Understanding of new FIGO staging of endometrium

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Revised FIGO staging of endometrial cancer

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SPECIAL ARTICLE

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FIGO staging of endometrial cancer: 2023

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to better define prognostic groups and create substages that indicate more appropriate surgical, radiation, and systemic therapies

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 involvement
IIIC1	Pelvic node involvement
IIIC2	Paraaortic node involvement
IVA	Tumor invasion into bladder or bowel mucosa
IVB	Distant metastases (including abdominal metastases) or inguinal lymph node involvement

2009 FIGO Staging Grade, Mm inv

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

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

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage IAm$_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICm$_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

2023 FIGO Staging Grade, Mm inv, Histologic type, LVSI, Mol classification, actual prognosis

Brief summary from 2023 FIGO staging

- "Challenges and opportunities for gynecologic onocologic pathologists"

- Notable points
  - Extent of LVSI
  - Size of LN metastasis
  - Synchronous endometrial and ovarian endometrioid carcinoma
  - Integrating molecular classification

Histologic type : Central feature of new staging

Non-aggressive	Aggressive
low-grade (grades 1 and 2) endometrioid carcinoma (EEC)	**high-grade EEC (grade 3)** Serous carcinoma (SC) clear cell carcinoma (CCC) mixed carcinoma (MC) undifferentiated carcinoma (UC) carcinosarcoma (CS) Other unusual types, such as mesonephric-like gastrointestinal type mucinous carcinoma

- **High-grade EEC (grade 3)** is a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that **benefits most from applying molecular classification.**
  - POLEmut : excellent prognosis
  - p53abn : bad prognosis
  - NSMP (esp, ER-) : bad prognosis
  - MMRd : grade does not matter
- For practical purposes and **to avoid undertreatment** of patients, if the molecular classification was unknown, high-grade EECs were grouped together with the aggressive histological types in the actual FIGO classification.

Tumor Grade

- Binary grading system of WHO Classification
  - Low-grade : Grade 1 and Grade 2 EECs
  - High-grade : Grade 3 ECCs, serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are considered high-grade
- Three-tiered system is still of value in patients requesting fertility-preserving strategies
- Grading is especially important in NSMP endometrioid cancers.
- MMRd and *POLEmut* endometrioid cancers can seem high-grade because of their frequent mutations.

Myometrial Invasion

- It is recommended that the assessment of the percentage of myometrium involved should be expressed as the percentage of the overall myometrial thickness infiltrated by carcinoma using three categories: **none; <50%; or ≥50%.**

Lymphovascular Space invasion (LVSI)

- Evaluation of extent of LVSI
  - "Substantial" or "extensive" LVSI vs. "focal" or "no" LVSI
  - WHO 2020 recommendation: ≥5 vessels on a single H&E glass slide
- Paucity of data on sub-criteria for prognosis and survival
  - 3-4 counts on a single slide → *advisable to document such findings for future research*
- Mimickers, such as a microcystic elongated and fragmented (MELF) pattern of myometrial invasion and retraction artifacts
  - Challenge in distinguishing true LVSI from its artifactural mimics

Adnexal Involvement

- Ovarian metastasis vs synchronous primary tumors
- In the case of high-grade tumors, ovarian involvement is almost always categorized as metastatic.
- for low-grade EECs, the situation is complex. Recent molecular studies have shown that there is a clonal relationship between the endometrial and ovarian tumor in the vast majority of cases, suggesting that the tumor arises in the endometrium, and secondarily extends to the ovary.
- the category of Stage IA3 when the following criteria are met in a low-grade EEC
  - (1) no more than superficial myometrial invasion is present (<50%);
  - (2) the absence of substantial LVSI;
  - (3) the absence of additional metastases;
  - (4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/breach (equivalent to pT1a).
- Tubal involvement
  - IIIA1
  - DDx from serous tubal intraepithelial carcinoma (SEE-FIM protocol & IHC and molecular pathology)
- Intraluminal tubal floating tumor fragment, positive washing cytology : not considered for staging purpose

Synchronous endometrial and ovarian tumors

- Synchronous endometrial and ovarian endometrioid carcinoma
- Traditionally, low-grade tumors have been considered as dual primary carcinomas, associated with a favorable prognosis.
- Recent molecular studies, however, have suggested that such tumors in the uterine corpus and the ovary are clonal, indicative of metastasis from one site to the other, typically from the endometrium to the ovary
  - These clonally related tumors, though likely representative of metastasis from the endometrium, generally have an excellent prognosis.
  - This leads to concerns about potential overtreatment through the unnecessary application of adjuvant therapy, given that they would technically qualify as stage IIIA endometrial carcinomas prior to FIGO 2023.

