Cancer Endometrium PO - Recent Insights

AROICON 2024
ICRO Preconference Workshop
Interactive Modules for Problem-based Assessment and Case-based Teaching

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My Team…

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The objectives of the session…

- To know the recent changes in the understanding of endometrial cancer
- To understand various molecular subtypes of EC
- To know their clinical applications
- To understand the limitations of molecular profiling for EC

What are new concepts in EC…

- Pathology..
  - CGA looked into the transcriptional, proteomic and genomic aspects done on formalin fixed paraffin blocks
- Staging 2023..
  - In early stages,prefix of m
- Surgery..
  - Lap/Robotic, SLND, Avoid LND, Fertility preservation
- Radiation/systemic therapy..
  - Personalised

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Changes in stage I

FIGO 2023

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 an 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

- IA3-low grade, uterus and ovary (unilateral, limited to ovary and capsule intact, less than 5 LVSI)
- IC-aggressive histopathology, polyp/endometrium

Changes in stage II

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

- IIA -stroma/nonaggressive
- IIB-LVSI/non aggressive
- IC-aggressive with MI

Clinico-pathology based Risk stratification…

Low risk	Stage 1A (G1,2), endometrioid type No LVSI
Intermediate risk	Stage 1B (G1,2), endometrioid type No LVSI
High Intermediate risk	Stage IA G3 ±LVSI Stage IG1-2+ LVSI ±MI
High risk	Stage 1B (G3), endometrioid type ± LVSI Stage II, Stage III with no residual disease All stages non-endometrioid type or carcinosarcoma
Advanced	Stage III with presence of residual disease and stage IV A
Metastatic	Stage IV B

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Cancer Genomic Atlas	Pole Mutation	MMR d, MSI-H	NSMP	P53abn
What is it?	Mutations in exonuclease domain of POLE gene	Copy number High	Copy number low	high somatic Copy-number alterations and mutation profiles
Mutation rate	232 X10 $^{-6}$/Mb	18 X10 $^{-6}$/Mb	2.9 X10 $^{-6}$/Mb	2.3 X10 $^{-6}$/Mb
Occurrence(PORTEC III)	12%	33%	32%	23%
Immunogenicity	Very high (ultramutated-pembrolizumab ?)	High/immune evasive tu cells	Nil	Nil
How detected?	NGS	IHC/PCR	IHC	IHC
Prognosis	Very good	variable	Intermediate, 50% endometrioid	Bad,mostly non endometrioid
Treatment	De-escalate? PORTEC-4A/Rainbo	Role for Immunotherapy?	Hormone sensitive	RTCT and adjuvant chemo
Outcome (5 yr RFS)	98%vs 73%	72%	74%	48%
Remarks	hypersensitivity to adjuvant therapy	More of LVSI	HT	Very aggressive

Indications for Molecular Testing…

- All patients
  - Risk stratification
  - Selection of adjuvant therapy
- Specially grade III
  - Its an heterogenous group of cancers
  - Differs with respect to prognosis/clinical/molecular
- Stage Im_{p53abn}..aggressive treatment results in better RFS $p<0.001$ as per PORTEC III

Shifts in staging with molecular analysis

Table 1. Molecular classification of Endometrial Cancer and correlation with previous classification systems.

TCGA Subgroup	Mutated Genes	Genetic Abberation	Surrogate Marker	Prevalence	Histology	FIGO Grade	Stage	Risk Group	Recurrence Status	Prognosis
Hypermutated MSI/MSI-H/MMRd	MLH1, MSH2, MSH6, PMS2	Microsatellite instability, somatic or germline mutations in MMR genes and epigenetic changes (i.e., MSH1 silencing)	MSH6, PMS2 IHC expression	24.7% of G1–2 tumors	EEC	Low (G1–2)	IA	Low risk	LVSI (−) or focal	Variable
							IB	Intermediate		
						High (G3)	IA			
							IB		Regardless of LVSI status	
				39.7% of G3 tumors		Regardless of the grade	I	High-intermediate	Substanial LVSI	
							II		(−)	
					Non-EEC *	High	III–IVA	High risk	No RD	
							I–IVA		MI, no RD	
Copy-number-low (CNL)/non specific molecular profile (NSMP)	TP53 wild type	Low number of mutations, microsatellite stability	Normal p53 IHC expression	63.5% of G1–2 tumors	EEC	Low	IA	Low risk	LVSI (−) or focal	Variable
							IB	Intermediate		
						High	IA			
							IB		Regardless of LVSI status	
				28% of G3 tumors		Regardless of the grade	I	High-intermediate	Substanial LVSI	
							II		(−)	
					Non-EEC *	High	III–IVA	High risk	No RD	
							I–IVA		MI, no RD	
Copy-number-high (CNH)/p53abn	TP53	TP53 somatic mutation (91% of cases)	Aberrant p53 IHC expression or aneuploidy with simultaneous testing to exclude MSI-H or POLE	4.7% of G1–2 tumors	Non-EEC *	N/A	IA	Intermediate	Without MI	Unfavorable
				25% of G3 EEC	EEC or non-EEC *		I–IVA	High	MI, no RD	
POLE ultramutated (POLEmut)	POLE	Somatic mutation of POLE, TP53 mutation in 35% of cases	Exonuclease domain POLE gene/molecular analysis	6.2% of G1–2 tumors	EEC or non-EEC *	Low (G1–2)	I–II	Low	No RD	Excellent
				12.1% of G3 tumors		High (G3)				

