POLE mutated endometrial cancer

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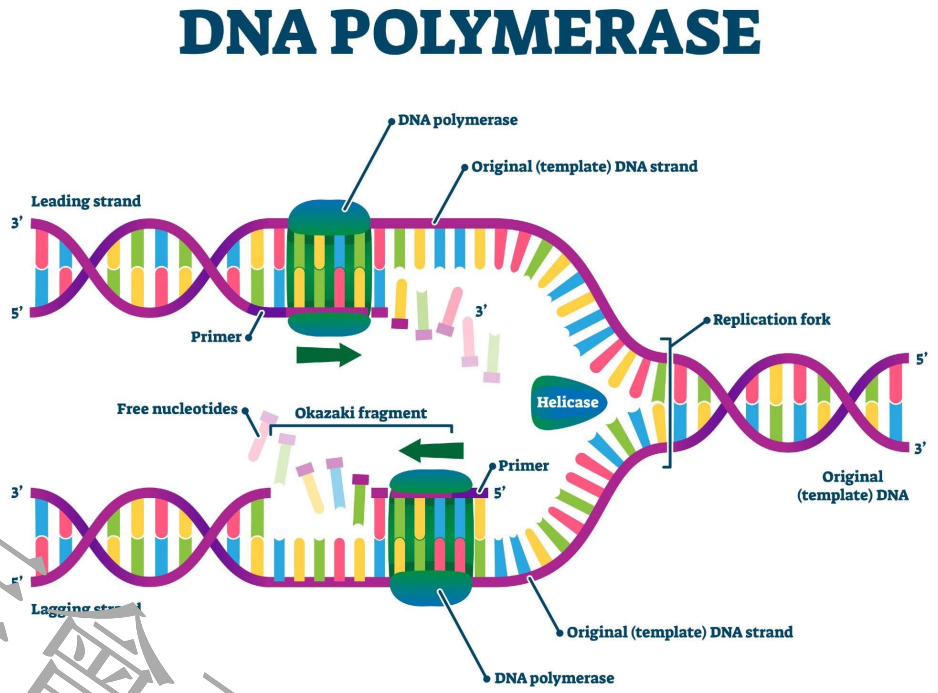
POLE gene and encoding protein

- Chr 12q24.33 (132.62-132.69 Mb)
- DNA polymerase epsilon catalytic subunit is an enzyme encoded by the POLE gene. It is the central catalytic subunit of DNA polymerase epsilon.
  - A critical protein involved in DNA proofreading and replication through recognition and excision of mismatched base pairs.
  - Somatic and germline POLE proofreading defects, particularly mutations occurring in the exonuclease domain representing codons 268-471, are more often found in mismatch repair proficient tumors and associated with hypermutagenesis



