Naveena Singh, London, UK

Typing endometrial carcinoma in biopsies



- Consultant Pathologist, Barts Health NHS Trust
- Honorary Professor, Queen Mary University of London
- Invited authorship of recent guidelines: WHO 2020; NICE guidance on screening for Lynch Syndrome in endometrial carcinoma 2020; ICCR 2020-2021; ISGyP Endocervical adenocarcinoma project 2019-2021; Joint ESMO-ESGO ovarian carcinoma 2018-2019; RCPath Datasets for endometrial and cervical carcinoma 2019-2021
- Participant in multiple collaborative research projects
- Past President BAGP (2016-2019); Past Meetings Secretary BAGP (2007-2013)
- Current co-Chair, Education Committee, ISGyP

The British Association of Gynaecological Pathologists

17th Annual Meeting

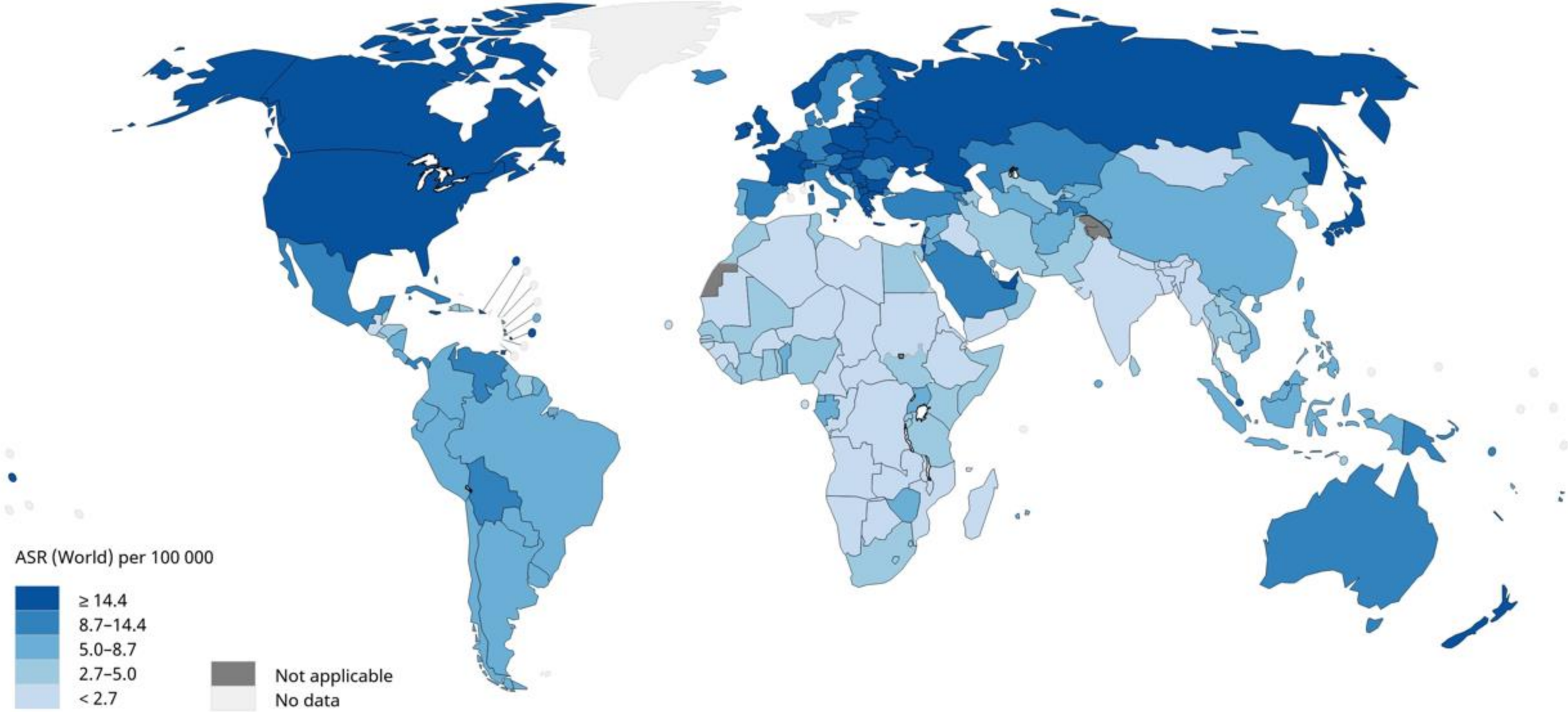
- Typing endometrial carcinoma in biopsies
- Naveena Singh
- Consultant Pathologist, Barts Health NHS Trust
- 10th June, 2021

The British Association of Gynaecological Pathologists

Speaker disclosures

I have the following disclosures: Invited member of advisory boards for Astra-Zeneca/MSD (2019); GSK-UK (2021)

Estimated age-standardized incidence rates (World) in 2018, corpus uteri, all ages

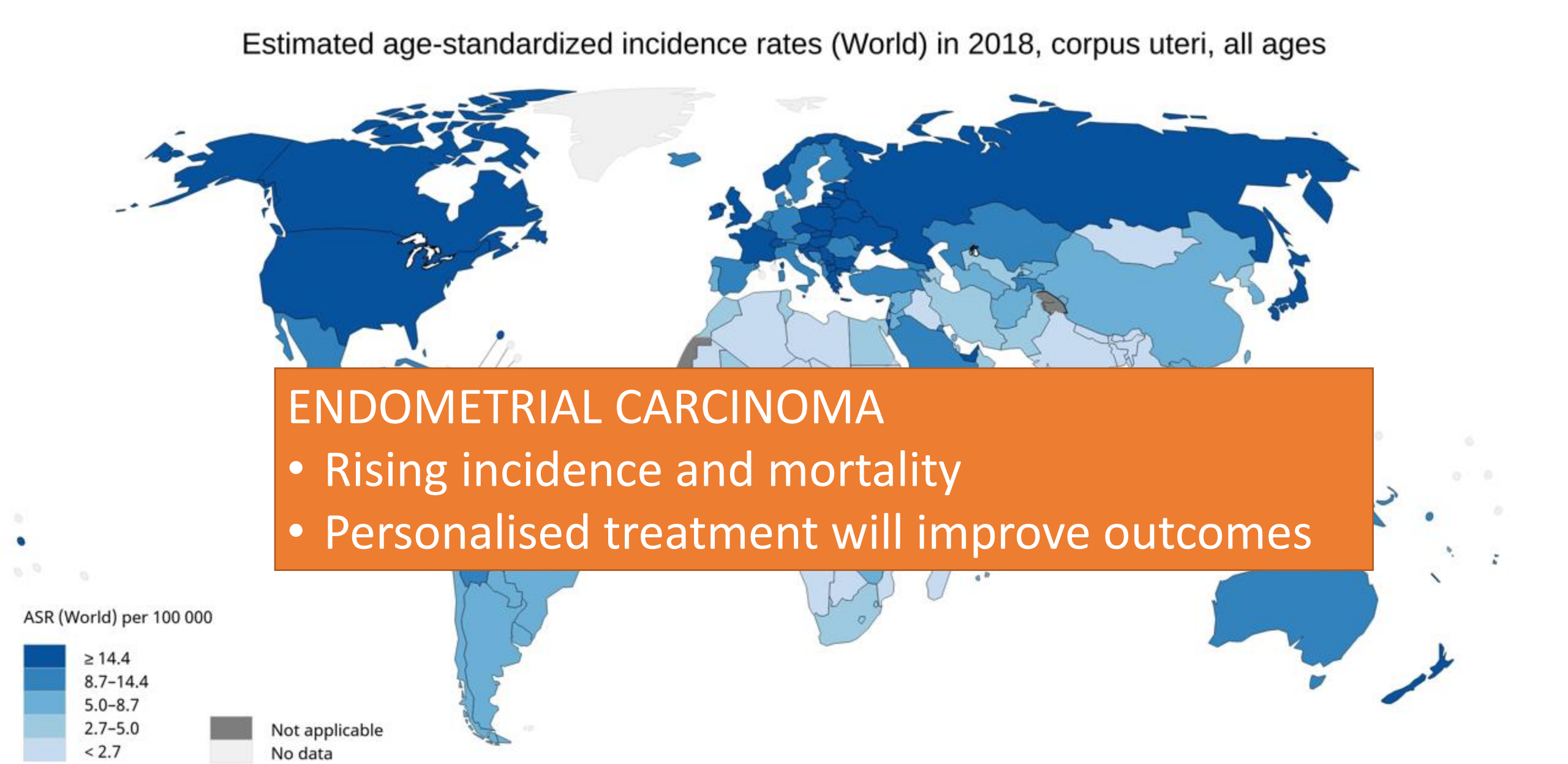


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Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

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Data source: GLOBOCAN 2018
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World Health Organization

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© International Agency for Research on Cancer 2018

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB

Treatment decisions in endometrial carcinoma:

- Surgery: location; extent including nodal procedure
- Adjuvant Rx: whether to give; what to give
- Non-surgical treatment

2020 Risk categorization:

- Endometrioid vs non-endometrioid
- If endometrioid:
  - Grade
  - Stage
  - LVSI

Concin *et al*, IJGC 2020

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Treatment decisions in endometrial carcinoma:

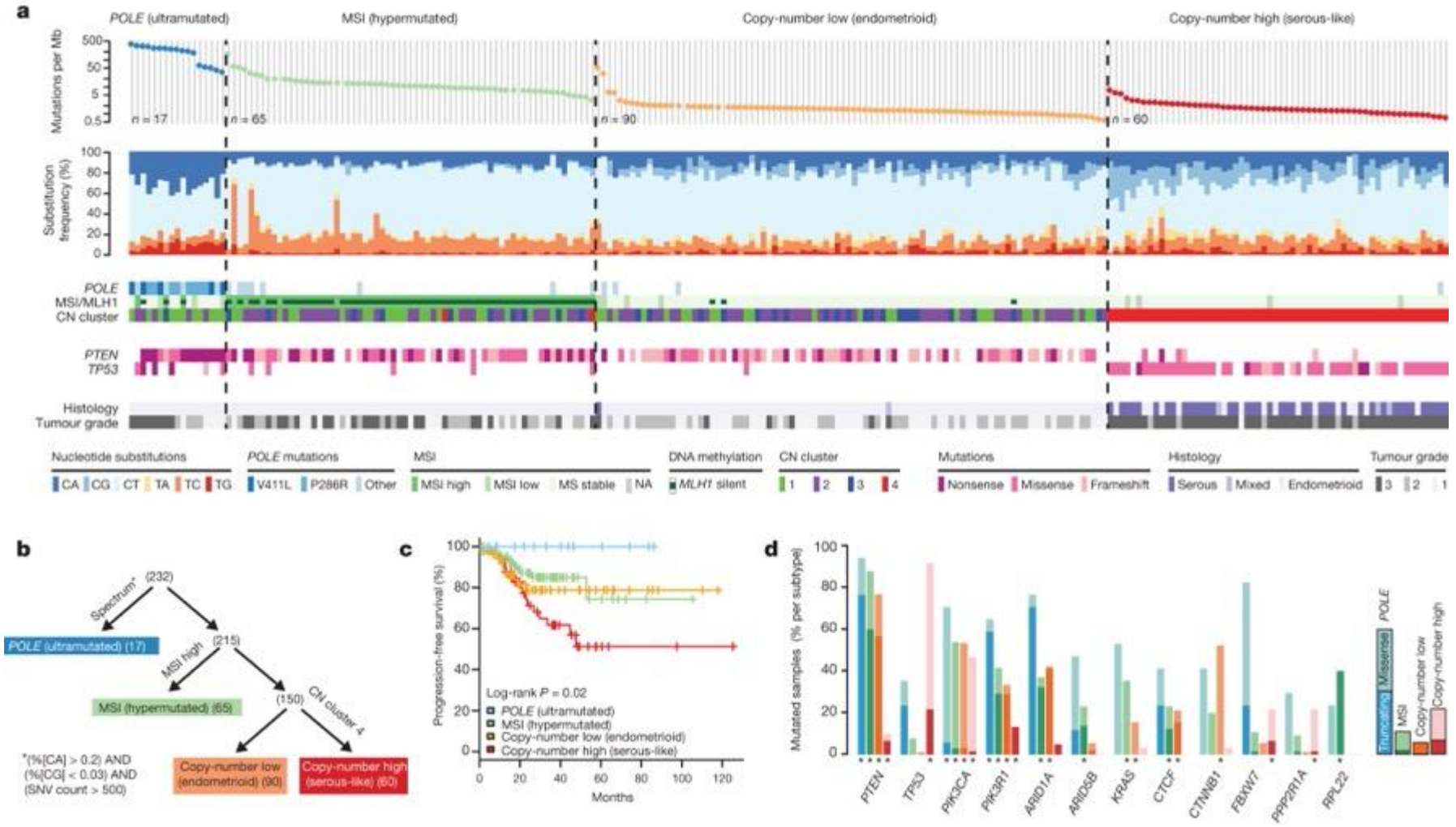
- Surgery: location; extent including nodal procedure
- Adjuvant Rx: whether to give; what to give
- Non-surgical treatment

2020 Risk categorization:

- Endometrioid vs non-endometrioid
- **Non-endometrioid** = High risk except for rare Stage IA without myoinvasion
- **Endometrioid**:
  - Grade
  - Stage
  - LVSI

Concin *et al*, IJGC 2020

Mutation spectra across endometrial carcinomas



G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

nature

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

Concin *et al*, IJGC 2020

Risk Category without and with molecular classification

	MOLECULAR CLASSIFICATION UNKNOWN						
MOLECULAR CLASS KNOWN		Low	Intermediate	High-intermediate	High	Advanced/ metastatic	TOTAL
	Low	**346 (99.4)**	**10 (8.0)**	**21 (12.9)**	**8 (4.3)**	0 (0)	385 (45.7)
	Intermediate	0 (0)	**110 (88.0)**	0 (0)	0 (0)	0 (0)	110 (13.0)
	High-intermediate	0 (0)	0 (0)	**122 (75.3)**	0 (0)	0 (0)	122 (14.5)
	High	**2 (0.6)**	**5 (4.0)**	**19 (11.7)**	**180 (95.7)**	0 (0)	206 (24.4)
	Advanced/ metastatic	0 (0)	0 (0)	0 (0)	0 (0)	**20 (100)**	20 (2.4)
	TOTAL	348 (41.3)	125 (14.8)	162 (19.2)	188 (22.3)	20 (2.4)	**843 (100)**

65/843 (7.7%) of cases move to lower (4.6%) or higher (3.3%) risk category. *Talhouk et al, manuscript in preparation.*

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
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High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

2020 risk stratification, molecular classification known:

- MMRd/NSMP:
  - ***Histoype***
  - Grade
  - Stage
  - LVSI
- P53 abn:
  - High-risk except for rare Stage IA without myoinvasion
- POLEmut stage I/II
  - Low-risk

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WHO 2020: Classification of EC

- Endometrioid
  - *POLE*-ultramutated
  - Mismatch repair-deficient
  - p53-mutant
  - No specific molecular profile
- Serous
- Clear cell
- Carcinoma, undifferentiated
- Mixed cell
- Mesonephric
- Squamous cell
- Mucinous, intestinal type
- Mesonephric-like
- Carcinosarcoma

Importance of Histotype and Grade in 2021

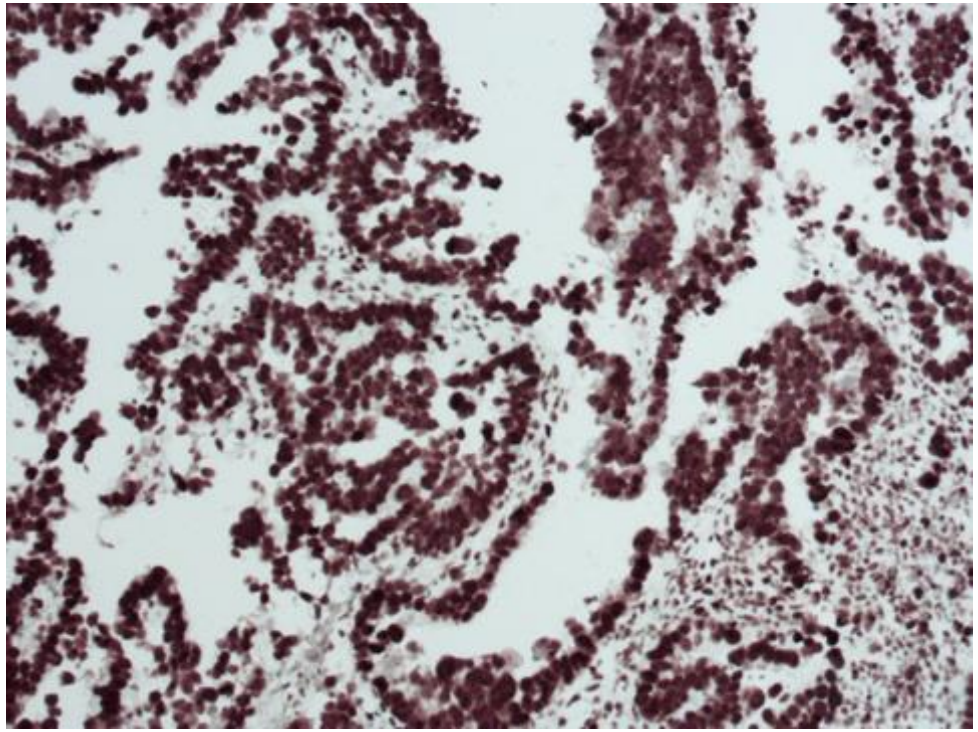
- PARAMOUNT! – Determines all treatment decisions
- BINARY: Endometrioid or non-endometrioid
- EEC and ESC together account for the vast majority of cases

Importance of Histotype and Grade in 2021

- Major impact of molecular classification is on endometrioid ca
- Effect of molecular classification on rarer (high-risk) histotypes is unknown)
- Molecular classification will have a greater impact in the future for ***personalised*** Rx:
  - whether to give adjuvant Rx
  - what to give
  - Implications for both conventional and targeted

Molecular Classification of EC in 2021

- Molecular classification can be delivered economically within NHS:
  - **MMR IHC on ALL EC regardless of histotype (NICE, 2020)**
    - **Lynch Syndrome screening**
    - **Molecular classification; prognosis**
    - **Immune checkpoint inhibitor Rx**
    - **Disease classification (endometrioid, not 'serous')**
  - P53 on all EC (or low threshold)
  - POLE on selected cases *where this will affect treatment*



How Good is Biopsy Diagnosis?