* Non-endometrioid: clear cell, serous, undifferentiated, carcinosarcoma, mixed; LVSI = LymphoVascular Space Invasion, RD = residual disease, MI = myometrial invasion, EEC = endometrioid carcinoma; IHC = immunohistochemical, N/A = not applicable.

Cancers 2022, 14, 4500. https://doi.org/10.3390/cancers14184500

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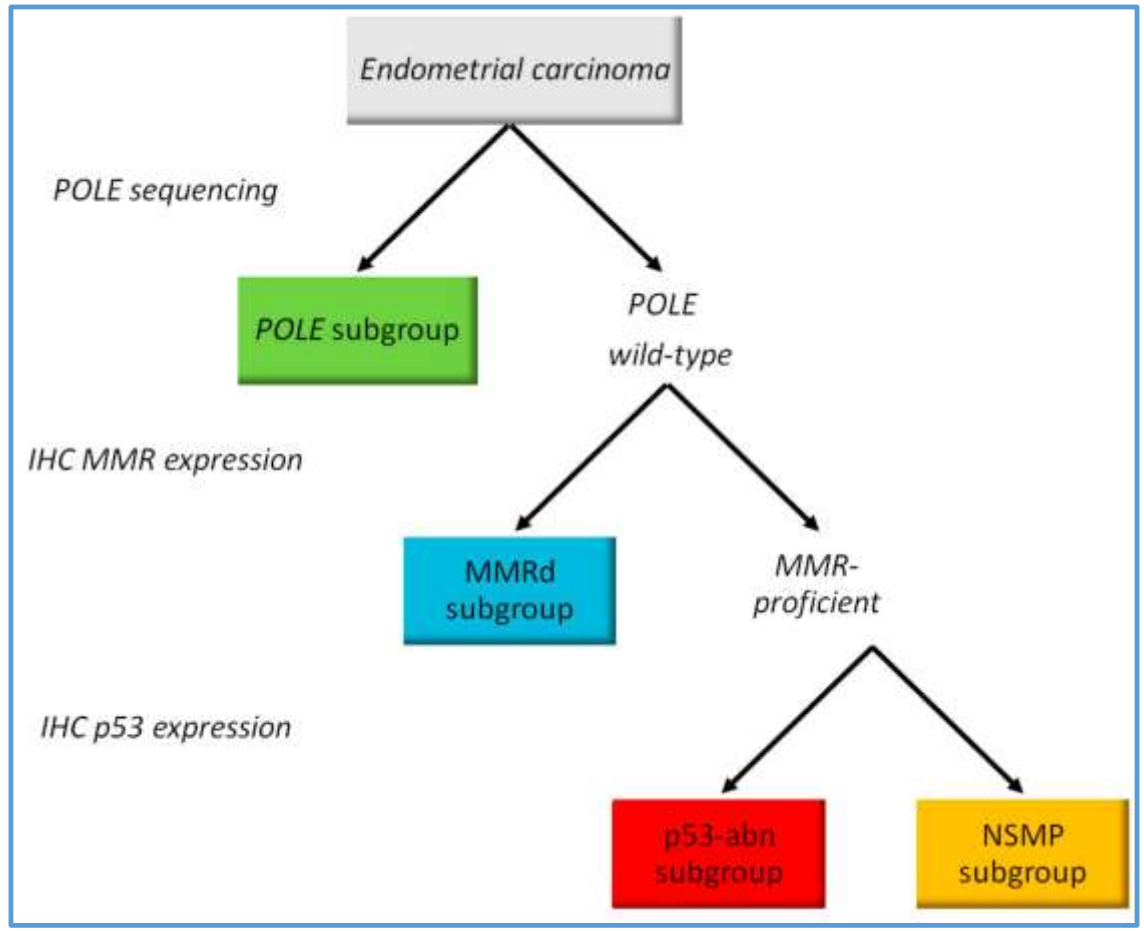
Case 1

