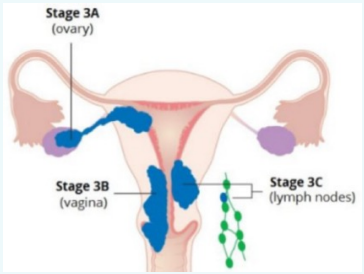
The 9th International
Clinical Oncology Congress
نوزدهمین کنگره سالیانه کلینیکال انکولوژی
فیزیک پزشکی، تکنولوژی پرتودرمانی،
رادیوبیولوژی و پرستاری انکولوژی
29-31 January 2025
Olympic hotel,Tehran ,IRAN

Adjuvant Radiotherapy and Systemic Therapy in Endometrial Cancer in Post Molecular Sub-Typing Era

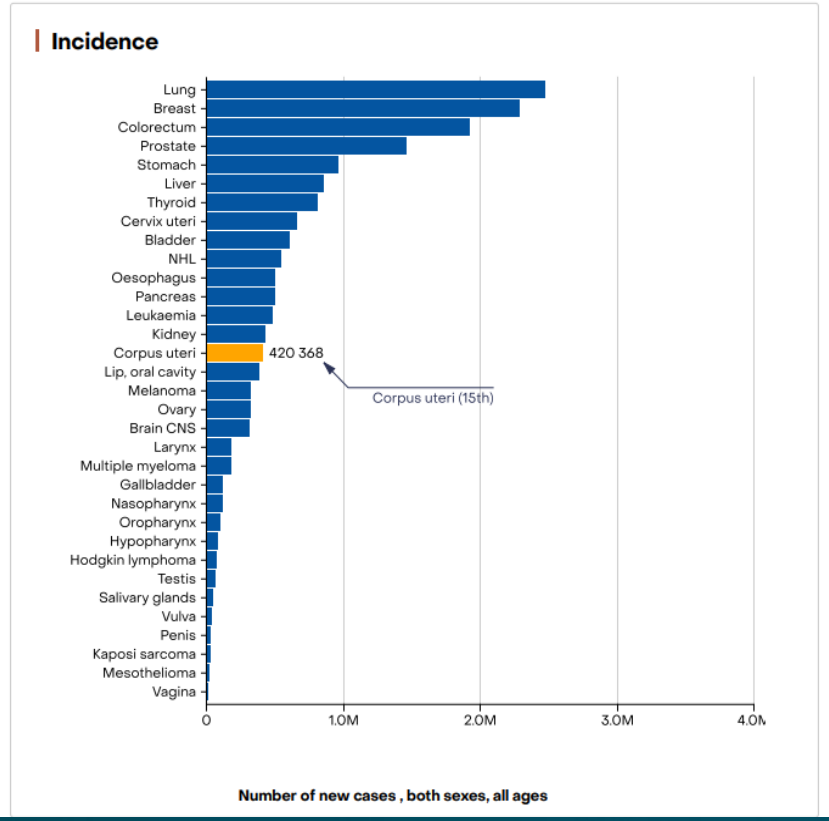


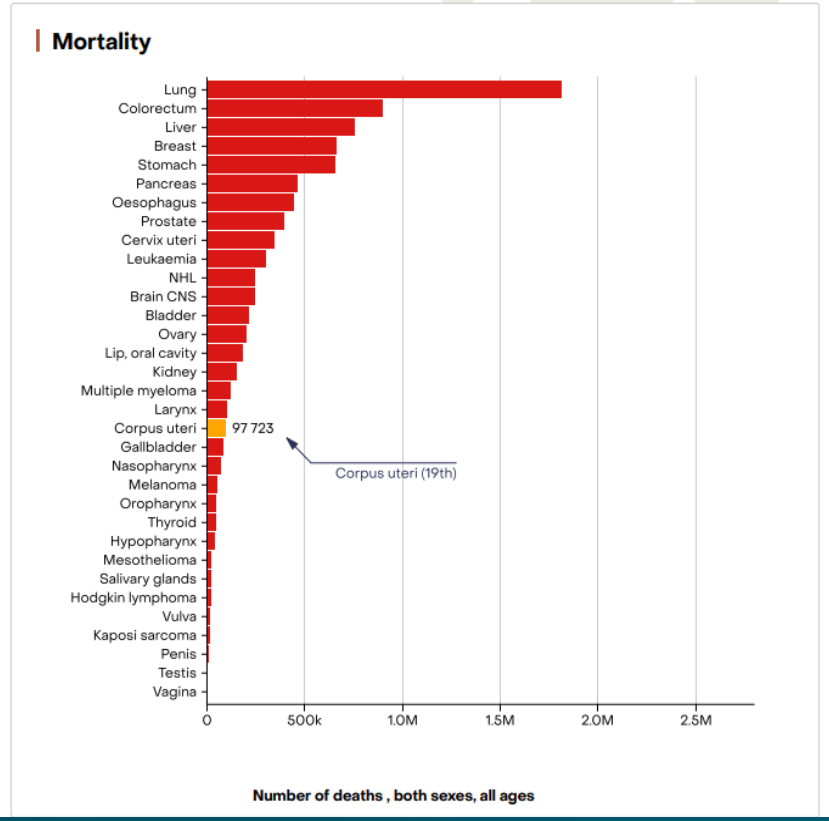
Fatemeh Homaei Shandiz, MD.
Prof. in Radiation Oncoloy
29 January 2025

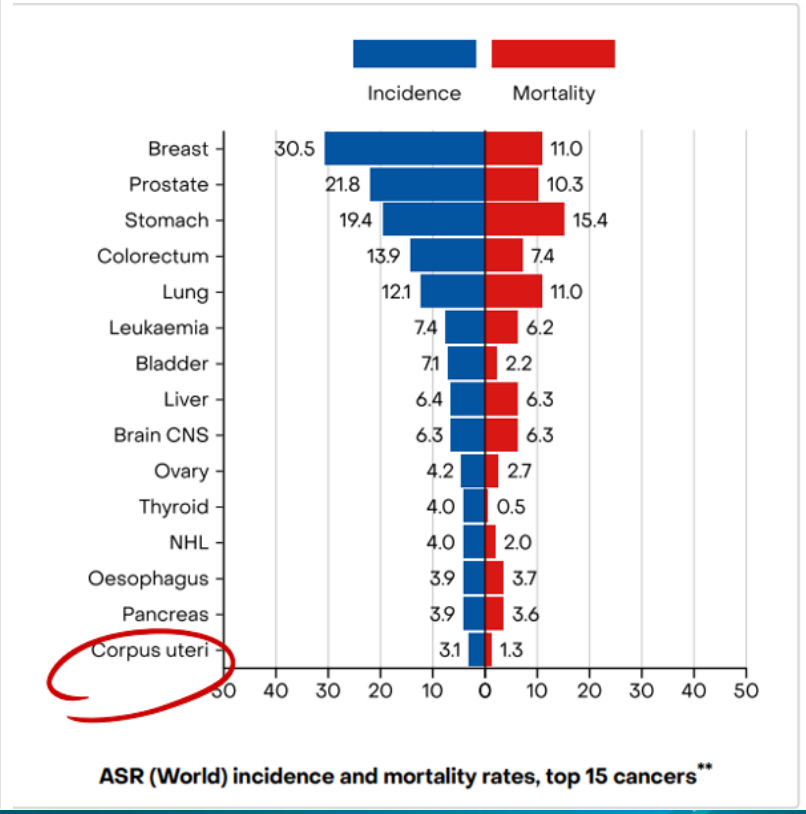
Endometrial Cancer | Why Endometrial Cancer?

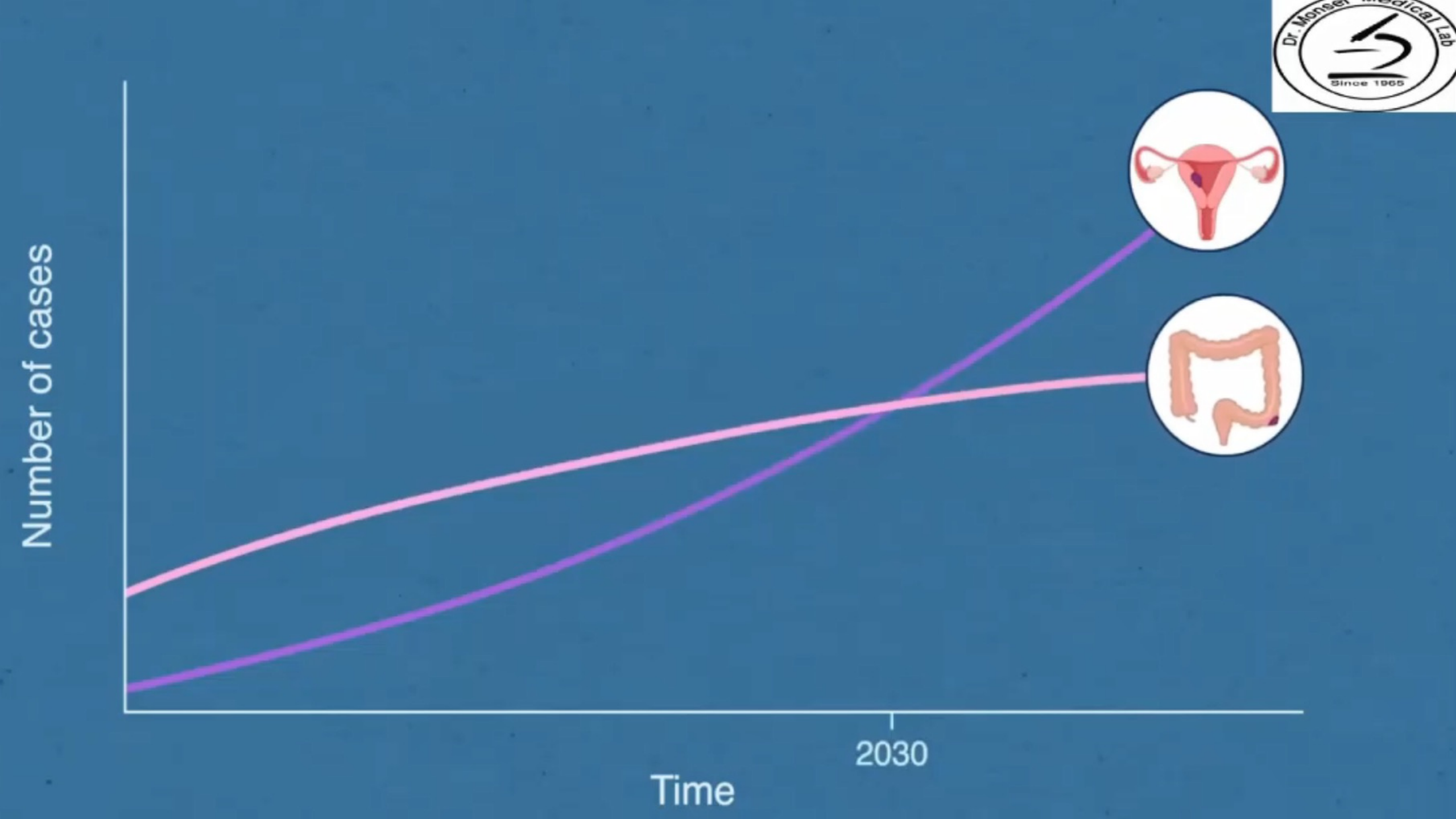
The endometrial cancer landscape
has changed markedly over the last 30 years

Endometrial cancer (EC) is a heterogeneous disease
with a rising incidence worldwide.



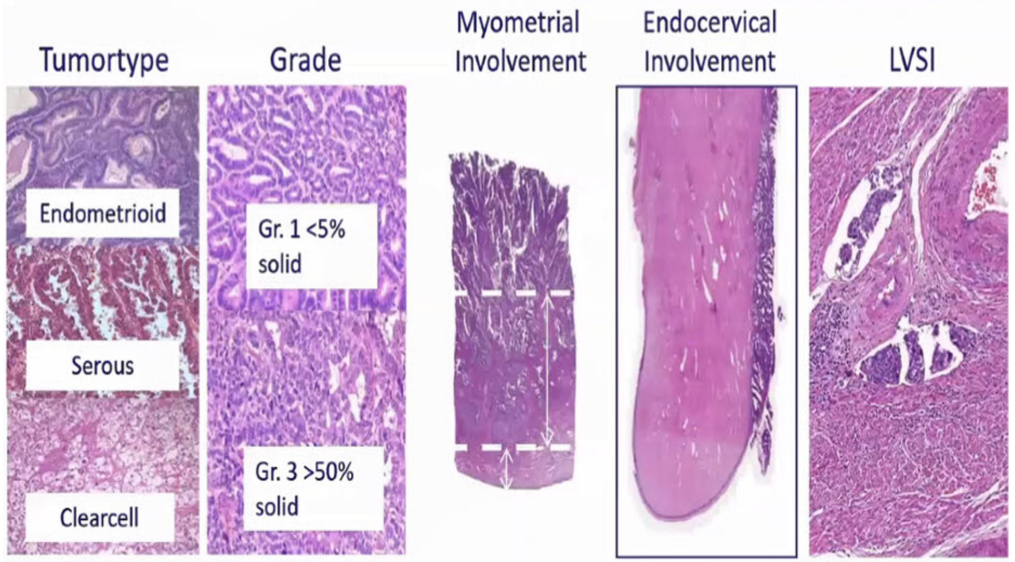





Dr. Monser Medical Lab
Since 1965
Number of cases
2030
Time

Endometrial Cancer | Why Endometrial Cancer?

Endometrial cancer presents in most women at an early stage confined to the uterus and initial treatment is by hysterectomy.
Postoperative treatment is indicated for **intermediate** and **high risk** patients defined by age, tumor type, stage, grade and
the presence or absence of lymphovascular space invasion

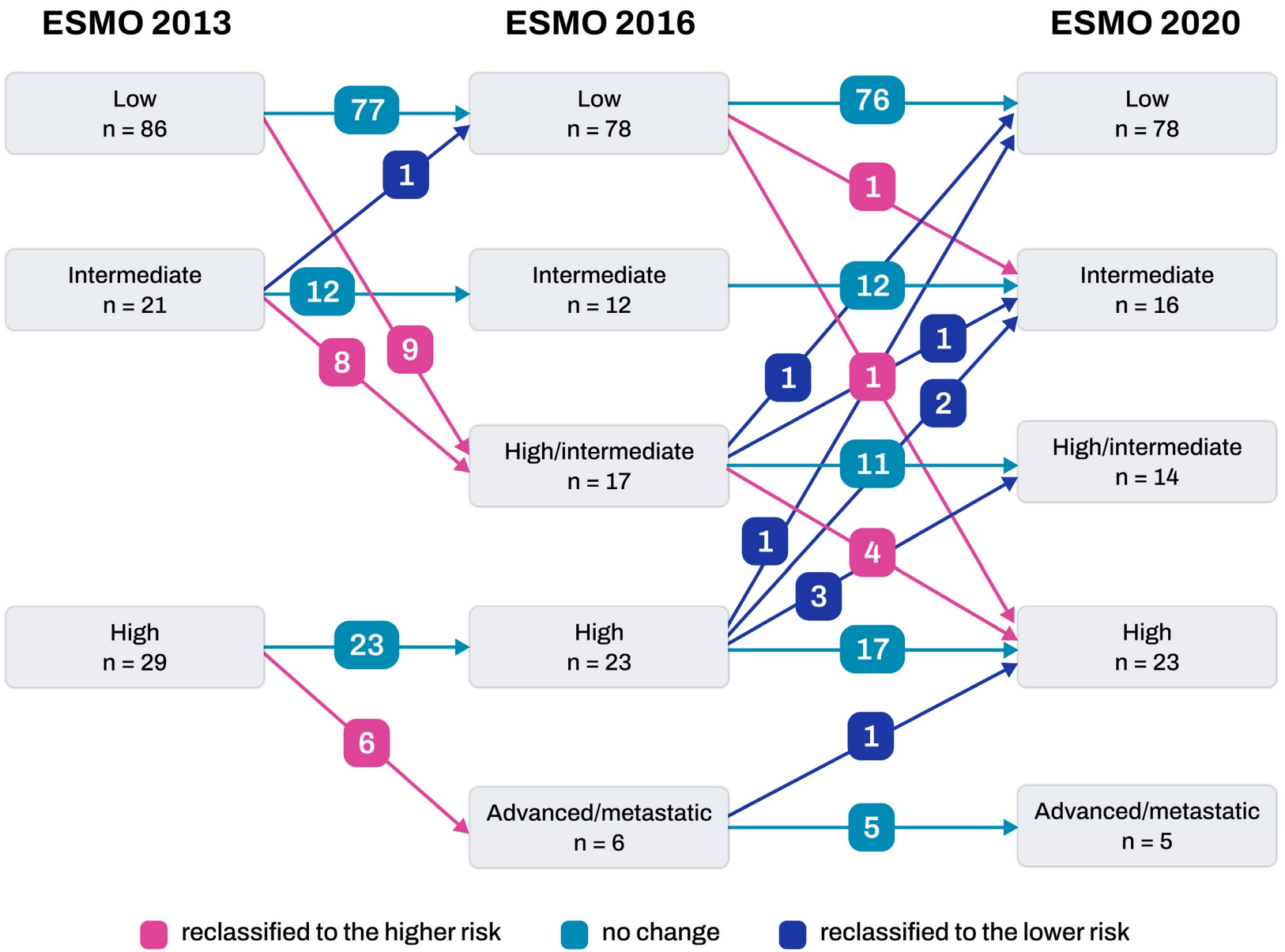


Endometrial Cancer | Why Endometrial Cancer?

Endometrial cancer (EC) is a heterogeneous disease

The treatment of endometrial cancer has recently undergone a **paradigm shift** from using traditional clinical-pathologic factors to **molecular characterization** for prognosis and selection of treatment.

Swift BE, Gien LT. Incorporating Molecular Diagnostics into Treatment Paradigms for Endometrial Cancer. Curr Treat Options Oncol. 2022 Aug;23(8):1121-1134. doi: 10.1007/s11864-022-00993-x. Epub 2022 Jul 6. PMID: 35793055.


