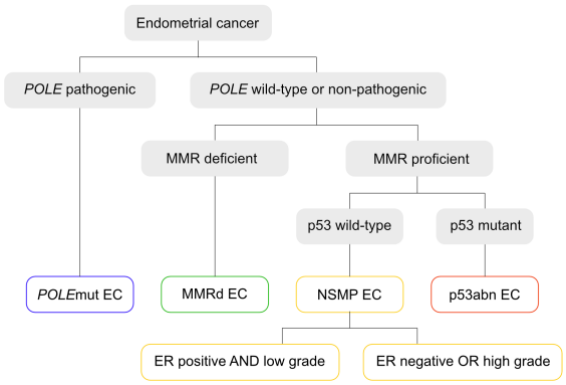
ENDOMETRIAL CANCER

General Overview

- 6th most common female cancer worldwide, Europe 4th (2022)
- Age 65-75
- Risk factors: high BMI, hyperinsulinemia, hypertension, prolonged exposure to unopposed estrogen (nulliparity, infertility with polycystic ovarian syndrome, tamoxifen)
- Symptoms: postmenopausal vaginal blood loss (often early diagnosis)
- > 90% sporadic, 5-10% genetic: Lynch syndrome (risk 10x higher, also risk for colon and ovarian cancer); genetic testing indicated if diagnosis < 50y
- Classification
    - Histological: type 1 (endometrioid) or type 2 (non-endometrioid)
    - Molecular: POLEmut, mismatch repair deficient (MMRd), no specific molecular profile (NSMP), TP53 abnormal (p53abn)
        - Prognostic and therapeutic relevance
        - To determine on biopsy specimen: IHC for MMR-TP53-ER, NGS for POLE(-MMR-TP53)



Staging (FIGO 2023) and Prognosis

- Clinical and gynecological examination
- Transvaginal ultrasound
- MRI: most accurate for determining depth of invasion in myometrium and invasion of cervix
- CT thorax/abdomen: for review of extra-pelvic disease
- FDG-PET-CT: for review of distant metastases in recurrent setting
- Tissue: via D&C, pipelle biopsy - possibly hysteroscopy for representative biopsy
- Prognostic factors: grade, histological subtype, age, stage, myometrial invasion, presence of substantial LVSI, molecular classification

FIGO 2023 classification
Stage 1: Confined to the uterine corpus and ovary **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 types 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 **IB**: Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI **IC**: Aggressive histological types limited to a polyp or confined to the endometrium **Stage 2: 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 of non-aggressive histological types **IIC**: Aggressive histological types with any myometrial involvement **Stage 3: Local and/or regional spread of the tumor of any histological subtype** **IIIA**: Invasion of uterine serosa, adnexa, or both by direct extension or metastasis **IIIA1**: Spread to ovary or fallopian tube (except when meeting stage IA3 criteria) **IIIA2**: Involvement of uterine subserosa or spread through the uterine serosa **IIIB**: Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum **IIIB1**: Metastasis or direct spread to the vagina and/or the parametria **IIIB2**: Metastasis to the pelvic peritoneum **IIIC**: Metastasis to the pelvic or para-aortic lymph nodes or both **IIIC1**: Metastasis to the pelvic lymph nodes **IIIC1i:** Micrometastasis **IIIC1ii:** Macrometastasis **IIIC2:** Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes **IIIC2i:** Micrometastasis **IIIC2ii:** Macrometastasis **Stage 4: Spread to the bladder mucosa and/or intestinal mucosa and/or distant metastasis** **IVA:** Invasion of the bladder mucosa and/or the intestinal/bowel mucosa **IVB:** Abdominal peritoneal metastasis beyond the pelvis **IVC:** Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone
FIGO stage with molecular classification (Stages 1 and 2 after surgical staging) **IAm$_{POLEmut}$**: POLEmut endometrial carcinoma confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type **IICm$_{p53abn}$**: p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

