Caratterizzazione istologica e biomolecolare del carcinoma dell'endometrio e nuova classificazione

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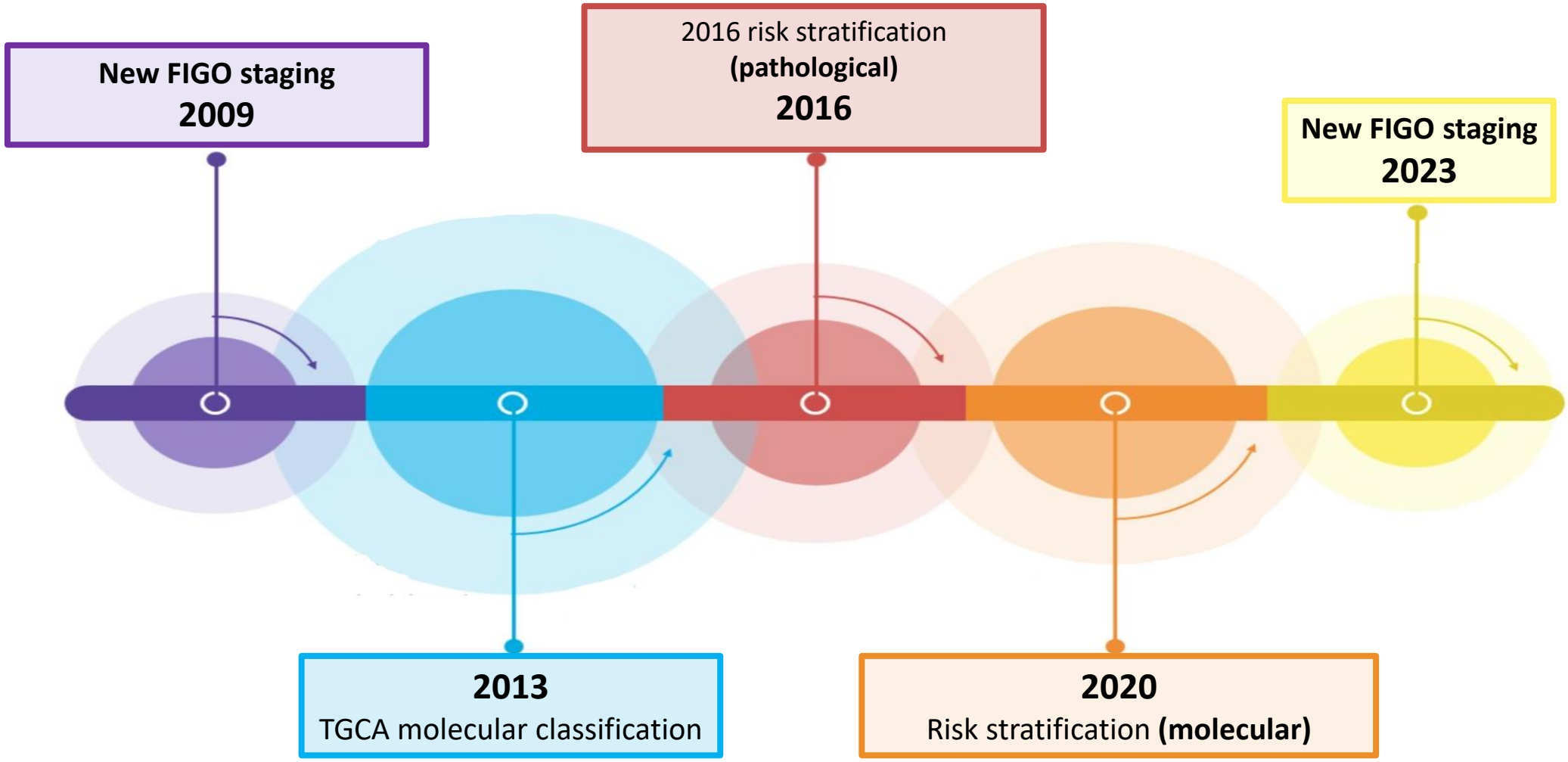
Disclosures

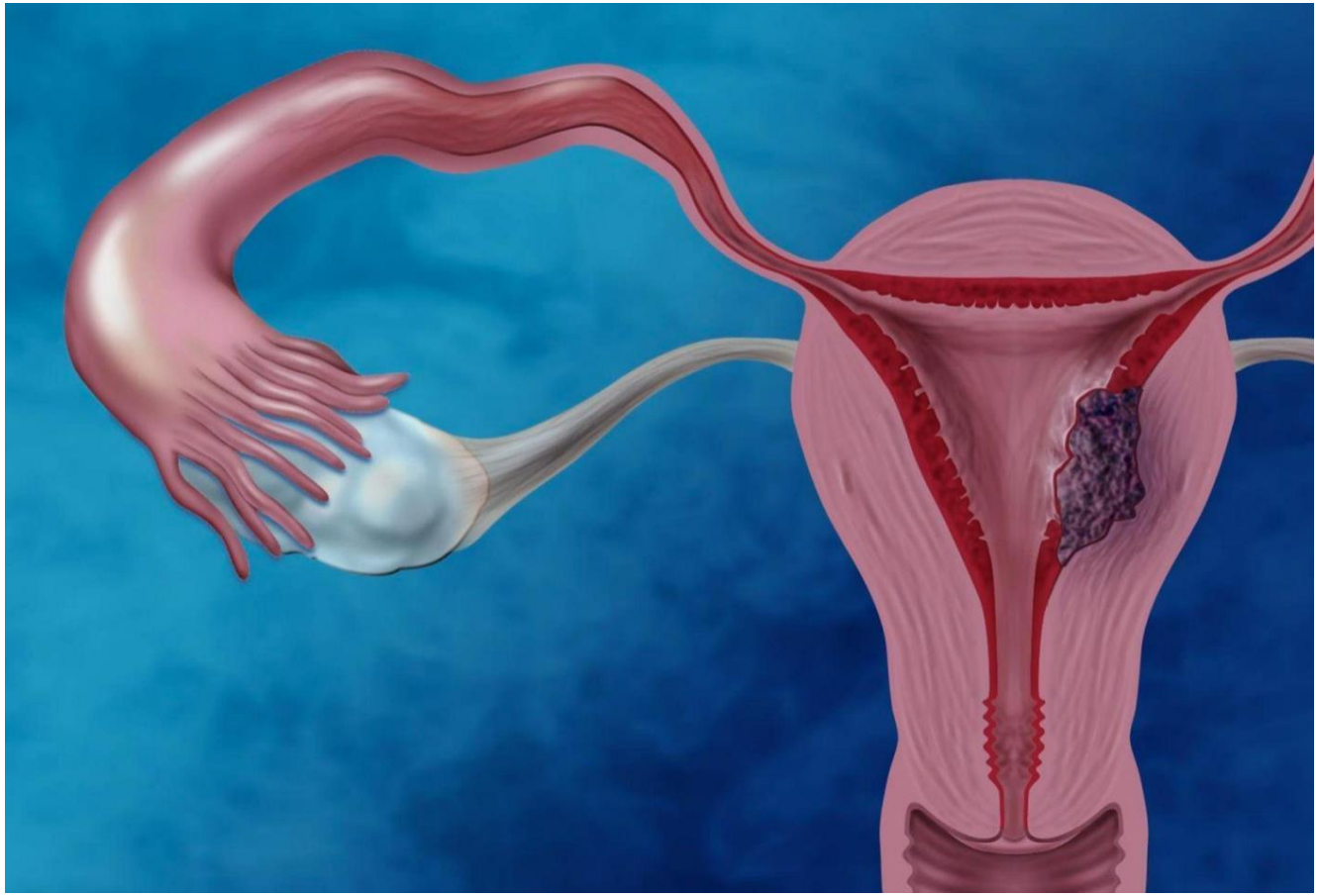
Consultancy: GSK, Clovis, Pharmamar, Arquer Diagnostics, MSD, Astrazeneca

Travel Support: Roche, Astrazeneca, Pharmamar



FIGO, International Federation of Gynecology and Obstetrics; TGCA, The Cancer Genome Atlas.

Classification of Endometrial Cancer



CONVENTIONAL

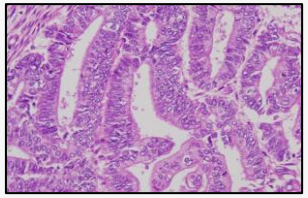
- Tumor type
- Histopathological grade
- Stage (clinical, surgical, pathological)
- Lymphovascular space invasion (LVSI)

BIOMOLECULAR

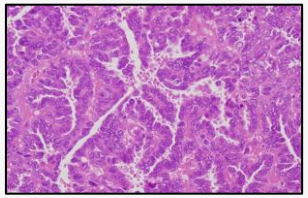
- P53 immunoreactivity/TP53 mutations
- MMR deficiency/microsatellite instability (MSI)
- Pathogenic POLE mutations

Endometrial carcinoma: Histological types

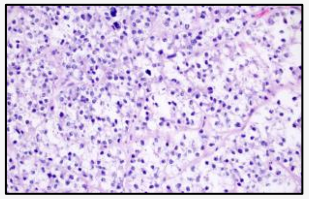
Endometrioid carcinoma



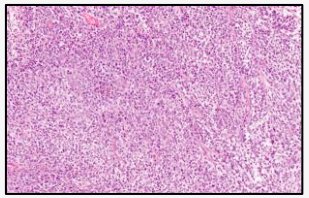
Serous carcinoma



Clear cell carcinoma

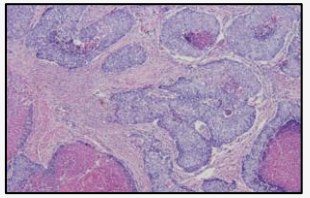


Undifferentiated/dedifferentiated carcinoma

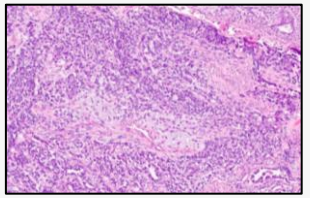


Other carcinomas

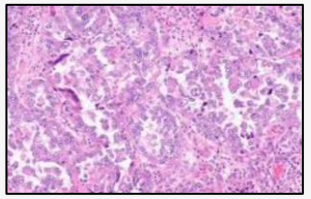
- **mesonephric-like**
- **mucinous intestinal type**
- **neuroendocrine**



Carcinosarcoma



Mixed carcinoma



WHO 2020

Less types compared to WHO 2014

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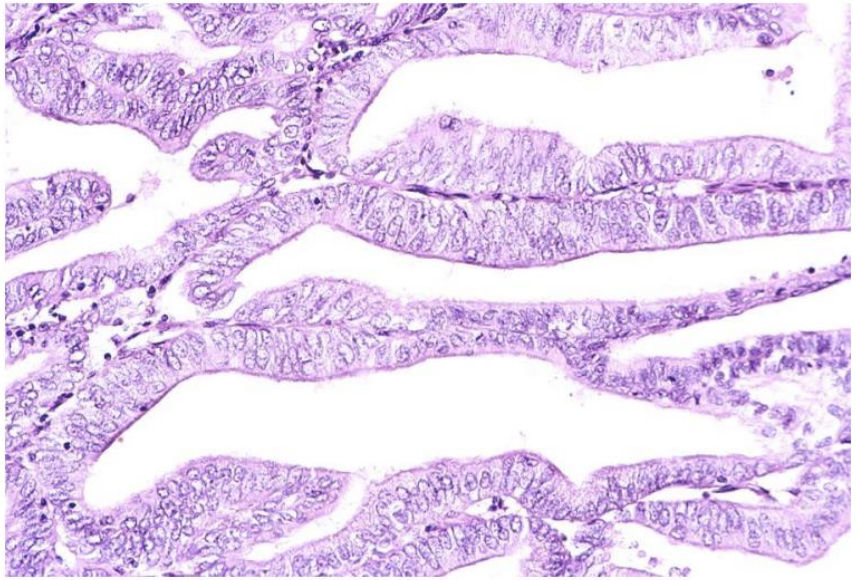
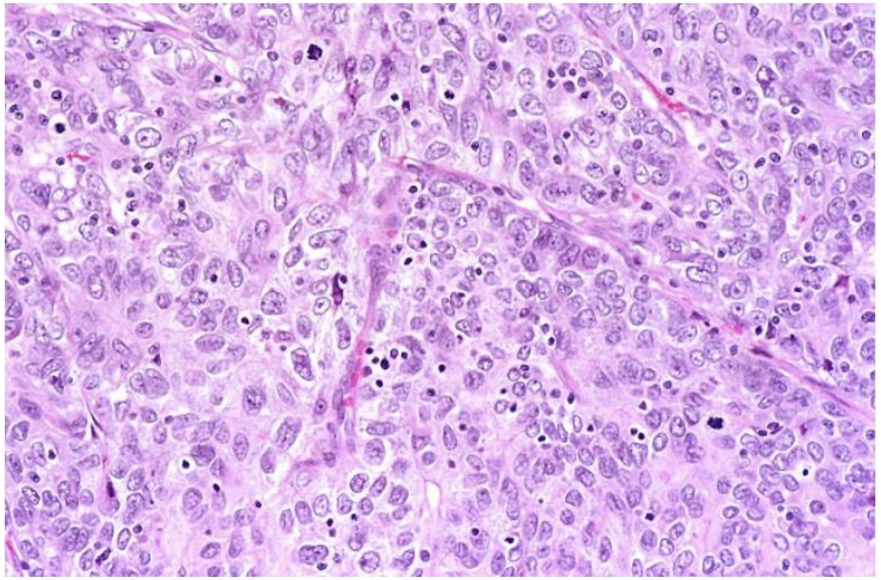
Endometrial carcinoma: Histological types

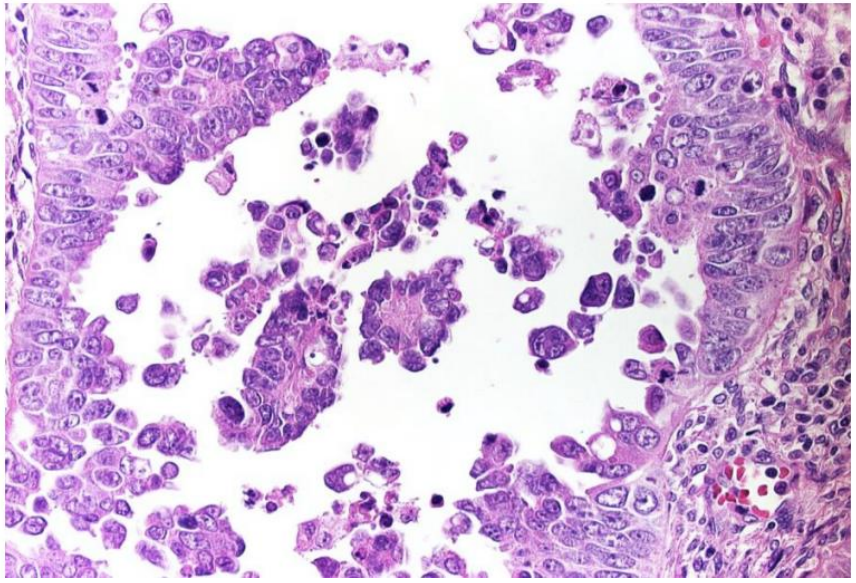
Low grade (G1,2) endometrioid

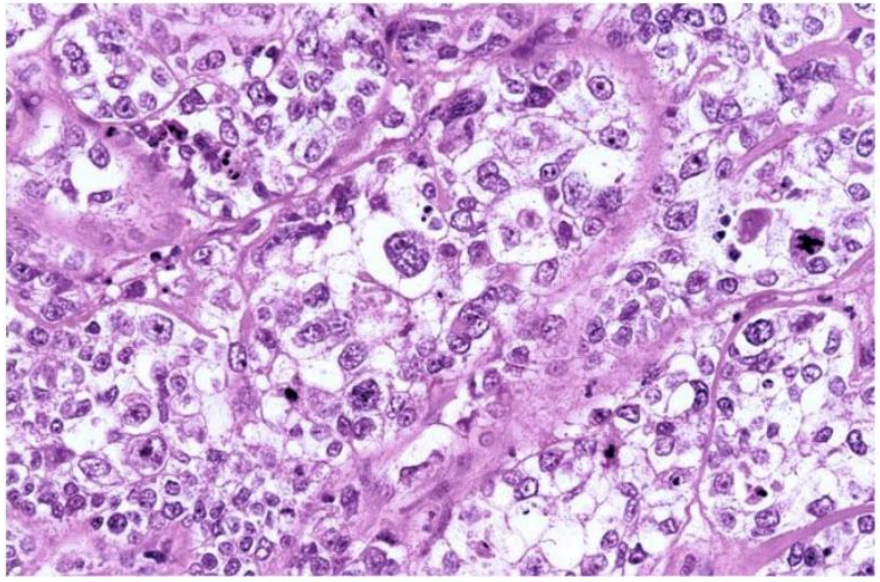




High grade (G3) endometrioid

Serous





Clear cell

Grading of Endometrial Carcinoma

Histological Type	Grading Method
Endometrioid	Modified FIGO (G1, 2: low grade)
Serous	No grading (high grade)
Clear cell	No grading (high grade)
Undifferentiated	No grading (high grade)