ESMO 2013
ESMO 2016
ESMO 2020
Low
n = 86
Intermediate
n = 21
High
n = 29
Low
n = 78
Intermediate
n = 12
High/intermediate
n = 17
High
n = 23
Advanced/metastatic
n = 6
Low
n = 78
Intermediate
n = 16
High/intermediate
n = 14
High
n = 23
Advanced/metastatic
n = 5
77
1
12
8
9
23
6
76
1
12
1
1
1
2
11
1
4
3
17
1
5
reclassified to the higher risk
no change
reclassified to the lower risk

Endometrial carcinoma classification

Bokhman classification — **2016** → **2020** — **The Cancer Genome Atlas classification**

Histology-driven
Endometrial Carcinoma Classification

H&E
+
IHC upon indication

Type I
- Endometrioid Carcinoma (EEC) Grade 1-3

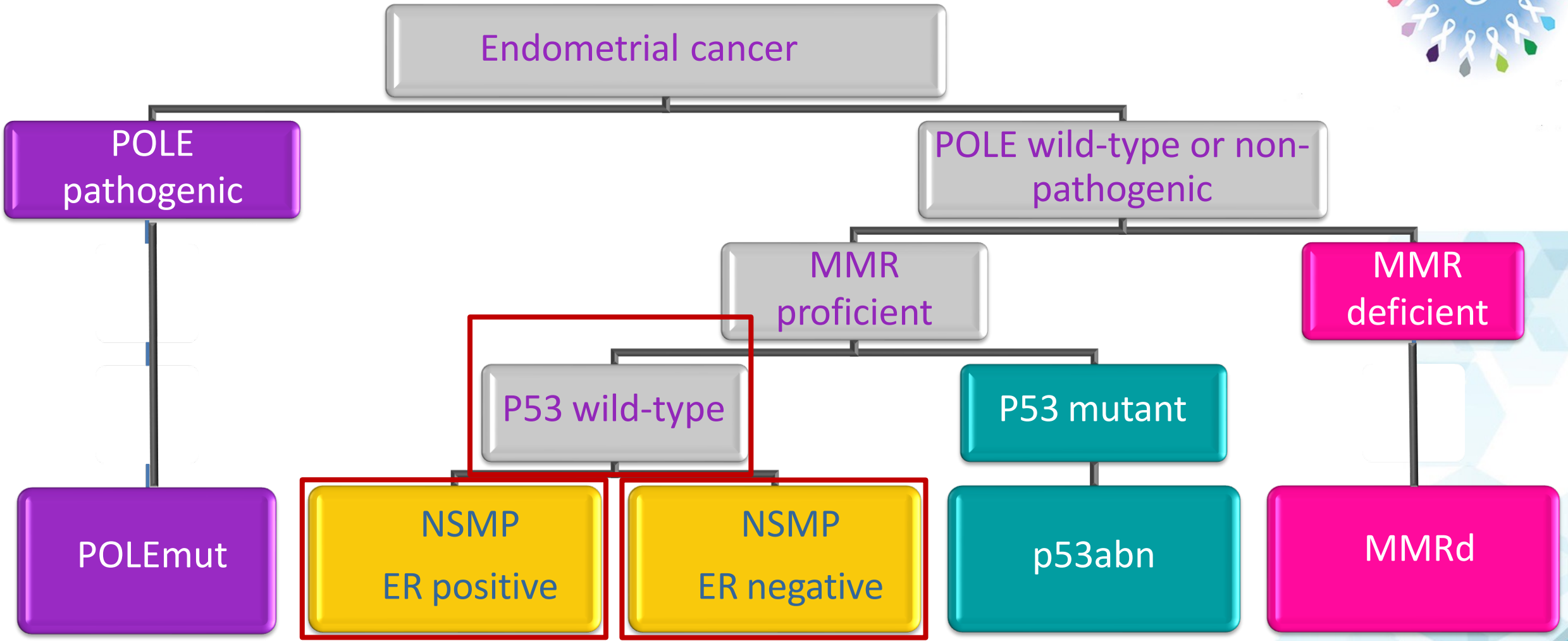
Type II
- Uterine Serous Carcinoma (USC)
- Clear Cell Carcinoma (CCC)
- Uterine Carcinosarcoma (UCS)
- Mixed Endometrial Carcinoma
- Un-/De-differentiated Carcinoma

Molecular-driven
Endometrial Carcinoma Classification

POLE sequencing
+
MMR and p53 IHC

- *POLE*mut Endometrial Carcinoma (***POLE*mut** EC)
- MMRd Endometrial Carcinoma (**MMRd** EC)
- p53-abnormal Endometrial Carcinoma (**p53abn** EC)
- No Specific Molecular Profile Endometrial Carcinoma (**NSMP** EC)

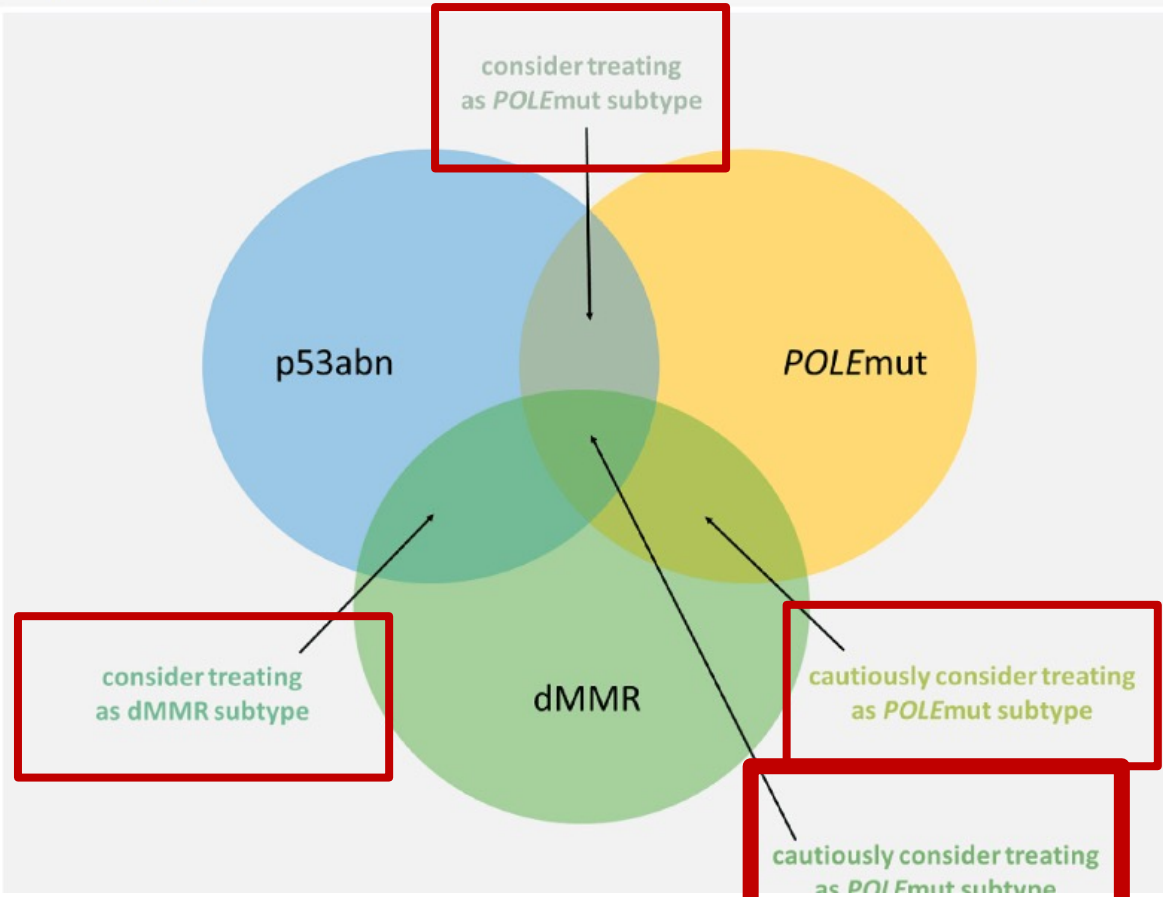
Molecular classification of endometrial cancer



Vermij et al., British Journal of Cancer (2023) 128:1360 – 1368

Multiple Classifiers

Figure 2. Proposed approach to therapy decision-making in multiple classifiers. Based on [97,98,99].



Galant, N.; Krawczyk, P.; Monist, M.; Obara, A.; Gajek, Ł.; Grenda, A.; Nicoś, M.; Kalinka, E.; Milanowski, J. Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection. *Int. J. Mol. Sci.* **2024**, *25*, 5893. https://doi.org/10.3390/ijms25115893

Selective ProMisE Testing Protocol

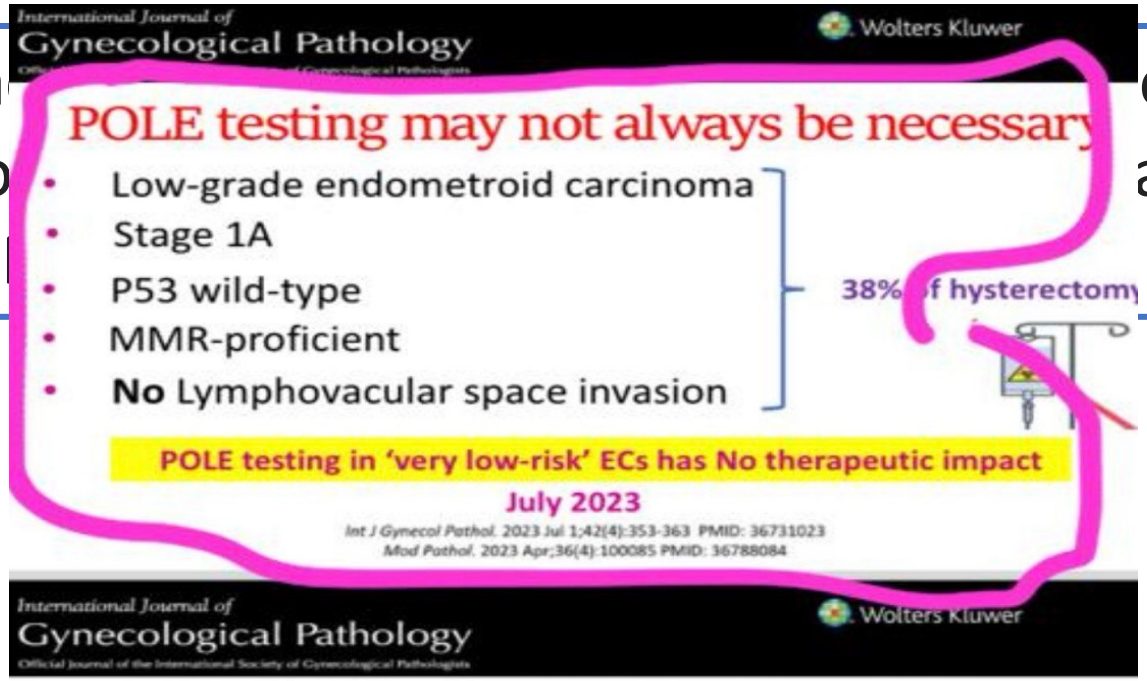
Cost and **a**

active M o

(

esting Pro

al Cancer



POLE testing strongly recommended

Stage I
- Intermediate risk
- or
- High-intermediate risk

Talhouk, Aline Ph.D; Jamieson, Amy M.B.Ch.B., F.R.A.N.Z.C.O.G., F.R.C.S.C.; Crosbie, Emma J. B.Sc., M.B.Ch.B., Ph.D., F.R.C.O.G.; Taylor, Alexandra M.B.B.S., M.R.C.P., F.R.C.R., M.D.; Chiu, Derek M.Sc.; Leung, Samuel M.Sc.; Grube, Marcel M.D.; Kommoss, Stefan M.D.; Gilks, C. Blake M.D., F.R.C.P.C.; McAlpine, Jessica N. M.D.; Singh, Naveena M.D.,

Talhouk A, Jamieson A, Crosbie EJ, T … n N. Targeted Molecular Testing in Endometrial Carcinoma: Validation of a Clinically … 42(4):353-363. doi: 10.1097/PGP.0000000000000898. E…

ESGO-ESTRO-ESP Endometrial Cancer Guidelines: major ADVANCEMENT

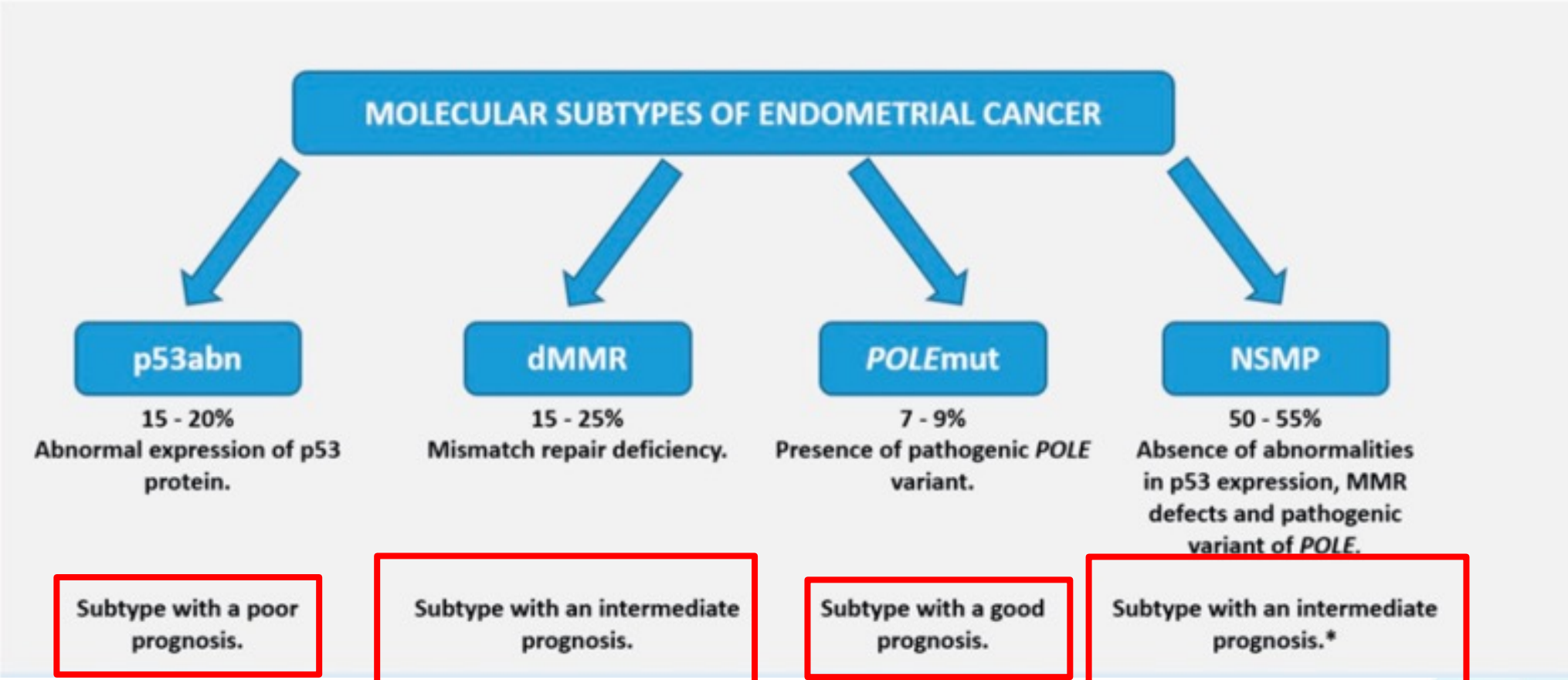
PROGNOSTIC RISK GROUPS

NOW

Integration of molecular markers

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, [illegible] 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

Endometrial Cancer | Why Endometrial Cancer?



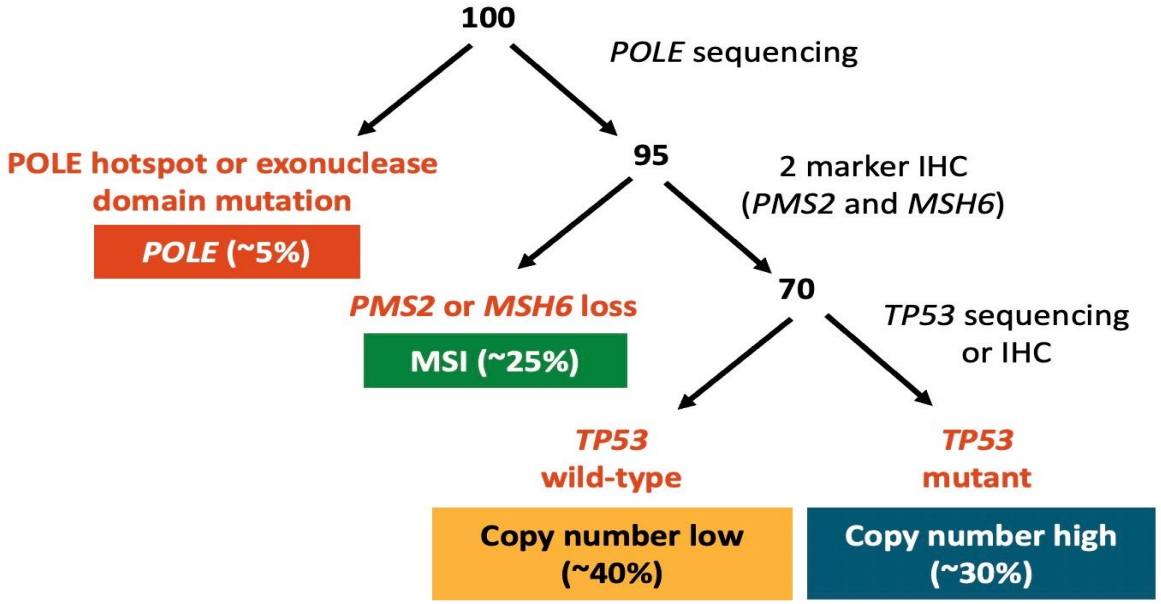
Galant, N.; Krawczyk, P.; Monist, M.; Obara, A.; Gajek, Ł.; Grenda, A.; Nicoś, M.; Kalinka, E.; Milanowski, J. Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection. *Int. J. Mol. Sci.* **2024**, *25*, 5893. https://doi.org/10.3390/ijms25115893

Endometrial Cancer : Molecular Classification and Outcomes

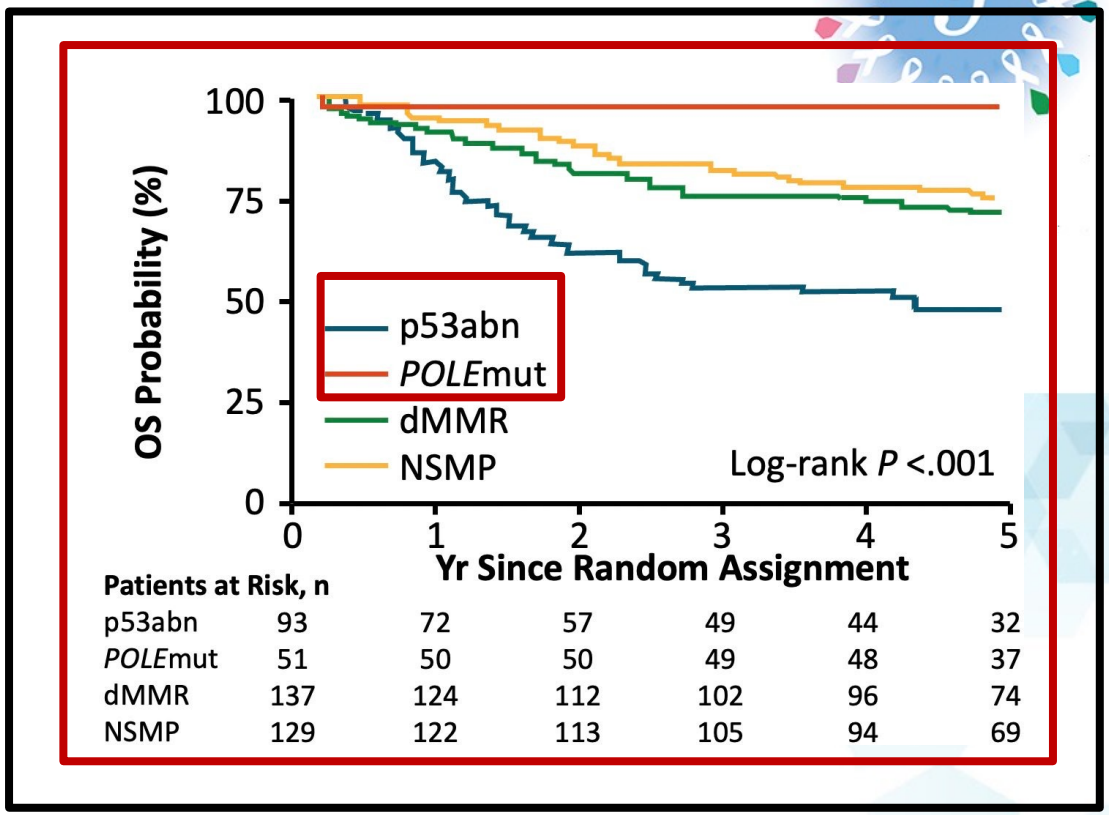
Molecular subtyping: prognostic and predictive value

Patients Divided Into TCGA subgroups

100 hypothetical patients with newly diagnosed endometrial cancer



- Prognostic value of molecular classification of high-risk endometrial cancer for benefit from chemotherapy
- 83% and 17% of endometrial cancer can be classified as endometrioid and non endometrioid, respectively



410 patients with successful molecular testing

- **23%** *p53*abn: *p53* abnormal
- **12%** *POLE*mut: *POLE* ultramutated
- **33%** dMMR: mismatch repair deficient
- **32%** NSMP: no specific molecular profile

MacKay. Oncotarget. 2017;8:84579. Leon-Castillo. JCO. 2020;38:3388.