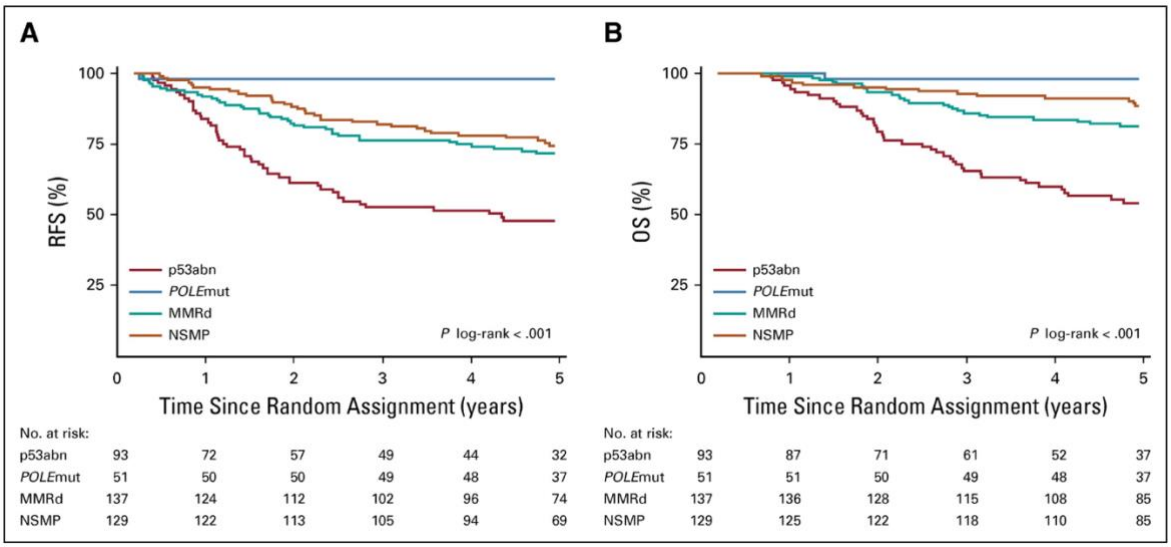
- Prognosis [1]

	Molecular classification				
	POLEmut	**MMRd**	**NSMP low grade and ER+**	**NSMP high grade or ER- ***	**p53abn**
Confined to the uterine corpus					
No myoinvasion, limited to polyp/endometrium	$IAm_{POLEmut}$	IA1/IC^	IA1	IA1/IC^	IA1/IC^
Myoinvasion < 50%, no/focal LVSI	$IAm_{POLEmut}$	IA2 / IIC^	IA2	IA2/IIC^	$IICm_{p53abn}$
Myoinvasion ≥ 50%, no/focal LVSI	$IAm_{POLEmut}$	IB/IIC^	IB	IB/IIC^	$IICm_{p53abn}$
Confined to the uterus (uterine corpus ± cervical invasion)					
Cervical stromal invasion, no/focal LVSI	$IAm_{POLEmut}$	IIA/IIC^	IIA	IIA/IIC^	$IICm_{p53abn}$
Uterine corpus ± cervical invasion, substantial LVSI	$IAm_{POLEmut}$	IIB/IIC^	IIB	IIB/IIC^	$IICm_{p53abn}$
Low-grade endometrioid carcinoma of both the endometrium + ovary					
Myoinvasion < 50%, no/focal LVSI, ovarian tumor pT1a	IA3			IA3*	IA3
Local and/or regional spread beyond uterus					
Spread to ovary or fallopian tube (except for #)	IIIA1	IIIA1			
Involvement of uterine subserosa or spread through uterine serosa	IIIA2	IIIA2			
Metastasis or direct spread to vagina and/or parametrium	IIIB	IIIB			
Metastasis to pelvic peritoneum	IIIC	IIIC			
Metastasis to pelvic lymph nodes	IIIC1	IIIC1			
Metastasis to para-aortic lymph nodes	IIIC2	IIIC2			
Locally advanced					
Invasion of bladder mucosa and/or intestinal mucosa	IVA	IVA			

