Update on Endometrial Carcinoma HK IAP 2022

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Global Cancer Incidence in Women

Rank	Cancer	New cases in 2020	% of all cancers
	All cancers*	8,751,759	
1	Breast	2,261,419	25.8
2	Colorectal **	865,630	9.9
3	Lung	770,828	8.8
4	Cervix uteri	604,127	6.9
5	Thyroid	448,915	5.1
6	Corpus uteri	417,367	4.8

World Cancer research Fund International

Classification Systems of Endometrial Cancer

- Bokhman Classification
- Clinical and epidemiological features

- WHO Classification
- Histomorphological features

- Molecular Classification
- Integrated genomic analysis

Histological type (WHO 5th Ed)

Endometrial carcinoma

- Endometrioid
- Serous
- Clear cell
- Undifferentiated and dedifferentiated ca
- Mixed ca
- Carcinosarcoma

- Binary grading
- Synchronous endometrial and ovarian carcinoma

- IHC: p53, p16 and Her2

hers

- sonephric adenocarcinoma
- quamous cell carcinoma NOS
- Mucinous carcinoma, intestinal type
- Mesonephric-like adenocarcinoma

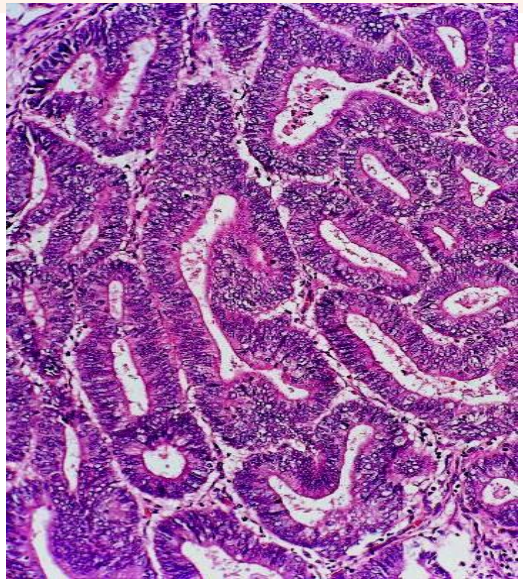
Endometrioid Carcinoma - Grading

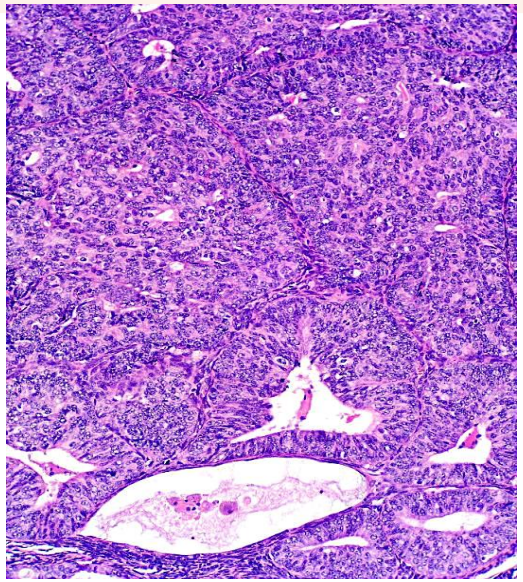
FIGO Grade	Definition
1	≤ 5% of solid (non-squamous/morular) growth
2	6-50% solid growth
3	>50% solid growth

The presence of grade 3 nuclei (rounded, contain prominent, often multiple, nucleoli and show variability in size) involving >50% of tumour → upgrade tumour by 1 grade

Low grade

High grade

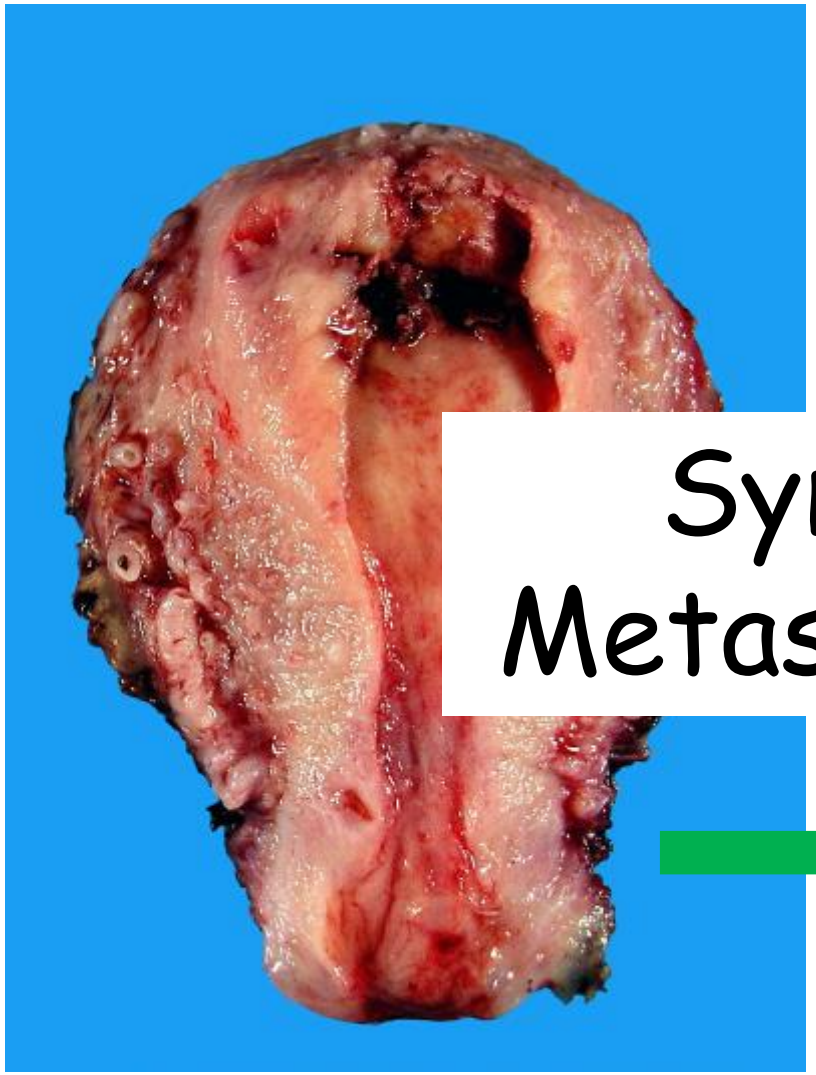


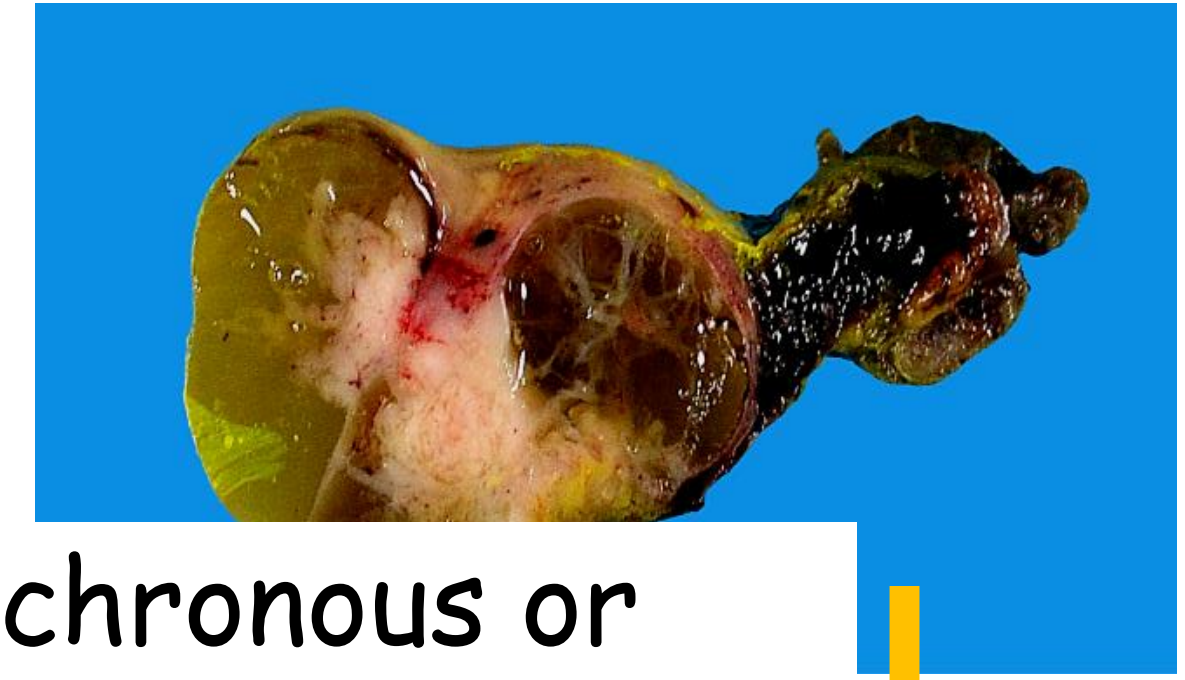


Exception: patients who wish to preserve fertility

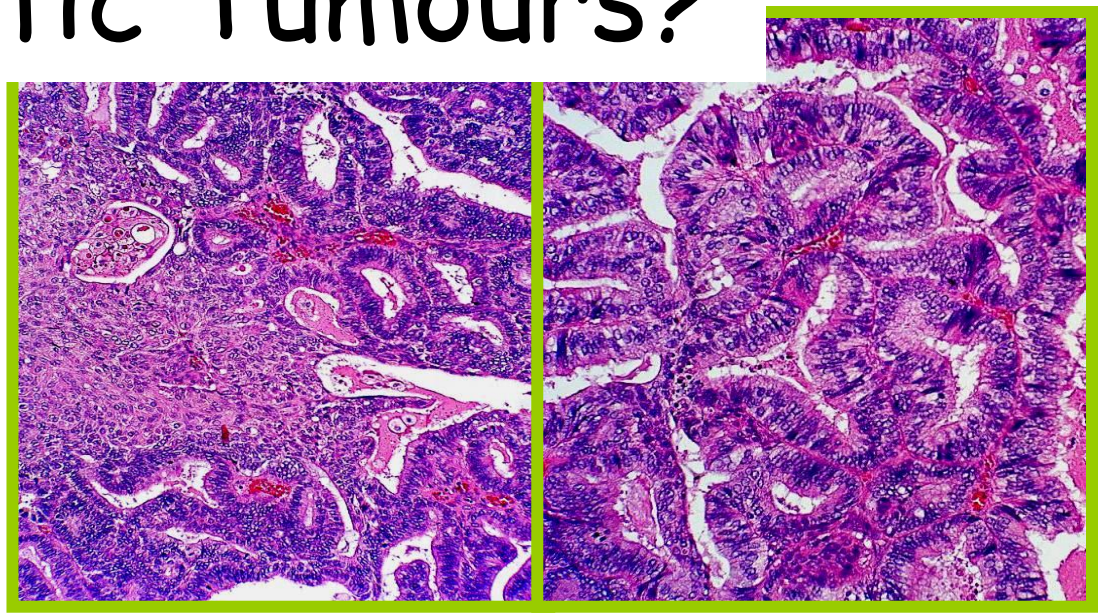
Endometrioid Carcinoma- Grading

- Binary grade: equal/superior to 3-tiered FIGO system in terms of interobserver variability kappa score
- Presence of microacini should not be considered “glandular” for the purposes of assigning binary or FIGO grade (ISGYP recommendation)
- A tumour is considered FIGO grade 3 if the solid areas resemble poorly differentiated nonkeratinizing squamous cell carcinoma (ISGYP recommendation)





Synchronous or Metastatic Tumours?



Endometrioid Carcinoma

Synchronous endometrial and ovarian carcinoma

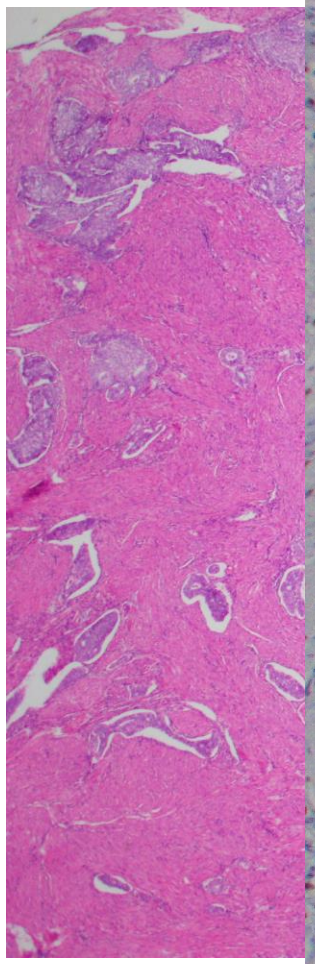
- Favorable outcome (akin to 2 low-stage primaries)
- Recent studies demonstrated clonal relationship ➔ favour metastases (endometrium to ovary)

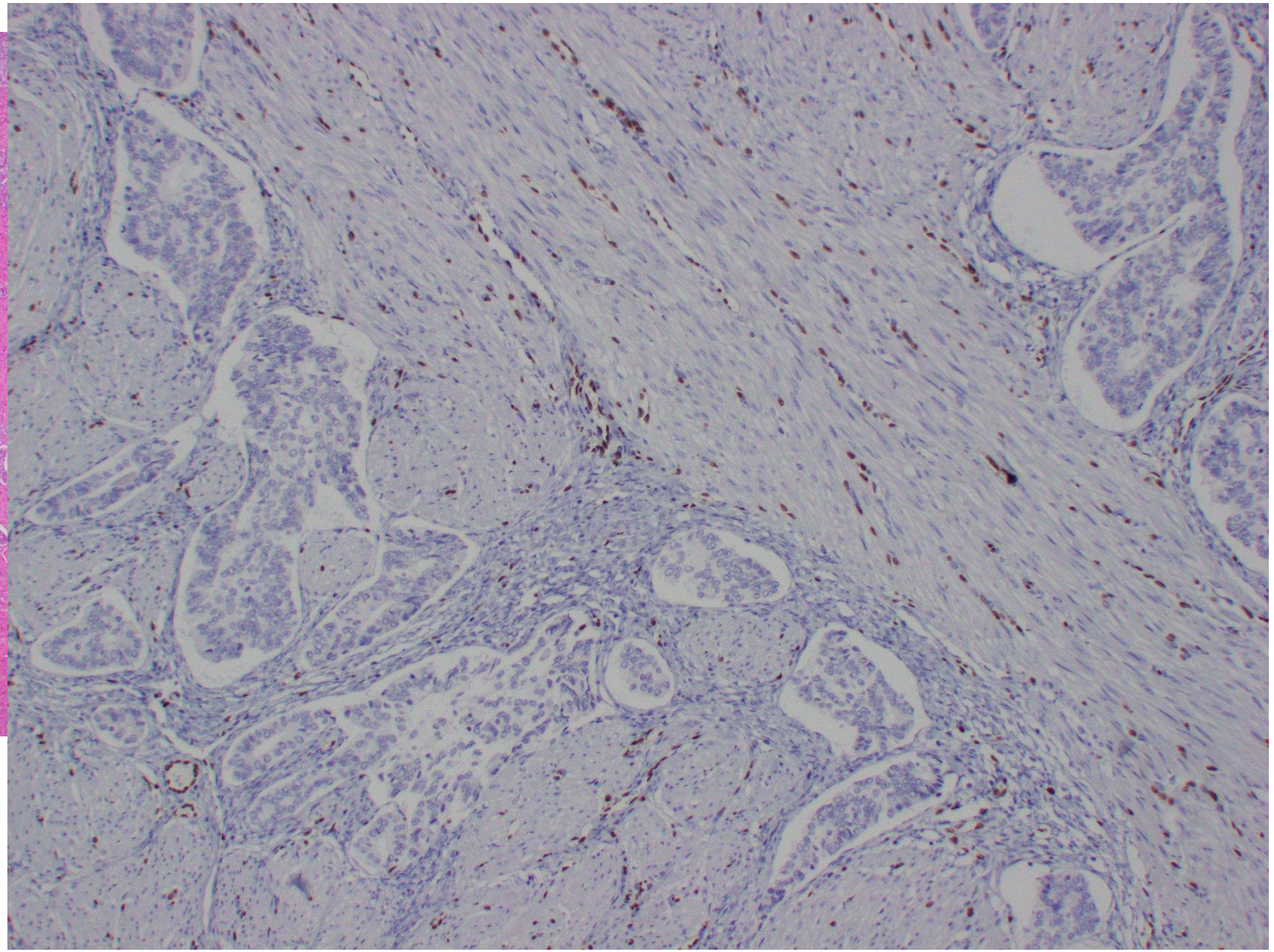
- Conservative management should be considered when:
  - Both low-grade
  - <50% myometrial invasion
  - No involvement of any other site
  - Absence of extensive LVSI