ESGO-ESTRO-ES and ESMO Guidelines, Endometrial Cancer

Virchows Archiv (2021) 478:153–190
https://doi.org/10.1007/s00428-020-03007-z

ORIGINAL ARTICLE

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

Nicole Concin[1,2] · Carien L. Creutzberg[3] · Ignace Vergote[4] · David Cibula[5] · Mansoor Raza Mirza[6] · Simone Marnitz[7] · Jonathan A. Ledermann[8] · Tjalling Bosse[9] · Cyrus Chargari[10] · Anna Fagotti[11] · Christina Fotopoulou[12] · Antonio González-Martín[13] · Sigurd F. Lax[14,15] · Domenica Lorusso[11] · Christian Marth[16] · Philippe Morice[17] · Remi A. Nout[18] · Dearbhaile E. O'Donnell[19] · Denis Querleu[11,20] · Maria Rosaria Raspollini[21] · Jalid Sehouli[22,23] · Alina E. Sturdza[24] · Alexandra Taylor[25] · Anneke M. Westermann[26] · Pauline Wimberger[27] · Nicoletta Colombo[28] · François Planchamp[29] · Xavier Matias-Guiu[30,31]

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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

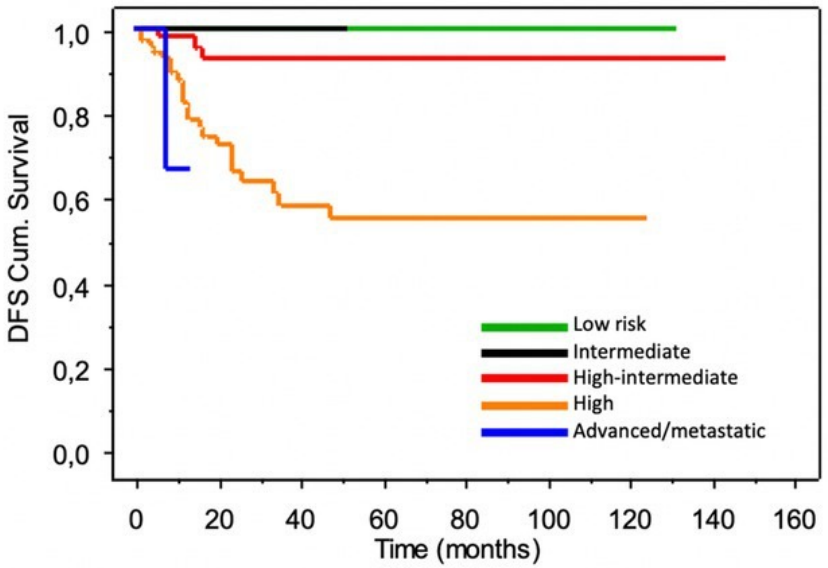
Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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

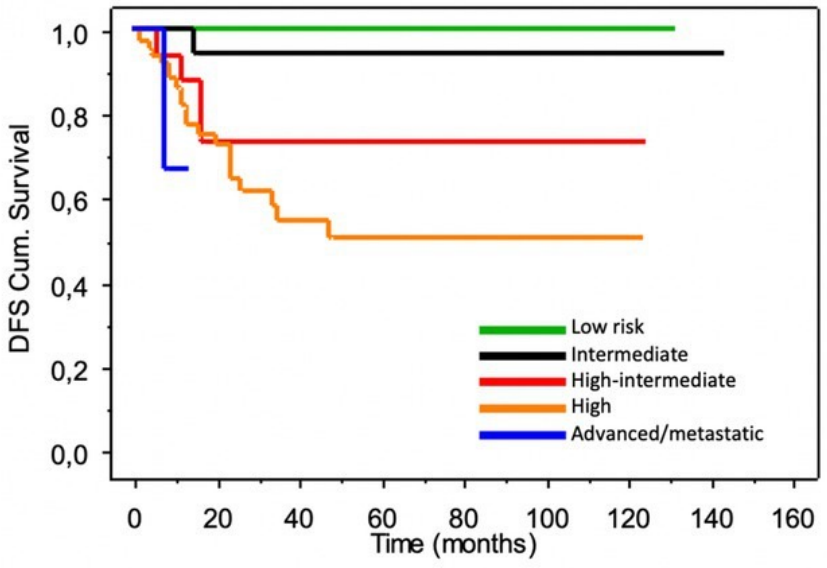
Risk group	Description[a]
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[b] and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers[c]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, 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]

ESMO 2016



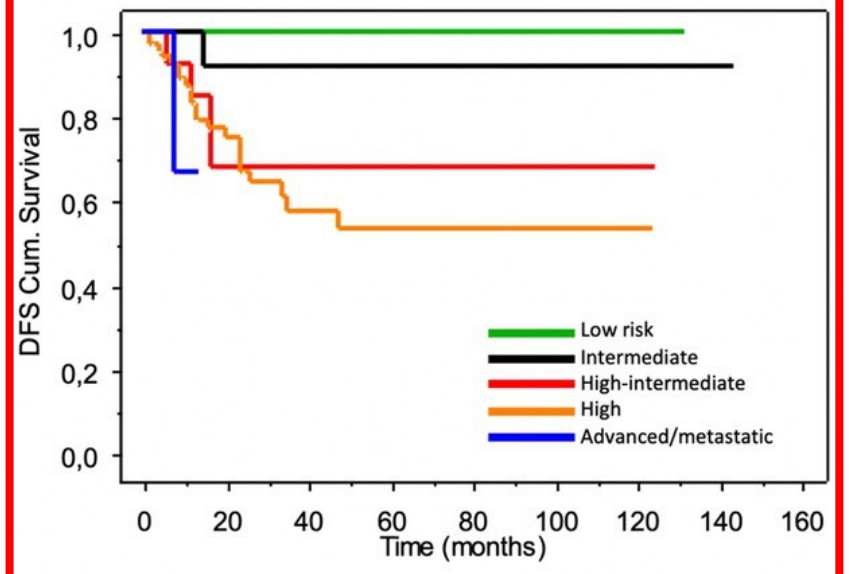
p-value < 0.0001

ESGO/ESTRO/ESP 2020 Molecular classification unknown



p-value < 0.0001

ESGO/ESTRO/ESP 2020 Molecular classification known



p-value < 0.0001

2023 Figo Stage	Defining Criteria
IA1	non-aggressive histological type limited to the endometrium or an endometrial polyp
IA2	non-aggressive histological type involving <50% myometrium, with no/focal LVSI
IA3	low-grade EEC limited to the uterus and ovary
$IAm_{POLEmut}$	*POLEmut EC, confined to the uterine corpus or with cervical extension, regardless of LVSI or histological type*
IB	non-aggressive histological type involving ≥50% myometrium, and with no/focal LVSI
IC	aggressive histological type limited to the endometrium or an endometrial polyp
IIA	non-aggressive histological type with invasion of the cervical stroma
IIB	non-aggressive histological type with substantial LVSI
IIC	aggressive histological type with any myometrial infiltration
$IICm_{p53abn}$	*p53abn EC, confined to the uterine corpus with any myometrial infiltration, with or without cervical invasion, and regardless of LVSI or histological type*
IIIA1	spread to ovary or fallopian tube (except if it meets the Stage IA3 criteria)
IIIA2	involvement of uterine subserosa/serosa
IIIB1	metastasis or direct spread to the vagina and/or the parametria
IIIB2	metastasis to the pelvic peritoneum

Open Access Review

Management of Endometrial Cancer: A Comparative Review of Guidelines

Management of endometrial cancer

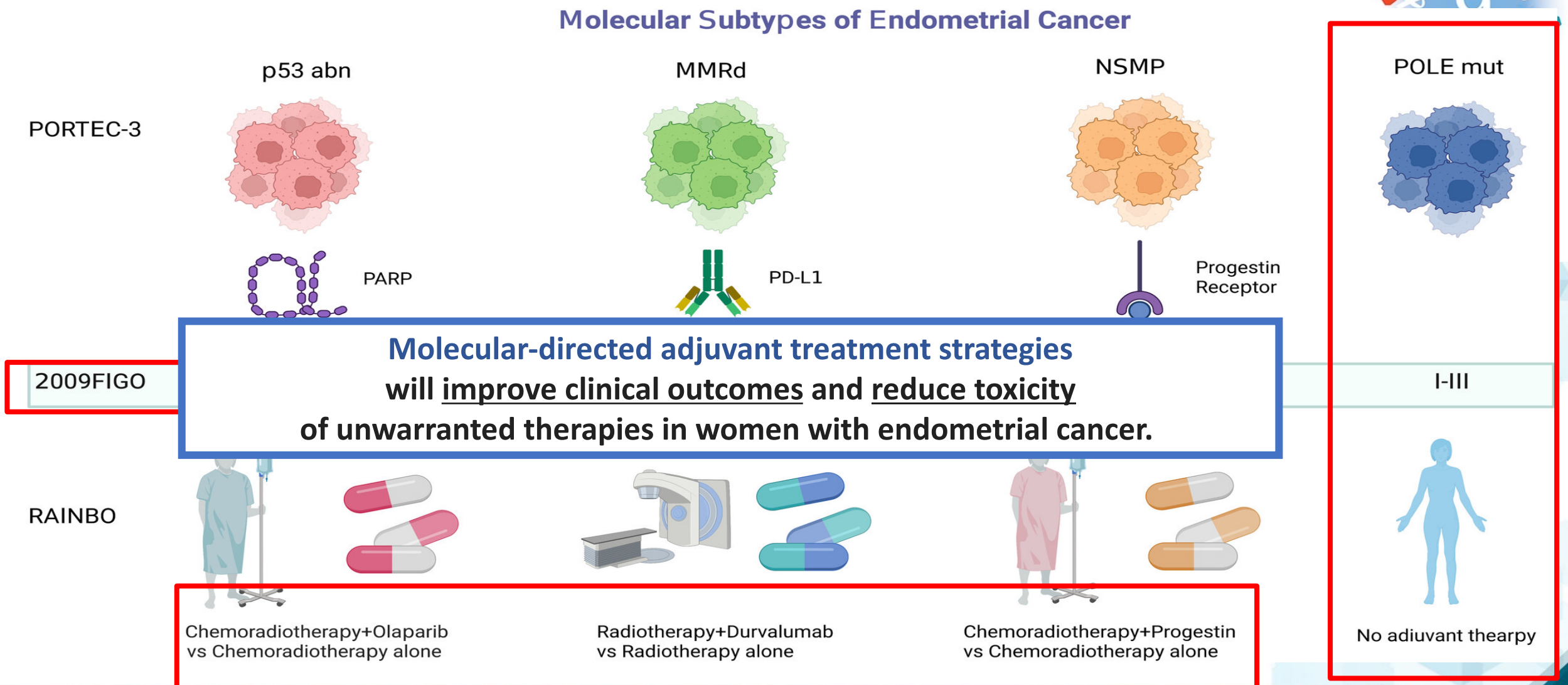
Agreement

- Endometrial biopsy as the first diagnostic tool for women with uterine bleeding.
- MRI to assess myometrial infiltration and metastases in high-risk cases.
- Molecular classification to assess risk or relapse.
- Minimal invasive procedure for early stages.

Discrepancies

- Extended lymphadenectomy for high-risk patients.
- Molecular classification for treatment adjustment.
- Adjuvant treatment.

Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies



Intl J Gynecology & Obste, Volume: 164, Issue: 2, Pages: 436-459, First published: 31 July 2023, DOI: (10.1002/ijgo.14969)

ESGO-ESTRO-ESP Endometrial Cancer Guidelines

TOPICS

TUMOR BIOLOGY:
-Molecular Markers
-LVSI

SURGERY:
-MIS
-Sentinel Lymph Node

11:45 | رادیوتراپی ادجوانت و درمان سیستمیک در سرطان آندومتر در دوران ارزیابی مولکولی

1403/11/10

11:45 - 13:00 (75 دقیقه)

دکتر ریحانه بیانی (رادیوانکولوژیست)، دکتر مریم¬السادات حسینی (ژنیکوانکولوژیست)، دکتر سهیلا سرمدی (پاتولوژیست)، دکتر فاطمه محمدیان (رادیوانکولوژیست)، دکتر بهناز مرادی (رادیولوژیست)

اداره کننده: دکتر فاطمه همایی شاندیز (رادیوانکولوژیست)

Case Presentation

A 58 y/o woman (G3P3) with a history of **post menopausal vaginal bleeding** from 3 months ago.

- BMI=**32** kg/m2
- PMH: **Diabetes**, **HTN** and **breast cancer** luminal A from 10 years ago **that is disease free**
- DH: **Tamoxifen** 20 mg/day/5 years
- **FH**: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is **bigger** than normal size
- Pap smear: (-)
- Performance status: 1

آیا بیمار از نظرابتلا به سرطان رحم در خطر بالا هست؟

آیا به این فرد اگر علامت نداشت توصیه خاصی برای پیشگیری از ابتلا به سرطان رحم می شود؟

با توجه به تاریخچه آیا بیمار نیاز به مشاوره ژنتیک و انجام تست خاصی دارد؟

Risk Factors of Endometrial Cancer

- ✓Hypertension
- ✓Diabetes
- ✓Other diseases associated with elevated estrogen levels, such as:
  - late menopause
  - high body mass index (BMI).
- ✓Tamoxifen

- Certain patterns of dietary intake have also been associated with a higher risk of endometrial cancer.

On the contrary,

the use of certain contraceptive medications reduces

the risk of developing endometrial cancer.

Baker-Rand, H.; Kitson, S.J. Recent Advances in Endometrial Cancer Prevention, Early Diagnosis and Treatment. *Cancers* **2024**, *16*, 1028. https://doi.org/10.3390/cancers16051028

Advances in Endometrial Cancer Prevention

- Given the strong association with modifiable risk factors, endometrial cancer appears eminently suited to primary disease prevention, with modelling suggesting that

- **up to 60% of endometrial cancer cases could be potentially prevented.**

- ✓ *Weight Management*
- ✓ *Hormonal Chemoprevention*
- ✓ *Aspirin*
- *Metformin (-)*

Baker-Rand, H.; Kitson, S.J. Recent Advances in Endometrial Cancer Prevention, Early Diagnosis and Treatment. *Cancers* **2024**, *16*, 1028. https://doi.org/10.3390/cancers16051028

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

NCCN Guidelines Index
Table of Contents
Discussion

CRITERIA FOR TESTING FOR LYNCH SYNDROME[m]

Testing is clinically indicated in the following scenarios:

- Known LS PV in the family
- Personal history of a LS-related cancer (CRC, EC, or other[e]) and any of the following:
  - Diagnosed <50 y[n,o]
  - A synchronous or metachronous LS-related cancer[e] regardless of age
  - 1 first-degree or second-degree relative with an LS-related cancer[e] diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with an LS-related cancer[e] regardless of age
- Family history[p] of any of the following:
  - ≥1 first-degree relative with a CRC or EC diagnosed <50 y
  - ≥1 first-degree relative with a CRC or EC and a synchronous or metachronous LS-related cancer[e] regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancers[e] including ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers[e] regardless of age
- Increased model-predicted risk for LS
  - An individual with a ≥5% risk of having an MMR gene PV based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict)
    - Individuals with a personal history of CRC and/or EC with a $PREMM_5$ score of ≥2.5% should be considered for MGPT.
    - For individuals without a personal history of CRC and/or EC, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decre in specificity.

- Personal history of CRC, EC, or of other tumor with MMR deficiency determined by polymerase chain reaction (PCR), next-generation sequencing (NGS), or IHC diagnosed at any age[q,r]
- Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline[s,t]

Additional tumor-based testing (LS-A) OR Germline MGPT for LS and other hereditary cancer syndromes[y] Strategies for Testing for LS (LS-1)

Testing may be considered in the following scenarios:

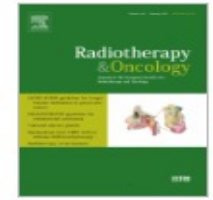
- Personal history of CRC or EC at age ≥50 y and any of the following (category 2B):[u,v]
  - untested for MMR deficiency status in tumor[w]
  - absence of MMR deficiency in tumor[x]

See Rationale, pros, and cons of multigene panel testing for Lynch syndrome and other cancer risk genes (HRS-A)

Lynch Syndrome
Amsterdam Criteria

- 3 or more relatives with lynch cancers (one of which is a 1st degree relative of the other 2)
- 2 or more successive generations affected
- 1 or more person with lynch syndrome diagnosed before age 50

ELSEVIER
Radiotherapy and Oncology
Volume 154, January 2021, Pages 327-353



Recommendations:

• To identify patients with Lynch syndrome and triage for germline mutational analysis, MMR IHC (plus analysis of MLH1 promotor methylation status in case of immunohistochemical loss of MLH1/PMS2 expression) or MSI tests should be performed in all endometrial carcinomas, irrespective of histologic subtype of the tumour [III, B].

• Endometrial carcinoma patients identified as having an increased risk of Lynch syndrome, should be offered genetic counselling [III, B].

• Surveillance for endometrial carcinoma in Lynch syndrome mutation carriers should in general start at the age of 35 years, however individual factors need to be taken into consideration (tailored surveillance programmes). The decision on the starting age of surveillance should integrate knowledge on the specific mutation and history of onset of events in the family [IV, B].

• Surveillance of the endometrium by annual transvaginal ultrasound (TVUS) and annual or biennial biopsy until hysterectomy should be considered in all Lynch syndrome mutation carriers [IV, B].

Hysterectomy and bilateral salpingo-oophorectomy, to prevent endometrial and ovarian cancer, should be performed at the completion of childbearing and preferably before the age of 40 years.

All the pros and cons of prophylactic surgery must be discussed including the risk of occult gynaecological cancer detection at prophylactic surgery.

Oestrogen replacement therapy should be suggested if bilateral salpingo-oophorectomy is performed in premenopausal women [IV, B].

Identifying High-Risk Women
Lynch syndrome (HNPCC):

- Highest-risk group
- A 40–60% lifetime risk of endometrial cancer
- Was checked for DNA mismatch repair genes mutations ***(MLH1, MSH2, MSH6* and *PMS2)*** by IHC.
- Benefit from surveillance for colorectal malignancies

Whose affected female relatives

should be offered a risk-reducing hysterectomy +_BSO from the age of 40 years.