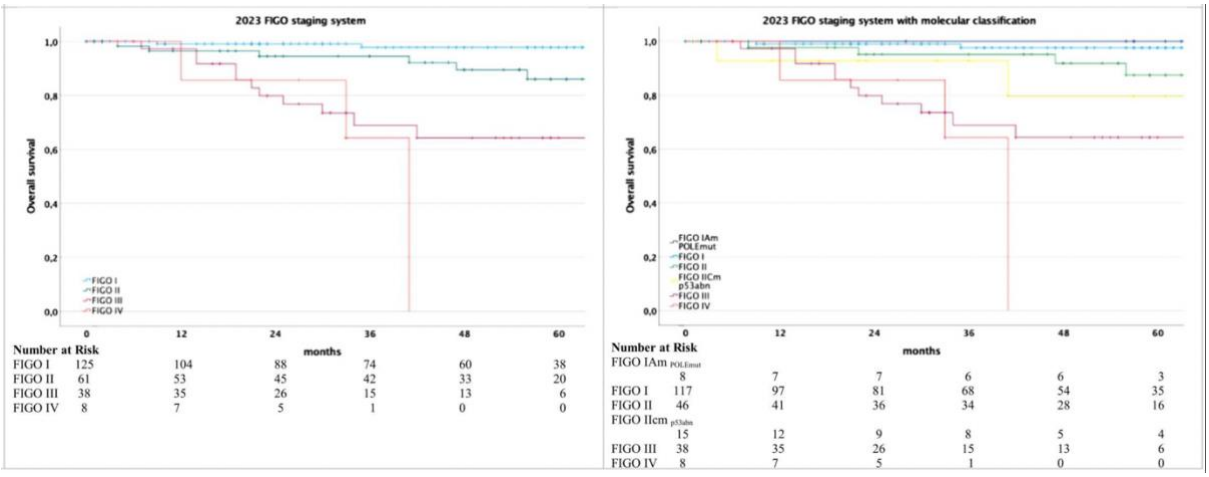
dMMR, mismatch repair deficient; ER, estrogen receptor; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53-abn, p53-abnormal; POLEmut, polymerase epsilon-ultramutated.
^ high-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3), serous and clear cell carcinoma, carcinosarcoma, undifferentiated, mixed, mesonephric-like and gastro-intestinal mucinous type carcinoma
***** the molecular subgroup NSMP high-grade/ER negative consists of either high-grade NSMP or ER-negative NSMP cases. In low-grade endometrioid carcinomas of both endometrium + ovary, only the ER-negative cases of the molecular subgroup NSMP high-grade/ER negative apply.
myoinvasion < 50% + no/focal LVSI + ovarian tumor pT1a
£ overall 5-year risk of any recurrence

Low risk (£ < 8%)	**Intermediate (£ 8-15%)**	**High-intermediate (£ 15-25%)**	**High (£ > 25%)**	**Uncertain (lack of data)**

- Recurrence free survival (A) and overall survival (B) in patients with histologically high-risk endometrial cancer by molecular classification [2]



- Overall survival according to FIGO 2023 classification [3]



Treatment

1. Local and locoregional setting

SURGERY

FIGO STAGE I-II

- Aim: remove macroscopic tumor, examine for microscopic metastases, staging
- Total hysterectomy with bilateral salpingo-oophorectomy via minimally invasive technique [4]
    - + staging infracolic (total or partial) omentectomy in serous carcinoma, carcinosarcoma, and undifferentiated carcinoma
    - consider ovary preservation in premenopausal patients with stage IA1 or IA2 disease and absence of genetic risk factors
        - low risk of recurrence by molecular classification and < 45 years: bilateral salpingectomy and ovarian preservation
        - high risk of recurrence by molecular classification or ≥ 45 years: bilateral salpingo-oophorectomy
- Sentinel lymph node biopsy (SLNB) [5–8]