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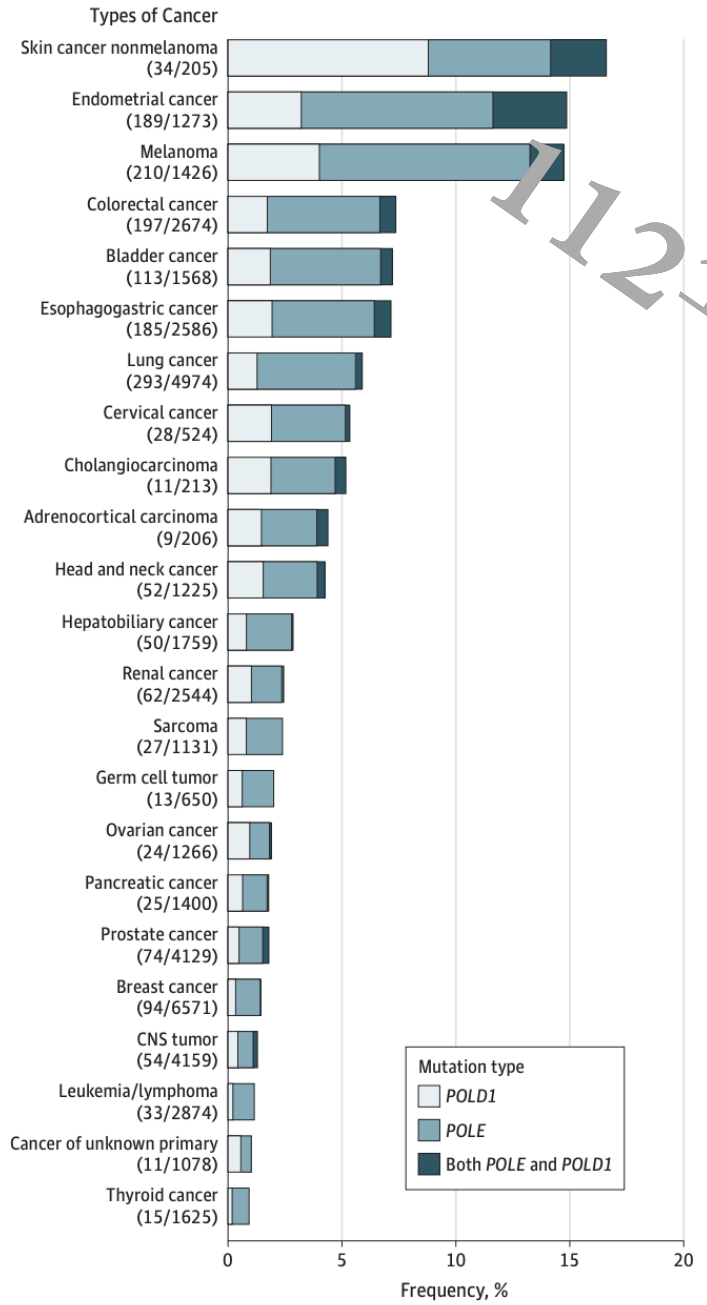
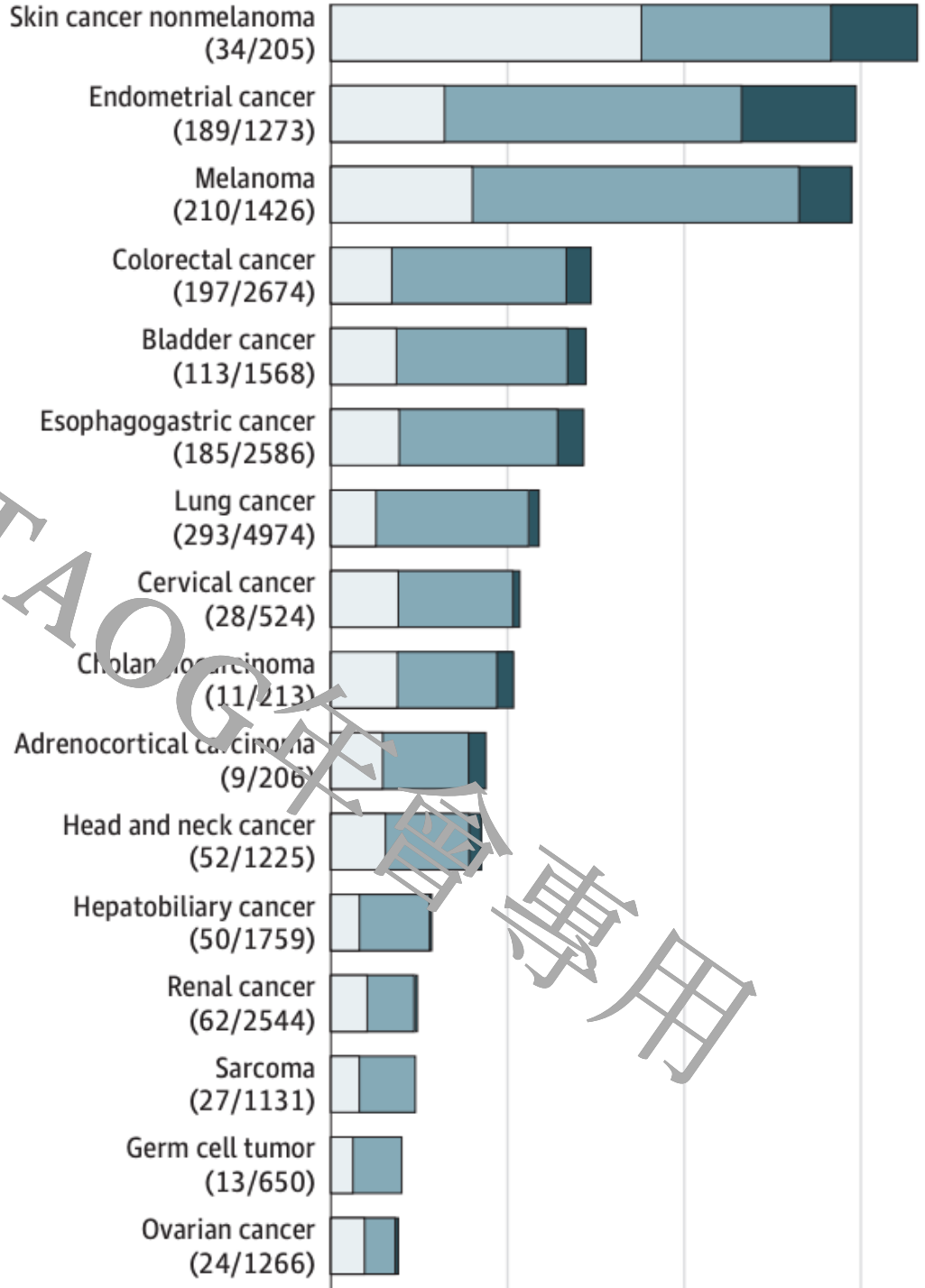