Endometrioid Carcinoma

Lymphovascular invasion

- Presence of tumour cells in a space lined by endothelial cells outside the immediate invasive border
- 5–15% of tumours
- Frequently associated with MELF pattern of invasion and MMRd
- Should be distinguished from artefactual vascular involvement => beware in poorly fixed tumours and those with necrosis ++





Endometrioid Carcinoma

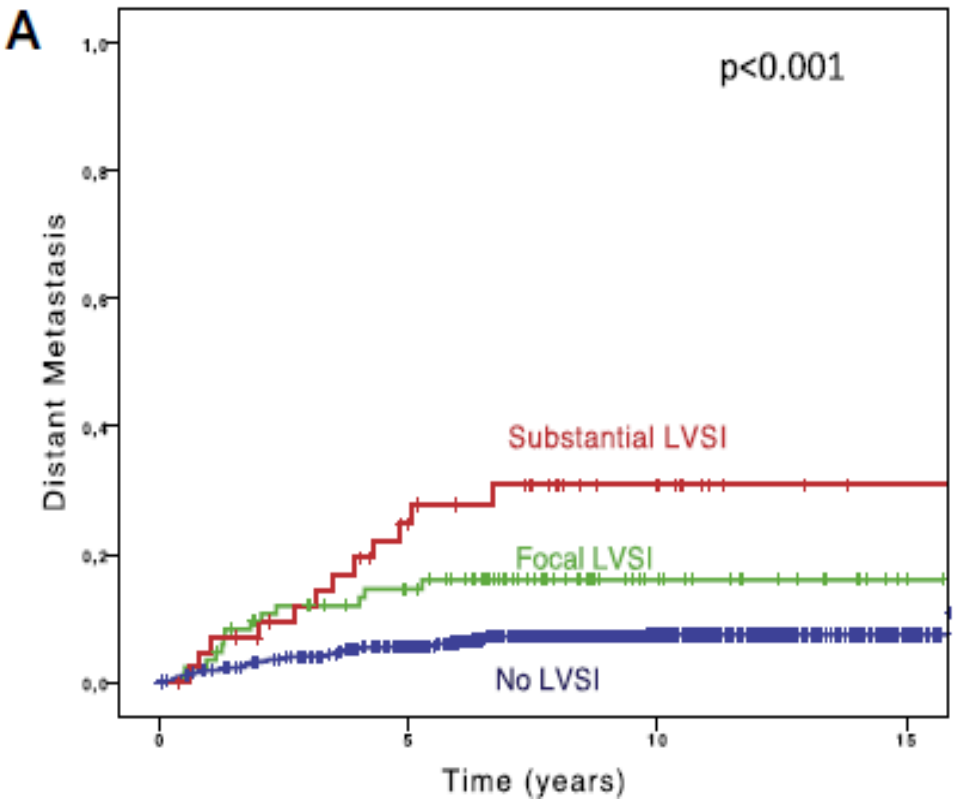
Lymphovascular invasion

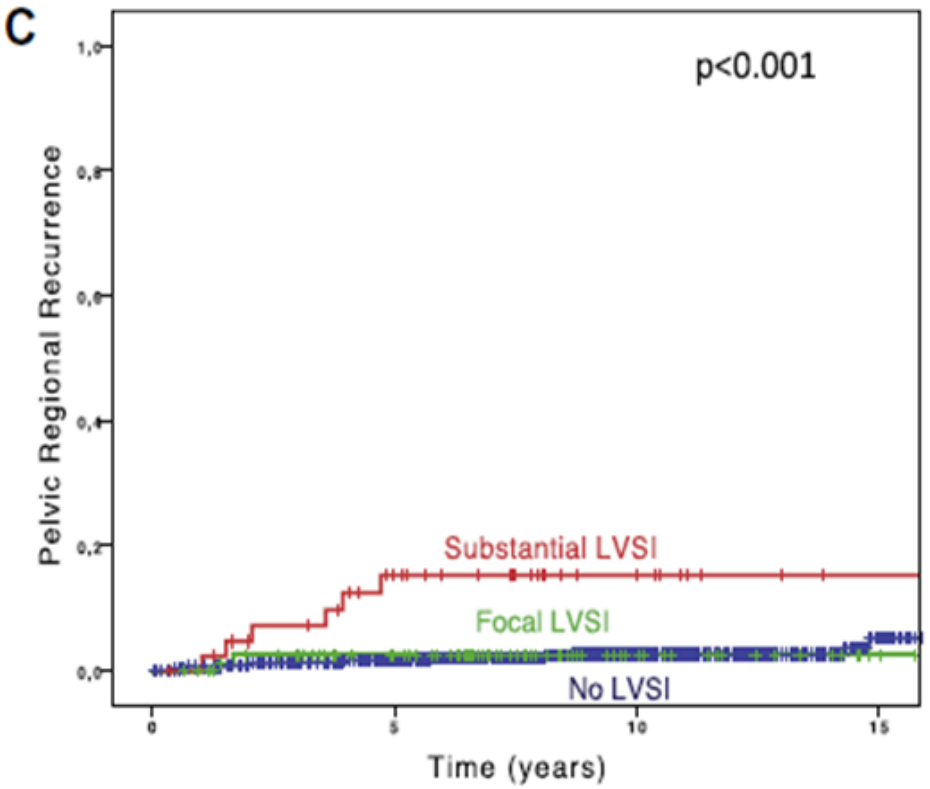
- Extensive/substantial LVSI: presence of tumour cells in ≥5 vessels → PROGNOSTIC SIGNIFICANCE
- Presence does not upstage the tumour

Reporting recommendation

- Absent
- Present, focal (1 focus)
- Present (state number of foci)
- Present, substantial (≥5 foci)

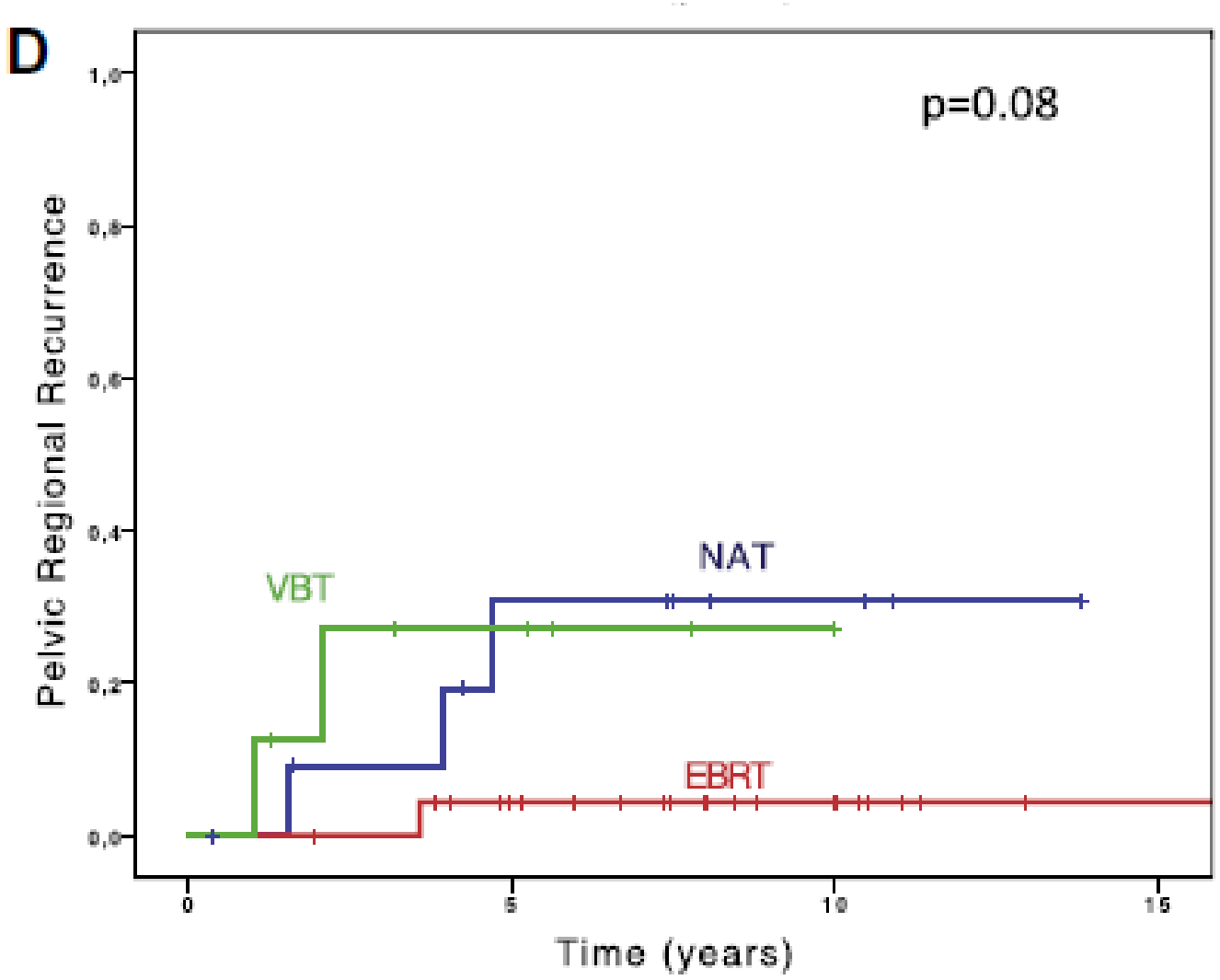
PORTEC 1 and 2: Kaplan Meier Curves for Risk of Distant Mets and Pelvic Recurrences





T. Bosse et al. Eur J Cancer 51 (2015) 1742–1750

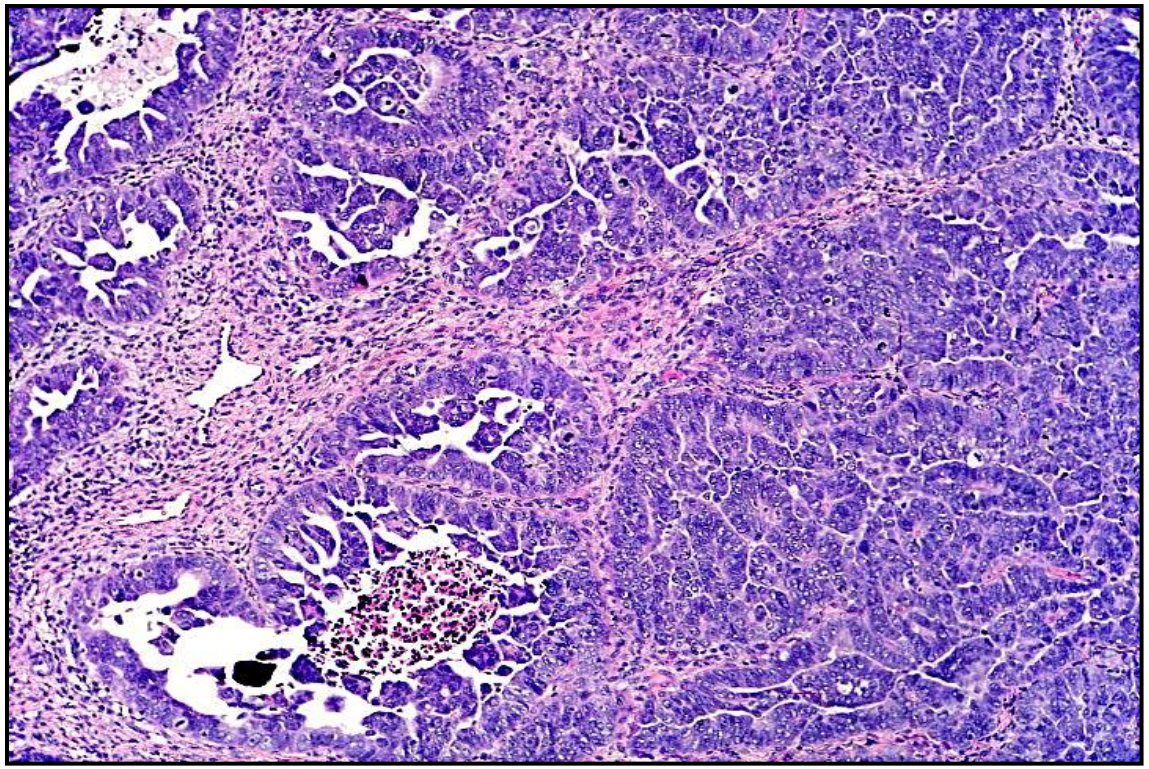
Patients with substantial LVSI (≥5 vessels)