Histopathological types and behavior

NON-AGGRESSIVE

- Low grade endometriod

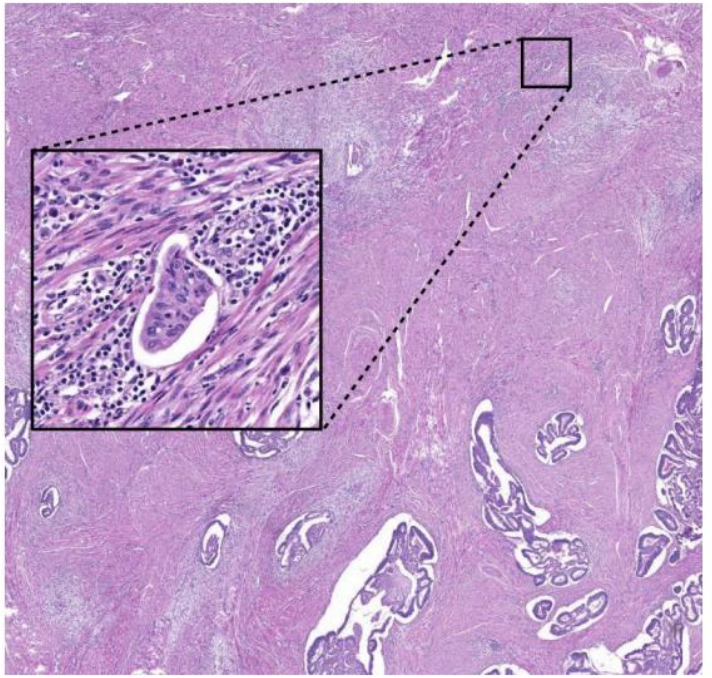
AGGRESSIVE

- High grade endometrioid
- Serous
- Clear cell
- Undifferentiated
- Carcinosarcoma
- Mixed
- Others
  - mesonephric-like
  - intestinal mucinous
  - neuroendcrine

According to WHO 2020, ESGO guidelines, FIGO staging 2023

Lymphovascular space invasion (LVSI)

- Also: lymphvascular invasion (LVI)
- Tumor cells within endothelial-lined spaces (lymphatics, blood vessels)
- No, focal, substantial (extensive)
- Cut-off varies between ESGO (≥4 within one slide), WHO (≥5), IJGP (≥3) and published studies
- Only few cases between 3 and 5 and numbers usually not reported

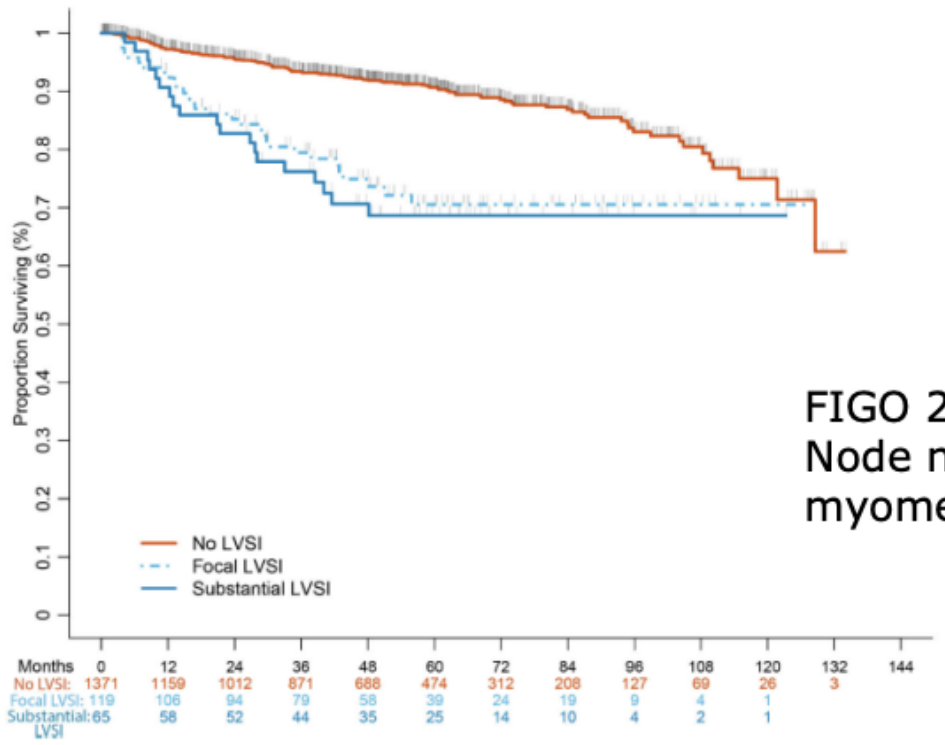


Prognostic impact of LVSI	• Threshold for clinicaally relevant LVSI needed • Methods differ between studies: review of slides • Controversy about impact of focal LVSI • Limited data with molecular classification

ROLE OF LVSI (STAGE 1)

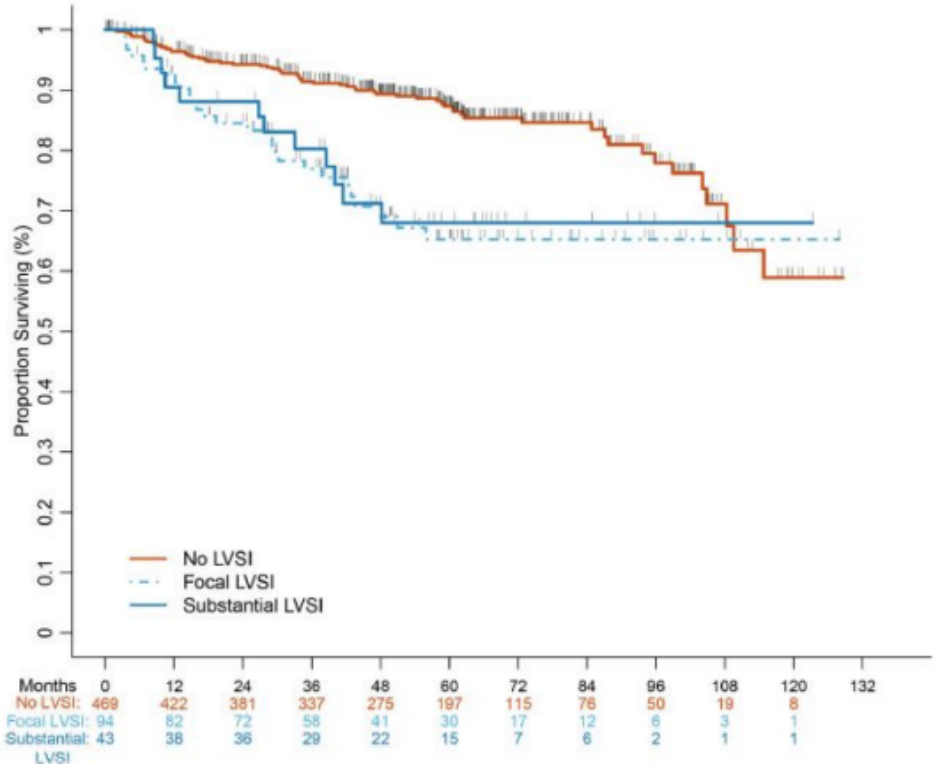
Memorial Sloan Kettering Cancer Center and Norwegian Radium Hospital/Oslo University Hospital

Stage I, endometrioid



FIGO 2009
Node negative
myometrial invasion

Stage I, G1 and 2, endometrioid



Dagher C, et al. Int *J Gynecol Cancer* 2024

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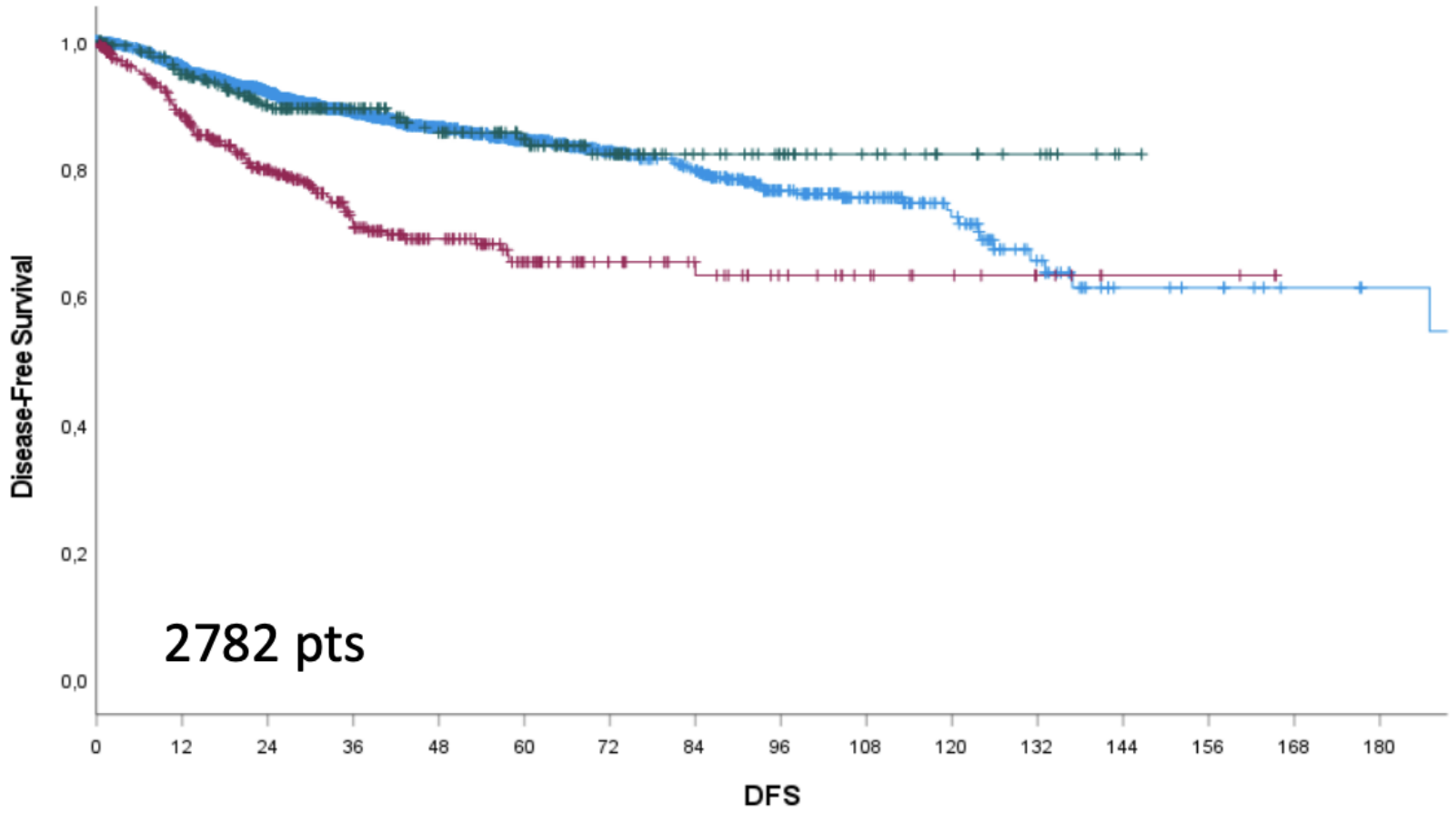
All histologies, stage I-II



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LVSI focal
LVSI negative
LVSI substantial

Overall p<0.001

No vs focal p=0.61

No vs substantial p<0.001

Focal vs substantial p<0.001

Capasso I, et al. manuscript in preparation

All histologies, stage I-II, according to molecular subgroups

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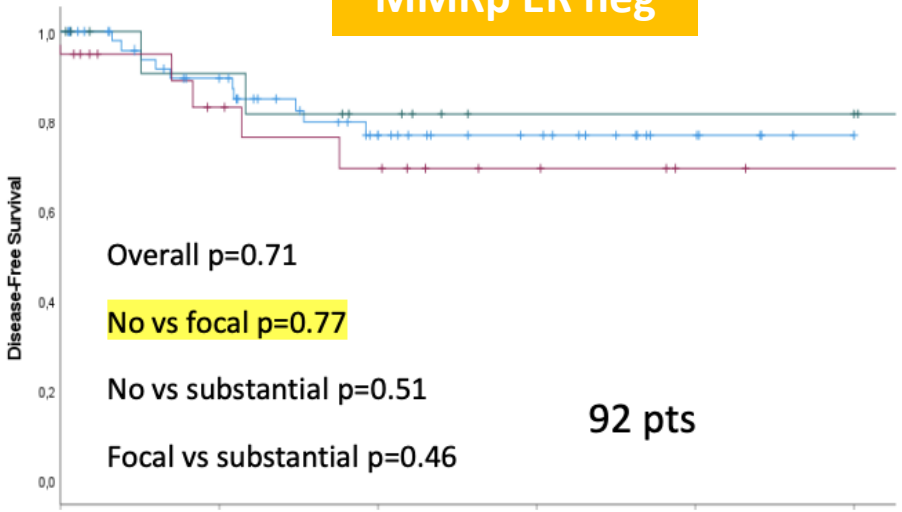
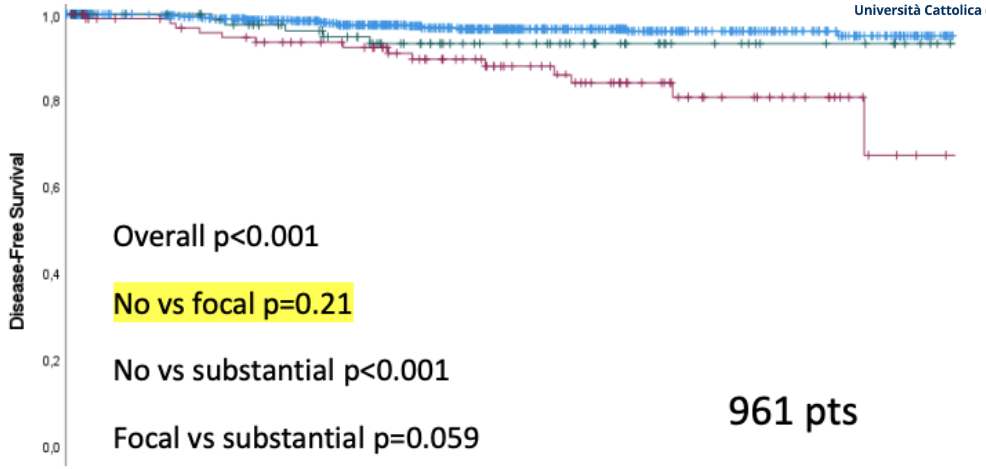
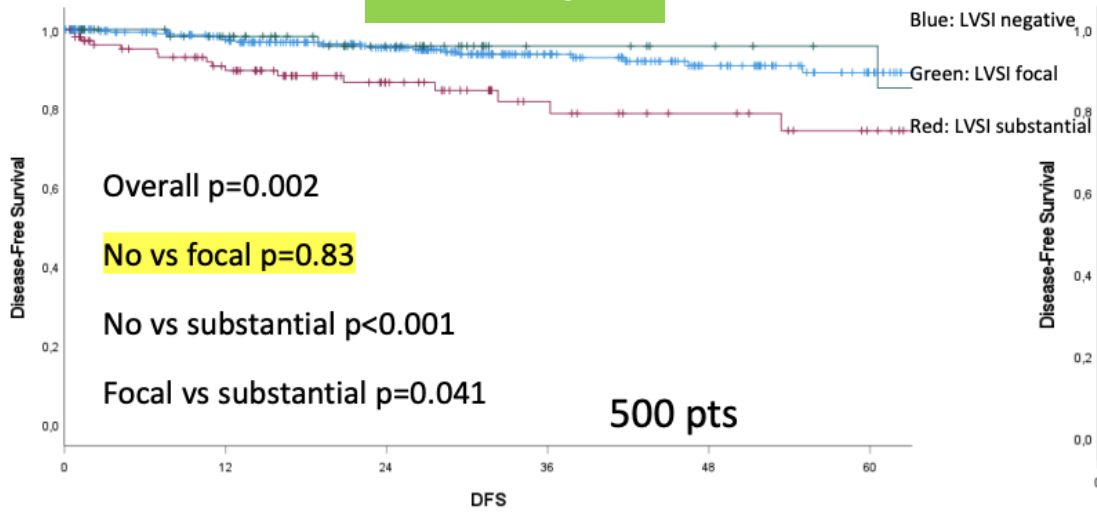
MMRp ER neg