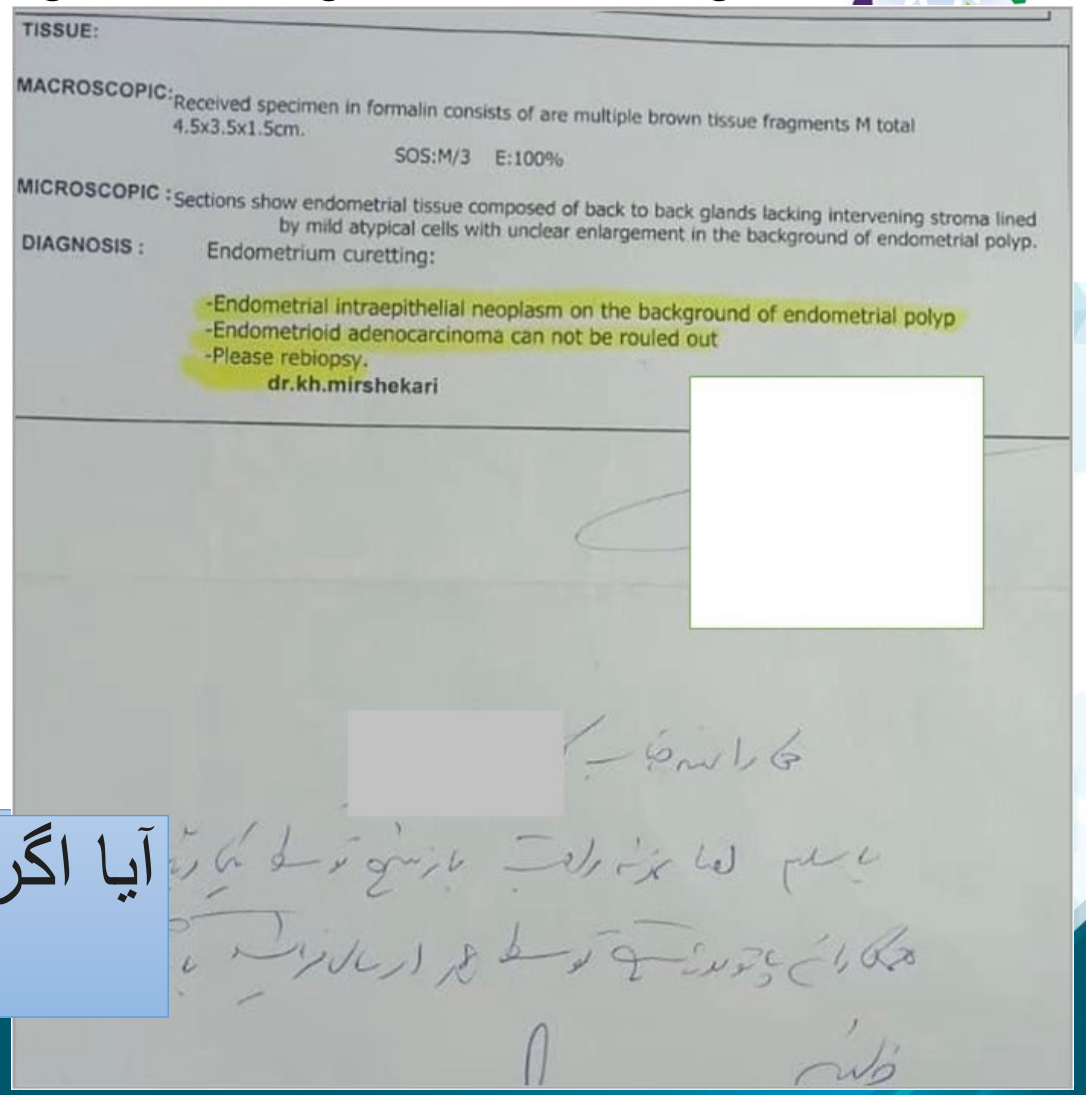
آیا برای این بیمار هر 4 تست را توصیه می کنید یا فقط PMS2+MSH6؟

Dominguez-Valentin, M., *et al.* Risk-reducing hysterectomy and bilateral salpingo-oophorectomy in female heterozygotes of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report. *Genet Med* **23**, 705–712 (2021).

Case Presentation

A 58 y/o woman (G3P3) with a history of post menopausal vaginal bleeding from 3 months ago.

- BMI=32 kg/m2
- PMH: Diabetes, HTN and breast cancer luminal A from 10
- DH: Tamoxifen 20 mg/day/5 years
- FH: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is **bigger** than normal size
- Pap smear: (-)
- Performance status: 1
- Genetic consultant **not** done
- Ca 125 = 21.1 U/mL


TISSUE:

MACROSCOPIC: Received specimen in formalin consists of are multiple brown tissue fragments M total 4.5x3.5x1.5cm.

SOS:M/3 E:100%

MICROSCOPIC : Sections show endometrial tissue composed of back to back glands lacking intervening stroma lined by mild atypical cells with unclear enlargement in the background of endometrial polyp.

DIAGNOSIS : Endometrium curetting:

-Endometrial intraepithelial neoplasm on the background of endometrial polyp
-Endometrioid adenocarcinoma can not be rouled out
-Please rebiopsy.

dr.kh.mirshekari

آیا اگرگزارش آسیب شناسی قطعی بود، باز هم درخواست بررسی مجدد لازم بود؟

All staging in guideline is based on 2009 FIGO staging. (ST-1, ST-2, ST-3 and ST-4)

INITIAL EVALUATION[a]

- History and physical (H&P)
- Complete blood count (CBC), liver function test [LFT], renal function tests, chemistry profile; and consider CA-125
- Expert pathology review with additional endometrial biopsy as clinically indicated[b,c]
- Imaging[d]
- Recommend molecular evaluation of tumor and evaluation for inherited cancer risk (ENDO-A and UTSARC-A)
- For patients who are older with uterine cancer also see the NCCN Guidelines for Older Adult Oncology
- Consider germline and/or multigene panel testing

INITIAL CLINICAL FINDINGS[c]

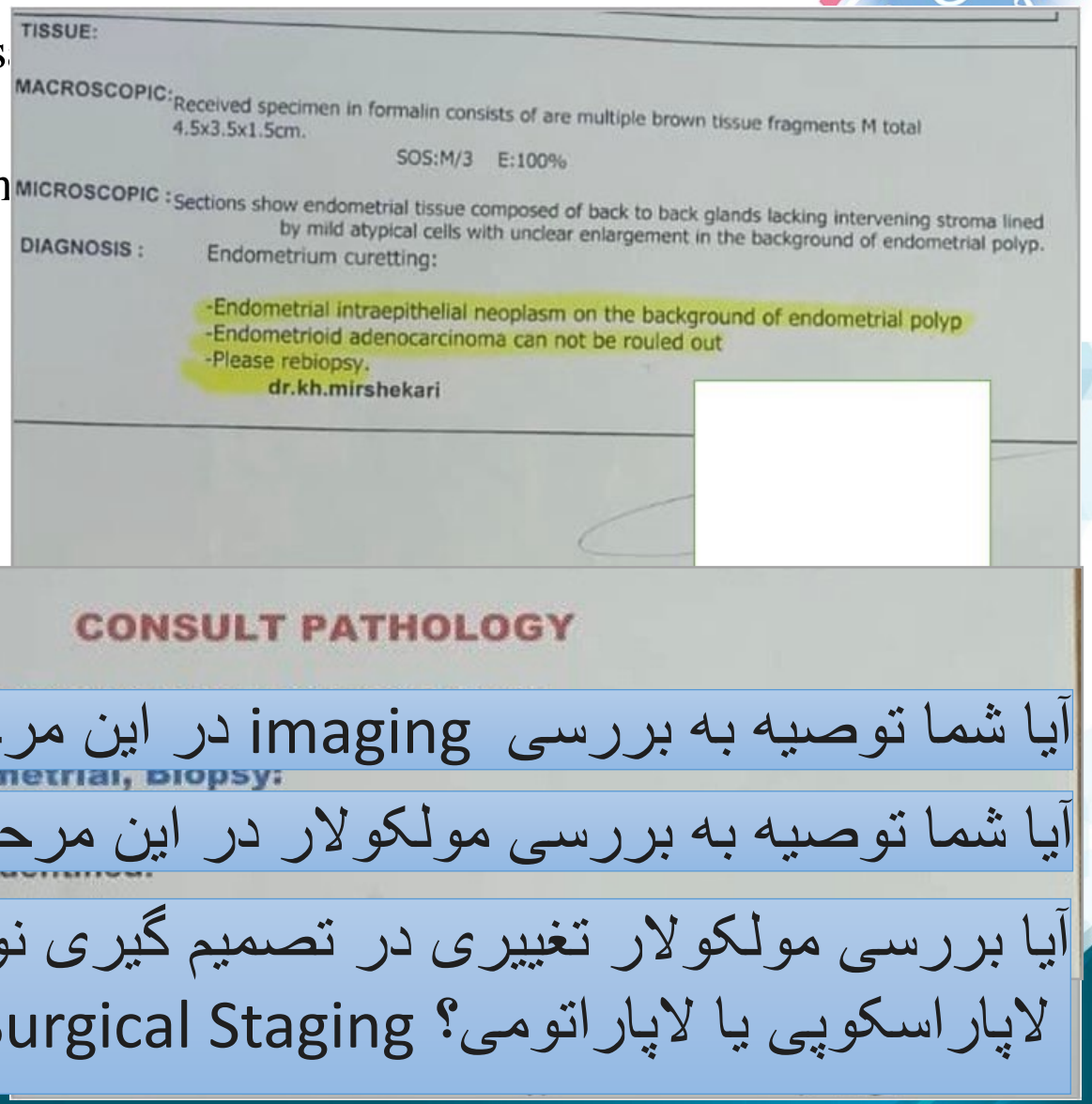
- Malignant epithelial (carcinoma)
  - Pure endometrioid carcinoma
    - Disease limited to uterus → Primary Treatment (ENDO-1)
    - Suspected or gross cervical involvement → Primary Treatment (ENDO-2)
    - Suspected extrauterine disease → Primary Treatment (ENDO-3)
  - High-risk endometrial carcinoma histology
    - Serous carcinoma → Primary Treatment (ENDO-11)
    - Clear cell carcinoma → Primary Treatment (ENDO-12)
    - Undifferentiated/dedifferentiated carcinoma → Primary Treatment (ENDO-13)
    - Carcinosarcoma[f,g] → Primary Treatment (ENDO-14)
- Malignant mesenchymal (sarcoma)[e]
  - Low-grade endometrial stromal sarcoma (ESS) or adenosarcoma
  - High-grade ESS
  - Undifferentiated uterine sarcoma (UUS)
  - Leiomyosarcoma (LMS)
  - Other sarcomas (eg, perivascular epithelioid cell tumor [PEComa])

→ Primary Treatment (UTSARC-1)

Case Presentation

A 58 y/o woman (G3P3) with a history of post menopaus

- BMI=**32** kg/m2
- PMH: Diabetes, HTN and breast cancer luminal A from
- DH: Tamoxifen 20 mg/day/5 years
- FH: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is **bigger** than normal size
- Pap smear: (-)
- Performance status: 1
- Genetic consultant **not** done
- Ca 125 = 21.1 U/mL


TISSUE:

MACROSCOPIC: Received specimen in formalin consists of are multiple brown tissue fragments M total 4.5x3.5x1.5cm.

SOS:M/3 E:100%

MICROSCOPIC : Sections show endometrial tissue composed of back to back glands lacking intervening stroma lined by mild atypical cells with unclear enlargement in the background of endometrial polyp.

DIAGNOSIS : Endometrium curetting:

-Endometrial intraepithelial neoplasm on the background of endometrial polyp
-Endometrioid adenocarcinoma can not be rouled out
-Please rebiopsy.

dr.kh.mirshekari

CONSULT PATHOLOGY

Designated Endometrial, Biopsy:

آیا شما توصیه به بررسی imaging در این مرحله می کنید؟

آیا شما توصیه به بررسی مولکولار در این مرحله می کنید؟

آیا بررسی مولکولار تغییری در تصمیم گیری نوع جراحی شما ایجاد می کند؟
لاپاراسکوپی یا لاپاراتومی؟ Surgical Staging ؟

All staging in guideline is based on 2009 FIGO staging. (ST-1, ST-2, ST-3 and ST-4)

INITIAL EVALUATION[a]

- History and physical (H&P)
- Complete blood count (CBC), liver function test [LFT], renal function tests, chemistry profile; and consider CA-125
- Expert pathology review with additional endometrial biopsy as clinically indicated[b,c]
- Imaging[d]
- Recommend molecular evaluation of tumor and evaluation for inherited cancer risk (ENDO-A and UTSARC-A)
- For patients who are older with uterine cancer also see the NCCN Guidelines for Older Adult Oncology
- Consider germline and/or multigene panel testing

INITIAL CLINICAL FINDINGS[c]

Malignant epithelial (carcinoma)

- Pure endometrioid carcinoma
  - Disease limited to uterus → Primary Treatment (ENDO-1)
  - Suspected or gross cervical involvement → Primary Treatment (ENDO-2)
  - Suspected extrauterine disease → Primary Treatment (ENDO-3)
- High-risk endometrial carcinoma histology
  - Serous carcinoma → Primary Treatment (ENDO-11)
  - Clear cell carcinoma → Primary Treatment (ENDO-12)
  - Undifferentiated/dedifferentiated carcinoma → Primary Treatment (ENDO-13)
  - Carcinosarcoma[f,g] → Primary Treatment (ENDO-14)

Malignant mesenchymal (sarcoma)[e] → Primary Treatment (UTSARC-1)

- Low-grade endometrial stromal sarcoma (ESS) or adenosarcoma
- High-grade ESS
- Undifferentiated uterine sarcoma (UUS)
- Leiomyosarcoma (LMS)
- Other sarcomas (eg, perivascular epithelioid cell tumor [PEComa])

Initial Workup
- Non–Fertility-Spar
  - Consider chest i
  - Consider pelvis
  - Consider preope
  - For high-grade c
  - For patients who
    uterine risk facto
  - Consider neck/cl
  - Other initial imag
- Fertility-Sparing T
  - Pelvis MRI (prefe
    unavailable.
  - Consider chest i
  - Consider neck/cl
  - Other imaging sh

Follow-up/Surveilla
- Non–Fertility-Spar
  - Imaging should b
- Fertility-Sparing T
  - Repeat pelvis MR
    considering furth
  - Other imaging sh
  - Consider pelvis

Suspected Recurre
- Abdomen/pelvis C
- Consider whole bo

[a] MRI is performed with
[b] High-grade endometr
[c] Uterine risk factors id
[d] Indications may includ
abdominal or pulmon
[e] Indications may includ

is <5 mm, the risk of endometrial cancer is minimal; the false-negative rate is approximately 4%.

Computed tomography (CT) imaging is not very useful in determining myometrial invasion (sensitivity 83%, specificity 42%) or in assessing cervical stromal invasion.[8] It is helpful, however, in assessing potential spread, especially for those with higher grade histology and high-risk histologic subtypes such as serous or clear cell carcinoma as opposed to those with endometrial hyperplasia or endometrioid low-grade carcinoma.

Magnetic resonance imaging (MRI), especially dynamic contrast-enhanced MRI, is very useful in detecting myometrial invasion, with an accuracy of 98%.[8] In patients with suspected cervical involvement, preoperative MRI may also help determine whether the uterine tumor involves the lower uterine segment or truly extends into the cervix. Gross cervical involvement in endometrial cancer is rare but important to document because it could influence surgical treatment (radical hysterectomy as opposed to simple hysterectomy). *Positron emission tomography (PET) plus CT* is of little benefit in assessing the primary tumor extension, of moderate benefit in detecting nodal metastasis with an overall diagnostic accuracy of 88%, and even greater benefit in detecting distant metastasis and relapse with an overall diagnostic accuracy of 93%.[9] *Serum cancer antigen (CA) 125* levels may be a predictor of extrauterine disease. In a study of 214 endometrial cancer patients, serum CA 125 was found to be an independent risk factor for pelvic and para-aortic lymph node metastasis.[10] Elevated levels of CA 125 may also assist in predicting treatment response or in posttreatment surveillance.

Devita 2023

NDO-7) with

ntraindicated or

especially if

CT.

tumor >2 cm.
ent; and

monary

Endometrial Cancer Stratification?

Table 1. Summary of recommendations on the preoperative management of endometrial cancer.

با توجه به عوامل پیش آگهی، تمامی دستورالعمل های مهم بر نقش محوری طبقه بندی بیماران سرطان آندومتر به گروه های کم، متوسط و پرخطر توافق دارند.
بویژه از نظر برآورد احتمال عود و پیش آگهی نامطلوب درآینده

ولی در مورد تصمیم گیری برای لنفادنکتومی
و استفاده یا عدم استفاده از درمان های کمکی
مانند شیمی درمانی یا رادیوتراپی
توافق قطعی در حال حاضر وجود ندارد.

Molecular classification	Encourages use	Encourages use	Not specified	Use only to characterize the degree of cancer risk	Use only to characterize the degree of cancer risk	Use only to characterize the degree of cancer risk

Kopatsaris, S.; Tsakiridis, I.; Kapetanios, G.; Zachomitros, F.; Michos, G.; Papanikolaou, E.; Athanasiadis, A.; Dagklis, T.; Kalogiannidis, I. Management of Endometrial Cancer: A Comparative Review of Guidelines. *Cancers* **2024**, *16*, 3582. https://doi.org/10.3390/cancers16213582

Surgery in endometrial carcinoma: Mainstay of treatment

Major Advancements in Surgery **in Early Stage Disease**

2015

ESMO-ESGO-ESTRO Consensus Conference

2020

ESGO-ESTRO-ESP Guidelines

Minimal invasive surgery

Sentinel Lymph Node

Minimal invasive surgery (MIS)

ESMO-ESGO-ESTRO
Consensus Conference 2015

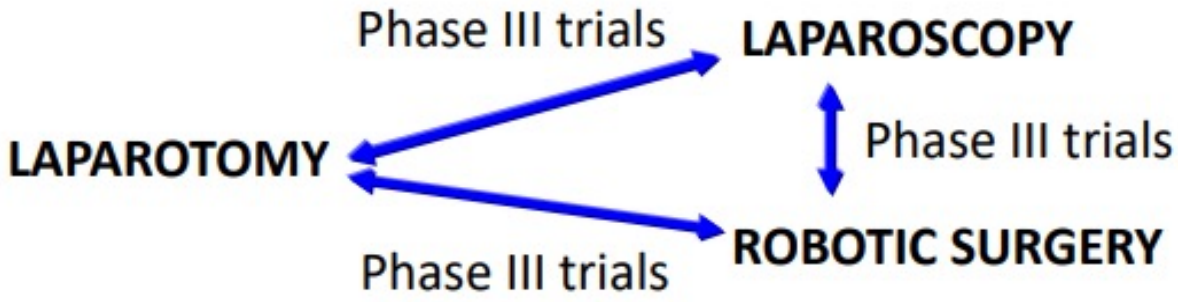
MIS **is recommended** in the surgical management of **low-and intermediate-risk** endometrial cancer
*Level of evidence: **I***
Strength of recommendation: A

MIS **can be considered** in the management of **high-risk endometrial cancer**
*Level of evidence: **IV***
Strength of recommendation: C

Colombo N et al, Ann Oncol. 2016 & Int J Gynecol Cancer 2016 & Radiother Oncol 2015

ESGO-ESTRO-ESP Guidelines NOW

Minimally invasive surgery is the preferred surgical approach, including patients with high-risk endometrial carcinoma (I, A).



Concin N et al, Int J Gynecol Cancer 2020 & Radiother Oncol 2021 & Virchows Arch 2021

Surgical management in apparent stage I/II endometrial carcinoma

- Total Hysterectomy (HE) & bilateral salpingo-oophorectomy (BSO) [II, A]
- Staging infracolic omentectomy in serous, undifferentiated carcinoma & carcinosarcoma [IV, B]
- Stage II: HE+BSO & lymph node staging, more extensive procedures admitted only to achieve free surgical margins [IV, B]

Minimally Invasive Surgery preferred surgical approach (I,A)

Intraperitoneal tumour spillage, including tumour rupture or morcellation (including in a bag), should be avoided [III, B]

If vaginal extraction risks uterine rupture, other measures should be taken

(eg. mini-laparotomy, use of endobag [III, B]

Tumours with metastasis outside the uterus and cervix (excluding lymph node metastases) are relative contra-indications [III, B]

Concin N *et al*, Int J Gynecol Cancer & Radiother Oncol & Virchows Arch 2020/21

Lymph node staging in apparent stage I/II endometrial carcinoma

ESGO
European Society of Gynaecological Oncology

ESMO-ESGO-ESTRO
Consensus Conference 2015

Sentinel Lymph Node biospy is still experimental

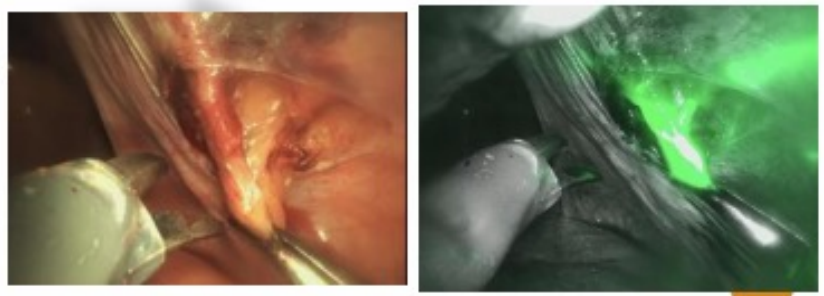
Level of evidence: IV
Strength of recommendation: D

Colombo N et al, Ann Oncol 2016 & Int J Gynecol Cancer 2016 & Radiother Oncol 2015

ESGO-ESTRO-ESP Guidelines NOW

Sentinel Lymph Node biopsy as an alternative to systematic lymphadenctomy for LYMPH NODE STAGING

A negative SLN is accepted to confirm pN0



Concin N et al, Int J Gynecol Cancer 2020 & Radiother Oncol 2021 & Virchows Arch 2021

Lymph node staging in apparent stage I/II endometrial carcinoma

- **Sentinel lymph node biopsy can be considered** for staging purposes in patients with **low/intermediate risk disease**. It can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended in this group [II, A].