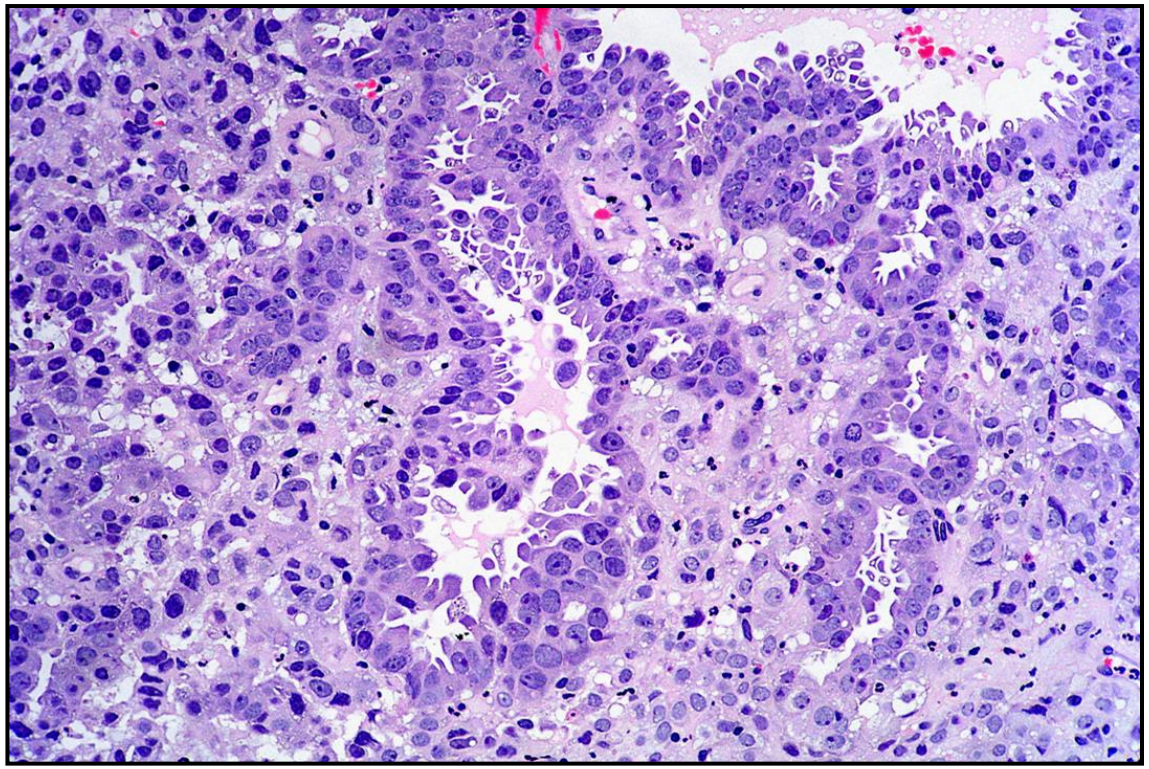


T. Bosse et al. Eur J Cancer 51 (2015) 1742–1750

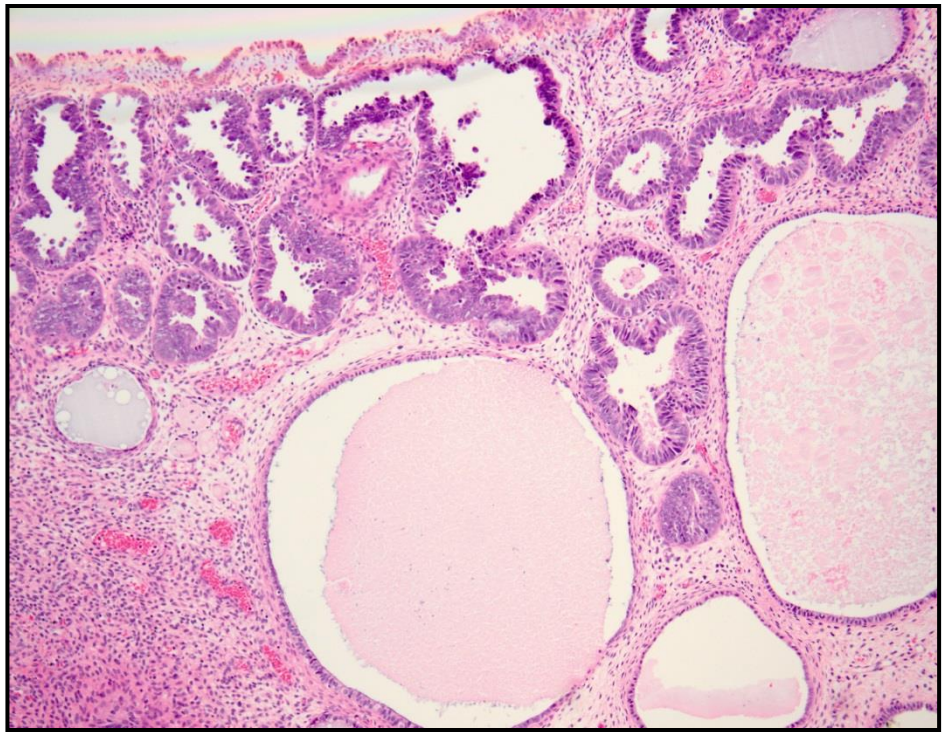
Serous Carcinoma

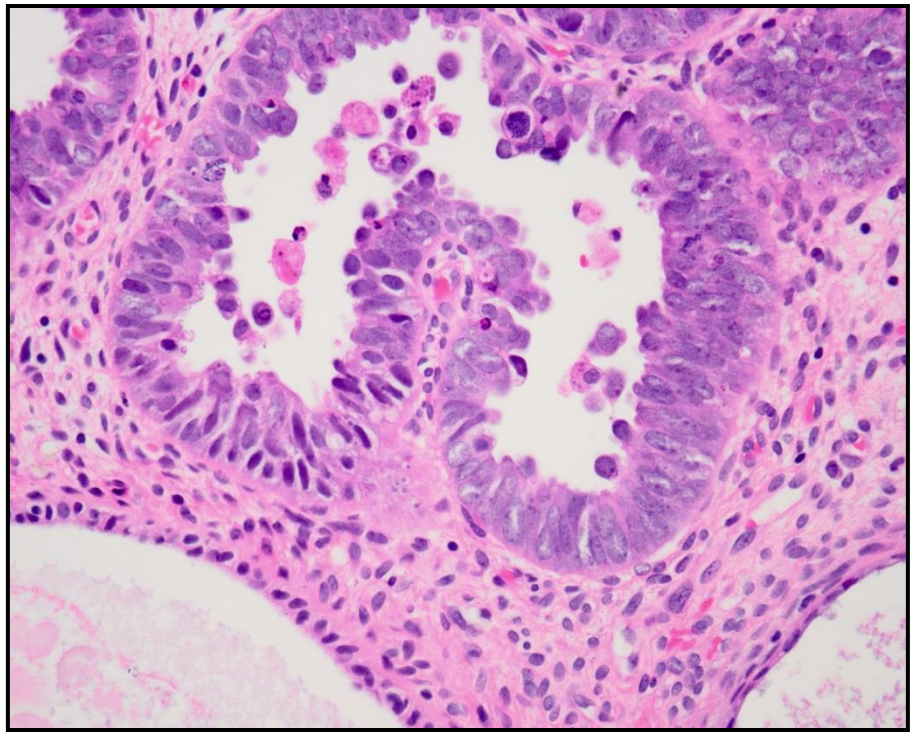
- Marked and diffuse nuclear pleomorphism
- Solid, papillary and/or glandular growth patterns





Serous Endometrial Intraepithelial Carcinoma





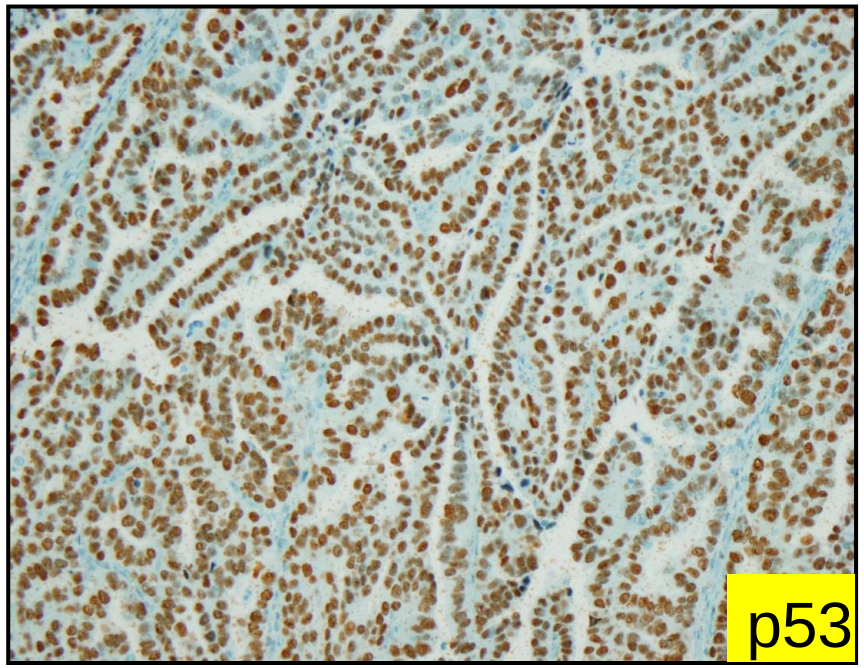
Does not behave like an ‘in-situ’ lesion -

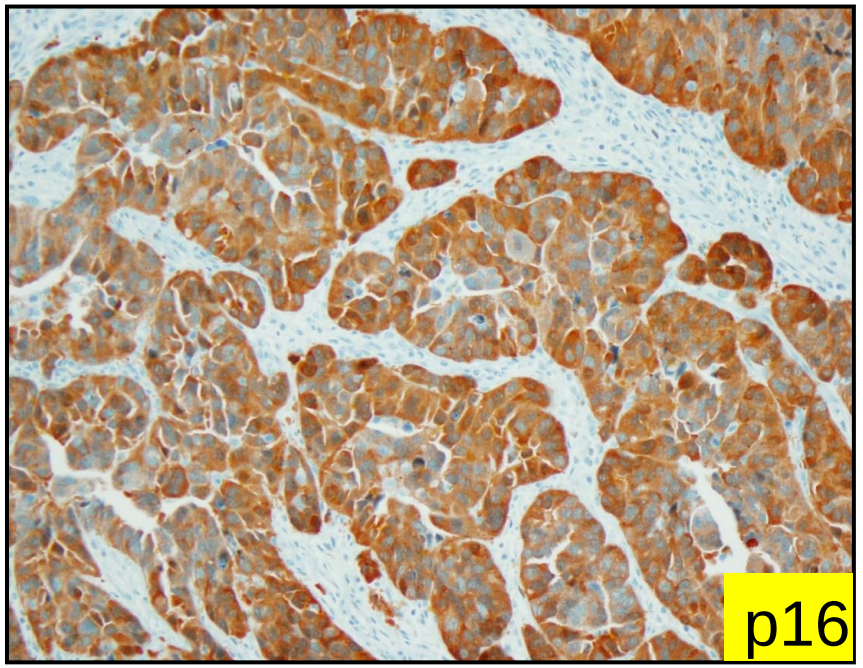
can be associated with metastases !

Serous Carcinoma

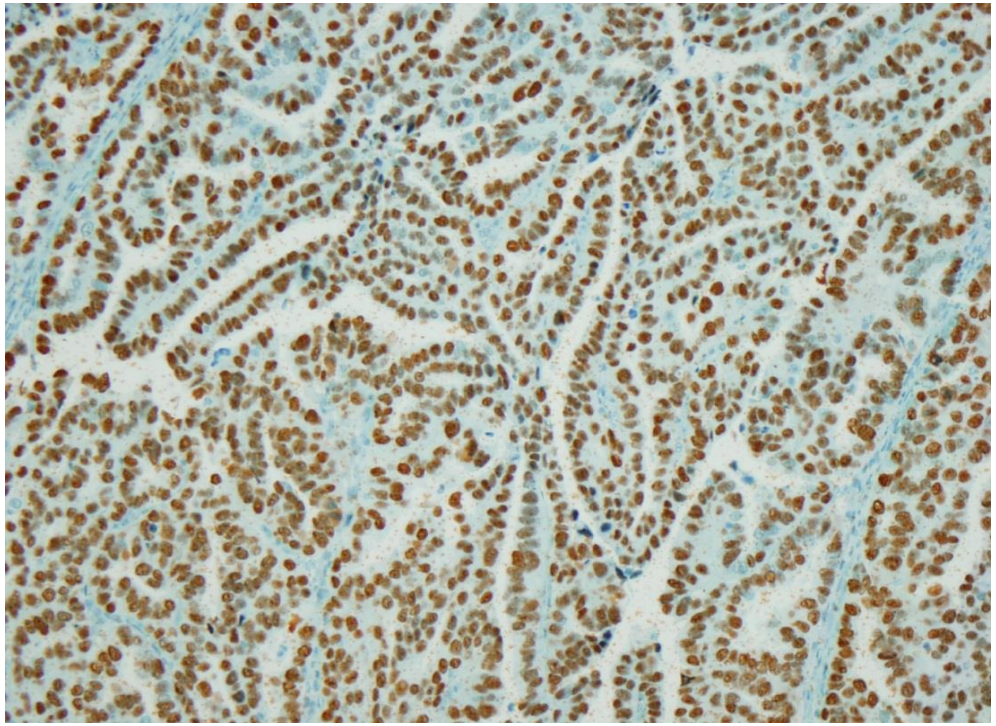
Immunohistochemical profile

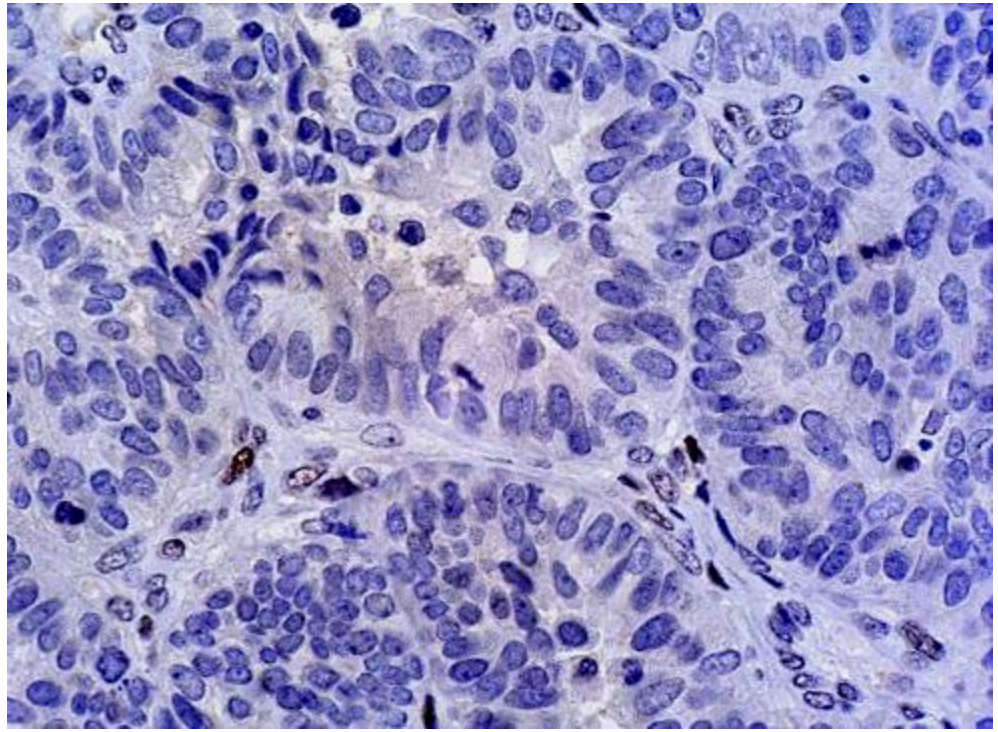
- Majority show mutation-pattern p53 staining
- diffuse expression of p16
- WT-1: focally positive in 30% of cases





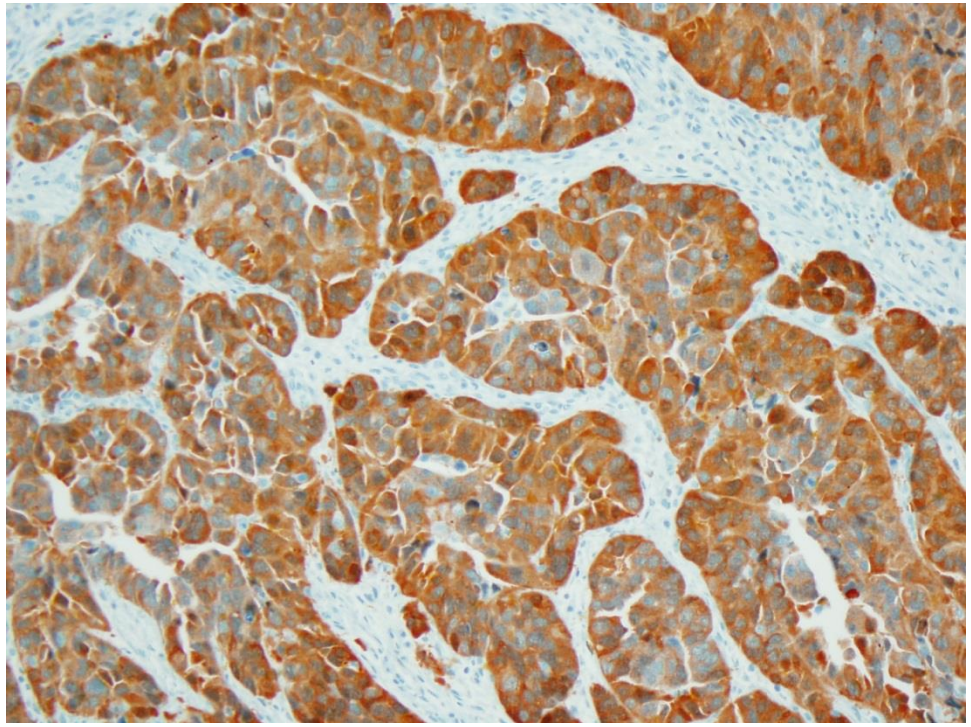
Aberrant p53 expression



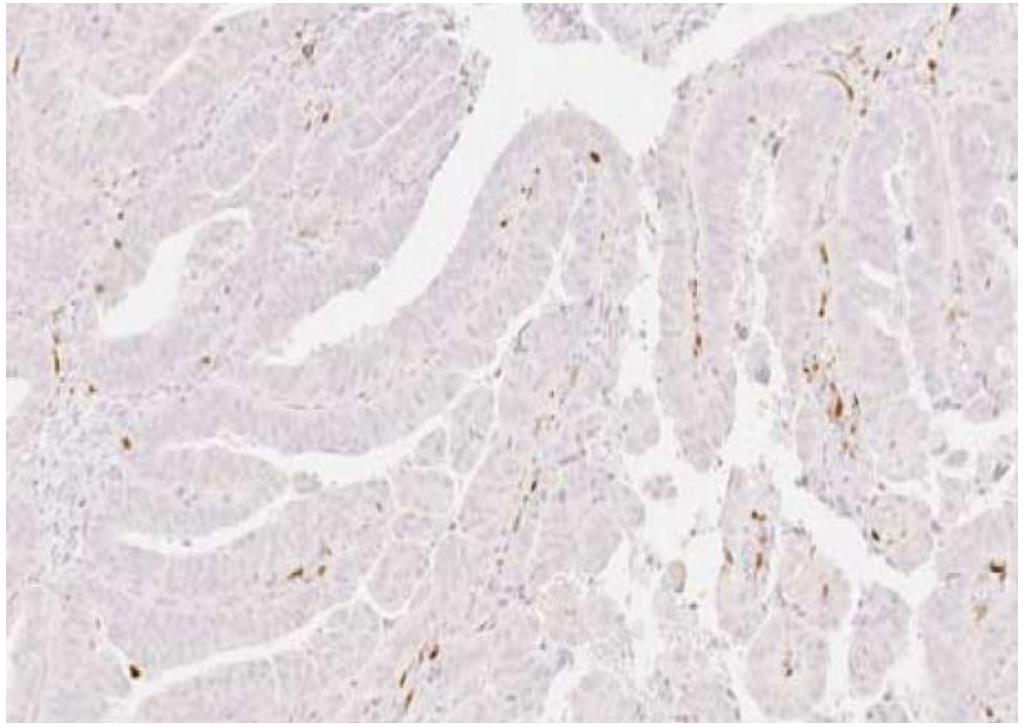


Strong and diffuse staining in >80% of tumour cells
or
Complete absence of staining