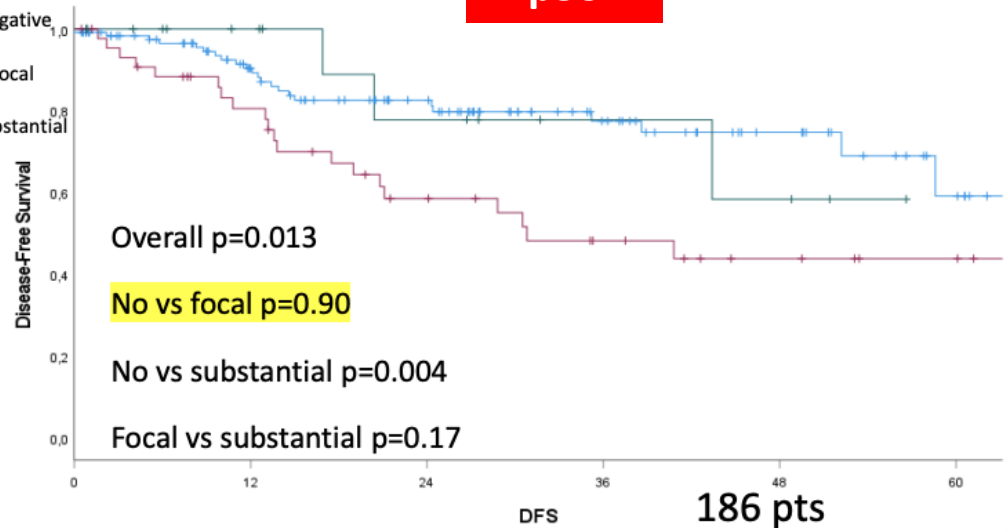
MMRp ER pos



MMRd



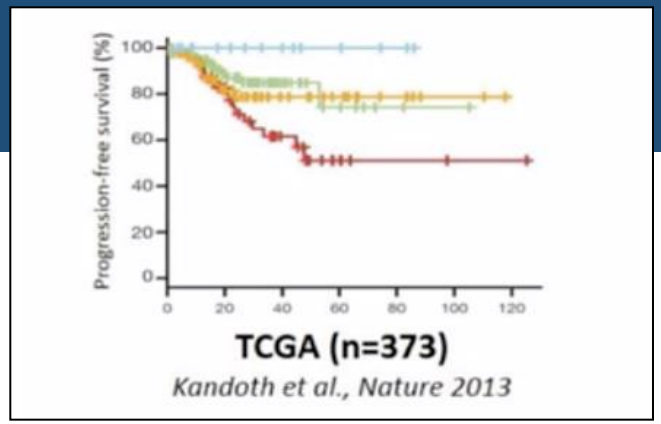
p53

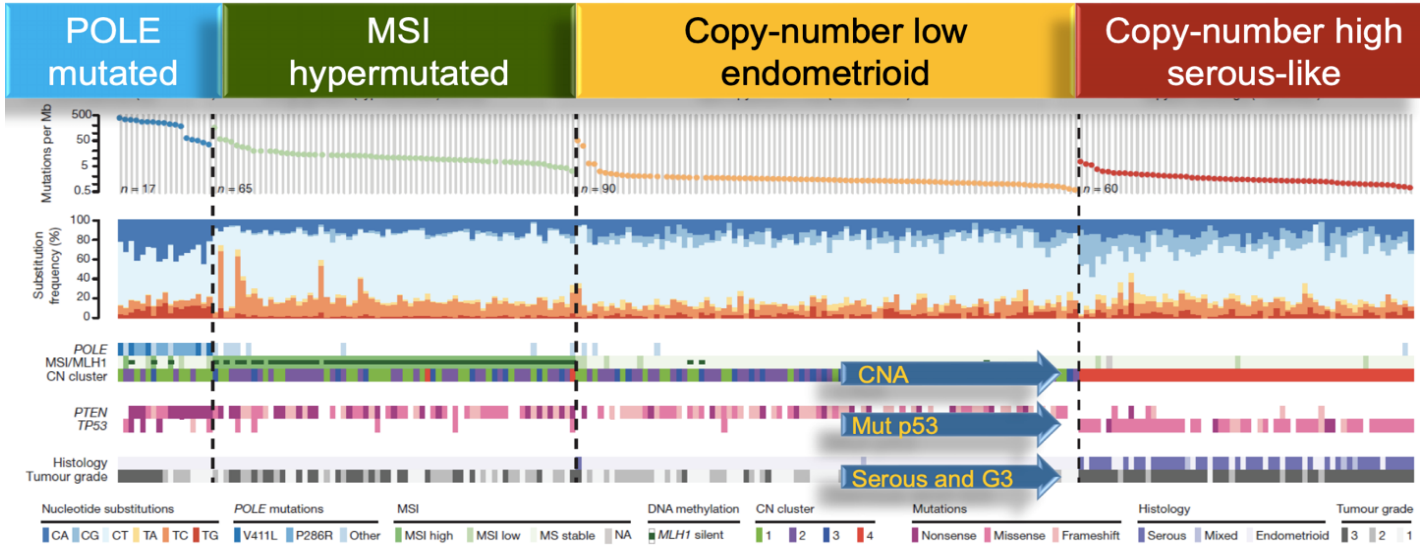


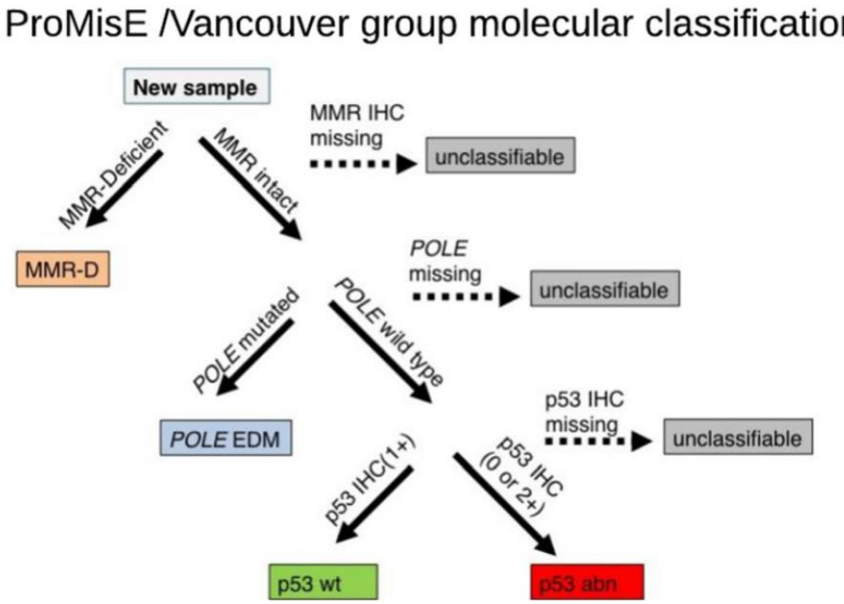
Capasso I, et al. manuscript in preparation

A genomic-based approach has identified four distinct molecular subgroups of endometrial cancer[1,2]

POLE ultramutated EC	MMRdeficient EC	NSMP EC	P53mutant EC
5-15%	25-30%	30-40%	5-15%







POLE and MSI-high subgroups have high tumor mutational load and are often characterized by high TILs and high expression of immune checkpoints[3]

CNA, copy number alteration; MSI, microsatellite instability; NSMP, no specific molecular profile; TIL, tumor-infiltrating lymphocyte.

1. Cancer Genome Atlas Research Network. *Nature.* 2013;497(744):67-73; 2. Morice P, et al. *Lancet.* 2016;387(10023):1094-1108;
3. Mittica G, et al. *Oncotarget*. 2017;8(52):90532-90544.

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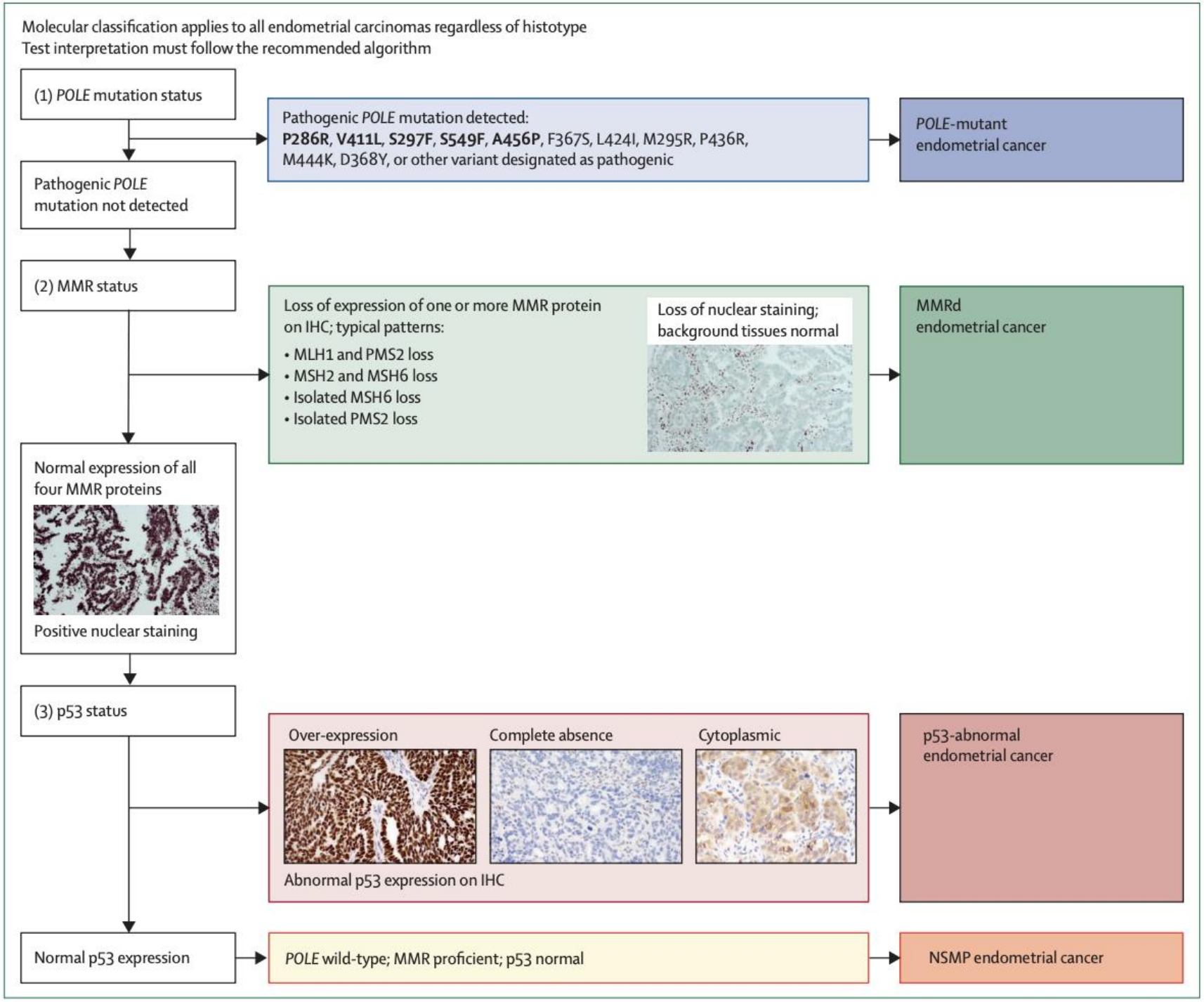
WHO-endorsed pragmatic approach to molecular classification of endometrial carcinoma in clinical practice

… should be performed on biopsies…

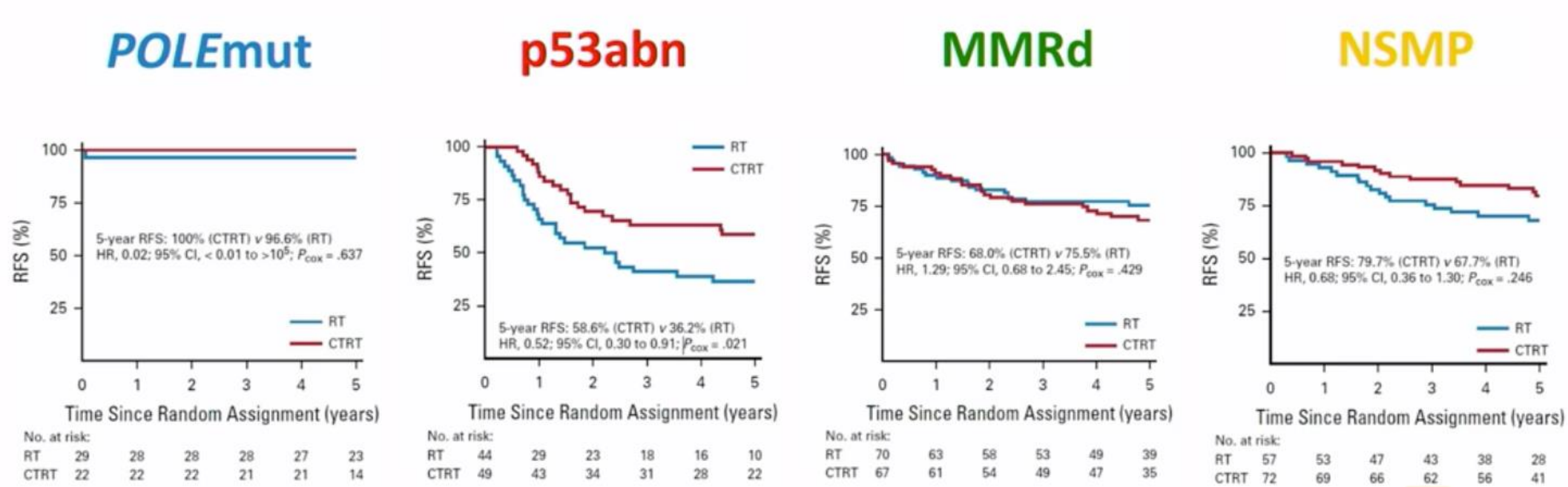


IHC, immunohistochemistry.

Cancer Genome Atlas Research Network. *Nature.* 2013;497(744):67-73; Talhouk A, et al. *Br J Cancer.* 2015;113(2):299-310; Talhouk A, et al. *Cancer*. 2017;123(5):802-813; Kommoss S, et al. *Ann Oncol.* 2018;29(5):1180-1188; Stelloo E, et al. *Mod Pathol.* 2015;28(6):836-844; Herrington CS. *WHO Classification of Tumours: Female Genital Tumours*. International Agency for Research on Cancer, 2020.

PORTEC-3 translational results

Predictive potential of molecular classification for adjuvant platinum-based treatment



ESGO-ESTRO-ESP EC Guidelines

Specific treatment recommendations for *POLE*mut stage I/II and p53mut EC based on current level of evidence

CI, confidence interval; ESP, European Society of Pathology; IRT, interventional radiotherapy.

León-Castillo A, et al. *J Clin Oncol.* 2020;38(29):3388-3397.