- Benefit: Good fixation; pre-treatment information

- Disadvantage: Sampling
  - Sensitivity is c 90% for diagnosis of cancer
  - Discordance in grade
  - Discordance in histotype

- Biopsy diagnosis of histotype can be as accurate as on hysterectomy; good awareness of the range of entities; low threshold for unusual variants/non-endometrial primary

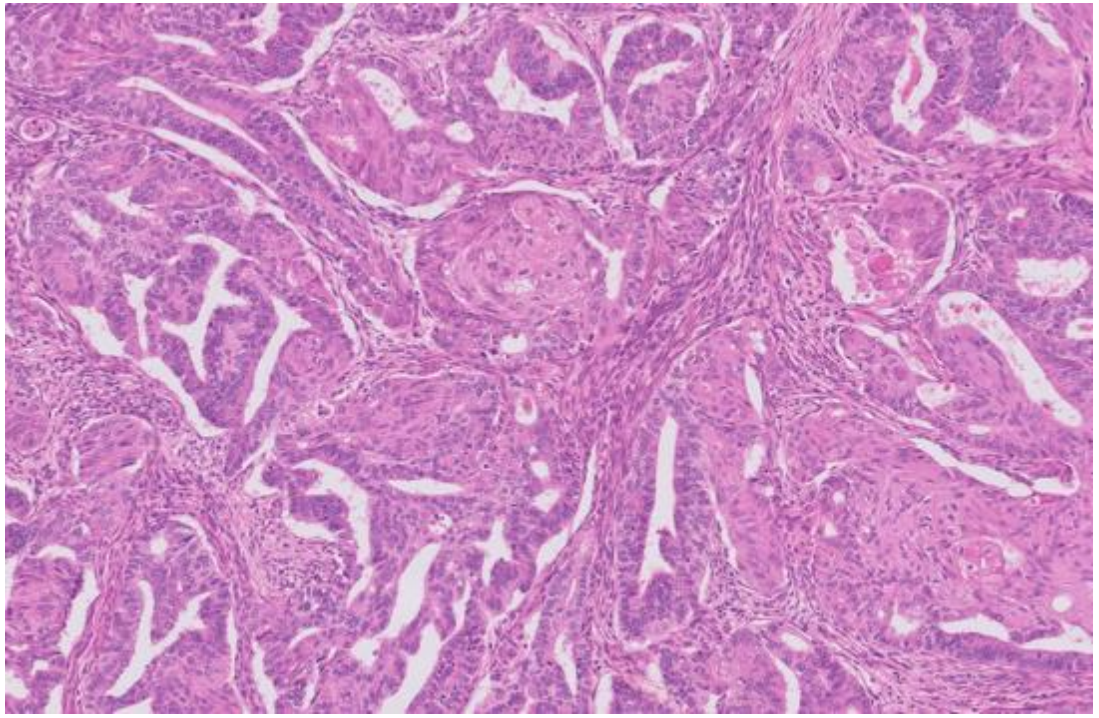
Immunohistochemistry in diagnosis of EC (ESGO 2020)

- Required ancillary techniques (IHC for p53, MSH-6 and PMS-2) complemented with MLH-1 and MSH-2, MLH-1 promoter methylation analysis in cases of MLH-1/PMS-2 decrease expression)

- Additional immunohistochemical markers may be important for pathologic diagnosis (PTEN, p16, ER, Napsin A, Racemase, Pax8, E-Cadherin) or prognosis (L1CAM).

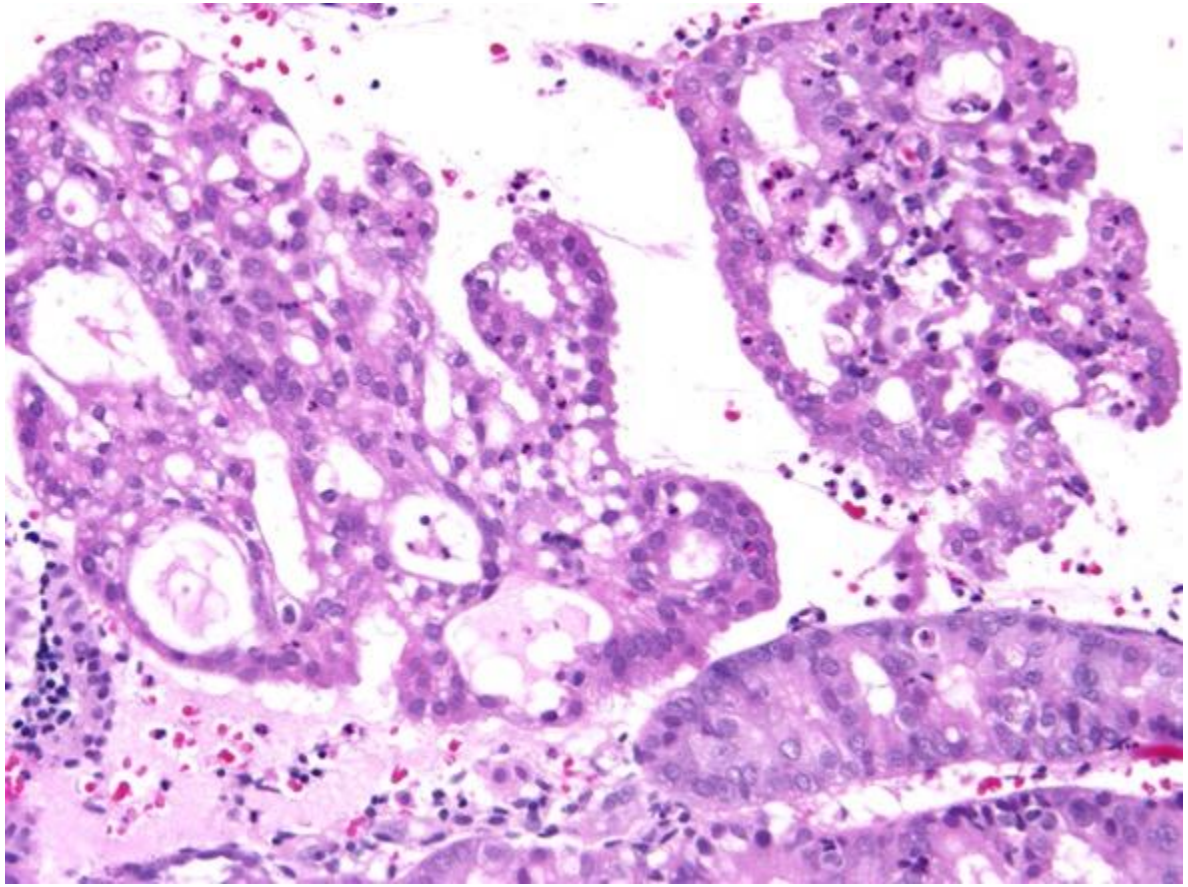
- Our approach: MMR x 2, p53 and ER on all cases

Endometrioid carcinoma



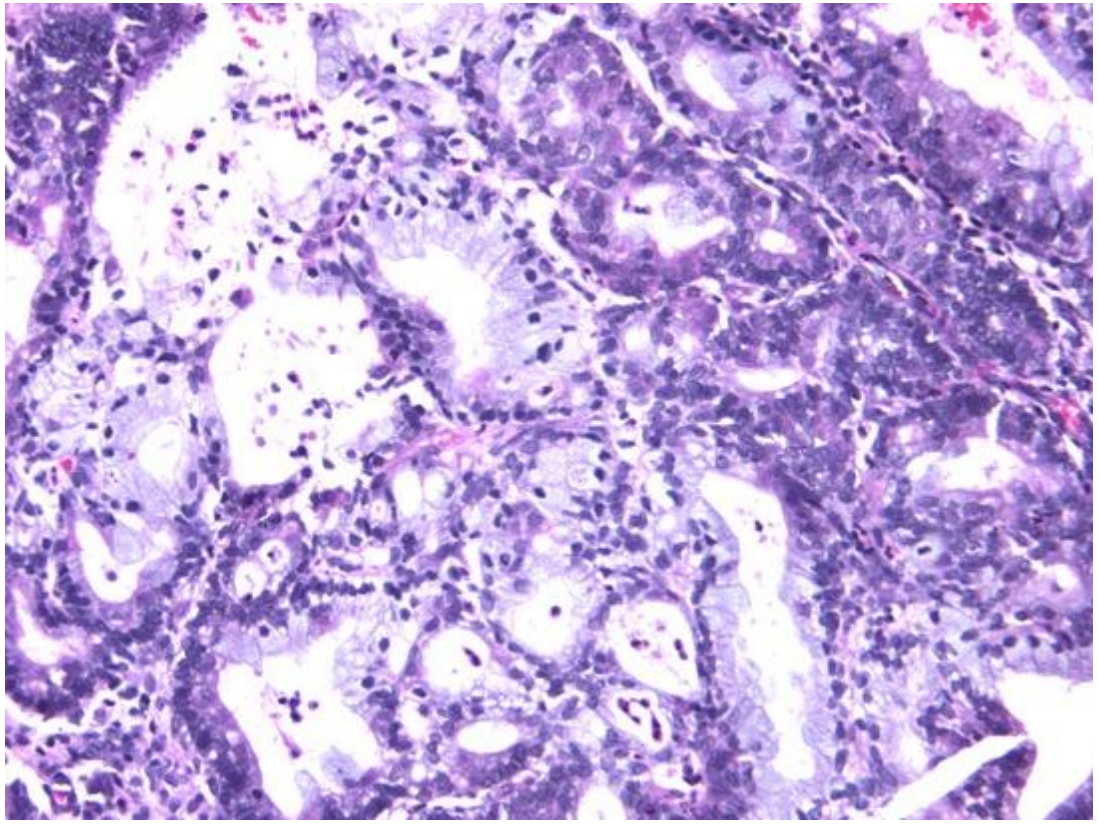
- Carcinoma displaying varying proportions of glandular, papillary and solid architecture, with the neoplastic cells showing endometrioid differentiation

Endometrioid ca with microglandular architecture



- Beware of fragments appearing as microglandular hyperplasia of cervical origin
- Deceptively bland
- No IHC really helps

Endometrioid ca with mucinous differentiation



- Mucinous pattern may be present to varying degrees and may predominate
- Not identified as a prognostic variant IF ENDOMETRIOID
- **Exclude Intestinal variant (NEW)**
- **Consider cervical (or GIT) origin**

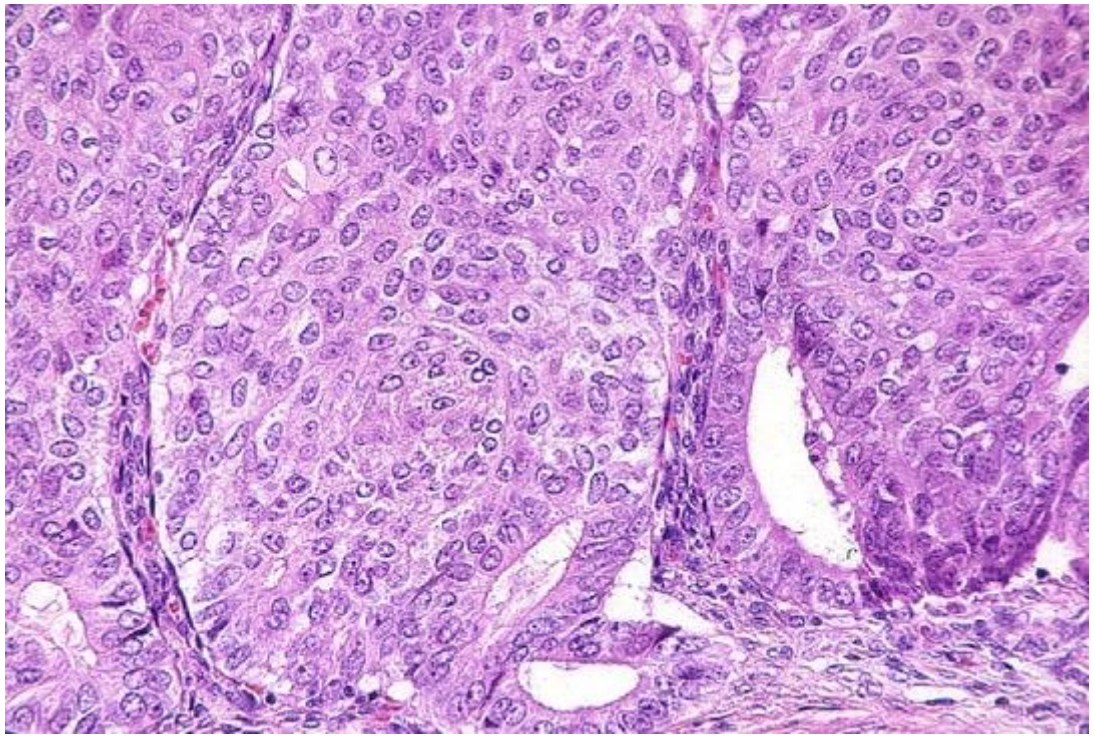
Problems in diagnosis of endometrioid ca: Grade

FIGO grading:

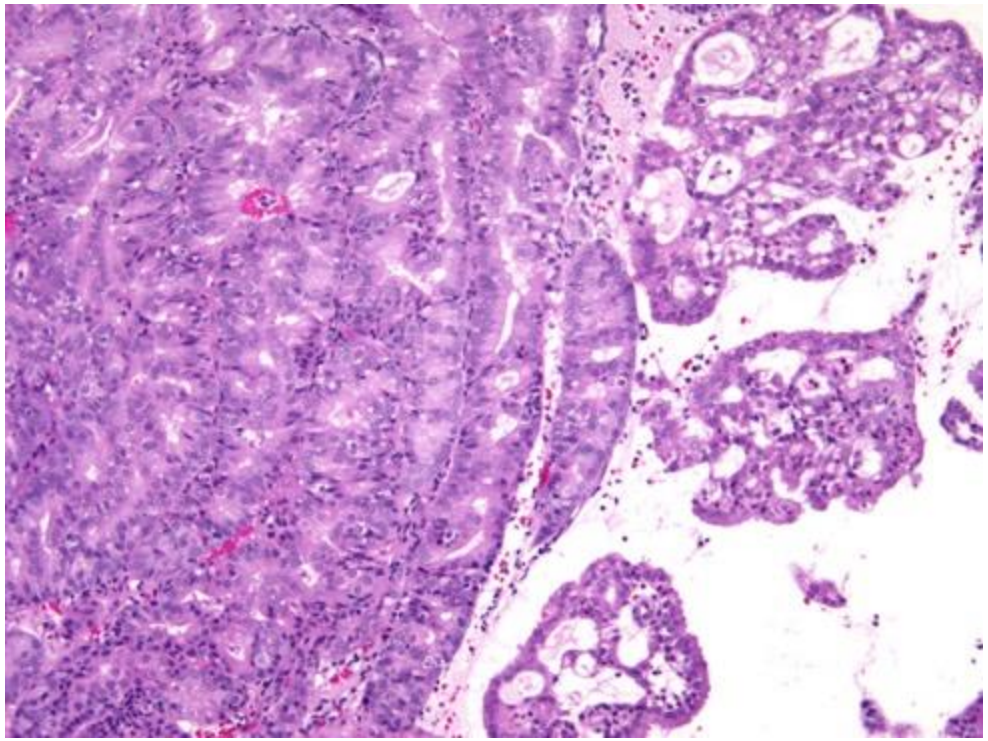
- Grade 1, 2 and 3 tumours respectively exhibit </=5%, 6-50% and >50% solid architecture