    - Staging SLNB in all patients with presumed uterus-confined disease
        - Indocyanine green with cervical injection is preferred technique
        - Pathologic ultrastaging of sentinel lymph nodes is recommended
    - Sampling lymphadenectomy
        - If sentinel is not detected on either pelvic side, indicated in high-intermediate and high-risk disease, and to consider in presumed intermediate-risk disease
- If contra-indication to undergo surgery
    - Vaginal hysterectomy + BSO if minimally invasive surgery is contra-indicated
    - Definitive curative radiotherapy
        - High-grade tumors and/or deep myometrial invasion: EBRT + brachytherapy
        - Low-grade tumors: consider brachytherapy alone
    - Systemic therapy if unfit for radiotherapy
- Fertility preservation
    - Consider if atypical hyperplasia, endometrioid intra-epithelial neoplasia (AH/EIN), or grade 1 endometrioid carcinoma without myometrial invasion and without genetic risk factors

FIGO STAGE III-IV

- Consider cytoreductive surgery with goal of complete resection and after completing preoperative staging in all subtypes, without systematic LNE
- Primary systemic therapy if upfront surgery is not feasible due to local extent of the disease (not because of unresectable disseminated disease, in this case see treatment for advanced setting below), consider delayed surgery in case of good response

ADJUVANT TREATMENT

LOW RISK GROUP

- No adjuvant treatment

INTERMEDIATE RISK GROUP

- Vaginal brachytherapy (VBT) to reduce vaginal recurrence [9–11]
    - Consider omitting, especially if <60y and/or low grade: risk of relapse higher (14%) but no OS difference due to successful treatment of relapse

HIGH-INTERMEDIATE RISK GROUP

- Adjuvant EBRT is recommended to reduce locoregional recurrence [12,13]
- Adjuvant VBT instead of EBRT is an alternative option, especially for those who underwent lymph node staging and are pN0
- Omission of any adjuvant therapy on a case-by-case decision, especially if pN0, without substantial LVSI and low-grade disease

HIGH RISK GROUP

- Adjuvant EBRT with concomitant and adjuvant chemo [14]
    - Cisplatin 50mg/m^2 q3w 2x during radiotherapy (week 1 and week 4), carboplatin AUC 5 + paclitaxel 175 mg/m^2 q3w 4x after radiotherapy (from week 8 onwards)
- Consider sequential chemotherapy and EBRT [15]
    - Doxorubicin/epirubicin 50mg/m^2 + cisplatin 50mg/m^2 q4w 4x
    - Paclitaxel 175mg/m^2 + epirubicin 60mg/m^2 4x

  - Doxorubicin 40mg/m^2 + carboplatin AUC 5 4x
  - Paclitaxel 175mg/m^2 + carboplatin AUC 5-6 q3w 4x
  - Doxorubicin 60mg/m^2 + cisplatin 50mg/m^2 q3w 3x
- Consider chemotherapy alone [16]
  - Carboplatin AUC 6 + paclitaxel 175 mg/m^2 q3w 6x
  - ± brachytherapy
- Consider adjuvant chemotherapy + pembrolizumab ± EBRT for stage IIIm-IVAm MMRd endometrial cancer [17]

2. Advanced or recurrent setting

LOCAL THERAPY

- Radiotherapy
  - Isolated vaginal or locoregional recurrence if not previously irradiated: combination of EBRT with VBT
  - Consider adding systemic therapy, especially in case of pelvic recurrence
- Surgery
  - Isolated local recurrence at vaginal apex: surgery and/or radiotherapy
  - Isolated local recurrence in an irradiated area: consider exenteration if no metastases are present elsewhere, only if complete resection of macroscopic disease seems achievable with acceptable morbidity
  - Role of adjuvant chemotherapy is unclear: assess on an individual basis