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‘Multiple classifier’ endometrial cancer (3–5%)

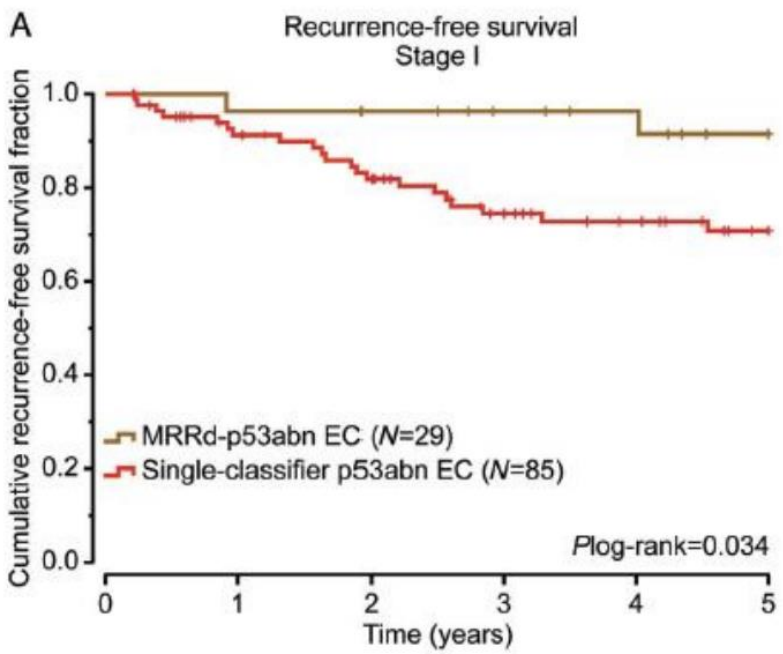
POLE		MMR		p53	MOLECULAR CLASS
POLE mut	+	MMR-p	+	p53 normal	*POLE* MUT
POLE wt	+	MMR-d	+	p53 normal	MMR-d
POLE wt	+	MMR-p	+	p53 normal	p53wt/NSMP
POLE wt	+	MMR-p	+	p53 abnormal	p53 abnormal
POLE mut	+	MMR-d	+	p53 normal	Double classifier -> *POLE* MUT
POLE mut	+	MMR-p	+	p53 abnormal	Double classifier -> *POLE* MUT
POLE wt	+	MMR-d	+	p53 abnormal	Double classifier -> MMR-d
POLE mut	+	MMR-d	+	p53 abnormal	Multiple classifier -> *POLE* MUT

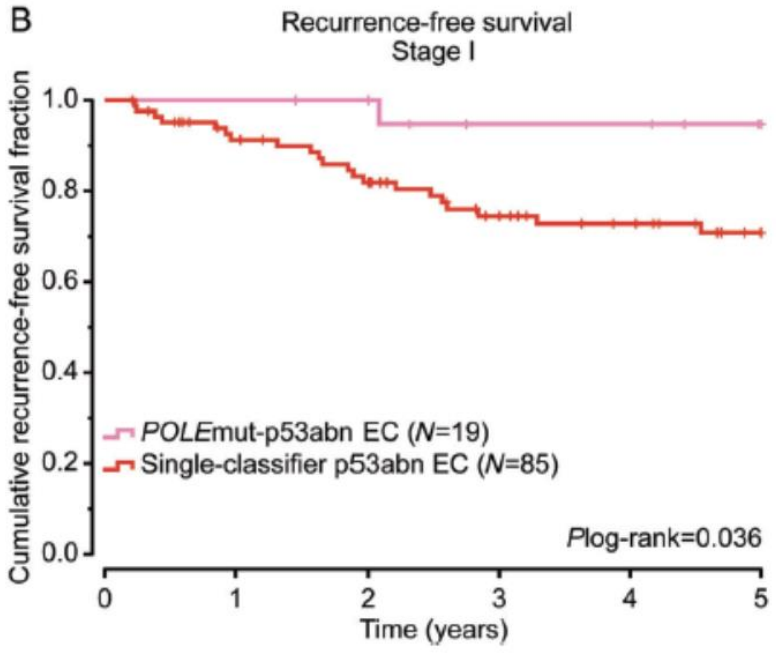
Courtesy of Caterina Fumagalli, Paola Rafaniello Raviele and Ilaroa Betella

MMRd, mismatch repair deficient.

Cancer Genome Atlas Research Network. *Nature.* 2013;497(744):67-73; Stelloo E, et al. *Mod Pathol.* 2015;28(6):836-844; Bosse T, et al. *Am J Stelloo, et al. Gyn Once 2014; Talhouket, et al. Gyn Onc 2016; Kommoss, McAlpine, Talhouk. Annals Oncol 2018; Abdulfatachet, et al. Gyn Onc 2019; Leon-Castillo, et al. J Pathol 2019; Talhouk A. Cancer 2017; Hussein YR. Mod Pathol 2015.*

Molecular subtypes and prognosis





Multiple classifier

- **Rare** (about 3.5% of endometrial carcinomas):
  - **MMRd/p53abn (60%)**
  - **POLEmut/p53abn (29%)**
  - **POLEmut/MMRd/p53abn (11%)**
- **Prognosis** significantly **better** than for p53abn tumor
- **TP53 mutations** seem to be **passengers** without impact
- **POLEmut/MMRd are considered POLEmut**

Leon-Castillo et al. J Pathol, 2020

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Molecular and clinicopathological features of molecular subgroups

	POLEmut EC	MMRd EC	NSMP EC	P53abn EC
Frequency[3]	5-15%	20-30%	30-60%	10-25%
Age at diagnosis (median)	57[1]	64[2]	61[2]	69[2]
Surrogate markers[3]	NGS (POLE sequencing)	MMR proteins IHC: PMS, MSH6 (MLH1, MSH2)		P53-IHC
	Sanger	MSSI assay		NGS (TP53 sequencing)
	Hot-spot targeted tecniques			
Molecular features[3]	Ultramutated (>100mut/Mb)	Hypermutated (>10mutations/Mb)	Low TMB	Low TMB
	Somatic copy number alteration-low	Somatic copy number alteration-low	Somatic copy number alteration-low	Somatic copy number alteration-high
	20% with MMR deficiency or MSI	MSI	MSS	MSS
	20% with p53 mutant-expression/TP53 mutations	10% with p53 mutant-expression/TP53 mutations	TP53 wild-type	TP53 mutated
			PTEN mutations	
			PI3CA mutations	
			CTNNB1 mutations	
Associated histological features[3]	Mostly high-grade endometrioid	Mostly high-grade endometrioid	Mostly low-grade endometrioid	Mostly high-grade, all histologies
	Ambiguos moorphology	Substantial LVSI	Squamous metaplasia	Substantial LVSI
	Tumor giant cells	MELF-like invasion	ER/PR positive	High-grade atypia
	High immune infiltrate (intra-epithelial CD8+ lymphocytes and TLS)	High immune infiltrate (intra-epithelial CD8+ lymphocytes and TLS)		
Early stage (I-II)	90.2%[1]	85.9%[2]	91.5%[2]	81.6%[2]
Tumor Grade G3	50.7%[1]	27.7%[2]	12.5%[2]	96.5%[2]
Not-endometrioid hystotype	10.6%[1]	10.9%[2]	6.2%[2]	88.6%[2]
LVSI negative	68.4%[1]	75.1%[2]	83.7%[2]	61.3%[2]
ER status				
Negative		7.1%[2]	2.9%[2]	22.1%[2]
1+		13.7%[2]	10.9%[2]	28.3%[2]
Associated clinical features[3]	Low BMI	High BMI	High BMI	Low BMI
	Early stage			Advanced stage
	Younger patients	10% Lynch syndrome carriers		Older patients
		Local recurrences		Distant recurrences
Prognosis[3]	Excellent	Intermediate	Intermediate-poor; stage and histologic-grade dependent	Poor
Potential biomarkers for prognosis refinement[3]		TLS	CD8 intra-epithelial lymphocytes	CD8 intra-epithelial lymphocytes

TP53mut worst prognosis

NSMP and **MMRd intermediate prognosis** without statistical significance for total collective but varies for subgroups

TP53mut, **NSMP** and **MMRd affected by adverse clinicolpathological** factors (stage, grade, LVSI)

POLEmut best prognosis, **not affected by adverse clinicolpathological factors**

1. Mc

ESGO2025 Congress
26th European Congress on Gynaecological Oncology
FEBRUARY 20-23, 2025 | ROME, ITALY

Improving Endometrial Cancer Assessment By Combining The New TechniqUe Of GENomic Profiling With Surgical Extra UterIne DisEase Assessment (EUGENIE). Second Interim Analysis After Two Years Of Enrolment.

Rita Trozzi, Luigi Congedo, Giulia Pellecchia, Elisa Ervas, Giovanni Esposito, Camilla Nero, Emilia Palmieri, Luca Palmieri, Daniela Annibali, Annouschka Laenen, Anne-Sophie Van Rompuy, Giuseppe Vizzielli, Stefano Restaino, Franco Odicino, Jure Knez, Thaïs Baert, Giovanni Scambia, Francesco Fanfani, Frédéric Amant

21st of February 2025
Rita Trozzi

congress.esgo.org

Results – clinical and molecular characteristics of the Cohort

64
Median age, years

58.7% Endometrioid G1-G2
21.3% Endometrioid G3
9.5% Serous
1.6% Clear cells
4,1% Mixed
2,7% MMMT
1,8% Other

74,6% Early 2023-FIGO stage
25,3% Advanced 2023-FIGO stage

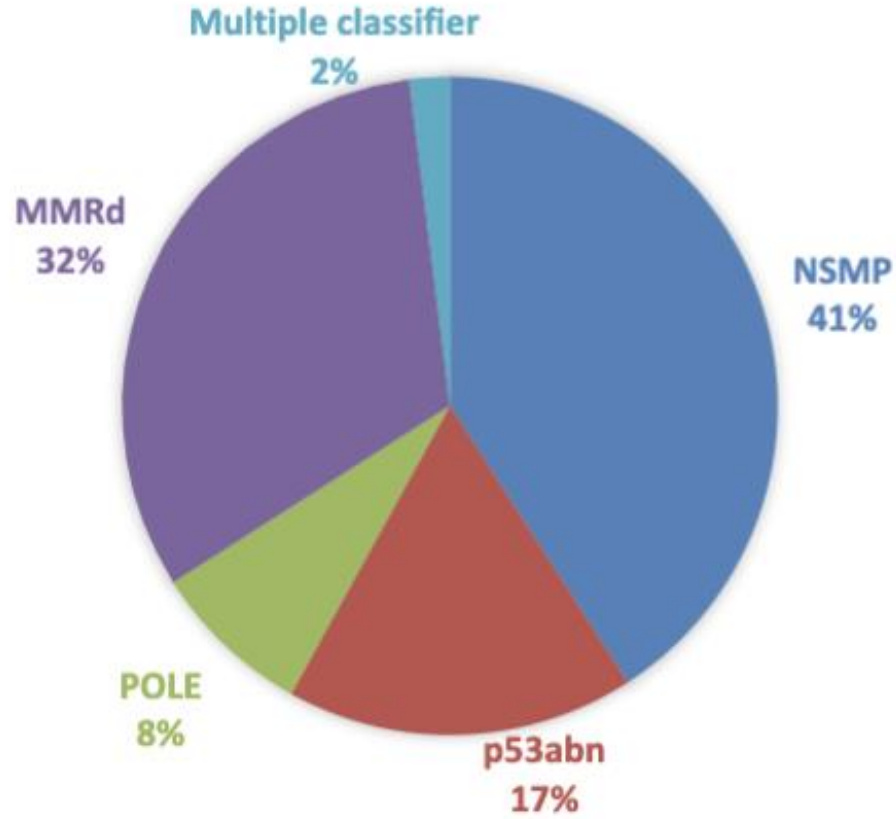
74,5% Early 2009-FIGO stage
25,5% Advanced 2009-FIGO stage

63,1% LVSI negative
9,9% LVSI focal
26,9% LVSI substantial

34,9% Low risk
14,6% Intermediate risk
16% High-intermediate risk
24,7% High risk
9,5% Advanced/metastatic

9,7% No miometrial invasion
43% < 50%
46,2% > 50%
0,9% Unknown

MOLECULAR CLASSIFICATION



ESGO2025 Congress | 26th European Congress on Gynaecological Oncology
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MMMT: Malignant mixed Mullerian tumour; LVSI: Lymphovascular Space Invasion

Results - Metastatic Sites in the Full Cohort

	All pts (n=553)	NSMP (n=226)	MMRd (n=181)	p53abn (n=95)	POLE (n=51)	P value
FIGO 2023						<0.001
Early	413 (74.7%)	189 (83.6%)	131 (72.4%)	48 (50.5%)	45 (88.2)%	
Advanced	140 (25.3%)	37 (16.4%)	50 (27.6%)	47 (49.5%)	6 (11.8%)	
HISTOLOGY						<0.001
Endometrioid	442 (79.9%)	214 (94.6%)	163 (90.1%)	18 (18.9%)	47 (92.2%)	
Other	111 (20.1%)	12 (5.4%)	18 (9.9%)	77 (81.1%)	4 (7.8%)	
GRADING						<0.001
G1	87 (15.7%)	60 (26.5%)	17 (9.4%)	6 (6.3%)	4 (7.8%)	
G2	238 (43.0%)	127 (56.2%)	88 (48.6%)	3 (3.2%)	20 (39.2%)	
G3	222 (40.1%)	38 (16.8%)	76 (42.0%)	81 (85.3%)	27 (52.9%)	
Missing	6 (1.1%)	1 (0.4%)	0	5 (5.3%)	0	
LVSI						0.028
Negative	349 (63.1)	157 (69.5)	103 (56.9)	51 (53.7)	38 (74.5)	
Focal	55 (9.9)	20 (8.8)	21 (11.6)	12 (12.6)	2 (3.9)	
Substantial	149 (26.9)	49 (21.7)	57 (31.5)	32 (33.7)	11 (21.6)	
MYOMETRIAL INVASION						<0.001
Absent	54 (9.9%)	29 (12.9%)	8 (4.4%)	9 (9.9%)	8 (15.7%)	
<50%	238 (43.4%)	107 (47.6%)	70 (38.7%)	31 (34.1%)	30 (58.8%)	
>50%	256 (46.7%)	89 (39.6%)	103 (56.9%)	51 (56.0%)	13 (25.5%)	

	All pts (n=553)	NSMP (n=226)	MMRd (n=181)	p53abn (n=95)	POLE (n=51)	P value
ADNEXES	38 (6.9%)	7 (3.1%)	13 (7.2%)	17 (17.9%)	1 (2.0%)	<0.001
LYMPH-NODES	85 (15.4%)	29 (12.8%)	31 (17.1%)	22 (23.2%)	3 (5.9%)	0.023
PERITONEAL	48 (8.7%)	10 (4.4%)	11 (6.1%)	27 (28.4%)	0	<0.001
OMENTAL	28 (5.1%)	5 (2.2%)	4 (2.2%)	19 (20.0%)	0	<0.001
SYSTEMIC	13 (2.4%)	1 (0.4%)	3 (1.7%)	8 (8.4%)	1 (2.0%)	<0.001
NUMBER OF METASTATIC SITES						<0.001
0	418 (75.6%)	191 (84.5%)	134 (74.0%)	46 (48.4%)	47 (92.2%)	
1	90 (16.3%)	26 (11.5%)	36 (19.9%)	25 (26.3%)	3 (5.9%)	
>=2	45 (8.1%)	9 (4.0%)	11 (6.1%)	24 (25.3%)	1 (2.0%)	

Results - Metastatic Sites in Patients with Extrauterine Disease

	All pts (n=135)	NSMP (n=35)	MMRd (n=47)	p53abn (n=49)	POLE (n=4)	P value
ADNEXES	38 (28.1%)	7 (20.0%)	13 (27.7%)	17 (34.7%)	1 (25.0%)	0.53
LYMPH-NODES	85 (63.0%)	29 (82.9%)	31 (66.0%)	22 (44.9%)	3 (75.0%)	0.004
PERITONEAL	48 (35.6%)	10 (28.6%)	11 (23.4%)	27 (55.1%)	0	0.003
OMENTAL	28 (20.7%)	5 (14.3%)	4 (8.5%)	19 (38.8%)	0	0.001
SYSTEMIC	13 (9.6%)	1 (2.9%)	3 (6.4%)	8 (16.3%)	1 (25.0%)	0.11
NUMBER OF METASTATIC SITES						0.036
1	90 (66.7%)	26 (74.3%)	36 (76.6%)	25 (51.0%)	3 (75.0%)	
>=2	45 (33.3%)	9 (25.7%)	11 (23.4%)	24 (49.0%)	1 (25.0%)	