Synchronous endometrial and ovarian tumors

- WHO 2020 guidelines: these two tumors as synchronous primary neoplasms when following 4 criteria are met:
  - Both tumors are low-grade
  - Less than 50% myometrial invasion
  - No other sites are involved
  - No substantial LVSI at any location.

- The FIGO 2023 staging system incorporated this approach with a new designation, stage IA3.
  - Explicitly excludes stage IA3 when following features are identified → remain as stage IIIA1, warranting the standard adjuvant treatment
    - Adnexal involvement
    - > 50% myometrial invasion
    - Substantial LVSI
    - Bilateral ovarian involvement
    - Capsular rupture
    - Presence of additional metastatic lesions are present

Q. But how about low-grade EC with 60% myometrial invasion without any metastasis?

Uterine Serosal Involvement

- Defined as a tumor reaching submesothelial fibroconnective tissue or the mesothelial layer, regardless of whether tumor cells may or may not be present on the serosal surface of the uterus

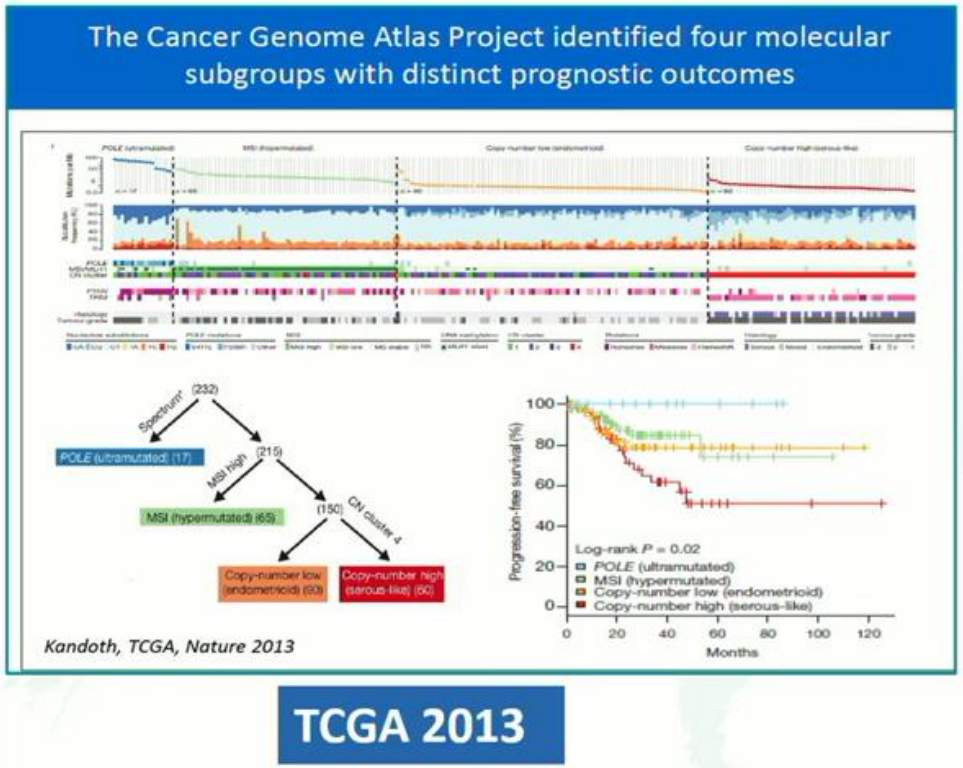
Lymph Node Status

- Macrometastases are larger than 2 mm,
- Micrometastases are 0.2–2mm in size and/or more than 200 cells, and
- Isolated tumor cells are up to 0.2 mm in size and up to 200 cells.
- Isolated tumor cells does not upstage a carcinoma.
- Ultrastaging is recommended for the analysis of sentinellymph nodes.