p16 expression in Serous Carcinoma



Strong and diffuse

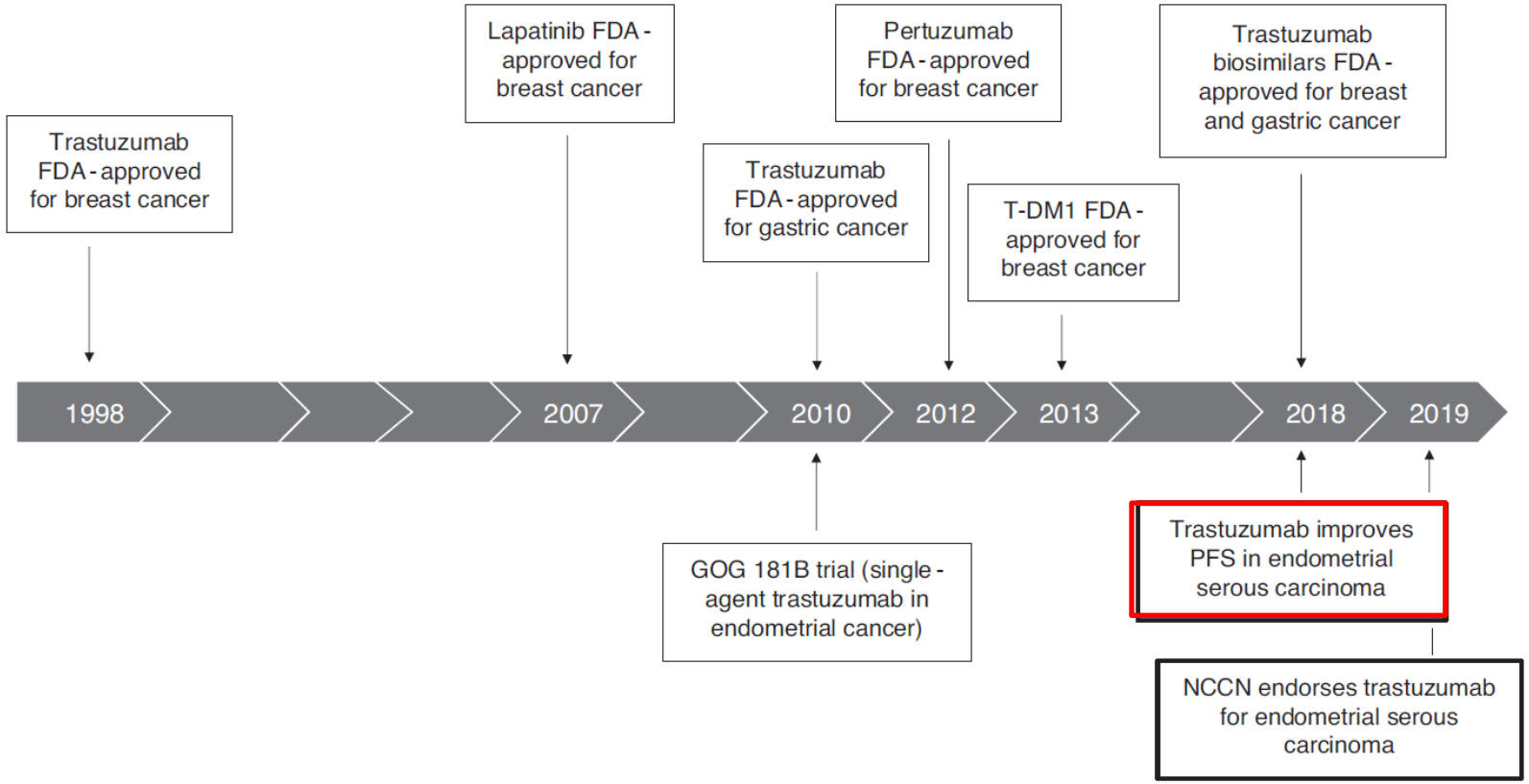


Null pattern

Matson DR et a. Int J Gynecol Pathol 2021; 41:378–388

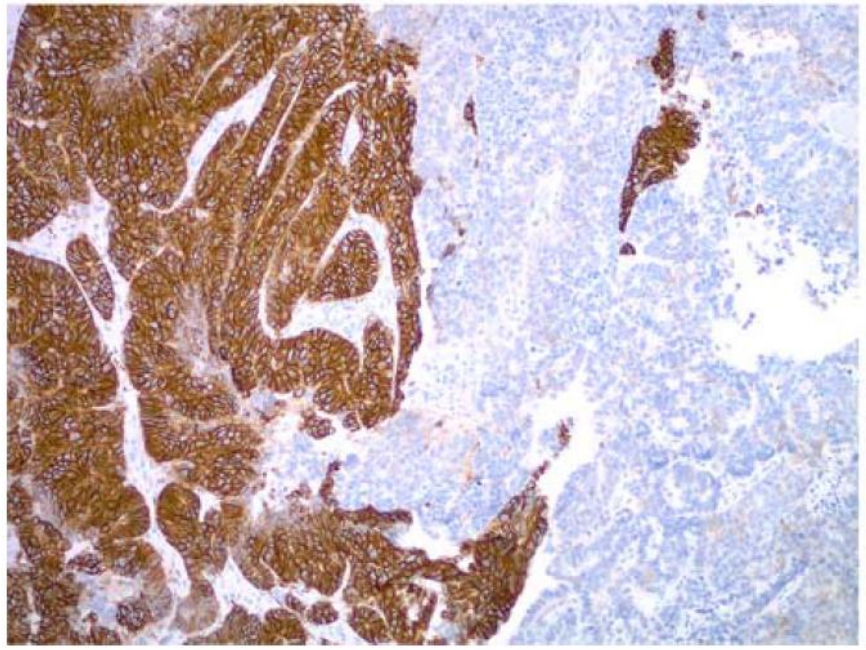
Her2 Testing in Endometrial Serous Carcinoma

ERBB2 (HER2) overexpression and/or gene amplification is seen in > 30%

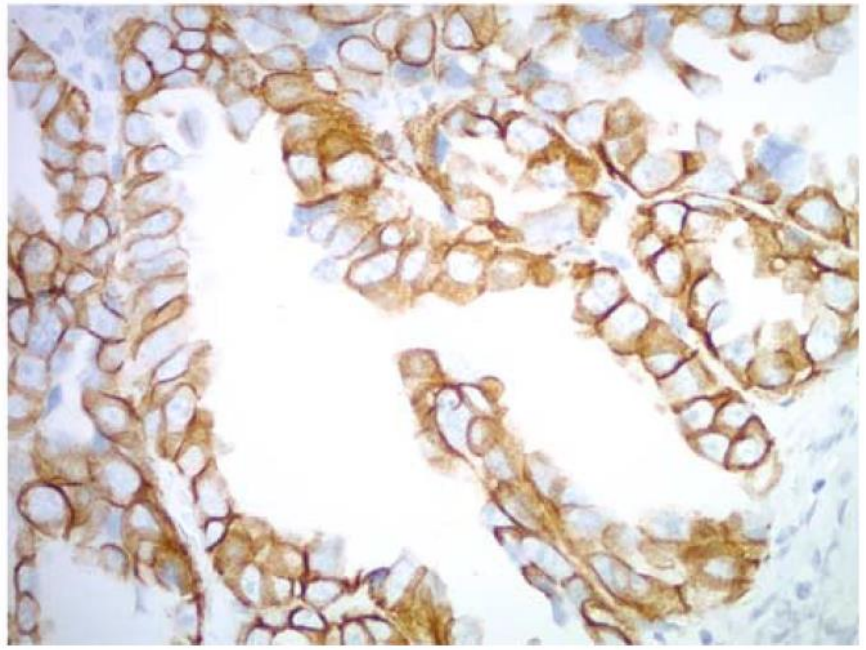


Buza N. Int J Gynecol Pathol. 40:17–23

Her2 IHC in Endometrial Serous Carcinoma

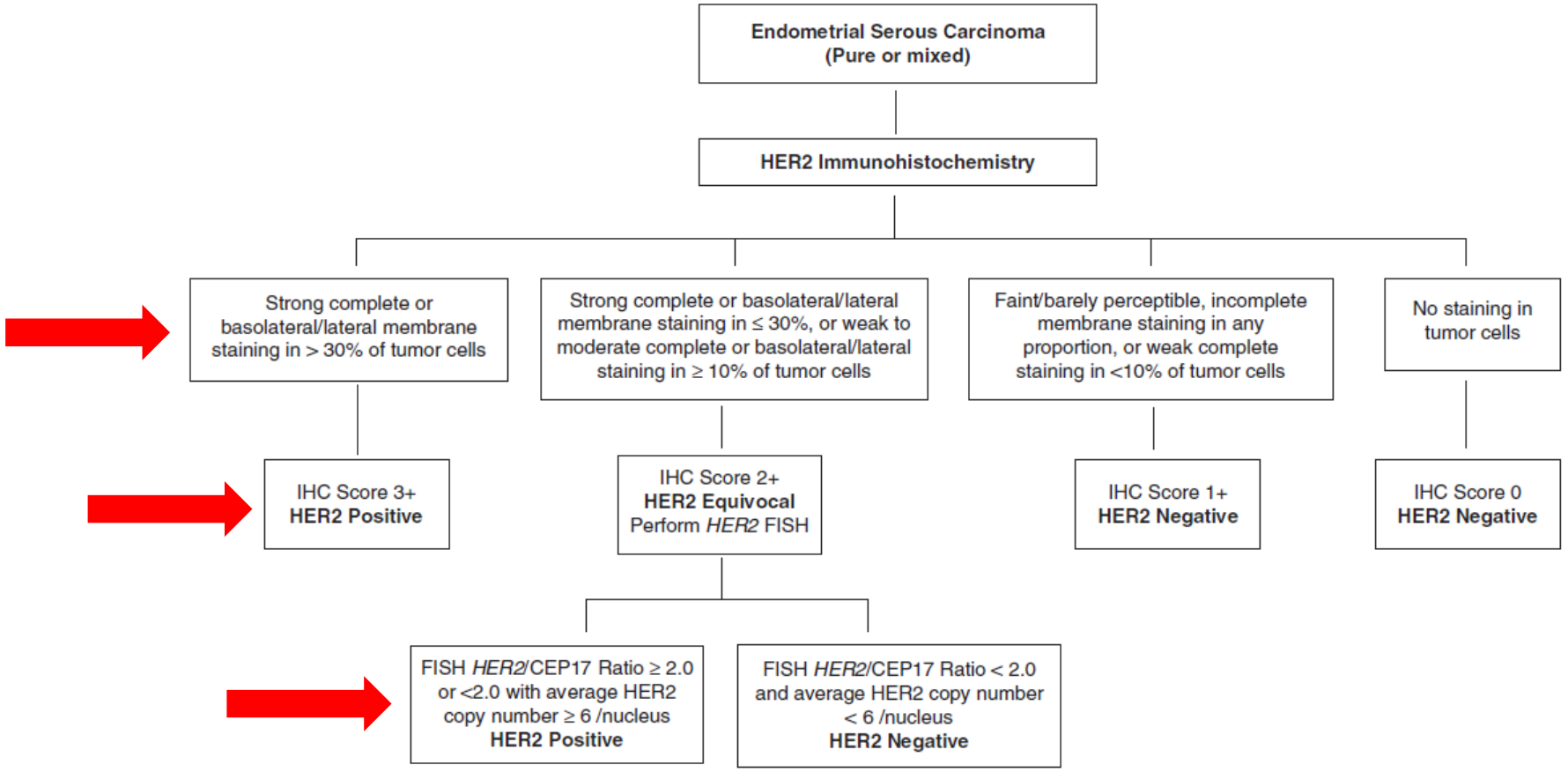


Heterogenous expression



Basolateral/lateral membranous staining

Her2 Testing in Endometrial Serous Carcinoma



Buza N. Int J Gynecol Pathol. 40:17–23

Histopathologic features and molecular genetic landscape of HER2-amplified endometrial carcinomas

Ross D et al Modern Pathology (2022) 35:962–971

Table 1. Frequency of *HER2* amplification across histologic subtypes of endometrial carcinoma.