- 65 yrs,P4L4,22 yrs postmenopausal bleed,HTN,5 kg weight loss
- U/S Hyperechoic solid lesion,34X25mm
- MRI 19X35X30mm,hyperintense,thin myometrium
- Robotic TAHBSO
- Serous carcinoma,pT1aN0M0,Her 2neu+++

Case 2

- 54 yrs, Ca Breast,pT4bN2M0,ER/PR+/Her2 –ve
- Surgery-CT-RT-Letrozole
- 8 yrs later, Postmenopausal bleed, O/E mild yellowish discharge
- U/S 4.5X3.6X4.3cm,mild internal vascularity
- PET lesion uterus SUV 12
- MRI fundus to internal os, RT ext iliac 0.9X1.7cm
- Pipelle aspirate poorly dif ca


Endometrial carcinoma
POLE sequencing
POLE subgroup
POLE wild-type
IHC MMR expression
MMRd subgroup
MMR-proficient
IHC p53 expression
p53-abn subgroup
NSMP subgroup

Histomolecular Report…

- 6X3.8X3.5 cm, High Gr EC
- MI <1/3rd
- LVSI-ve, serosa-ve,para –ve
- 0/2 LNs
- pT1aN0M0

- MSI-High,
- P53 Wild type
- POLE not mutated

Case 3

TEST NAME
MMR Panel
SPECIMEN INFORMATION
Received two paraffin blocks. Test performed on block no. 2728/24 (G)
CLINICAL HISTORY
Postmenopausal bleeding with thickened endometrium.
METHODOLOGY
Immunohistochemistry

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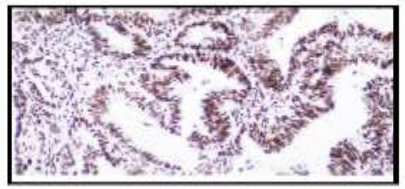
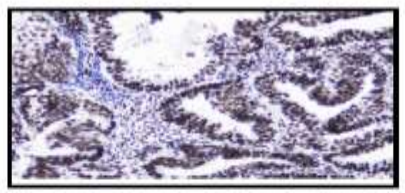
DIAGNOSIS		
MARKERS	**RESULT**	**IMAGE**
hMSH-6(EP-49)	INTACT NUCLEAR EXPRESSION	
hMSH-2(RED2)	INTACT NUCLEAR EXPRESSION	
hMLH-1(GM011)	INTACT NUCLEAR EXPRESSION	

MUTATION TYPE	GENES TESTED	RESULTS
SNVs and short indels	**TP53**	**Not detected**
SNVs and short indels	**POLE**	**Not detected**

Adjuvant therapy based on subtypes

	CTRT (5yr PFS)	RT (5yr PFS)	P value
POLE mutation	100%	97%	0.637
P53abn	59%	36%	0.019
MMRd	68%	76%	0.428
NSMP	80%	68%	0.243
	5 yr OS	5yr OS	
MMRd	79%	84%	0.445
MMRd vs MMRp	adding RT improved DFS in MMRd for Ib and II,gr3 EC		

Interpretation:

- **Adding chemo helps pts with mutant p53**
- **Adding RT and not chemo helps MMRd**
- **De-escalation possible in POLE mut**
- **HT helpful for NSMP**

Limitations of molecular profiling

- Non availability
- Only few mutations are known
- Lack of robust data for day to day use
- Results of PORTEC 4a/TAPER/TRANSPORTEC RAINBO yet to come
- Financial liability

