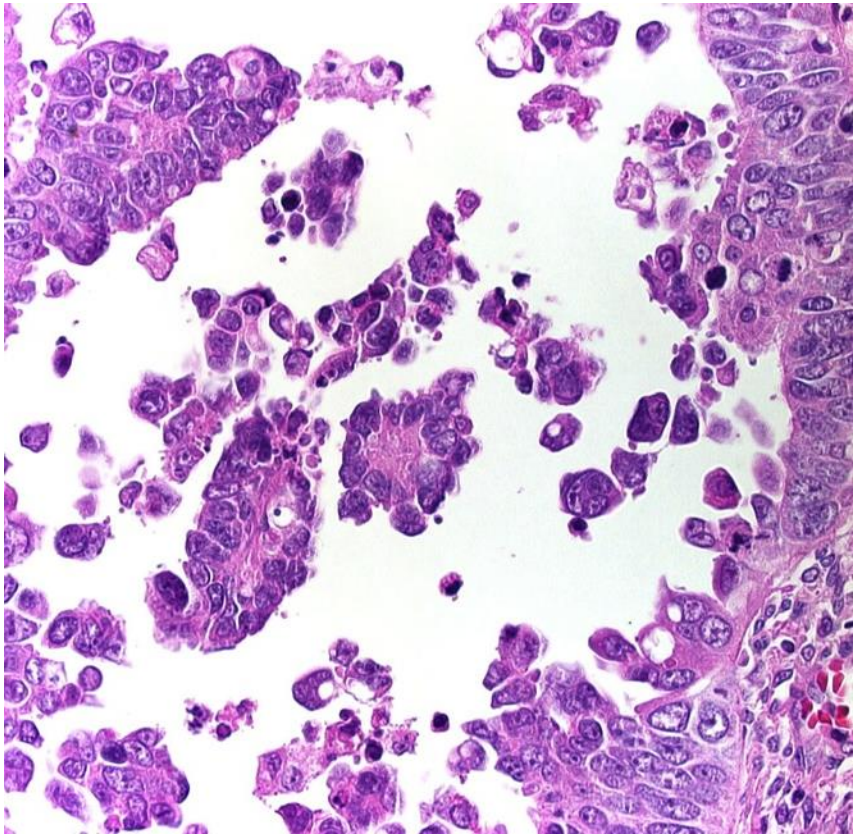
- Well formed glands
- Straight luminal borders
- Squamous differentiation
- Resembling the glands of proliferative endometrium



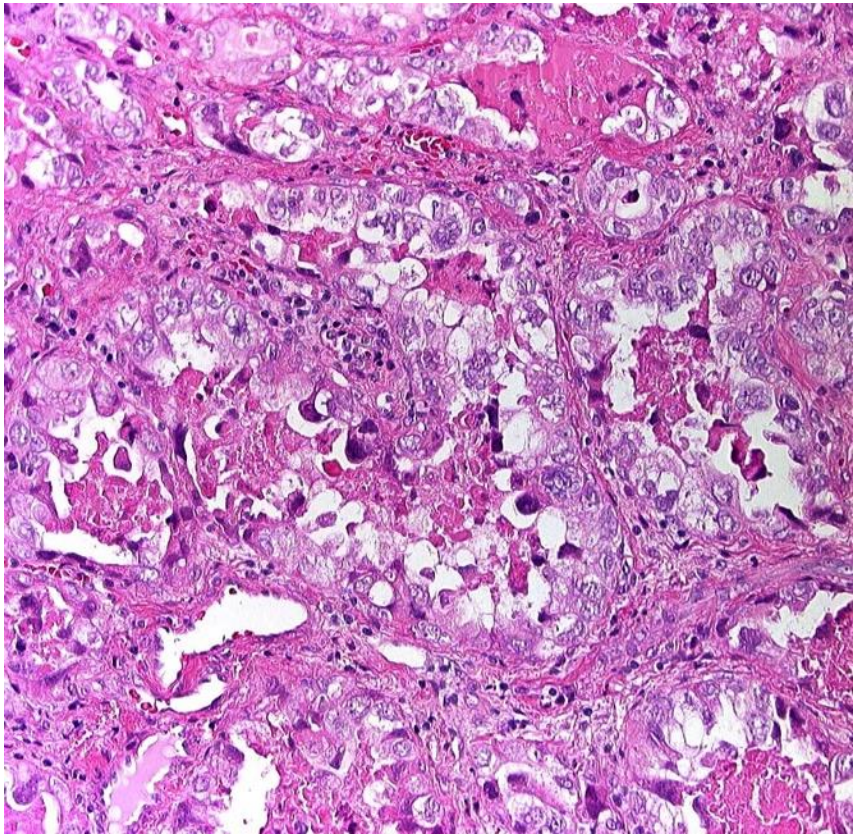


Non-endometrioid Carcinomas

Serous carcinoma



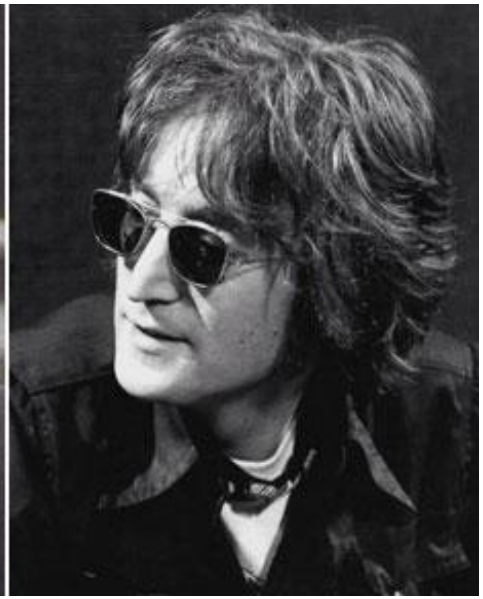
Clear cell carcinoma



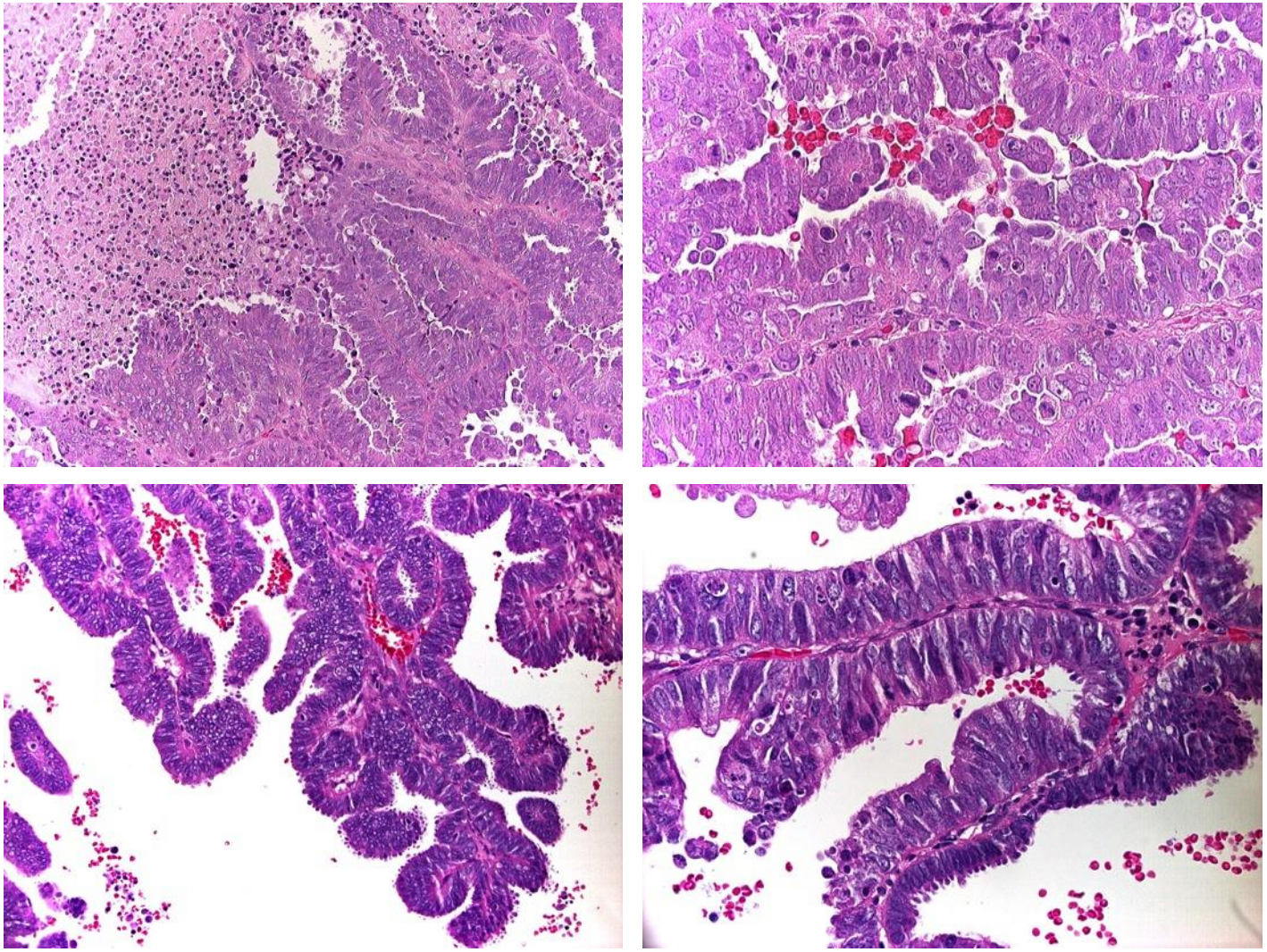
Endometrioid Carcinoma: Variants

- Variant with squamous differentiation
- Variant with secretory differentiation
- Villoglandular variant
- Ciliated cell variant
- Variant with mucinous differentiation

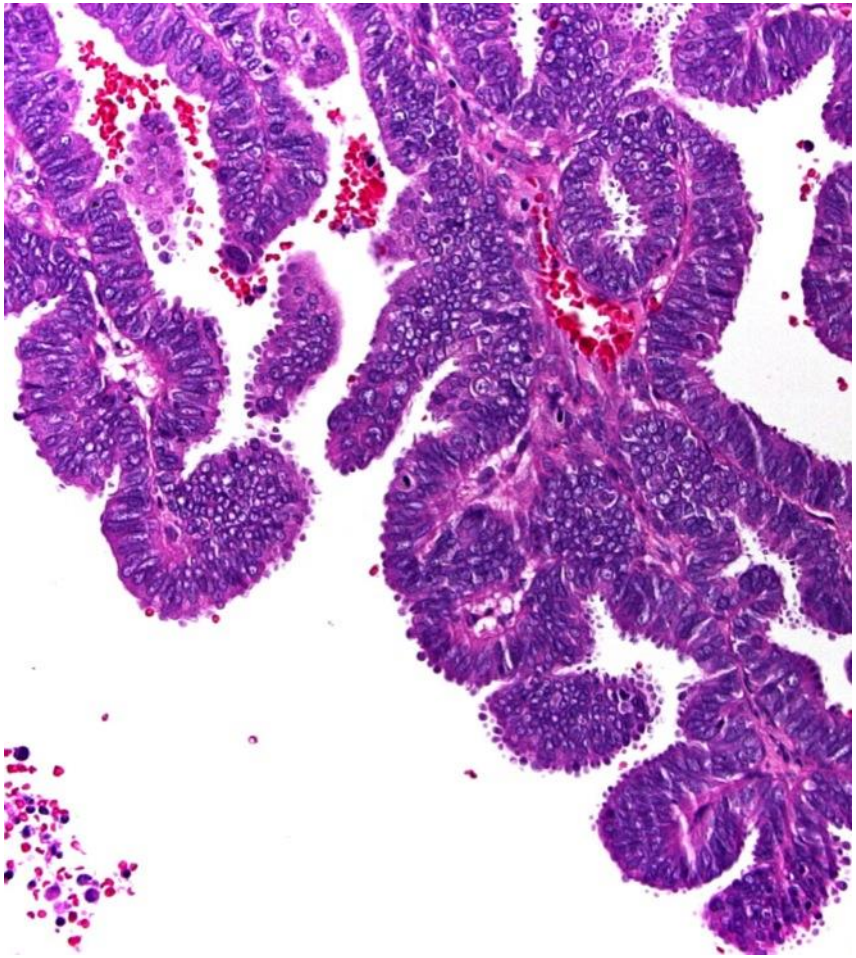
“Lookalikes“

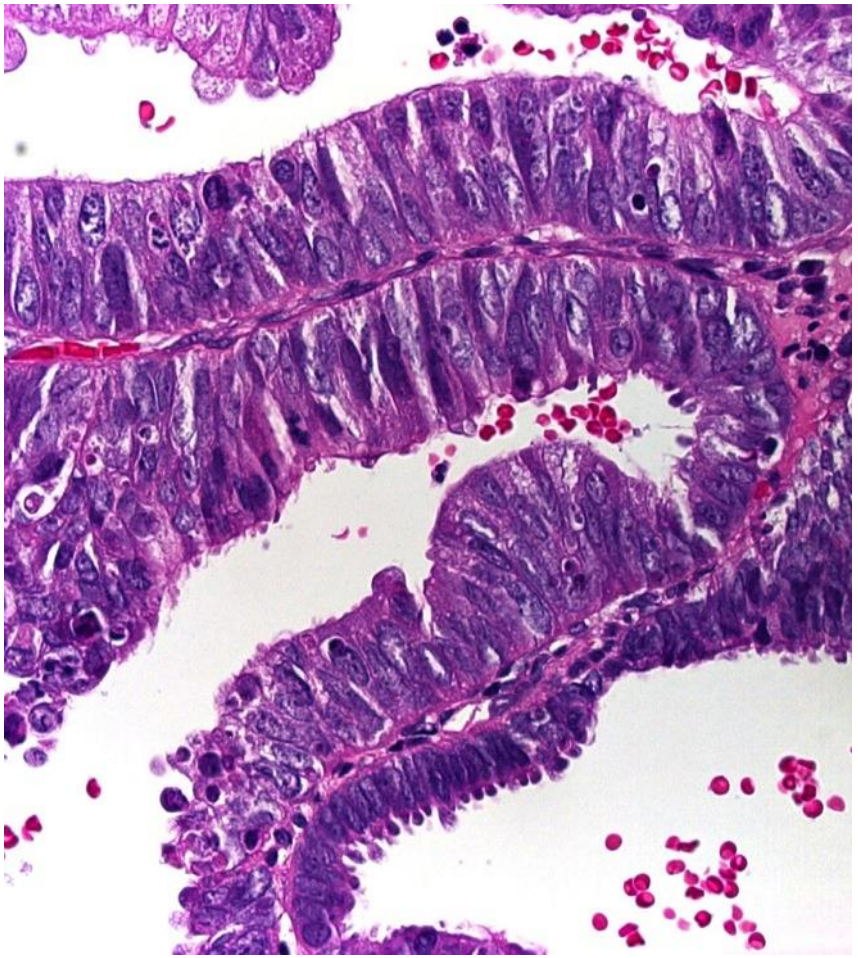


Look alikes

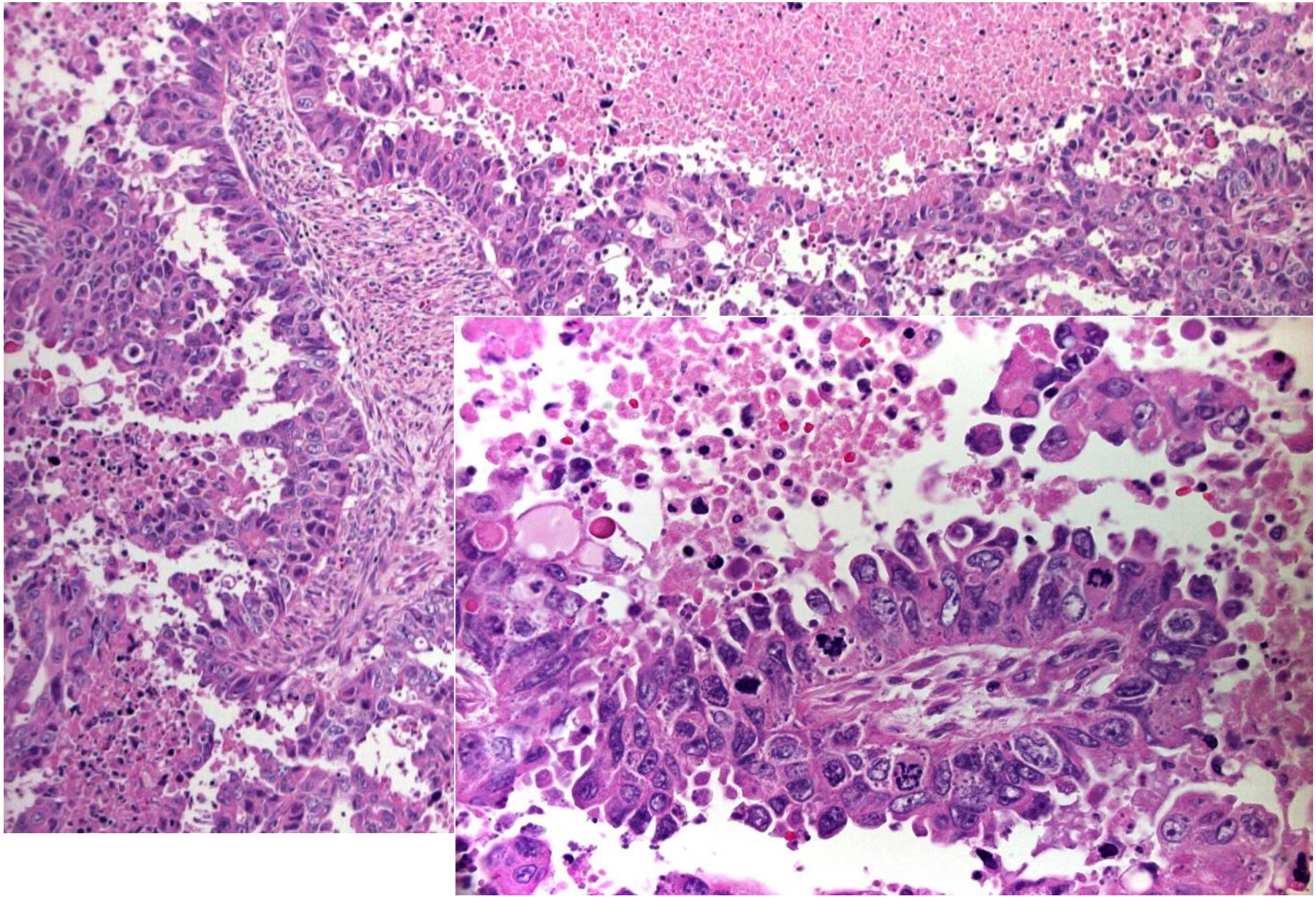


Endometrioid carcinoma: Villoglandular variant





Serous adenocarcinoma



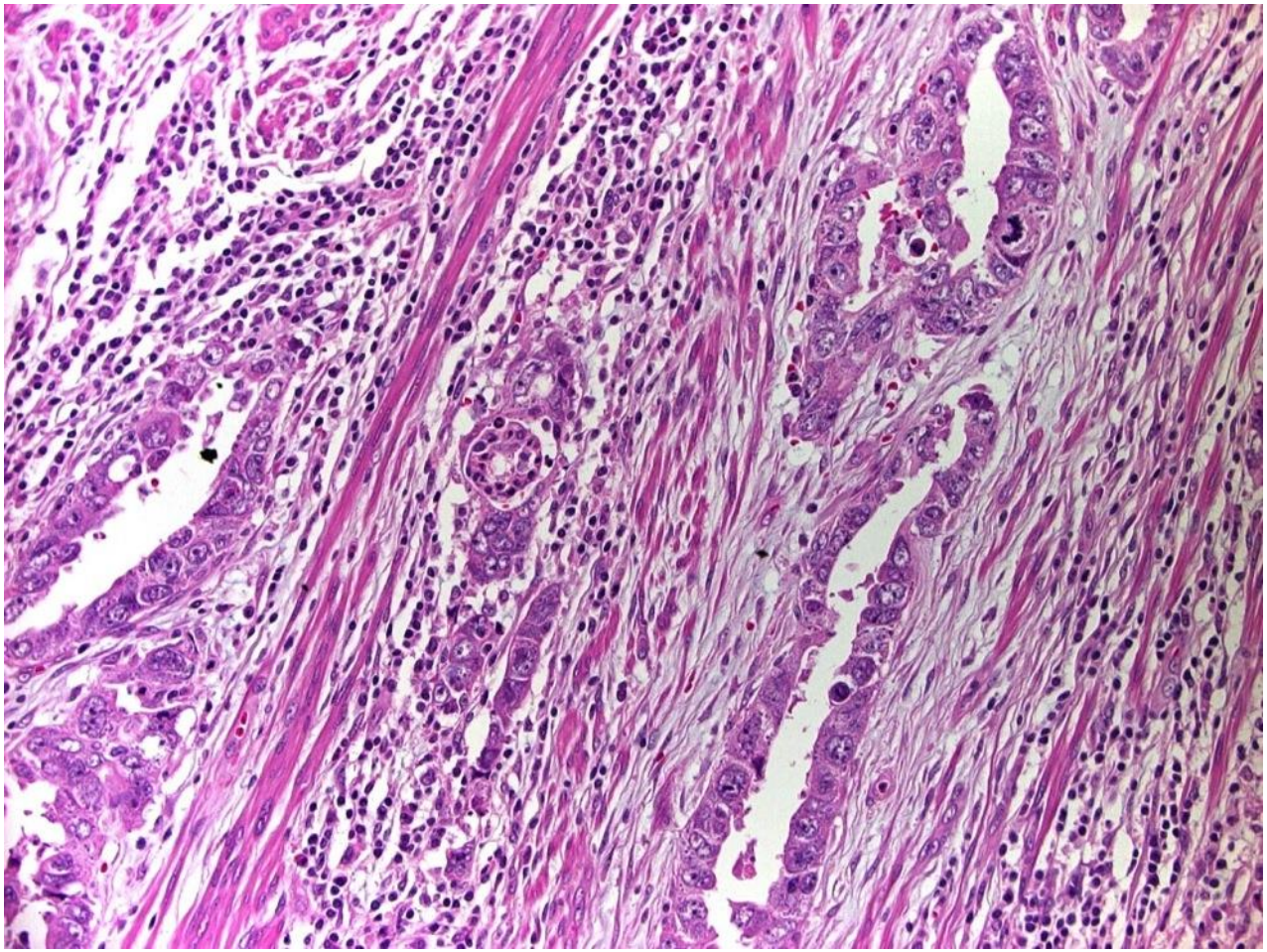
Serous carcinoma: Diagnostic rules

- Hallmark: Well differentiated architecture combined with high grade nuclear atypia
- Cells often loosely cohesive
- It may not be exclusively papillary, may even be solid or glandular
- Therefore, the term “serous-papillary” is misleading

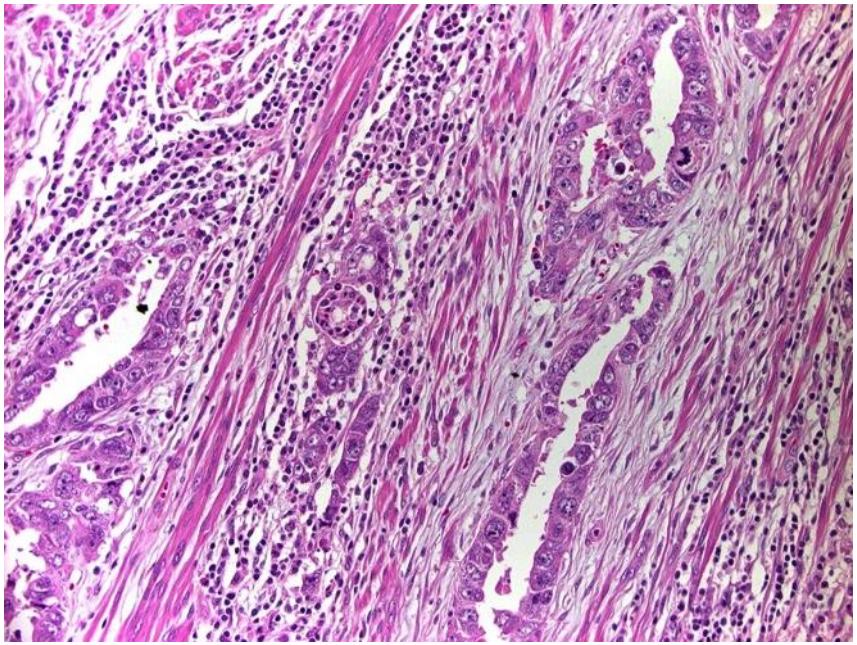
Serous versus Villoglandular Carcinoma

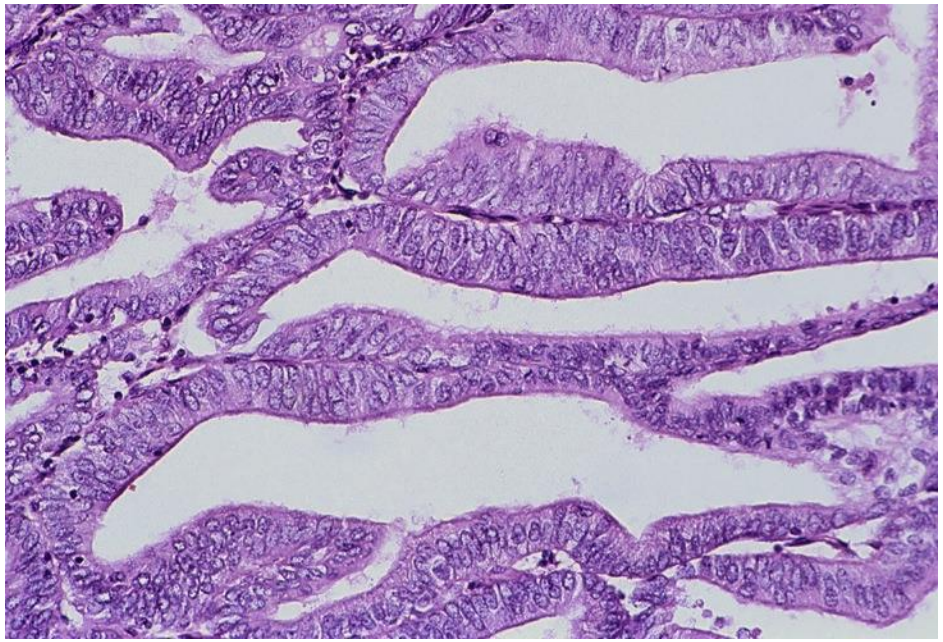
	Serous carcinoma	Villoglandular carcinoma
Papillae	Shorter, thicker, densely fibrotic	Thin and delicate
Cells	Columnar/ polygonal, proliferated (tufting/ budding), luminal borders scalloped	Columnar, pseudostratified
Nuclei	Marked polymorphism, frequent mitosis	Mild polymorphism, infrequent mitosis
Immuno	P53 diffusely positive ER negative/focal pos. Ki-67 high	P53 negative/focal positive ER diffusely positive Ki-67 low/moderate