- Surgical lymph node staging should be performed in patients with **high intermediate risk/high risk** disease. **Sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II** [III, B].

Case Presentation

A 58 y/o woman (G3P3) with a history of post menopausal vaginal bleeding from 3 months ago.

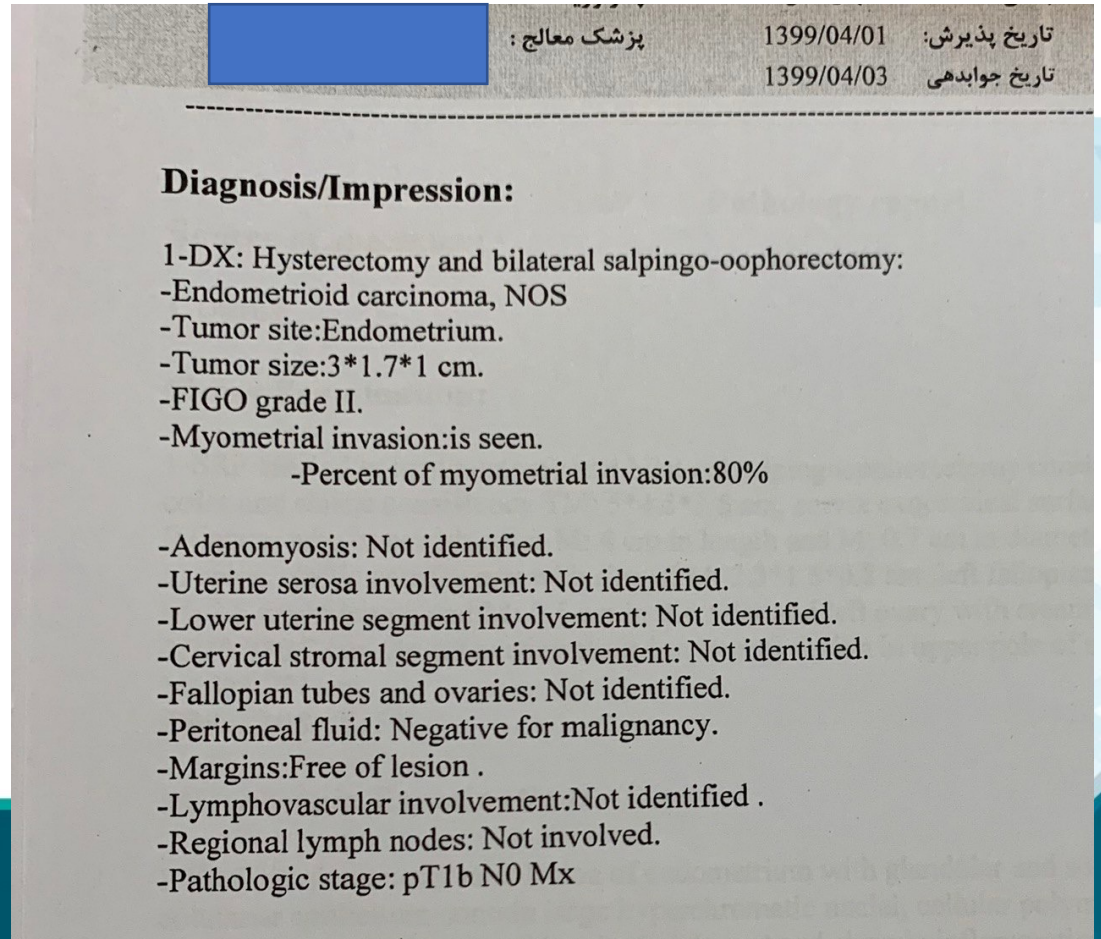
- BMI=**32** kg/m2
- PMH: Diabetes, HTN and breast cancer luminal A from 10 years ago **that is disease free**
- DH: Tamoxifen 20 mg/day/5 years
- FH: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is bigger than normal size
- Pap smear: (-)
- Performance status: 1
- Genetic consultant **not** done
- Ca 125 = 21.1 U/mL
- **Not** done molecular evaluation
- **Not** done additional imaging
- **TAH/BSO/SLNB was done by laparoscopy without any morcellation**

Case Presentation

A 58 y/o woman (G3P3) with a history of post menopausal vaginal bleeding from 3 months ago.

- BMI=**32** kg/m2
- PMH: Diabetes, HTN and breast cancer luminal A from 10 years ago **that is disease free**
- DH: Tamoxifen 20 mg/day/5 years
- FH: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is bigger than normal size
- Pap smear: (-)
- Performance status: 1
- Genetic consultant **not** done
- Ca 125 = 21.1 U/mL
- **Not** done molecular evaluation
- **Not** done additional imaging
- TAH/BSO/SLNB was done by laparoscopy

بیماری؟ Stage
FIGO 2009 or 2023?
Molecular evaluation?



پزشک معالج :
تاریخ پذیرش: 1399/04/01
تاریخ جوابدهی 1399/04/03

Diagnosis/Impression:

1-DX: Hysterectomy and bilateral salpingo-oophorectomy:
-Endometrioid carcinoma, NOS
-Tumor site:Endometrium.
-Tumor size:3*1.7*1 cm.
-FIGO grade II.
-Myometrial invasion:is seen.
-Percent of myometrial invasion:80%

-Adenomyosis: Not identified.
-Uterine serosa involvement: Not identified.
-Lower uterine segment involvement: Not identified.
-Cervical stromal segment involvement: Not identified.
-Fallopian tubes and ovaries: Not identified.
-Peritoneal fluid: Negative for malignancy.
-Margins:Free of lesion .
-Lymphovascular involvement:Not identified .
-Regional lymph nodes: Not involved.
-Pathologic stage: pT1b N0 Mx

FIGO STAGING SYSTEM FOR ENDOMETRIAL CANCER - 2009	
STAGE	**DESCRIPTION**
IA	Tumor confined to uterus, **< 50%** myometrial invasion
IB	Tumor confined to uterus, **≥ 50%** myometrial invasion
II	Cervical stromal invasion
IIIA	Tumor invasion into serosa or adnexa
IIIB	Vaginal or parametrial involvment
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvment
IVA	Tumor invasion into bladder or bowel mucosa
IVB	Distant metastases

2023 Figo Stage	Defining Criteria
IA1	non-aggressive histological type limited to the endometrium or an endometrial polyp
IA2	non-aggressive histological type involving <50% myometrium, with no/focal LVSI
IA3	low-grade EEC limited to the uterus and ovary
$IAm_{POLEmut}$	*POLEmut EC, confined to the uterine corpus or with cervical extension, regardless of LVSI or histological type*
IB	non-aggressive histological type involving ≥50% myometrium, and with no/focal LVSI
IC	aggressive histological type limited to the endometrium or an endometrial polyp
IIA	non-aggressive histological type with invasion of the cervical stroma
IIB	non-aggressive histological type with substantial LVSI
IIC	aggressive histological type with any myometrial infiltration
$IICm_{p53abn}$	*p53abn EC, confined to the uterine corpus with any myometrial infiltration, with or without cervical invasion, and regardless of LVSI or histological type*
IIIA1	spread to ovary or fallopian tube (except if it meets the Stage IA3 criteria)
IIIA2	involvement of uterine subserosa/serosa
IIIB1	metastasis or direct spread to the vagina and/or the parametria
IIIB2	metastasis to the pelvic peritoneum

Staging–Uterine Carcinomas and Carcinosarcoma

Table 1
AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Endometrial Cancer

Definitions for T, N, M

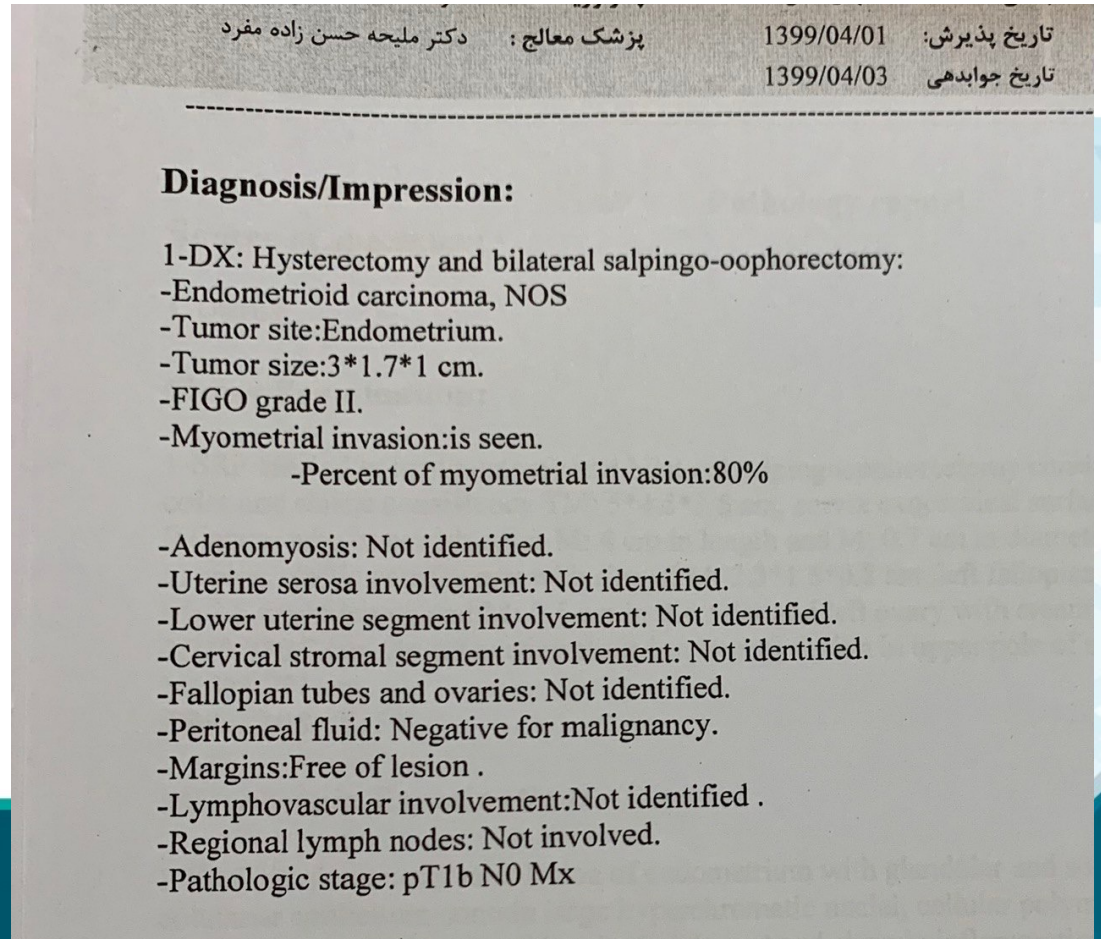
T	FIGO Stage	Primary Tumor
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor confined to the corpus uteri, including endocervical glandular involvement
T1a	**IA**	Tumor limited to the endometrium or invading less than half the myometrium
T1b	**IB**	Tumor invading one half or more of the myometrium
T2	**II**	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus. Does NOT include endocervical glandular involvement
T3	**III**	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	**IIIA**	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
T3b	**IIIB**	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	**IVA**	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

Case Presentation

A 58 y/o woman (G3P3) with a history of post menopausal vaginal bleeding from 3 months ago.

- BMI=32 kg/m2
- PMH: Diabetes, HTN and breast cancer luminal A from 10 years ago that is disease free
- DH: Tamoxifen 20 mg/day/5 years
- FH: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is bigger than normal size
- Pap smear: (-)
- Performance status: 1
- Genetic consultant **not** done
- Ca 125 = 21.1 U/mL
- **Not** done molecular evaluation
- **Not** done additional imaging
- TAH/BSO/SLNB was done by laparoscopy **without any morcellation**
- **EEC /G2 /LVsI(-) /FIGO Stage2009 IB**

آیا بیمار Low risk هست؟



تاریخ پذیرش: 1399/04/01 پزشک معالج : دکتر ملیحه حسن زاده مفرد
تاریخ جوابدهی 1399/04/03

Diagnosis/Impression:

1-DX: Hysterectomy and bilateral salpingo-oophorectomy:
-Endometrioid carcinoma, NOS
-Tumor site:Endometrium.
-Tumor size:3*1.7*1 cm.
-FIGO grade II.
-Myometrial invasion:is seen.
-Percent of myometrial invasion:80%

-Adenomyosis: Not identified.
-Uterine serosa involvement: Not identified.
-Lower uterine segment involvement: Not identified.
-Cervical stromal segment involvement: Not identified.
-Fallopian tubes and ovaries: Not identified.
-Peritoneal fluid: Negative for malignancy.
-Margins:Free of lesion .
-Lymphovascular involvement:Not identified .
-Regional lymph nodes: Not involved.
-Pathologic stage: pT1b N0 Mx

THE GEC ESTRO HANDBOOK OF BRACHYTHERAPY | Part II: Clinical Practice Version 1 - 25/04/2016

1. SUMMARY

Endometrial cancer presents in most women at an early stage confined to the uterus and initial treatment is by hysterectomy. Post-operative treatment is indicated for intermediate and high risk patients defined by age, stage, grade and the presence or absence of lymphovascular space invasion.

Vaginal vault brachytherapy is indicated in intermediate risk patients having one of the following risk factors: grade = 2 or 3, myometrial invasion >50%, lymphovascular space invasion or cervical stromal invasion. The PORTEC 2 trial confirmed that it is as effective as external beam pelvic radiotherapy in this group of patients and associated with less toxicity. Vaginal relapse is reduced to only 2-3%. Mucosal atrophy occurred in 36% of patients in PORTEC 2 as the main toxicity; grade 3 GI toxicity was <1%.

Intrauterine brachytherapy is indicated for patients with endometrial cancer who are unfit for surgery either alone (stage I or II) or with external beam therapy (stage III). Accurate staging is now possible with MR scanning. Specific applicators are required, either Heymans or Norman Simon capsules, or the Rotte Y applicator to ensure good coverage of the IR-CTV which includes the entire wall of the uterus and vaginal cuff to which a minimum dose of 60Gy should be delivered. With MR imaging a HR-CTV incorporating the GTV can be defined which receives a higher dose. Outcome in this group of patients is predominantly defined by their comorbidities rather than the endometrial cancer. Toxicity is mainly vaginal dryness and shortening with occasional grade≥3 urinary and bowel toxicities in <5%.

اگر طبقه بندی مولکولار برای بیمار انجام می شد، آیا ریسک بیمار متفاوت بود؟

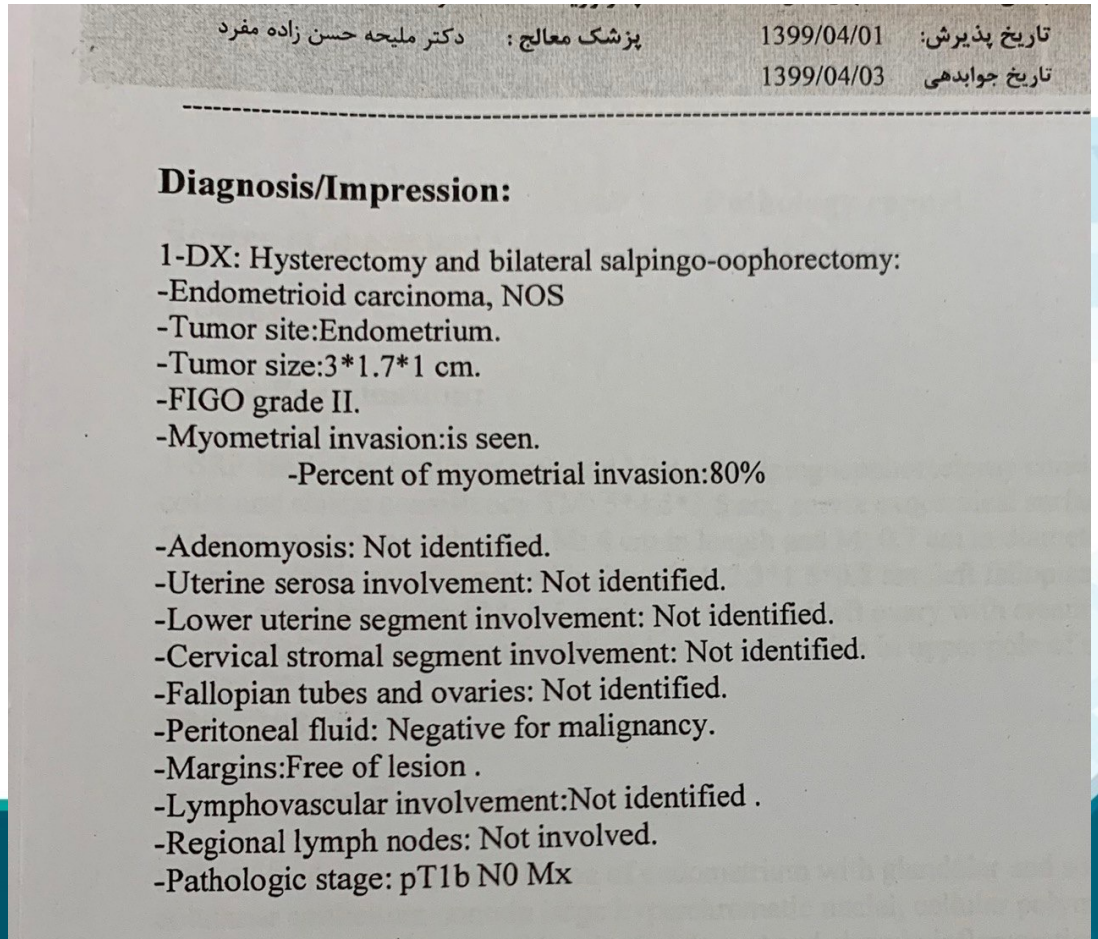
Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal
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-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

Case Presentation

A **58** y/o woman (G3P3) with a history of post menopausal vaginal bleeding from 3 months ago.