Tumor histologic subtype	*HER2* amplification (n)	Total number of cases (n)	Frequency (%)
Serous	29	361	8.0
Endometrioid	3	1177	0.2
Clear cell	4	72	6
Carcinosarcoma	18	255	7.1
HGEC/Mixed	23	164	14
Other (undifferentiated, de-differentiated, mesonephric-like, neuroendocrine)	0	13	0

- Co-existing *TP53* mutation identified in **94%** (72/77) of HER2-amplified Ecs

- Other genetic alterations included
  - amplification of *CCNE1* (22%) and *ERBB3* (10%)
  - *FBXW7* mutations or deletions (13%)
  - Mutations in *PIK3CA* (40%) and *PPP2R1A* (13%)

Mixed Endometrial Carcinomas

- Definition – 2 or more spatially distinct tumour subtypes, at least 1 of which is serous carcinoma or clear cell carcinoma
- Most common combination – endometrioid + serous
- Excludes
  - Morphologic variants of endometrioid, serous or clear cell
  - Endometrioid carcinoma with mucinous differentiation
  - Dedifferentiated endometrial carcinoma
  - Carcinosarcoma

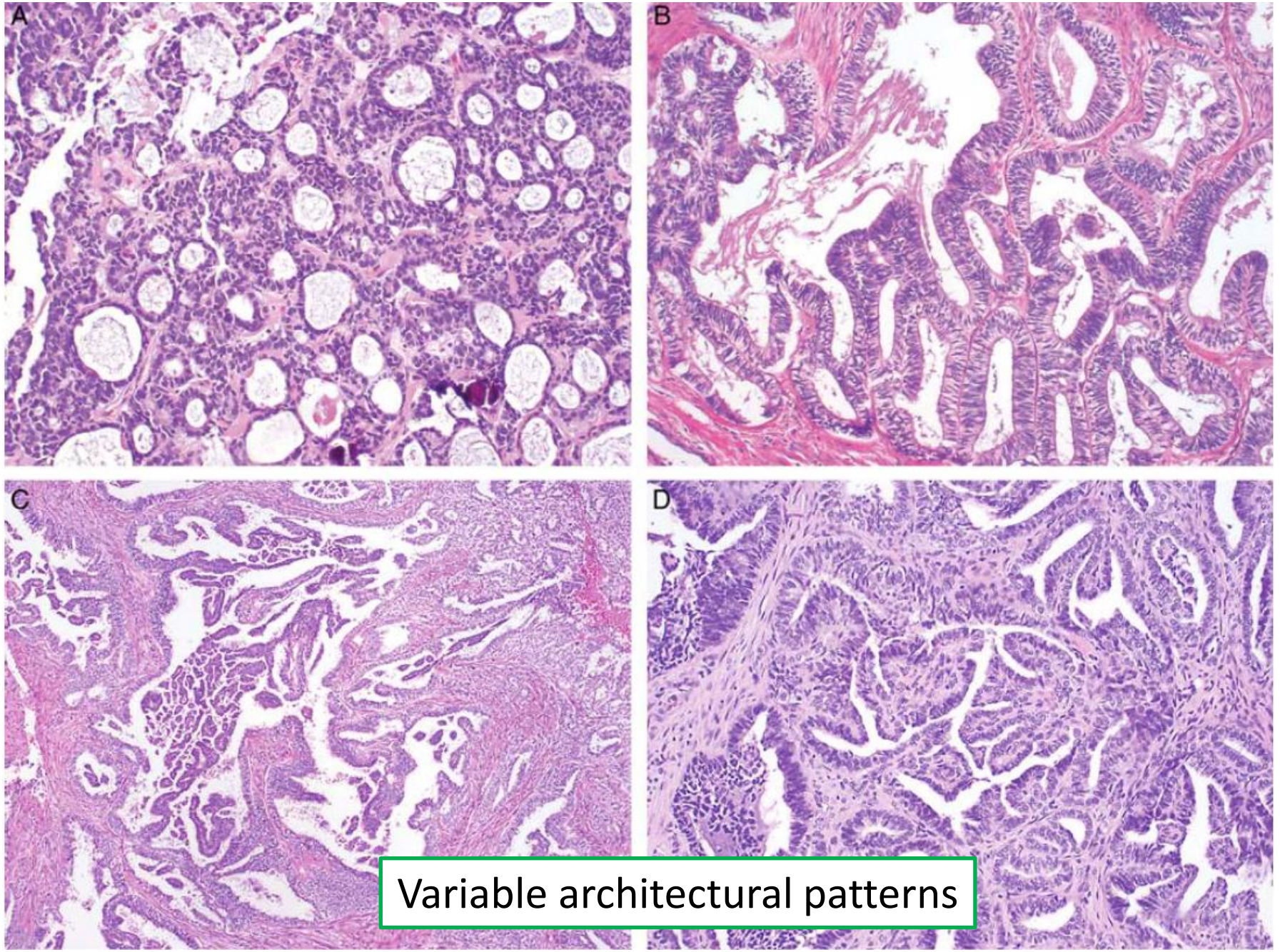
Mixed Endometrial Carcinomas

- No minimum amount of serous or clear cell carcinoma needed
- Immunohistochemical support for 2 distinct types is desirable
- Avoid using this category for tumours with ambiguous morphology
- Report should include
  - tumour types present and their grade
  - Their respective percent composition

Mesonephric-like adenocarcinomas (MLA)

- Similar histologic and immunophenotypic features as mesonephric carcinoma
- Diff: mucosal location and lack of mesonephric remnants/hyperplasia
- Sites of occurrence: endometrium and ovary

- Uncertain histogenesis
  - ?Mesonephric carcinomas
  - ?Mullerian carcinomas with mesonephric differentiation



Variable architectural patterns

Am J Surg Pathol. 2020 Apr;44(4):429-443

MLA-Immunoprofile

- GATA3 + (91% sensitivity, 94% specificity)
  - Loss of expression in solid, spindled and undifferentiated areas of tumor
- TTF1 +
- CD10 + (apical/luminal staining)
- Calretinin +/-
- PAX8 +/-
- CK7 +
- Negative for ER/PR
- Wild type p53
- Mosaic pattern p16

	Features in Common With Mullerian Carcinoma	Features in Common With True Mesonephric Adenocarcinoma
Pathology	Distribution within uterine corpus (predominantly endometrial-based)	Very similar morphology; absence of squamous, ciliated and mucinous differentiation; absence of adjacent endometrial hyperplasia
Immunophenotype	Focal ER positivity	Very similar immunophenotype (classically ER and PR negative; TTF1, GATA3, CD10 positive)
Associated findings	Endometriosis; other ovarian Mullerian lesions; lack of mesonephric remnants	
Molecular features	*PIK3CA, PTEN, ARID1A* mutations	*KRAS* and *NRAS* mutations

Adv Anat Pathol 2022;29:208–216

Prognosis of MLA

- Aggressive biological behavior
- a/w risk of recurrent disease with tendency for lung metastasis

Features a/w increased risk of metastasis

✓large tumor size (>4 cm)
✓ ill-defined tumor border
✓advanced FIGO stages (III to IV),
✓presence of coagulative tumor cell necrosis
✓high mitotic activity (>10/10 high-power fields)
✓presence of LVI

Am J Surg Pathol 2019;43(1):12–25

Mucinous carcinoma, gastric (gastrointestinal)-type

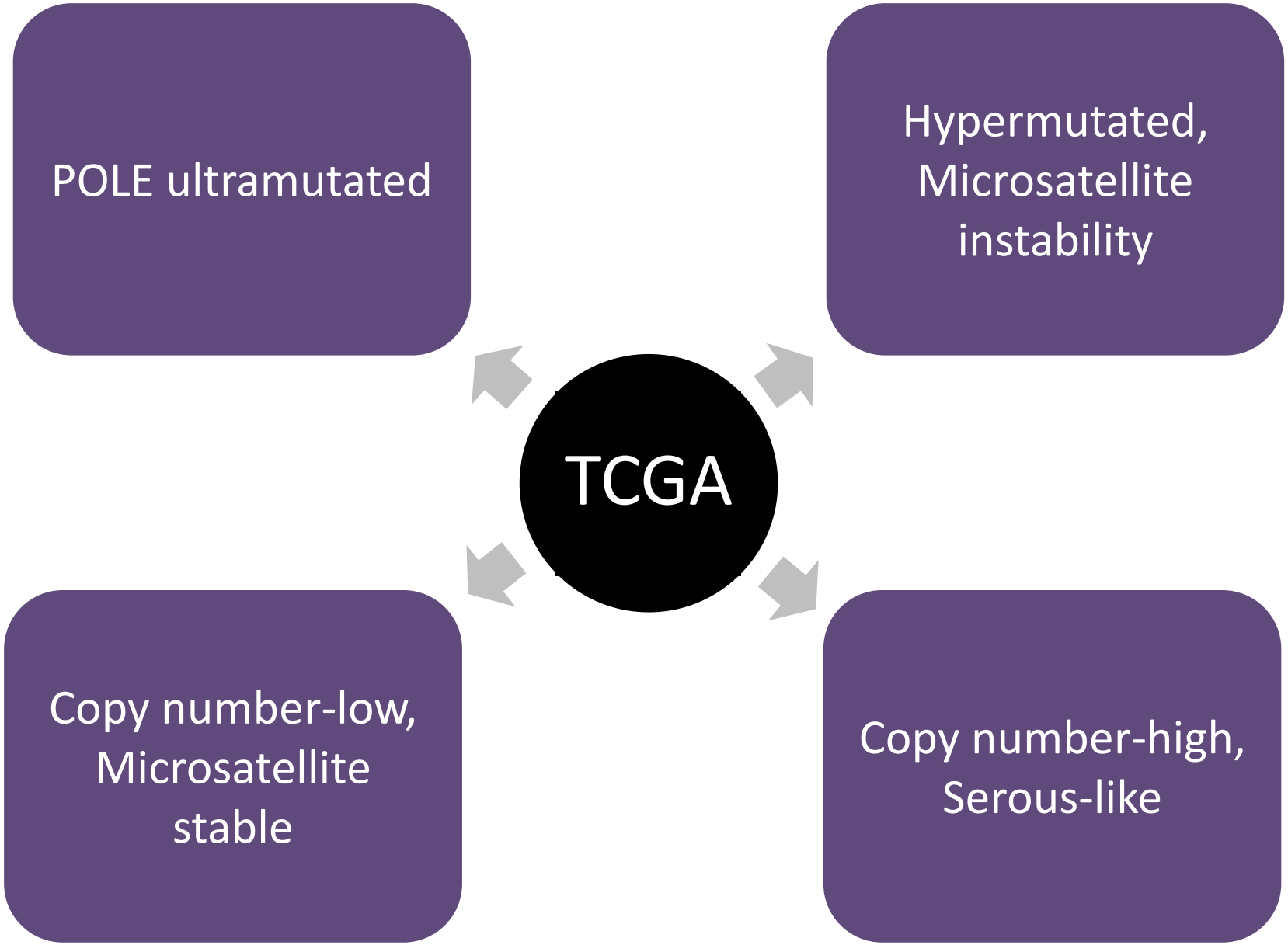
- Mucinous differentiation may be seen in endometrioid carcinoma ≠mucinous ca

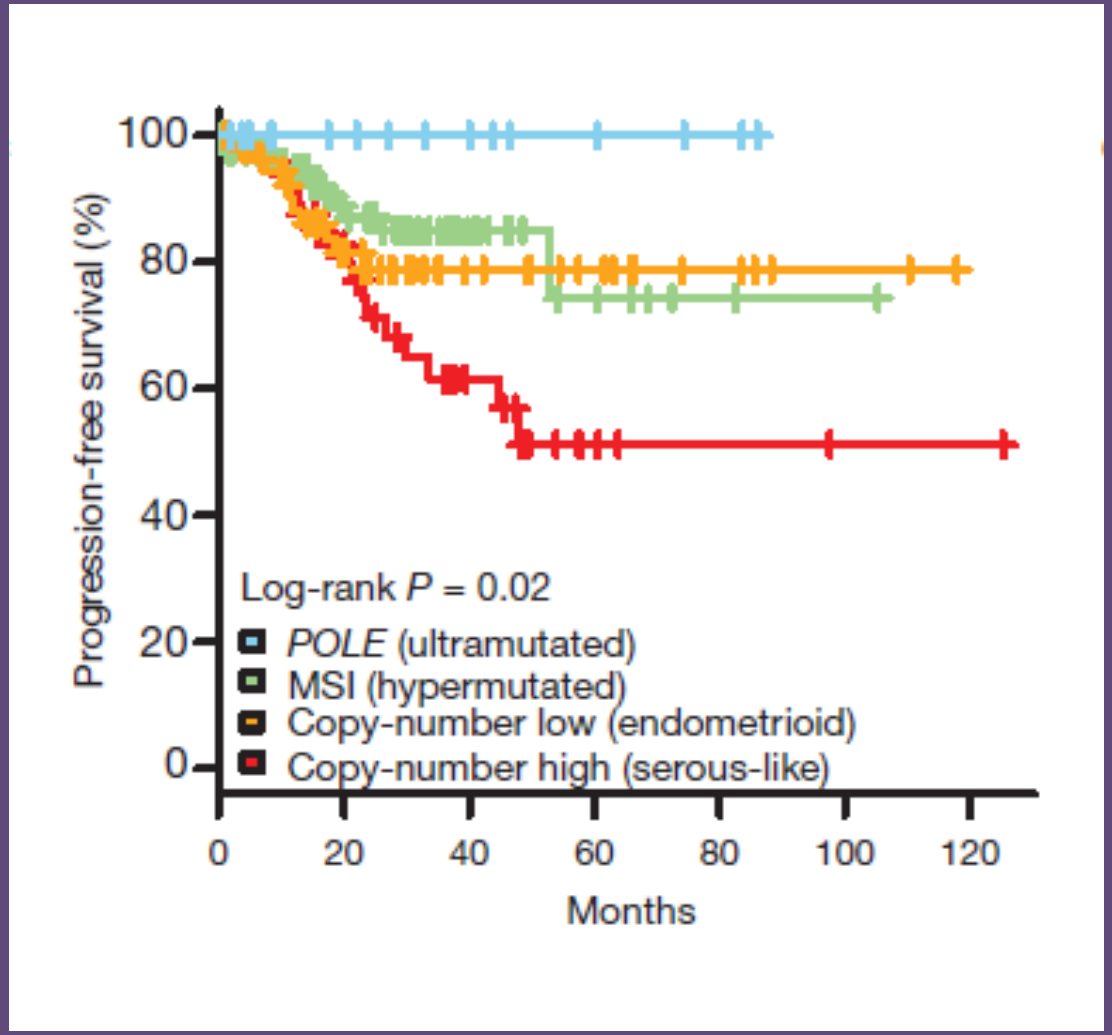
- Rare; similar to gastric type endocervical adenocarcinomas
  - Presence of gastric-type morphology and/or goblet cells
  - Absent/minimal expression of ER
  - Expression of gastrointestinal markers

- Differentials:
  - Cervical primary
  - metastasis from GIT

- Aggressive behaviour

Molecular Classification of Endometrial Carcinoma


POLE ultramutated
Hypermutated, Microsatellite instability
TCGA
Copy number-low, Microsatellite stable
Copy number-high, Serous-like