Serous carcinoma may contain glands



Look alike





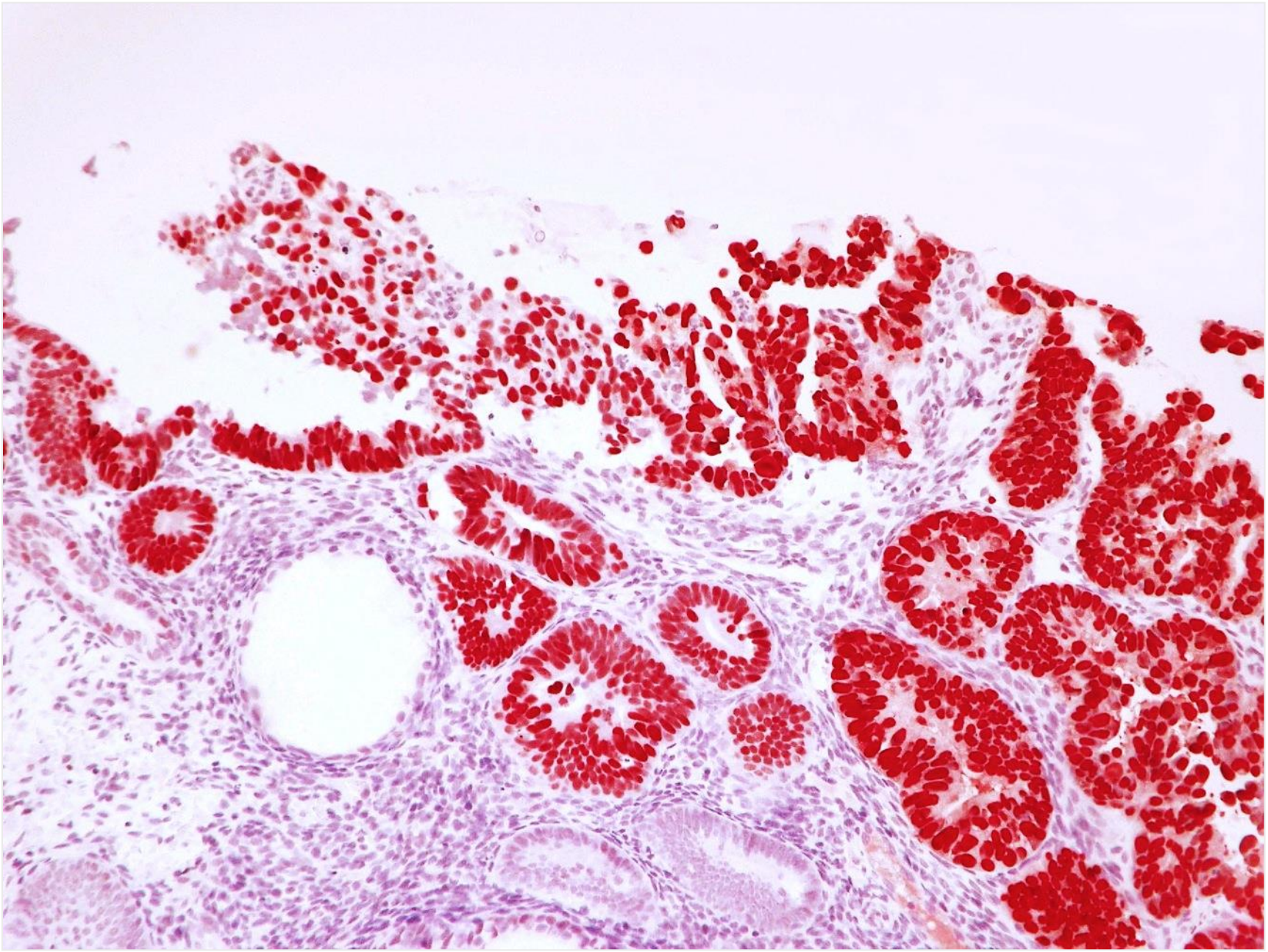
A tubuloglandular pattern may be confusing

Serous Endometrial Cancers That Mimic Endometrioid Adenocarcinomas

A Clinicopathologic and Immunohistochemical Study of a Group of Problematic Cases

Farbod Darvishian, MD, Amanda J. Hummer, MS,† Howard T. Thaler, PhD,† Rohit Bhargava, MBBS,* Irina Linkov, BS,* Marina Asher, BS,* and Robert A. Soslow, MD**

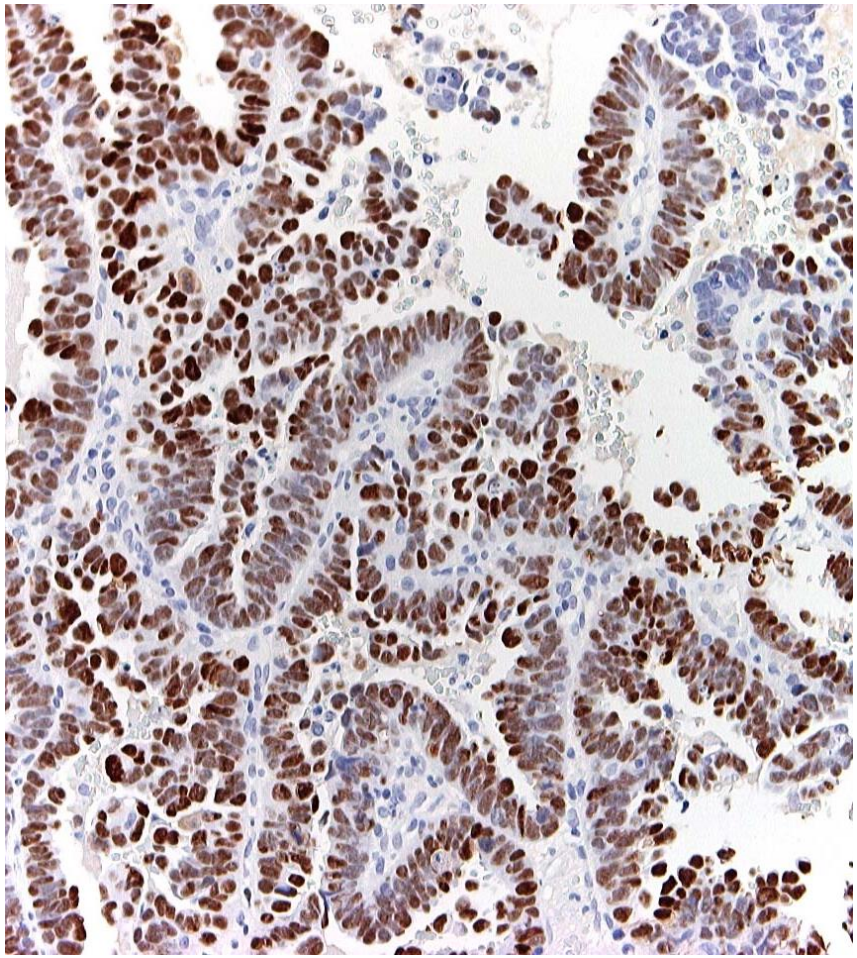
AJSP 2004



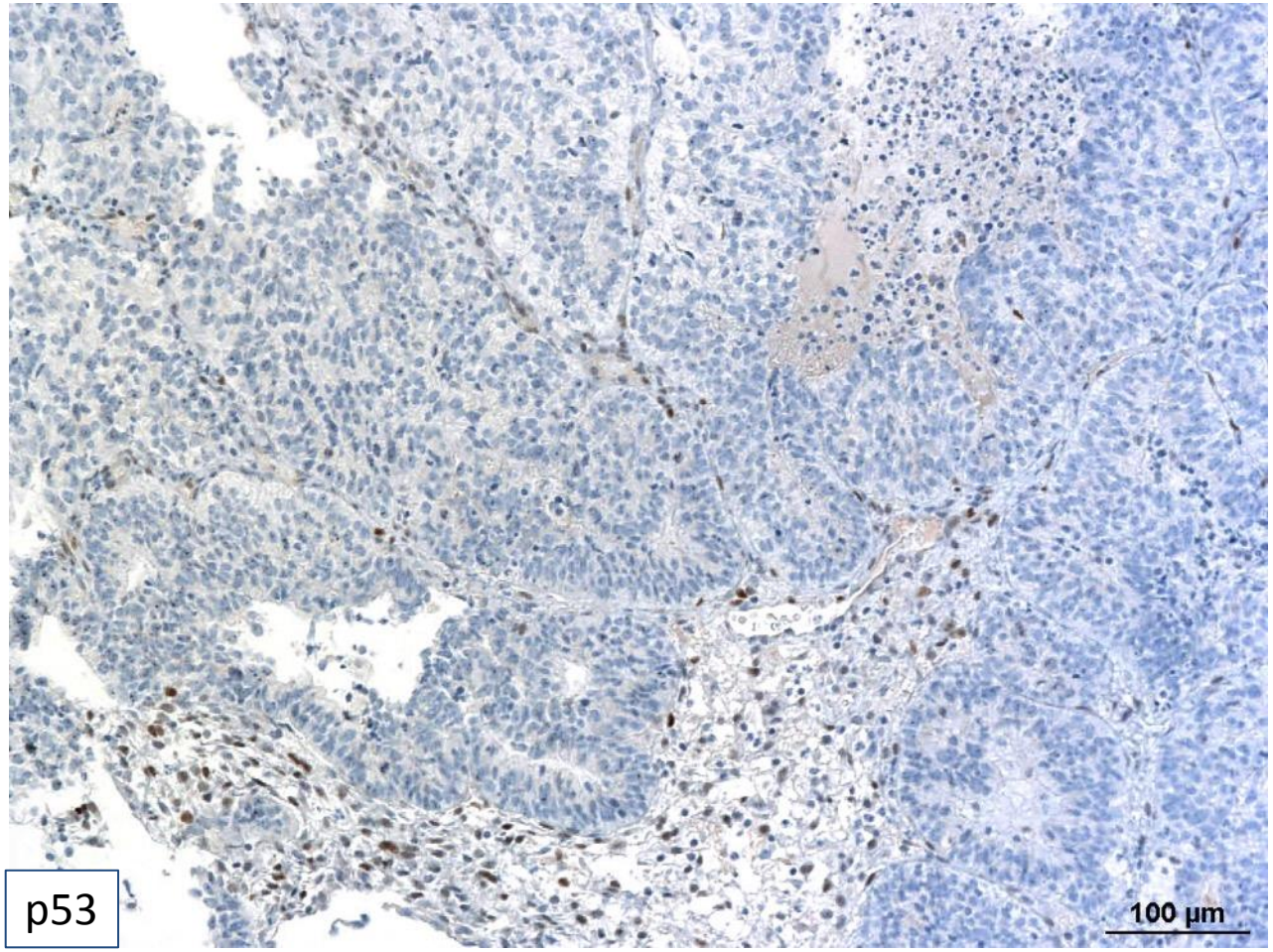
P53 and Endometrial Serous Carcinoma

Tashiro et al. AJP 1997

- P53 mutations in > 90% of serous carcinoma, associated with LOH
- 90% of mutations are point mutations, thus p53 is over expressed
- < 10% frameshift or missense mutations, leading to truncated protein and flat negative immunohistochemistry
- P53 mutations in 50% of EIC but without LOH



TP53 germ line mutation with splicing



Diagnostic support by Immunohistochemistry: p53, PR

TABLE 5. Stepwise Discriminant Analysis Procedure

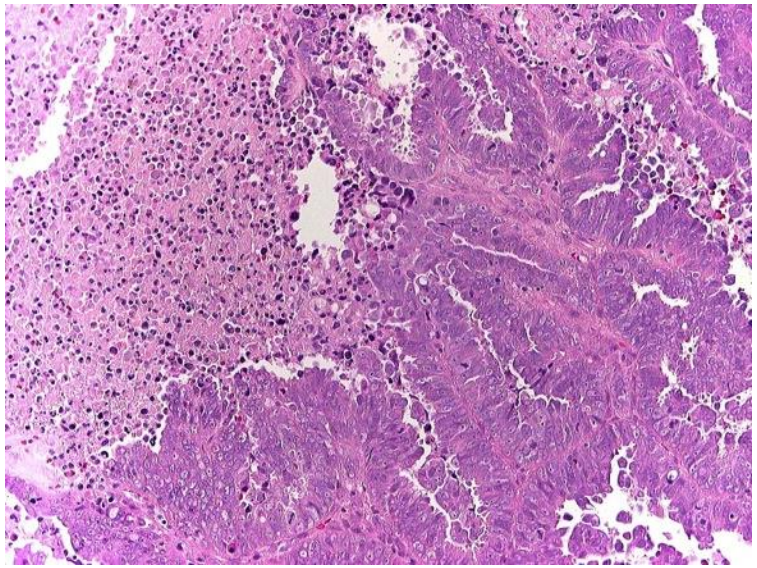
Marker	Univariate R^2	Univariate *P* Value	Multivariate Partial R^2	Multivariate *P* Value
p53	0.63	<0.001	0.26	0.008
β-Catenin	0.55	<0.001		
Cyclin D1	0.13	0.05		
ER	0.37	<0.001		
PR	0.63	<0.001	0.43	<0.001
PTEN	0.53	<0.001	0.15	0.05

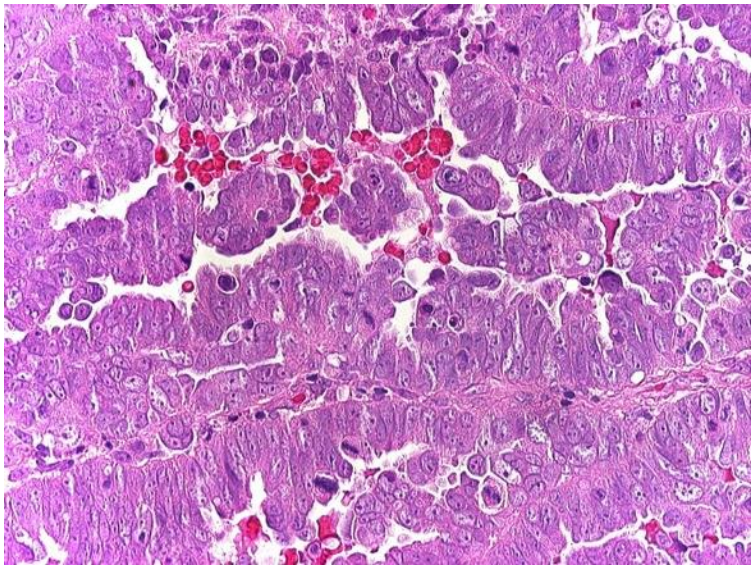
Note: All 6 markers were entered into the initial model. Stepwise discriminant analysis yielded 3 markers (p53, PR, and PTEN).

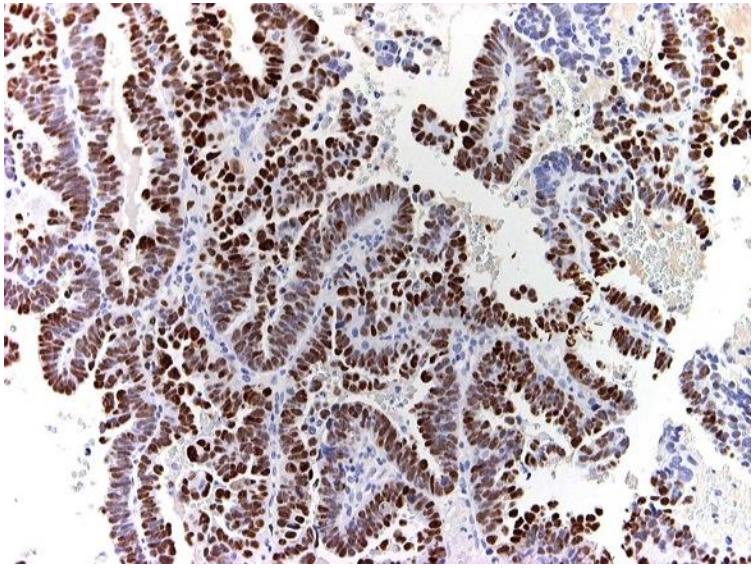
ER, estrogen receptor; PR, progesterone receptor.

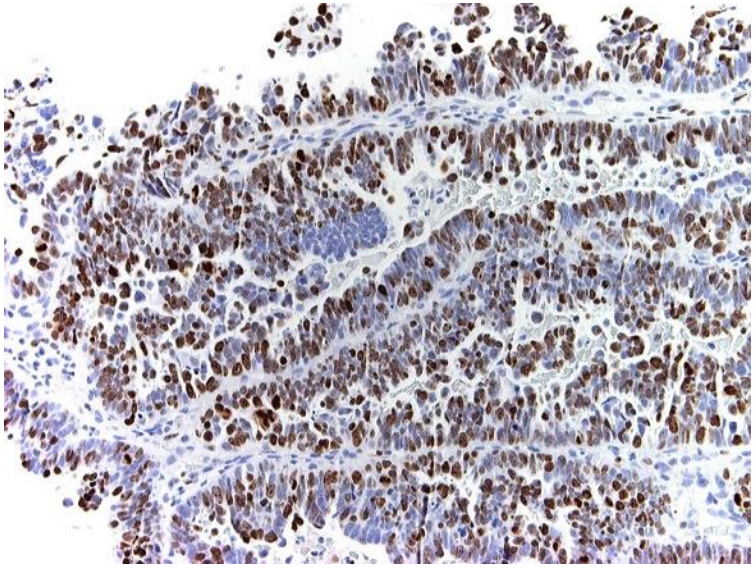
Darvishian et al., AJSP 2004

Serous adenocarcinoma





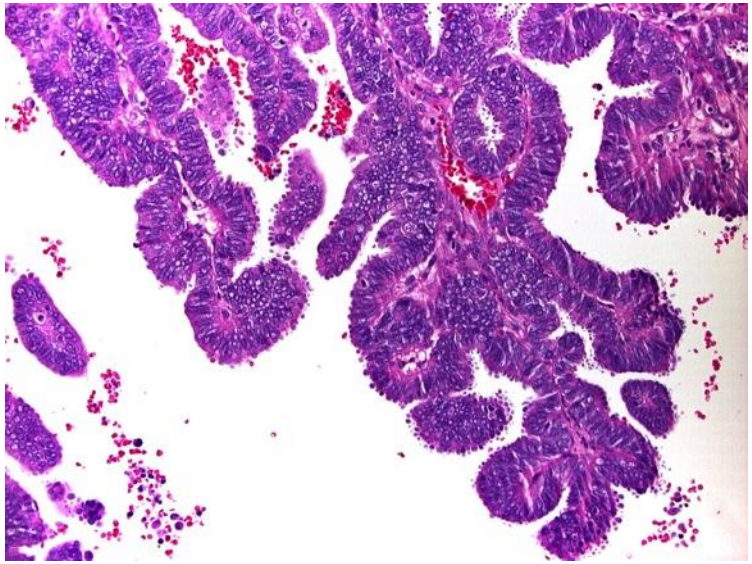


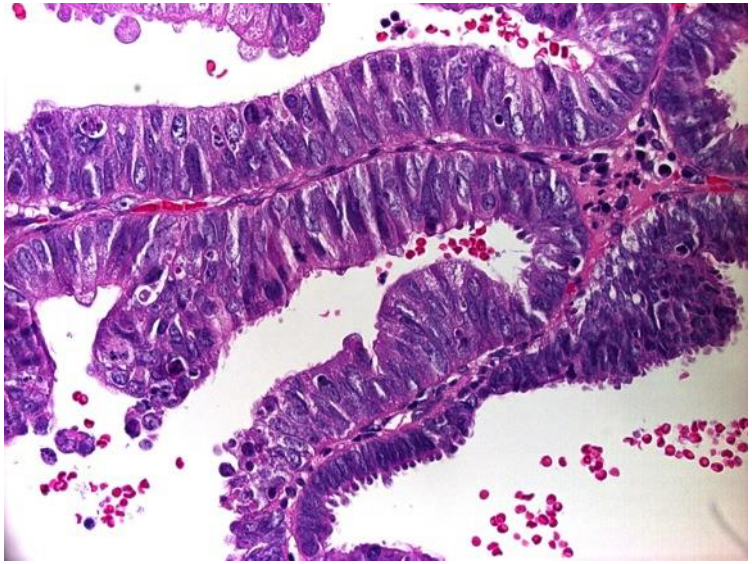


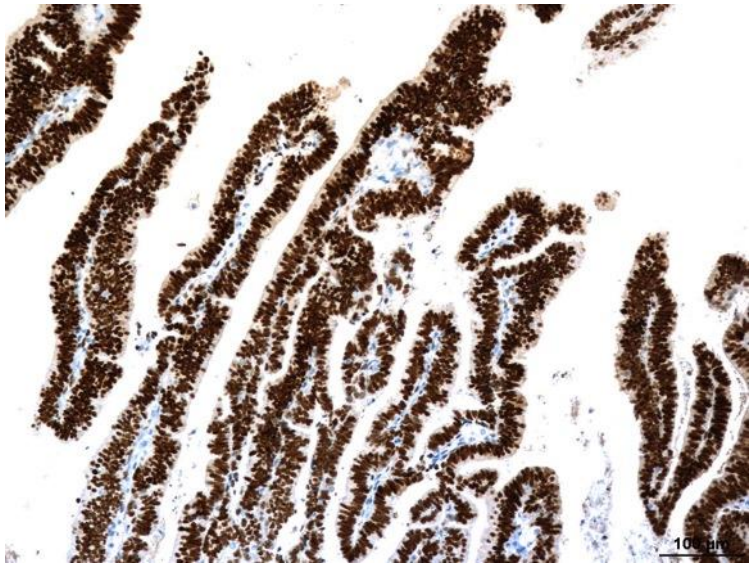
p53

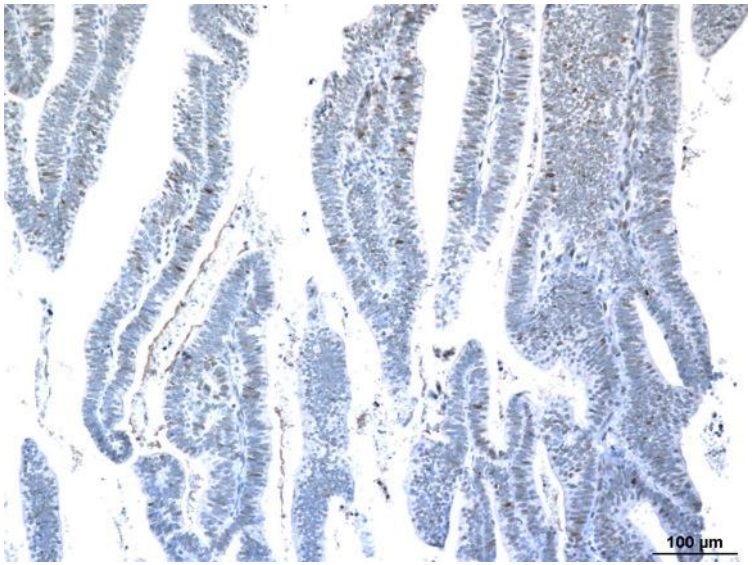
Ki-67

Villoglandular adenocarcinoma









ER

p53

Immunophenotyping of Endometrial Carcinoma

Lax et al., Hum Pathol 1998; Reid-Nicholson et al., Mod Pathol 2006

Tumor type	P16	ER	PR	p53	Ki67
Endometrioid G1,2	+/-	++	++	-	<20%
Endometrioid G3	++/-	+/-	+/-	++/-	20-50%
Serous	+++	-/+	+/-	+++	>40%
Clear cell	++/-	-	-/+	++/-	30-50%
P-value	<0.001	<0.001	<0.001	<0.001	<0.001

Differential Diagnosis between Endometrioid and Serous Carcinoma

Alkushi et al., Int J Gynecol Pathol, 2010

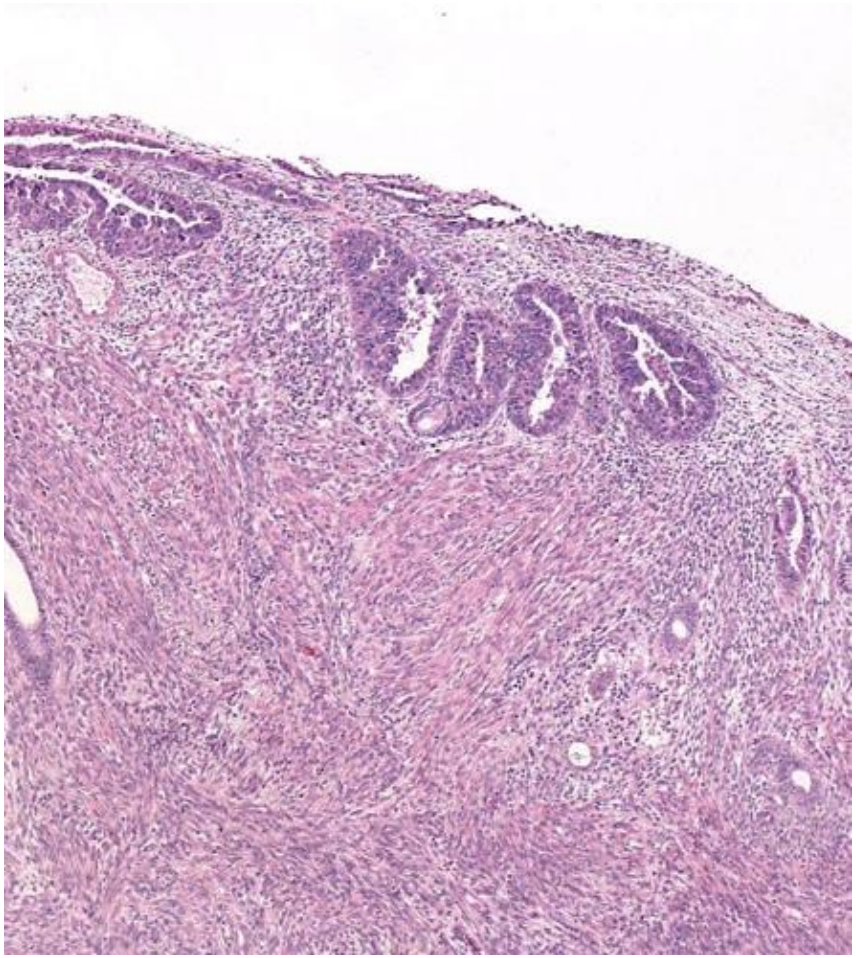
TABLE 4. *P values for differences in expression of immunohistochemical markers*

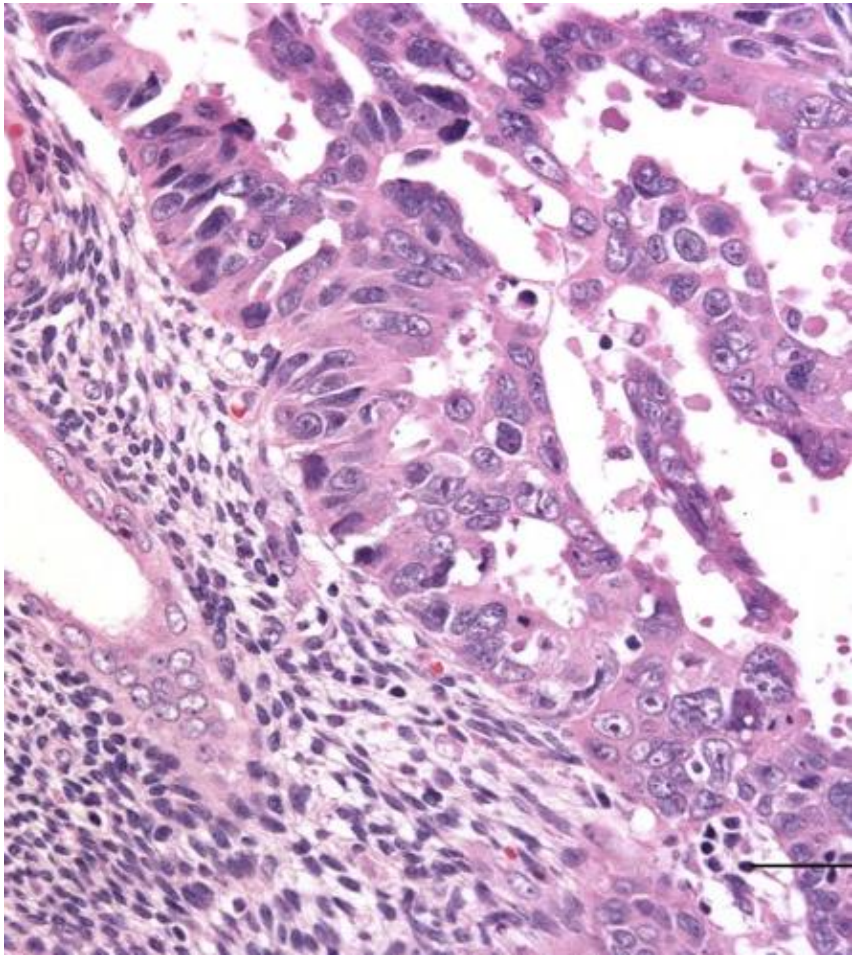
	ER (*P*)	IMP3 (*P*)	p16 (*P*)	p53 (*P*)	PR (*P*)	PTEN (*P*)
EC-1/2 versus EC-3	0.01	0.008	<0.0001	<0.0001	0.002	0.427
EC-3 versus SC	0.055	0.031	<0.0001	0.068	0.281	0.021
All groups	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Mixed serous carcinomas

- Often difficult to be recognized
- Clinically even a minor serous component considered as equivalent to a pure serous carcinoma
- 10% is considered as quantitative minumum for one component
- Little evidence for prognostic impact