SYSTEMIC THERAPY

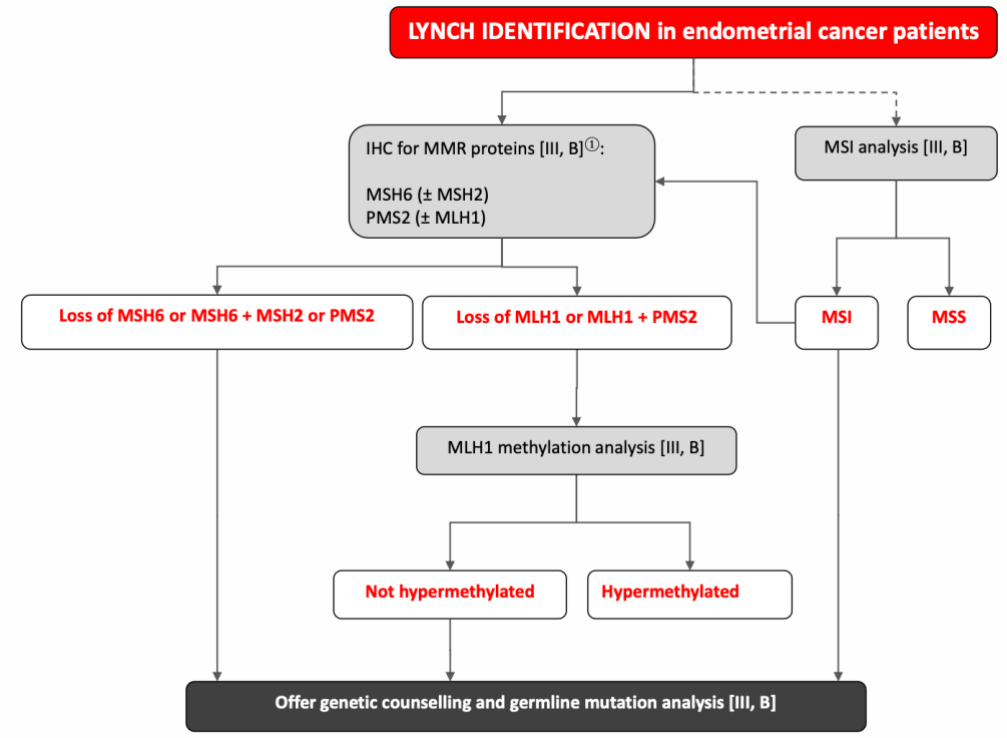
- pMMR subtype
  - 1st line:
    - carboplatin + paclitaxel + pembrolizumab q3w x6, followed by pembrolizumab for a total of 2 years (prespecified pMMR and dMMR cohort, PFS, OS not mature, crossover) – ESMO MCBS score 4 [18]
    - carboplatin AUC 5-6 + paclitaxel 175 mg/m^2 + durvalumab q3w x6, followed by durvalumab + olaparib until progression (approval based on pre-specified, exploratory subgroup analysis in pMMR all histologies, PFS gain 5.5mo) – ESMO MCBS score 4 [19]
  - 2nd line: pembrolizumab + lenvatinib after platin-based chemotherapy (if not received prior immunotherapy) – ESMO MCBS score 4 [20]
  - 3rd line and further: participation in clinical trials, weekly paclitaxel, weekly doxorubicin, consider platinum-rechallenge if recurrence > 6 months after last platinum
- dMMR subtype
  - 1st line:
    - carboplatin + paclitaxel + pembrolizumab, followed by pembrolizumab for a total of 2 years (prespecified pMMR and dMMR cohort, PFS, OS not mature, crossover) – ESMO MCBS score 4 [18]
    - carboplatin + paclitaxel + dostarlimab, followed by dostarlimab for a total of 3 years (PFS, OS in overall population, OS prespecified exploratory endpoint in dMMR population) – ESMO MCBS score 4 [21,22]
    - carboplatin + paclitaxel + durvalumab, followed by durvalumab until progression (PFS, waiting for secondary endpoint OS and QoL data) – ESMO MCBS score 4 [19]
- Hormonal therapy