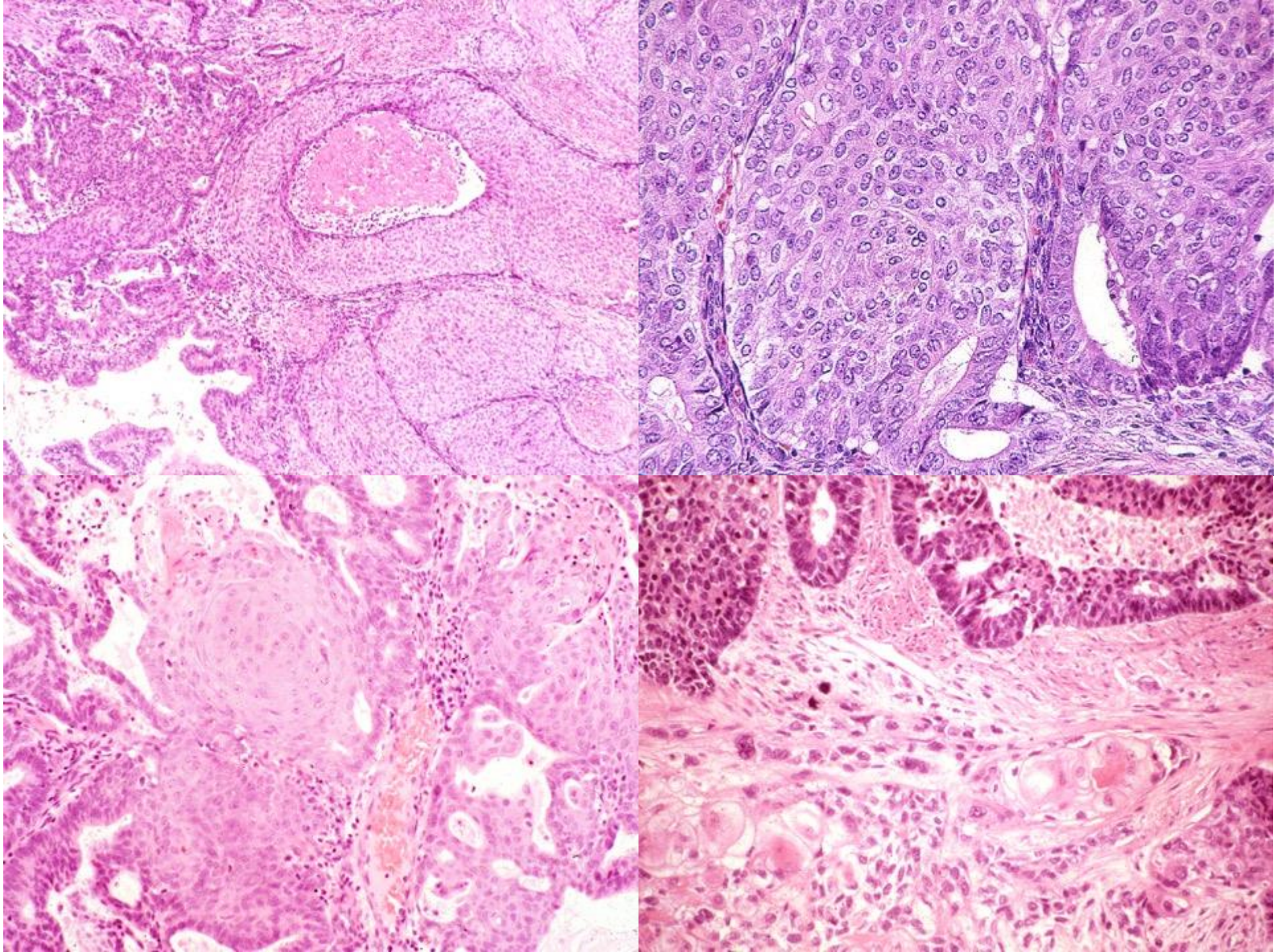
Problems in diagnosis of endometrioid ca: Grade

Exclude squamous differentiation



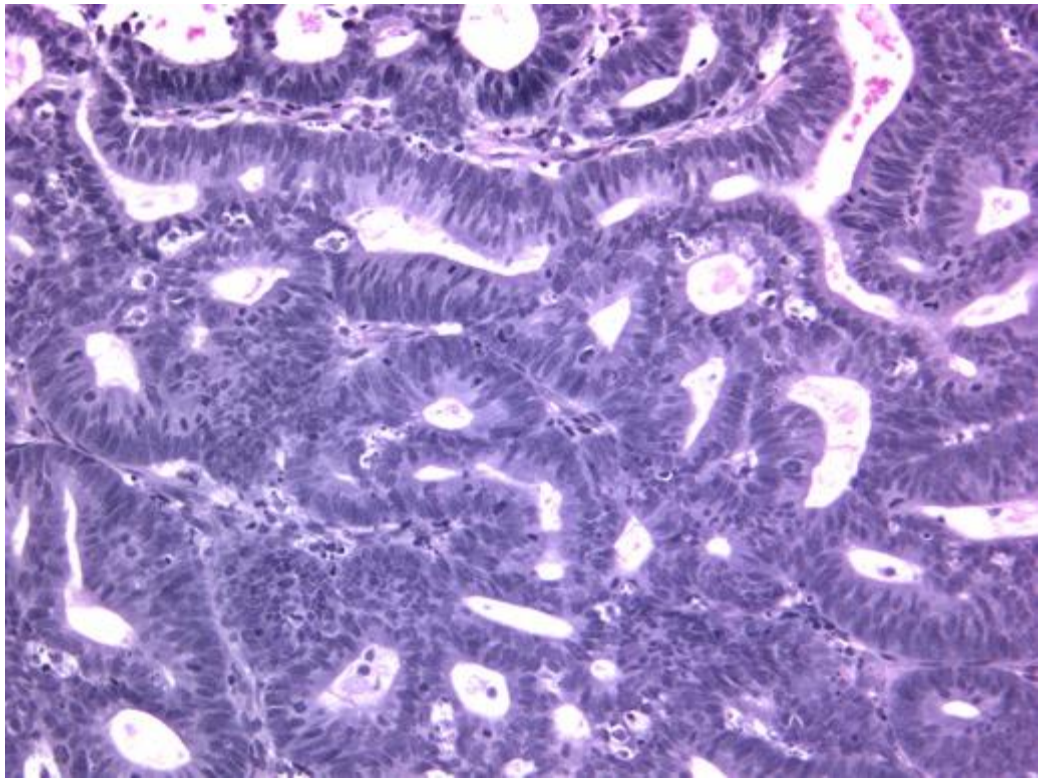
Confluent microacinar architecture qualifies as solid



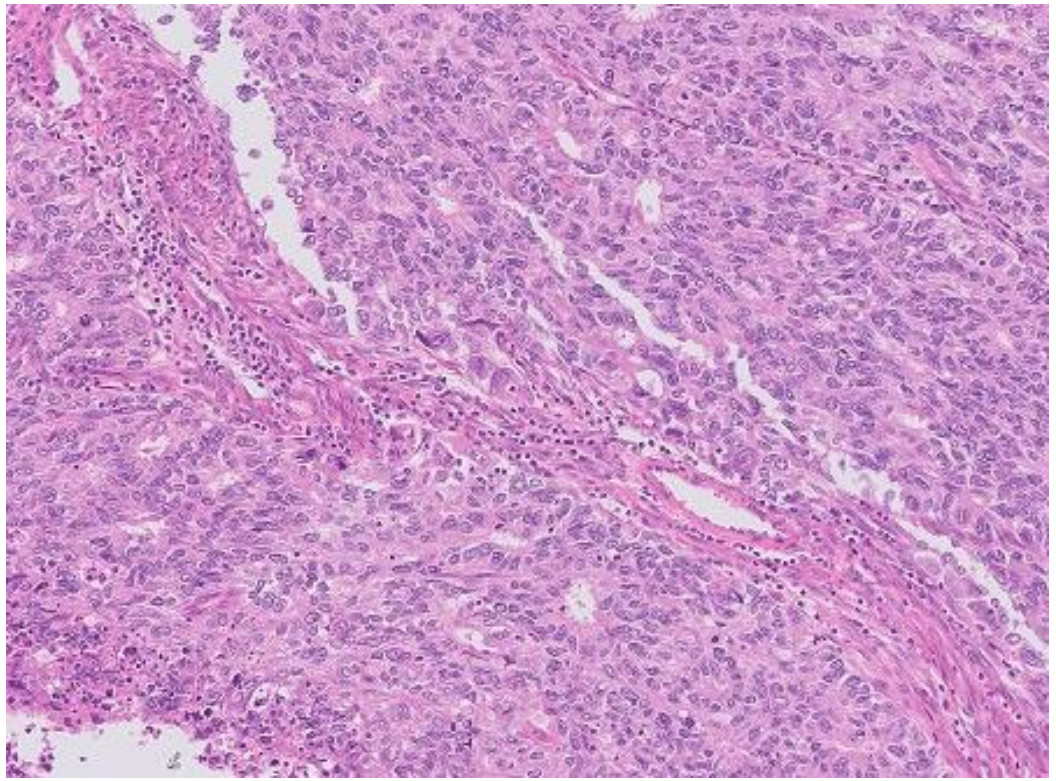


Problems in diagnosis of endometrioid ca: Grade

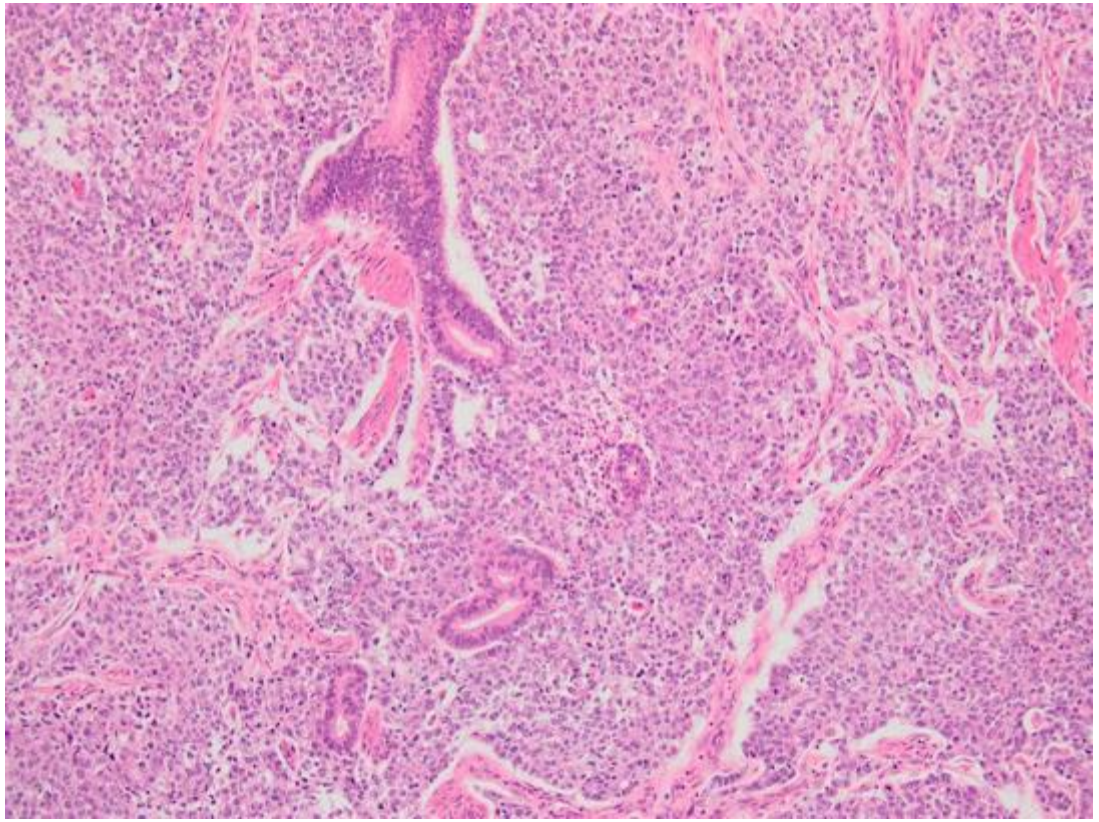
Glandular architecture



Confluent microacinar architecture

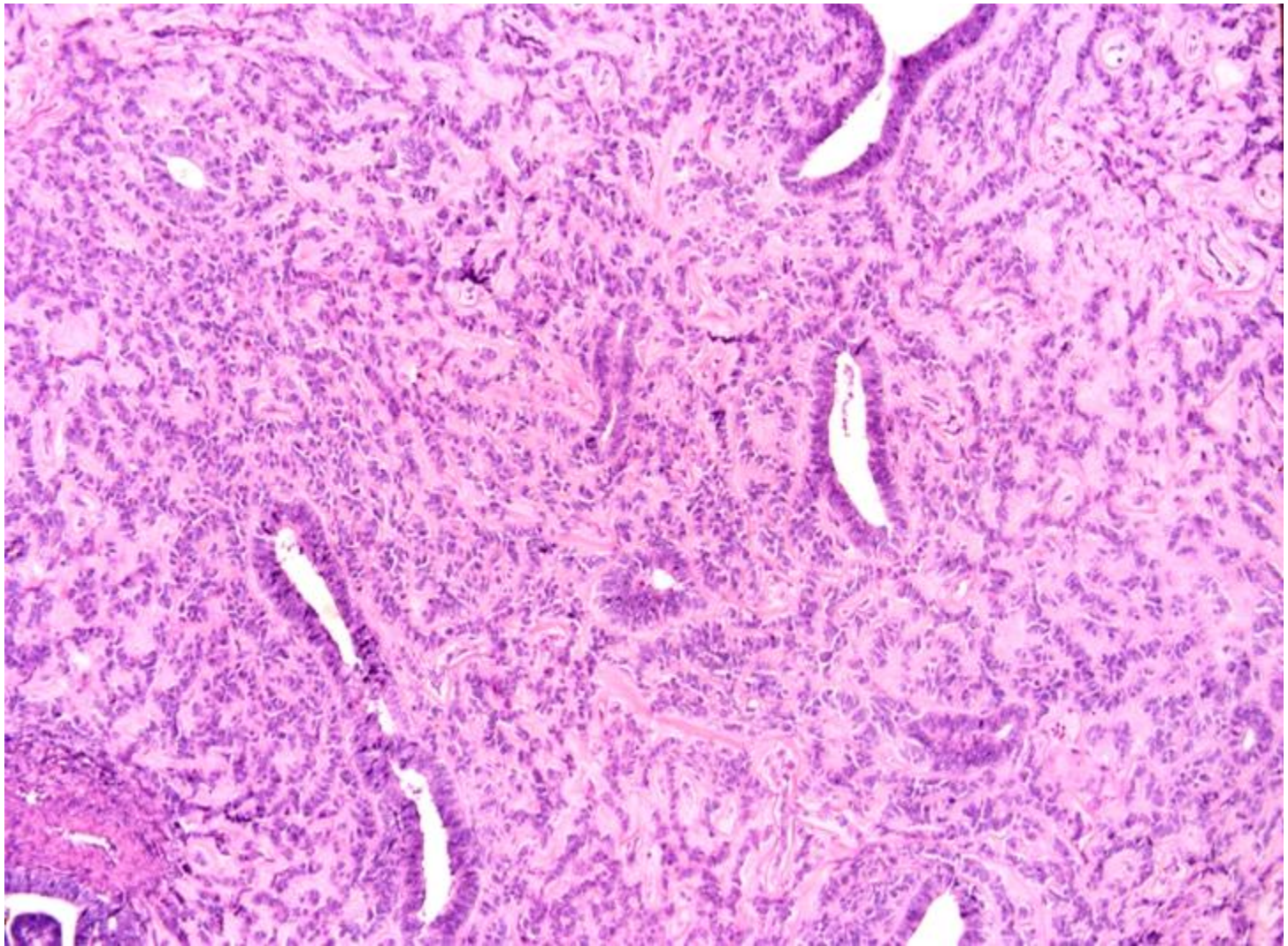


Problems in diagnosis of endometrioid ca: Solid pattern vs undifferentiated component