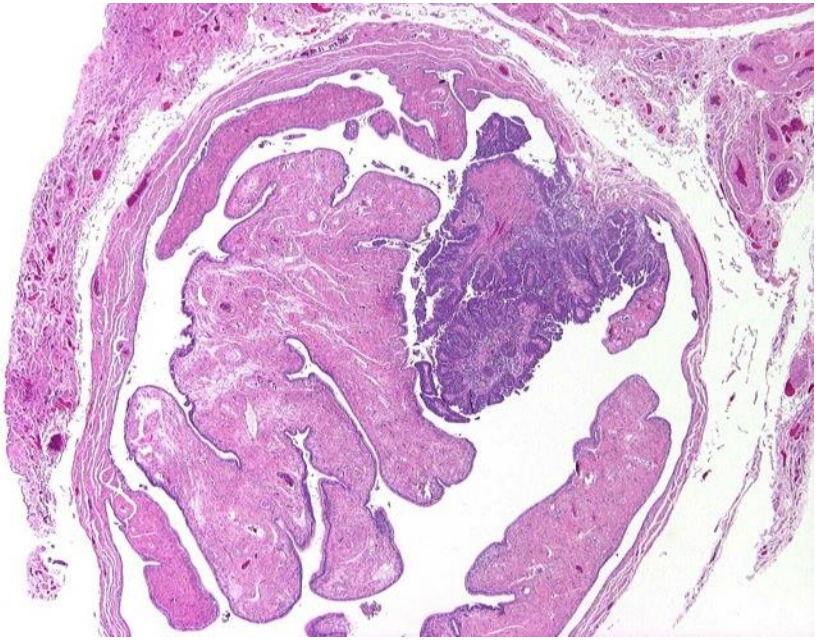
Serous Endometrial Intraepithelial Carcinoma (SEIC)

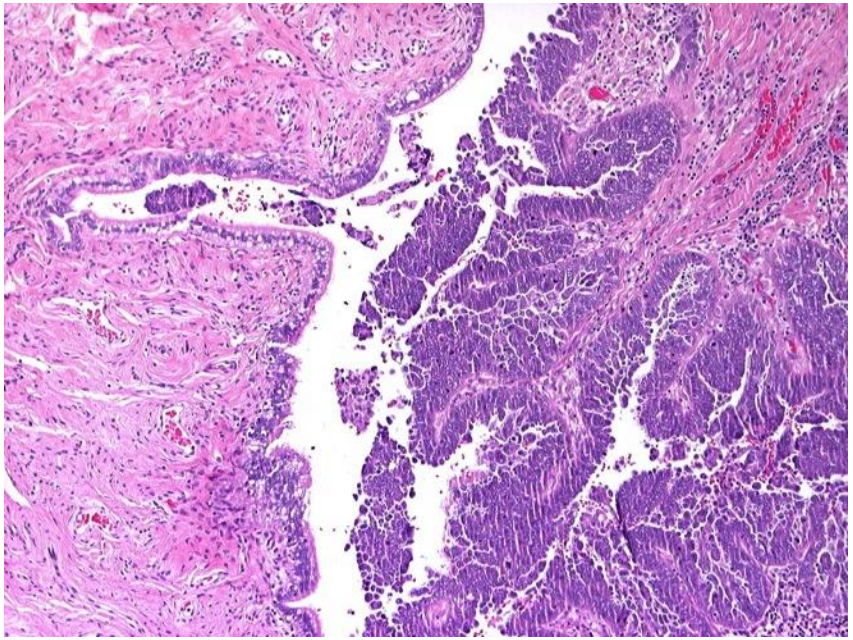


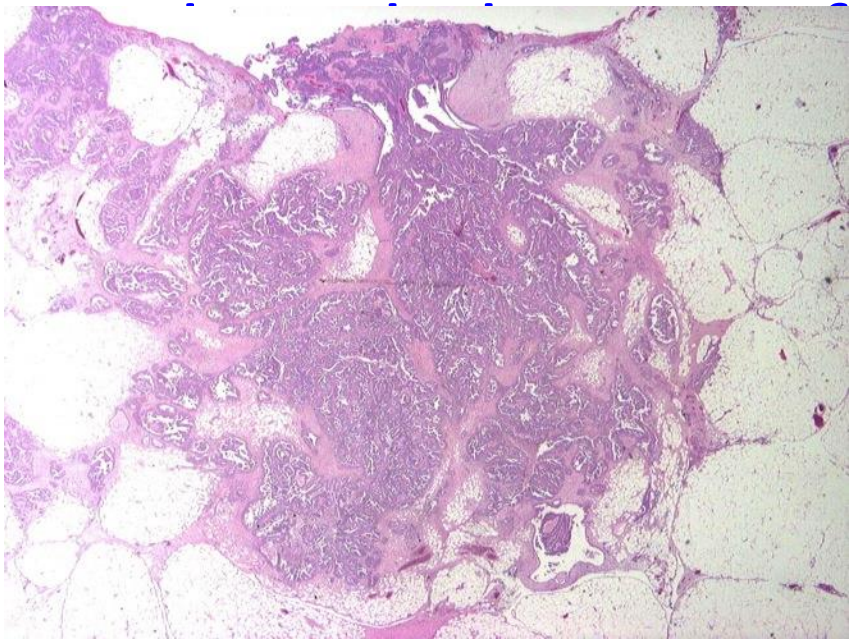


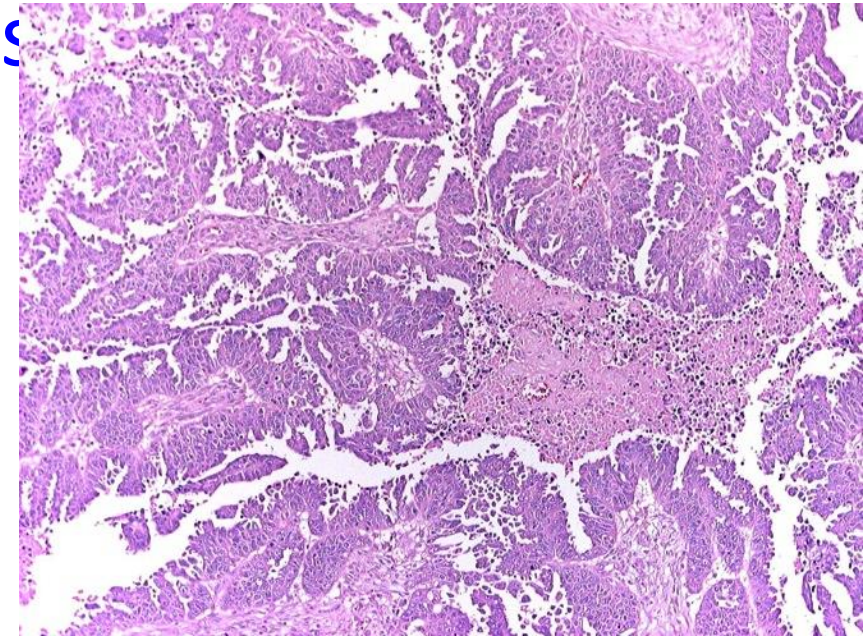
SEIC

- Putative precursor of serous carcinoma
- Flat highly atypical lesion on the endometrial surface and/or within glands replacing the original epithelium
- May occur in endometrial polyps
- May be associated with extensive extrauterine disease and/ or involvement of the cervix
- Distinction from early invasion may be difficult (minimally invasive serous carcinoma)



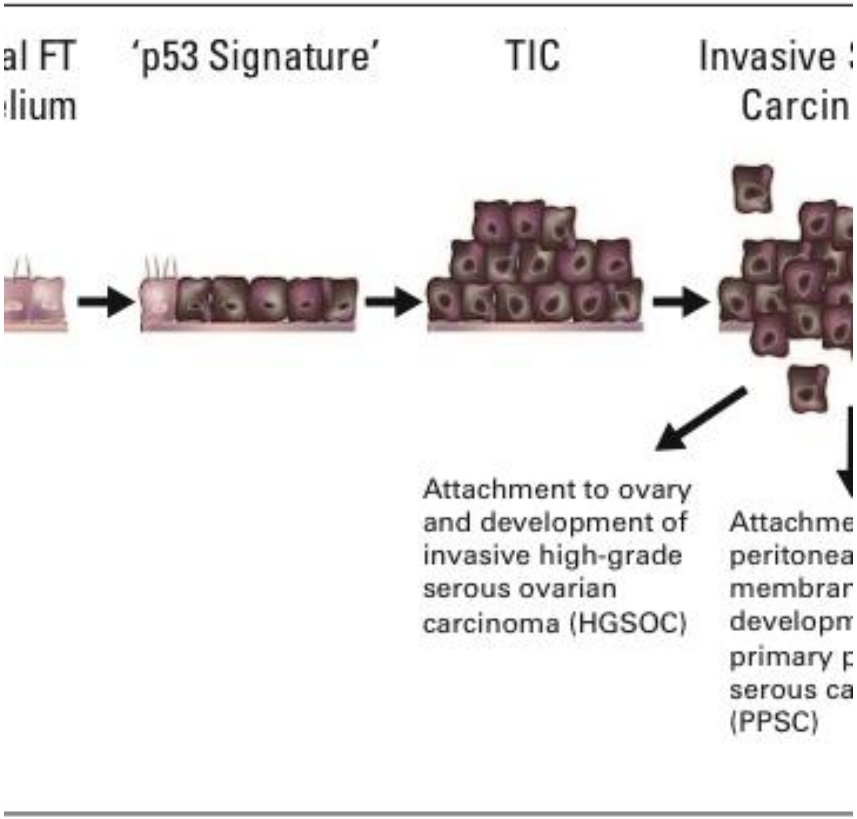




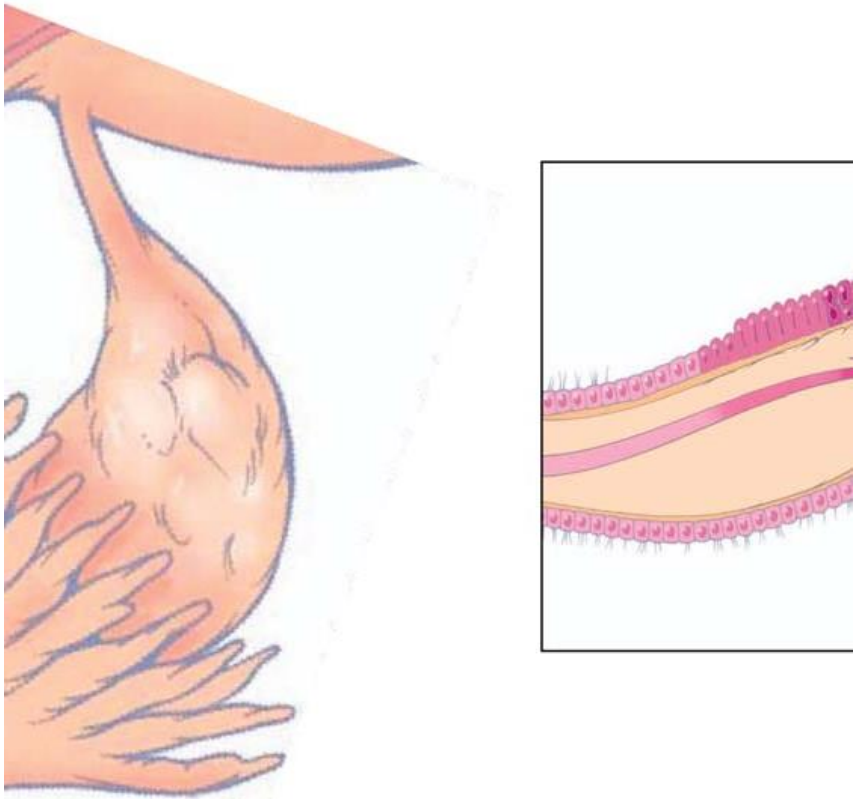


The tubal origin of serous carcinoma

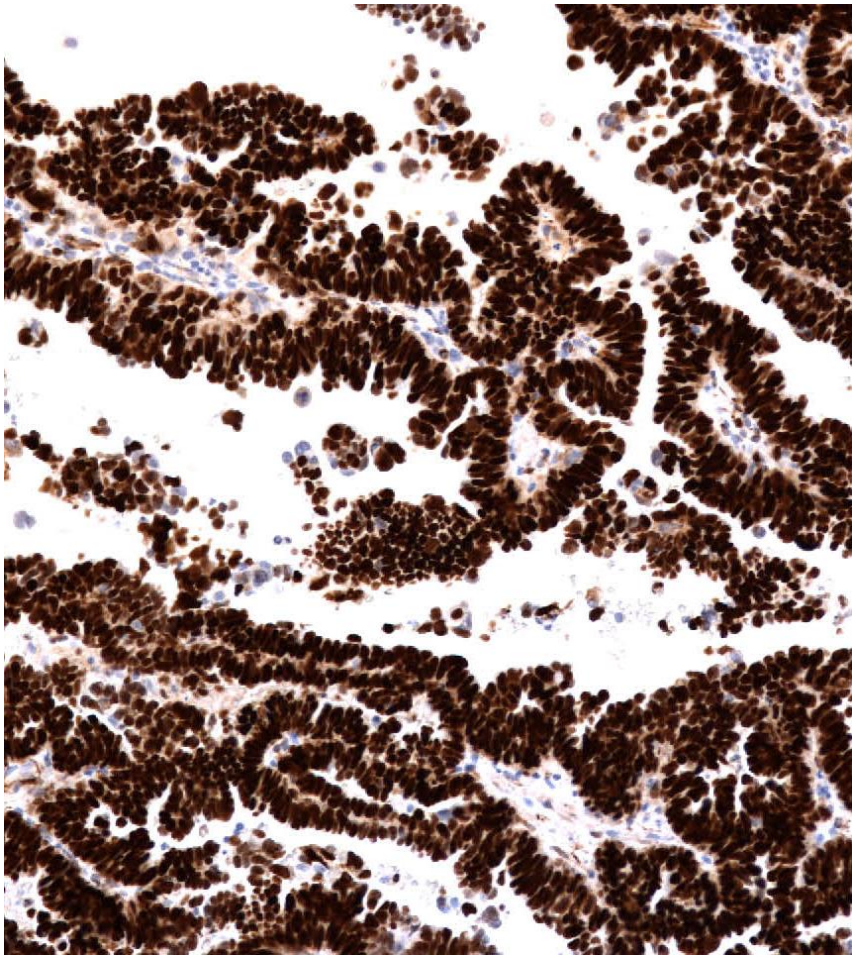
Levanon et al., JCI 2008

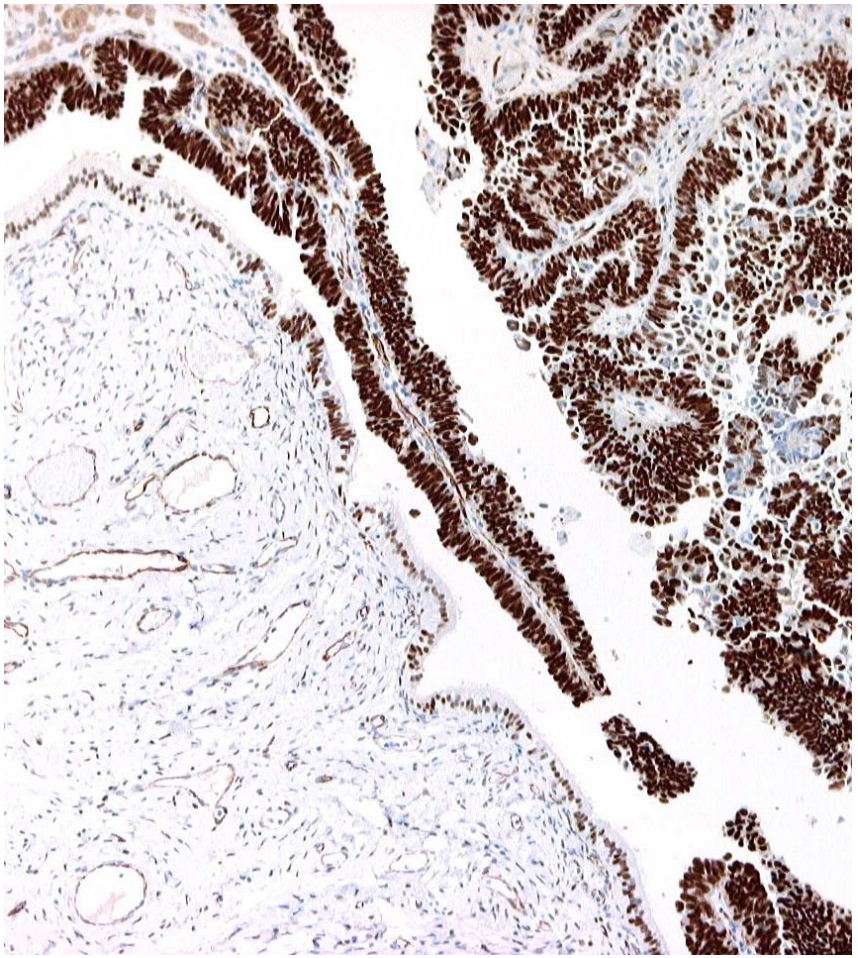


Kurman and Shih, AJSP 2010



High grade pelvic serous carcinoma with tubal origin





WT1

WT-1 and Female Genital Tract Neoplasia

Goldstein AJCP 2002; Al-Hussaini et al. Histopathology 2004; Euscher et al. AJSP 2005

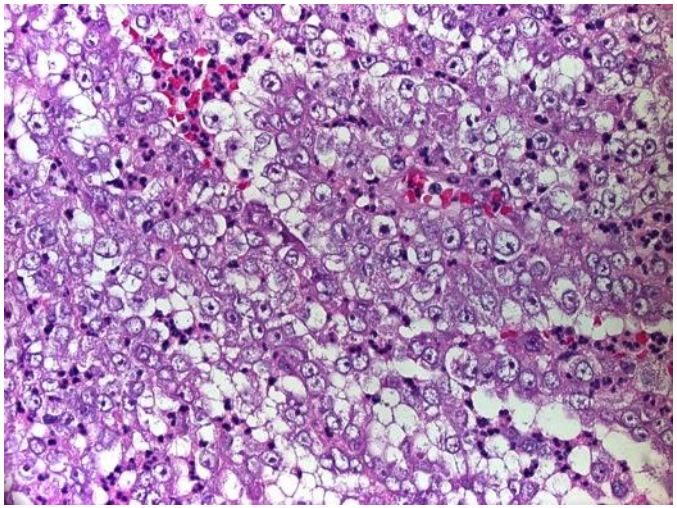
	Uterus	Ovary
Endometrioid	Negative	Negative
Serous	80-100% negative	95-100% positive

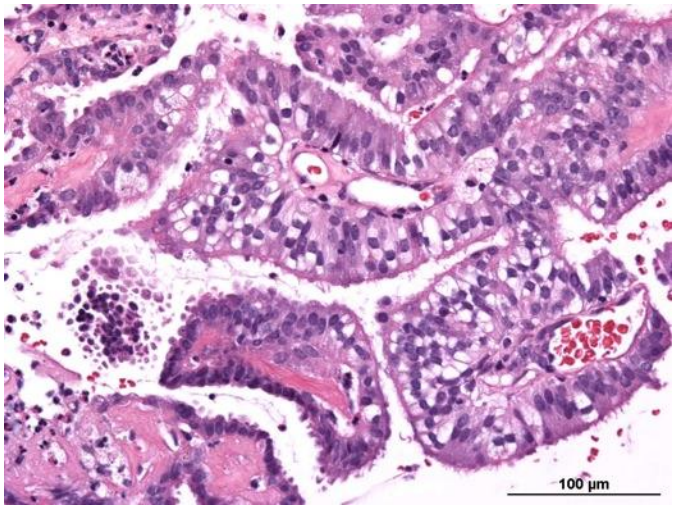
- WT-1 seems to assist in the determination of the origin of a serous carcinoma

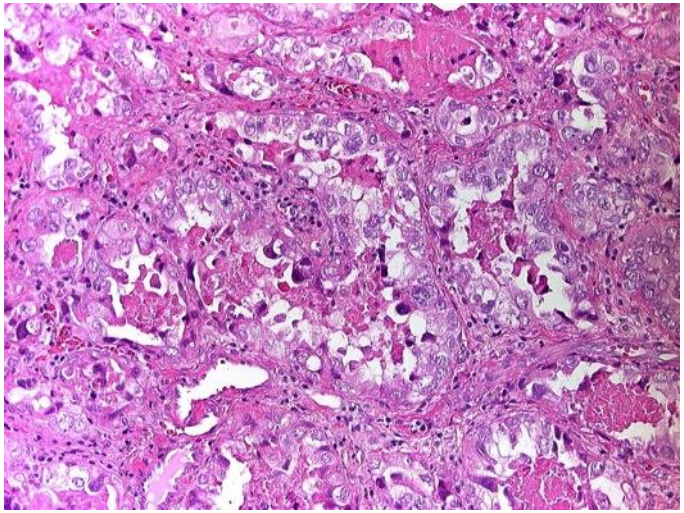
Multifocal serous carcinoma

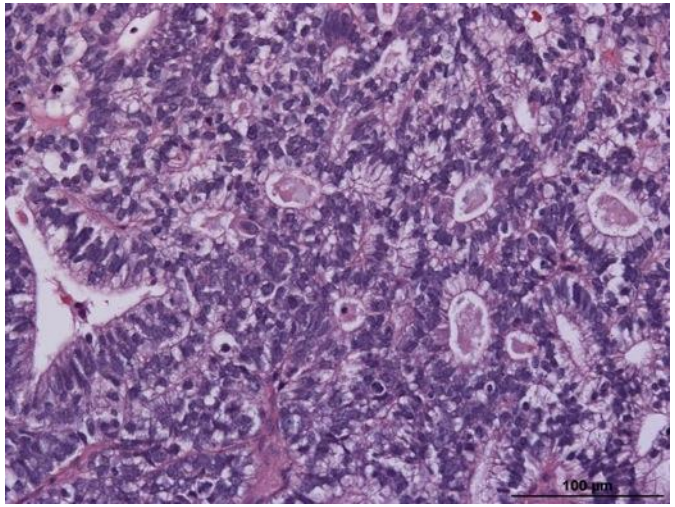
- Endometrium, peritoneum, ovary and Fallopian tubes may be involved
- Molecular analyses show clonality by same p53 mutation (Kypryanczik et al. Modern Path 1996)
- Site of origin seems to be frequently the Fallopian tube

“Carcinoma with Clear Cells”



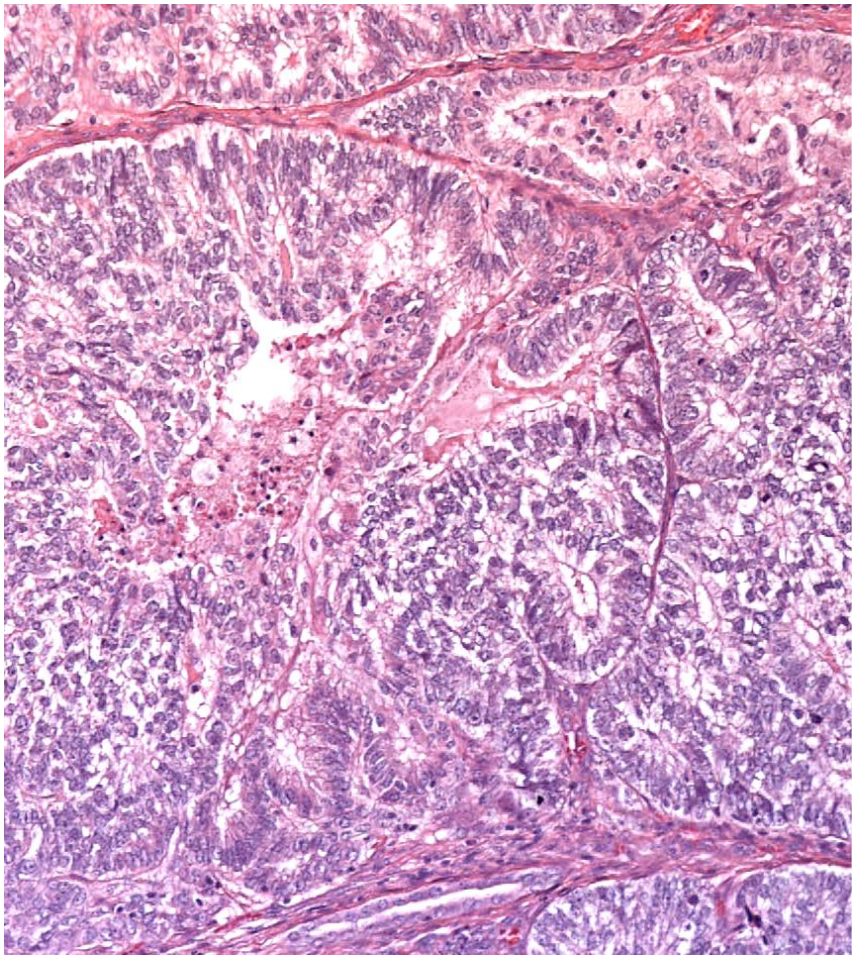


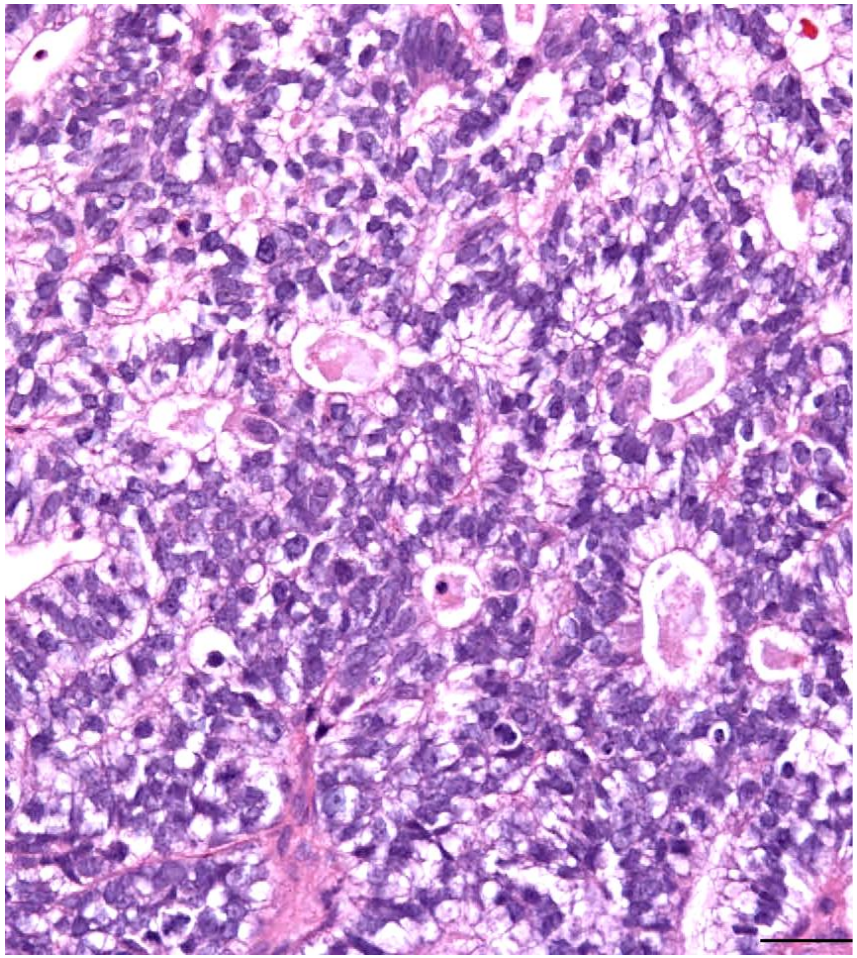


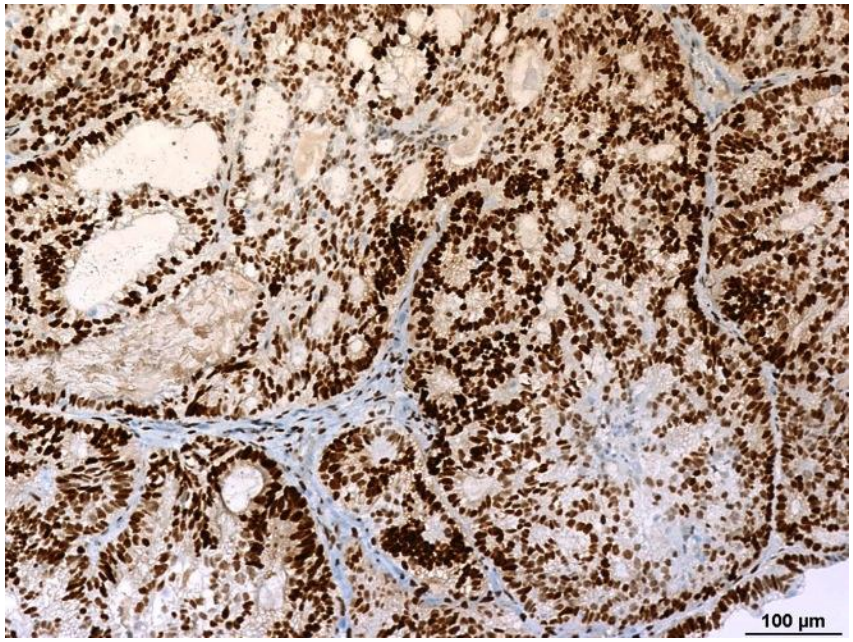


Lookalikes

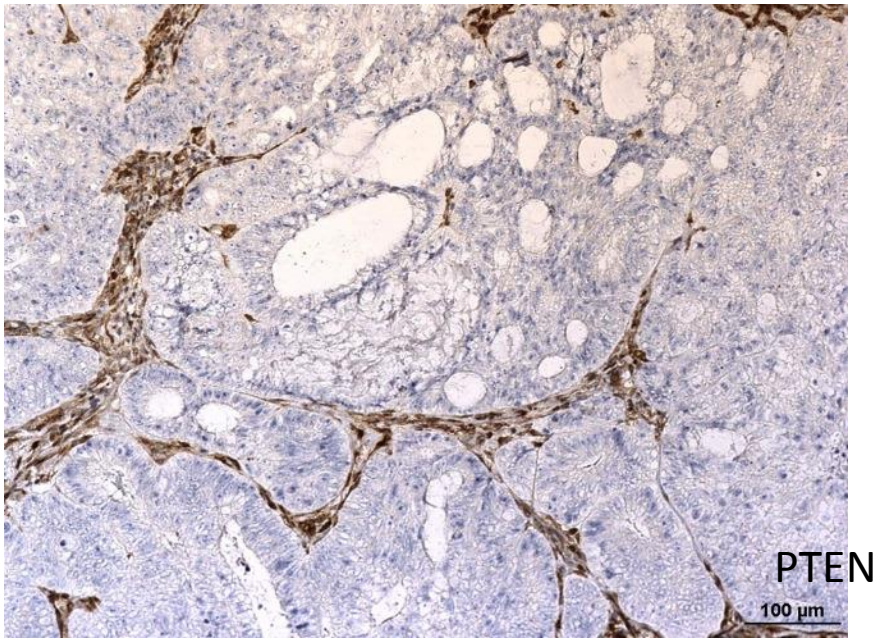
Endometrioid carcinoma with secretory differentiation (secretory endometrioid carcinoma)