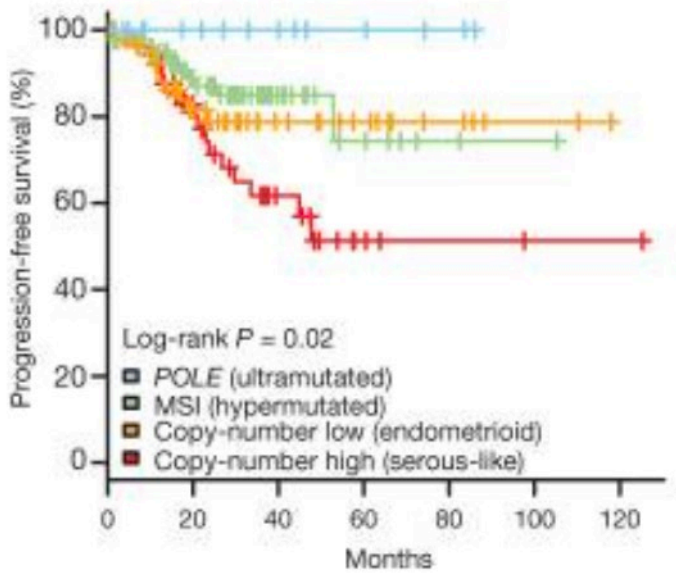
https://www.news-medical.net/life-sciences/What-is-DNA-Polymerase.aspx