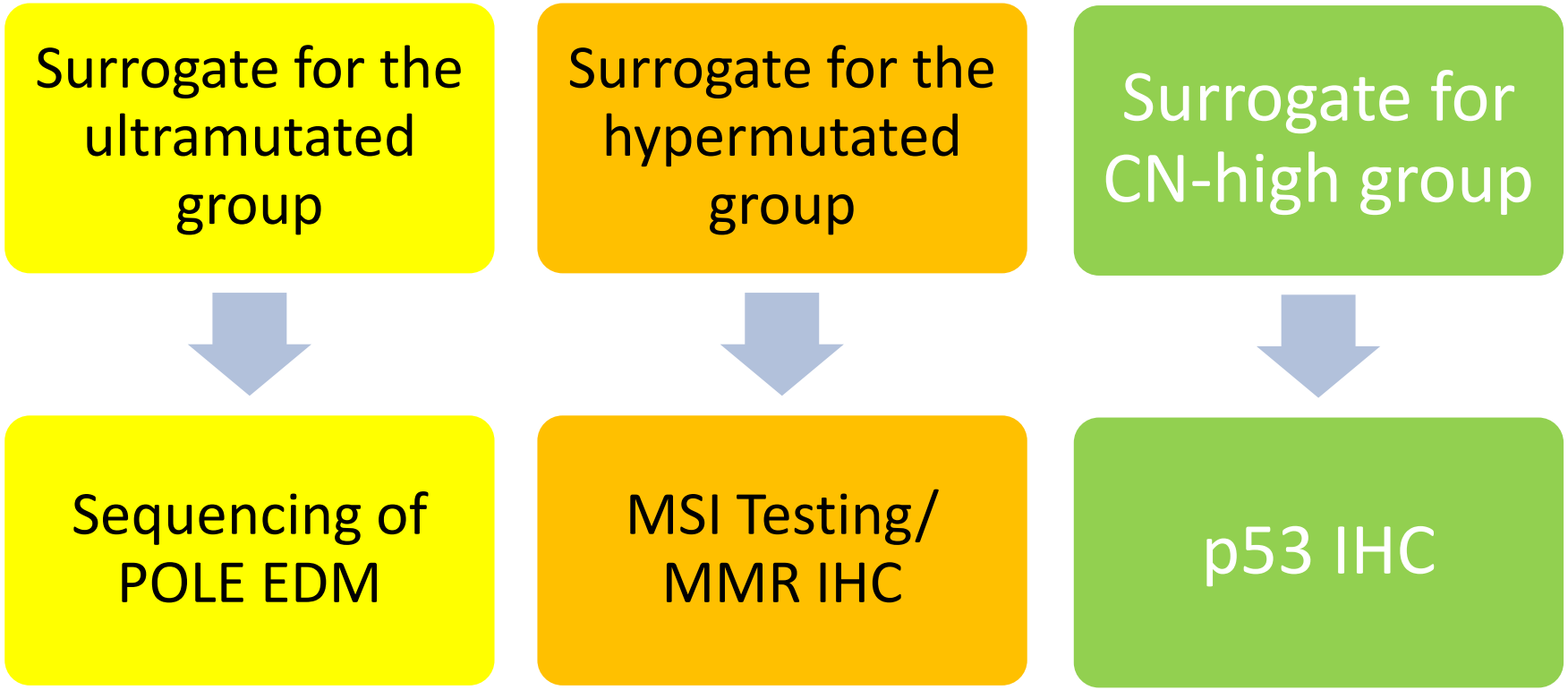
TCGA. *Nature* 2013;497(7447):67-73

Clinicopathological and Molecular Characteristics of the Molecular Subgroups

	POLE-mutant (i.e. *POLE* EDM)		MMRd (i.e. MSI)		NSMP (i.e. p53 wt)		p53-aberrant (i.e. p53 abn, p53-mutant)	
Mutational frequency	> 100 mutations/Mb		100–10 mutations/Mb		< 10 mutations/Mb		< 10 mutations/Mb	
Somatic copy-number alterations	Very low		Low		Low		High	
Top five recurrent gene mutations (%)	*POLE*	(100%)	*PTEN*	(88%)	*PTEN*	(77%)	*TP53*	(92%)
	DMD	(100%)	*PIK3CA*	(54%)	*PIK3CA*	(53%)	*PIK3CA*	(47%)
	CSMD1	(100%)	*PIK3R1*	(42%)	*CTNNB1*	(52%)	*FBXW7*	(22%)
	FAT4	(100%)	*RPL22*	(37%)	*ARID1A*	(42%)	*PPP2R1A*	(22%)
	PTEN	(94%)	*ARID1A*	(37%)	*PIK3R1*	(33%)	*PTEN*	(10%)
Associated histological features	Endometrioid		Endometrioid		Endometrioid		Serous	
	Grade 3		Grade 3		Grade 1–2		Grade 3	
	Ambiguous morphology		LVSI substantial		Squamous differentiation		LVSI	
	Broad front invasion		MELF-type invasion		ER/PR expression		Destructive invasion	
	TILs, peri-tumoural Lymphocytes		TILs, Crohn's-like peri-tumoural reaction				High cytonuclear atypia	
							Giant tumoural cells	
	Giant tumoural cells		Low uterine segment involvement				Hobnailing	
							Slit-like spaces	
Associated clinical features	Lower BMI		Higher BMI		Higher BMI		Lower BMI	
	Early stage (IA/IB)		Lynch syndrome				Advanced stage	
	Early onset						Late onset	
Prognosis in early stage (I–II)	Excellent		Intermediate		Excellent/intermediate/poor		Poor	
Diagnostic test	Sanger/NGS (exons 9, 13, 14 or 9–14)		MMR-IHC (MLH1, MSH2, MSH6, PMS2)				p53-IHC	
	Tumour mutation burden		MSI assay				NGS	
			Tumour mutation burden				SCNA	
Suggested treatment options in recurrent/metastatic disease*	Checkpoint inhibitors		Checkpoint inhibitors		Hormonal therapy mTOR inhibitors		Small molecule activators of p53	
							PARPi	

McAlpine J et al. J Pathol 2018; 244: 538–549

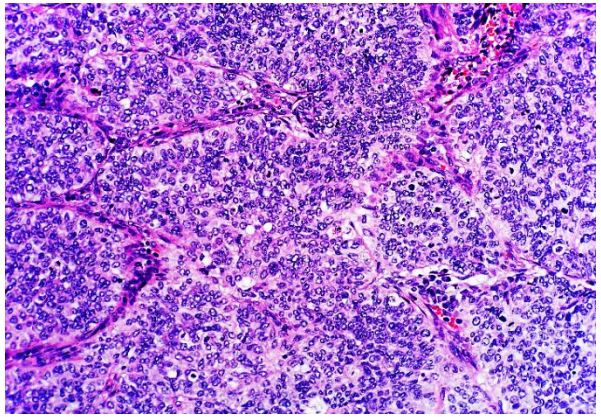
How can we molecularly classify endometrial cancers in routine clinical practice?

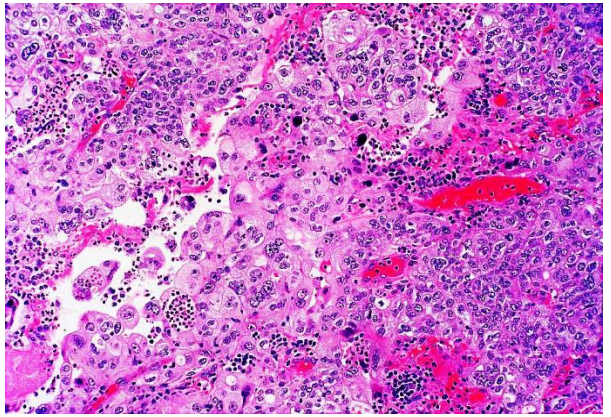


POLE TESTING

Clinicopathological Features of EC with *POLE* Mutation

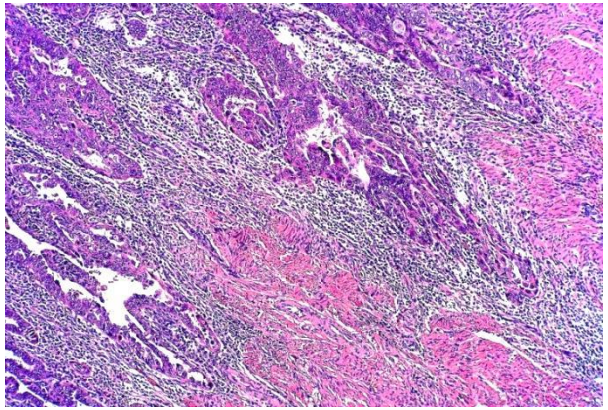
High grade tumours

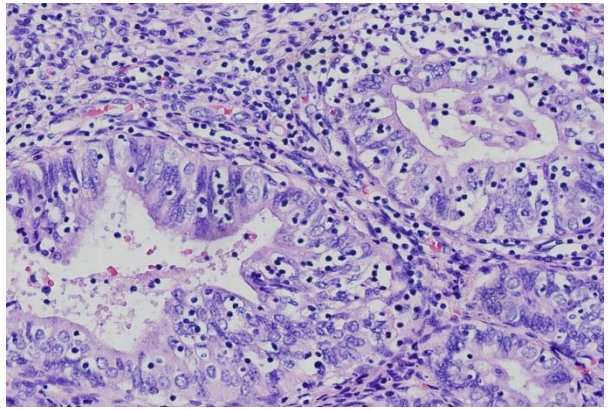




Ambiguous morphology

Peritumoral lymphocytes





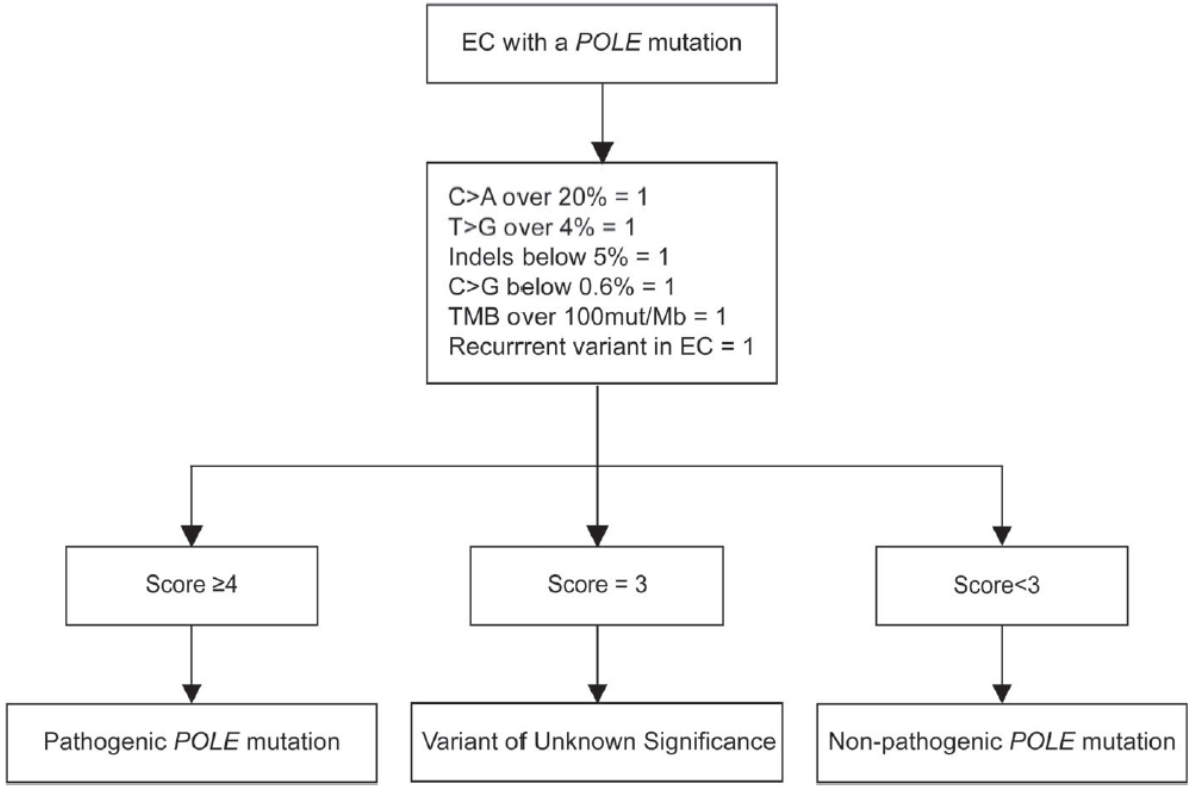
Tumour infiltrating lymphocytes

Testing for *POLE* Mutations

- *POLE* exonuclease domain mutations
  - Single gene assays eg Sanger Sequencing
  - Next generation sequencing
- Tumour mutational burden

- Majority of mutations outside the exonuclease domain are not pathogenic

POLE Score

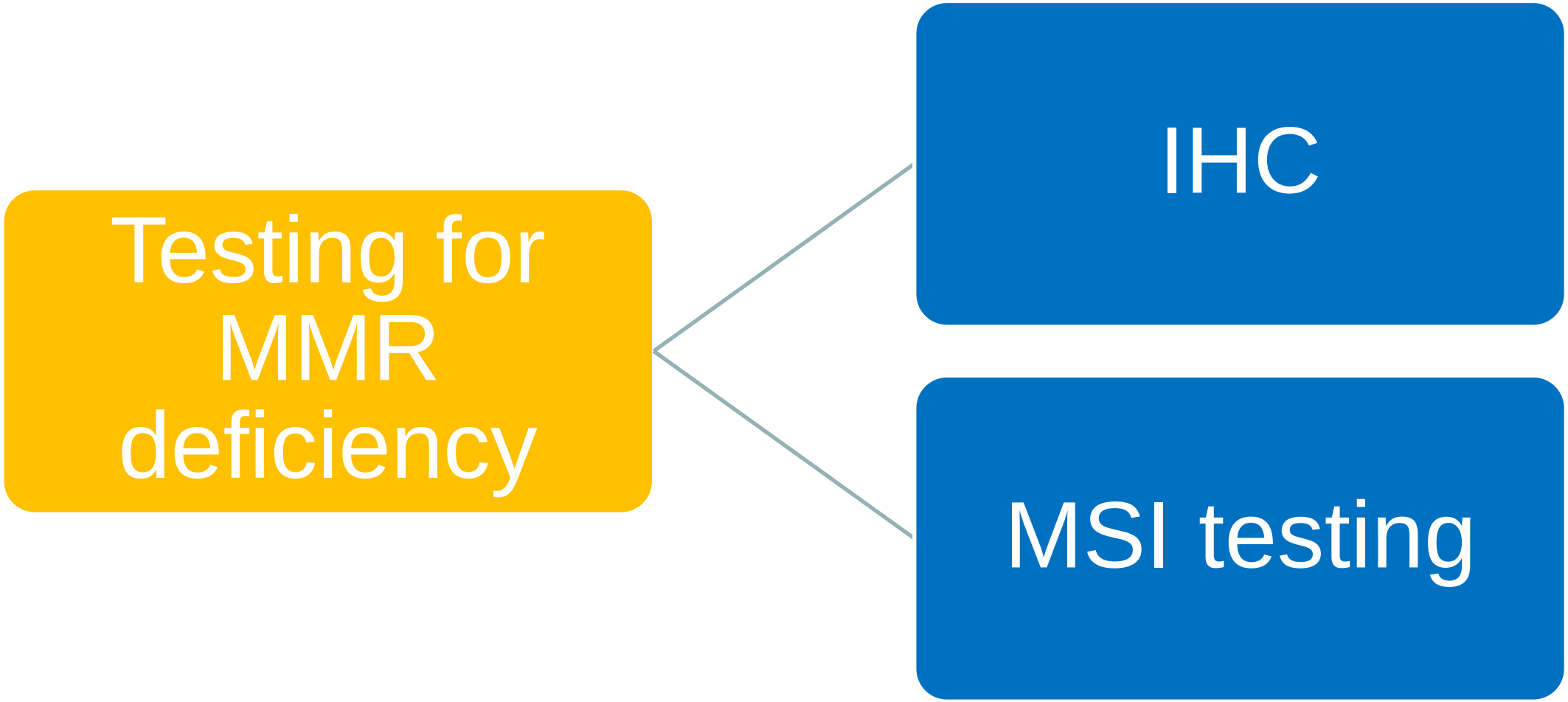


Pathogenic POLE EDM based on POLE-score

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

Alicia León-Castillo et al. J Pathol 2020; 250: 323–335

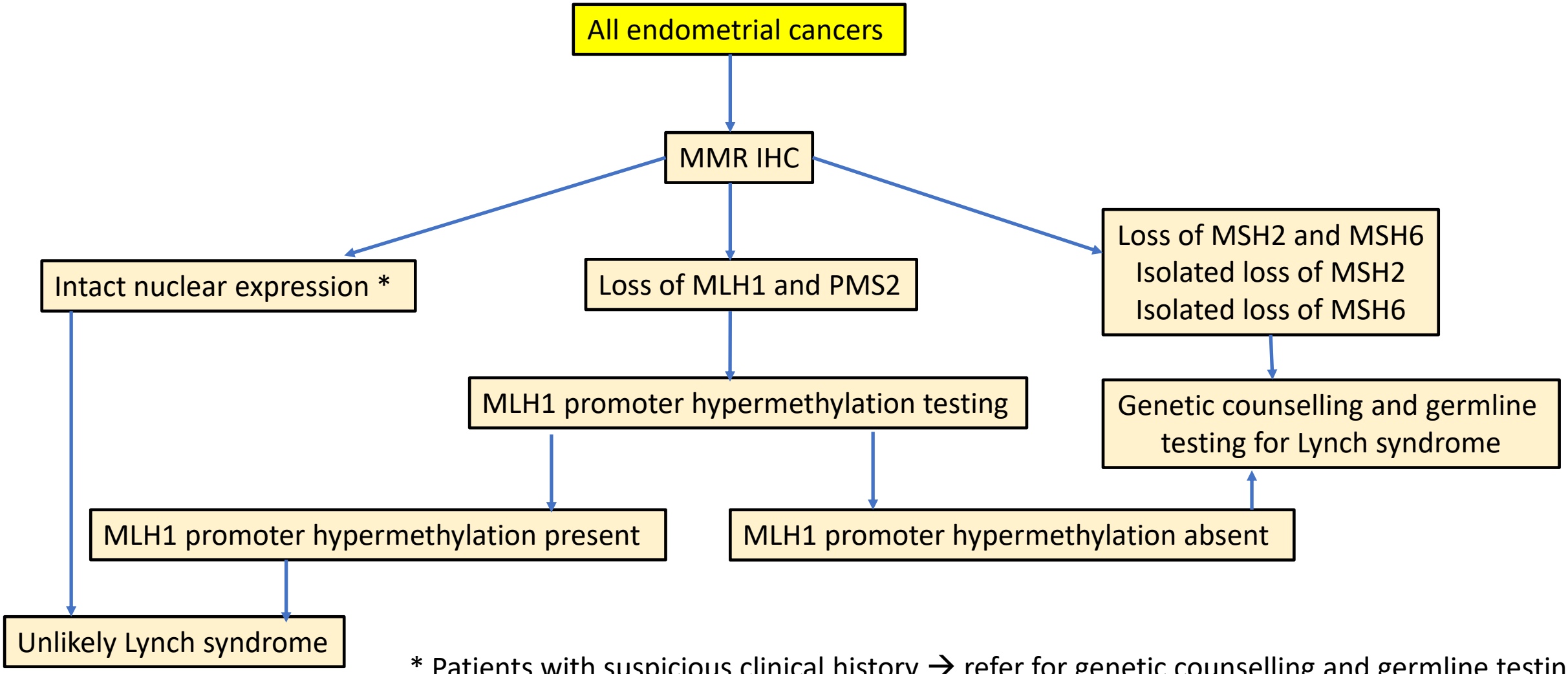
MMR/MSI TESTING


Testing for MMR deficiency
IHC
MSI testing

MMR IHC

- Stain for MMR proteins: MLH1,MSH2, MSH6, PMS2
- High concordance with MSI assay (>90%)
- A simplified two-antibody (PMS2 and MSH6) approach has been proposed as a cost-effective alternative

Universal Screening Model



* Patients with suspicious clinical history → refer for genetic counselling and germline testing

Why test for MMR/MSI in EC?