Lymph Node Status

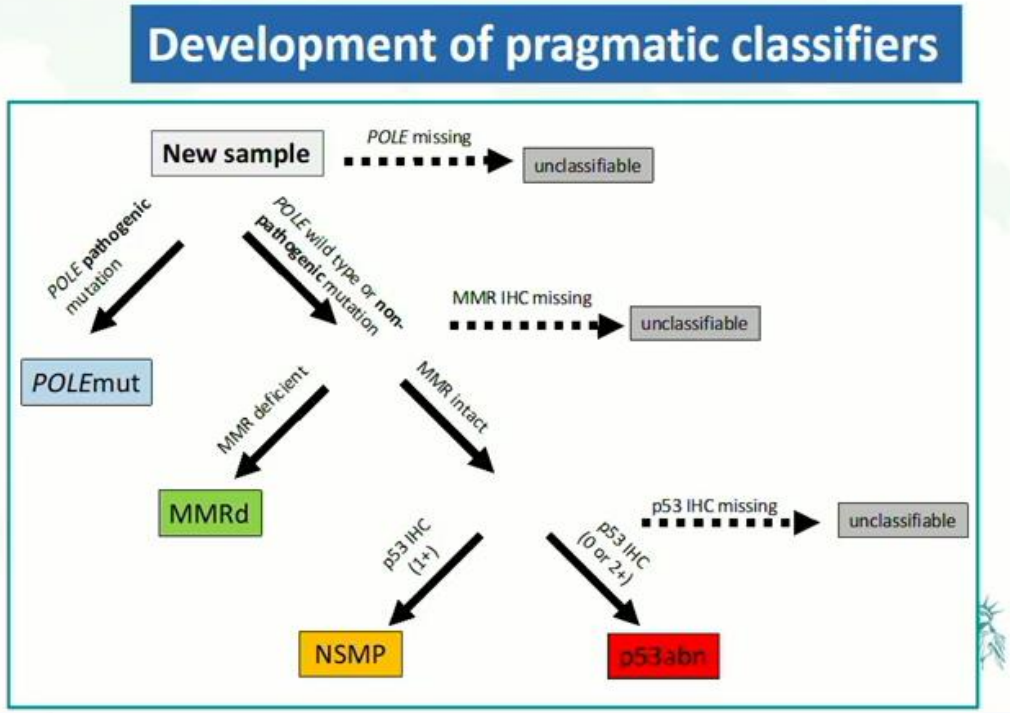
- Low-volume metastasis (LVM): isolated tumor cell (ITCs), micrometastasis
  - Approximatrely 8% increase in nodal positivity over standard pathologic staging
  - Better prognosis than macrometastasis (>2mm)
  - No significant differences in terms of recurrence and survival rates
  - Clear benefits of FIGO 2023 system over Figo 2009 system remain challenging, as these cases are currently treated as stage IIIC disase in real-world clinical practice.
- Sentinel lymph node (SLN) ultrastaging
  - Evidences on superiorty of SLN over standard lymphadenectomy are growing, with adoption of molecular classification for more accurate risk stratification, compared to conventional histology.

Molecular Classification of Endometrial Cancer



TCGA 2013

- Simplified TCGA-surrogate Approach
  - three immunohistochemical markers (p53, MSH6, and PMS2)
  - one molecular test (analysis for pathogenic *POLE* mutations)



Molecular Classification

Molecular classification – When feasible, the addition of molecular subtype to staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all endometrial cancer cases for prognostic risk-group stratification and as potential influencing factors of adjuvant treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen.

