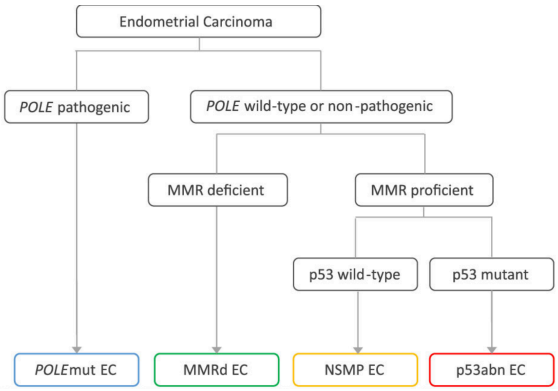
ENDOMETRIAL CANCER

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, 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

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 type limited to an endometrial polyp OR confined to the endometrium **IA2:** Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI **IA3:** Low-grade endometrioid carcinomas limited to the uterus and ovary **IB**: Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI

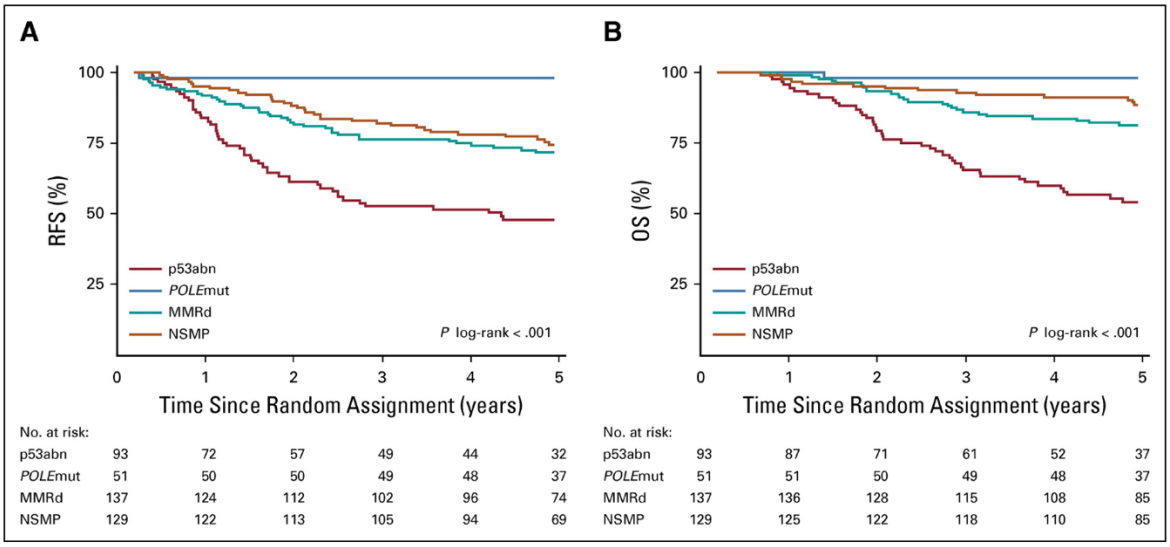
IC: Aggressive histological types limited to a polyp or confined to the endometrium
Stage 2: Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA: Invasion of the cervical stroma of non-aggressive histological 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

- Prognosis

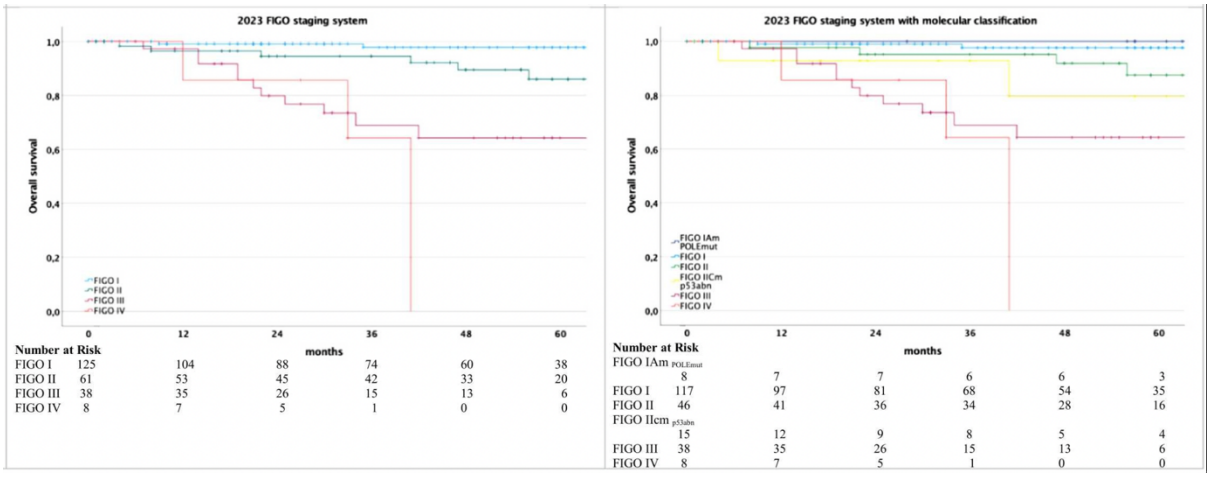
Prognostic risk groups[a]	
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[a] and NSMP) and no or focal LVSI Stage I/II POLEmut cancer; for stage III POLEmut cancers[b]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type* and/or 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[c]