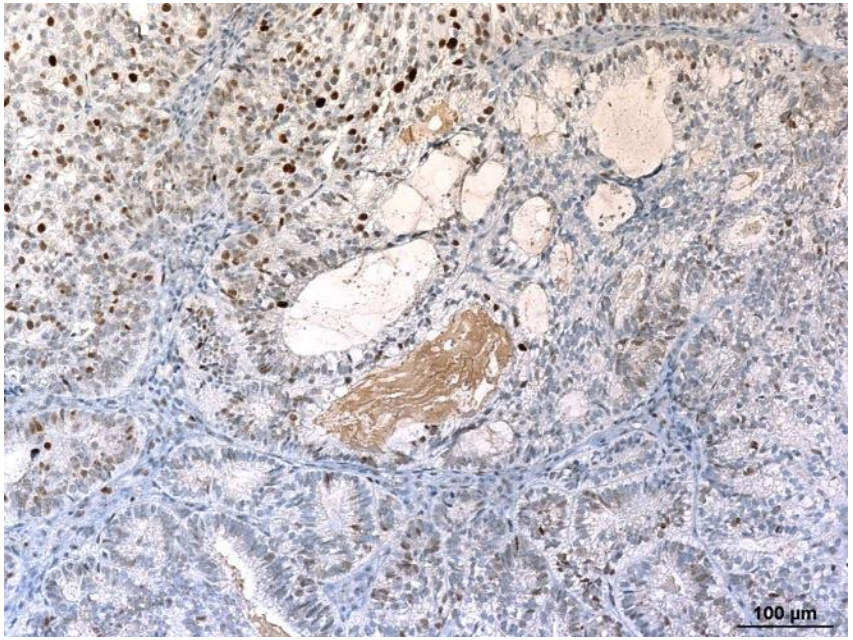




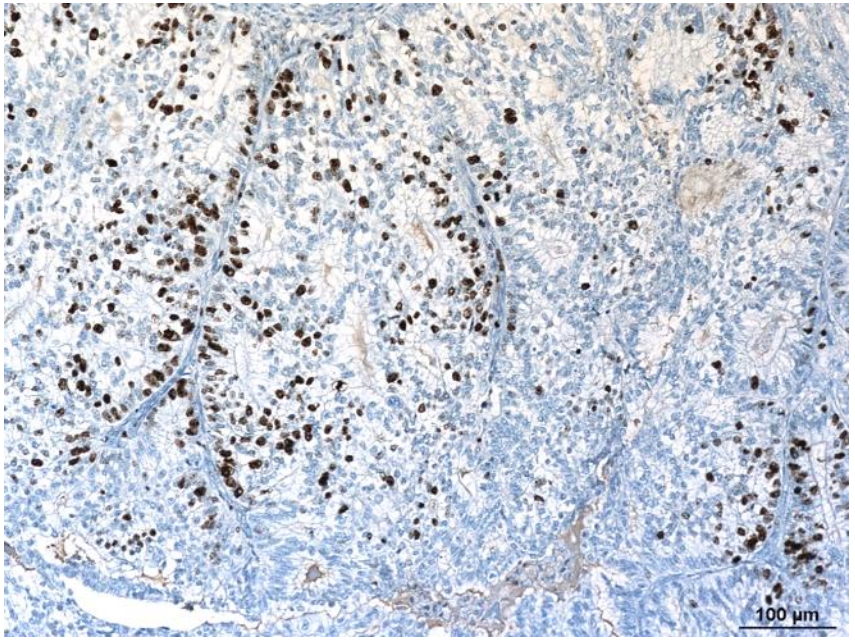
ER



PTEN

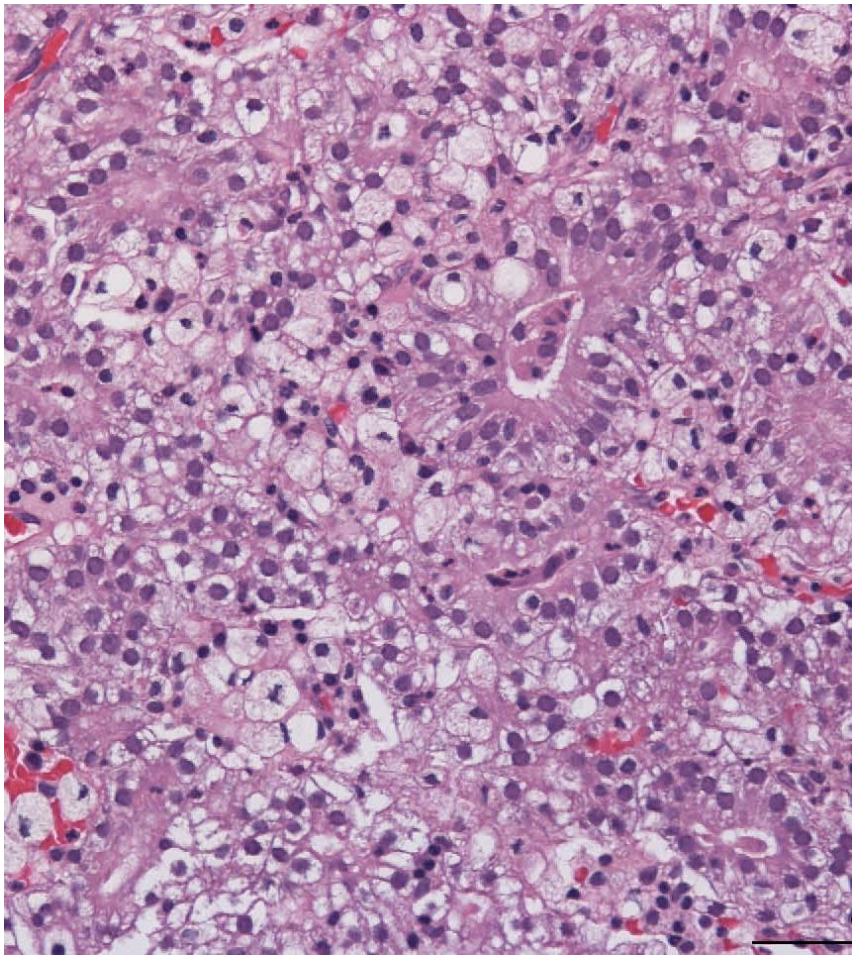


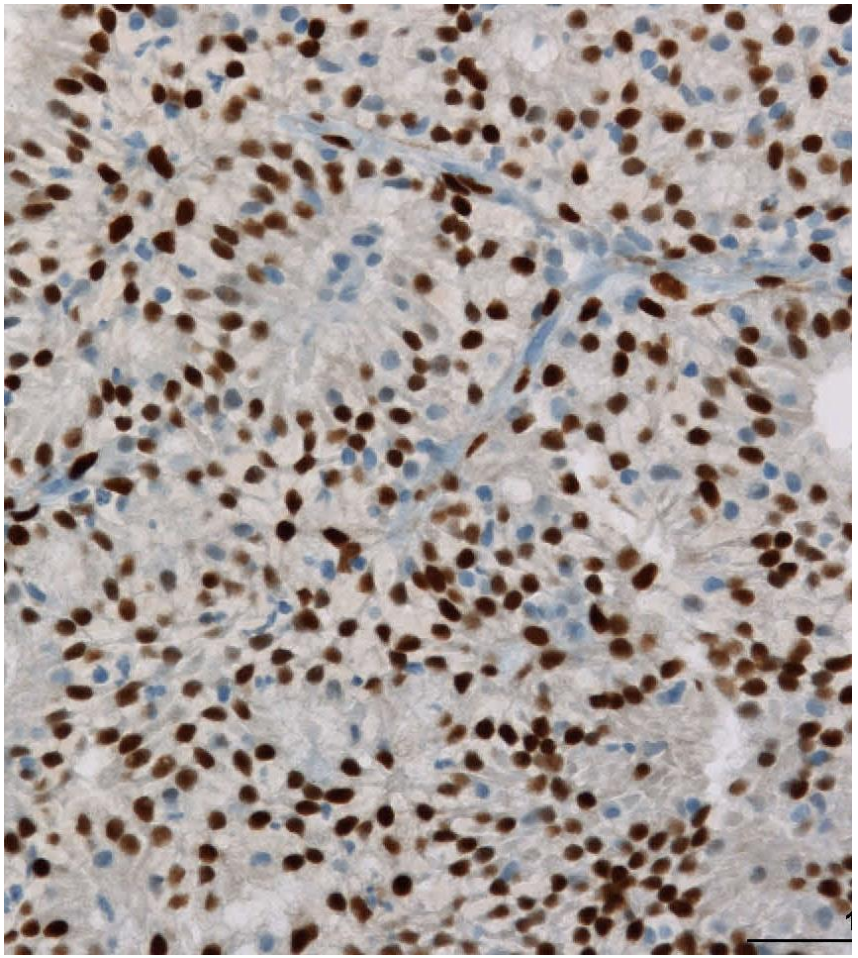
p53

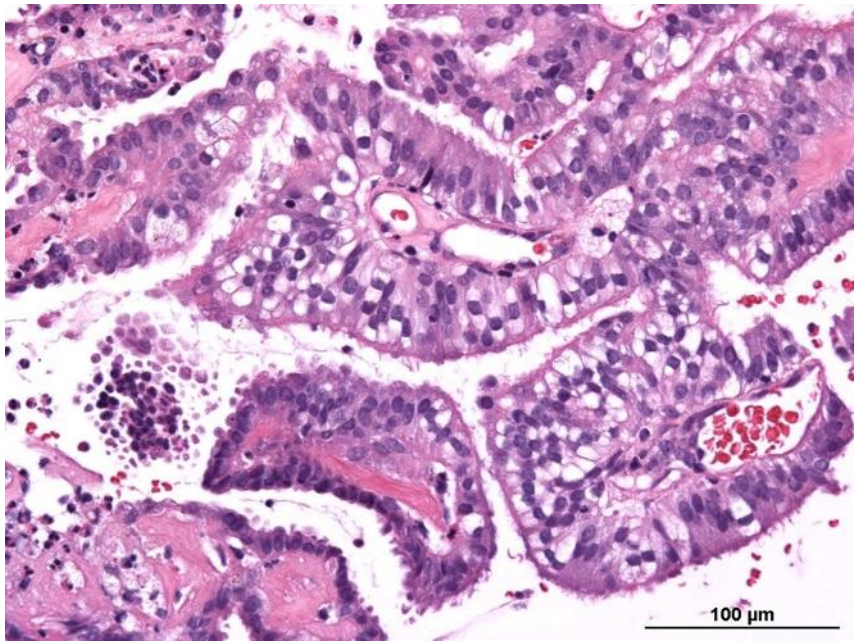


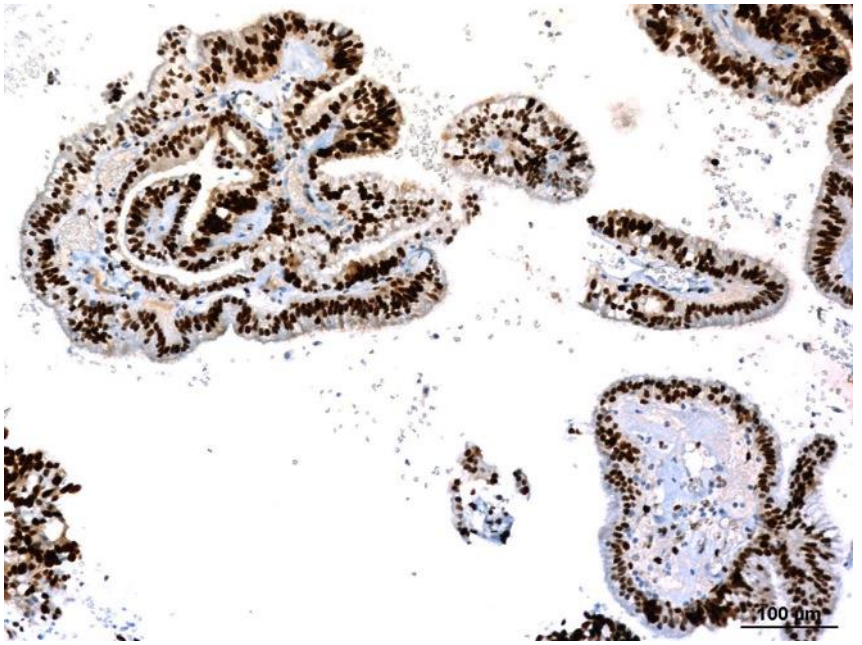
Ki-67

Secretory variant of endometrioid carcinoma may be solid

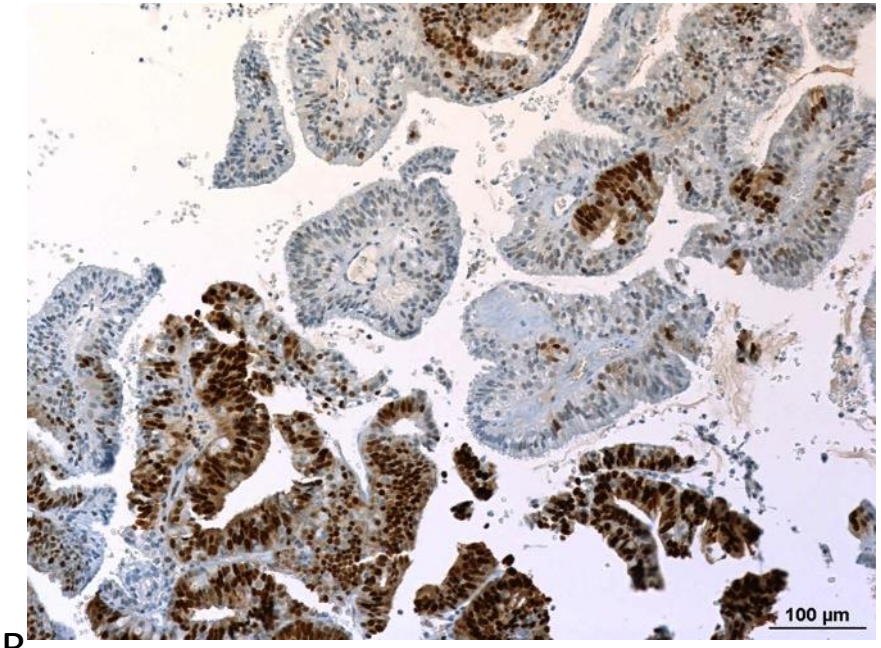




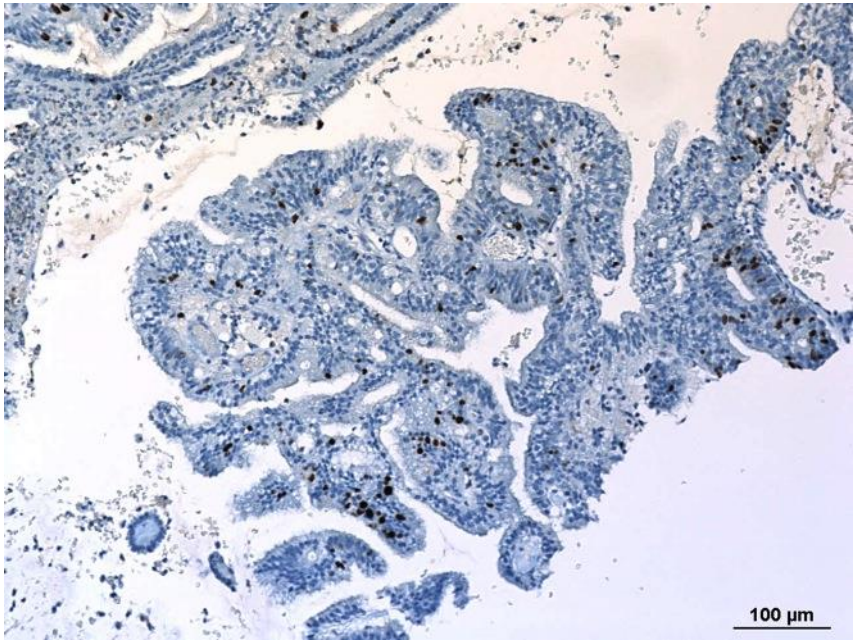




ER

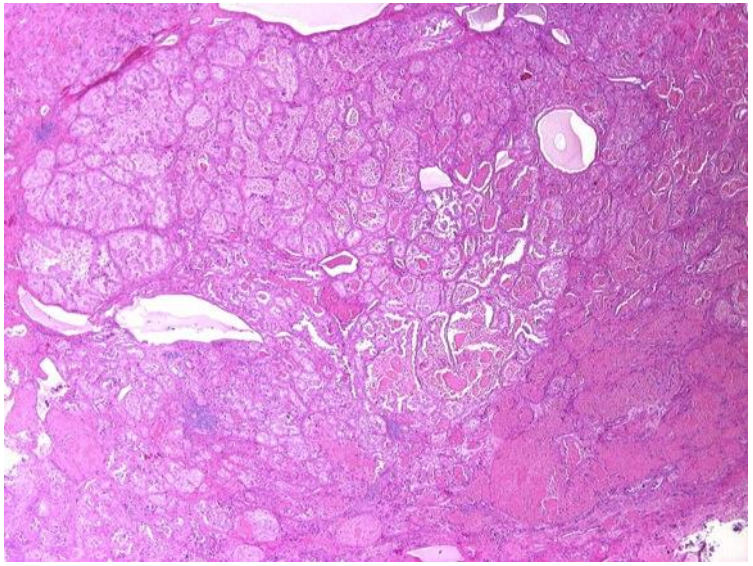


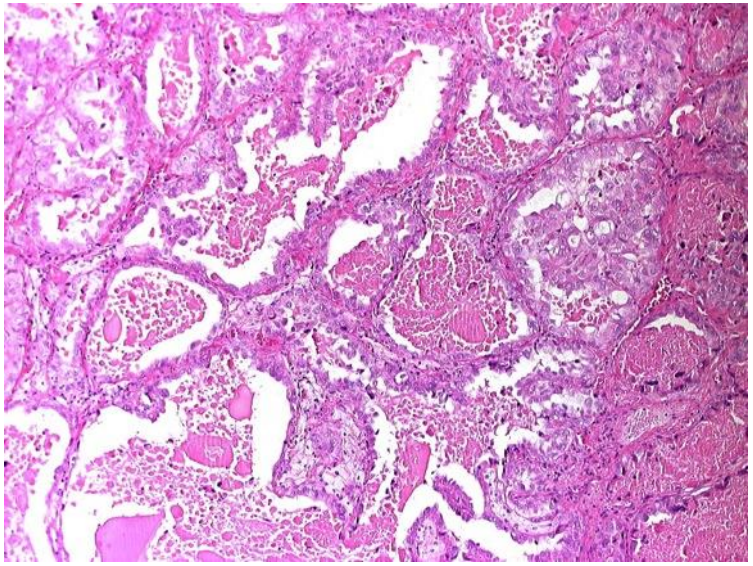
PR

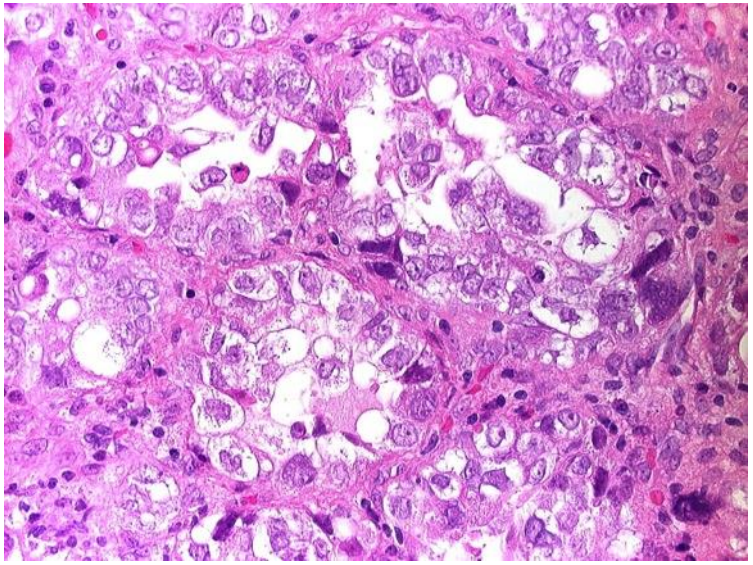


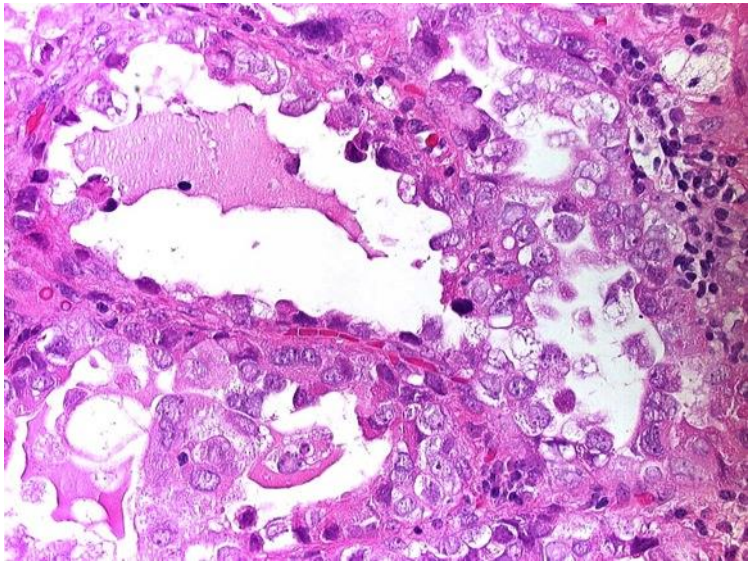
Ki-67

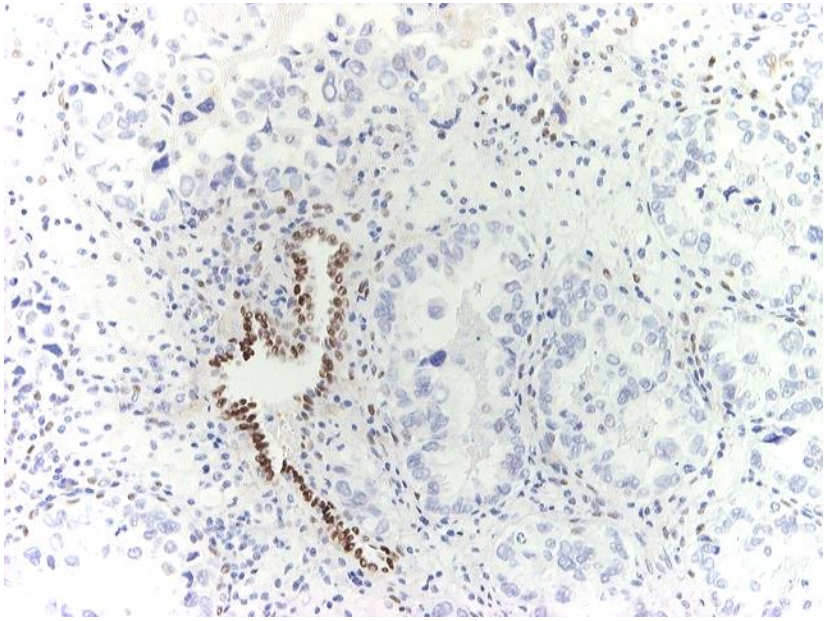
Clear cell carcinoma











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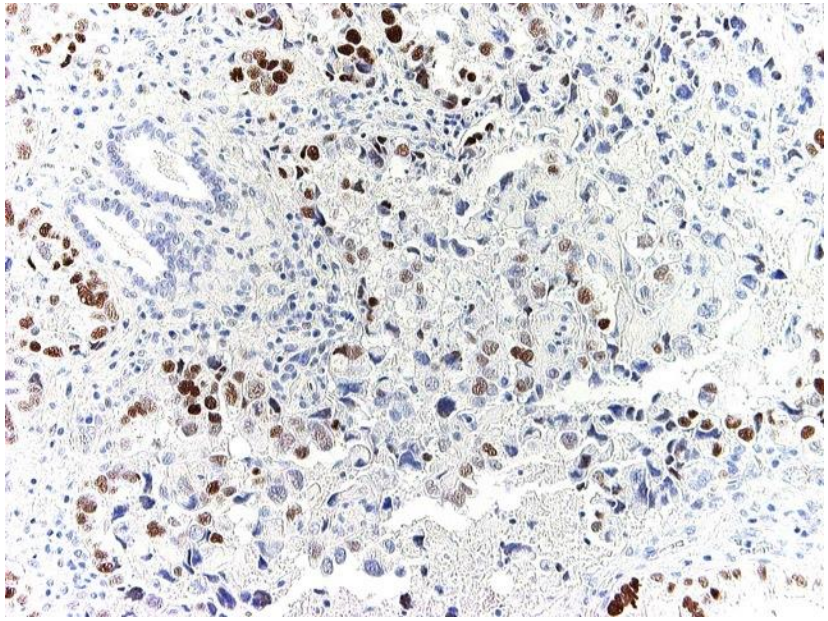