Results - Predictors of Extra-Uterine and Lymph Node Metastases

EXTRA-UTERINE SPREAD

	UNIVARIATE	MULTIVARIABLE
AGE (in years)	1.01 (0.99-1.02) p=0.44	--
BMI (kg/m2)	1.01 (0.99-1.04) p=0.36	--
HISTOLOGY	P<0.001	-- P=0.11
Low-risk	Ref.	
High-risk	4.06 (2.69-6.13)	
GRADING	P<0.001	-- P=0.11
G1-G2	Ref.	
G3	4.01 (2.65-6.07)	
DEPTH OF MYOMETRIAL INVASION	P<0.001	P=0.008
<50%	Ref.	Ref.
>50%	5.04 (3.23-7.87)	2.14 (1.22-3.75)
LVSI	P<0.001	P<0.001
No	Ref.	Ref.
Focal	2.60 (1.33-5.09)	1.97 (0.92-4.20)
Substantial	7.22 (4.60-11.33)	5.64 (3.20-9.93)
MOLECULAR CLASS	P<0.001	P<0.001
p53abn	Ref.	Ref.
NSMP	0.17 (0.10-0.30)	0.20 (0.11-0.37)
MMRd	0.33 (0.19-0.56)	0.31 (0.16-0.56)
POLE	0.08 (0.03-0.24)	0.10 (0.03-0.34)

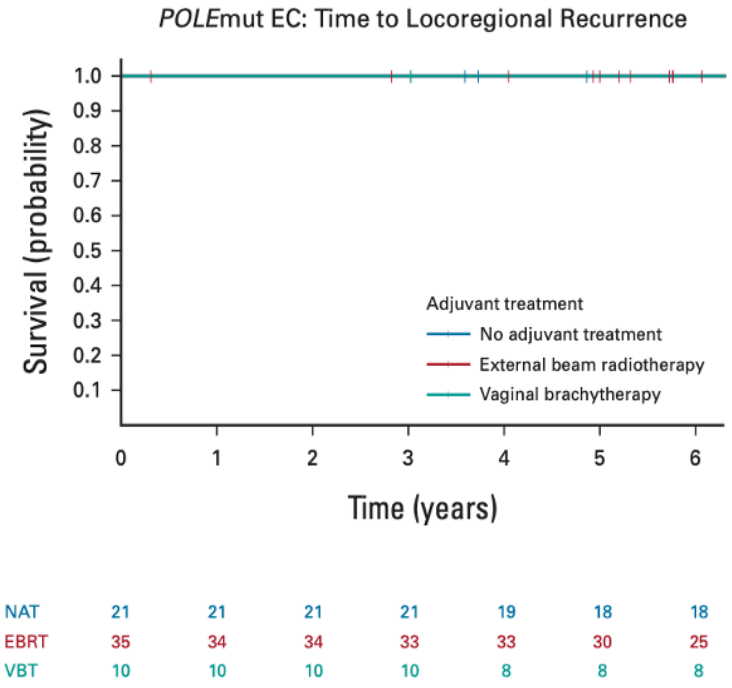
ONLY LYMPH-NODE SPREAD

	UNIVARIATE	MULTIVARIABLE
AGE (in years)	0.99 (0.97-1.02) p=0.61	--
BMI (kg/m2)	1.01 (0.97-1.05) p=0.66	--
HISTOLOGY	P=0.01	-- P=0.95
Low-risk	Ref.	
High-risk	2.02 (1.17-3.46)	
GRADING	P=0.02	-- P=0.95
G1-G2	Ref.	
G3	1.94 (1.12-3.35)	
DEPTH OF MYOMETRIAL INVASION	P<0.001	P=0.03
<50%	Ref.	Ref.
>50%	5.38 (2.79-10.39)	2.33 (1.08-5.01)
LVSI	P<0.001	P<0.001
No	Ref.	Ref.
Focal	3.25 (1.26-8.37)	2.51 (0.92-6.84)
Substantial	7.62 (4.04-14.38)	4.99 (2.36-10.56)
MOLECULAR CLASS	P=0.27	--
p53abn	Ref.	
NSMP	0.68 (0.33-1.41)	
MMRd	0.92 (0.44-1.91)	
POLE	0.26 (0.06-1.19)	

POLE-mutated population

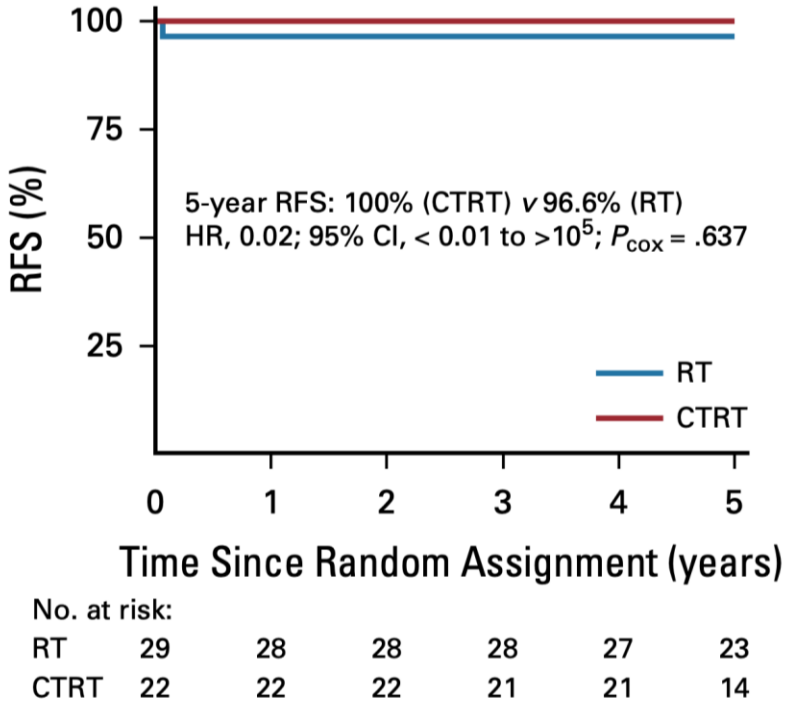
PORTEC-1/2

66 patients



PORTEC-3

51 patients



Meta-analysis

McAlpine

109 *POLE*mut patients
No adjuvant treatment

Only 3 recurrences
(all in high-risk patients)

LAY SUMMARY

Additional therapy (radiation and chemotherapy) does not appear to improve outcomes for women with *POLE*-mutated endometrial cancer, and this supports the move to less therapy and less associated toxicity

León-Castillo A, et al. *J Clin Oncol.* 2020;38(29):3388-3397; Horeweg N, et al. *J Clin Oncol.* 2023;41(27):4369-4380; McAlpine JN. *Cancer*. 2021;127(14):2409-2422.

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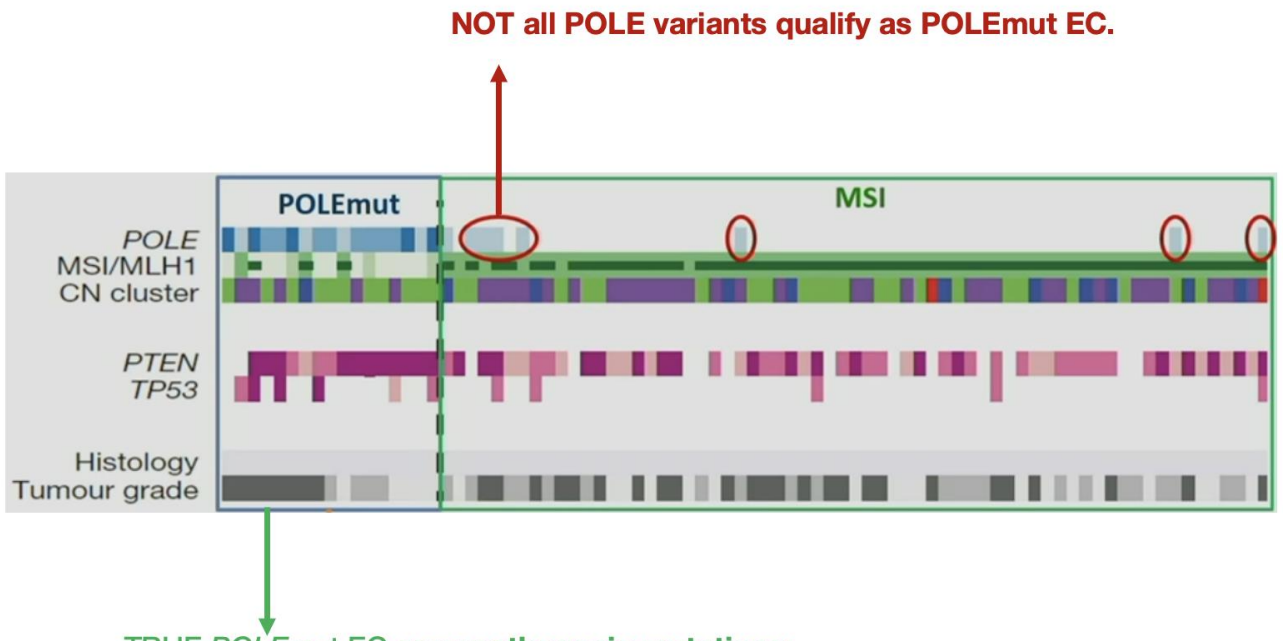
*POLE*mut endometrial cancer



_POLE_mut endometrial cancer

- Majority high grade (G3); atypia comparable to serous EC
- High levels of tumor-infiltrating lymphocytes
- High levels of tertiary lymphoid structures
- Mostly endometrioid, but present as all histological types (including dedifferentiated/undifferentiated, carcinosarcomas, serous carcinomas, and clear cell)

IHC:

- Mutant-type p53 staining: ~25% (mostly subclonal)
- MMRd: ~2%

12 pathogenic somatic missense mutations across 11 loci within exons 9, 11, 13, and 14 of the *POLE* EDM have been internationally recognized to qualify as *POLE*mut EC

Histology not specific enough to identify *POLE*mut EC – sequencing is required!

Cancer Genome Atlas Research Network. *Nature.* 2013;497(744):67-73; León-Castillo A, et al. *J Pathol.* 2020;250(3):312-322; Van den Heerik A, et al. *JCO Glob Oncol.* 2023;9:e2200384; Van Gool IC, et al. *Histopathology.* 2018;72(2):248-258.

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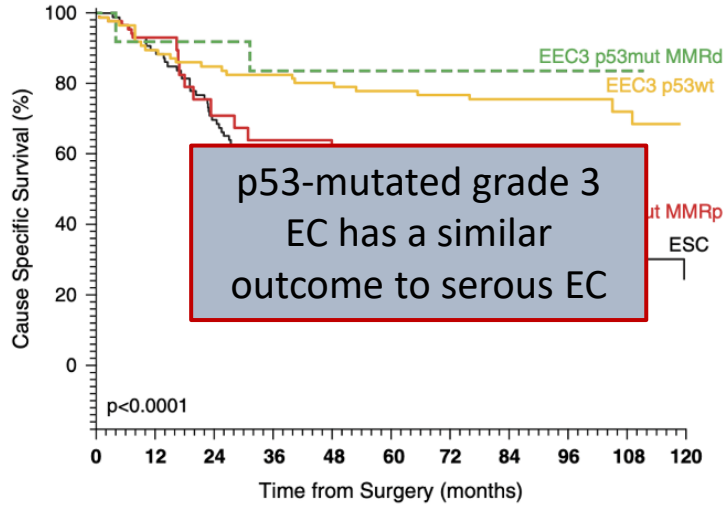
p53abn endometrial cancers: should they all be considered “high risk”? Encompasses more than just serous carcinoma…

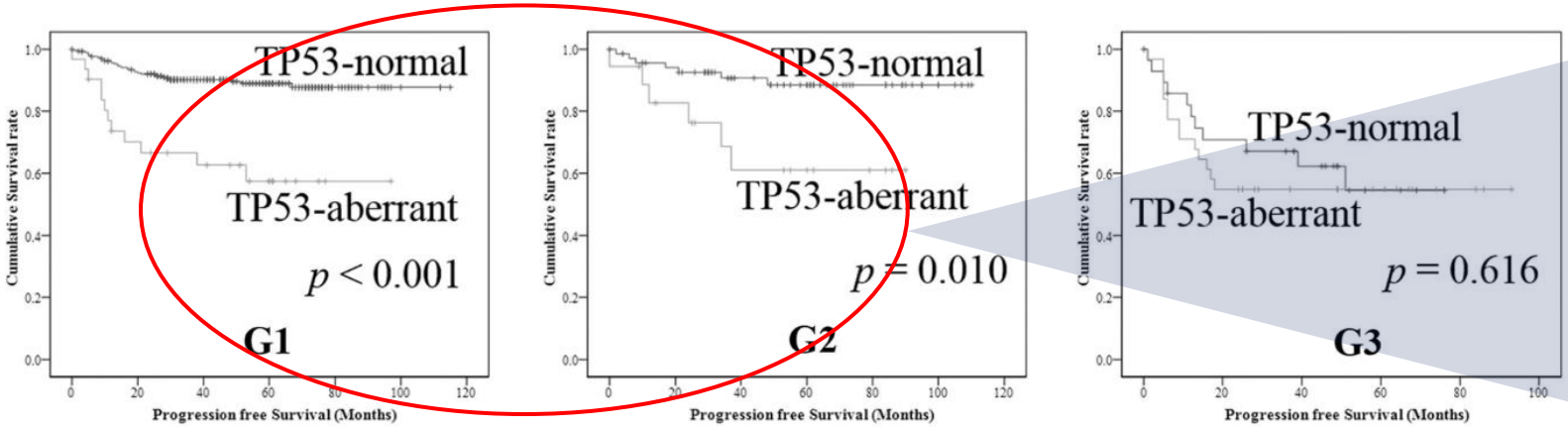
Proportion of p53abn endometrial cancer for each histotype from published endometrial cancer cohorts which have been molecularly classified

Histotype	Total	p53abn (n(%))
Endometrioid endometrial carcinoma grades 1–2	2515	130 (5.2)
Endometrioid endometrial carcinoma grade 3	900	199 (22.1)
Serous endometrial carcinoma	122	133(92.6)
Clear cell carcinoma	61	23 (37.7)
Carcinosarcoma	171	146 (85.4)
Total	3769	611 (16.2)

Jamieson A, et al. *Int J Gynecol Cancer.* 2021;31(6)907-913.



Brett MA, et al. *Int J Gynecol Cancer.* 2021;40(2):116-123.



Yano M, et al. *Mod Pathol.* 2019;32(7):1023-1031.

p53abn grade 1 and 2 endometrioid ECs:

- Older women
- Lower BMI
- More had advanced-stage disease, i.e., behave more like serous carcinoma
- Worse survival outcomes vs those with p53wt ECs

Expert pathology review of PORTEC-1/2 series confirmed presence of low-grade endometrioid p53abn ECs; not just glandular variants of serous carcinoma, and these patients had markedly worse outcomes *(Jamieson A, et al. IGCS 2022 abstract)*

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Mismatch repair protein and MLH1 methylation status as predictors of response to adjuvant therapy in endometrial cancer

Disease-specific survival analyses for MMRd subgroup

	MMR-D (n = 287)		
	N	HR (95% CI)	*p*
Age >65 years	180	1.4 (0.81–2.6)	0.219
Stage II–IV	81	1.4 (0.68–2.8)	0.372
Histology			0.567
Endometrioid grade 1–2	210	1	
Endometrioid grade 3	54	1.4 (0.74–2.6)	0.299
Nonendometrioid	23	1.1 (0.45–2.5)	0.908
Myometrial invasion ≥50%	120	2.2 (1.2–4.1)	0.016*
Lymphovascular space invasion	80	2.3 (1.3–4.1)	0.004**
Adjuvant therapy			0.345
None	35	1	
VBT	129	0.52 (0.15–1.8)	0.293
WPRT	47	1.3 (0.39–4.0)	0.698
Chemotherapy	10	1.8 (0.40–8.3)	0.443
Chemotherapy and VBT/ WPRT	66	1.4 (0.45–4.7)	0.538

WPRT, whole pelvic radiotherapy. Loukovaara M, et al. *Cancers (Basel).* 2021;13(13):3124.