dMMR, mismatch repair deficient; EC, endometrial cancer; G1-G3, grade 1-3; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MSI-H, microsatellite instability high/hypermutated; NSMP, no specific molecular profile; p53-abn, p53-abnormal; POLEmut, polymerase epsilon-ultramutated.
a dMMR and MSI-H: Both terms identify a similar EC population. Identification of a defective mismatch repair pathway by IHC (i.e. dMMR) or sequencing to determining microsatellite instability (i.e. MSI-H).
b POLEmut stage III might be considered as low risk. Nevertheless, currently there are no data regarding safety of omitting adjuvant therapy.
c Stage III-IVA if completely resected without residual disease; table does not apply to stage III-IVA with residual disease or for stage IV.
* serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed

- Prognostic factors: grade, histological subtype, age, stage, myometrial invasion, presence of substantial LVSI, molecular classification
- Recurrence free survival (A) and overall survival (B) in patients with histologically high-risk endometrial cancer by molecular classification [1]



- Overall survival according to FIGO 2023 classification [2]



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 [3]
  - + staging infracolic omentectomy in stage I serous endometrial carcinoma, carcinosarcoma, and undifferentiated carcinoma
  - consider ovary preservation in premenopausal patients with stage IA G1 endometrioid EC if no genetic risk factors
- Systemic lymphadenectomy (LNE) / sentinel node biopsy (SNB) [4–7]
  - Staging SNB indicated in low-risk/intermediate-risk disease
    - Pathologic ultrastaging of sentinel lymph nodes is recommended

    - LNE indicated in high-intermediate-risk and high-risk disease, SNB is an alternative in stage I/II
        - If sentinel is not detected on either pelvic side, side-specific systematic lymphadenectomy is indicated
        - If peroperative positive pelvic lymph nodes are present, do para-aortic lymphadenectomy to the renal vessels [8]
- If contra-indication to undergo surgery
    - 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, 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: risk of relapse higher (14%) but no OS difference due to successful treatment of relapse
- FIGO IA p53-abn without myometrial invasion or restricted to a polyp: not included in trials, case-by-case decision

HIGH-INTERMEDIATE RISK GROUP

- pN0 / cN0-pNx (no lymph node staging performed)
    - Adjuvant EBRT to reduce locoregional recurrence [12,13]
        - pN0: consider
        - cN0-pNx: recommended, especially for substantial LVSI
        - and/or for stage II
    - Adjuvant VBT instead of EBRT
        - pN0: recommended
        - cN0-pNx: consider if no substantial LVSI or stage II G1 endometroid carcinoma
    - Consider adding (concomitant or sequential) chemotherapy, especially if G3 and/or substantial LVSI [14,15]
        - EBRT: 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)

        - VBT: sequential paclitaxel 175mg/m^2 + carboplatin AUC 6 q3w 3x
    - Omission of any adjuvant therapy on a case-by-case decision

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 [16]
    - 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 [17]
    - Carboplatin AUC 6 + paclitaxel 175 mg/m^2 q3w 6x

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 AUC 5-6 + paclitaxel 175 mg/m^2 + durvalumab q3w x6, followed by durvalumab + olaparib (approval based on pre-specified, exploratory subgroup analysis in pMMR all histologies, PFS gain 5.5mo, olaparib via **MNP**) [18]
    - 2nd line: pembrolizumab + lenvatinib after platin-based chemotherapy if not received prior immunotherapy [19]
    - 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 + dostarlimab, followed by dostarlimab (PFS, OS in overall population, OS prespecified exploratory endpoint in dMMR population) [20,21]
        - carboplatin + paclitaxel + durvalumab, followed by durvalumab (PFS, waiting for secondary endpoint OS data) [22]
    - after prior treatment with a platinum-containing therapy at any treatment phase: pembrolizumab monotherapy (not if received prior dostarlimab) [23,24]

- Hormonal therapy
  - 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)
  - To consider if poor PS or in 2nd and 3rd line
  - Standard: progestin - medroxyprogesterone acetate 200mg and megestrol acetate 160mg (ORR 23.3%, mPFS 2.0mo, mOS 9.2mo)
  - Alternative: tamoxifen, fulvestrant, aromatase inhibitors [25]
- HER2-positive
  - trastuzumab via **samples** based on phase 2 study [26]: 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

What's new

- Dostarlimab monotherapy after progression on platinum-based chemotherapy in MMRd subtype, EMA label, not reimbursed in Belgium [27]

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