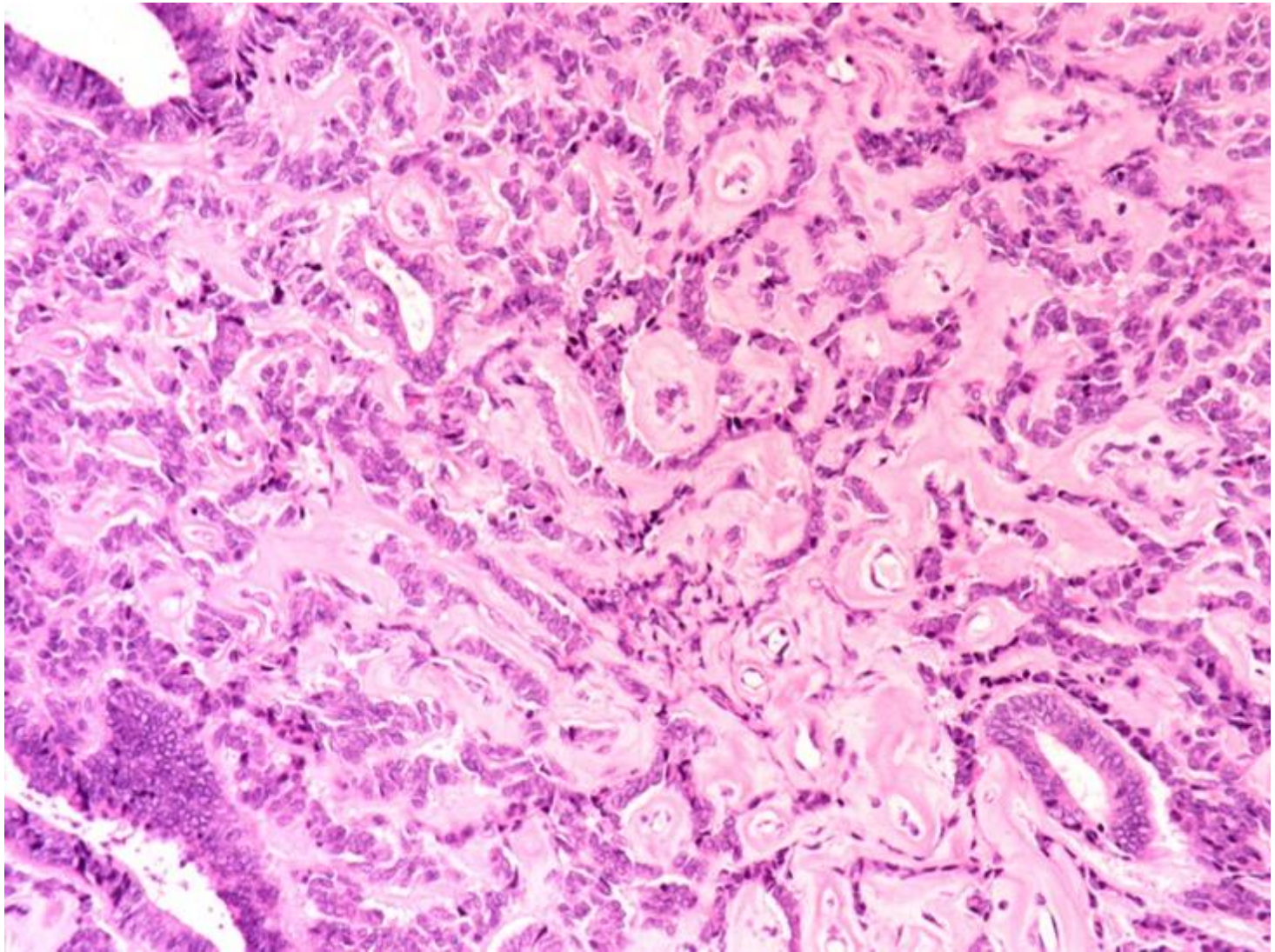


- Dedifferentiated ca
  - Solid component may be misleadingly monotonous/bland-appearing
  - Have a low threshold for this possibility

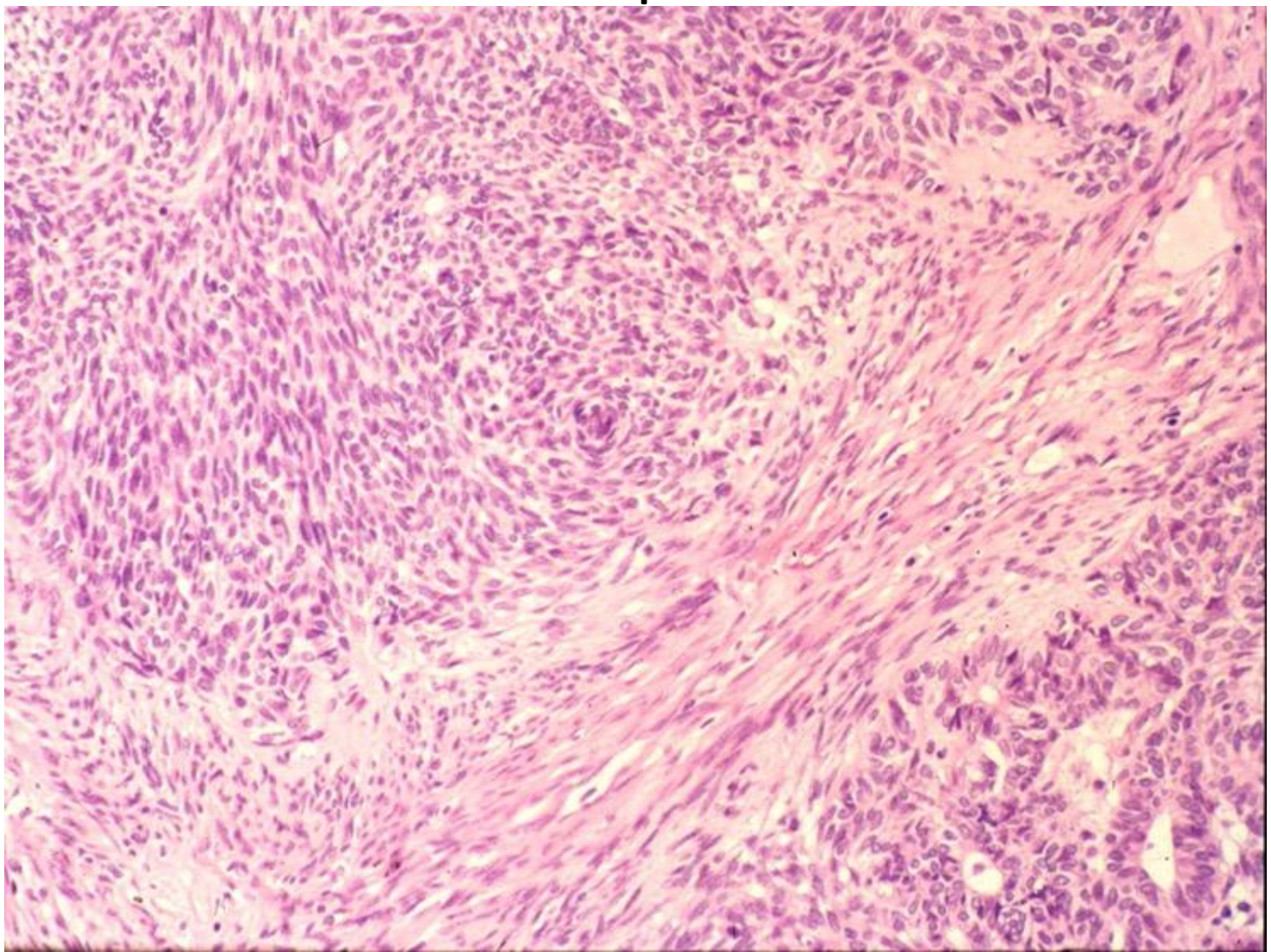
Problems in diagnosis of endometrioid ca: Corded and hyalinized endometrioid ca



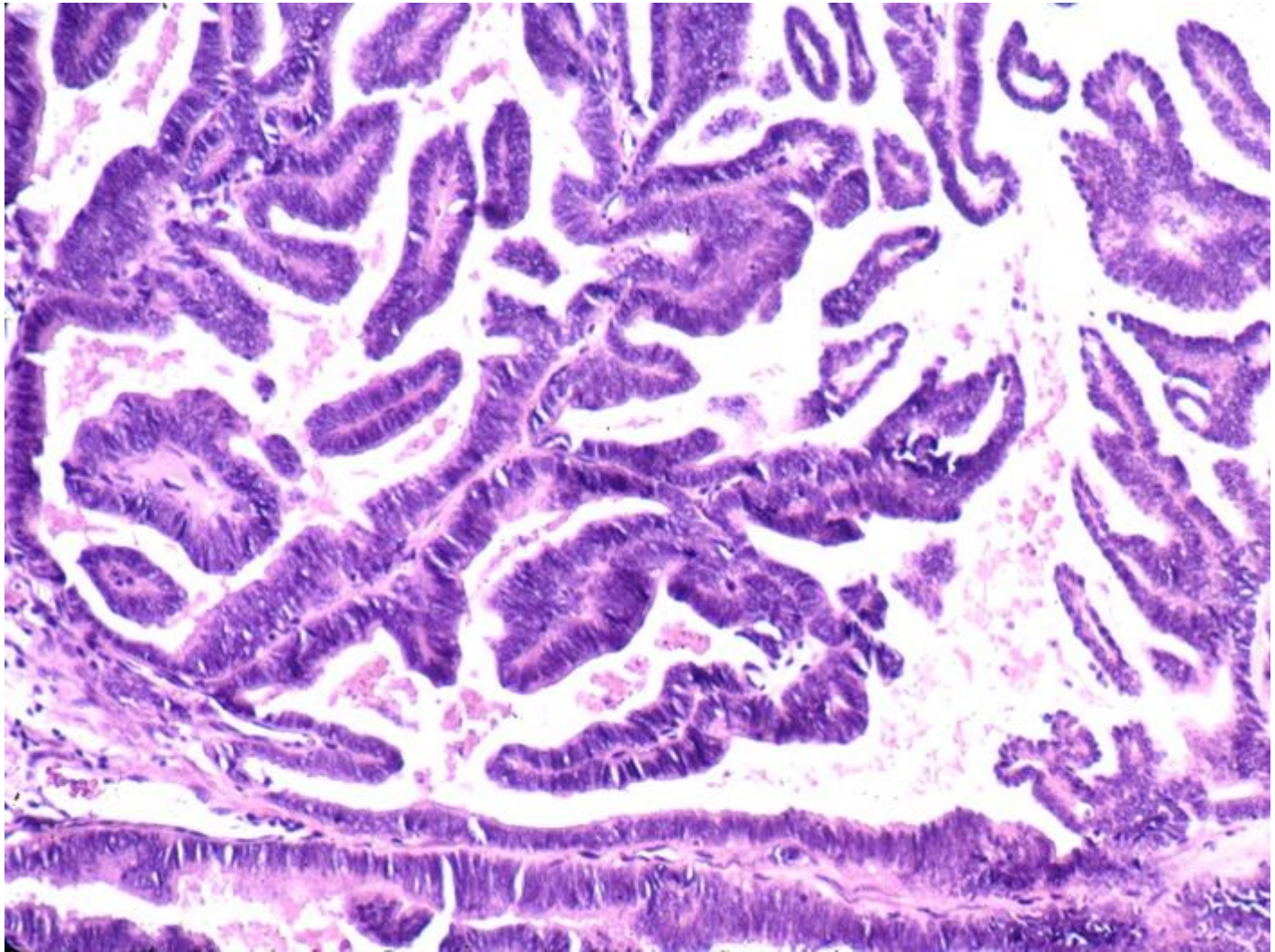
Problems in diagnosis of endometrioid ca: Corded and hyalinized endometrioid ca



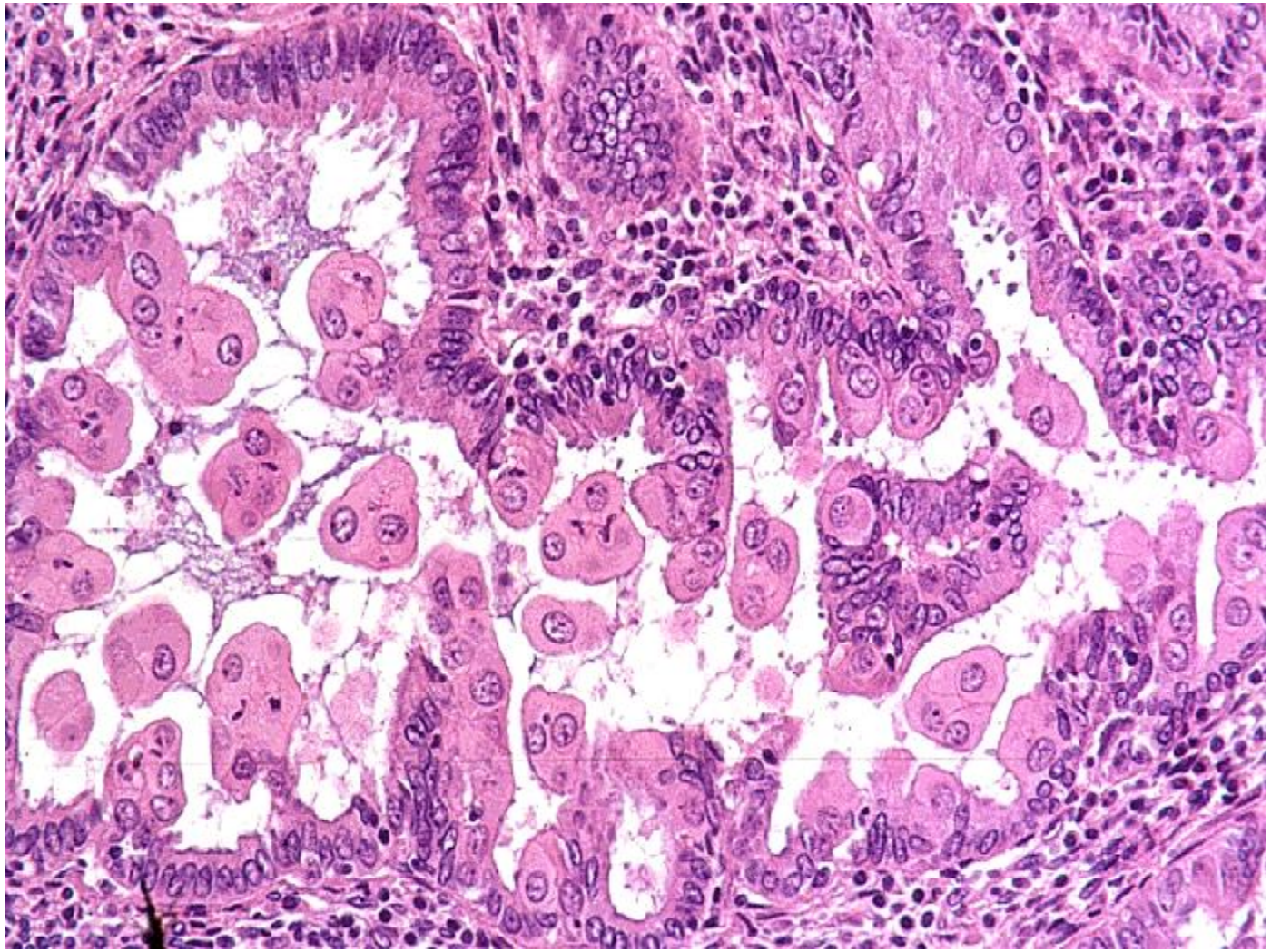
Problems in diagnosis of endometrioid ca: Endometrioid ca with spindle cells



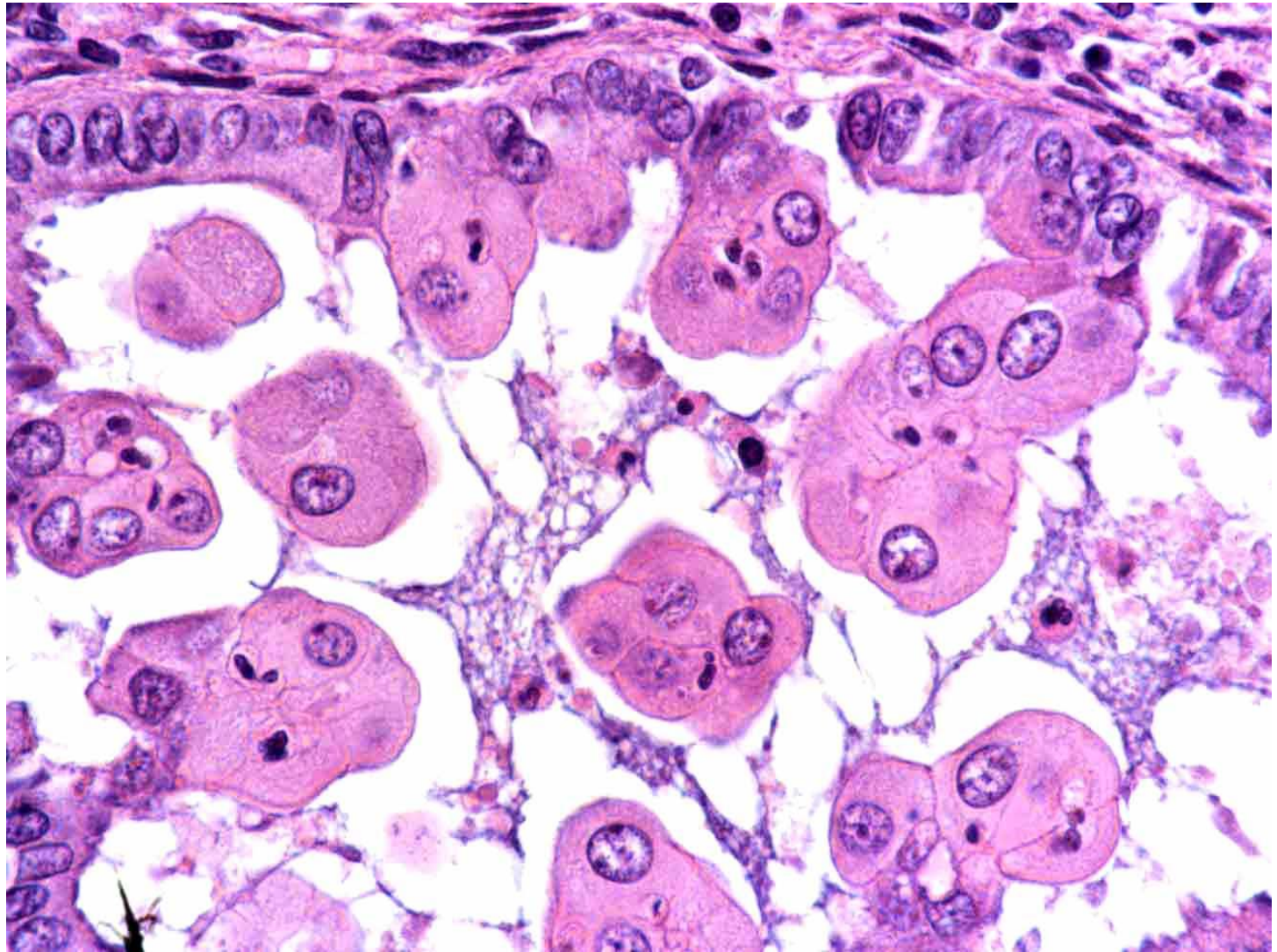
Endometrioid ca with papillary architecture: Villoglandular