- Good prognosis-- pathogenic *POLE* mutation (*POLEmut*) De-escalate Adj Tx
- Intermediate prognosis: mismatch repair deficiency (MMRd) /microsatellite instability and no specific molecular profile (NSMP)
- Poor prognosis-- p53 abnormal (p53abn) Intensify Adj Tx

- Multiple classifier

Molecular Classification

When molecular classification is known—

- **FIGO Stages I and II—based initially on surgical/ anatomical and histological findings, should then be modified by the inclusion of molecular classification, and a subscript ("m" for molecular classification) is added to denote this addition as shown below.**
- **FIGO Stage III—stage is based on surgical/ anatomical findings, and stage category is not modified by molecular profiling; however, when molecular classification reveals p53 abnormality, it should be recorded as Stage $III_{m\text{-}p53abn}$ for purposes of data collection.**
- **FIGO Stages IV—based on the surgical/ anatomical findings and stage category is not modified by molecular profiling.**

Molecular Classification

Molecular Finding	Stage Designation
*POLE*mut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histologic type	Stage $IA_{m\text{-}POLEmut}$
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 histologic type	Stage $IIC_{m\text{-}p53abn}$

Molecular Classification

- Challenges in real-world practice for POLE mutations
- Prerequisite for molecular sequencing to identify pathologic POLE mutations
  - No significant benefits in conditions that:
    - Endometrial serous carcinoma: most fall into the p53abn group
    - Mesonephric-like adenocarcinoma: no reported benefit of POLEmut
    - Non-aggessive or low-grade EC with p53wt and/or pMMR
    - "Very-low risk" EC (G1/G2 grade, endometrioid, pMMR, p53wt, stage IA, LVSI-)
- POLE mutation analysis is advisable to avoid misclassification into the p53abn and MMRd groups
- Pathogenic POLE mutations
  - Location within the exonuclease domain and association with an ultrahigh tumor mutation burden (>100 mut Mb)
  - Quantitiatve hotspot PCR assay as an alternative of NGS: e.g. QPOLE (Van den Heerik et al)

Molecular Classification

- Pathogenic POLE mutations in endometrial carcinoma as per TCGA data, compiled following the study by León-Castillo et al.

Protein Change	No. of Cases	Nucleotide Substitution	Exon	MSI-H Cases (%)	Mutation Recurrence in EC	Mutation Recurrence Pan-Cancer	No. of "Benign" Results by In Silico Tools	POLE Score	EDM	Signature 10 Contribution
P286R	21	c.857C>G	9	1 (4.8)	Recurrent	Recurrent	0	5–6	Y	0.225–0.978
V411L	13	c.1231G>T/C	13	1 (7.7)	Recurrent	Recurrent	1	4–6	Y	0.000–0.751
S297F	3	c.890C>T	9	2 (66.7)	Recurrent	Recurrent	0	5–6	Y	0.123–0.611
S459F	2	c.1376C>T	14	0 (0)	Recurrent	Recurrent	1	5–6	Y	0.940–0.955
A456P	2	c.1366G>C	14	0 (0)	Recurrent	Recurrent	0	5–6	Y	0.277–0.837
F367S	2	c.1100T>C	11	2 (100)	Recurrent	Recurrent	0	6	Y	0.095–0.100
L424I	2	c.1270C>A	13	2 (100)	Recurrent	Recurrent	1	5 or 3	Y	0.000–0.000
M295R	1	c.884T>G	9	1 (100)	Recurrent	Recurrent	0	6	Y	0.785
P436R	1	c.1307C>G	13	0 (0)	Recurrent	Recurrent	0	6	Y	0.230
M444K	1	c.1331T>A	13	0 (0)	Recurrent	Recurrent	0	5	Y	1.000
D368Y	1	c.1102G>T	11	1 (100)	Novel	Recurrent	0	4	Y	0.042

EDM: exonuclease domain mutations; Y = yes; N = no.

Zheng et al (2023)

Molecular Classification

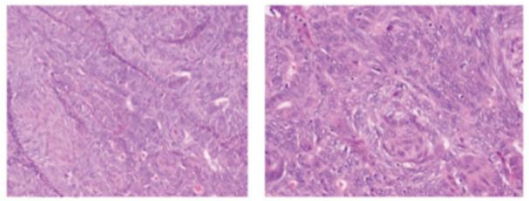
- Questions remaining

1. Implications of additional molecular markers
   - For all molecular subtype (universal)?
   - For a specific group only?
     - L1CAM overexpression: no prognostic value in p53abn, potential for NSMP group
     - Clinicopathological and molecular parameters do not add value or stratify outcomes for patients with POLEmut EC but do for those with NSMP
2. "Actionable" molecular markers?
3. Additional costs vs. benefit?