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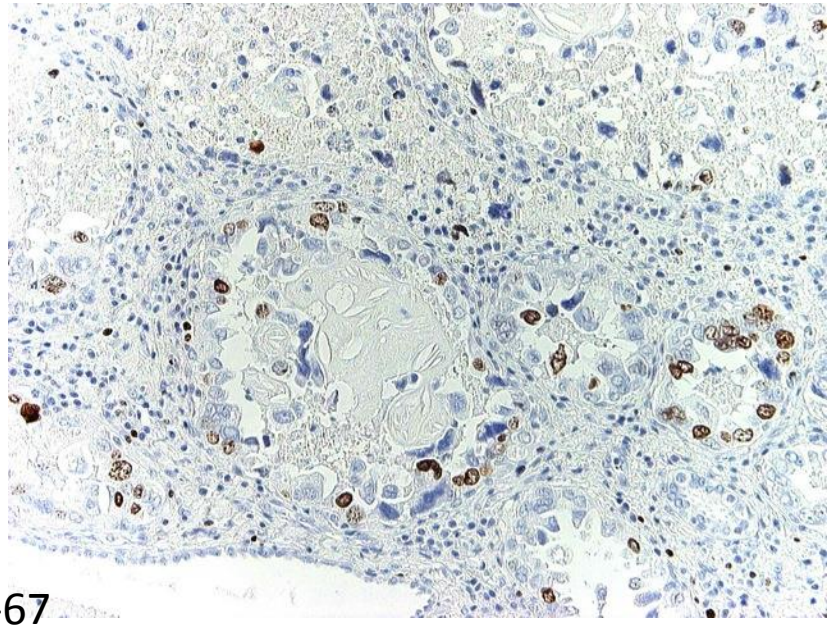
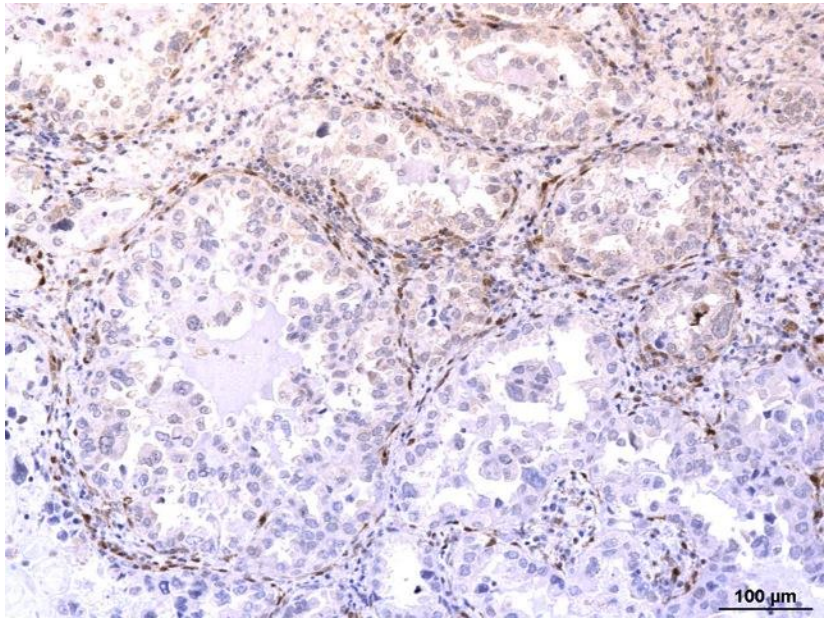
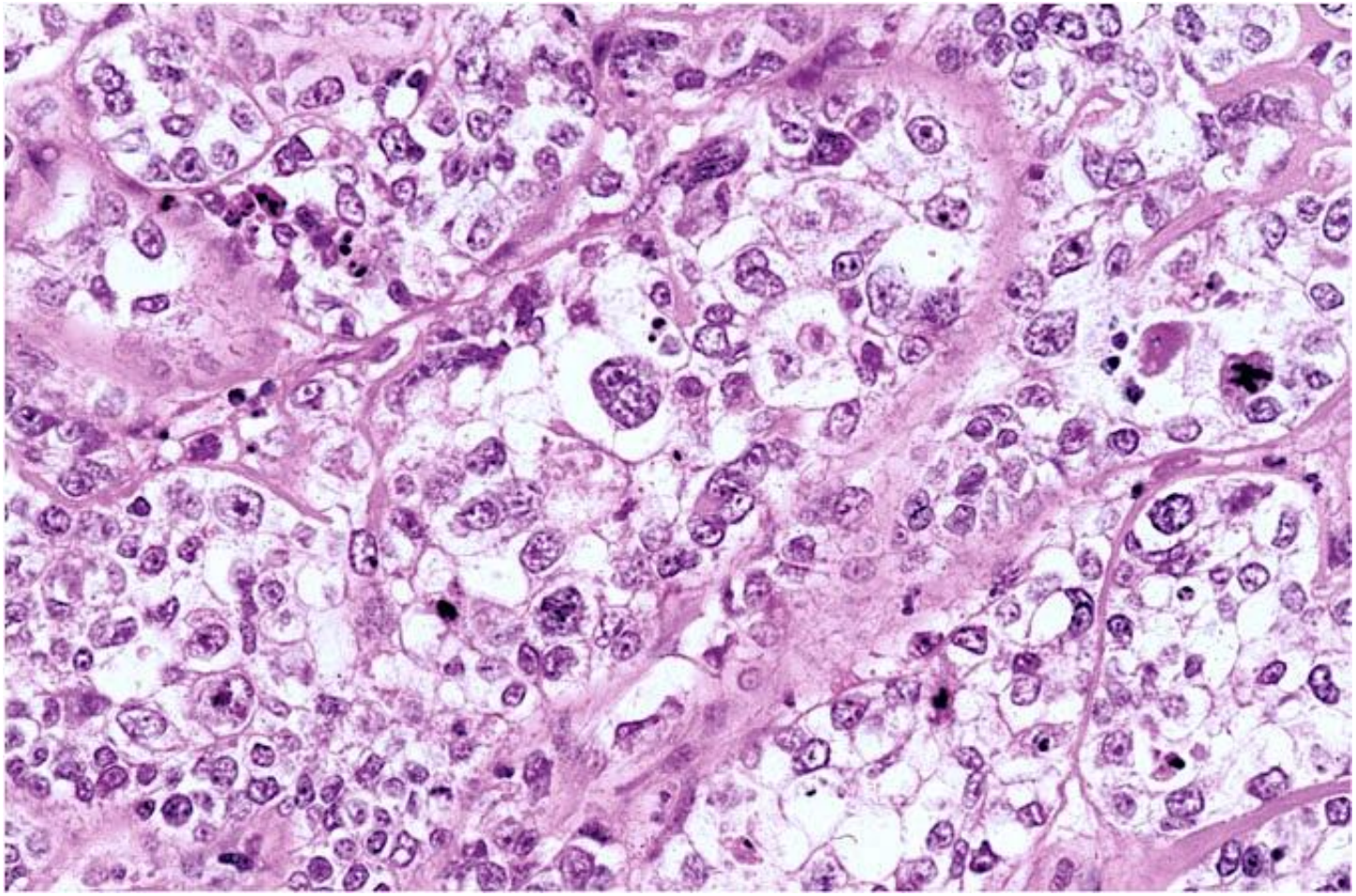


Ki-67

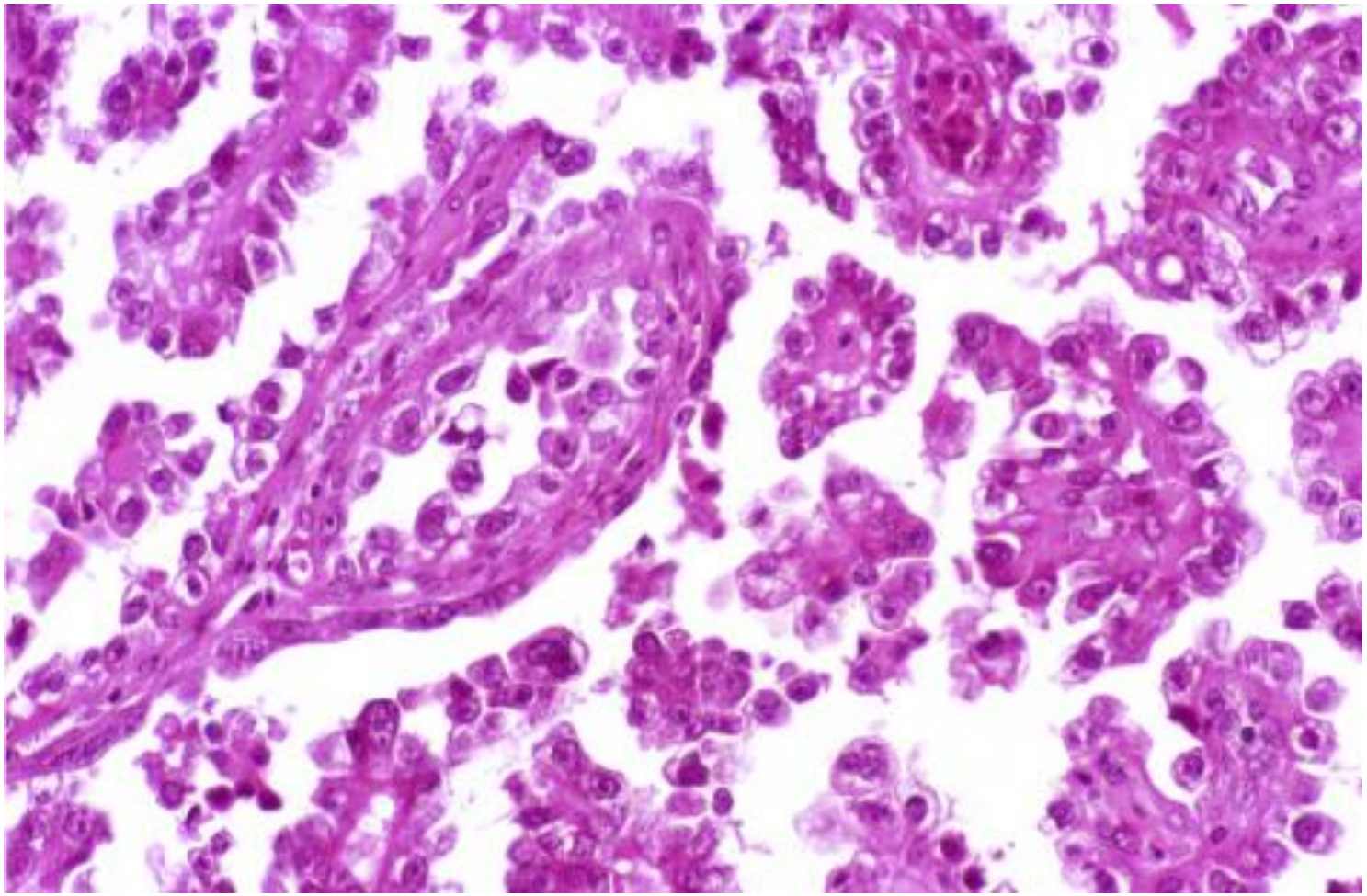


PTEN

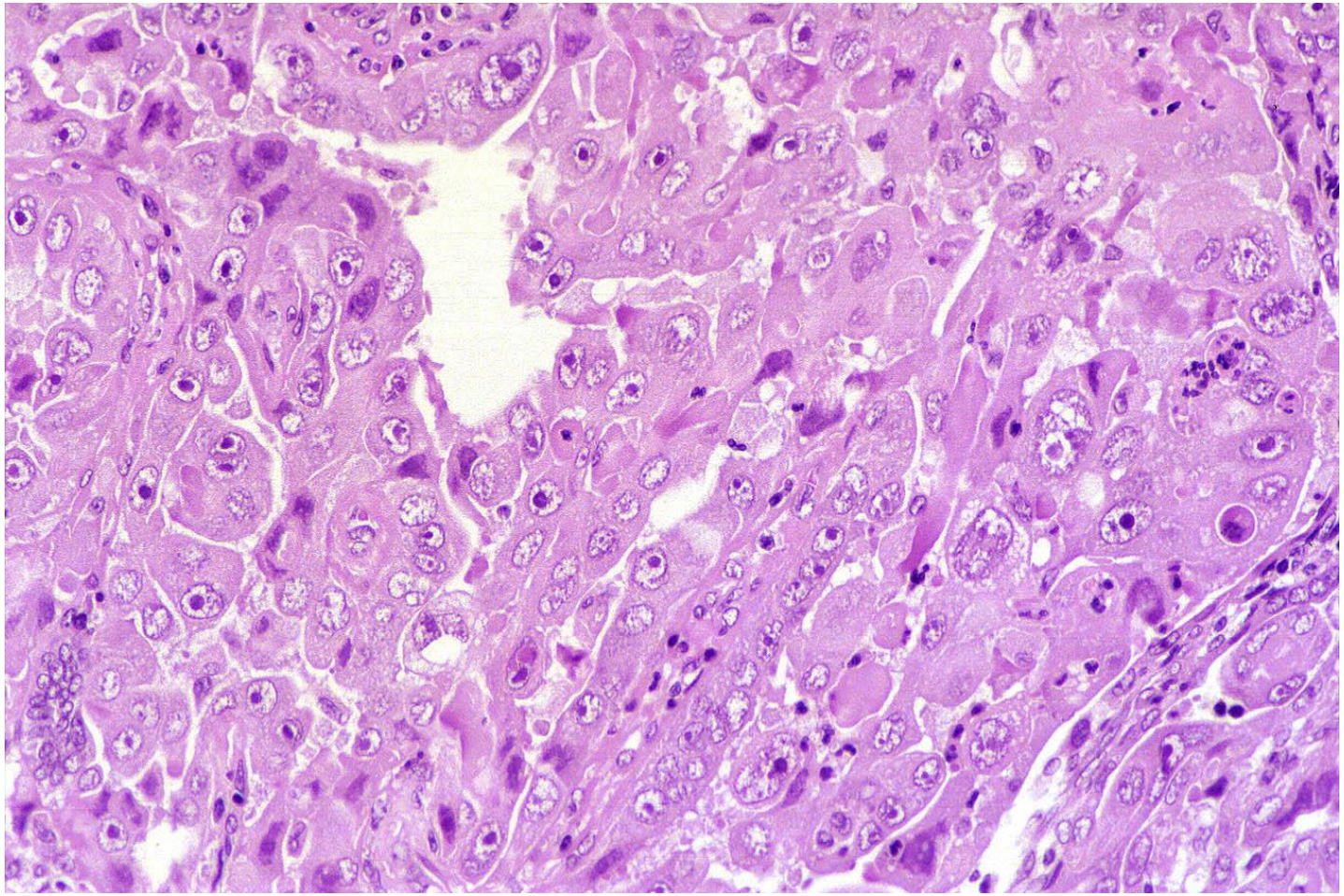
Clear cell carcinoma



Clear cell carcinoma



Clear cell carcinoma, eosinophilic



Clear Cell versus secretory endometrioid carcinoma

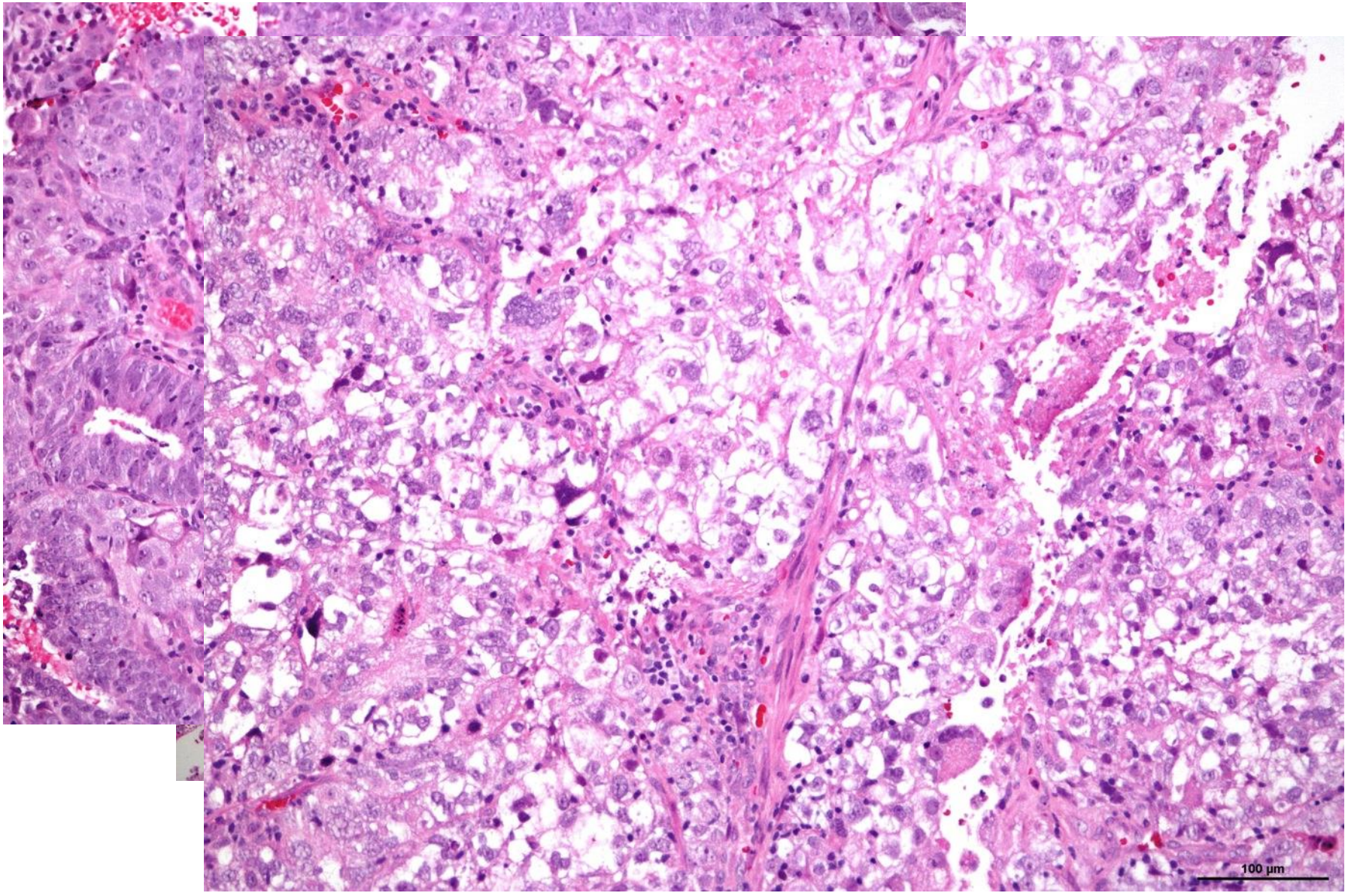
Clear cell carcinoma

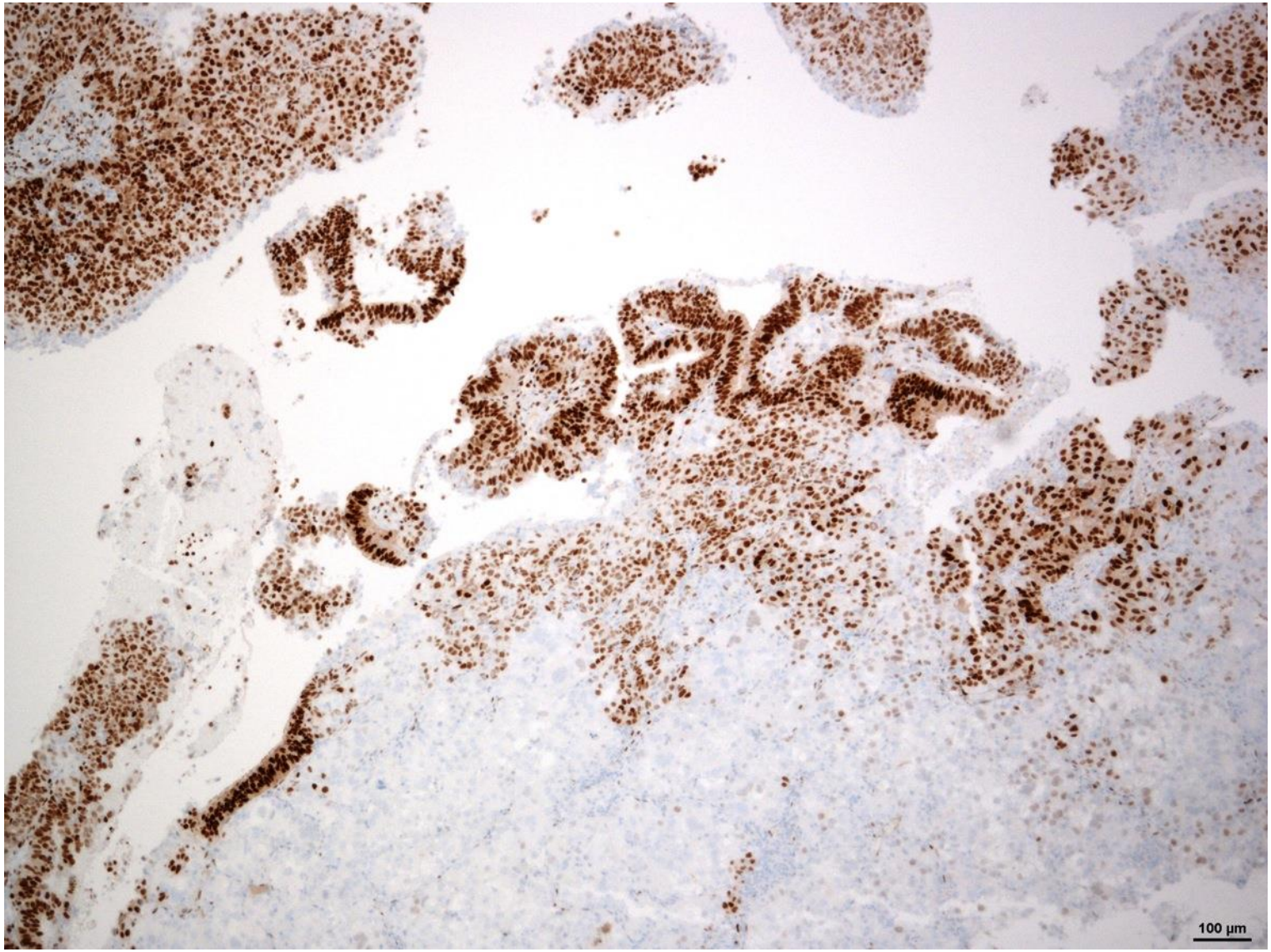
- Tubulo-cystic, solid or papillary
- May rarely be oxiphilic
- High nuclear grade
- Eosinophilic material in lumen

Secretory endometrioid ca

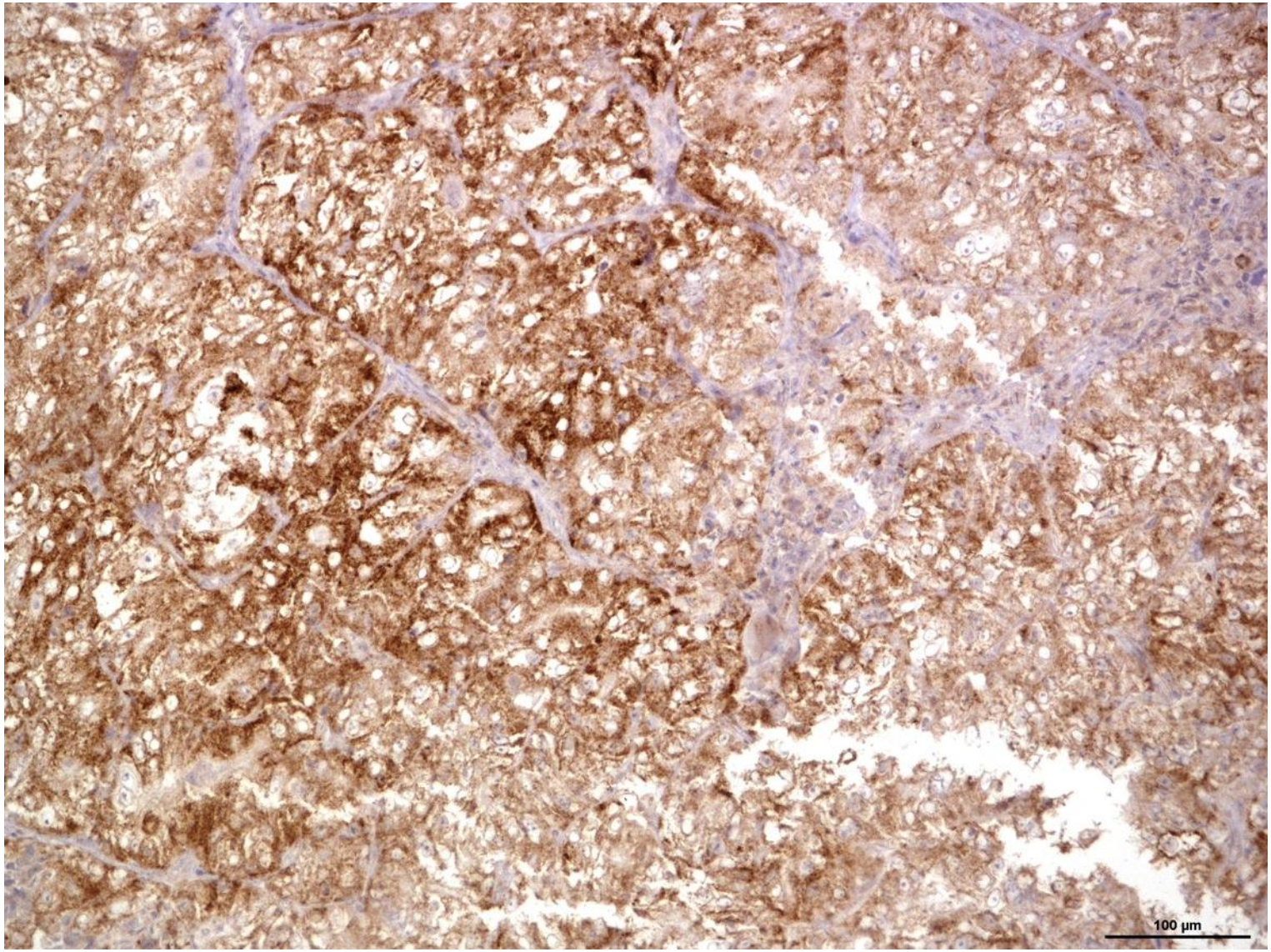
- Glandular, solid or papillary
- Oxiphilic cell type not described
- Low nuclear grade
- Mimickry of early secretory phase

Mixed clear cell-endometrioid ca

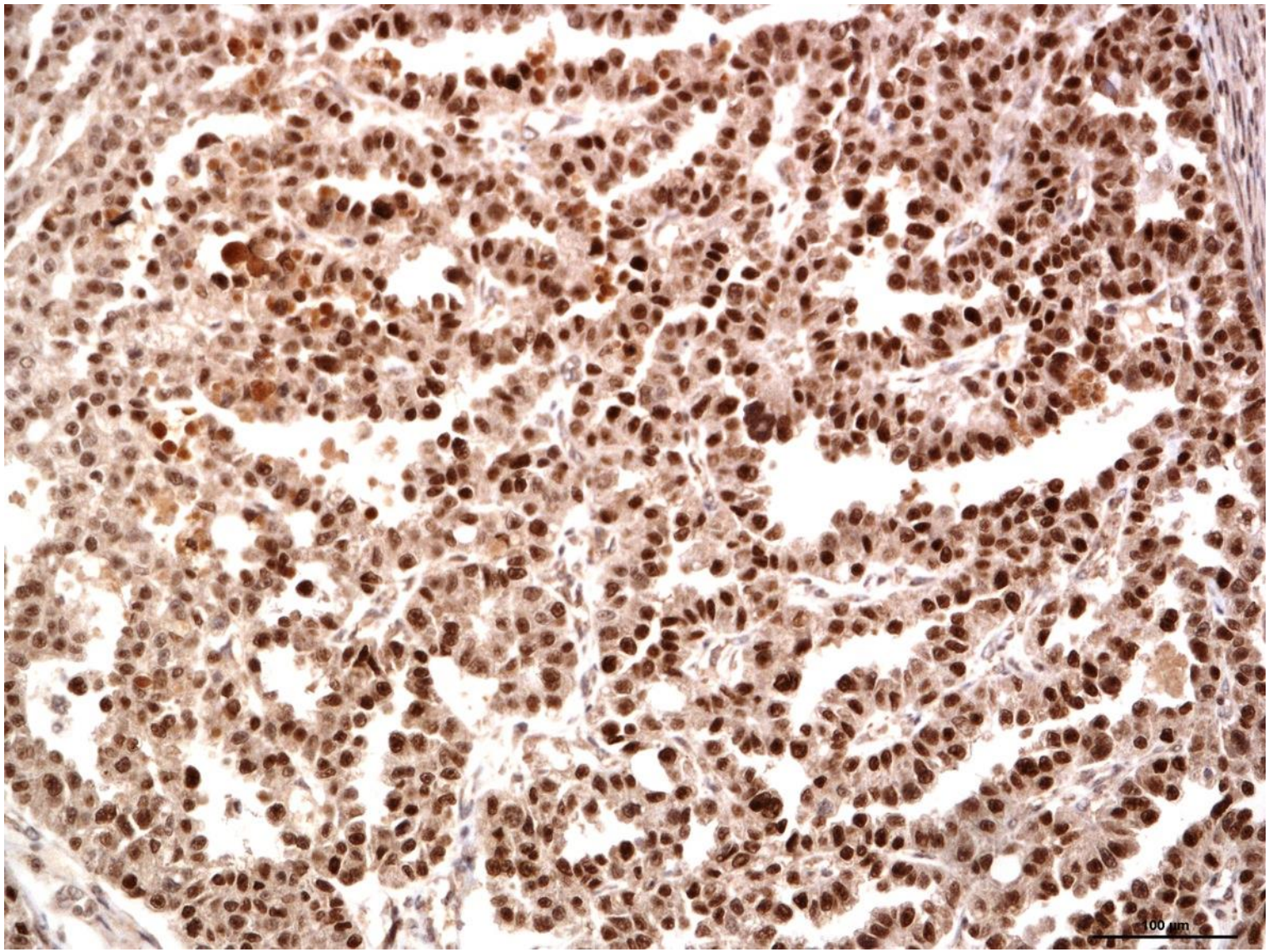




ER



racemase



HNF1ß

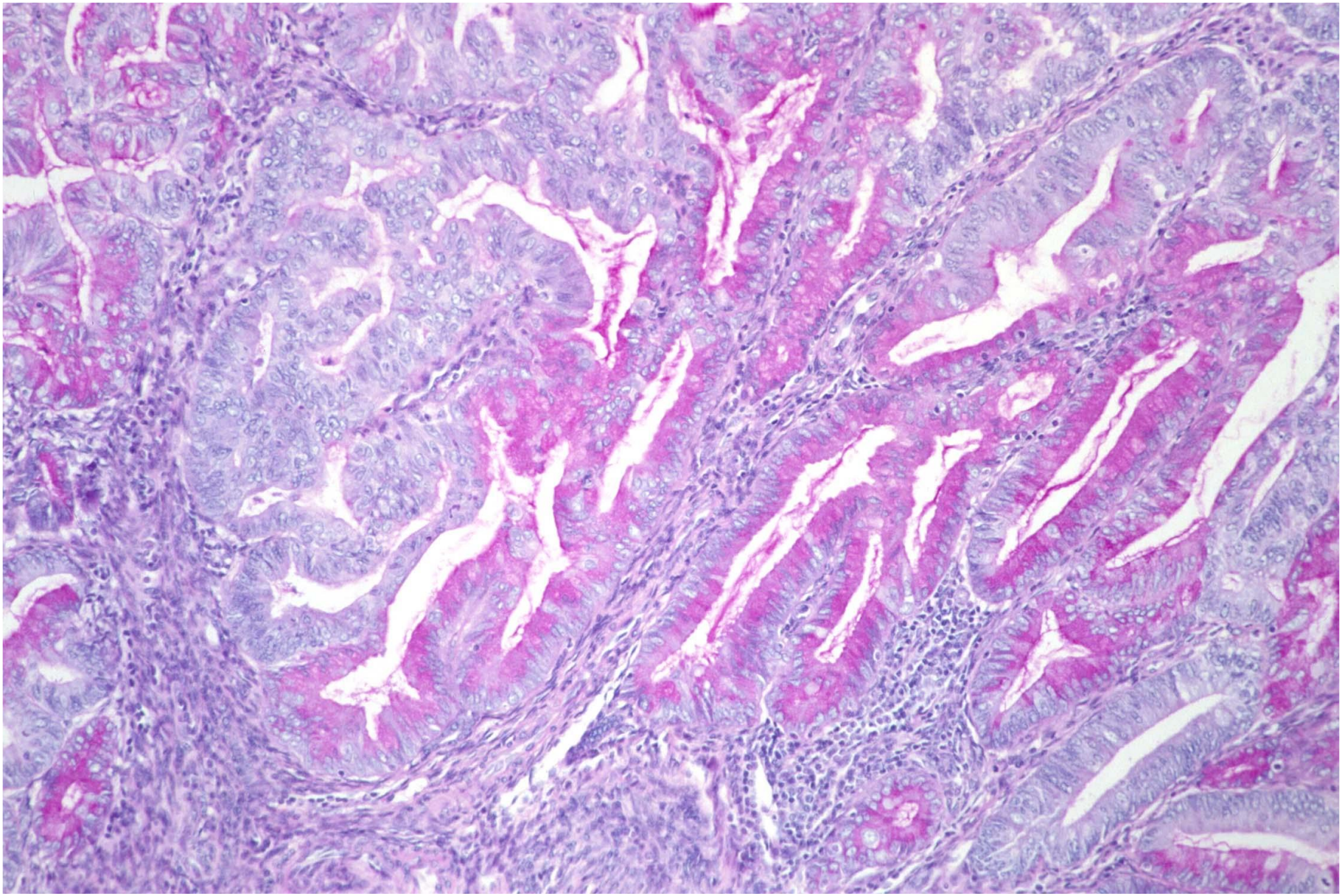
Immunohistochemistry of clear cell carcinoma