Endometrioid ca with papillary architecture: EEC with small non-villous papillae



Endometrioid ca with papillary architecture: EEC with small non-villous papillae

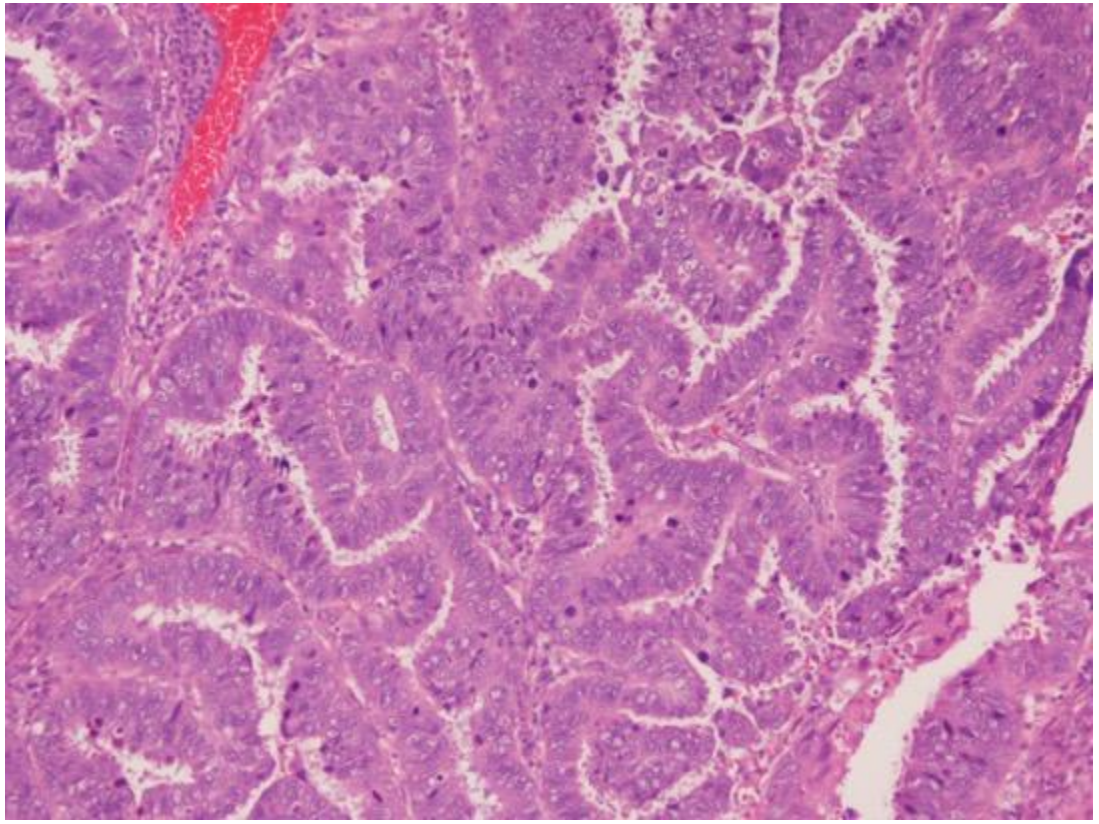


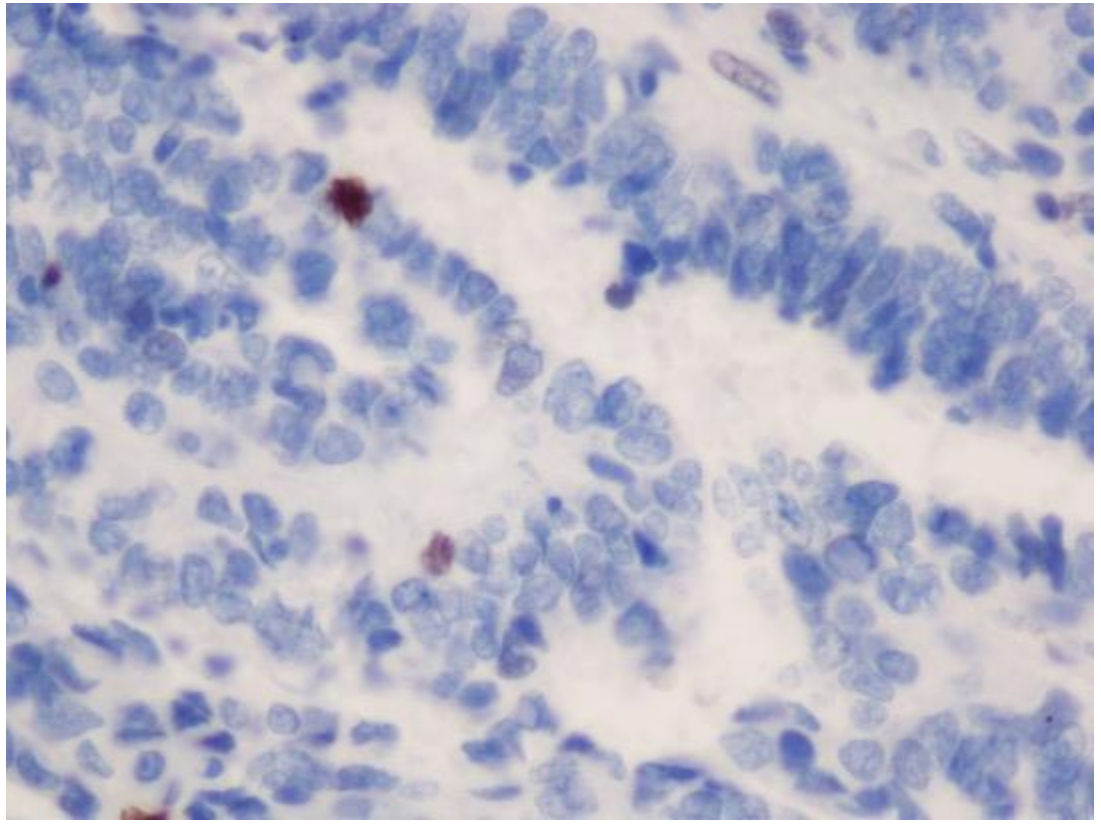
Problems in diagnosis of endometrioid ca: Grade

FIGO grading:

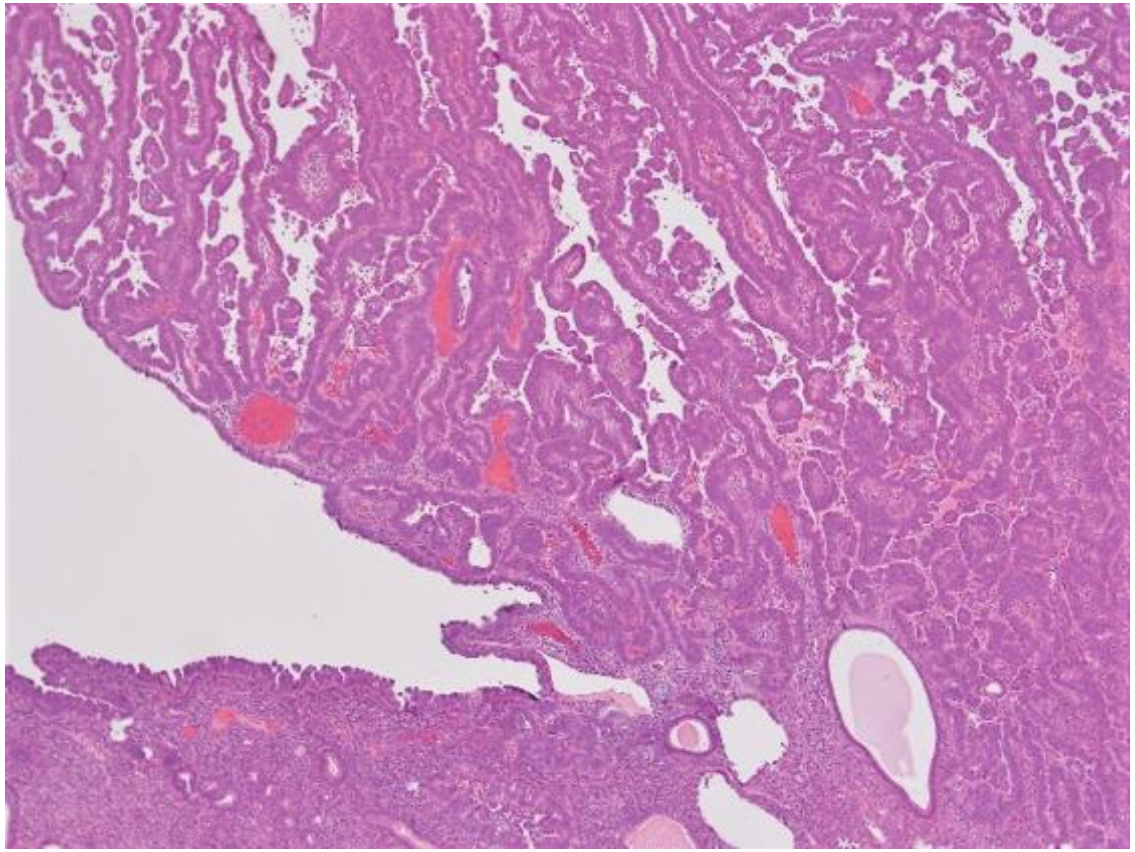
- Presence of severe cytological atypia in the majority of cells (>50%) increases the grade by one level, ***but serous carcinoma should be excluded***

Problems in diagnosis of endometrioid ca: Grade: low threshold for testing for p53 if nuclei are atypical!

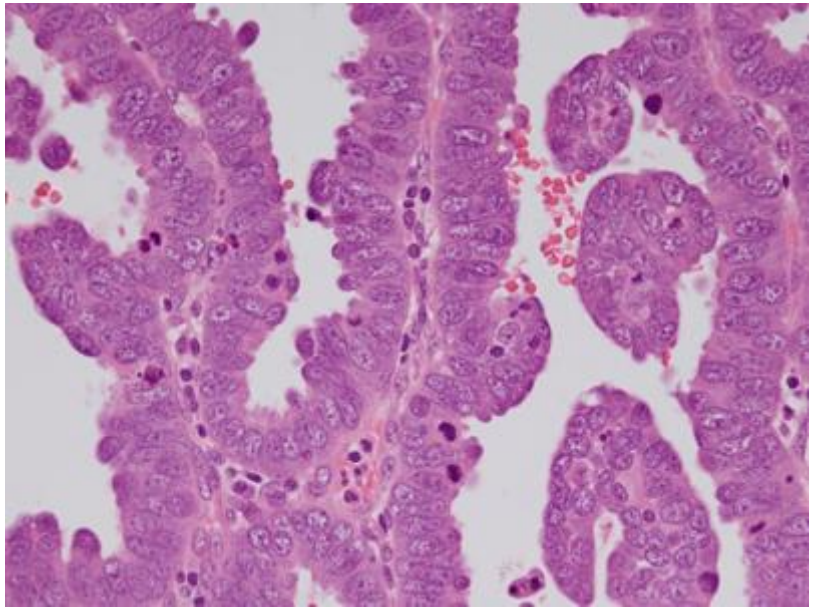




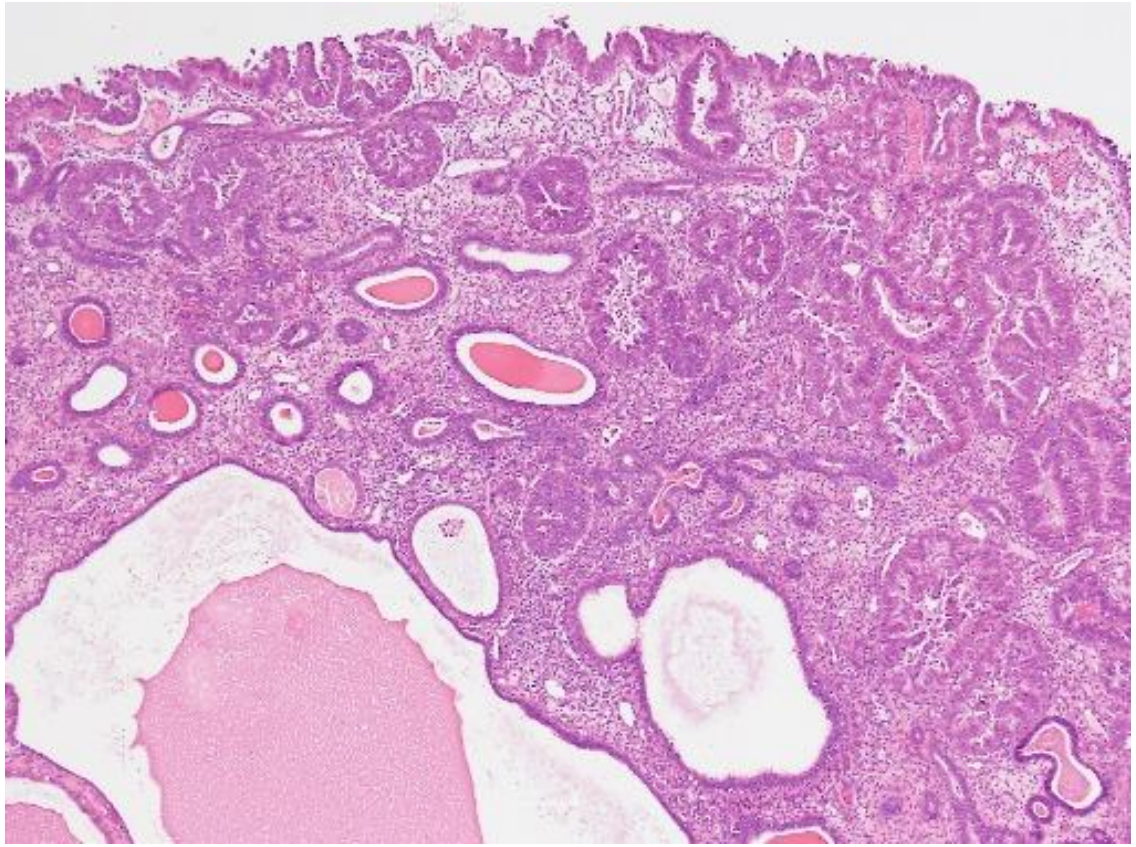
Serous carcinoma



- Carcinoma with diffuse marked nuclear pleomorphism, typically exhibiting papillary and/or glandular growth patterns