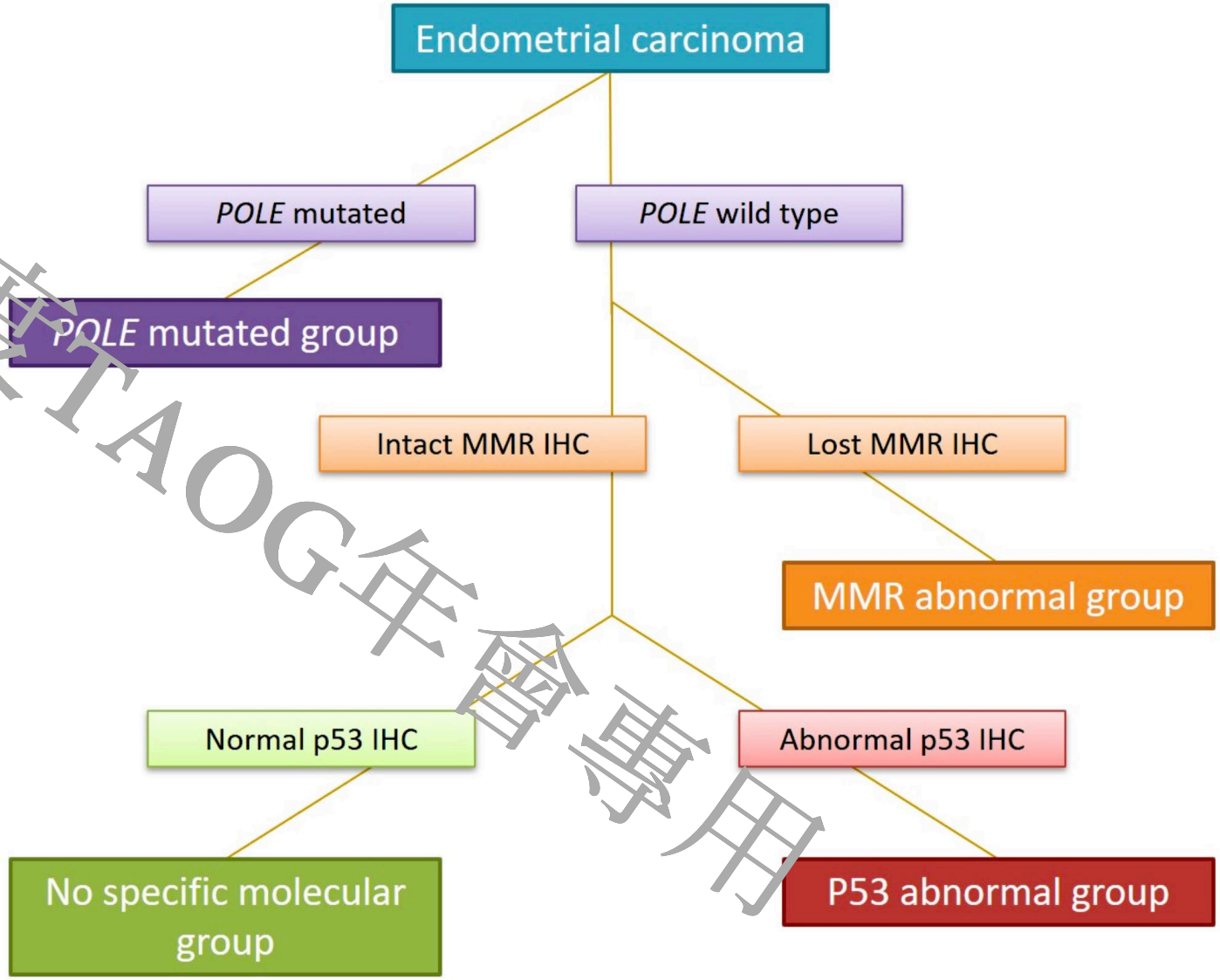
Figure 1. Prevalence of *POLE*/*POLD1* Mutations in 47 721 Patients With Different Cancer Types