Molecular Classification

Jamieson et al (2023)

Potential molecular candidate for NSMP



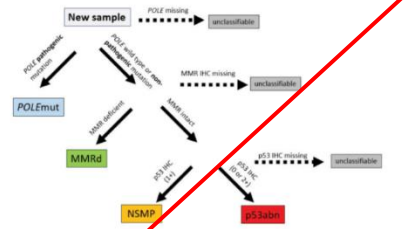
Endometrial Biopsy or Curettage

↓

Pathology + Molecular Classification

↓

Impact surgical decision /staging



POLEmut

- Early ~90% → De-escalation e.g., surgery only
- Advanced ~10% → ? De-escalation ? Radiation only

Clinicopathologic and molecular parameters; e.g., LVI, grade, myoinvasion, L1CAM do not add prognostic or predictive stratification

Adjuvant Clincal Trials

PORTEC-4a (de-escalation)
RAINBO Blue (de-escalation)
TAPER (de-escalation)

MMRd

Adjuvant Radiation

? No additional benefit from chemotherapy

- Loss of MSH6, MSH2, PMS2 → Hereditary Cancer Referral → Consider ICB
- Loss of MLH1
  - Not Methylated → Hereditary Cancer Referral → Consider ICB
  - Methylated → ? Less response to ICB ? Pembro + Lenvat

Further stratified by MLH1 and immune profile?

Adjuvant Clincal Trials

NRG GY 020 (+ICB; pembrolizumab)
RAINBO Green (+ICB; durvalumab)
ADELE Trial (+ICB; tislelizumab)

NSMP

Additional Stratification

- LVI
- Grade
- ER/PR
- L1CAM?
- *CTNNB1?*
- Immune, e.g., CD8?

- Highly Favourable
  - De-escalation
  - Vault brachy
  - Endocrine therapy
- Unfavourable
  - ?Chemo RT
  - ? Pembro + Lenvat

Clinicopathologic parameters do add prognostic and possible predictive stratification

Adjuvant Clincal Trials

RAINBO Orange (+endocrine therapy)
TAPER (de-escalation)

p53abn

- Stage IA No myoinvasion
  - ?Surgery only
  - ?Vault brachy
  - ?ChemoRT
- Stage IA with myoinvasion/Stage IB+ → Significant benefit from chemotherapy
  - HRD (20-25%) PARPi
  - HER2 (20-25%) Anti-HER2 Rx
  - CCNE1 (20-30%) Wee1-i
  - Pembro + Lenvat (50% response in serous)

Aggressive tumors regardless of grade and histotype

Molecular parameters for predictive stratification

Adjuvant Clincal Trials

RAINBO Red (+PARPi; olaparib)
CAN-STAMP (+PARPi; niraparib)
NRG GY 026 (+HER2; trastuzumab/pertuzumab)