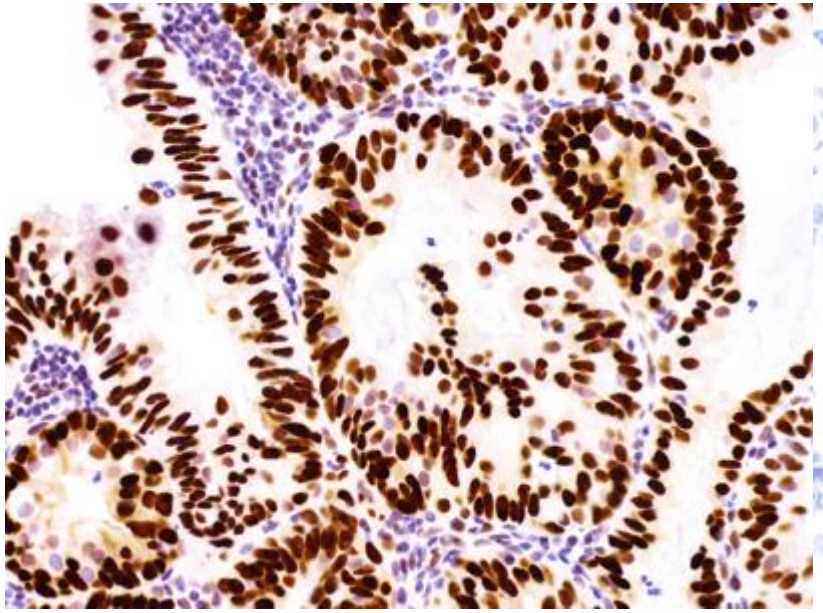


Serous carcinoma

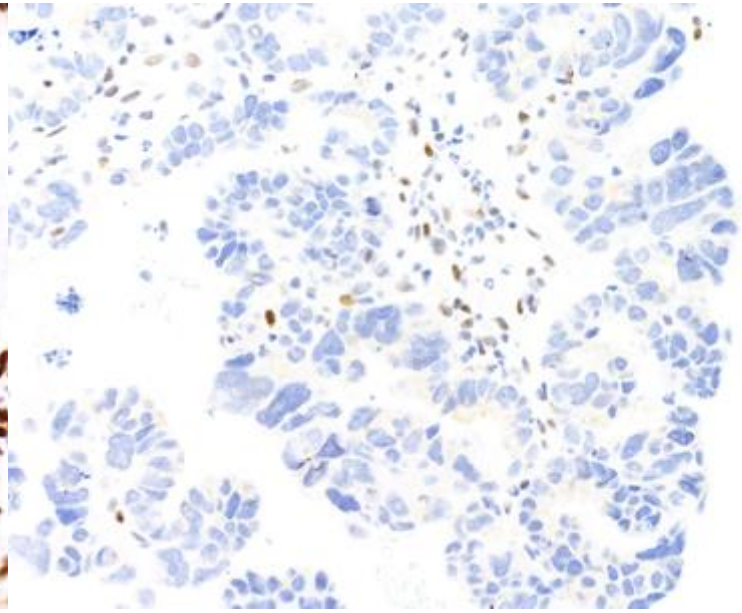


- 10% of EC
- 40% of EC deaths
- Carcinomas without invasion are staged the same way
- (EIC no longer exists)
- Abnormal p53 is supportive of diagnosis (desirable)
- Do not rely on p16, ER/PR – can give variable results

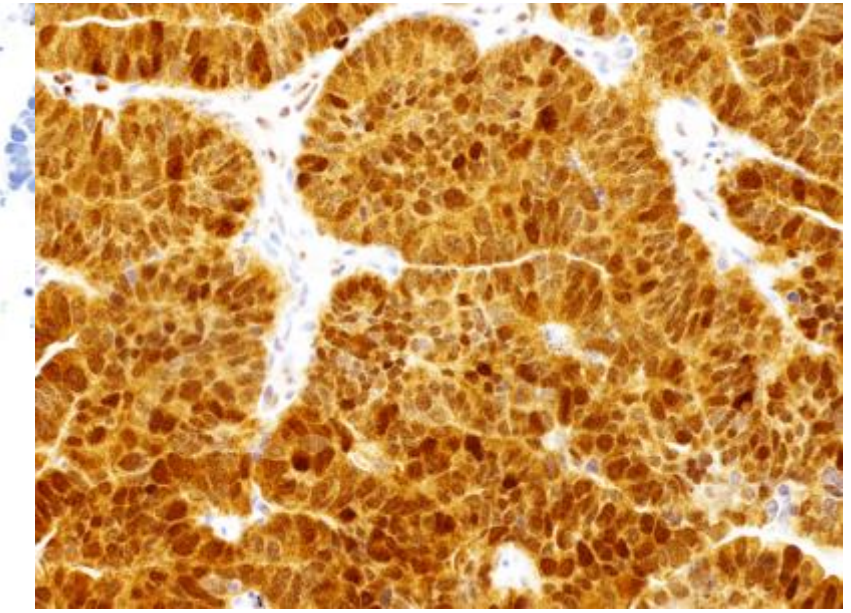
P53 IHC in endometrial ca: 3 patterns of abnormal expression