- BMI=32 kg/m2
- PMH: Diabetes, HTN and breast cancer luminal A from 10 years ago **that is disease free**
- DH: Tamoxifen 20 mg/day/5 years
- FH: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is bigger than normal size
- Pap smear: (-)
- Performance status: 1
- Genetic consultant **not** done
- Ca 125 = 21.1 U/mL
- **Not** done molecular evaluation
- **Not** done additional imaging
- TAH/BSO/SLNB was done by laparoscopy without any morcellation
- **EEC /G2 /LVsI(-) /FIGO Stage2009 IB**
- **Not** done molecular evaluation

توصیه شما چیست؟



تاریخ پذیرش: 1399/04/01 پزشک معالج : دکتر ملیحه حسن زاده مفرد
تاریخ جوابدهی 1399/04/03

Diagnosis/Impression:

1-DX: Hysterectomy and bilateral salpingo-oophorectomy:
-Endometrioid carcinoma, NOS
-Tumor site:Endometrium.
-Tumor size:3*1.7*1 cm.
-FIGO grade II.
-Myometrial invasion:is seen.
-Percent of myometrial invasion:80%

-Adenomyosis: Not identified.
-Uterine serosa involvement: Not identified.
-Lower uterine segment involvement: Not identified.
-Cervical stromal segment involvement: Not identified.
-Fallopian tubes and ovaries: Not identified.
-Peritoneal fluid: Negative for malignancy.
-Margins:Free of lesion .
-Lymphovascular involvement:Not identified .
-Regional lymph nodes: Not involved.
-Pathologic stage: pT1b N0 Mx

International Journal of GYNECOLOGY & OBSTETRICS

REVIEW ARTICLE | Open Access

Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies

Risk group	Molecular classification unknown	Molecular classification known	Common treatment recommendations—for no fertility sparing
Intermediate	• Stage IB endometrioid, grade 1–2, LVSI negative or focal • Stage IA endometrioid, grade 3, LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB MMRd/p53 wt endometrioid carcinoma + low grade + LVSI negative or focal • Stage IA MMRd/p53 wt endometrioid carcinoma + high grade + LVSI negative or focal • Stage IA p53 abn and/or non-endometrioid without myometrial invasion	• Vaginal brachytherapy preferred • Consider observation if age < 60 year and no LVSI • Vaginal brachytherapy preferred or consider observation if no myoinvasion or consider EBRT if either age ≥ 70 year or LVSI • Staging omentectomy should be performed

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

All staging in guideline is based on 2009 FIGO staging. (ST-1)

CLINICAL FINDINGS (Endometrioid Histology)[a]

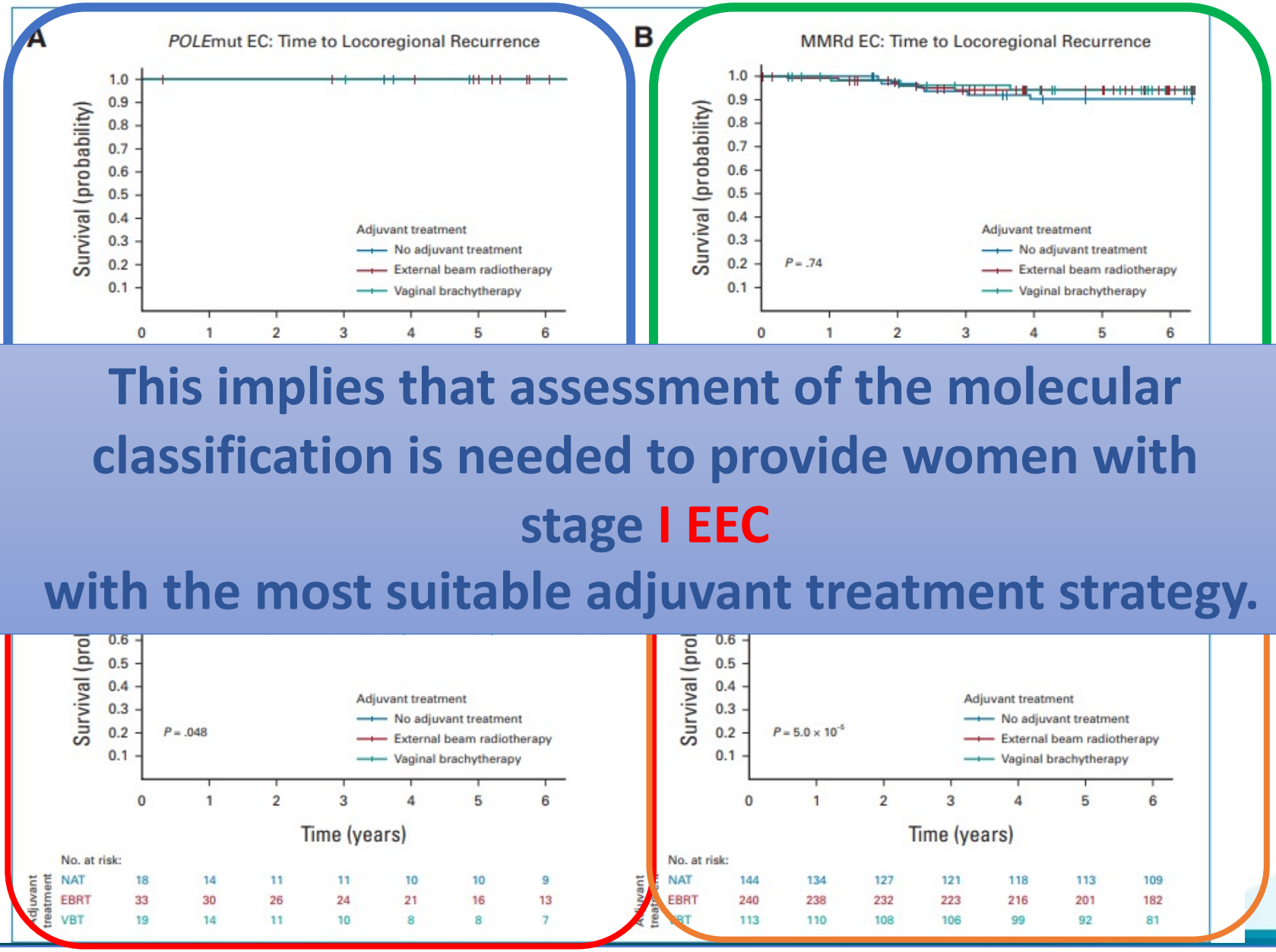
HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]

Surgically staged: Stage I[e] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥70 y or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age <60 y and no LVSI
	G2	Vaginal brachytherapy preferred or Consider EBRT if ≥60 y and/or LVSI or Consider observation if age <60 y and no LVSI
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

اگر طبقه بندی مولکولار برای بیمار انجام می شد، آیا در این stage تصمیم گیری در مورد درمان بیمار متفاوت بود؟

Endometrial Cancer Molecular Class Predicts Radiotherapy Response



This implies that assessment of the molecular classification is needed to provide women with stage I EEC with the most suitable adjuvant treatment strategy.

Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer: J Clin Oncol, . 2023 Sep 20;41(27):4369-4380. doi: 10.1200/JCO.23.00062. Epub 2023 Jul 24.

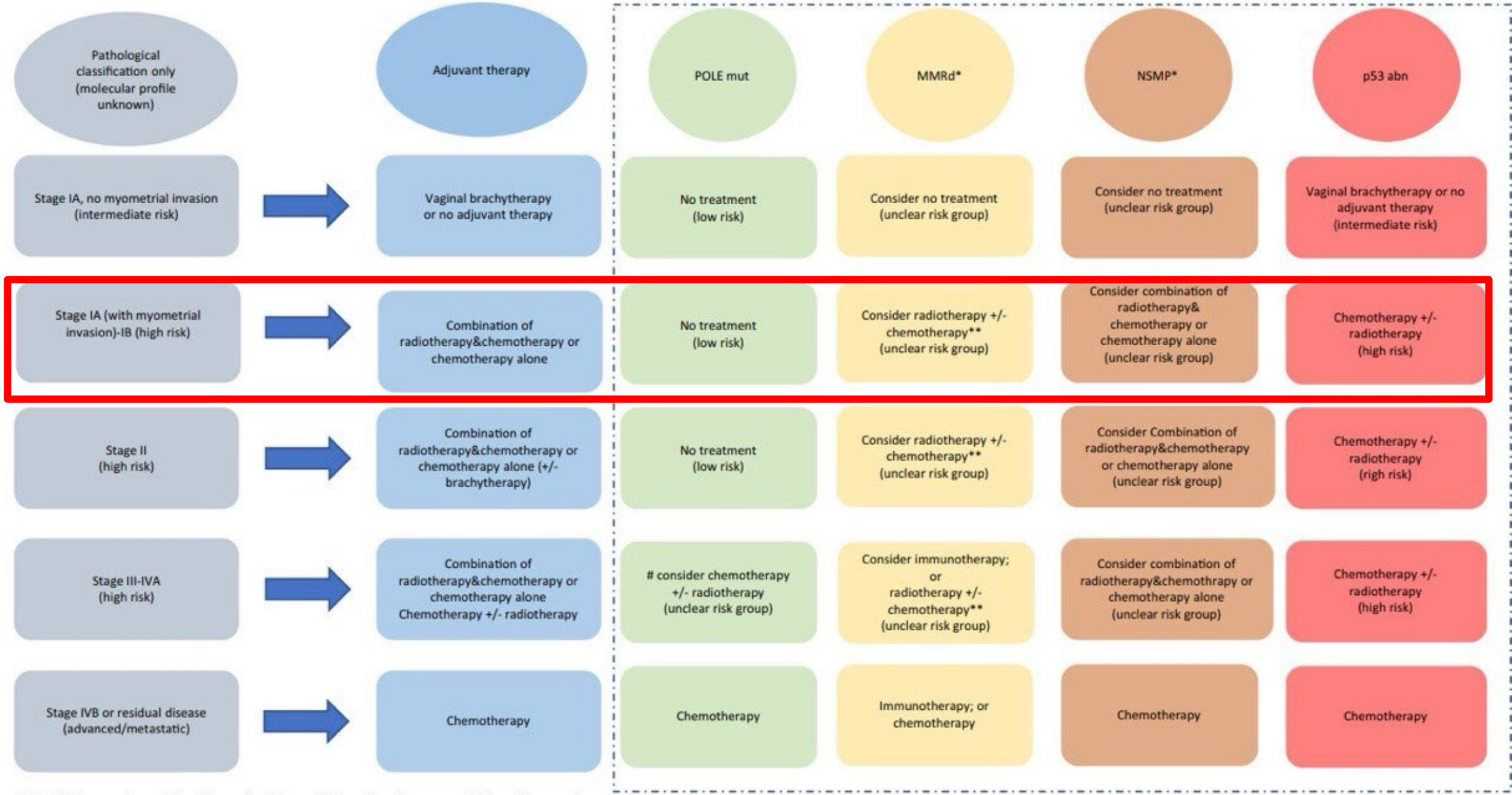
J Clin Oncol. 2023 Jul 24;41(27):4369–4380. doi: 10.1200/JCO.23.00062

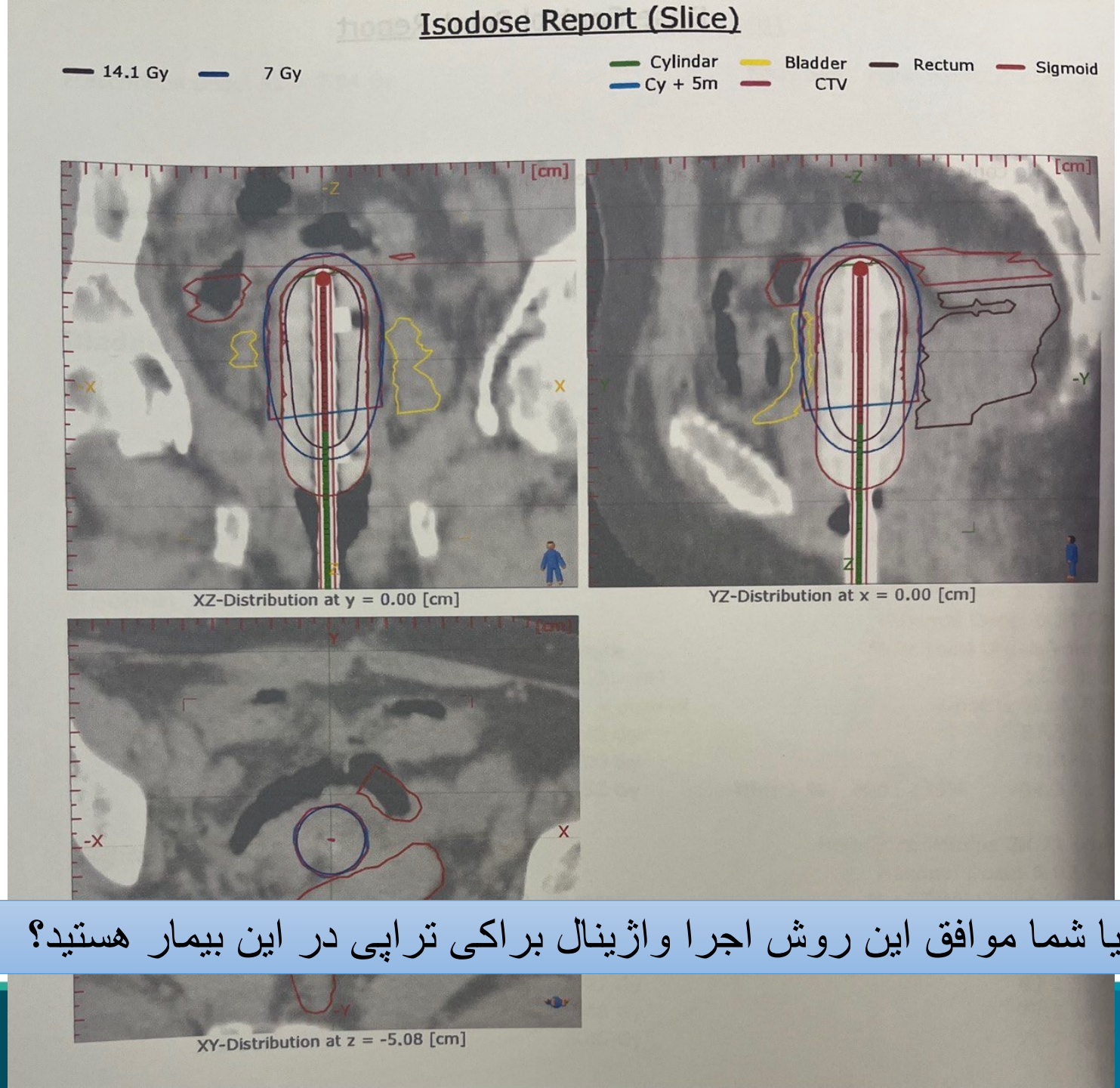
Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer

Nanda Horeweg [1,✉], Remi A Nout [1,2], Ina M Jürgenliemk-Schulz [3], Ludy CHW Lutgens [4], Jan J Jobsen [5], Marie AD Haverkort [6], Jan Willem M Mens [2], Annerie Slot [7], Bastiaan G Wortman [1,8], Stephanie M de Boer [1], Ellen Stelloo [9], Karen W Verhoeven-Adema [10], Hein Putter [11], Vincent THBM Smit [9], Tjalling Bosse [9], Carien L Creutzberg [1], for the PORTEC Study Group

CONCLUSION:

- ✓ **Omitting radiotherapy seems to be safe in *POLE*mut EC.**
- ✓ **The benefit of radiotherapy seems to be limited in MMRd EC.**
- ✓ **EBRT yields a significantly better locoregional recurrence-free survival than VBT or no adjuvant therapy in p53abn EC.**
- ✓ **VBT is the treatment of choice for NSMP EC as it is as effective as EBRT and significantly better than no adjuvant therapy for locoregional tumor control.**


Pathological classification only (molecular profile unknown)
Adjuvant therapy
POLE mut
MMRd*
NSMP*
p53 abn
Stage IA, no myometrial invasion (intermediate risk)
Vaginal brachytherapy or no adjuvant therapy
No treatment (low risk)
Consider no treatment (unclear risk group)
Consider no treatment (unclear risk group)
Vaginal brachytherapy or no adjuvant therapy (intermediate risk)
Stage IA (with myometrial invasion)-IB (high risk)
Combination of radiotherapy&chemotherapy or chemotherapy alone
No treatment (low risk)
Consider radiotherapy +/- chemotherapy** (unclear risk group)
Consider combination of radiotherapy& chemotherapy or chemotherapy alone (unclear risk group)
Chemotherapy +/- radiotherapy (high risk)
Stage II (high risk)
Combination of radiotherapy&chemotherapy or chemotherapy alone (+/- brachytherapy)
No treatment (low risk)
Consider radiotherapy +/- chemotherapy** (unclear risk group)
Consider Combination of radiotherapy&chemotherapy or chemotherapy alone (unclear risk group)
Chemotherapy +/- radiotherapy (righ risk)
Stage III-IVA (high risk)
Combination of radiotherapy&chemotherapy or chemotherapy alone Chemotherapy +/- radiotherapy
consider chemotherapy +/- radiotherapy (unclear risk group)
Consider immunotherapy; or radiotherapy +/- chemotherapy** (unclear risk group)
Consider combination of radiotherapy&chemothrapy or chemotherapy alone (unclear risk group)
Chemotherapy +/- radiotherapy (high risk)
Stage IVB or residual disease (advanced/metastatic)
Chemotherapy
Chemotherapy
Immunotherapy; or chemotherapy
Chemotherapy
Chemotherapy



آیا شما موافق این روش اجرا واژینال براکی تراپی در این بیمار هستید؟

PRINCIPLES OF RADIATION THERAPY FOR UTERINE NEOPLASMS

General Treatment Information (continued)

- **Dosing Prescription Regimen – External Beam**
  - External-beam doses for microscopic disease should be 45–50 Gy. CT treatment planning should be utilized, and intensity-modulated RT (IMRT) for normal tissue sparing should be considered, with appropriate attention to quality assurance (QA) and tissue interfraction mobility.
  - Treating with IMRT technique is preferred to minimize toxicities in definitive treatment of the pelvis with or without para-aortic treatment. Regular use of image-guided RT (IGRT) with orthogonal imaging and/or routine volumetric imaging (such as cone beam CT) at the time of treatment delivery is essential to ensure appropriate coverage of targets and sparing of normal tissues.
  - Postoperatively, if there is gross residual disease and the area(s) can be sufficiently localized, a boost can be added to a total dose of 60–70 Gy, respecting normal tissue sensitivity.
  - For gross nodal disease, consider boost to 60–65 Gy while respecting normal tissue constraints.
  - For neoadjuvant radiation, doses of 45–50 Gy are typically used. One could consider adding 1–2 high dose-rate (HDR) insertions to a total dose of 75–80 Gy low dose-rate (LDR) equivalent, to minimize risk of positive or close margins at hysterectomy.
  - For pelvic-confined recurrent endometrial cancer without a prior history of radiation, fields would mirror adjuvant radiation. For reirradiation, fields should be limited to gross disease and target dose prescribed to maximize control while minimizing risk to normal tissues.
- **Dosing Prescription Regimen – Brachytherapy**
  - Initiate brachytherapy as soon as the vaginal cuff is healed, preferably 6–8 weeks after surgery but in general initiation of brachytherapy should not exceed 12 weeks. For vaginal brachytherapy, the dose should be prescribed to the vaginal surface or at a depth of 0.5 cm from the vaginal surface; the dose depends on the use of EBRT. The target for vaginal brachytherapy after hysterectomy should be no more than the upper two-thirds of the vagina; in cases of extensive LVSI or positive margins, a longer segment of the vagina may be treated.
    - ◊ For postoperative HDR vaginal brachytherapy alone, regimens include 6 Gy x 5 fractions prescribed to the vaginal surface, or 7 Gy x 3 fractions or 5.5 Gy x 4 fractions prescribed to 5 mm below the vaginal surface. While 7 Gy x 3 fractions prescribed at a depth of 0.5 cm from the vaginal surface is a regimen used by many, the use of smaller fraction sizes may be considered to potentially further limit toxicity in selected patients.
    - ◊ When HDR brachytherapy is used as a boost to EBRT, doses of 4–6 Gy x 2 to 3 fractions prescribed to the vaginal mucosa are commonly used.
  - For medically inoperable uterine cancer, risk of extrauterine spread determines the combination of EBRT plus brachytherapy or brachytherapy alone. Brachytherapy doses for definitive therapy are individualized based on the clinical situation. When available, image-guided therapy should be used. Based on the best available evidence, an equivalent dose at 2 Gy (EQD2) fractions D90 of ≥48 Gy should be delivered to the uterus, cervix, and upper 1–2 cm of vagina if brachytherapy alone is used, and should be increased to 65 Gy for the combination of EBRT and brachytherapy. If an MRI is used as part of planning, the target dose for the gross tumor volume (GTV) would be an EQD2 of ≥80 Gy.