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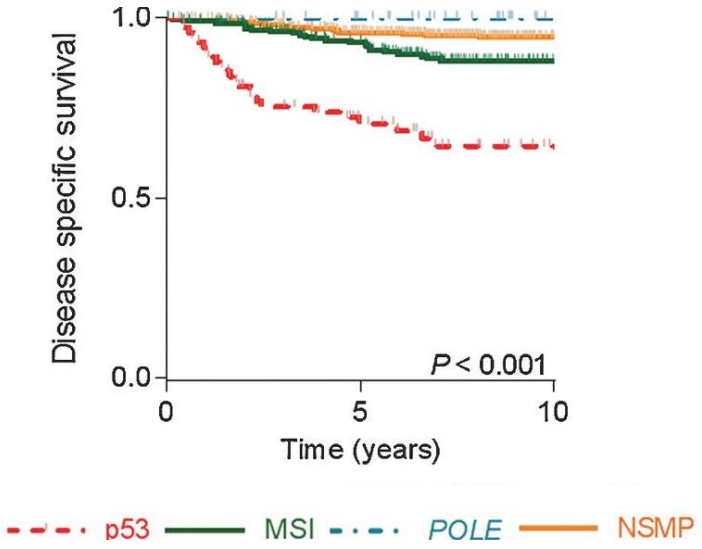
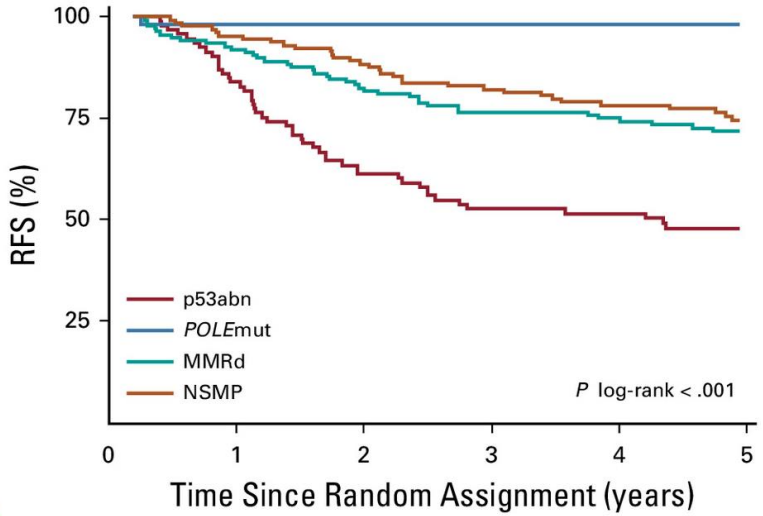
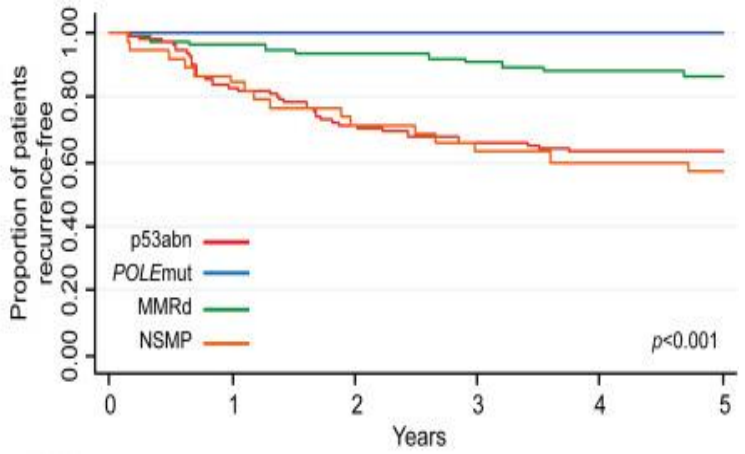
Different clinical outcomes of NSMP endometrial cancer



PORTEC 1/2 (n= 834)
Stello et all, CCR 2016



PORTEC- 3 (n= 410)
León-Castillo et al., JCO 2020



High-grade EC (n=251)
León-Castillo ESGO 2021

NSMP (n=129) patients with EC had an ***intermediate outcome***

5-year RFS: 74.4%

Stelloo E, et al. *Clin Cancer Res.* 2016;22(16):4215-4224; León-Castillo A, et al. *J Clin Oncol.* 2020;38(29):3388-3397; Vermij L, et al. *Int J Gynecol Cancer*. 2021;31(Suppl 3):A89-A90 [Abstract 397].

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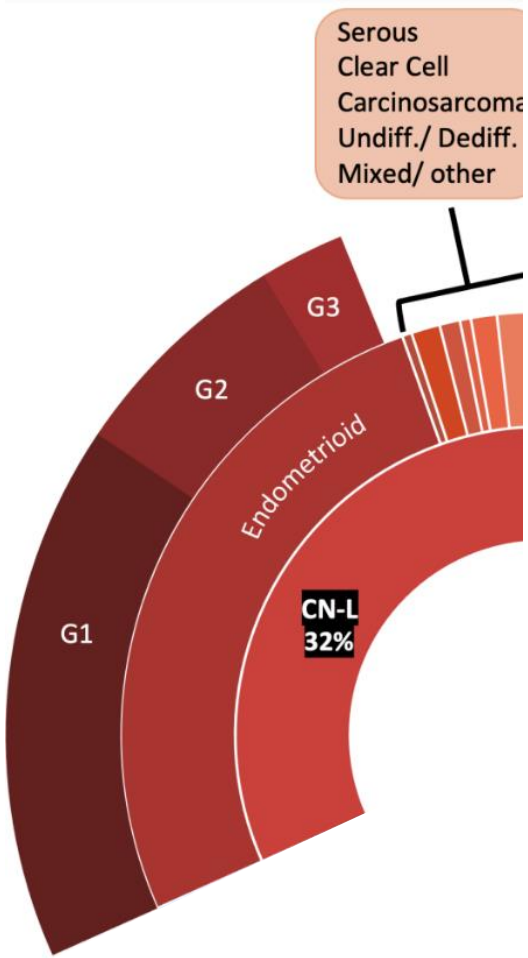
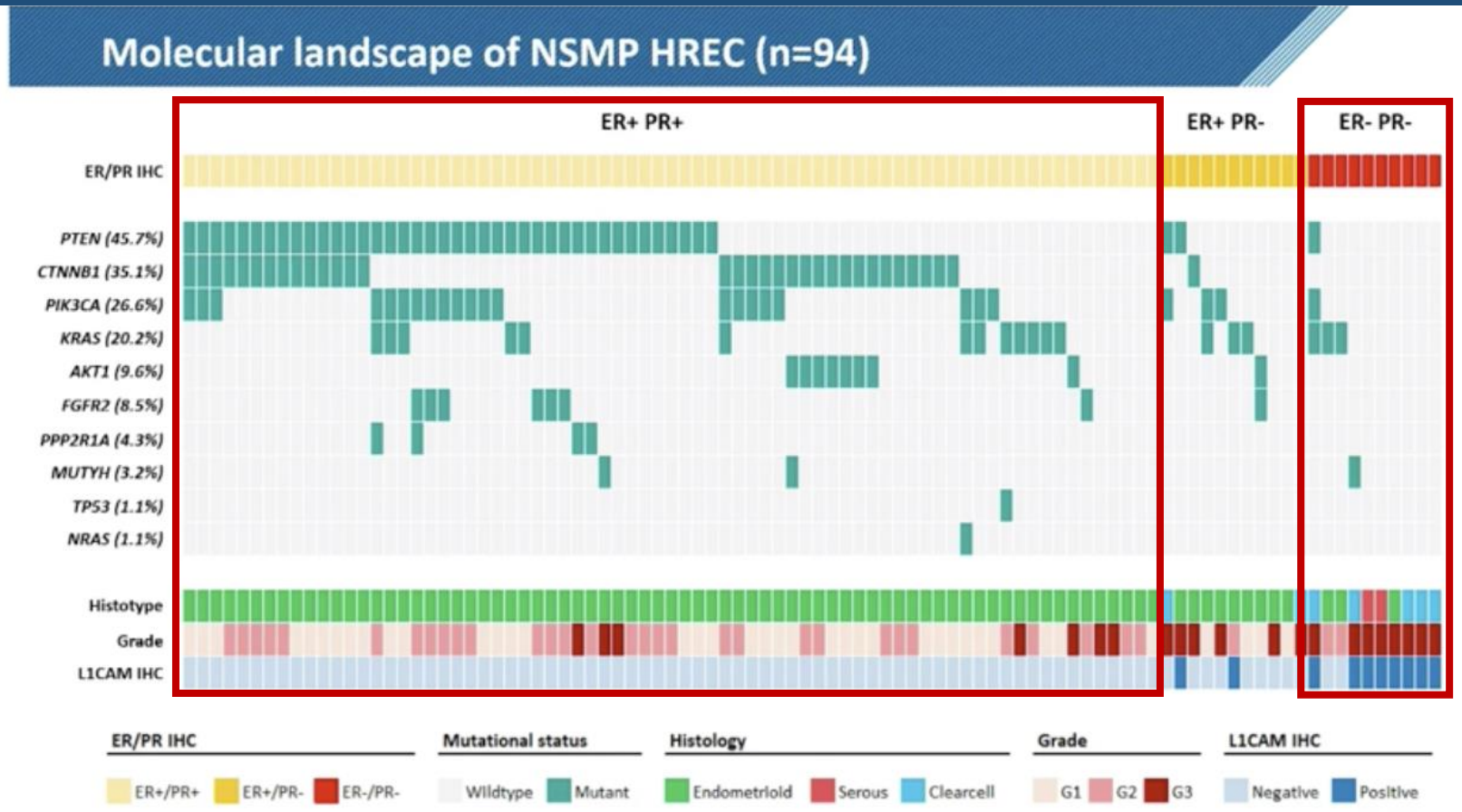
Characteristics of patients with NSMP endometrial cancer





I. NSMP HREC – **ER + / PR +**
- Frequent mutations in *PTEN, CTNNB1, PIK3CA* and *KRAS*
- **Favourable** characteristics: low grade, endometrioid, L1CAM-negative

II. NSMP HREC – **ER - / PR -**
- Relatively few somatic mutations
- **Unfavourable** characteristics: high grade, non-endometrioid, L1CAM-positive

HREC, high-risk endometrial cancer.

Rios-Doria E, et al. *Gynecol Oncol.* 2022;166(Suppl 1):S57-S58 [Abstract 084];
Vermij L, et al. *Int J Gynecol Cancer*. 2021;31(Suppl 3):A89-A90 [Abstract 397];
Rios-Doria E, et al. Gynecol Oncol. 2023;174:262-272..

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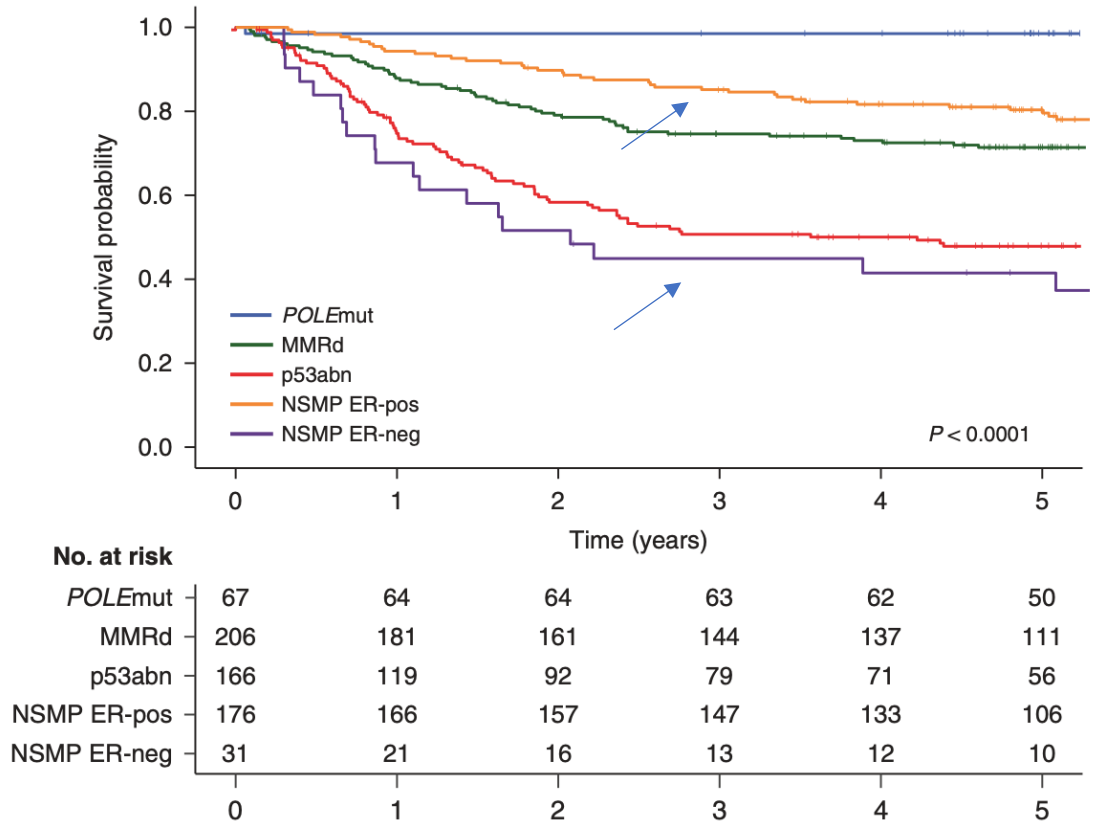
Role of other factors: ER, L1CAM, CTNNB1

- N=**648** patients with molecularly classified high-risk EC from the PORTEC-3 trial and an independent prospective cohort
- Age, stage, and adjuvant chemotherapy had an independent impact on risk of recurrence
- No *independent* prognostic value of ER, PR, L1CAM, and CTNNB1
- **In NSMP cancers**, ER positivity was independently and strongly associated with a reduced risk of recurrence (HR 0.33, 95% CI 0.15-0.75)



BJC British Journal of Cancer

neg, negative; pos, positive.

Vermij L, et al. *Br J Cancer.* 2023;128(7):1360-1368.

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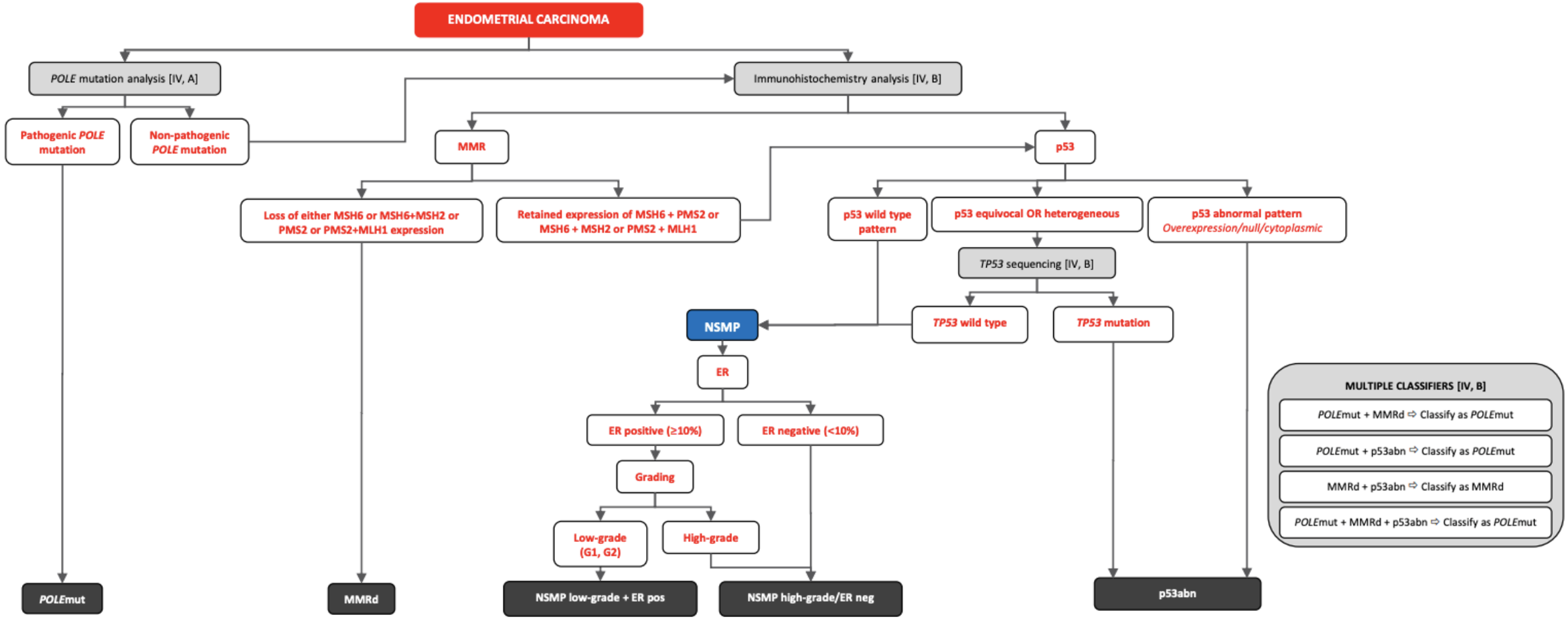
Assessment of molecular classification