1. Diagnostic (MMRd/MSI is considered a marker for endometrioid-type EC)
2. Pre-screening (to identify patients at higher risk for Lynch syndrome)
3. Prognostic
4. Predictive (for use of immunotherapy)

P53 TESTING

P53 IHC

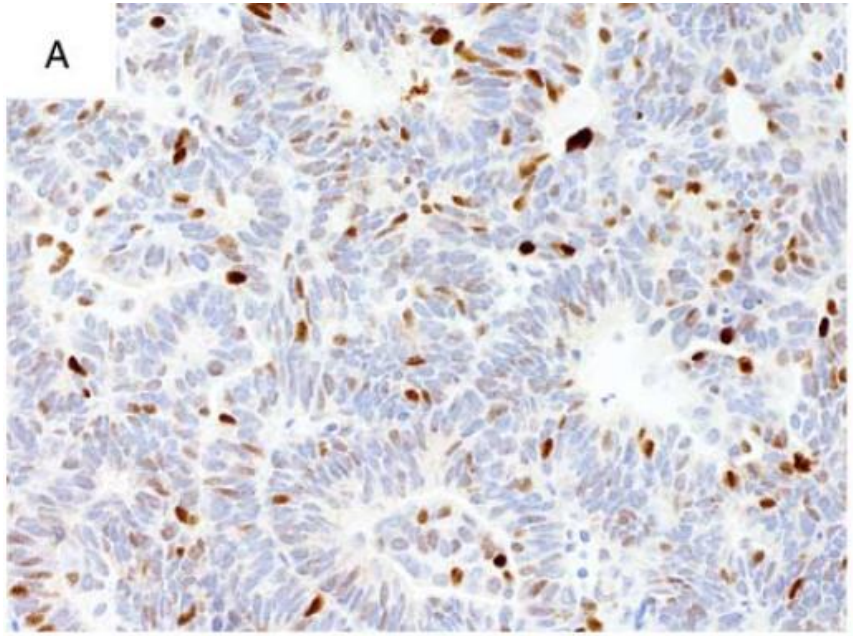
4 main patterns of staining

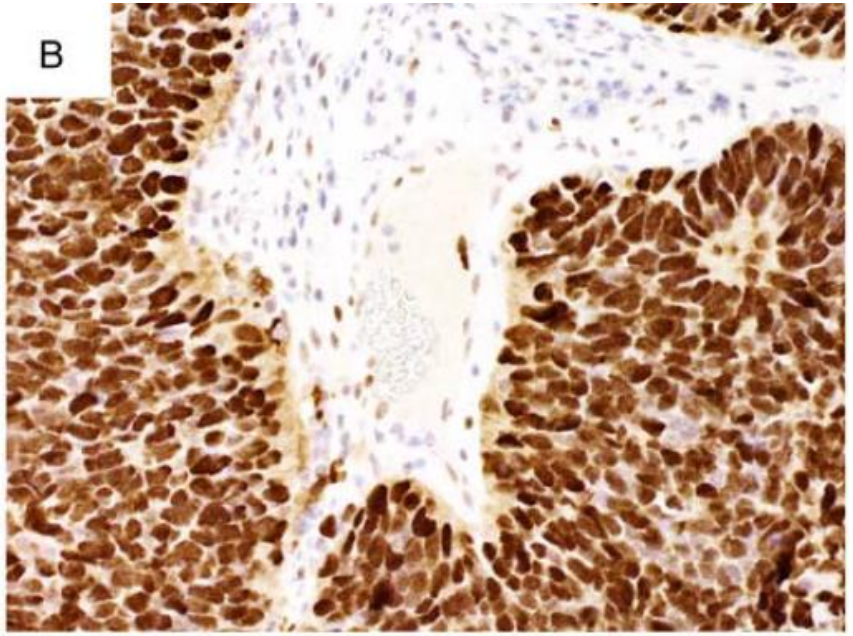
- Complete absence (null pattern)
- Overexpression
- Cytoplasmic
- Wild-type

Pattern of staining should be reported as

- wild-type or
- abnormal/aberrant/mutation type (describe pattern)
- do not report as positive or negative