Over-expression

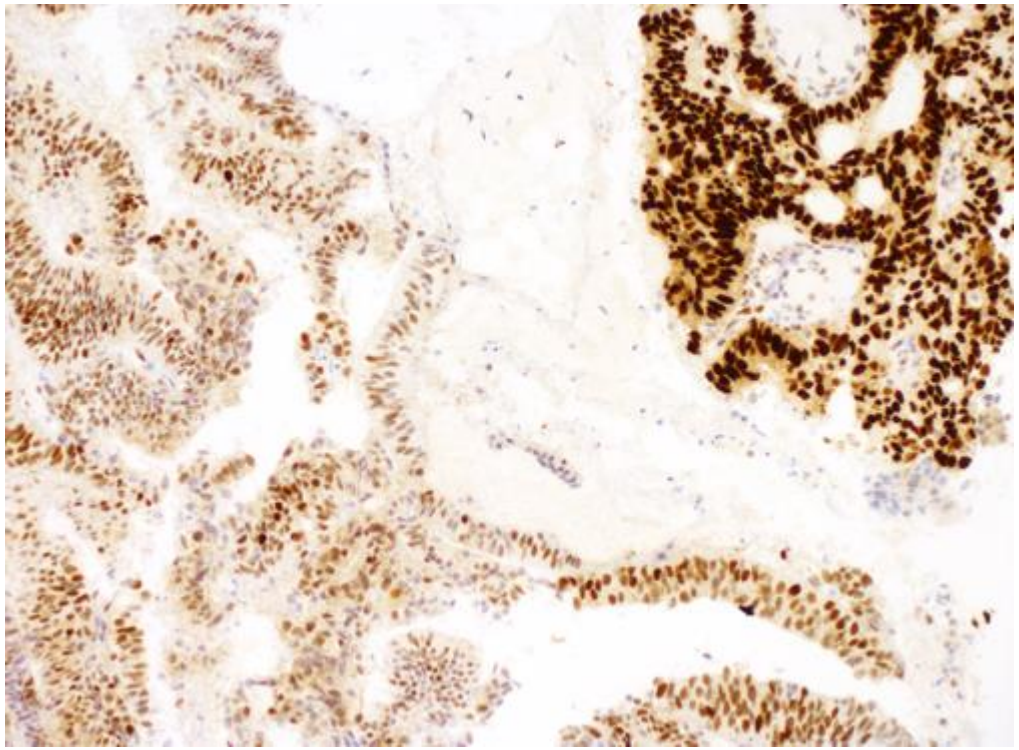


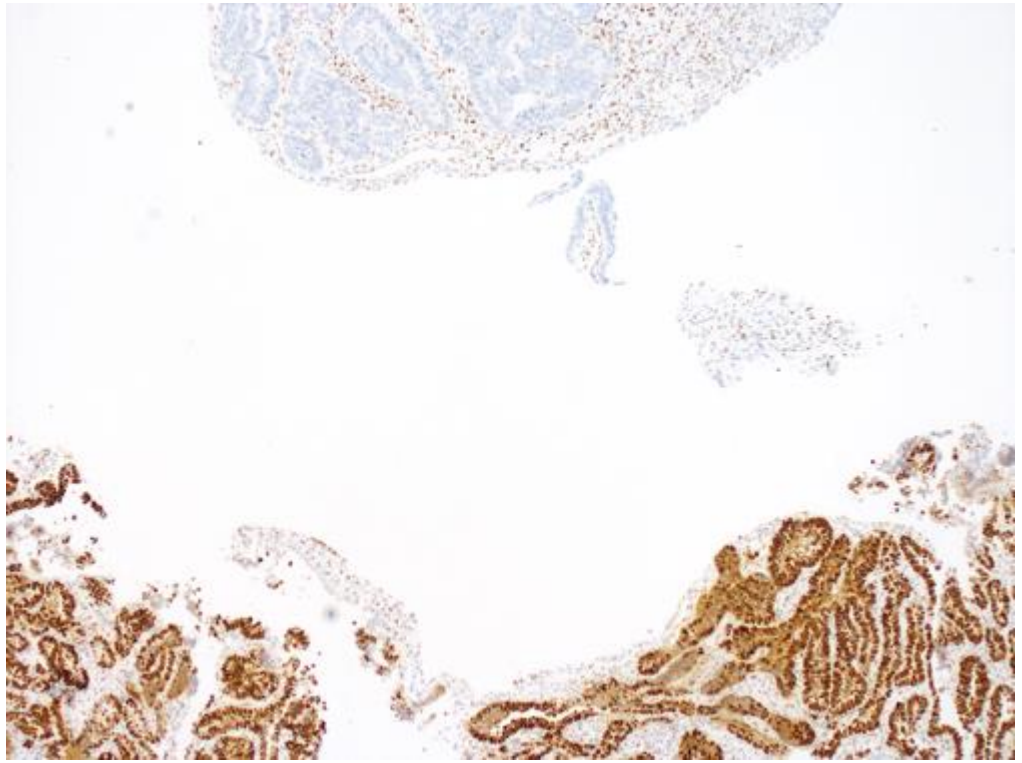
Complete absence



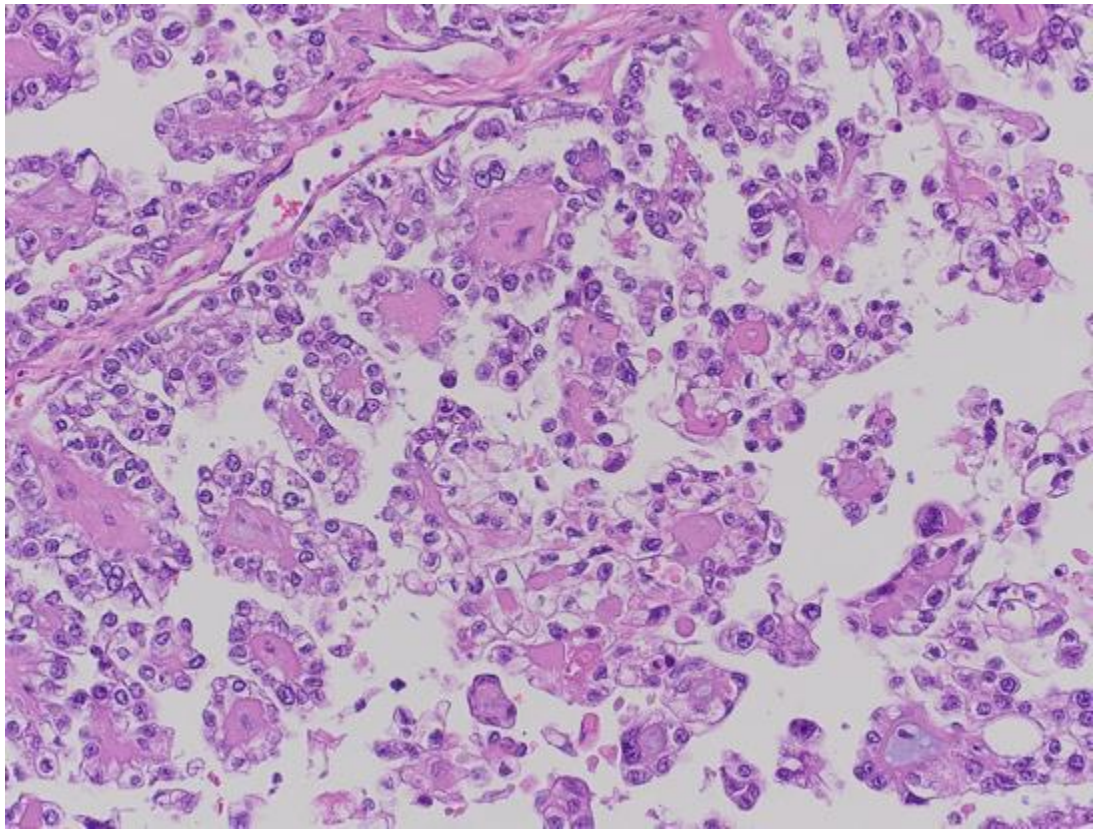
Cytoplasmic

P53 IHC in endometrial ca: Subclonal expression; most often in MMRd/POLEmut EC

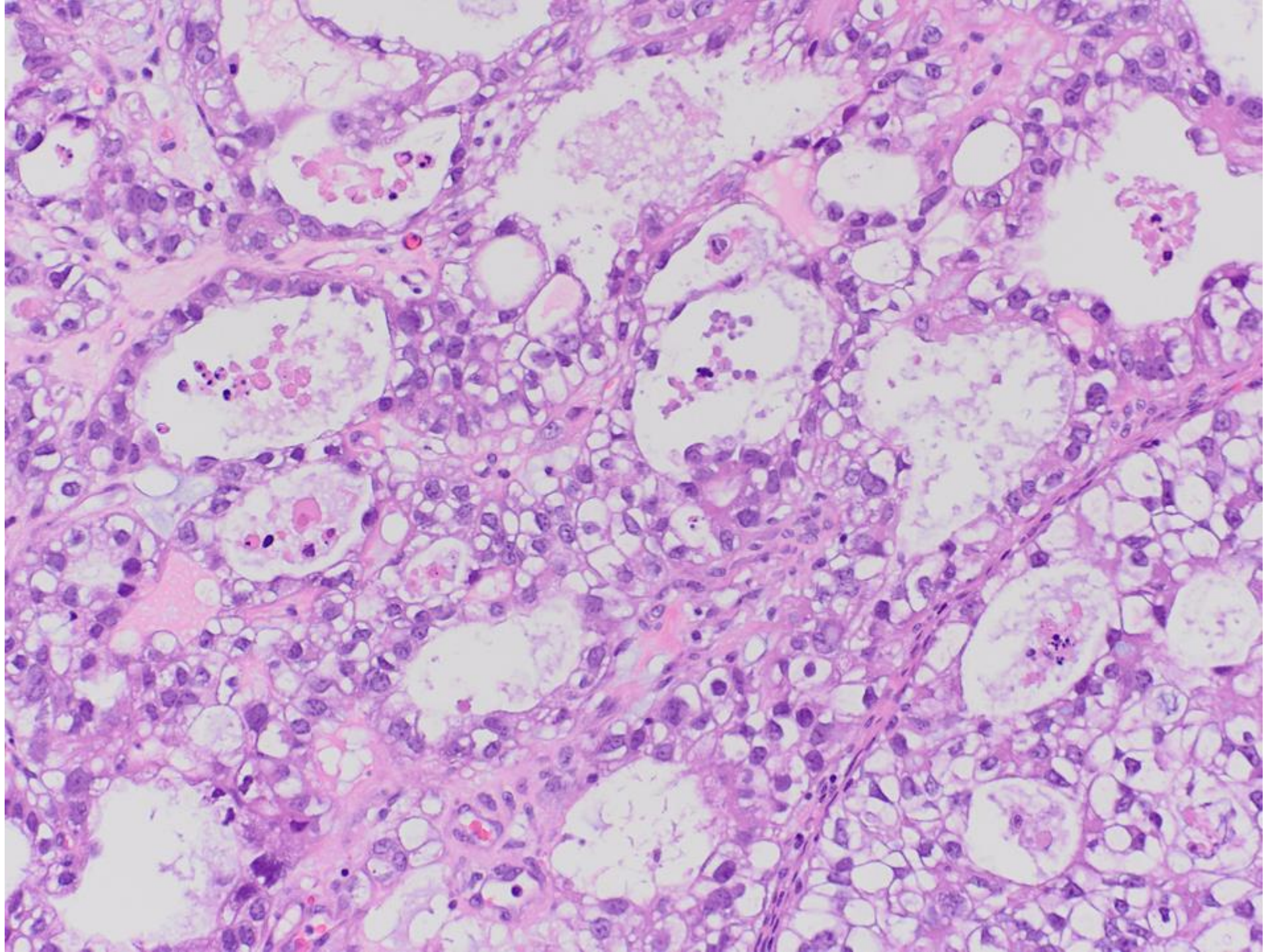


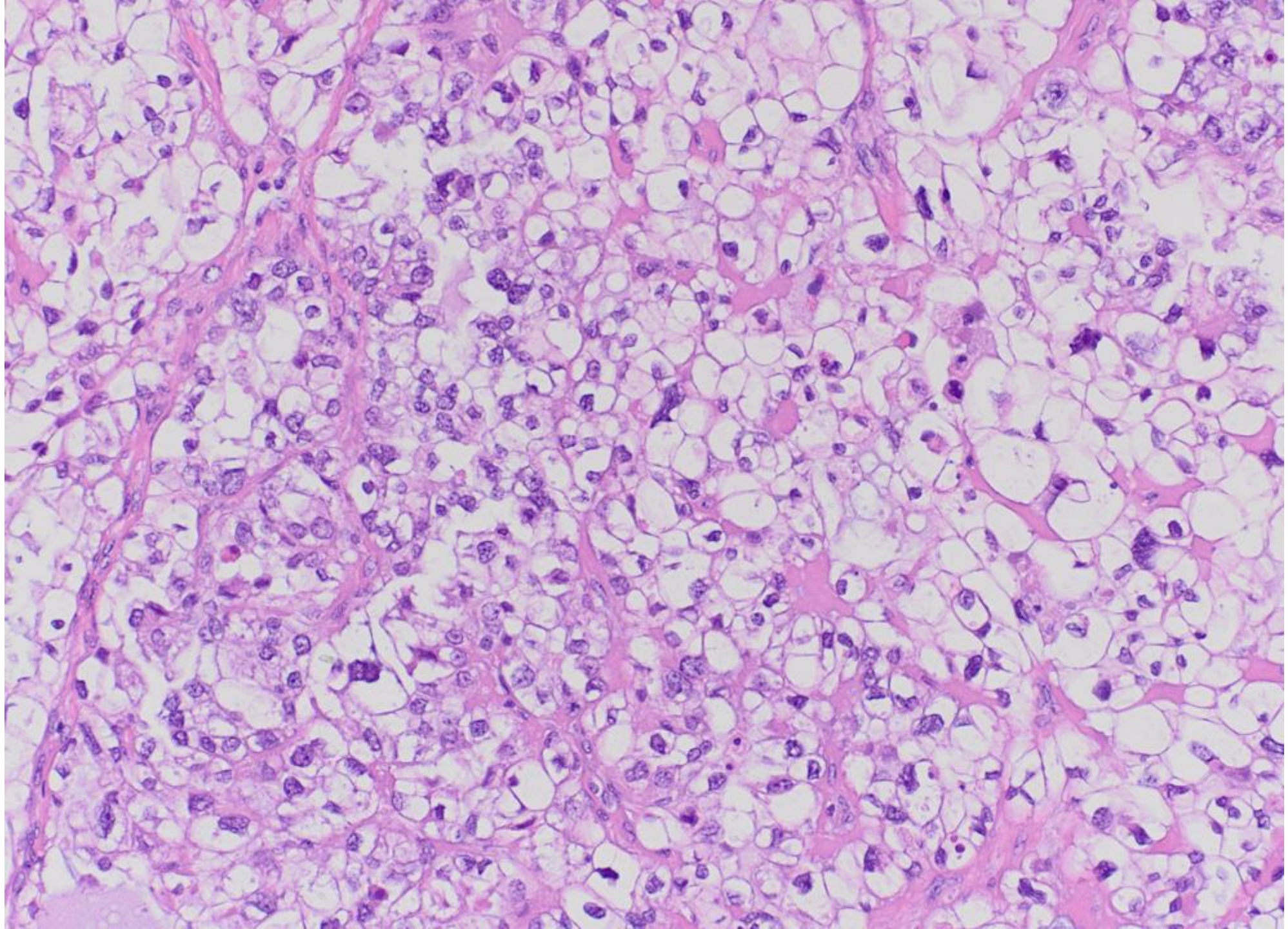


Clear cell carcinoma

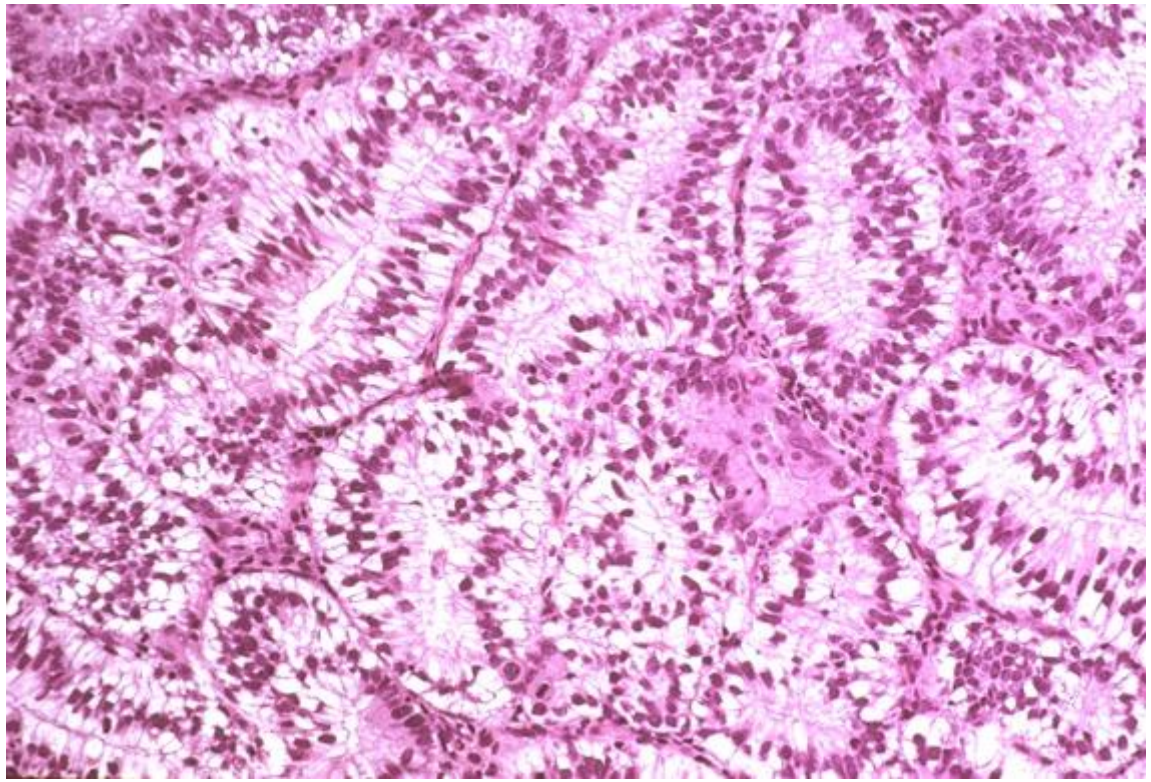


- Carcinoma demonstrating papillary, tubulocystic and/or solid architectural patterns and variably pleomorphic polygonal, cuboidal, flat or hobnail cells with clear or eosinophilic cytoplasm
- Rare, <10% (more likely about 2%) of EC
- **Stage I–IVA MMRd or NSMP clear cell carcinoma with myometrial invasion: insufficient data to allocate these patients to a prognostic risk group in the molecular classification (ESGO 2020)**
- **Prospective registries are recommended.**



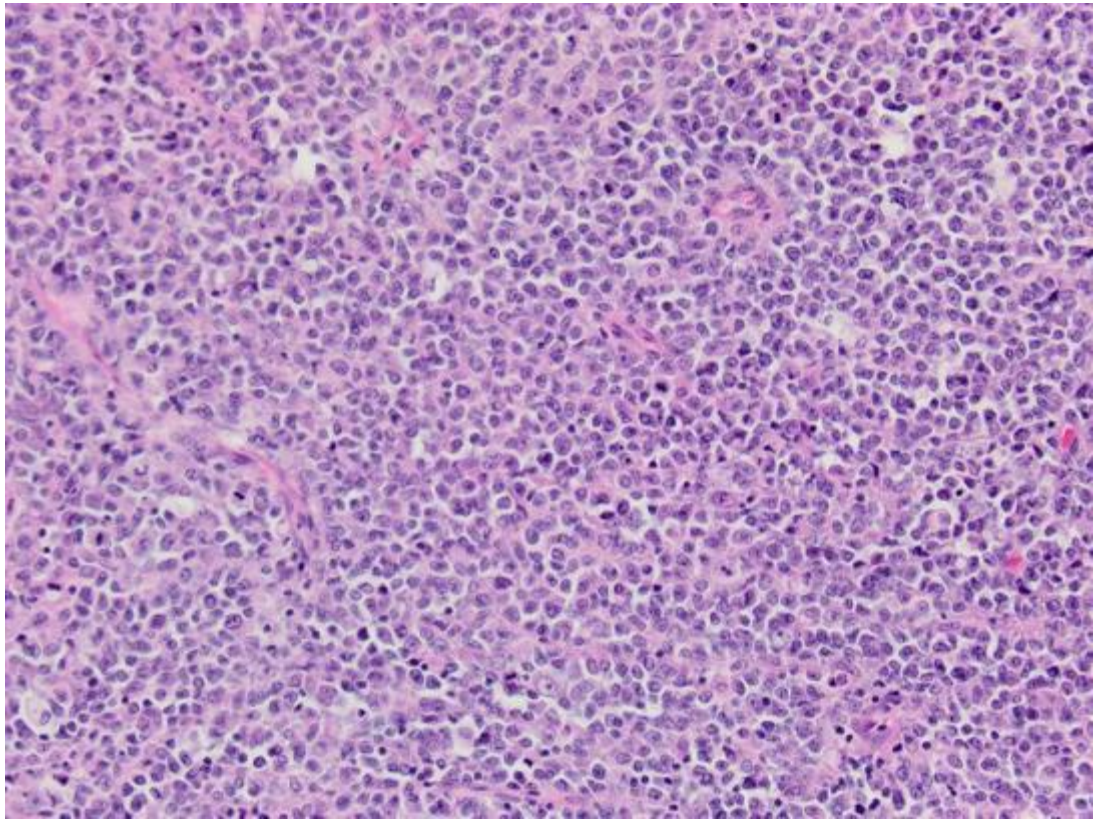


DD of CCC



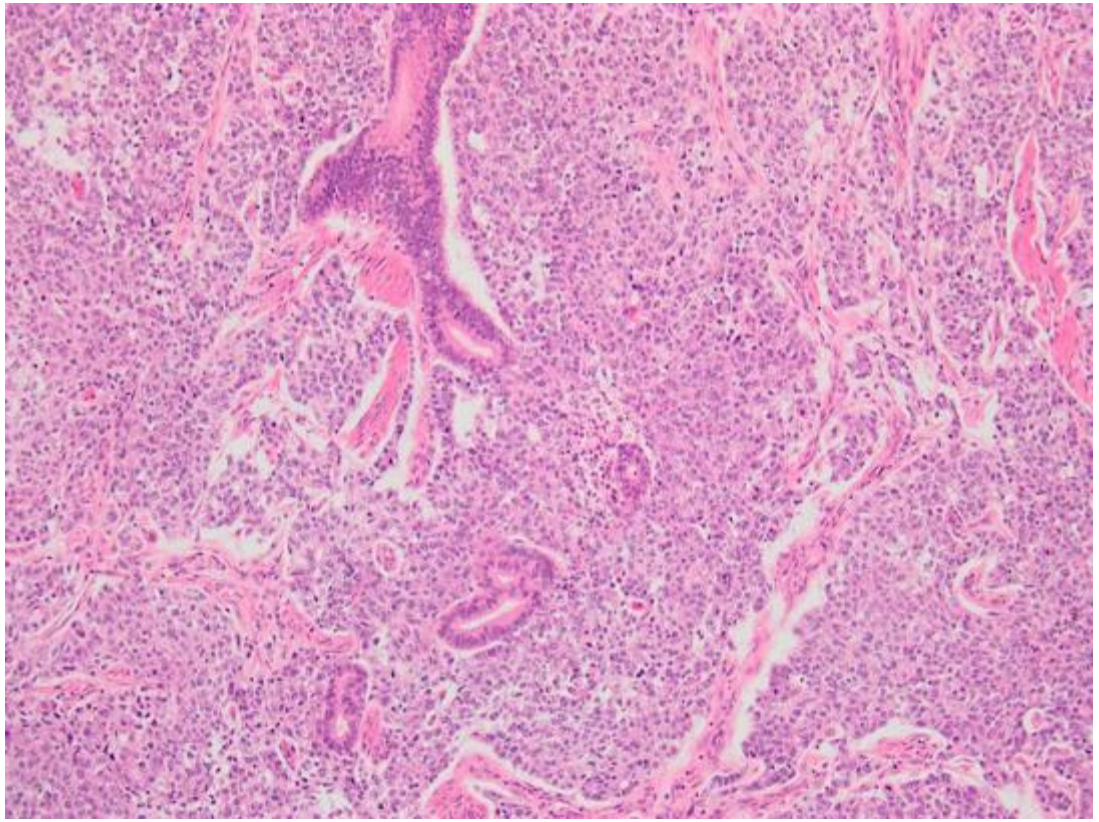
- Rare!
- Exclude other EC with clear cells:
  - Secretory change in EEC
  - Glycogenation of squamous component in EEC
  - Cytoplasmic clearing in serous ca

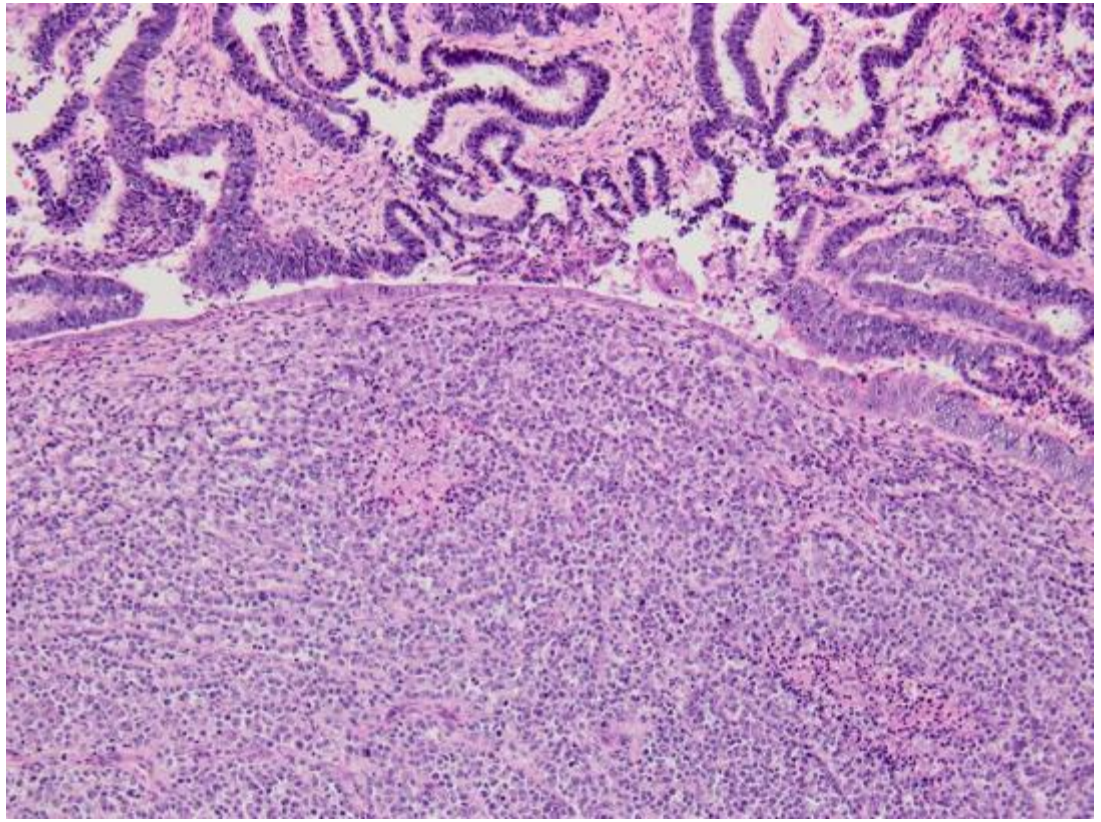
Undifferentiated and dediffentiated ca

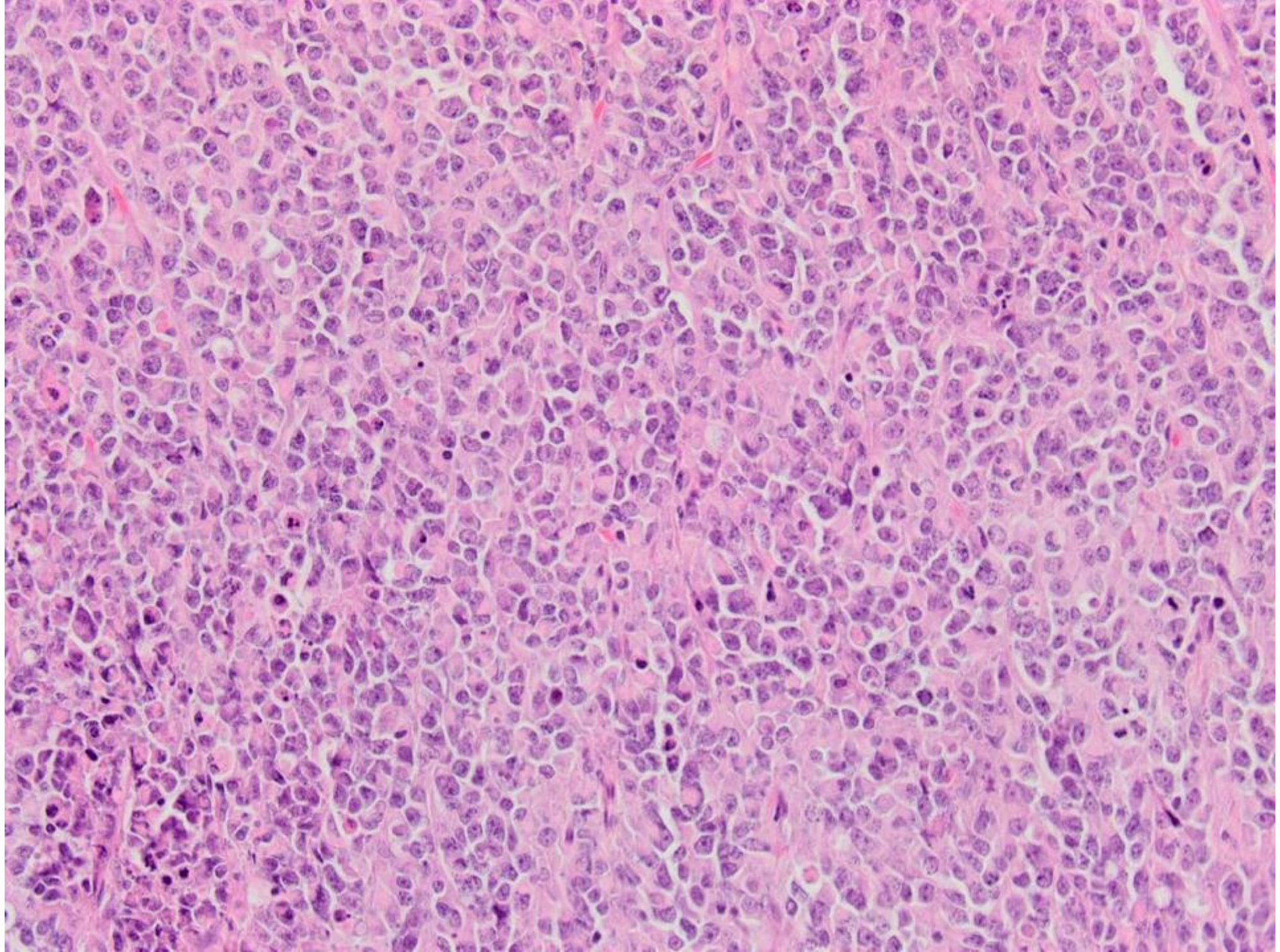


- Malignant epithelial neoplasm with no overt cell lineage differentiation
- Greater propensity for MMRd
- Dediff: undiff component is clonally related to EEC
- Only occasional tumour cells are positive for EMA or keratins (use >1 marker)
- ER, PR, PAX8 negative
- Chromo/synapto may be positive in a minority of cells