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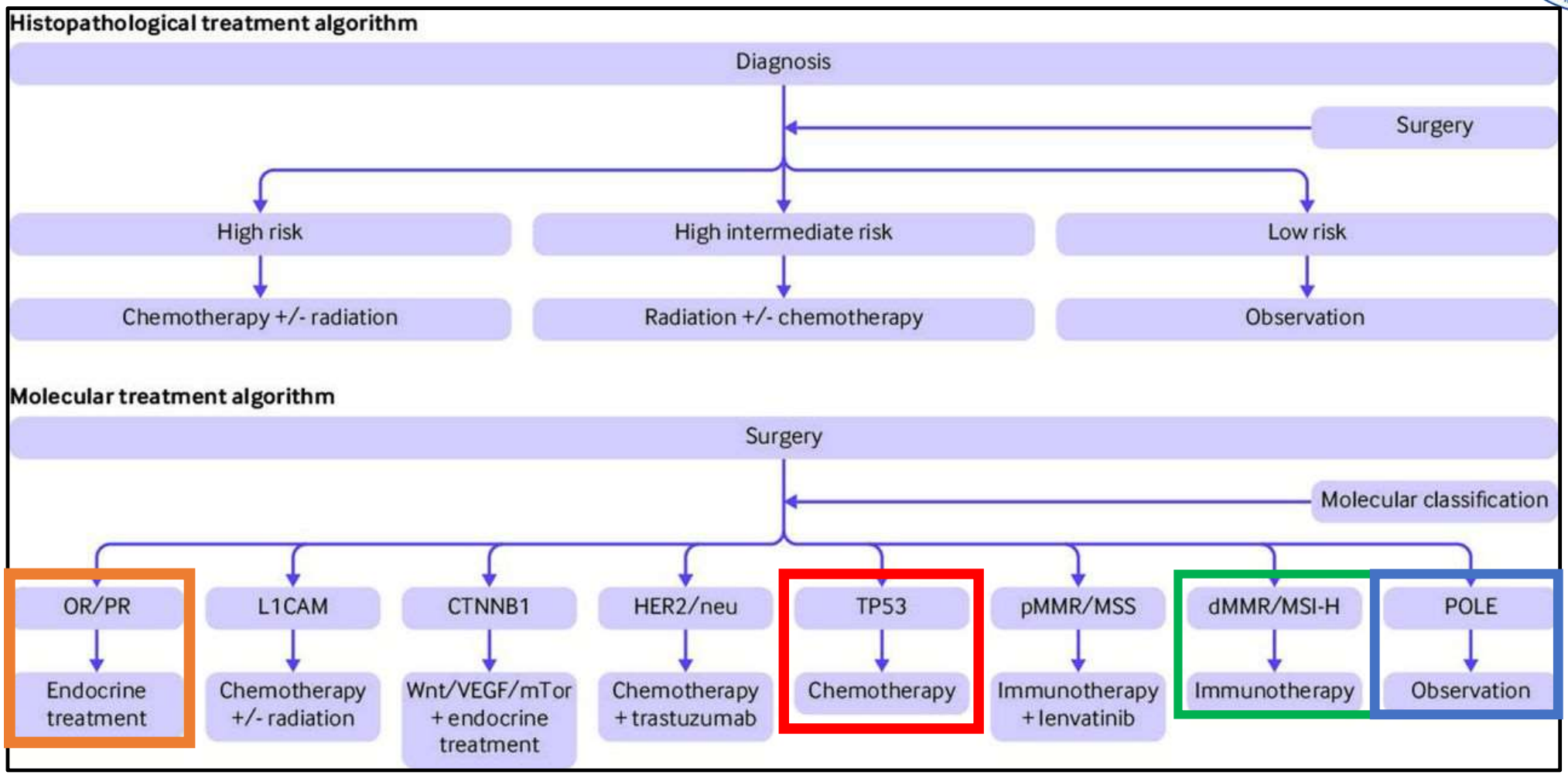
Risk	Criteria	Adjuvant Therapy:
low	➢ IA, grade 1–2 endometrioid carcinoma ➢ No LVSI ➢ POLE-mutated tumors, regardless of other features	➢ No adjuvant therapy is recommended. ➢ Excellent prognosis with surgery alone.
Intermediate	➢ I, grade 3 endometrioid carcinoma without LVSI ➢ IA, grade 3 with focal LVSI ➢ IB, grade 1–2 with no LVSI ➢ Exclusion: p53-abnormal tumors or MSI-high cases with aggressive features	➢ Vaginal brachytherapy is preferred to reduce local recurrence. ➢ No systemic chemotherapy.
High-Intermediate	➢ I–II with substantial risk factors: ➢ MI (≥50%) ➢ Grade 3 endometrioid histology ➢ Substantial LVSI ➢ Age >60 years with additional risk features	➢ Vaginal brachytherapy ± pelvic radiotherapy for local control. ➢ Systemic chemotherapy (e.g., carboplatin and paclitaxel) considered for higher risk patients, particularly those with p53-abnormal or NSMP tumors.
High Risk	➢ stage III–IVA endometrioid carcinoma ➢ Non-endometrioid histologies ➢ p53-abnormal tumors (any stage) ➢ extensive LVSI	➢ Chemotherapy (carboplatin and paclitaxel) and external beam radiation therapy (EBRT). ➢ sequential or sandwich approaches to chemo-radiotherapy. ➢ Hormone therapy may have a role for hormone receptor-positive tumors in selected cases.