Molecular classification based treatment

PORTEC-4a

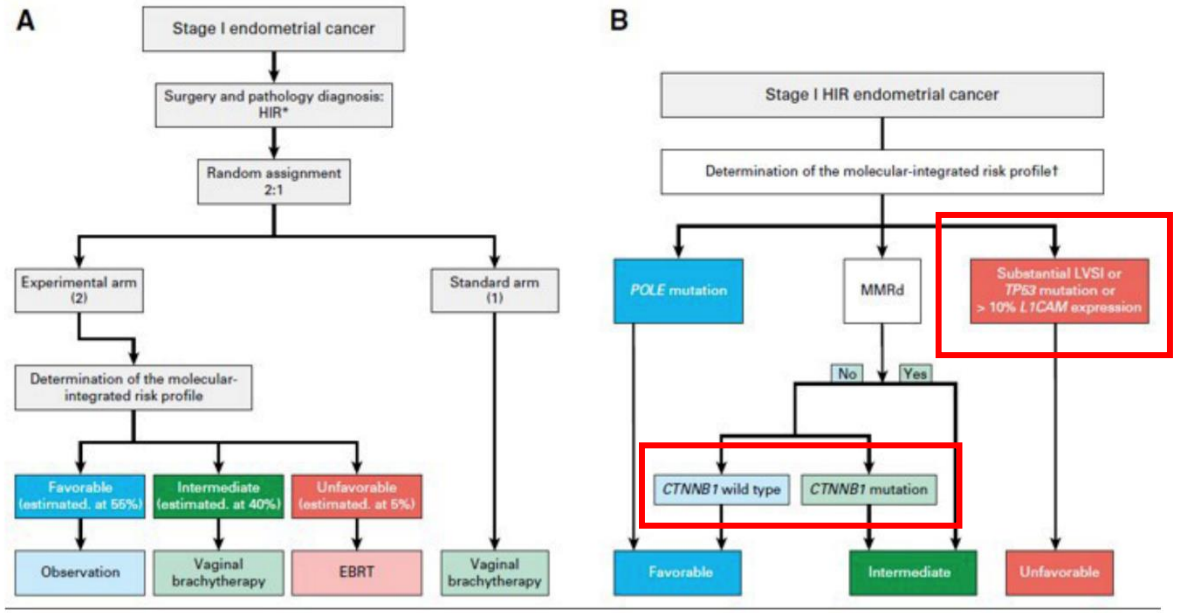


Figure 1 Study design PORTEC-4a trial. Reprinted from 'Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: evaluation of the pilot phase of the PORTEC-4a trial' by Wortman et al., 2018, *Gynecologic Oncology* 151; 69–75. A: trial design of the PORTEC-4a trial; B: decision tree for the molecular-integrated profile; *CTNNB1*, β-catenin; EBRT, external beam radiotherapy; LVSI; lymph-vascular space invasion; HIR, high-intermediate risk; L1-CAM, L1-cell adhesion molecule; *POLE*, polymerase-ε * stage I (with invasion) disease, grade 3 tumor; stage IB disease, grade 1 or 2 tumor, with either age 60 years or older or substantial LVSI; stage IB disease, grade 3 tumor, without LVSI; or stage II (microscopic) disease, grade 1 tumor.

van den Heerik et al (2020)