THE GEC ESTRO HANDBOOK OF BRACHYTHERAPY | Part II: Clinical Practice Version 1 - 25/04/2016

7. TARGET VOLUME

7.1 Postoperative vaginal brachytherapy

The rationale for post-operative vaginal vault brachytherapy is that the majority of vaginal recurrences occur at the vaginal cuff. The next most common site is the periurethral region but this accounts for only 10% of the total recurrences. The target volume for postoperative brachytherapy has therefore been limited to the vaginal wall of the upper third of the vagina. The resulting typical target length is 3 - 4 cm and the thickness may vary according to the thickness of the vaginal wall. Special care must be taken that the applicator has direct contact at the vaginal cuff with its often irregular surface and shape after surgery. Careful choice of an adequate applicator using a cylinder, ovoids, or individual mould applicators is crucial for target coverage. Verification with MR or CT to confirm close apposition should be considered.

Case Presentation

A 58 y/o woman (G3P3) with a history of post menopausal vaginal bleeding from 3 months ago.

- BMI=**32** kg/m2
- PMH: Diabetes, HTN and breast cancer luminal A from 10 years ago **that is disease free**
- DH: Tamoxifen 20 mg/day/5 years
- FH: Colon cancer in her sister in 45 y/o
- PE & BME & SPE: uterine is bigger than normal size
- Pap smear: (-)
- Performance status: 1
- Genetic consultant **not** done
- Ca 125 = 21.1 U/mL
- **Not** done molecular evaluation
- **Not** done additional imaging
- TAH/BSO/SLNB was done by laparoscopy
- **HDR VBT/21Gy/3Fr/2.5 weeks**
- **Not** done molecular evaluation

فالو اپ؟

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Endometrial Carcinoma

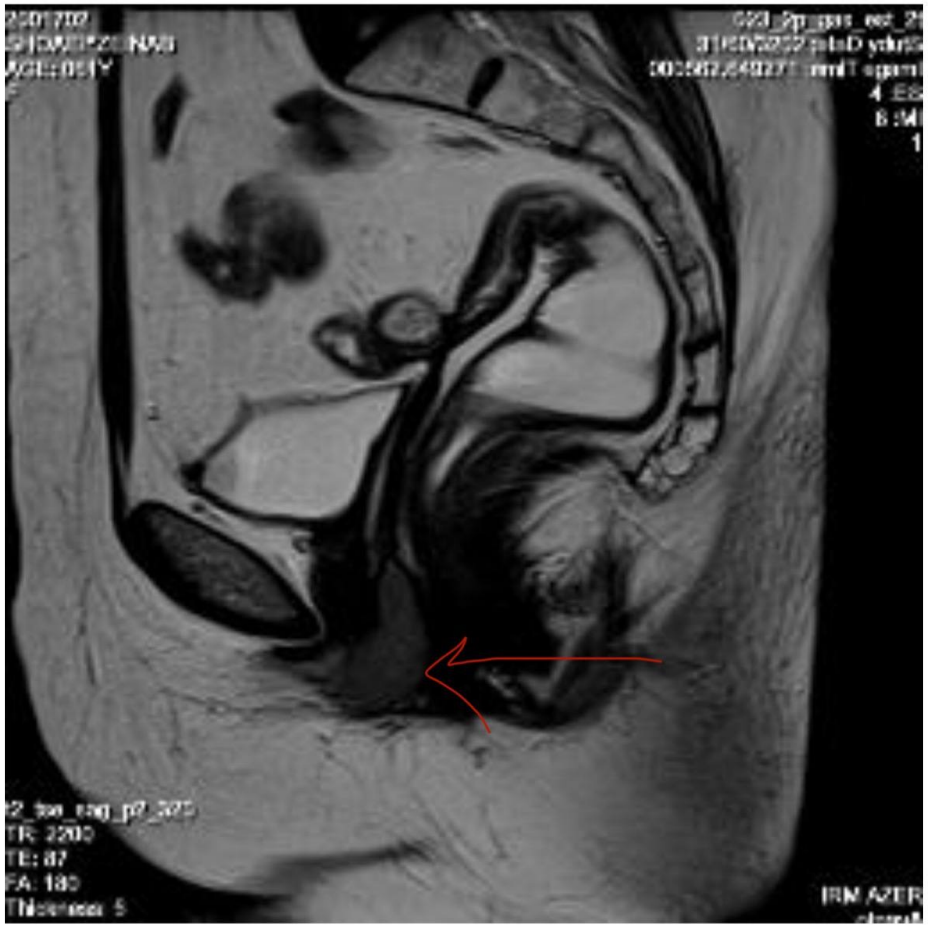
NCCN Guidelines Index
Table of Contents
Discussion

Vaginal brachytherapy was done without any molecular evaluation.

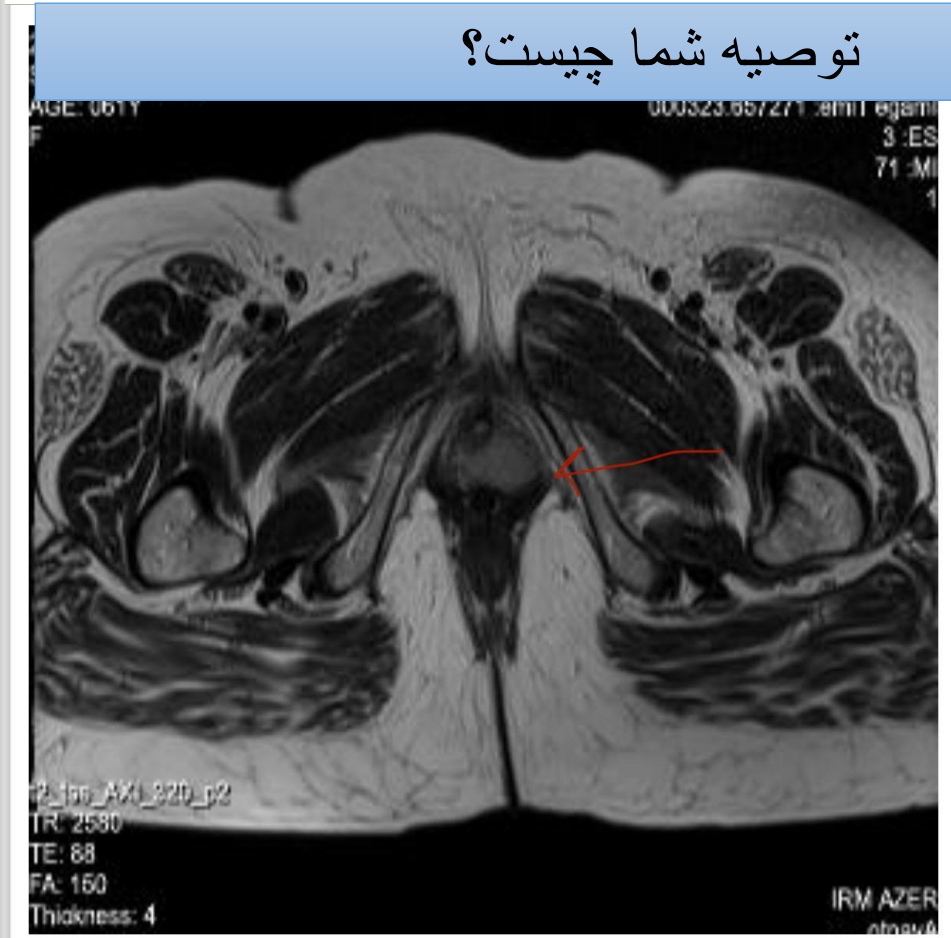
- Physical exam (including pelvis)
  - every 3–6 mo for 2–3 y,
  - then every 6–12 mo for up to year 5,
  - then annually
- CA-125 if initially elevated or serous histology
- Imaging as indicated based on symptoms or examination findings suspicious for recurrence[i]
- Clinical evaluation and management of potential long-term and late effects of treatment[v] (Also see Principles of Gynecologic Survivorship (UN-B), NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation)

CLINICAL PRESENTATION		THERAPY FOR RELAPSE			
Locoregional recurrence • Negative for distant metastases on radiologic imaging[i]	→	Therapy for Relapse (ENDO-10)			
Isolated metastases	→	• Consider resection and/or EBRT[g] or Ablative therapy[w] • Consider systemic therapy[h] (category 2B)	→	Not amenable to local treatment or Further recurrence	→ Treat as disseminated metastases (See below)
Disseminated metastases	→	Systemic therapy[h] ± palliative EBRT[g]	→		If progression, Best supportive care (NCCN Guidelines for Palliative Care)

- After 3 years (May 2023), she come back with vaginal bleeding and a mass with ulceration in lower part of her vagina.

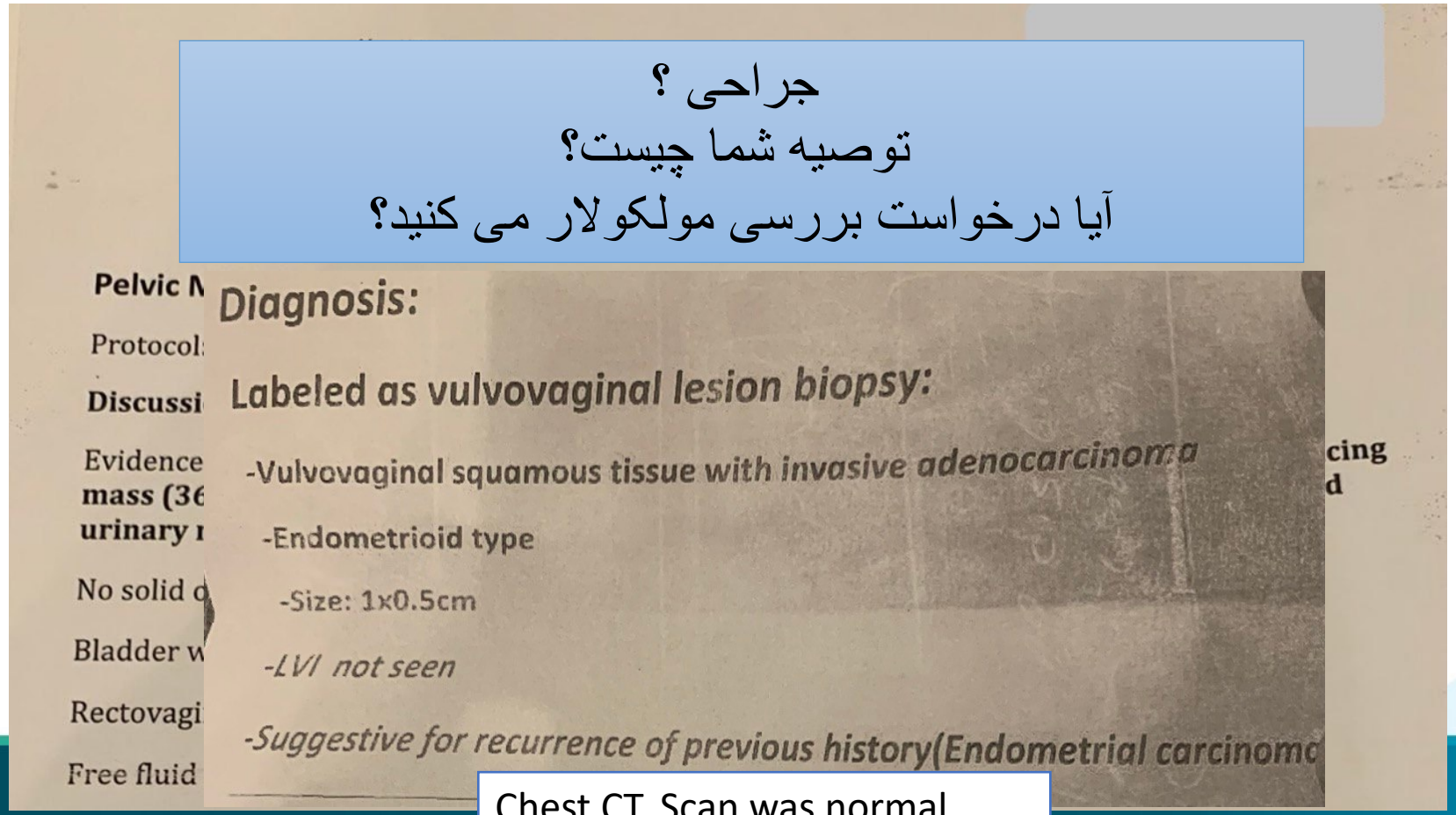


توصیه شما چیست؟



- After 3 years (May 2023), she come back with vaginal bleeding and a mass with ulceration in lower part of her vagina

جراحی ؟
توصیه شما چیست؟
آیا درخواست بررسی مولکولار می کنید؟



Chest CT. Scan was normal

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL PRESENTATION | **THERAPY FOR RELAP**

Locoregional recurrence[x]
- Negative for distant metastases on radiologic imaging[i]

→ No prior RT to site of recurrence or previous vaginal brachytherapy only
→ EBRT[g] ± brachytherapy[g] ± systemic therapy[h]
or
Surgical exploration[y] + resection ± intraoperative RT (IORT) (category 3 for IORT)

→ Prior EBRT to site of recurrence
→ Surgical exploration + resection ± IORT (category 3 for IORT) and/or Systemic therapy[h] ± palliative EBRT[g] or Brachytherapy[g,z] ± systemic therapy[h]

→ Upper abdominal/ peritoneal
- Microscopic residual disease → Systemic therapy[h] ± EBRT[g,bb]
- Gross upper abdominal residual disease → Therapy For Relapse [disseminated metastases (ENDO-9)]

First-Line Therapy for Recurrent Disease[j]

Preferred Regimens
- Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[c,d,k,8]
- Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,k,9]
- Carboplatin/paclitaxel/durvalumab (for dMMR only) (category 1)[c,d,k,10]
- Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma or carcinosarcoma)[d,g,11]
- Carboplatin/paclitaxel (category 1 for carcinosarcoma)[l,14]

Other Recommended Regimens
- Carboplatin/docetaxel[m]
- Carboplatin/paclitaxel/bevacizumab[d,12,13]

Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)
- MMR-proficient (pMMR) tumors
  - Lenvatinib/pembrolizumab (category 1)[c,15,16]
- TMB-high (TMB-H) tumorsn
  - Pembrolizumab[c,17]
- MSI-H/dMMR tumors[o]
  - Pembrolizumab[c,18]
  - Dostarlimab-gxly[c,19]

g Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
h Systemic Therapy for Endometrial Carcinoma (ENDO-D).

Endometrial Cancer

Diagnostic workup

Patient is candidate for systemic therapy

Disease status confirmed: advanced, metastic, or recurrent endometrial cancer

No prior systemic therapy for advanced stage disease

- Dostarlimab + carboplatin + paclitaxel
- Pembrolizumab + carboplatin + paclitaxel

Previously treated with chemotherapy for advanced-stage disease

MMR status

pMMR/MSS

Pembrolizumab + lenvatinib

dMMR/MSI-H

- Pembrolizumab monotherapy
- Dostarlimab monotherapy

آیا برای این بیمار درمان سیستمیک توصیه می کنید؟

Disis ML, Adams SF, Bajpai J, *et al*. Society for I
gynecologic cancer. *Journal for ImmunoTherapy of Cancer* 2023

Molecular evaluation by IHC

MMR-proficient (pMMR)
ER (+)

MSH6: Retained nuclear staining/ Non mutant

PMS2: Retained nuclear staining/ Non mutant

P53: positive in 60% tumoral cells (wild type)

ER: 30% in tumoral cells

PR: negative tumoral cells

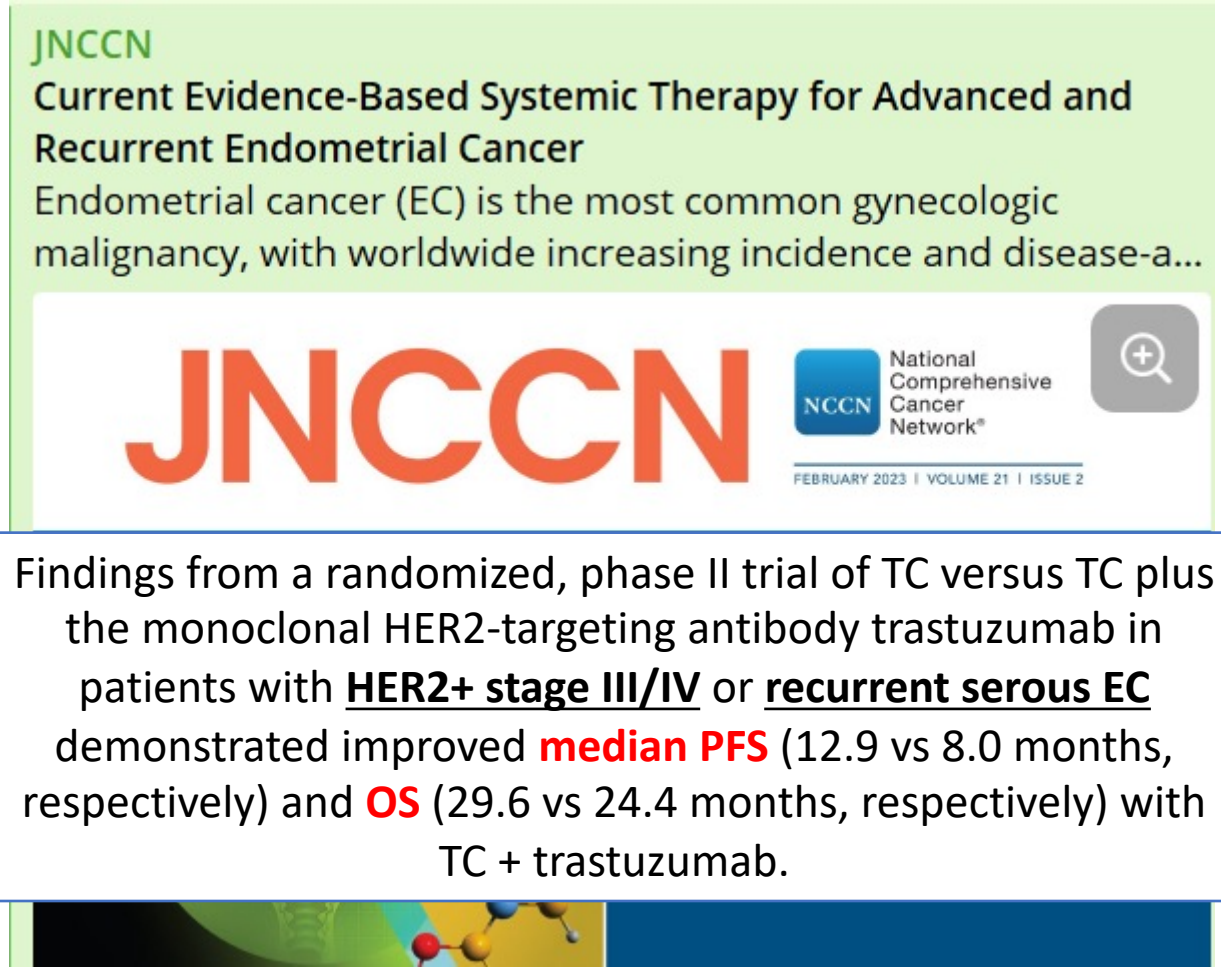
HER2: 20% strongly (+)

آیا چک MMR و P53 در این مرحله توصیه می شود؟
آیا HER2 باید چک می شد؟
آیا HER2 مثبت است؟
با درخواست ER و PR موافق هستید؟
توصیه شما چیست؟