Testing strategy recommendations

- IHC for MMR proteins (2 antibody approach), ER, p53 on all cases on biopsy/curettage
- POLEmut on all cases; at least on high grade, low stage carcinomas or if adjuvant therapy planned
- Molecular analysis for p53 (NGS) and MSI if IHC is equivocal
- HER2 testing for all p53abn/TP53mut carcinomas

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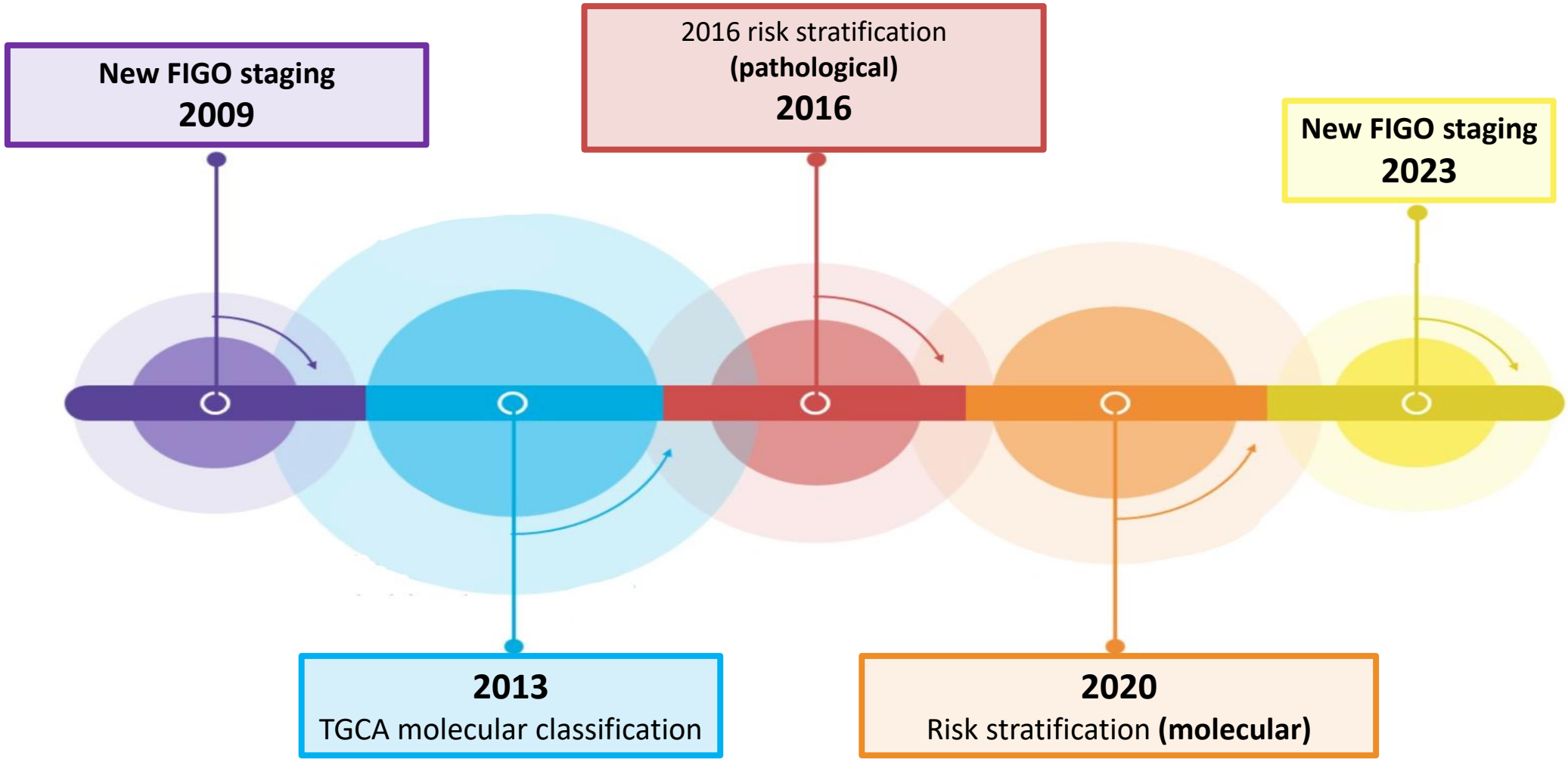


FIGO, International Federation of Gynecology and Obstetrics; TGCA, The Cancer Genome Atlas.

Endometrial cancer 2009 FIGO staging system

Stage I*	Tumor confined to the corpus uteri
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
Stage II*	Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III*	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae#
IIIB*	Vaginal and/or parametrial involvement#
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes#
IIIC1*	Positive pelvic nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumor invasion of bladder and/or bowel mucosa
IVB*	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

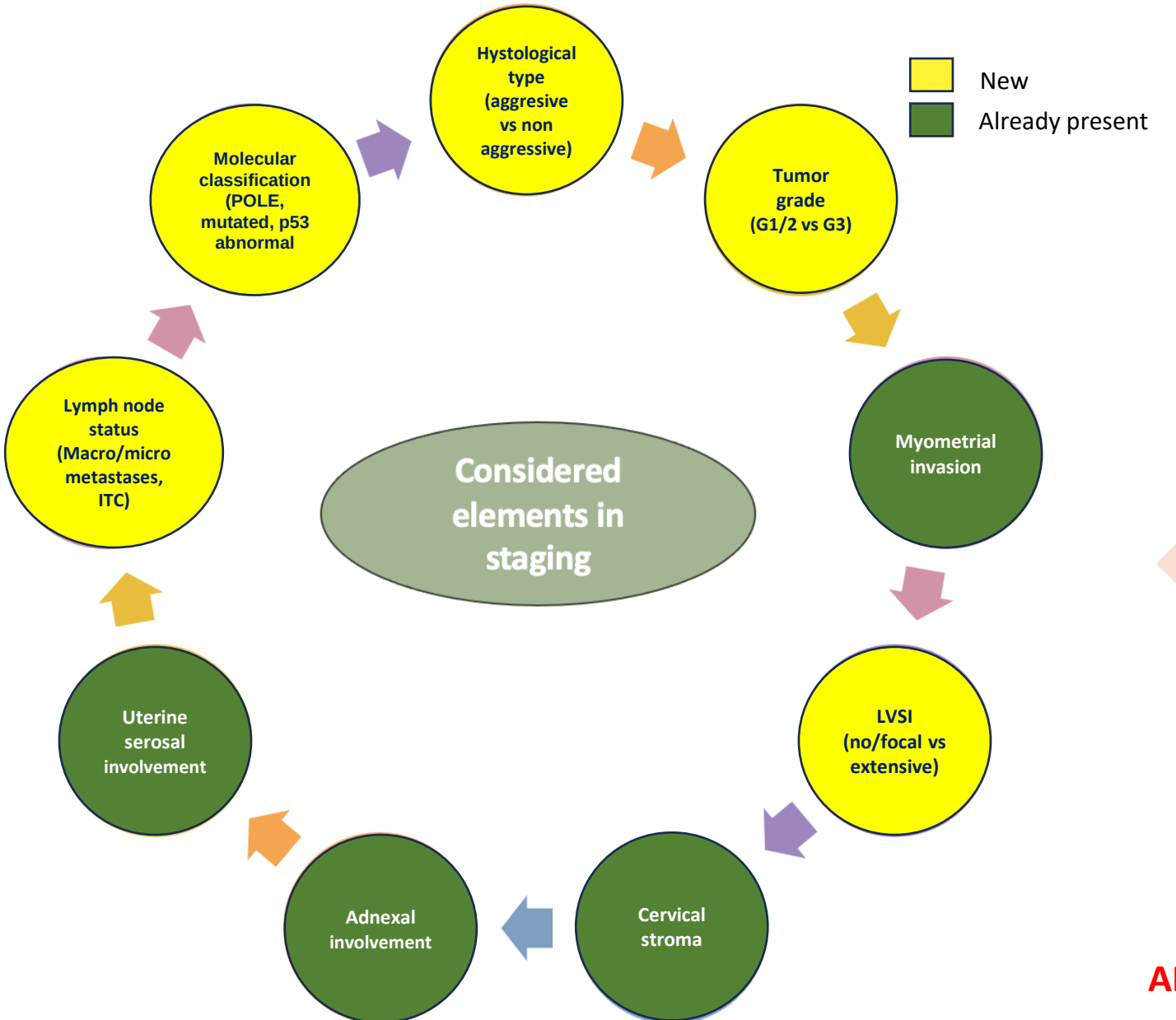
*Either G1, G2, or G3.

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

#Positive cytology has to be reported separately without changing the stage.

International Journal of Gynecology and Obstetrics , 2009

FIGO staging of endometrial cancer: 2023



KEY CHANGES

Incorporation of **histological subtype** and **subtleties of LVSI** to the actual determination of staging

Incorporation of **molecular profile** into the staging (if available)

Adaptation of anatomical spread in regards to the stage (adnexa, cervix, peritoneum)

Distinction between synchronous and metastatic cancers

ANATOMY + HISTOPATHOLOGY + MOLECULAR BIOLOGY

FIGO Endometrial cancer staging system over years

	FIGO 1988	FIGO 2009	FIGO 2023
Stage I	Tumor confined to the uterine corpus	Tumor confined to the uterine corpus	Tumor confined to the uterine corpus and ovary
Stage IA	Confined to the endometrium	MI < 50%	Confined to the endometrium OR non-aggressive histological type with MI < 50% with no substantial LVSI OR good prognosis disease
Stage IA1	-	-	Non-aggressive histological type confined to the endometrium or limited to a polyp
Stage IA2	-	-	Non-aggressive histological type with MI < 50% with no substantial LVSI
Stage IA3	-	-	Low grade endometrioid EC limited to the uterine corpus and ovary
Stage IAm $_{POLE\ MUT}$	-	-	*POLE* mut EC, confined to the uterus, regardless histology and degree of LVSI
Stage IB	MI < 50%	MI ≥ 50%	Non-aggressive histological type with MI ≥ 50%, with no extensive LVSI
Stage IC	MI ≥ 50%	-	Aggressive histological type confined to the endometrium or limited to a polyp
Stage II	Cervical involvement	Cervical involvement (only stroma)	Non-aggressive histological type with substantial LVSI
Stage IIA	Epithelial invasion	-	Non-aggressive histological type with cervical stromal involvement
Stage IIB	Stromal invasion	-	Non-aggressive histological type with substantial LVSI
Stage IIC	-	-	Aggressive histological type with any myometrial involvement
Stage IICm p53$_{abn}$	-	-	p53 abn EC, confined to the uterus, regardless of histology and degree of LVSI
Stage III	Local/regional spread	Local/regional spread	Local/regional spread
Stage IIIA	Serous of the corpus uteri and/or adnexa and/or malignant cytology	Serous of the corpus uteri and/or adnexa	Serous of the corpus uteri and/or adnexa
Stage IIIA1	-	-	Adnexal involvement (except when meeting stage IA3 criteria)
Stage IIIA2	-	-	Subserosa or serosal involvement
Stage IIIB	Vaginal involvement	Vaginal and/or parametrial involvement	Vaginal and/or parametrial and/or pelvic peritoneum involvement
Stage IIIB1	-	-	Vaginal and/or parametrial involvement
Stage IIIB2	-	-	Pelvic peritoneum involvement
Stage IIIC	Positive pelvic and/or para-aortic nodes	Positive pelvic and/or para-aortic nodes	Positive pelvic and/or para-aortic nodes
Stage IIIC1	-	Positive pelvic nodes	Positive pelvic nodes
Stage IIIC1i	-	-	Positive pelvic nodes (micrometastasis)
Stage IIIC1ii	-	-	Positive pelvic nodes (macrometastases)
Stage IIIC2	-	Positive para-aortic nodes	Positive para-aortic nodes (up to the renal vessels)
Stage IIIC2i	-	-	Positive para-aortic nodes (micrometastasis)
Stage IIIC2ii	-	-	Positive para-aortic nodes (macrometastases)
Stage IV	Tumor invades bladder and/or bowel mucosa and/or distant metastases	Tumor invades bladder and/or bowel mucosa and/or distant metastases	Tumor invades bladder and/or bowel mucosa and/or distant metastases
Stage IVA	Tumor invades bladder and/or bowel mucosa	Tumor invades bladder and/or bowel mucosa	Tumor invades bladder and/or bowel mucosa
Stage IVB	Distant metastases (including intra-abdominal metastases and inguinal nodes)	Distant metastases (including intra-abdominal metastseas and inguinal nodes)	Abdominal peritoneal (extra-pelvic) metastases
Stage IVC	-	-	Distant metastasis, including extra- and intra-abdominal nodes above the renal vessels, lungs, liver, and other organs

Note: EC, endometrial cancer; MI, myometrial invasion; LVSI, lymphovascular space invasion; *POLE* mut, *POLE* mutation; p53 abn, p52 abnormality.

Raspagliesi F,
Int J Gynaecol Obstet
2024

FIGO 2023

Stage I	Tumor confined to the uterine corpus and ovary
Stage IA	Confined to the endometrium OR non-aggressive histological type with MI < 50% with no substantial LVSI OR good prognosis disease
Stage IA1	Non-aggressive histological type confined to the endometrium or limited to a polyp
Stage IA2	Non-aggressive histological type with MI < 50% with no substantial LVSI
Stage IA3	Low grade endometrioid EC limited to the uterine corpus and ovary
Stage IAm $_{POLE\ MUT}$	*POLE* mut EC, confined to the uterus, regardless histology and degree of LVSI
Stage IB	Non-aggressive histological type with MI ≥ 50%, with no extensive LVSI
Stage IC	Aggressive histological type confined to the endometrium or limited to a polyp
Stage II	Non-aggressive histological type with substantial LVSI
Stage IIA	Non-aggressive histological type with cervical stromal involvement
Stage IIB	Non-aggressive histological type with substantial LVSI
Stage IIC	Aggressive histological type with any myometrial involvement
Stage IICm p53$_{abn}$	p53 abn EC, confined to the uterus, regardless of histology and degree of LVSI
Stage III	Local/regional spread
Stage IIIA	Serous of the corpus uteri and/or adnexa
Stage IIIA1	Adnexal involvement (except when meeting stage IA3 criteria)
Stage IIIA2	Subserosa or serosal involvement
Stage IIIB	Vaginal and/or parametrial and/or pelvic peritoneum involvement
Stage IIIB1	Vaginal and/or parametrial involvement
Stage IIIB2	Pelvic peritoneum involvement
Stage IIIC	Positive pelvic and/or para-aortic nodes
Stage IIIC1	Positive pelvic nodes
Stage IIIC1i	Positive pelvic nodes (micrometastasis)
Stage IIIC1ii	Positive pelvic nodes (macrometastases)
Stage IIIC2	Positive para-aortic nodes (up to the renal vessels)
Stage IIIC2i	Positive para-aortic nodes (micrometastasis)
Stage IIIC2ii	Positive para-aortic nodes (macrometastases)
Stage IV	Tumor invades bladder and/or bowel mucosa and/or distant metastases
Stage IVA	Tumor invades bladder and/or bowel mucosa
Stage IVB	Abdominal peritoneal (extra-pelvic) metastases
Stage IVC	Distant metastasis, including extra- and intra-abdominal nodes above the renal vessels, lungs, liver, and other organs

- **Incorporation of histological subtypes and LVSI**
- **Incorporation of molecular profile in the staging**
- **Dis** **static can**
- **Ada** **to the sta**
- **Dis** **etastasis**