Additional biomarkers for immunotherapy…

- Homologous recombination deficiency (HRD scoring)
  - More than 4 –poor survival
  - Higher scores – increased response to Cis/Pacli/olaparib
- HER 2
  - Similar to TP53,
- Immune markers
  - PD L1,TIL


Histopathological treatment algorithm
Diagnosis
Surgery
High risk
High intermediate risk
Low risk
Chemotherapy +/- radiation
Radiation +/- chemotherapy
Observation
Molecular treatment algorithm
Surgery
Molecular classification
OR/PR
L1CAM
CTNNB1
HER2/neu
TP53
pMMR/MSS
dMMR/MSI-H
POLE
Endocrine treatment
Chemotherapy +/- radiation
Wnt/VEGF/mTor + endocrine treatment
Chemotherapy + trastuzumab
Chemotherapy
Immunotherapy + lenvatinib
Immunotherapy
Observation

So, at the end…

- Endometrial cancers are a heterogenous group of cancers
- Molecular profiling could upstage/downstage the disease
- Complementary to clinic-pathological features
- Results of ongoing trials will help in either de-escalating or adjuvant therapy selection for EC
- Adjuvant radiation can be personalised to get maximum benefit.

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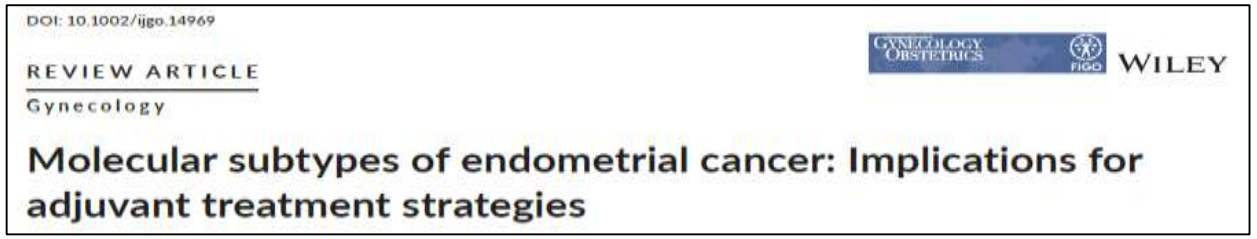
Our Reference Literature from…….

ASTRO/ESTRO/ESMO/ACOG/BCOG/ ESP and ICMR

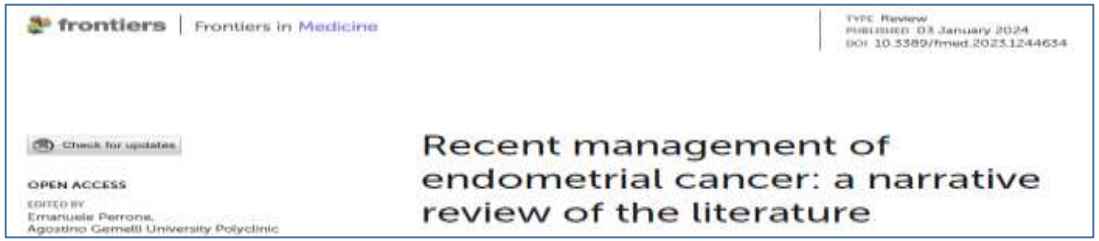

DOI: 10.1002/ijgo.14969

REVIEW ARTICLE

Gynecology

GYNECOLOGY OBSTETRICS FIGO WILEY

Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies


frontiers | Frontiers in Medicine

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Recent management of endometrial cancer: a narrative review of the literature

NCCN Guidelines

UpToDate


cancers

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Review

Management of Endometrial Cancer: A Comparative Review of Guidelines

Stergios Kopatsaris, Ioannis Tsakiridis *, Georgios Kapetanios, Fotios Zachomitros, Georgios Michos, Evangelos Papanikolaou, Apostolos Athanasiadis, Themistoklis Dagklis † and Ioannis Kalogiannidis †


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SPECIAL ARTICLE

GYNECOLOGY OBSTETRICS FIGO WILEY

FIGO staging of endometrial cancer: 2023

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