- ER: negative or weakly positive
- P53: heterogenous staining
- Napsin: positive
- Racemase: positive
- HNF1ß: positive

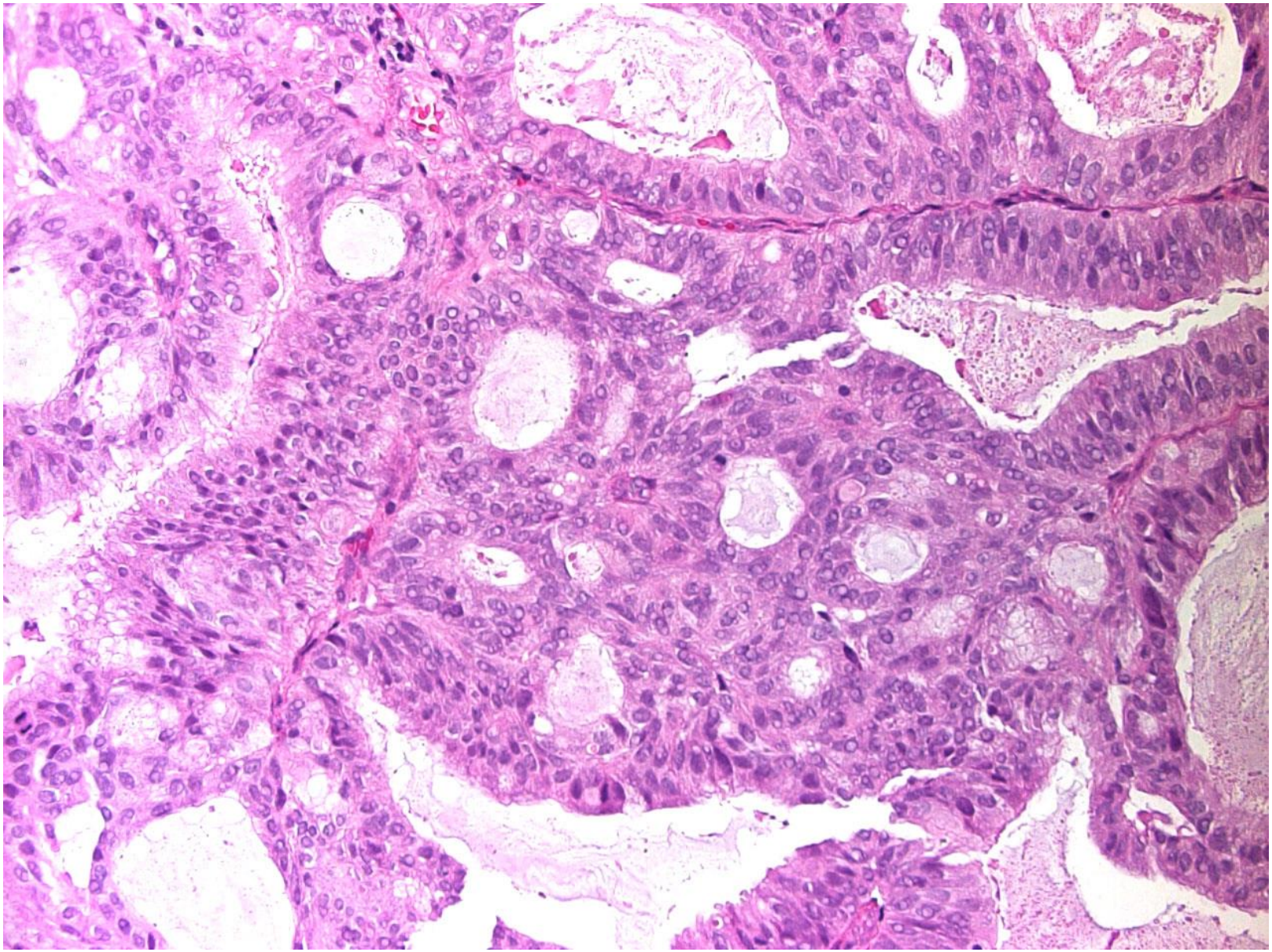
Mucinous carcinoma is related to endometrioid carcinoma

- Often associated with endometrioid histology
- Low stage
- Low grade
- Similar biology
- Term mucinous adenocarcinoma needs >50% mucinous differentiation
- Variant of endometrioid carcinoma?
- Minimal deviation mucinous carcinoma?!

Endometrioid carcinoma with mucinous differentiation



Microglandular Pattern

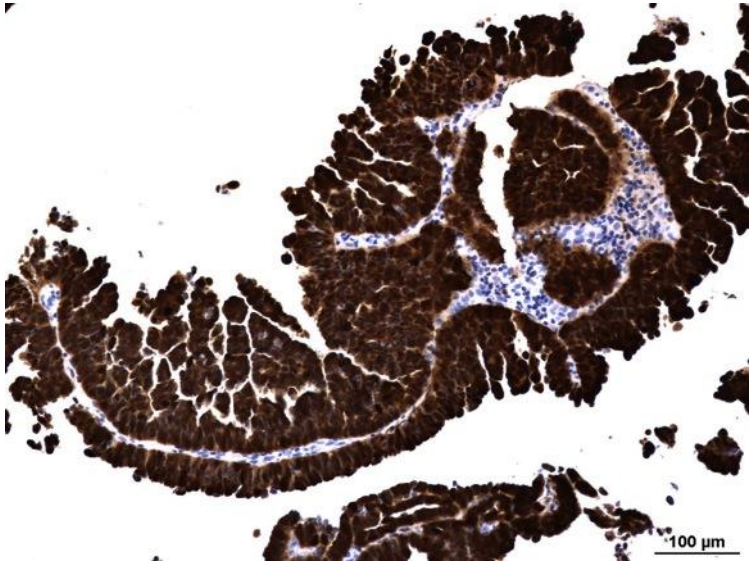


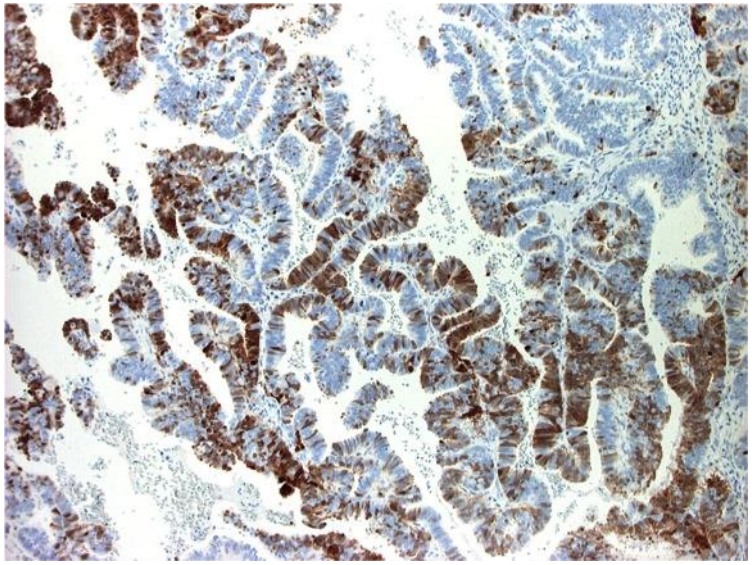
P16 Immunoreactivity in Endometrial Carcinoma

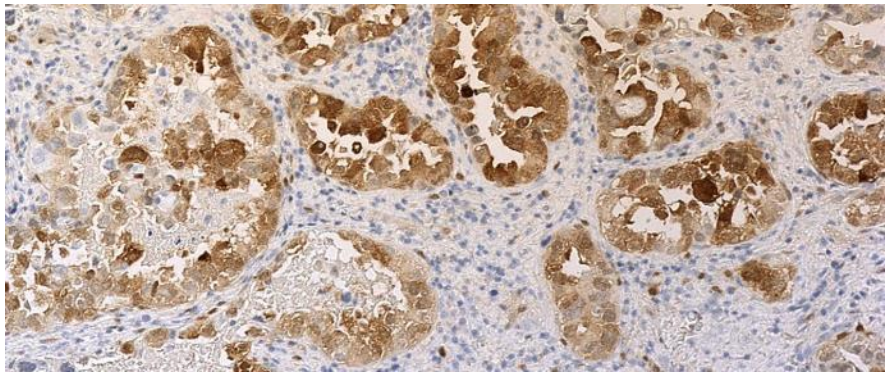
Reid-Nicholson et al., 2006; Chekmareva et al., 2008

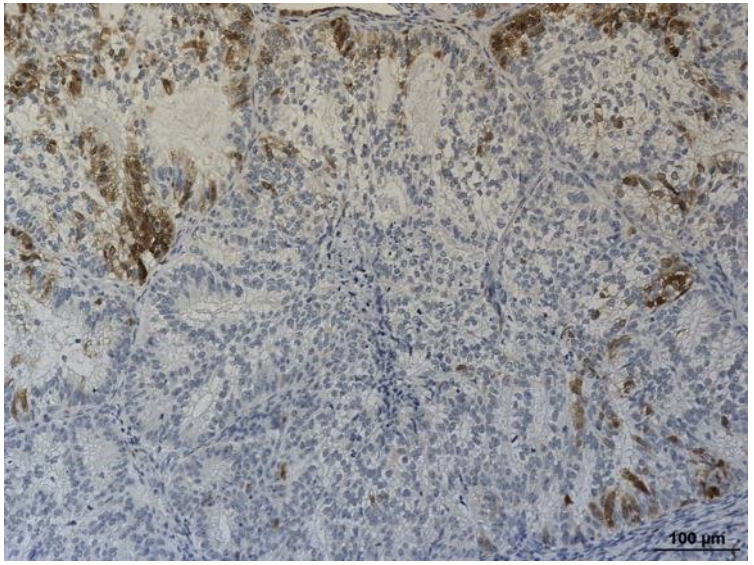
Tumor type	% of p16 positivity
Endometrioid G 1, 2	7 (focal, weak to moderate)
Endometrioid G 3	25 (focal, moderate)
Mucinous	96 (focal or diffuse)
Serous	92 (diffuse, strong)
Clear cell	45 (diffuse, strong)

P16 staining in endometrial carcinoma

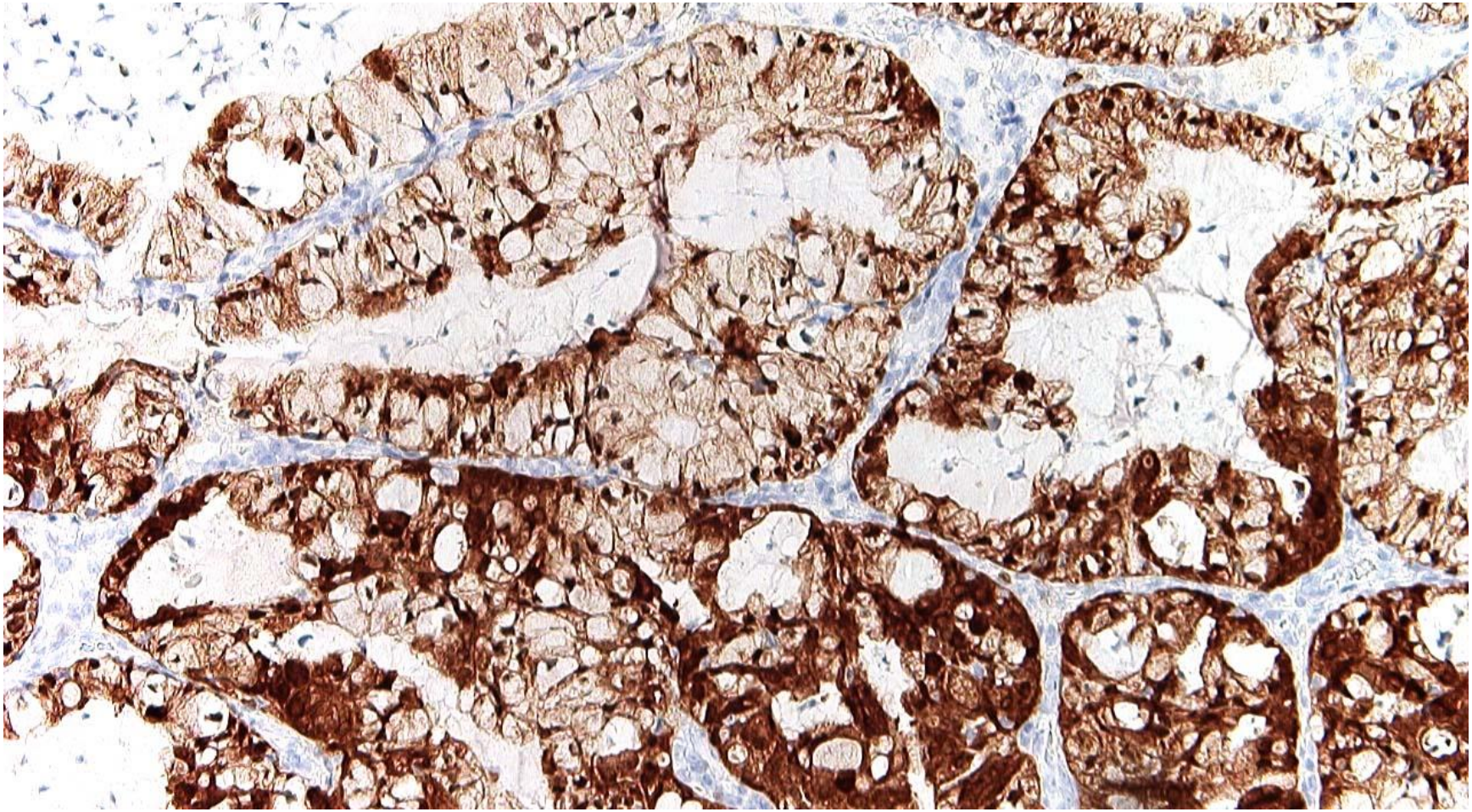








P16 in endometrial carcinoma with mucinous differentiation



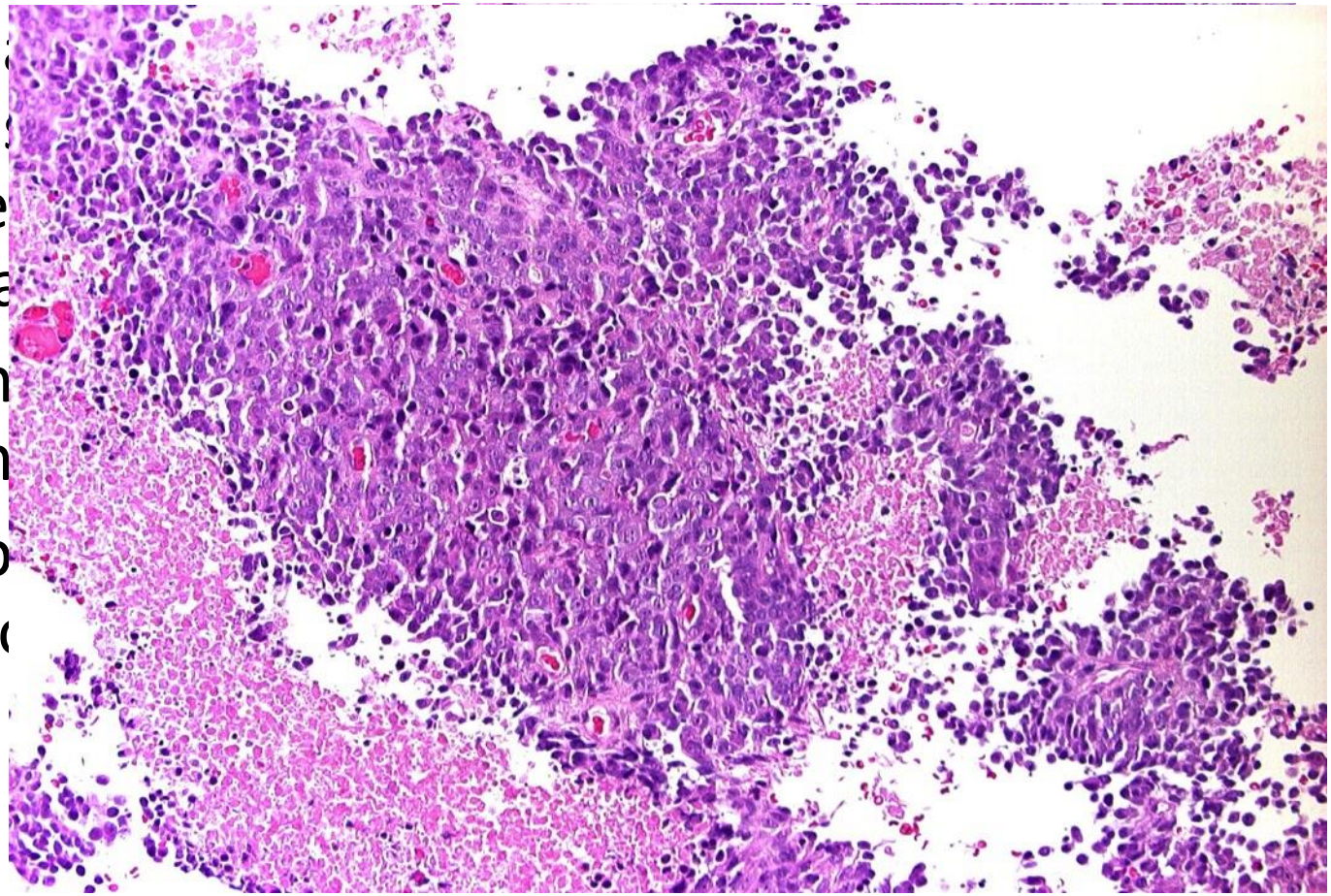
Antibodies for typing summarized

- ER
- PR
- P53
- Ki-67
- PTEN
- Racemase
- Napsin A
- HNF1ß

Dedifferentiated endometrioid carcinoma

Silva et al. IJGP 2006

- Undifferenti
  carcinoma a
  with G 1/2 e
  carcinoma (a
- DD G 3 EC: n
  2 componen
- Aggressive b
  Prognosis w
  G 3 EC



Challenge of grading

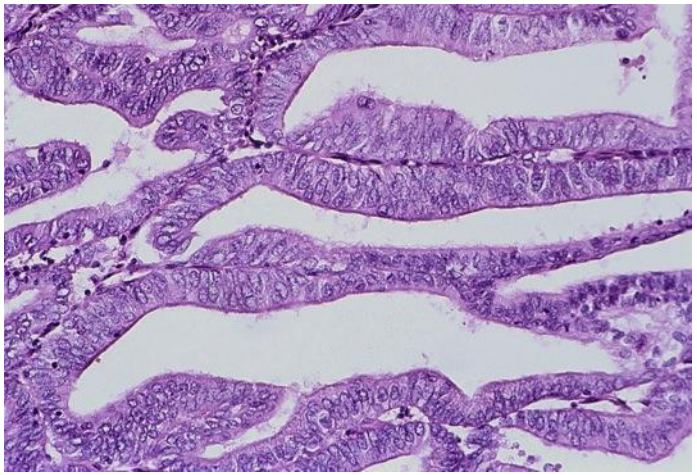
- FIGO for endometrioid adenocarcinoma
- Predicts outcome for low stage carcinomas
- Stratifies surgical and adjuvant therapy
- Required preoperatively but not consistently performed in curettage specimens
- Reproducibility varies and may be poor
- Alternative grading systems proposed

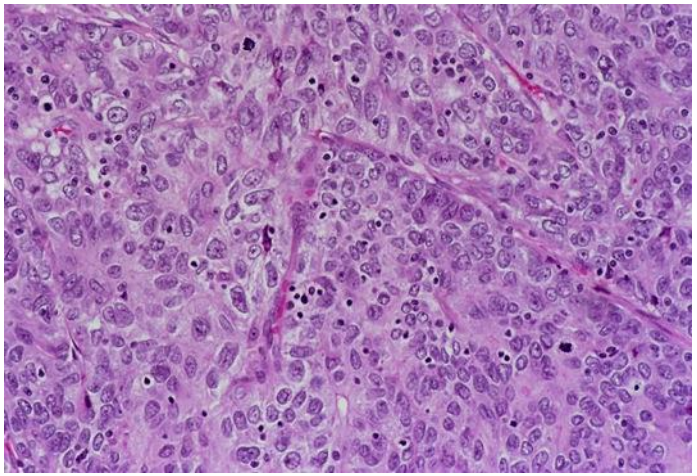
Grading of Endometrial Carcinoma

Histological Type	Grading Method
Endometrioid and variants	FIGO
Mucinous	FIGO
Serous	No grading (high grade)
Clear cell	No grading (high grade)

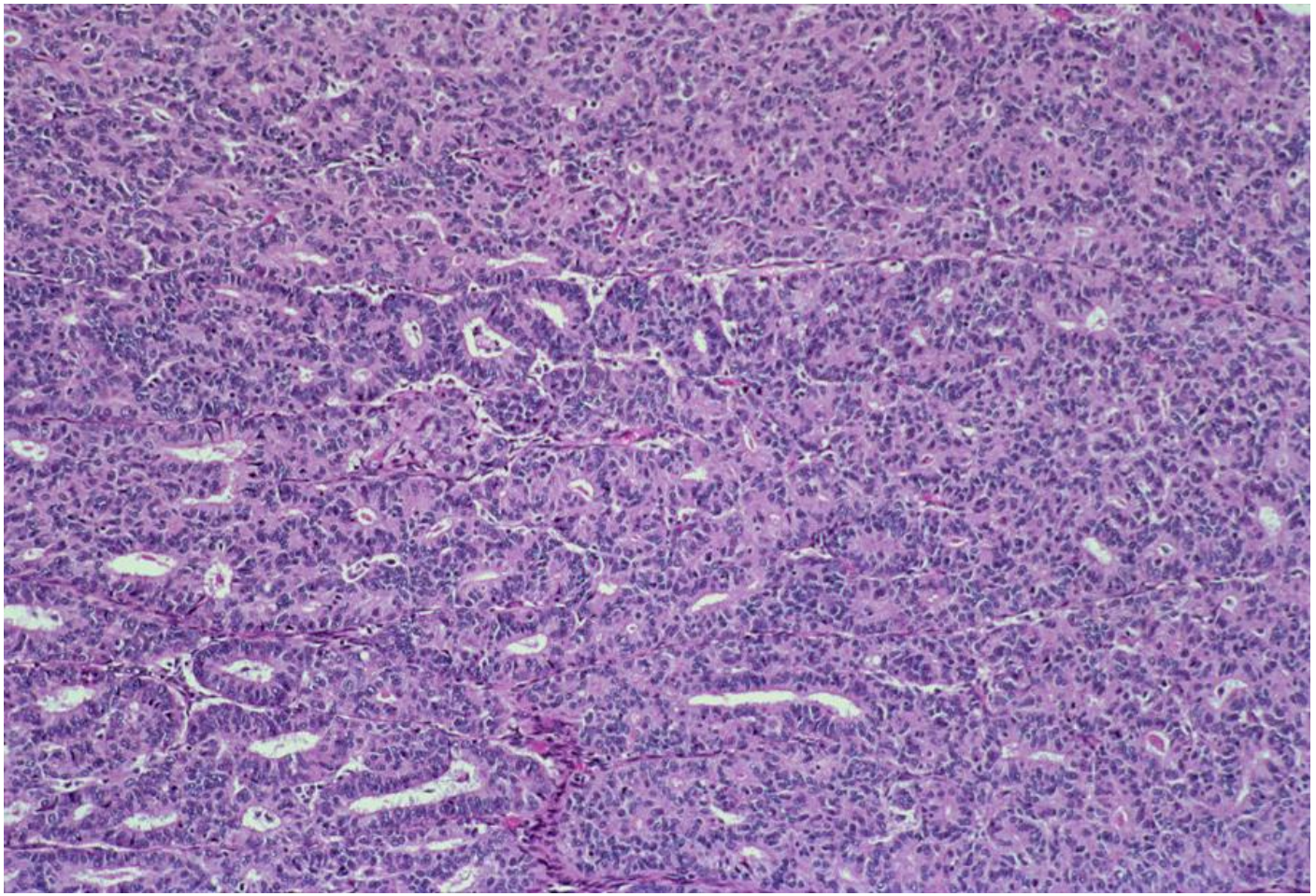
FIGO Grading of Endometrioid Carcinoma

- Solid, non squamous, non-morular growth pattern
- 5/6-50/>50% rule
- Bizarre nuclear atypia raises grade by one
- Cave: Bizarre nuclear atypia should raise suspicion for serous or clear cell carcinoma