HER2NEU CUT OFF IN DIFFERENT TUMOR TYPES

	Breast (ASCO/CAP 2018)[23]	Gastric (ASCO/CAP 2016)[36]	Colorectal (HERACLES Trial)[39]	Endometrial Serous (Fader et al Clinical Trial)[21]
HER2 IHC 3+	>10% circumferential, strong, complete	≥10%, strong complete, or basolateral/lateral	≥50% strong complete, or basolateral/lateral	>30% strong complete or basolateral/lateral
HER2 FISH amplification	*HER2*/CEP17 ratio ≥2.0 and *HER2* signal ≥4.0 per nucleus OR ratio <2.0 and *HER2* signal ≥6.0 per nucleus (if IHC score 2+ or 3+)	*HER2*/CEP17 ratio ≥2.0 OR ratio <2.0 and *HER2* signal >6.0 per nucleus	*HER2*/CEP17 ratio ≥2.0 in ≥50% of cells	*HER2*/CEP17 ratio ≥2.0

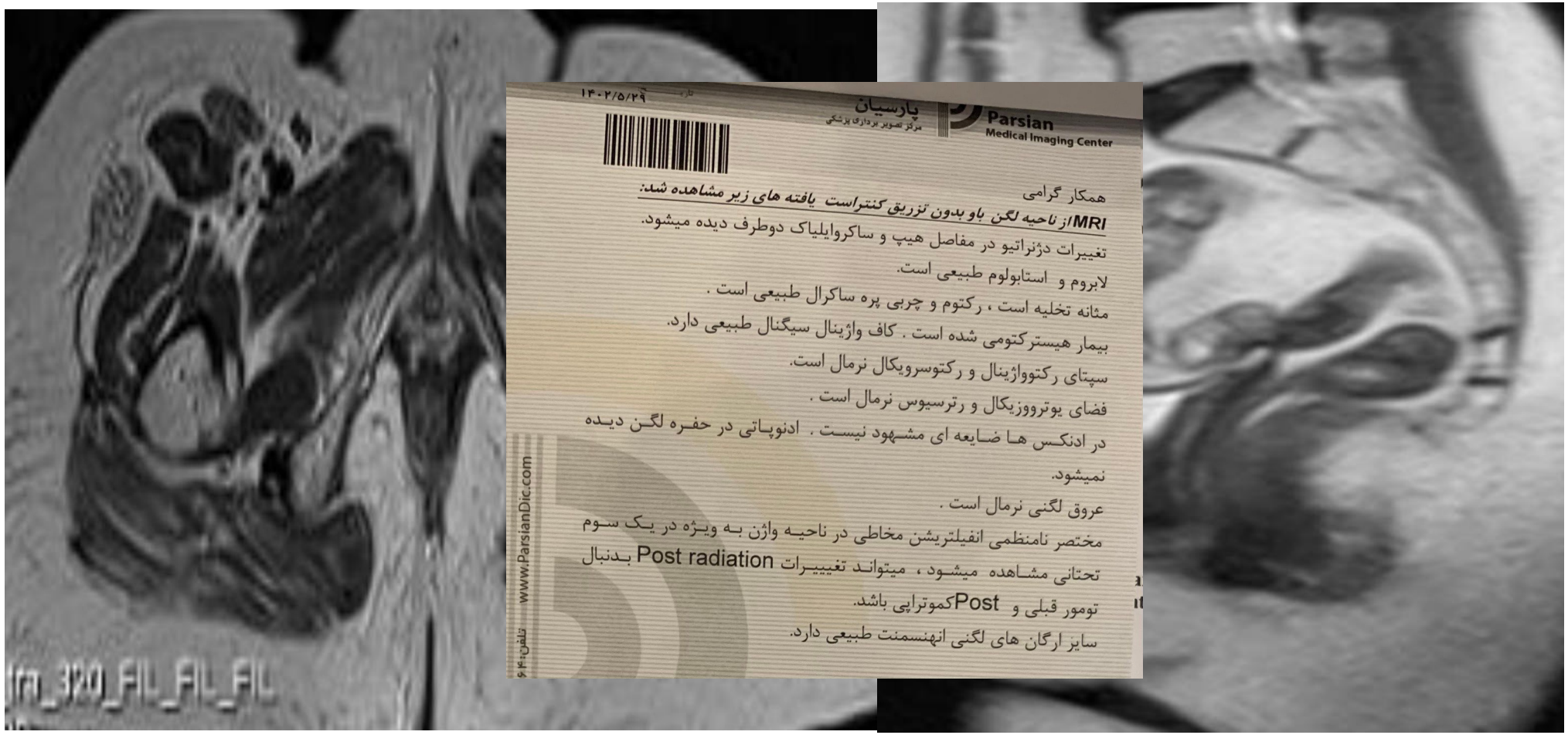
Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists.



Findings from a randomized, phase II trial of TC versus TC plus the monoclonal HER2-targeting antibody trastuzumab in patients with **HER2+ stage III/IV** or **recurrent serous EC** demonstrated improved **median PFS** (12.9 vs 8.0 months, respectively) and **OS** (29.6 vs 24.4 months, respectively) with TC + trastuzumab.

HER2 is overexpressed in approximately 25% to 30% of CN-H, serous/serous-like ECs and 13% of carcinosarcomas.

She treated with chemoradiotherapy (Cisplatin+ 45Gy/25Fr/ 3D conformal EBRT)



+ 20Gy vaginal brachytherapy
+ **Megace** (megestrol acetate) 160 m/day
After 1.5 years follow up, she is disease free.

Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies

Molecular Subtypes of Endometrial Cancer

	p53 abn	MMRd	NSMP	POLE mut
PORTEC-3	PARP	PD-L1 PD-1	Progestin Receptor	
2009FIGO	Invasive I-III	II and LVSI, III	ER+ II and LVSI, III	I-III
RAINBO	Chemoradiotherapy+Olaparib vs Chemoradiotherapy alone	Radiotherapy+Durvalumab vs Radiotherapy alone	Chemoradiotherapy+Progestin vs Chemoradiotherapy alone	No adiuvant thearpy

Intl J Gynecology & Obste, Volume: 164, Issue: 2, Pages: 436-459, First published: 31 July 2023, DOI: (10.1002/ijgo.14969)

Take Home Massage

Endometrial cancer (EC) is a heterogeneous disease

✓ We must look to relevant biologic targets to **individualize treatment**.

Although the incidence and number of deaths from EC has increased worldwide,
we must advocate for research to improve the quality of life and outcomes for patients with EC.

Open Access Review

Recent Advances in Endometrial Cancer Prevention, Early Diagnosis and Treatment

by Holly Baker-Rand [1] and Sarah J. Kitson [1,2,*]

[1] Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PL, UK

[2] Manchester Academic Health Science Centre, Department of Obstetrics and Gynaecology, Manchester University NHS Foundation Trust, Manchester M13 9WL, UK

* Author to whom correspondence should be addressed.

Cancers **2024**, *16*(5), 1028; **https://doi.org/10.3390/cancers16051028**

Submission received: 15 February 2024 / Revised: 26 February 2024 / Accepted: 27 February 2024 / Published: 1 March 2024

https://www.mdpi.com/2072-6694/16/21/3582

Open Access Review

Management of Endometrial Cancer: A Comparative Review of Guidelines

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

Third Department of Obstetrics and Gynaecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Konstantinoupoleos 49, 54642 Thessaloniki, Greece

* Author to whom correspondence should be addressed.

† These authors contributed equally to this work.

Cancers **2024**, *16*

https://www.mdpi.com/2072-6694/16/5/1028

Open Access Review

Tailoring Endometrial Cancer Treatment Based on Molecular Pathology: Current Status and Possible Impacts on Systemic and Local Treatment

by Pedro Ribeiro-Santos [1,2], Carolina Martins Vieira [1,2], Gilson Gabriel Viana Veloso [1,3], Giovanna Vieira Giannecchini [1,2], Martina Parenza Arenhardt [1,2], Larissa Müller Gomes [1,2], Pedro Zanuncio [1,4], Flávio Silva Brandão [1,3] and Angélica Nogueira-Rodrigues [1,2,5,6,*]

1 Oncoclínicas&Co—Medica Scientia Innovation Research (MEDSIR), São Paulo 04542-390, Brazil
2 Brazilian Group of Gynecologic Oncology (EVA), Rio de Janeiro 35500-025, Brazil
3 Department of Oncology, Santa Casa de Belo Horizonte, Belo Horizonte 30150-221, Brazil
4 Department of Radiotherapy, Hospital Beneficência Portuguesa de São Paulo, São Paulo 01323-001, Brazil
5 Department of Medicine, Federal University of Minas Gerais—UFMG, Belo Horizonte 30130-100, Brazil
6 DOM Oncologia, Belo Horizonte 30190-111, Brazil
* Author to whom correspondence should be addressed.

Int. J. Mol. Sci. **2024**, *25*(14), 7742; https://doi.org/10.3390/ijms25147742

https://www.mdpi.com/1422-0067/25/14/7742

ESGO-ESTRO-ESP Guideline for the management of Endometrial Cancer

Nicole Concin

Dept. of Gynaecology & Obstetrics,
Medical University of Innsbruck, Austria
ESGO accredited center for training & advanced ovarian cancer surgery

Dept. of Gynaecology & Gynaecologic Oncology,
KEM, Kliniken Essen-Mitte, Germany
ESGO accredited center for training & excellence center in advanced ovarian cancer surgery

NSGO Annual Meeting / Reykjavik, Iceland / 14th – 16th of June 2023

International Journal of Gynecology & Obstetrics /
Volume 164, Issue 2 / p. 436-459

REVIEW ARTICLE | Open Access

Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies

Ye Yang, Su Fang Wu, Wei Bao

First published: 31 July 2023
https://doi.org/10.1002/ijgo.14969
Citations: 1

https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.14969

Review > Curr Treat Options Oncol. 2022 Aug;23(8):1121-1134.

doi: 10.1007/s11864-022-00993-x. Epub 2022 Jul 6.

Incorporating Molecular Diagnostics into Treatment Paradigms for Endometrial Cancer

Brenna E Swift [1], Lilian T Gien [2 3]

Affiliations + expand

PMID: 35793055 DOI: 10.1007/s11864-022-00993-x

Swift BE, Gien LT. Incorporating Molecular Diagnostics into Treatment Paradigms for Endometrial Cancer. Curr Treat Options Oncol. 2022 Aug;23(8):1121-1134. doi: 10.1007/s11864-022-00993-x. Epub 2022 Jul 6. PMID: 35793055.

Open Access Review

Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection

by Natalia Galant [1], Paweł Krawczyk [1], Marta Monist [2], Adrian Obara [3], Łukasz Gajek [3], Anna Grenda [1,*], Marcin Nicoś [1], Ewa Kalinka [4] and Janusz Milanowski [1]

[1] Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, 20-090 Lublin, Poland
[2] II Department of Gynecology, Medical University of Lublin, 20-090 Lublin, Poland
[3] Institute of Genetics and Immunology GENIM LCC, 20-609 Lublin, Poland
[4] Department of Oncology, Polish Mother's Memorial Hospital-Research Institute, 93-338 Łódź, Poland
* Author to whom correspondence should be addressed.

Int. J. Mol. Sci. **2024**, *25*(11), 5893; **https://doi.org/10.3390/ijms25115893**

Submission received: 17 April 2024 / Revised: 21 May 2024 / Accepted: 27 May 2024 / Published: 28 May 2024

Galant, N.; Krawczyk, P.; Monist, M.; Obara, A.; Gajek, Ł.; Grenda, A.; Nicoś, M.; Kalinka, E.; Milanowski, J. Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection. *Int. J. Mol. Sci.* **2024**, *25*, 5893. https://doi.org/10.3390/ijms25115893

The GEC ESTRO Handbook of Brachytherapy

SECOND EDITION

PART II: CLINICAL PRACTICE

17

Endometrial Cancer

THE GEC ESTRO HANDBOOK OF BRACHYTHERAPY | Part II: Clinical Practice Version 1 - 25/04/2016

MMR-Proficient

Most patients with EC have MMR-proficient (MMRp) tumors, which have limited response to single-agent ICIs (ORR, 3%–14%).[33,38–40] However, recent studies have established the combination of the multikinase inhibitor lenvatinib + pembrolizumab as an effective 2L treatment option. Findings from the phase Ib/II Study 111/KEYNOTE-146 trial in patients with advanced EC demonstrated an ORR at week 24 (ORR_{wk24}) of 38.0%. The ORR_{wk24} was 63.6% for MSI-H tumors (n=11) and 36.2% for microsatellite-stable tumors (n=94). Regardless of MSI status, the median duration of response was 21.2 months, median PFS was 7.4 months, and median OS was 16.7 months in previously treated patients. Responses were seen regardless of PD-L1 expression or histology.[41] These results led to the FDA accelerated approval of lenvatinib + pembrolizumab for advanced EC that is not MSI-H/MMRd and has progressed following prior systemic therapy.

In the confirmatory phase III Study 309/KEYNOTE-775 trial, patients with recurrent EC with measurable disease and one prior platinum-based chemotherapy were enrolled regardless of MMR status. Patients were stratified based on MMR status and randomized 1:1 to lenvatinib + pembrolizumab or investigator's choice of doxorubicin or paclitaxel. The median PFS was longer with lenvatinib + pembrolizumab compared with chemotherapy (MMRp population: 6.6 vs 3.8 months; $P<.001$; overall: 7.2 vs 3.8 months; $P<.001$). The median OS was also longer (MMRp population: 17.4 vs 12.0 months; $P<.001$; overall: 18.3 vs 11.4 months; $P<.001$). PFS and OS analyses in all subtypes, including MMR status, histology, and prior lines of therapy, favored lenvatinib + pembrolizumab; no substantial differences in health-related quality of life scores were appreciated.[21]

Endocrine Therapy

In hormone (estrogen or progesterone) receptor–positive EC, endocrine therapy is a viable treatment option for advanced or recurrent EC. In a translational study of advanced EC tissues from study GOG 119, 40% and 45% of the 45 evaluable tumors were estrogen receptor (ER)–positive and progesterone receptor–positive, respectively.[42] Estrogen and progesterone receptors are typically evaluated with IHC, although timing of when this should be performed is not well established. Current NCCN Guidelines recommend hormone receptor testing for stage III, stage IV, or recurrent endometrioid carcinoma.[22]

Endocrine therapy is generally well tolerated and can be considered in patients with minimal symptoms and low-grade or more indolent disease. A systematic review from 2007 reported that up to 30% of advanced or recurrent ECs respond to endocrine therapy, with the highest response rates in low-grade EC (up to 56% in grade 1/2 endometrioid carcinoma).[43] In the phase II GOG 119 study in advanced EC, alternating tamoxifen and megestrol acetate demonstrated an ORR of 27%, median PFS of 2.7 months, and OS of 14.0 months.[44] Other endocrine therapies include progestational agents alone (medroxyprogesterone acetate or megestrol acetate), aromatase inhibitors, tamoxifen alone, or fulvestrant, a selective ER degrader.[22,45]

Anti-VEGF Therapy

Beyond the combination of bevacizumab with cytotoxic chemotherapy, anti-VEGF therapies have been studied as monotherapy and in combination with other agents in advanced EC. In GOG 229E, bevacizumab monotherapy in previously treated EC was associated with an ORR of 13.5%, and 40.4% of patients were progression-free at 6 months.[46] Lenvatinib monotherapy in a phase II trial in the 2L setting was associated with an ORR of 13.3% and median PFS of 5.6 months.[47]

The NRG-GY012 protocol compared the efficacy of olaparib (PARP inhibitor) monotherapy, cediranib (VEGF receptor TKI) monotherapy, and combination olaparib/cediranib in patients with advanced EC who had received at least 1 prior line of platinum-based chemotherapy and no more than 2 prior lines of chemotherapy; median PFS was 2.0, 3.8, and 5.5 months, respectively.[48] Findings from a randomized phase II trial in recurrent EC demonstrated median PFS for combination nivolumab/cabozantinib (a TKI) and single-agent nivolumab of 5.3 and 1.9 months, respectively; ORRs were 25% and 16.7%, respectively.[49]

Cell Signaling–Targeted Therapy

Cyclin-dependent kinase inhibitors (CDKis) such as palbociclib and abemaciclib function by selectively inhibiting CDK4 and CDK6, which are crucial for the cell cycle G1/S phase transition.[50] The randomized, phase II PALEO trial of letrozole with/without palbociclib demonstrated improved PFS with the combination (8.3 vs 3.0 months; HR, 0.56; *P*=.04).[51] Data from a phase II trial in patients with ER-positive recurrent EC demonstrated an ORR of 30% and median PFS of 9.1 months with abemaciclib + letrozole at a median follow-up of 12.5 months.[52] These studies suggest a role for CDK4/6 inhibitors in subsets of advanced ECs, warranting further investigation, which is the subject of ongoing trials (Table 2).

Wee1 Kinase Inhibitors

Wee1 kinase regulates cell cycle checkpoints of G2/M and S phase. *TP53*-mutant cancers such as serous EC are often disregulated at the G1/S phase checkpoint, allowing for early S phase entry, rendering them more vulnerable to Wee1 inhibition. Adavosertib is a highly selective inhibitor of Wee1 kinase that, in a phase II study in recurrent EC, resulted in an ORR of 30%, median PFS of 6.1 months, and median duration of response of 9 months.[53] Additional Wee1 inhibitors are being evaluated in ongoing studies.

XPO1 Inhibition

Selinexor is an orally available potent inhibitor of XPO1 resulting in retention of tumor suppressor proteins in the nucleus. A phase I open-label study of selinexor with TC in advanced ovarian cancer or EC demonstrated good safety and tolerability.[54] A subsequent phase II study of selinexor monotherapy in advanced EC showed a 35% disease control rate.[55] Results of the randomized phase III SIENDO trial of maintenance selinexor versus placebo following response to TC chemotherapy in EC showed the greatest therapeutic benefit in *p53* wild-type EC, with a 10-month PFS improvement over placebo.[56] The recently opened phase III XPORT-EC trial (NCT05611931) will evaluate selinexor as maintenance therapy after systemic therapy for *p53* wild-type advanced or recurrent EC (Table 2).

Unanswered Questions and Future Directions

Current NCCN Guidelines recommend universal testing for MMR proteins in EC to assess for genetic predisposition to Lynch syndrome and encourage molecular subtyping when available to inform future treatment decisions.[22] Although molecular analysis for all ECs is resource-intensive, molecular subtyping is considered more predictive of outcomes than other risk stratification criteria in patients with early-stage disease and is anticipated to play an increasing role in adjuvant therapeutic decision-making.[57–59]

In advanced and recurrent disease, molecular analysis is essential in informing optimal treatment options, delineating predictive biomarkers, and identifying patients eligible for clinical trials investigating emerging therapeutic options based on molecular drivers of EC subtypes. The refinement of MSI-H/MMRd predictive subgroups (eg, assessment of mutational thresholds and signatures) may identify patients whose disease will not respond or will rapidly progress after an initial response to single-agent ICIs and who could benefit from novel combination strategies. Clinical studies among larger cohorts of patients with Lynch/Lynch-like versus those with sporadic MSI-H disease treated with ICIs are warranted. The potential for response to immunotherapy after prior immunotherapy also warrants investigation, as does delineation of mechanisms of response to ICIs in the minority of responding MMRp ECs.

- **Conclusions**
- Understanding of EC biology has been greatly expanded by modern molecular characterization, which has defined molecularly and clinically distinct EC subtypes. Given the heterogeneity of this malignancy, patients with advanced disease should undergo molecular profiling to optimize treatment strategies and inform clinical trial eligibility. The therapeutic ceiling with traditional chemotherapy has been reached, and we must look to relevant biologic targets to individualize treatment. Although surgical resection or radiation therapy may be appropriate for localized disease, advanced EC requires systemic therapy. Ongoing phase III studies evaluating immunotherapeutic approaches will likely change the standard of care for 1L management of EC, which will necessitate refinement of 2L and beyond management. Although the incidence and number of deaths from EC has increased worldwide, we must advocate for research to improve the quality of life and outcomes for patients with EC.