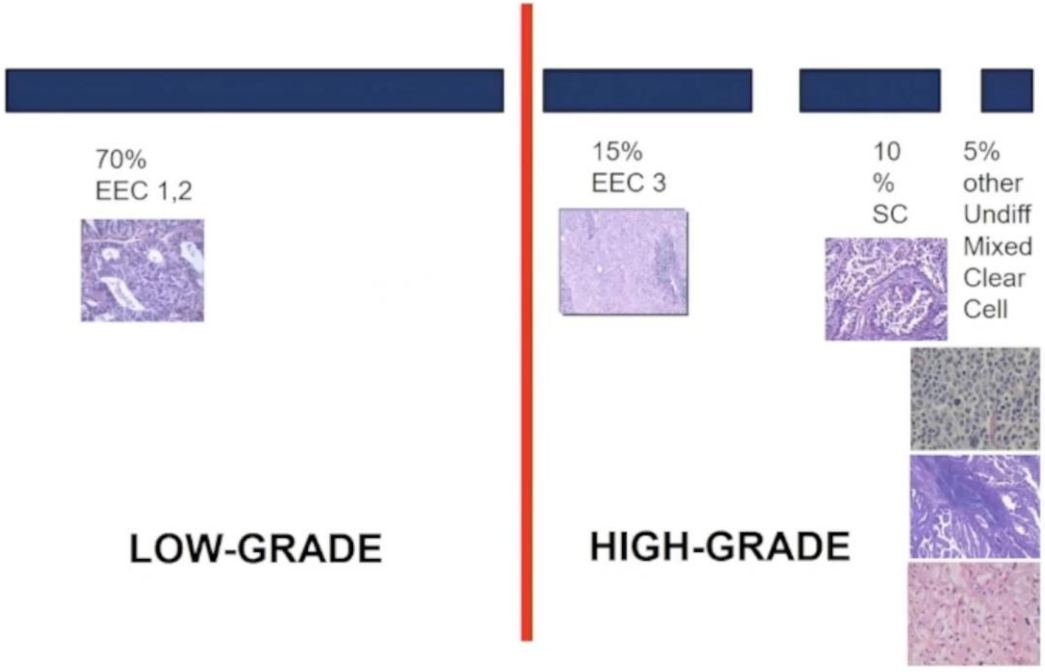
WHO, ESGO-ESTRO-ESP, CAP 2023

- Absent
- Focal (< 5 vessels)
- Substantial/extensive (> 5 vessels)

NCCN, ESMO

- Absent

LOW GRADE AND HIGH GRADE ENDOMETRIAL CARCINOMAS



- Ly m
- M th by

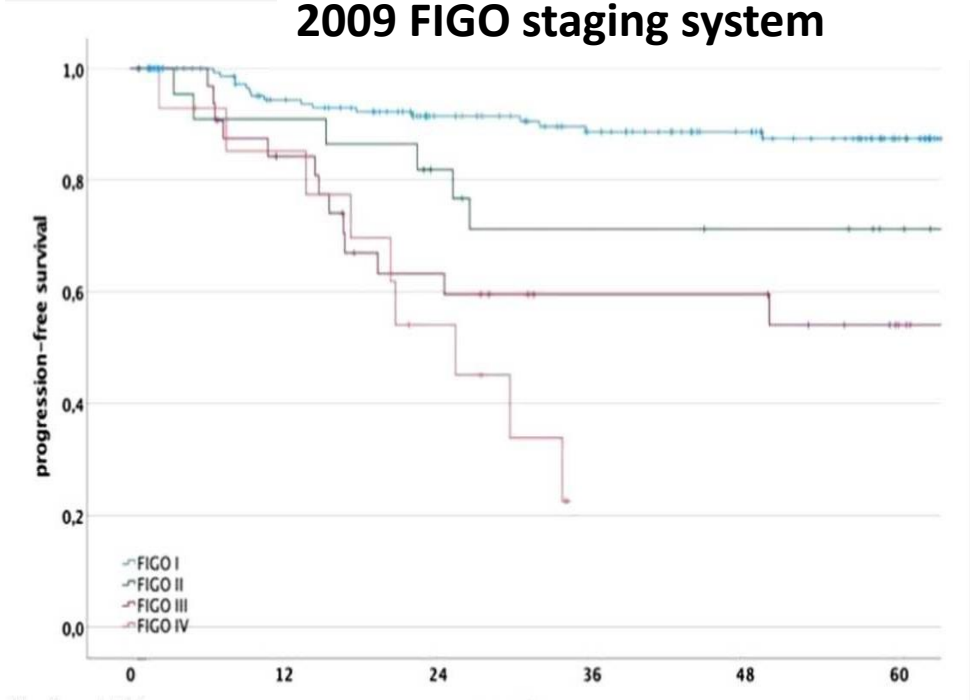
%
9%
.5%
.4.9%
2.7%

Berek.

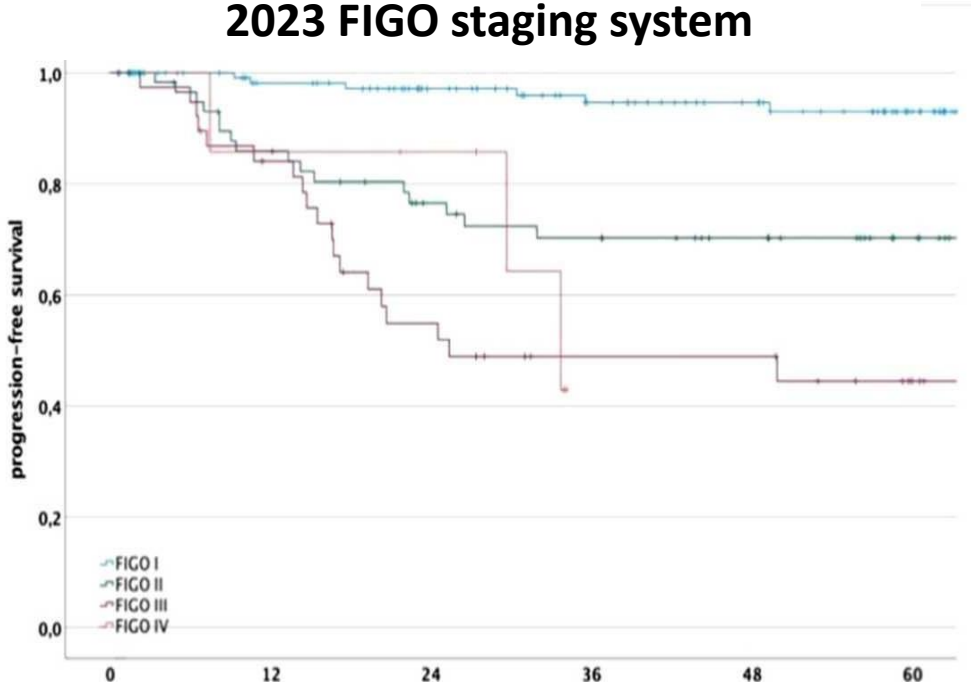
Survival according to FIGO staging system 2009 vs 2023

PFS

2009 FIGO staging system



2023 FIGO staging system



FIGO STAGING 2023 ALLOWS FOR A MORE PRECISE 'PROGNOSTICATION' COMPARED WITH FIGO 2009 PARTICULARLY IN EARLY STAGES OF DISEASE

	5-year PFS (FIGO 2009)	5-year PFS (FIGO 2023)
Stage I vs II	87.4% vs 71.2%	**93% vs 70.2%**
Stage I vs III	87.4% vs 54.1%	**93% vs 44.4%**

Schwameis R, et al. *Eur J Cancer*. 2023:193:113317.

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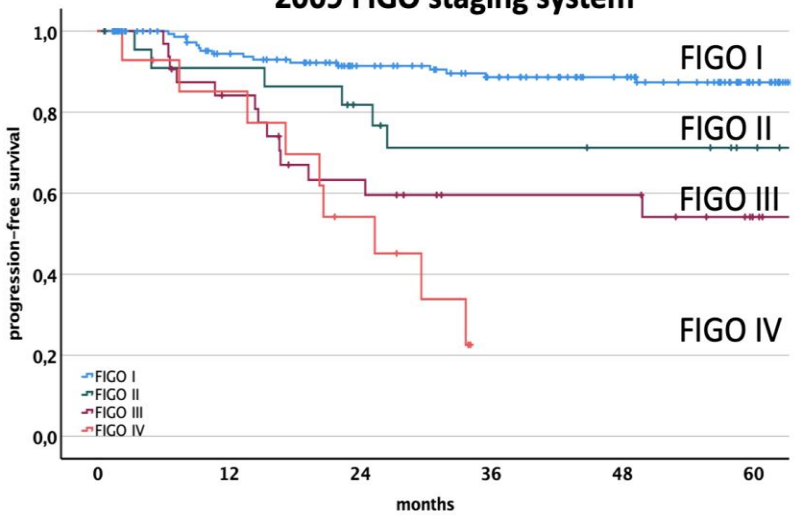
MOLECULAR STAGING: when molecular classification CHANGES the FIGO stage

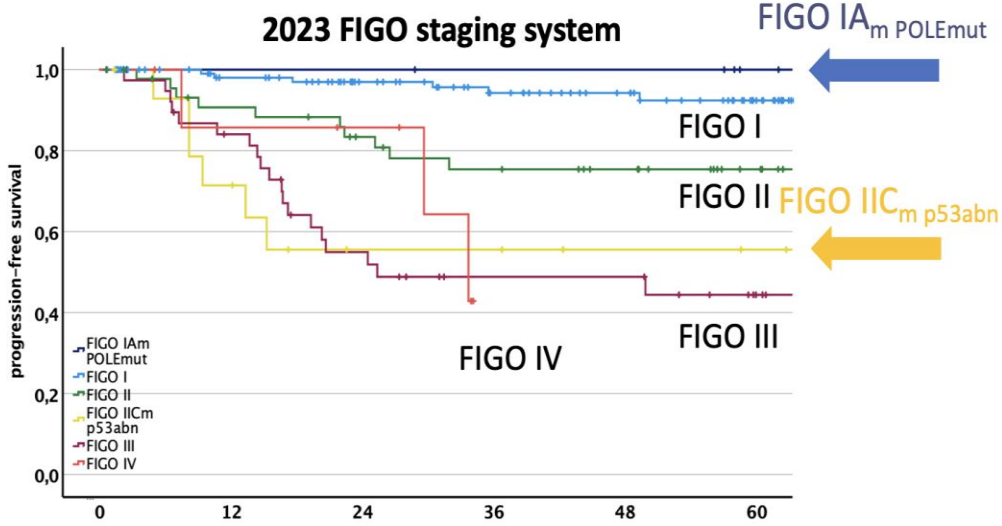
Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

2009 FIGO staging system



Figo Stage						
I	163	131	107	91	75	49
II	23	20	16	13	12	9
III	32	25	17	12	12	4
IV	14	11	6	0	0	0

2023 FIGO staging system



						Figo Stage
8	7	7	6	6	3	$IAm_{POLEmut}$
117	96	79	65	54	35	I
46	38	32	28	24	16	II
15	10	5	5	3	2	$IICm_{p53abn}$
38	30	18	12	12	4	III
8	6	5	0	0	0	IV

Excellent prognosis

POLEm

5-yr PFS 100%

Unfavourable prognosis

p53 protein expression

5-yr PFS 55.6%

R. Schwameis et al. Eur J Cancer 2023

ESGO-ESTRO-ESP GUIDELINES 2021

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** 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-gr… 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 … • 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

ESMO GUIDELINES 2022

Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

A. Oaknin[1], T. J. Bosse[2], C. L. Creutzberg[3], G. Giornelli[4], P. Harter[5], F. Joly[6,7], D. Lorusso[8,9], C. Marth[10], V. Makker[11,12], M. R. Mirza[13], J. A. Ledermann[14,15] & N. Colombo[16,17], on behalf of the ESMO Guidelines Committee*

Table 2. EC risk groups

Risk group	Description[a]
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[b] and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers[c]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype[b]

Less data in the ADVANCED stage for POLE; unable to advice; clincial trial or data collection when possible

Concin N, et al. *Int J Gynecol Cancer*. 2021;31(1):12-39; Oaknin A, et al. *Ann Oncol.* 2022;33(9):860-877.

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2023 FIGO staging[¶]			Molecular classification*				
			*POLE*mut	MMRd	NSMP low-grade+ERpos	NSMP high-grade/ERneg**	p53abn
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)	IAm *POLE*mut			**	
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#	IAm *POLE*mut			**	
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium	IAm *POLE*mut		n.a.		
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm *POLE*mut			**	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI***	IAm *POLE*mut			**	IICm p53abn
IIC		High-grade histologies^, myoinvasion	IAm *POLE*mut	Myoinvasion <50%, no/focal LVSI	n.a.		IICm p53abn
			IAm *POLE*mut	Myoinvasion ≥50%, no/focal LVSI			
			IAm *POLE*mut	Cervical stromal invasion, no/focal LVSI			
			IAm *POLE*mut	Substantial LVSI**			
III	**Local and/or regional spread**						
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)					
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa					
IIIB	IIIB1	Metastasis or direct spread to the vagina and/or the parametria					
	IIIB2	Metastasis to the pelvic peritoneum					
IIIC	IIIC1	Pelvic lymph node metastasis					
	IIIC1i	Micrometastasis					
	IIIC1ii	Macrometastasis					
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIIC2i	Micrometastasis					
	IIIC2ii	Macrometastasis					
IV	**Locally advanced and/or metastatic disease**						
IVA		Invasion of the mucosa and/or the intestinal mucosa					
	Metastatic disease or residual disease after surgery						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

Risk Groups

- Low risk
- Intermediate risk
- High-intermediate risk
- High risk
- Uncertain, lack of data

2023 FIGO stage IIC carcinomas other than p53 abnormal are not depicted in this table.

When molecular classification is known, the FIGO stage should be reported with an annotation of m (for molecular) followed by the specific molecular subtype. There are two specific molecularly defined FIGO stages, namely stage IAm *POLE*mut (stages I and II disease with a pathogenic *POLE* mutation) and stage IICm p53abn (stages I and II disease with a p53 abnormality and myometrial invasion).

*Details on determining the molecular classification, including allocation for double classifiers, are detailed in figure 2 and the webappendix, pp 18-20.

** The molecular subgroup NSMP high-grade/ERneg consists of either high-grade NSMP cases or ERneg NSMP cases. Thus, in *low-grade* endometrioid carcinomas of both the endometrium + ovary, only the ERneg cases of the molecular subgroup NSMP high-grade/ERneg apply.

***Substantial LVSI is defined according to WHO criteria by ≥4 vessels in at least one H&E slide (refer to appendix for information on LVSI, pp 18-20).

myoinvasion <50% + no/focal LVSI + ovarian tumour pT1a

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Definition of risk groups

Low | Intermediate | High-Intermediate | High | Uncertain

2023 FIGO staging[Ŧ]			Molecular classification*				
			***POLE*mut**	**MMRd**	**NSMP low-grade+ERpos**	**NSMP high-grade/ERneg****	**p53abn**
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)	IAm *POLE*mut			**	
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#	IAm *POLE*mut			**	IICm p53abn
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium	IAm *POLE*mut		n.a.		
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm *POLE*mut			**	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI***	IAm *POLE*mut			**	IICm p53abn
IIC		High-grade histologies^, myoinvasion	IAm *POLE*mut	Myoinvasion <50%, no/focal LVSI	n.a.		IICm p53abn
			IAm *POLE*mut	Myoinvasion ≥50%, no/focal LVSI			
			IAm *POLE*mut	Cervical stromal invasion, no/focal LVSI			
			IAm *POLE*mut	Substantial LVSI**			

ESGO 2025

Definition of risk groups

Low | Intermediate | High-Intermediate | High | Uncertain

2023 FIGO staging[T]			Molecular classification*				
			*POLE*mut	MMRd	NSMP low-grade+ERpos	NSMP high-grade/ERneg**	p53abn
III	**Local and/or regional spread**						
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)					
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa					
IIIB	IIIB1	Metastasis or direct spread to the vagina and/or the parametria					
	IIIB2	Metastasis to the pelvic peritoneum					
IIIC	IIIC1	Pelvic lymph node metastasis					
	IIIC1i	Micrometastasis					
	IIIC1ii	Macrometastasis					
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIIC2i	Micrometastasis					
	IIIC2ii	Macrometastasis					
IV	**Locally advanced and/or metastatic disease**						
IVA		Invasion of the mucosa and/or the intestinal mucosa					
	Metastatic disease or residual disease after surgery						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

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Conclusions

- Endometrial carcinomas include four non-overlapping disease categories: including these into routine diagnosis improves risk stratification
- MMR proteins, ER, p53 IHC and POLE status on all cases
- Molecular classification might have influence on adjuvant treatment: POLE status for all and HER2 IHC for all p53abn/TP53mut cases
- New FIGO 2023 classification is a major step forward in identifying better prognostic factors for patients with EC YES
- New FIGO 2023 classification is a major step forward in identifying better predictive factors for patients with EC MAYBE
- Integrated molecular classification into the WHO classification, 2023 FIGO staging and multidisciplinary guidelines by ESGO-ESTRO-ESP

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Thank you

Any questions?

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