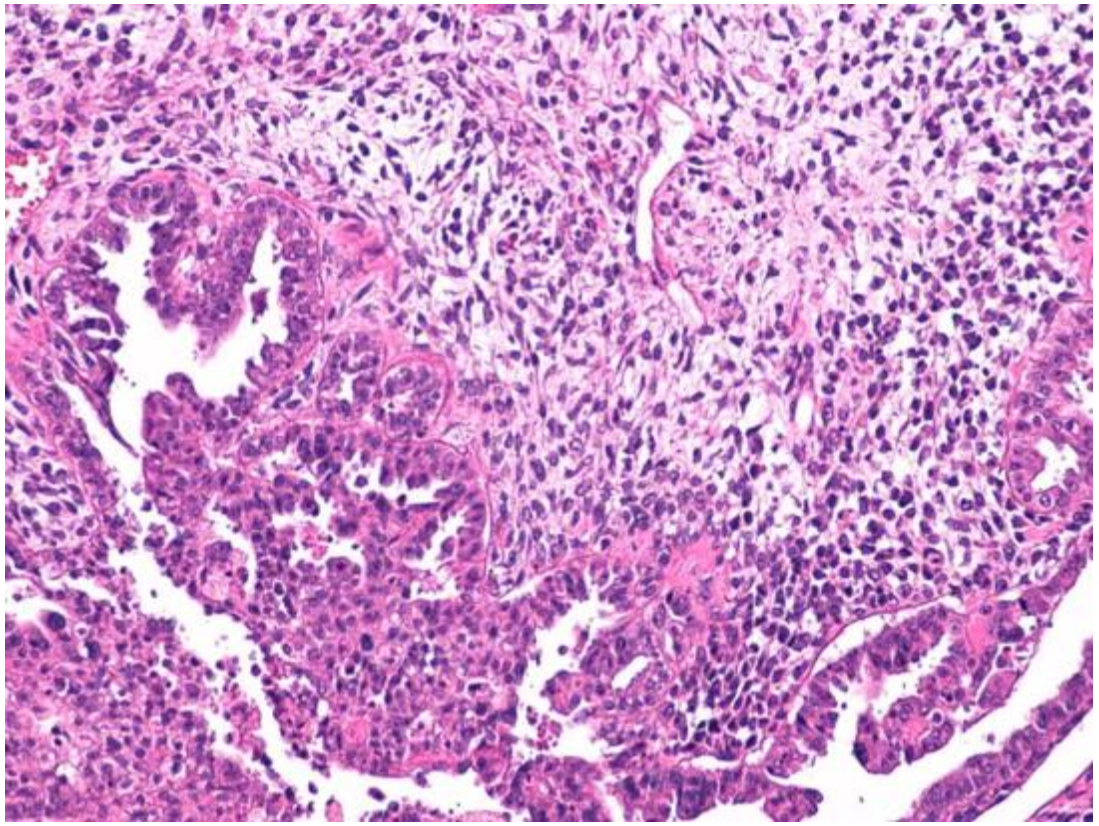
Dedifferentiated carcinoma

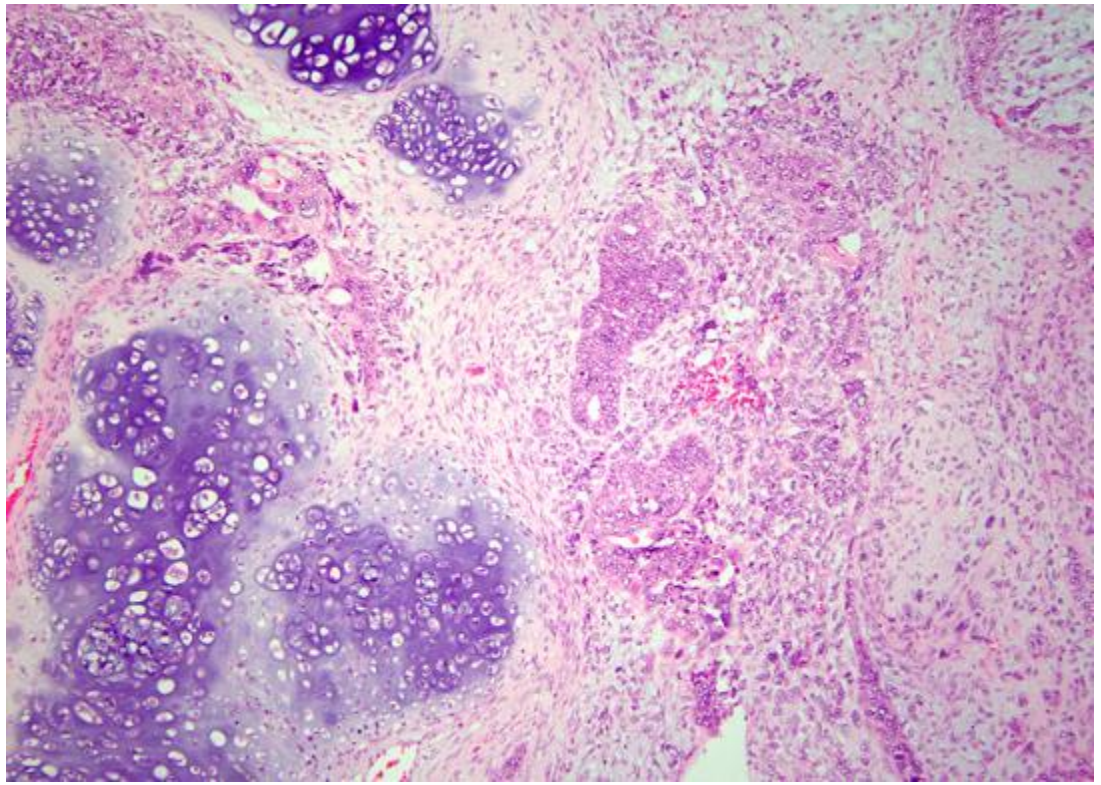




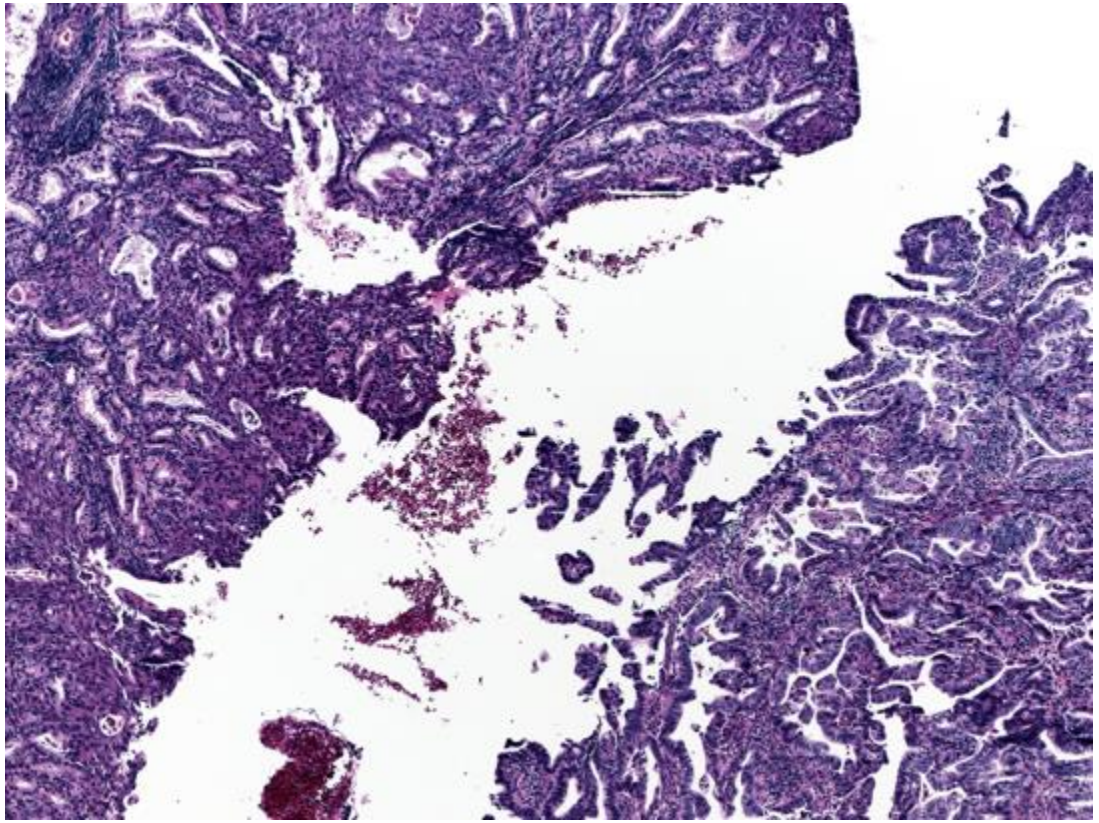


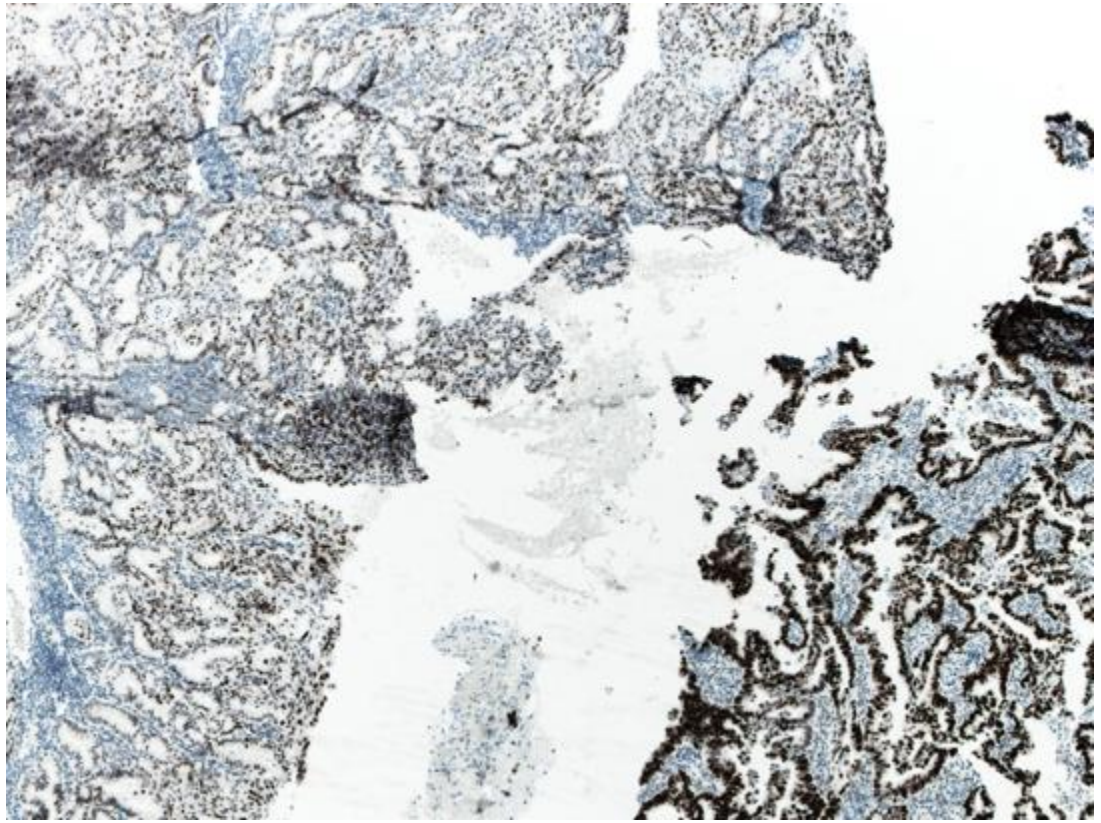
Carcinosarcoma: Biphasic tumour composed of ***high-grade*** carcinomatous and sarcomatous components



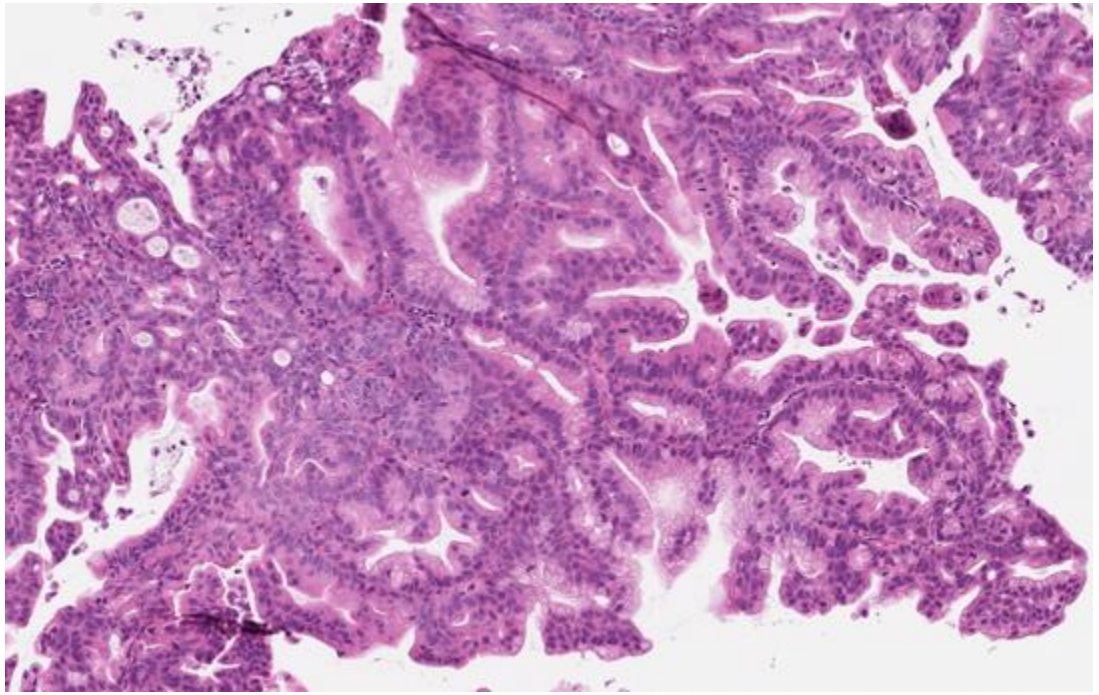


Mixed carcinoma: Composed of 2 or more discrete histological types where at least one component is either serous or clear cell





Other carcinomas



- Mesonephric carcinoma
- Mesonephric-like carcinoma
- Squamous cell carcinoma
- **Primary gastric (gastro-intestinal) type carcinoma: ER negative; p53 may be abnormal; gastric/colonic-type markers positive; exclude metastasis**

Typing endometrial carcinoma in biopsies

- Accurate histological typing and grading remains central to management, regardless of molecular classification
- Key to accuracy is awareness of rare patterns and new entities
- Limited panel of IHC allows for accurate diagnosis and molecular classification in >90% cases: ER, p53, PMS2, MSH6
- ER: alerts to possibility of non-endometrioid histotype; possible prognostic value in NSMP EC (new PORTEC3 data; ESGO 2021); hormonal therapy
- Additional IHC in selected cases: Napsin, WT1, p16

ELECTRA

Expanding the **L**aboratory Diagnosis of **E**ndometrial **C**arcinoma: **T**argeted Molecular Testing Based on **R**isk **A**ssessment

Prospective collaborative multi-centre data collection study to define optimal molecular testing strategies for endometrial cancer

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Thank you