    - Preferred first-line treatment in low-grade, ER positive, low volume/asymptomatic advanced or slowly growing recurrent tumors
    - Also to consider if poor PS or in 2nd and 3rd line, predictive factors for response: low grade endometrioid histology, ER/PR status (but also response in ER/PR negative tumors, status may differ between primary tumor and metastasis)
    - Standard: progestin - medroxyprogesterone acetate 200mg and megestrol acetate 160mg (ORR 23.3%, mPFS 2.0mo, mOS 9.2mo)
    - Alternative: tamoxifen, fulvestrant, aromatase inhibitors [23]
- HER2-positive
    - trastuzumab via **samples** based on phase 2 study [24]: any line, HER2-positive serous endometrial cancer; arm A: carboplatin+paclitaxel, arm B: carboplatin+paclitaxel + trastuzumab; OS B > A: 29.6 vs 24.4 mo. Use preferably in early line.

Follow-up

- General
    - Relapse usually happens in first 3 years after initial treatment, mostly symptomatic
    - CT-scan detects only 15%, routine use not recommended
    - CA 125 low sensitivity and specificity, not recommended
    - Patient education regarding signs and symptoms of relapse is crucial
    - Promote regular physical exercise, healthy diet, weight management
- Low-risk group
    - Year 1-2: every 6 months with clinical and gynecological examination
    - Year 3-5: every year with clinical and gynecological examination
- Intermediate to High-risk group
    - Year 1-3: every 3 months with clinical and gynecological examination
    - Year 4-5: every 6 months with clinical and gynecological examination
    - CT to be considered, especially if lymph node positive: every 6 months in first 3 years

Addendum: Lynch identification in patients with endometrial cancer



References

1 Concin, N. *et al. Lancet Oncol.* 26, e423–e435 (2025)

2 Lé On-Castillo, A. *et al. J Clin Oncol* 38, 3388–3397 (2020)

3 Schwameis, R. *et al. Eur. J. Cancer* 193, 113317 (2023)

4 Janda, M. *et al. JAMA* 317, 1224–1233 (2017)

5 Cusimano, M. C. *et al. JAMA Surg.* 156, 157–164 (2021)

6 Persson, J. *et al. Eur. J. Cancer* 116, 77–85 (2019)

7 May, K. *et al. Cochrane Database Syst. Rev.* CD007585 (2010)

8 Rossi, E. C. *et al. Lancet Oncol.* 18, 384–392 (2017)

9 Nout, R. A. *et al. The Lancet* 375, 816–823 (2010)

10 Sorbe, B. *et al. Int. J. Radiat. Oncol. Biol. Phys.* 82, 1249–55 (2012)

11 Wortman, B. G. *et al. Br. J. Cancer* 119, 1067–1074 (2018)

12 Creutzberg, C. L. *et al. Int. J. Radiat. Oncol. Biol. Phys.* 81, (2011)

13 Keys, H. M. *et al. Gynecol. Oncol.* 92, 744–751 (2004)

14 de Boer, S. M. *et al. Lancet Oncol.* 19, 295–309 (2018)

15 Hogberg, T. *et al. Eur. J. Cancer* 46, 2422–2431 (2010)

16 Matei, D. *et al. New England Journal of Medicine* 380, 2317–2326 (2019)

17 Van Gorp, T. *et al. Ann. Oncol.* 35, 968–980 (2024)

18 Eskander, R. N. *et al. N. Engl. J. Med.* 388, 2159–2170 (2023)

19 Westin, S. N. *et al. Journal of Clinical Oncology* 42, 283–299 (2024)

20 Makker, V. *et al. N. Engl. J. Med.* 386, 437–448 (2022)

21 Mirza, M. R. *et al. New England Journal of Medicine* 388, 2145–2158 (2023)

22 Powell, M. A. *et al. Annals of Oncology* 35, 728–738 (2024)

23 Mileshkin, L. *et al. Gynecol. Oncol.* 154, 29–37 (2019)

24 Fader, A. N. *et al. Clinical Cancer Research* 26, 3928–3935 (2020)