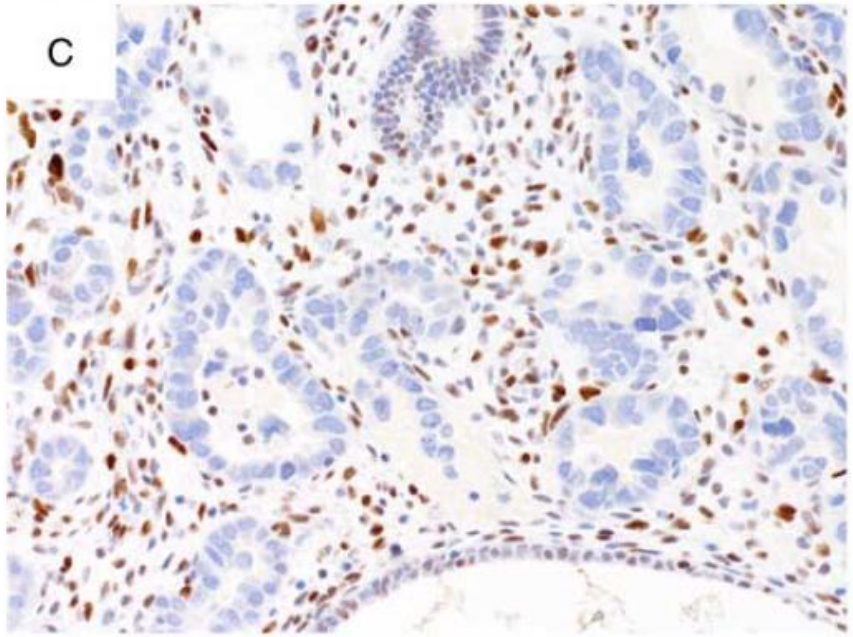
Wild-type

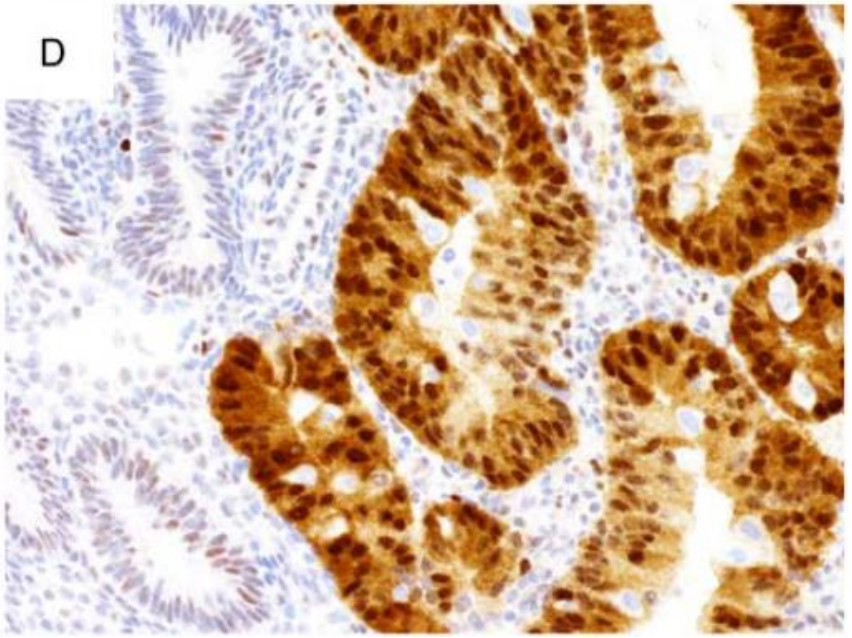




Overexpression

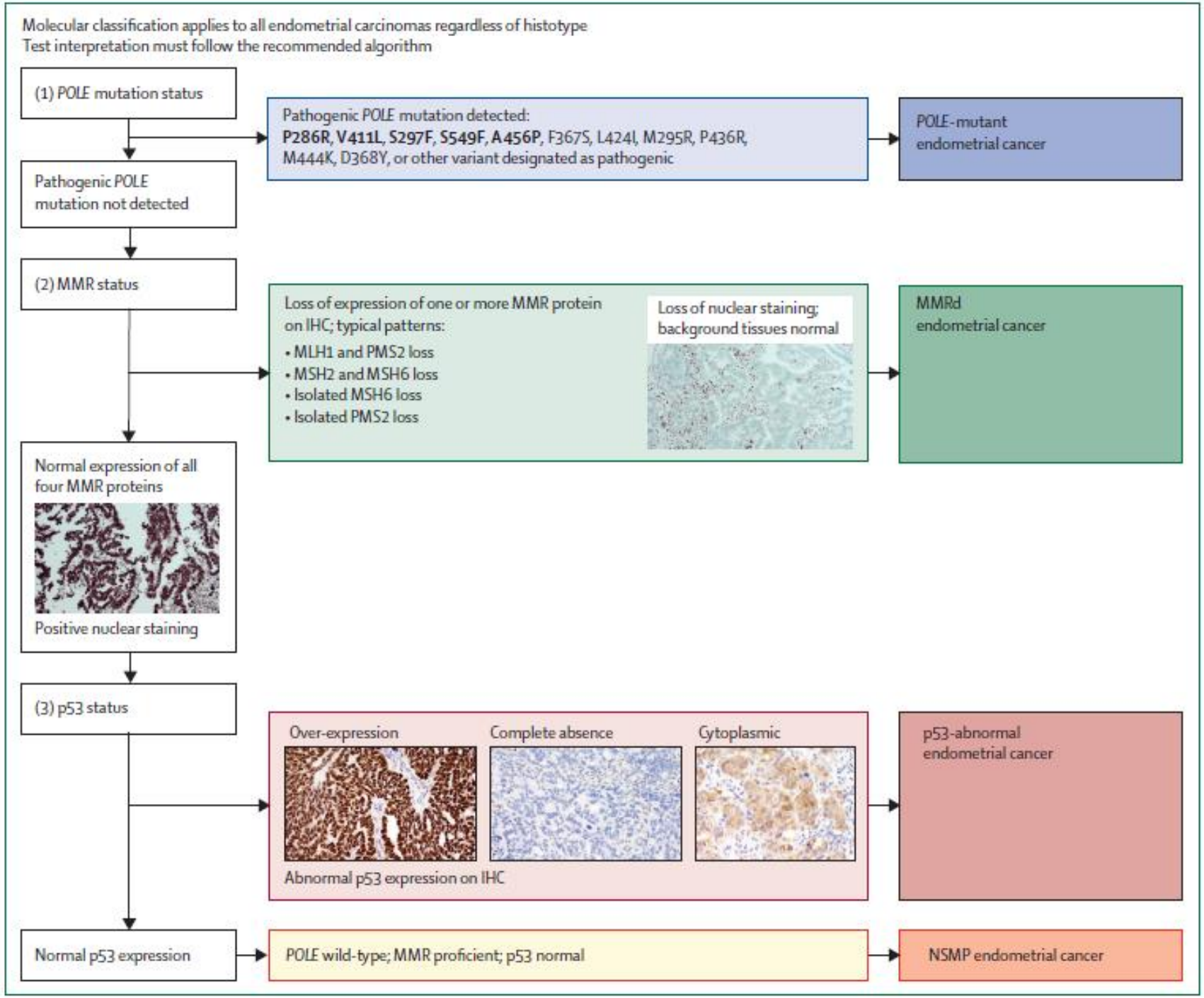
Null pattern





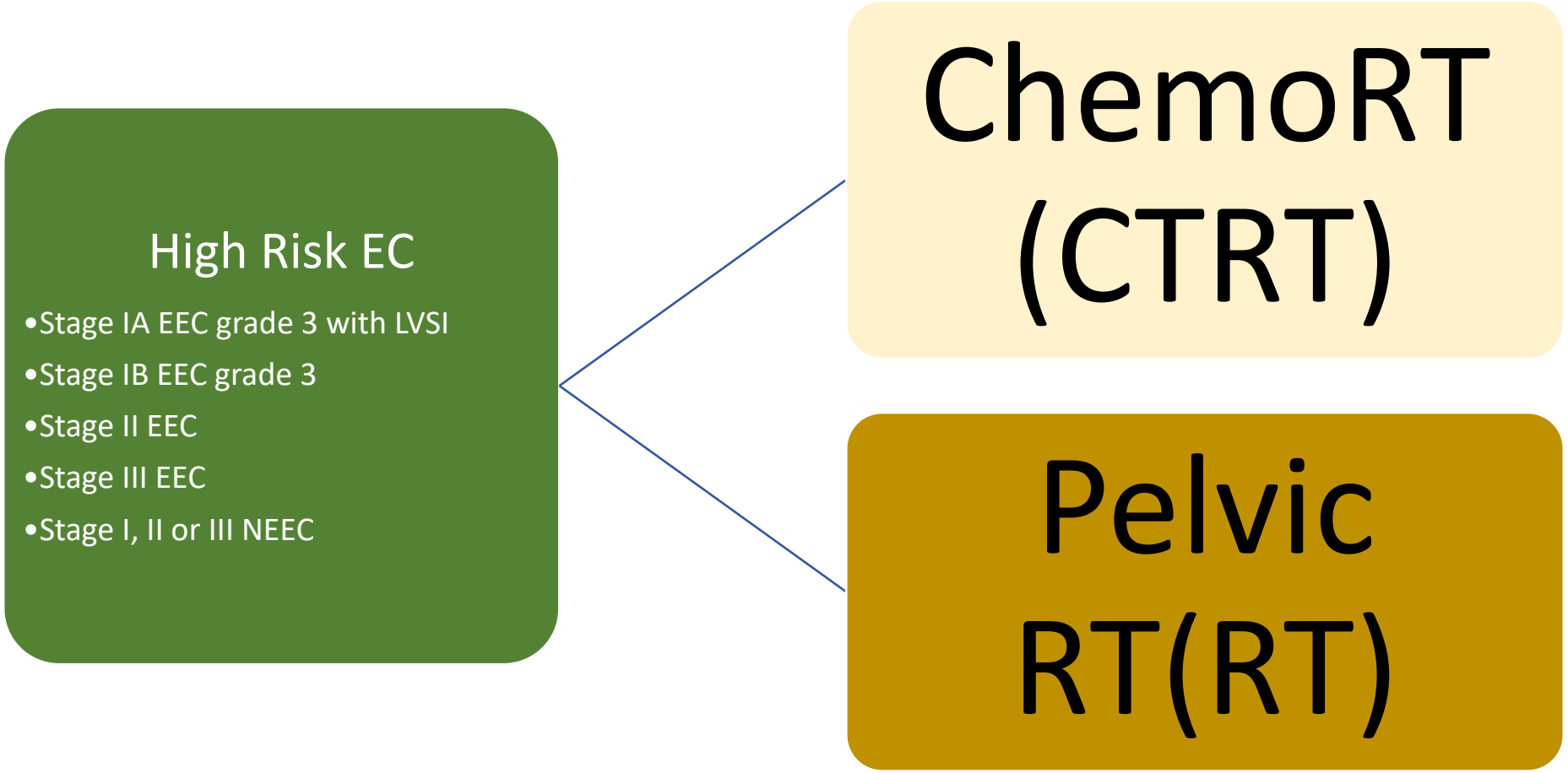
Cytoplasmic

Kobel M et al. Int J Gynecol Pathol 2019;38:S123–S131



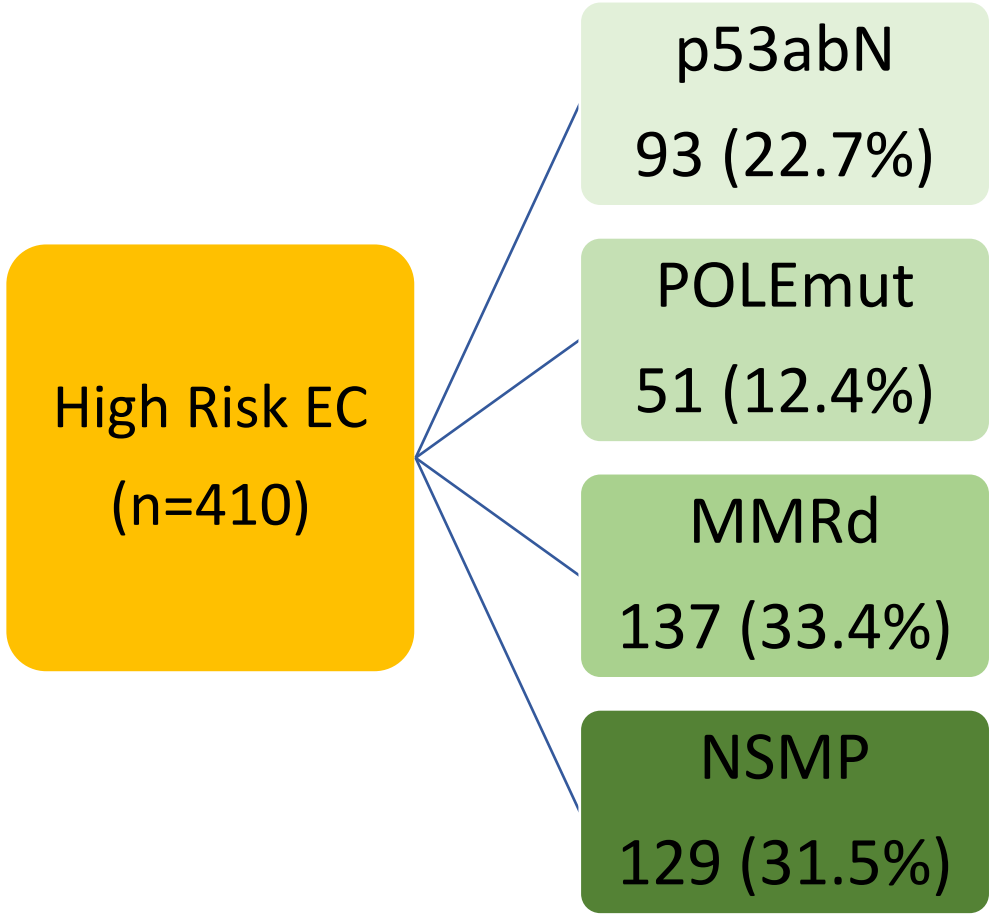
Lancet 2022; 399: 1412–28

PORTEC-3



León-Castillo et al. J Clin Oncol 2020 38:29, 3388-3397

PORTEC-3



Characteristic	Total	p53abn	*POLE*mut	MMRd	NSMP	*P*
No. of patients	410 (100)	93 (22.7)	51 (12.4)	137 (33.4)	129 (31.5)	
Age, years						< .001
Mean (range)	61.2 (26.7-80.5)	65.8 (47.3-80.5)	57.2 (42.7-72.3)	60.6 (33.5-76.5)	60.1 (26.7-78.6)	
Histotype						< .001
EEC grade 1-2	161 (39.3)	4 (4.3)	4 (7.8)	59 (43.1)	94 (72.9)	
EEC grade 3	113 (27.6)	21 (22.6)	29 (56.9)	47 (34.3)	16 (12.4)	
Serous carcinoma	65 (15.9)	46 (49.5)	6 (11.8)	7 (5.1)	6 (4.7)	
Clear-cell carcinoma	39 (9.5)	12 (12.9)	6 (11.8)	12 (8.8)	9 (7.0)	
Mixed carcinoma	19 (4.6)	6 (6.5)	3 (5.9)	7 (5.1)	3 (2.3)	
Other	13 (3.2)	4 (4.3)	3 (5.9)	5 (3.6)	1 (0.8)	
Stage						< .001
IA	54 (13.2)	23 (24.7)	12 (23.5)	13 (9.5)	6 (4.7)	
IB	73 (17.8)	14 (15.1)	20 (39.2)	26 (19.0)	13 (10.1)	
II	105 (25.6)	24 (25.8)	7 (13.7)	33 (24.1)	41 (31.8)	
IIIA	46 (11.2)	8 (8.6)	2 (3.9)	10 (7.3)	26 (20.2)	
IIIB	29 (7.1)	4 (4.3)	4 (7.8)	13 (9.5)	8 (6.2)	
IIIC	103 (25.1)	20 (21.5)	6 (11.8)	42 (30.7)	35 (27.1)	

No clear correlation between histological and molecular subtypes

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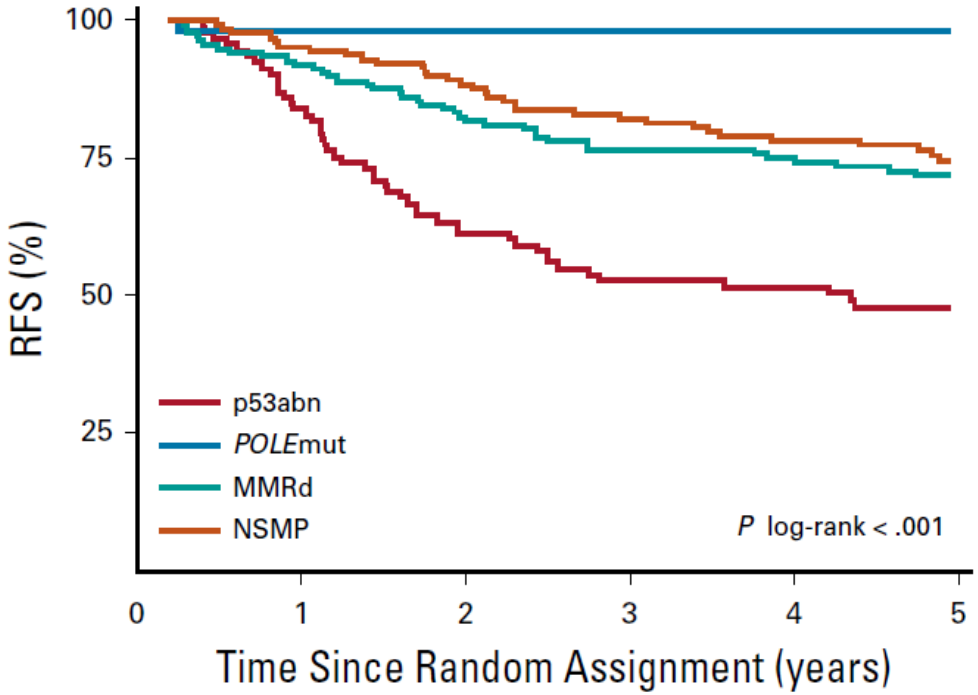
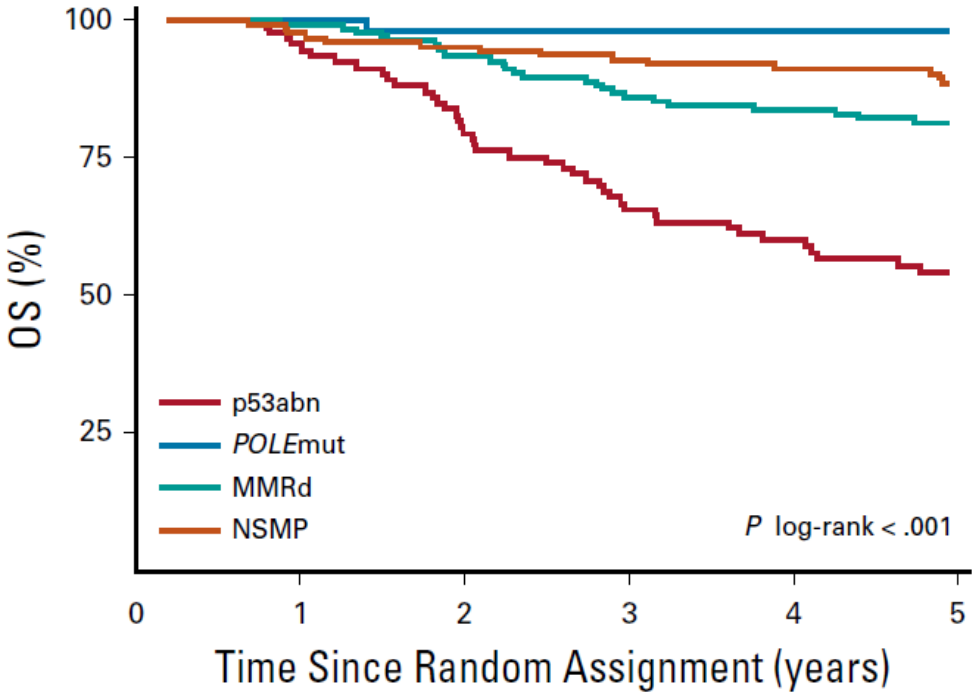
Kaplan-Meier Survival Curves for 5-year recurrence free survival (RFS) and overall survival (OS)





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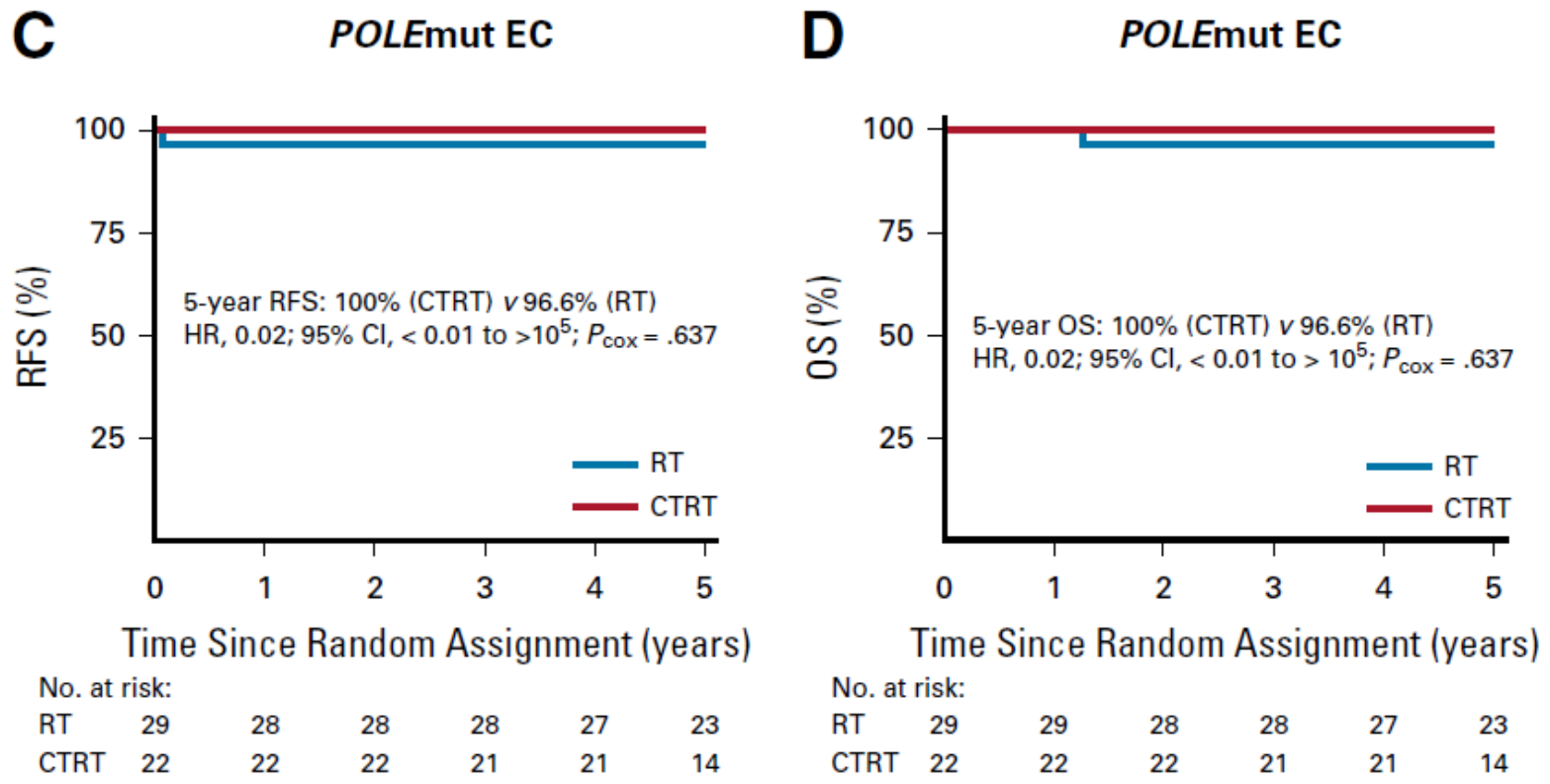

Patients with POLEmut EC had an excellent RFS and OS in both trial arms (even in those with advanced-stage and non-endometrioid histologies)

León-Castillo et al. J Clin Oncol 2020 38:29, 3388-3397

Joint statement

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin ,[1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann ,[9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou ,[13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu ,[12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Int J Gynecol Cancer 2021;31:12–39.

Recommendation:

- **Molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumors**

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

No need adjuvant Rx

Concin N, et al. Int J Gynecol Cancer 2021;31:12–39

Multiple Classifier EC

- Uncommon; simultaneous presence of two or three molecular signatures (3% of endometrial cancers)

- Outcomes correspond to those predicted by the driver molecular subtype e.g.
  - MMRd–p53abn EC behave like MMRd
  - POLEmut–p53abn EC behave like POLEmut

A León-Castillo et al J Pathol 2020; 250: 312–322

CTNNB1 Mutations in EC

- 20-25% of tumours; mostly NSMP subtype

- CTNNB1 encodes for β-catenin
  - ➢ cell to cell adhesion
  - ➢ Wnt/β-catenin signalling pathway

- Missense mutations in exon 3 ➔translocation of β-catenin to the nucleus which can be detected by IHC

- Detection
  - ✓ Sequencing (Sanger/NGS)
  - ✓ IHC (nuclear β-catenin expression)
    - ➢ Specificity (~100%)
    - ➢ Sensitivity (85-91%)

CTNNB1 Mutants – the Fifth Molecular subgroup?

- Clinicopathological features
  - usually occur in younger women
  - low grade histology
  - low rates of myometrial invasion
  - low rates of LVSI

- a/w worse outcomes with significantly increased rate of disease recurrence and lower overall survival

Future Directions

- Identify better biomarkers to guide prognosis and therapy e.g. further stratification of NSMP group using other markers e.g. CTNNB1 or ARID1A mutations and L1CAM expression

- More molecular biomarkers driven clinical trials e.g. PORTEC 4-a

- Studies involving combination therapies and new targeted agents e.g PARP inhibitors in patients with p53abn tumours