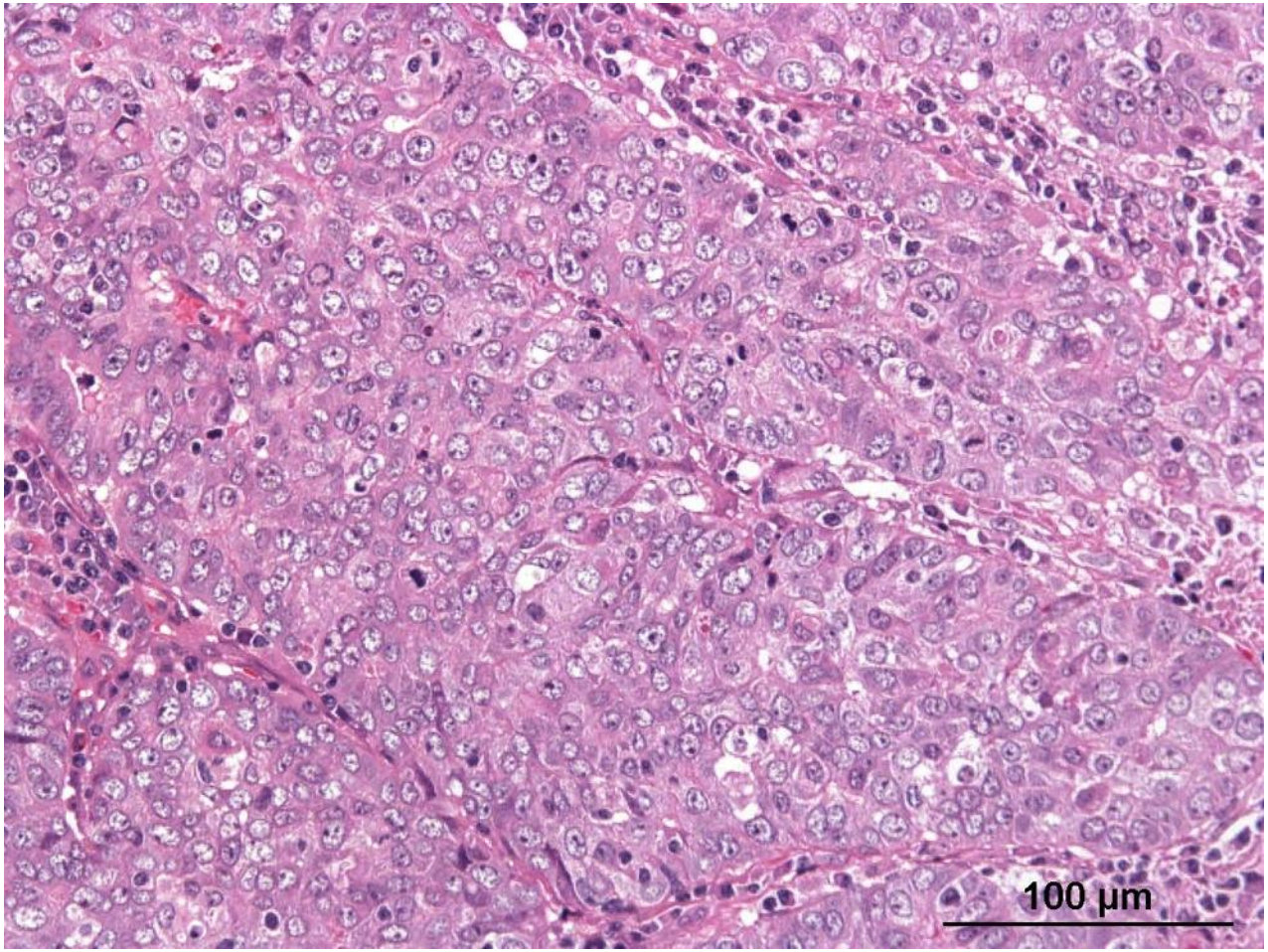




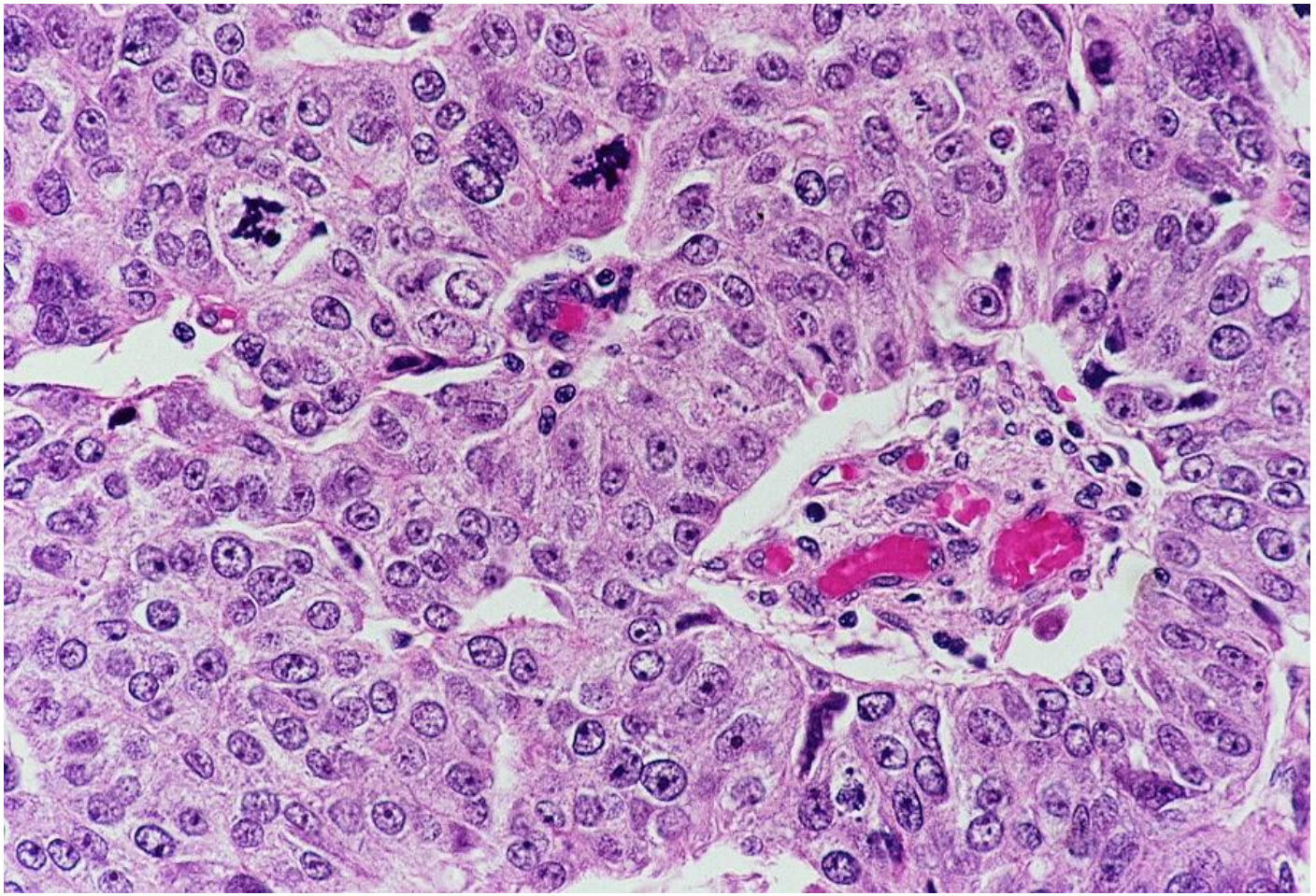
Endometrioid Carcinoma, FIGO G2

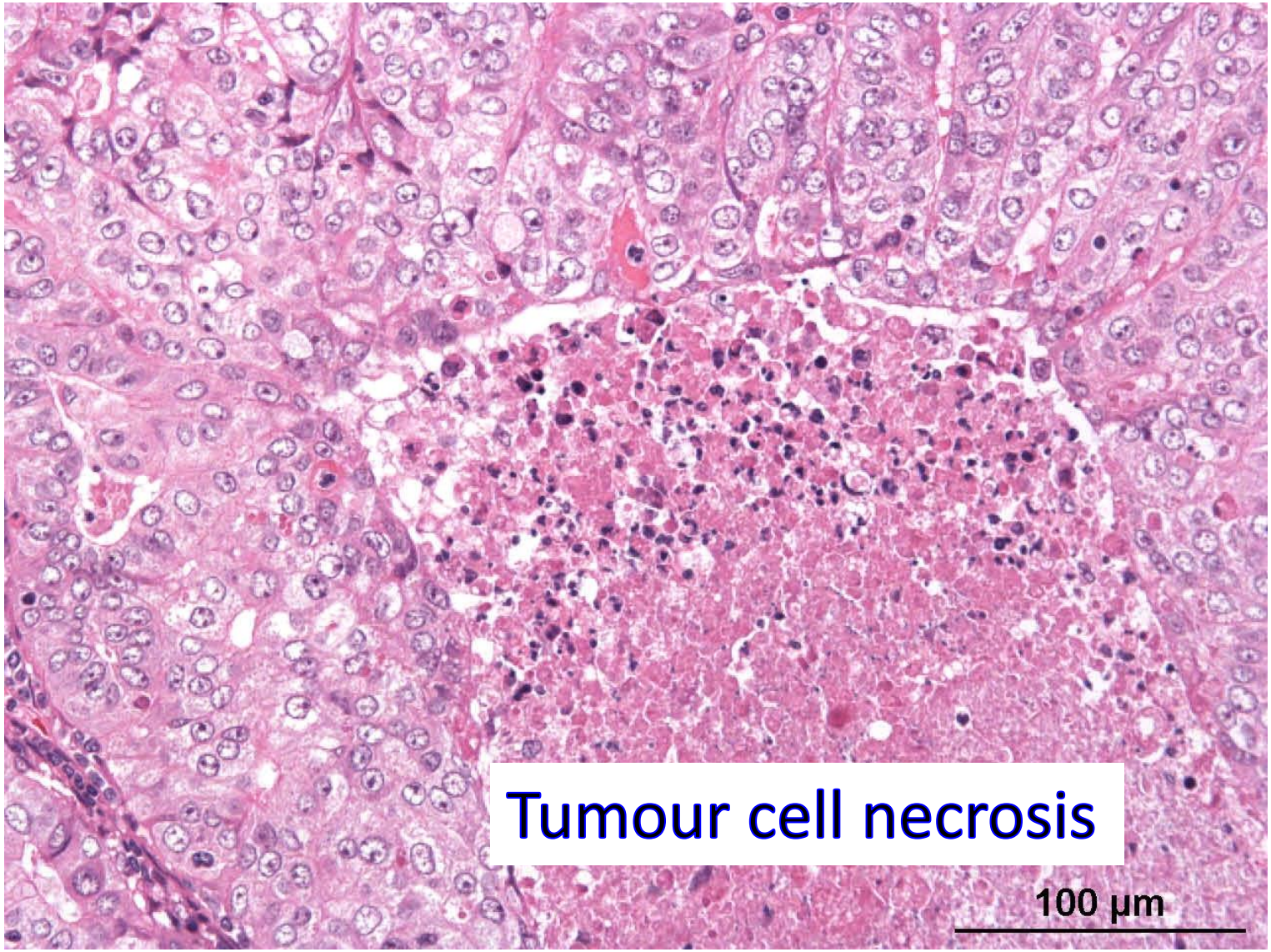


Endometrioid carcinoma Grade 3



Endometrioid carcinoma, nuclear grade 3




Tumour cell necrosis
100 µm

Advantages of FIGO garding

- Well established
- Long term experience
- High level of evidence
- Can be assessed in curettings

Problems of FIGO Grading

- Determination of low percentage (5%) of solid growth
- Distinction between solid non-squamous growth and immature squamous differentiation
- Recognition/definition of bizarre nuclear atypia
- Three-tiered systems less reproducible than 2-tiered systems

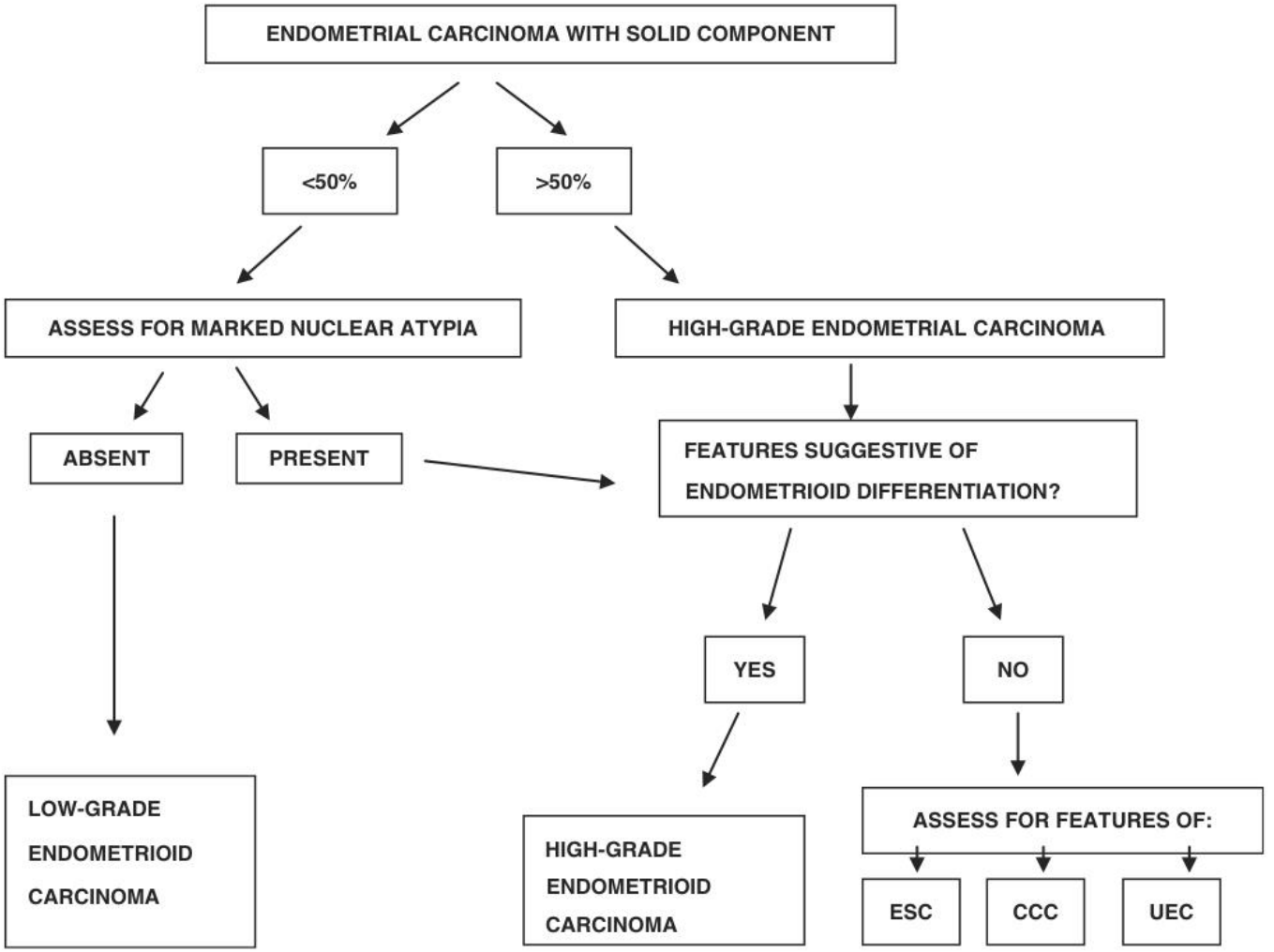


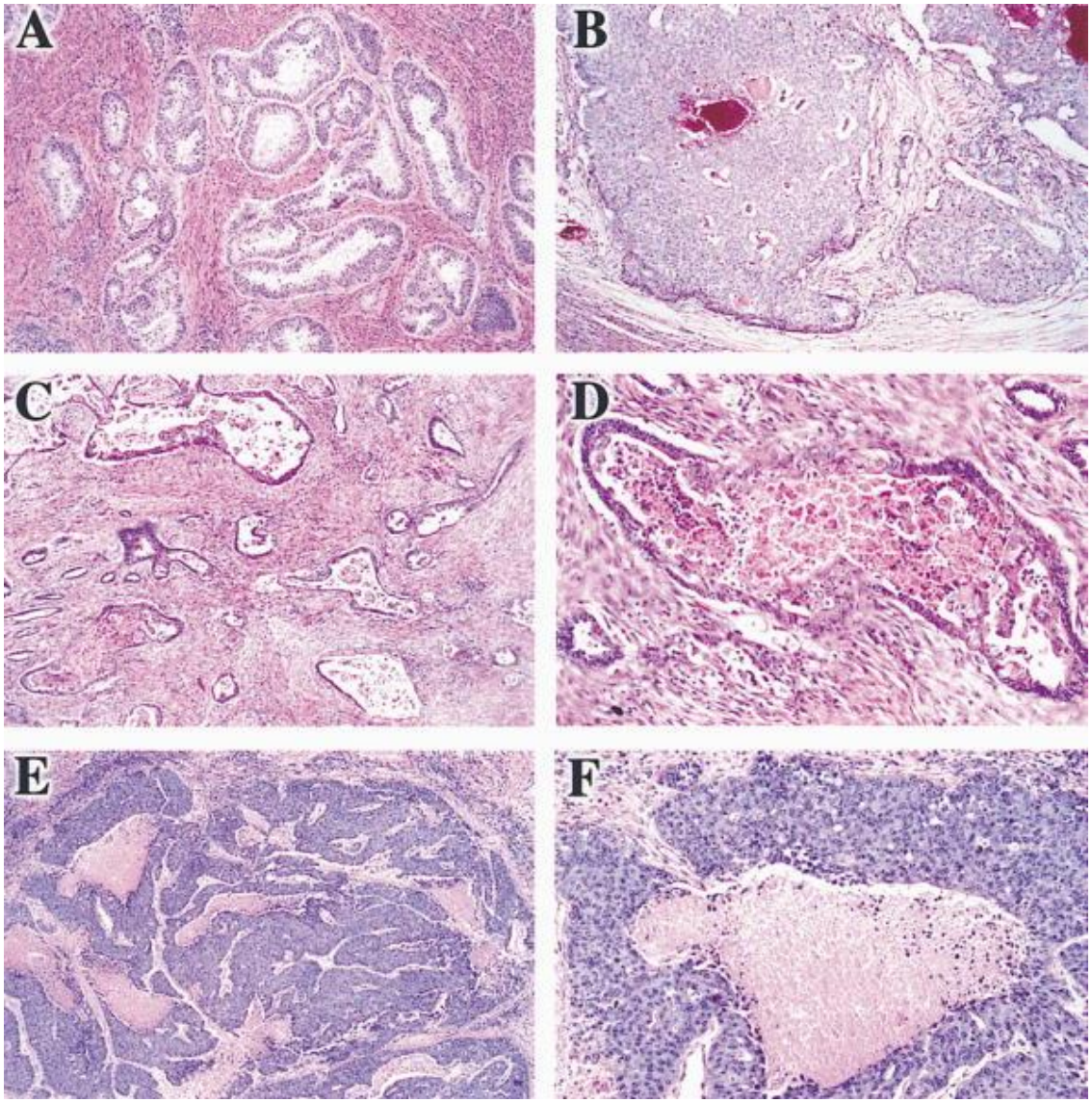
FIGURE 1. Algorithm for assessment of endometrial carcinoma. CCC indicates clear cell carcinoma; ESC, endometrial serous carcinoma; UEC, undifferentiated endometrial carcinoma.

Conlon AJSP 2014

Grading in curettage versus hysterectomy

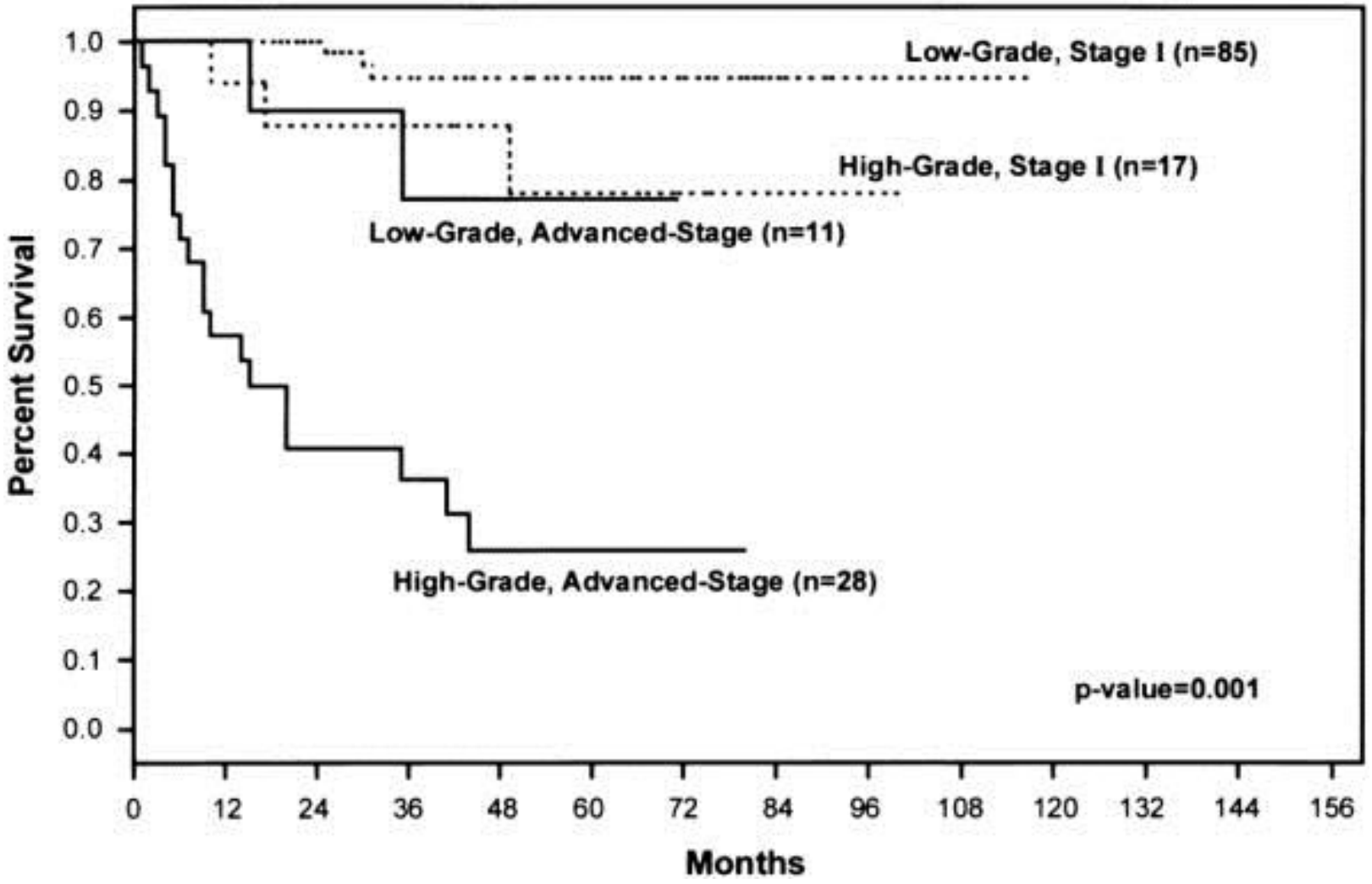
- Agreement in 65%
- Downgrading in hysterectomy more frequent than upgrading
- Heterogeneity of tumors or interpretation by pathologist responsible?