Molecular types in endometrial cancer





https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3704730/

https://www.pathologyoutlines.com/topic/uterusPOLEendometrialcarcinoma.html

Detection of POLE mutation

Molecular diagnostic tests

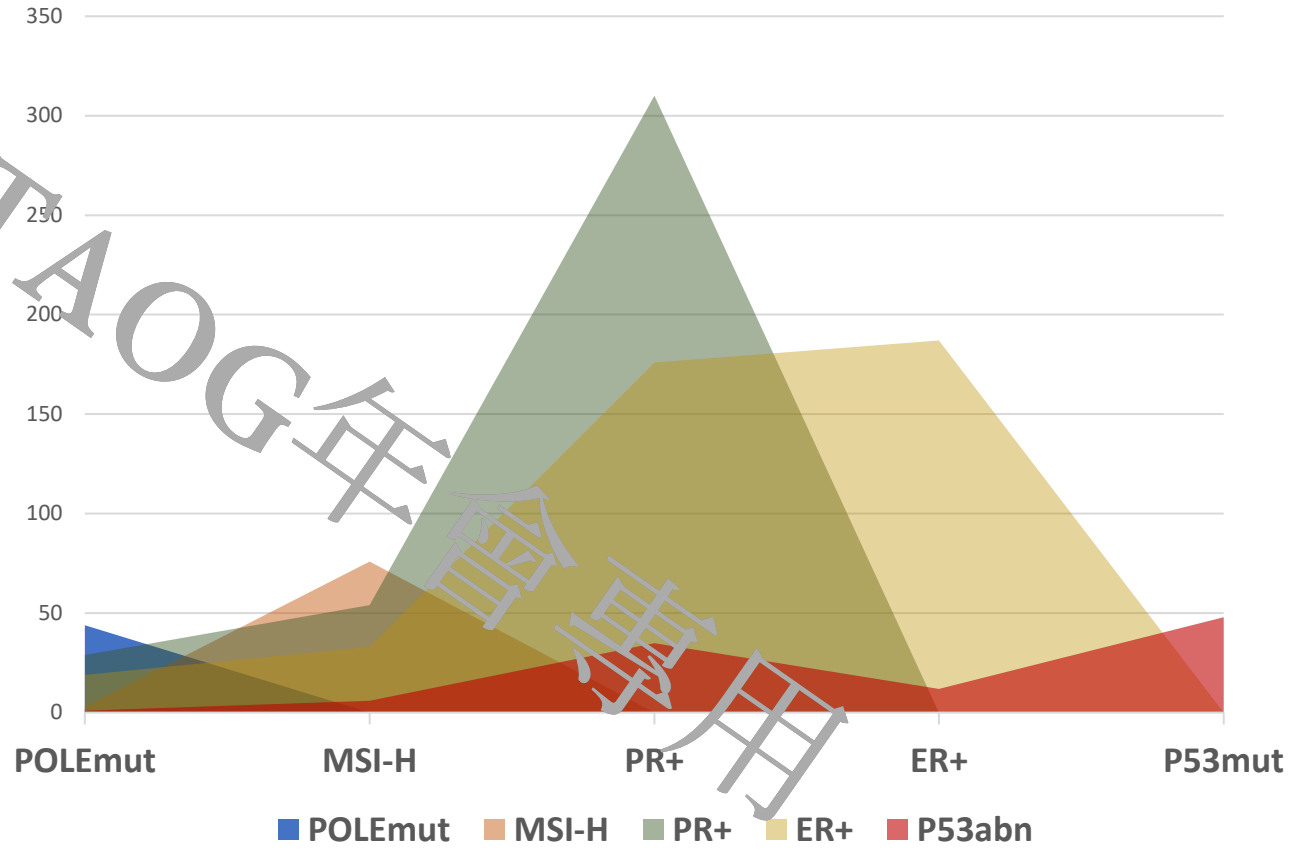
- next generation sequencing
- sanger sequencing,
- hotspot single nucleotide SNaPshot assay
- droplet digital PCR

No IHC surrogate marker currently available

- > 5% of endometrial carcinomas harbor > 1 molecular classifying alteration and are referred to as multiple classifier
- p53 alterations in the presence of POLE pathogenic mutation or MMR deficiency are likely secondary events acquired in tumor progression (passenger mutations) and are typically subclonal

Correlation of molecular markers of 397 patients with endometrioid endometrial cancer

	POLEmut	MSI-H	PR+	ER+	P53mut
POLEmut	44				
MSI-H	3	76			
PR+	29	54	310		
ER+	19	33	176	187	
P53abn	1	6	35	12	48



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Treatment of POLEmut endometrial cancer

- Surgery with or without adjuvant therapy (vaginal brachytherapy, pelvic radiotherapy and chemotherapy, depending on stage)
  - Ongoing clinical trials (e.g., PORTEC-4a) are investigating the potential for treatment de-escalation in high-intermediate-risk group patients
  - Immune checkpoint inhibitor therapy in an advanced stage or recurrent disease
    - “ultramutated”, very high tumor mutation burden

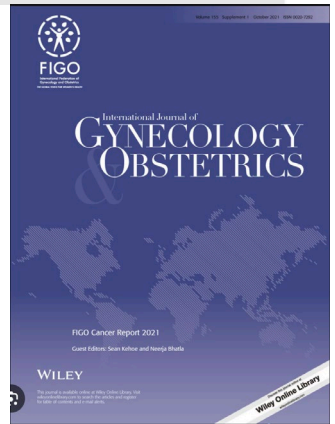
Incidence and outcome after treatment

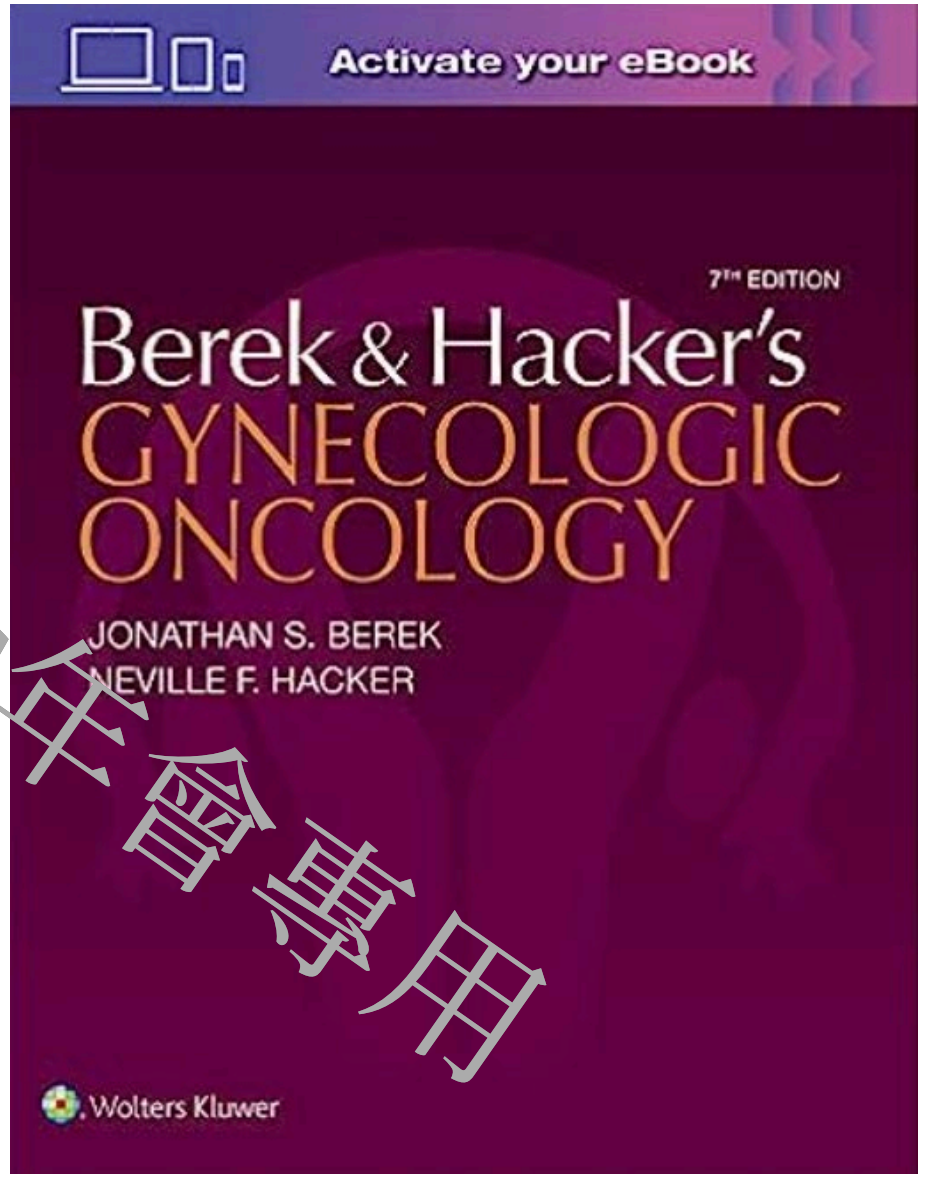
- 44/397 endometrioid cancer
- 6/120 type II cancer

- All but one ”cured” from cancer

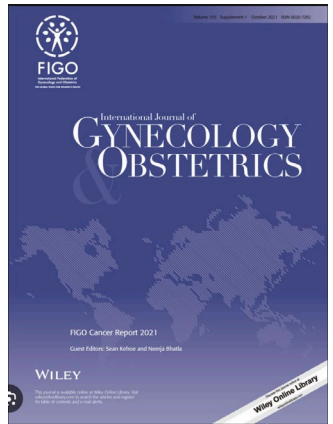
TABLE 1 2023 FIGO staging of cancer of the endometrium.[a,b]

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to a polyp OR endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium





Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum



IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes
	IIIC1i Micrometastasis
	IIICii Macrometastasis
	IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	IIIC2i Micrometastasis
	IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

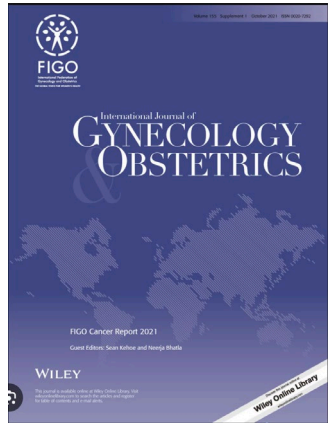
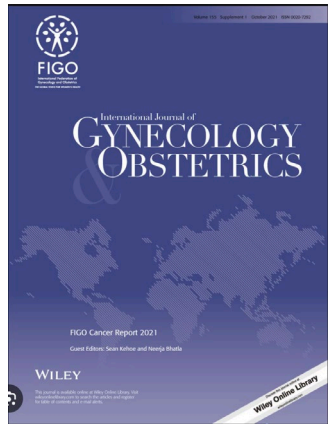


TABLE 2 FIGO endometrial cancer stage with molecular classification.[a]

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



FIGO stage?