An alternative approach: A combined binary grading system



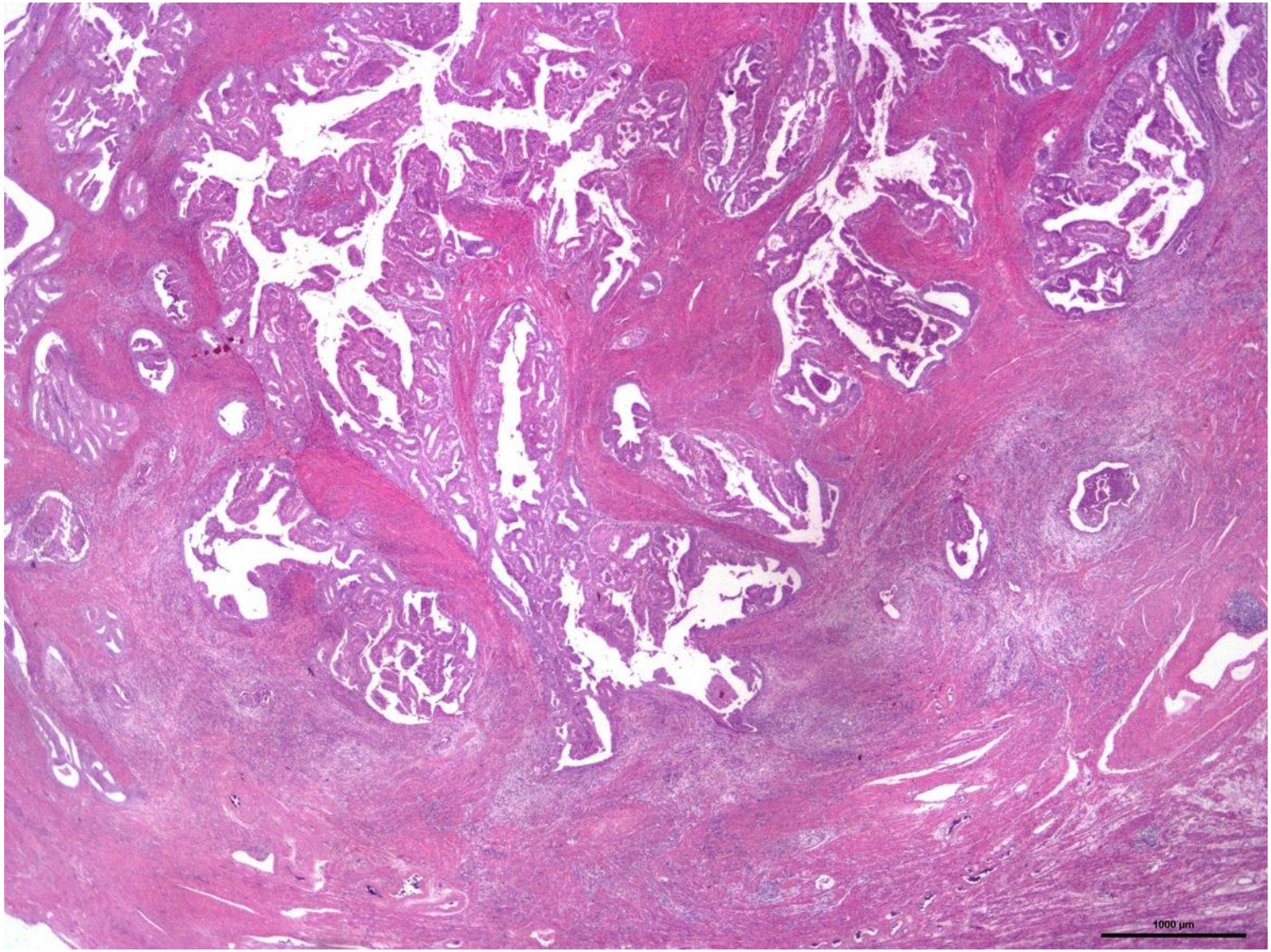
Lax et al., AJSP 2000

Binary Grading System

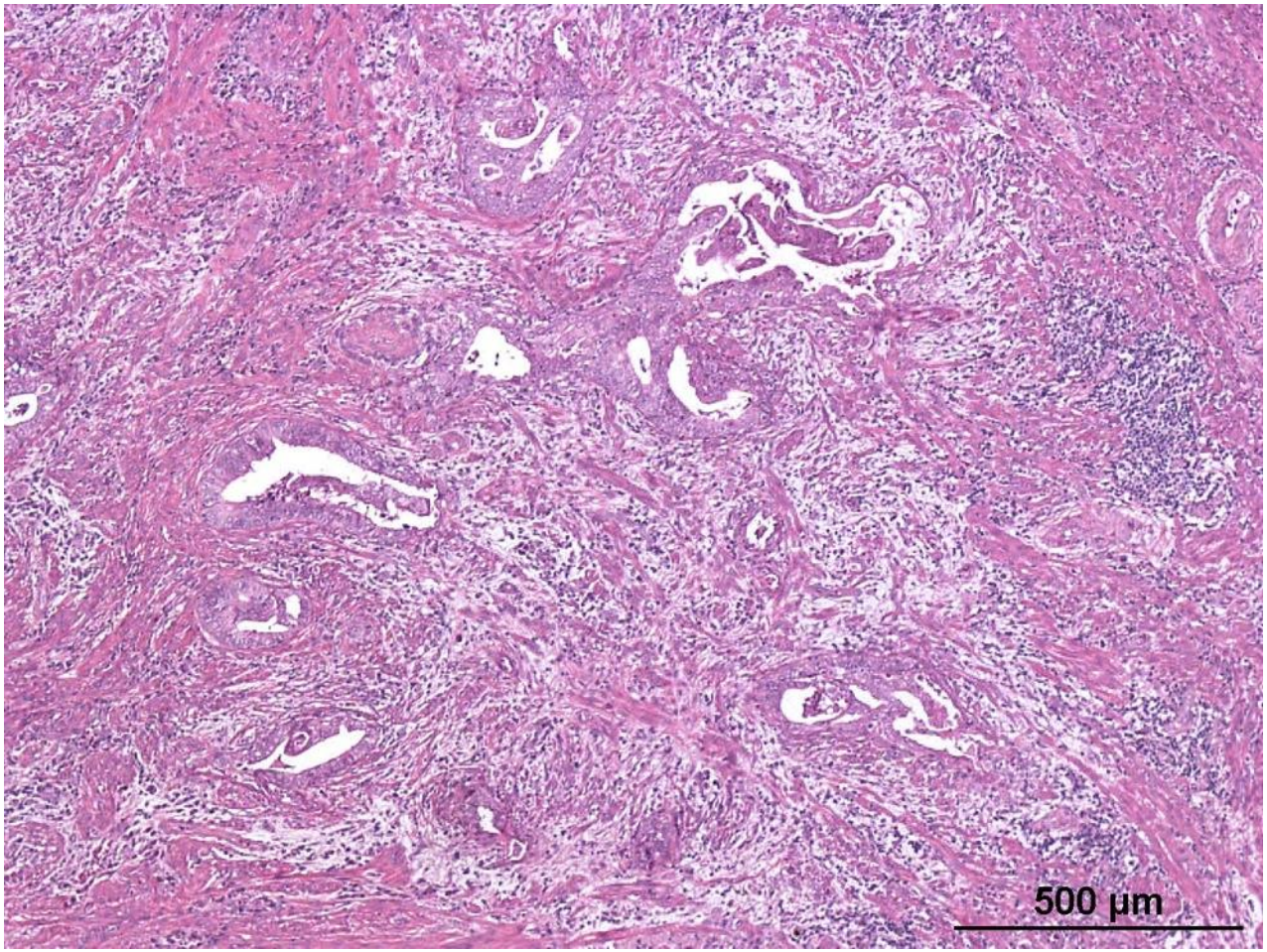


Lax et al., AJSP 2000

Infiltrative growth of well differentiated endometrioid carcinoma

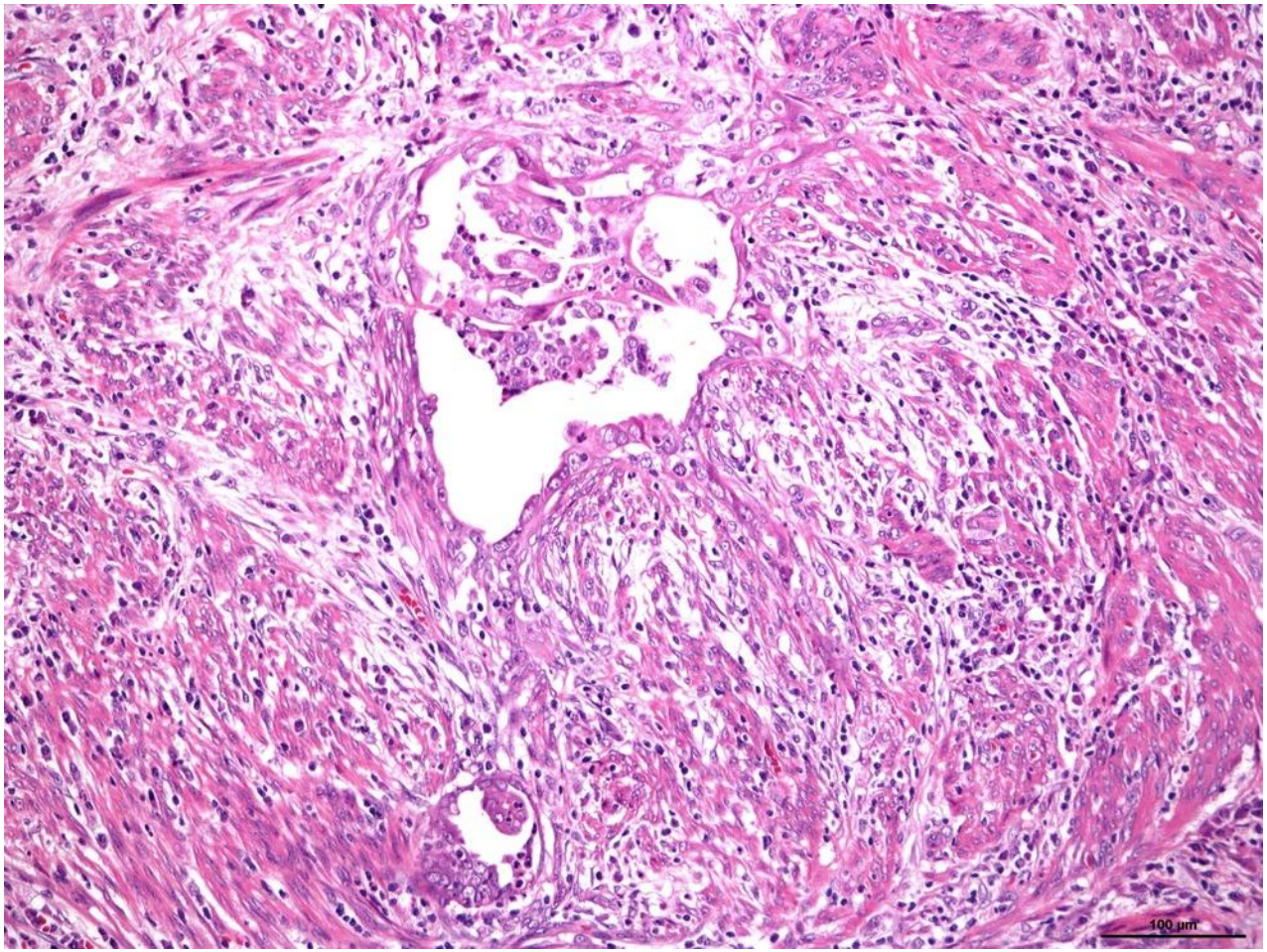


Fibromyxoid changes of the stroma



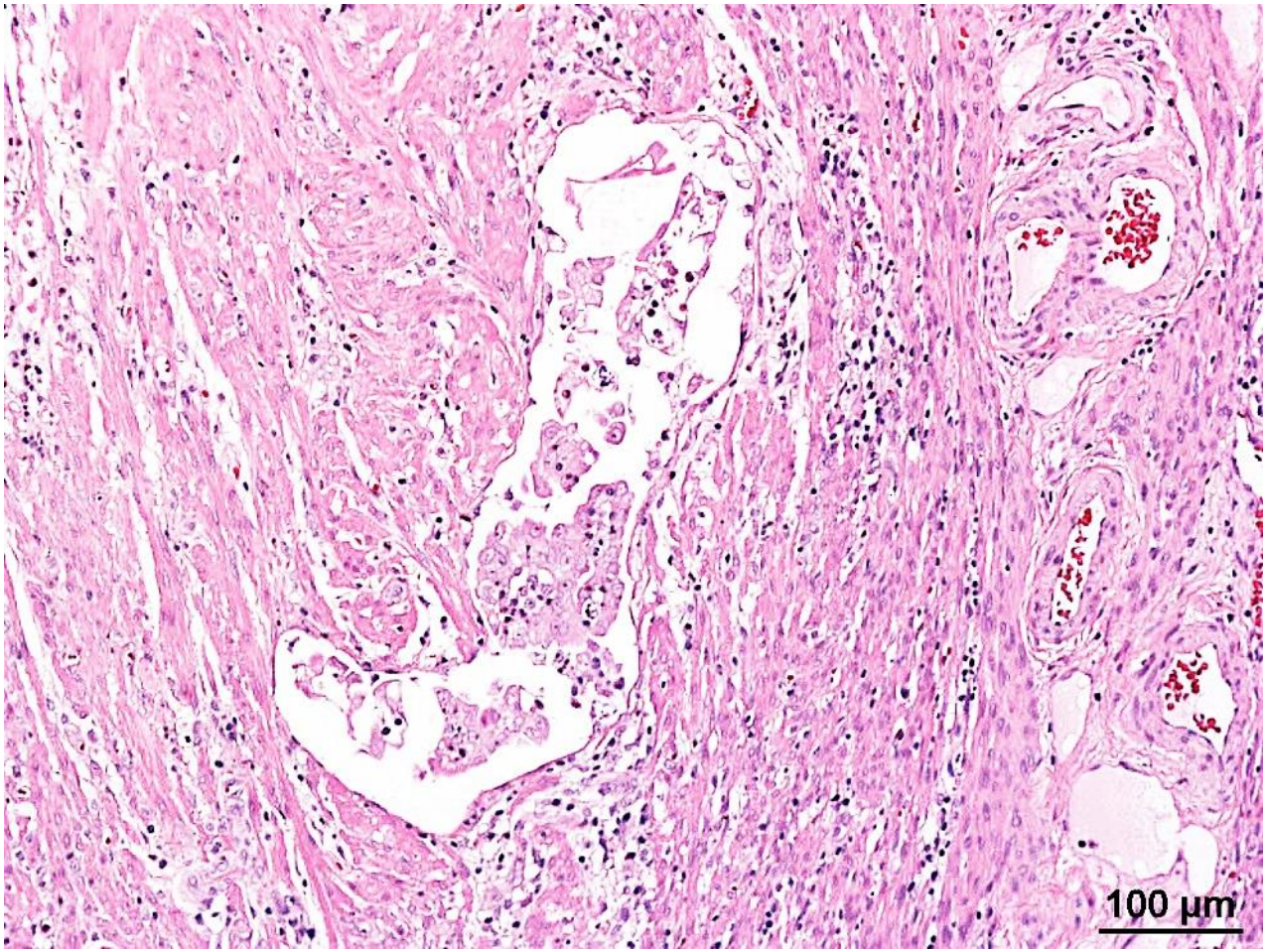
Murray, Young and Scully, ISGP 2003

MELF: microcystic, elongated, fragmented glands



Murray, Young and Scully, ISGP 2003

MELF is associated with LVSI



Murray, Young and Scully, ISGP 2003

The renaissance of growth pattern

Am J Surg Pathol. 2013 November ; 37(11): 1728–1736. doi:10.1097/PAS.0b013e318299f2ab.

The Pattern of Myometrial Invasion As a Predictor of Lymph Node Metastasis or Extrauterine Disease in Low Grade Endometrial Carcinoma

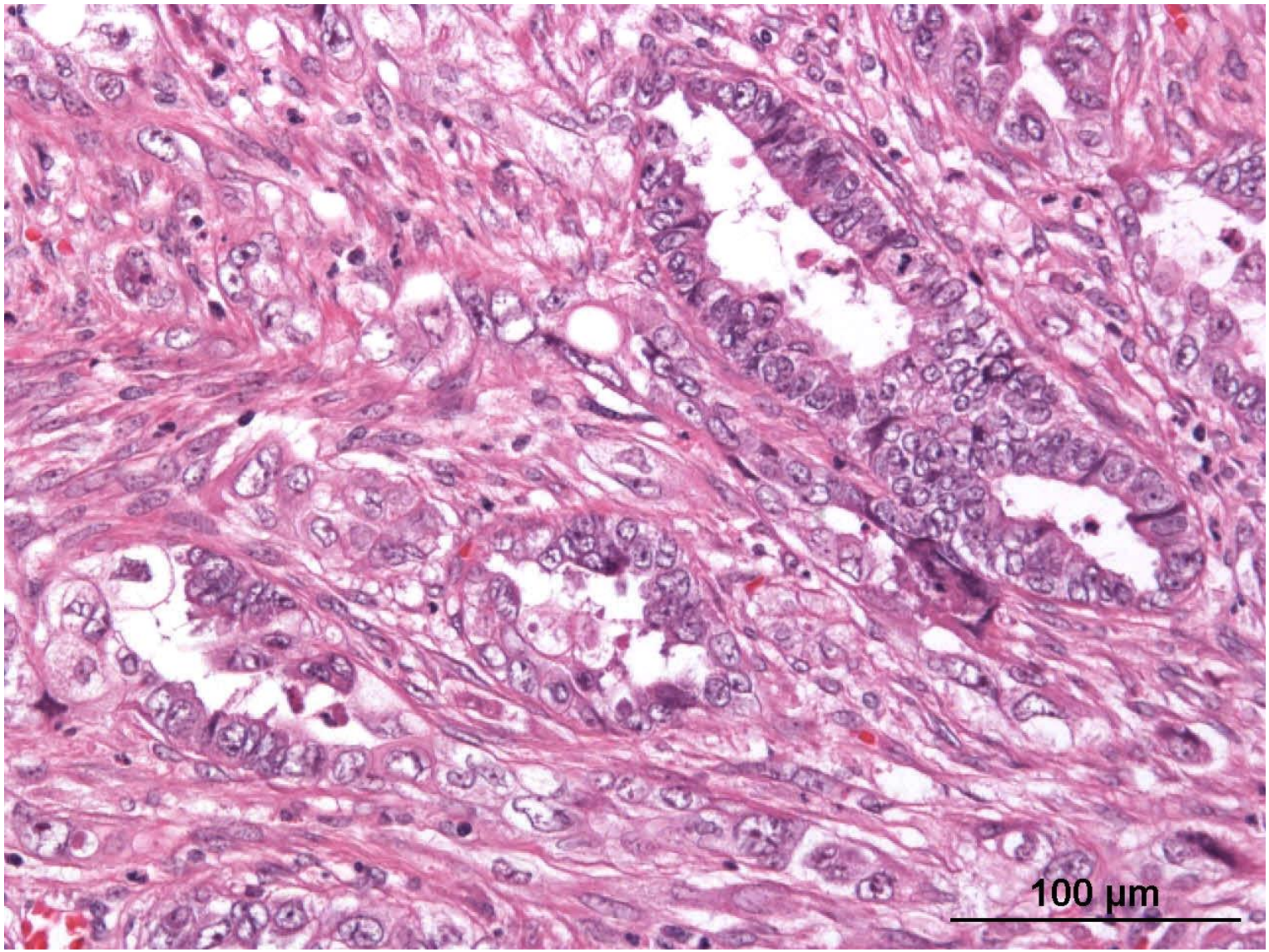
Elizabeth Euscher[1], Patricia Fox[1], Roland Bassett[1], Hayma Al-Ghawi[1], Rouba Ali-Fehmi[2], Denise Barbuto[3], Bojana Djordjevic[4], Elizabeth Frauenhoffer[5], Insun Kim[6], Sun Rang Hong[7], Delia Montiel[8], Elizabeth Moschiano[3], Andres Roma[9], Elvio Silva[1,3], and Anais Malpica[1]

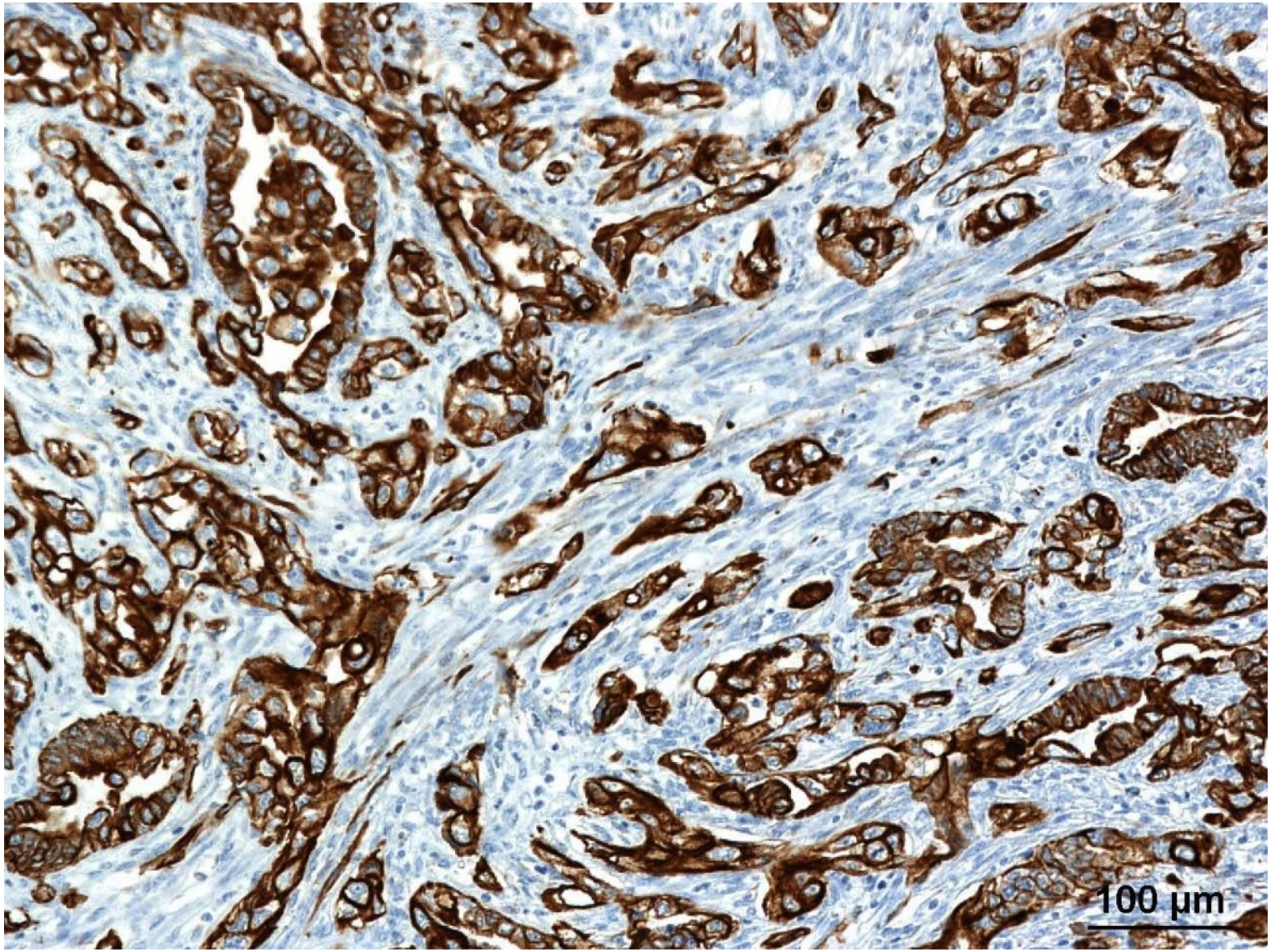
- Infiltrative, particularly, single cell pattern and lymph vascular space involvement as strong predictors of lymph node metastases

Multivariate Logistic Regression Results Modeling Lymph Node Metastases or Extrauterine Disease

Variable	Odds Ratio (95% CI)	p-value
Tumor (per cm)	1.10 (0.97 – 1.24)	0.1505
Lower uterine segment involvement	1.92 (0.96 – 3.87)	0.067
Cervical stromal involvement	3.15 (1.12 – 8.35)	0.0211
% Solid component (continuous, per 1%)	0.99 (0.97 – 1.02)	0.6704
%Myometrial invasion (per 10%)	1.15 (1.02 – 1.30)	0.0280
MELF pattern invasion present	1.34 (0.64 – 2.82)	0.4422
Single cell invasion present	3.46 (1.56 – 7.67)	0.0022
Lymphovascular invasion	4.92 (2.37 – 10.19)	<.0001

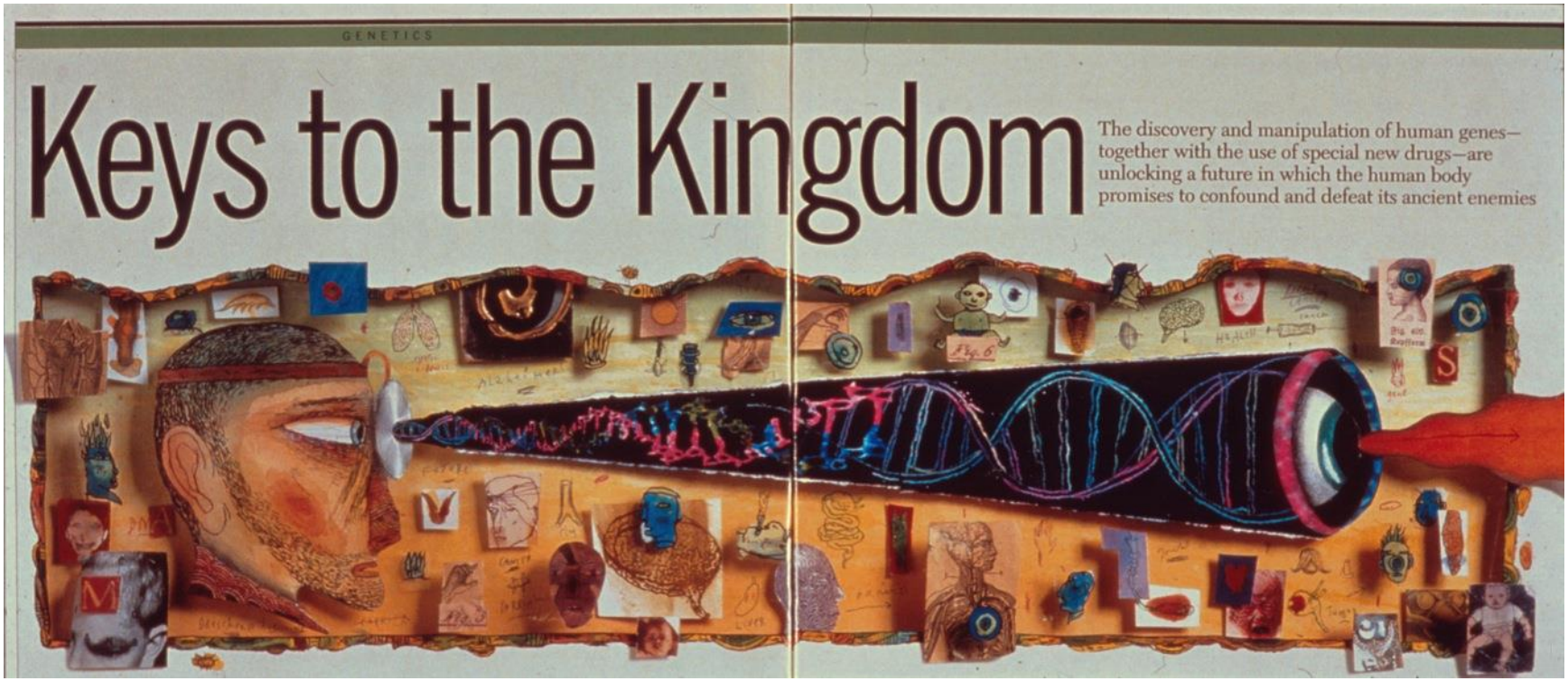
Euscher et al., AJSP 2013


100 µm



CK

The Molecular Microscope: Typing and grading being replaced?



Somatic copy number alterations

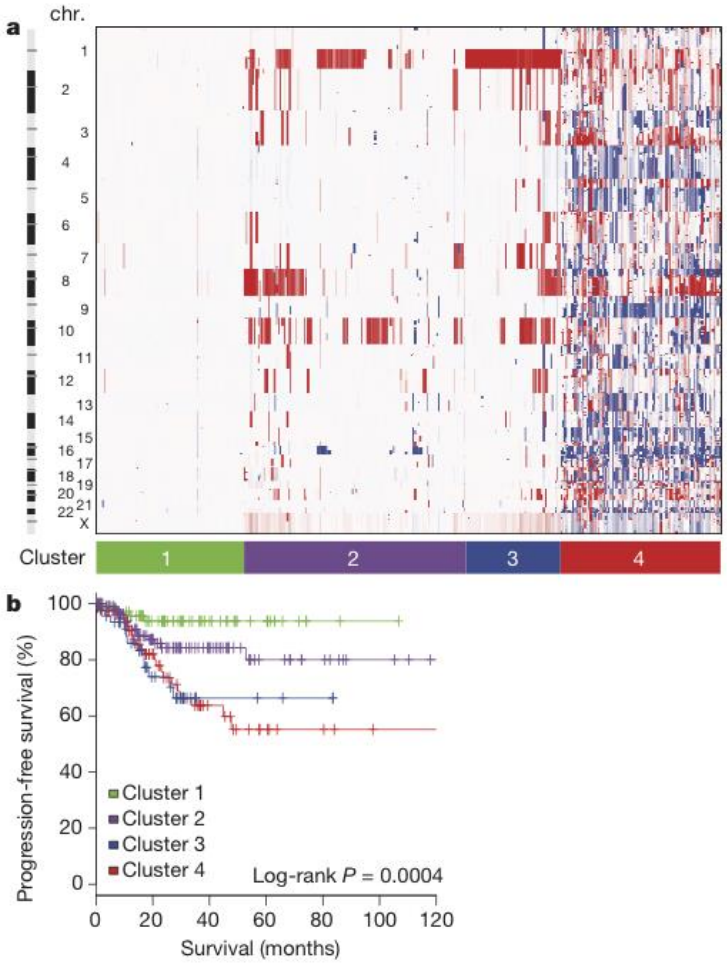
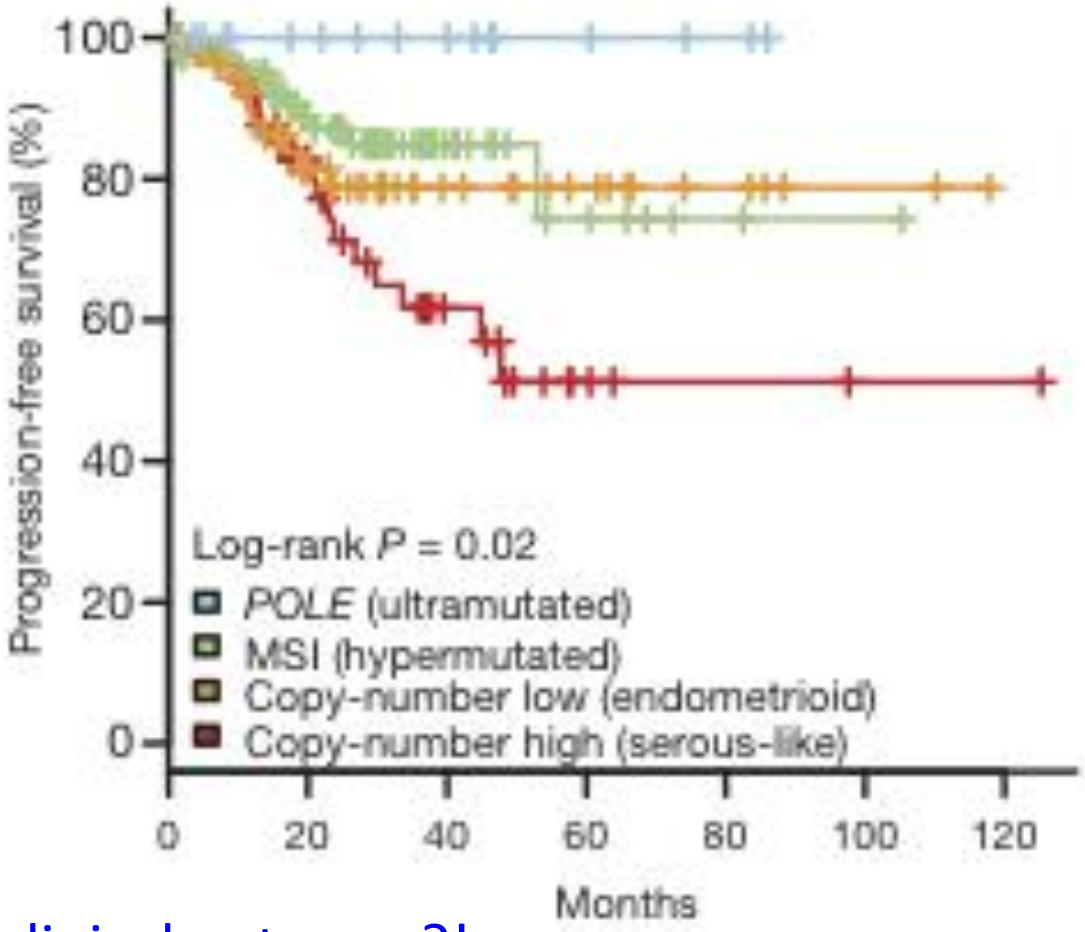


Figure 1 | SCNAs in endometrial carcinomas. **a**, Tumours were hierarchically clustered into four groups based on SCNAs. The heat map shows SCNAs in each tumour (horizontal axis) plotted by chromosomal location (vertical axis). Chr., chromosome. **b**, Kaplan–Meier curves of progression-free survival for each copy-number cluster.

The TCGA Research Network, Nature 2013

Molecular Classification of endometrial carcinoma



- Impact for clinical outcome?!

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Take home message

- HE histomorphology as solid basis for typing and grading
- Immunohistochemistry assists in typing
- Growth pattern is the basis for grading
- Binary FIGO grading (</>50%)?!
- Alternative approaches seem to provide additional information
- A molecular classification may be sooner available as expected

Thank you very much for your attention!