- 77 y/o, with a 58 mm endometrial tumor
- 75% myometrial invasion
- Endometrioid carcinoma, G3
- POLE mutated, c.1231G>C (exon 13)
- MLH1 (-), MSH2 (+), MSH6(-), PMS2(-)
- ER moderate, 10%, PR strong 10%
- P53wt

pT1bN0M0 (2009)

FIGO IIC Aggressive histological types with any myometrial involvement

Stage IAm$_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type

FIGO IAm$_{POLEmut}$

- 44 y/o, with a 14 mm tumor
- Superficial myometrial invasion, 1 mm/20 mm myometrial involvement
- Endometrioid carcinoma, G2
- Extensive LVSI
- POLEmut, c.1366G>C
- pMMR
- ER moderate, 70%
- PR strong, 100%
- p53wt

pT1bN0M0 (2009)

FIGO IIB Substantial LVSI of non-aggressive histological types

Stage IAm$_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type

FIGO IAm$_{POLEmut}$

FIGO 2009 vs. FIGO 2023 staging in POLE mutated endometrioid endometrial cancer without molecular classification

		FIGO 2023								Total
		IA	IB	IIC	IIIA1	IIIB2	IIIC1ii	IIIC2ii	IVB	
FIGO 2009	1A	18		5						23
	1B		9	5						14
	3A				1	3				4
	3C1						1			1
	3C2							1		1
	4B								1	1
Total		18	9	10	1	3	1	1	1	44

P < 0.001, Fisher's exact test

FIGO 2009 vs. FIGO 2023 staging in POLE mutated endometrioid endometrial cancer with molecular classification

		FIGO 2023						Total
		$IAm_{POLEmut}$	$IIIA1m_{POLEmut}$	$IIIB2m_{POLEmut}$	$IIIC1iim_{POLEmut}$	$IIIC2iim_{POLEmut}$	$IVBm_{POLEmut}$	
FIGO 2009	1A	23						23
	1B	14						14
	3A		1					4
	3C				1			1
	3C2					1		1
	4B						1	1
Total		37	1	3	1	1	1	44

P < 0.001, Fisher's exact test

FIGO 2023 in POLE mutated endometrioid endometrial cancer

		$IAm_{POLEmut}$	$IIIA1m_{POLEmut}$	$IIIB2m_{POLEmu}$	$IIIC1iim_{POLEmu}$	$IIIC2iim_{POLEmu}$	$IVBm_{POLEmu}$	Total
FIGO 2023 without molecular classification	IA	18						18
	IB	9						9
	IIC	10						10
	IIIAI		1					1
	IIIB2			3				3
	IIIC1ii				1			1
	IIIC2ii					1		1
	IVB						1	
Total		37	1	3	1	1	1	44

P < 0.001, Fisher's exact test

年齡	組織分類	LVSI	p53	2009 FIGO	FIGO 2023 w/o mol	FIGO 2023mol
47	Carcinosarcoma	(-)	p53wt	3C2	IIIC2ii	IIIC2ii
53	Carcinosarcoma	diffuse		2B	IIC	IA
56	Carcinosarcoma	not other specified		3B	IIIB2	IIIB2
57	Clear cell adenocarcinoma		p53wt	3C1	IIIC1ii	IIIC1ii
54	Serous carcinoma	diffuse	p53wt	1A	IIC	IA
56	Serous carcinoma	diffuse	p53abn	1B	IIIA2	IIIA2

FIGO 2023 in POLE mutated EMCA

		$IAm_{POLEmut}$	$IIIA1m_{POLEmut}$	$IIIA2m_{POLEmut}$	$IIIB2m_{POLEmu}$	$IIIC1iim_{POLEmu}$	$IIIC2iim_{POLEmu}$	$IVBm_{POLEmu}$	Total
FIGO 2023 without molecular classification	IA	18							18
	IB	9							9
	IIC	12							12
	IIIA1		1						1
	IIIA2			1					1
	IIIB2				4				4
	IIIC1ii					2			2
	IIIC2ii						2		2
	IVB							1	1
Total		39	1	1	4	2	2	1	50

Comments

App for FIGO 2023 endometrial cancer staging

- A friendly App according to the new staging
- “**Filemaker go**” App
  - Free download from **Apple store**
- ”Guest” for simulation and testing
- Feedback welcome