Molecular classification based treatment

RAINBO

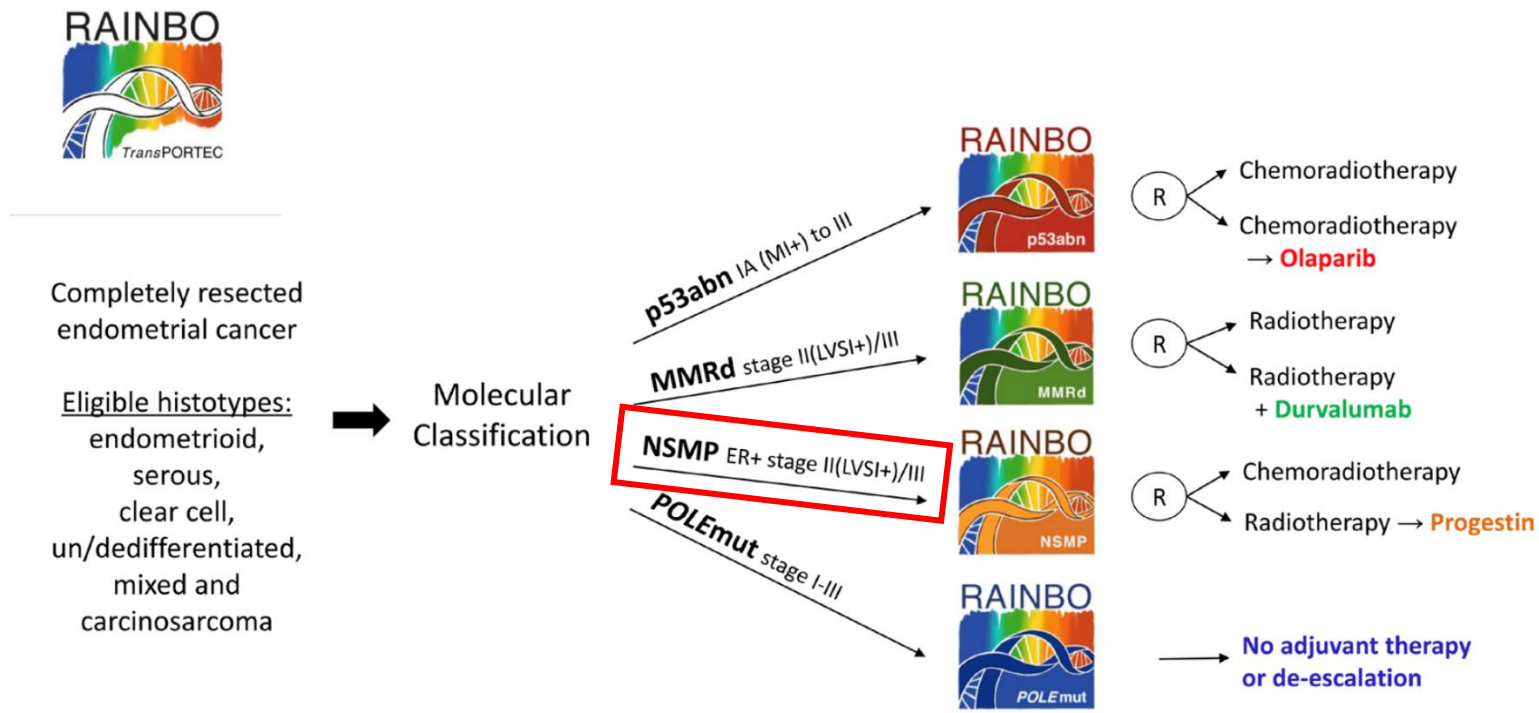


Figure 1 Design of the RAINBO program. ER, estrogen receptor status; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; p53abn, p53 abnormal; POLEmut, DNA polymerase-ε mutated; R, randomization; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features.

RAINBO Research Consortium (2022)

2023 FIGO staging of endometrial cancer

- Endometrial cancer is surgically staged and pathologically examined. In all stages, the grade of the lesion, the histological type and LVSI must be recorded.

- If available and feasible, **molecular classification testing** (POLEmut, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions.

2023 FIGO staging of endometrial cancer

- In early endometrial cancer, the standard surgery is a total hysterectomy with bilateral salpingo-oophorectomy via a minimally invasive laparoscopic approach. Staging procedures include infracolic omentectomy in specific histological subtypes, such as serous and undifferentiated endometrial carcinoma, as well as carcinosarcoma, due to the high risk of microscopic omental metastases. Lymph node staging should be performed in patients with intermediate-high/high-risk patients. Sentinel lymph node (SLN) biopsy is an adequate alternative to systematic lymphadenectomy for staging proposes. SLN biopsy can also be considered in low−/low-intermediate-risk patients to rule out occult lymph node metastases and to identifydisease truly confined to the uterus.
- The ESGO-ESTRO-ESP guidelines allow an approach of SLN in all patients with endometrial carcinoma.
- In assumed early endometrial cancer, an SLN biopsy in an adequate alternative to systematic lymphadenectomy in high-intermediate and high-risk cases for the purpose of lymph node staging and can also be considered in low–/ intermediate-risk disease to rule out occult lymph node metastases.
- An SLN biopsy should be done in association with ultrastaging as it will increase the detection of low-volume disease in lymph nodes.

2023 FIGO staging of endometrial cancer

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

- Low-grade EECs involving both the **endometrium** and the **ovary** are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met.
  (1) no more than superficial myometrial invasion is present **(<50%)**
  (2) **absence of extensive/substantial LVSI**
  (3) **absence of additional metastases**
  (4) **the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture**
  (equivalent to pT1a)

2023 FIGO staging of endometrial cancer

Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement

2023 FIGO staging of endometrial cancer

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

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Abbreviation: LVSI, lymphovascular space involvement.

[a]When feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial cancer for prognostic risk-group stratification and as potential influencing factors of adjuvant or systemic treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages.

- Good prognosis: pathogenic *POLE* mutation (*POLEmut*)
- Intermediate prognosis: mismatch repair deficiency (MMRd)/microsatellite instability and no specific molecular profile (NSMP)
- Poor prognosis: p53 abnormal (p53abn)When the molecular classification is known:
- FIGO Stages I and II are based on surgical/anatomical and histological findings. In case the molecular classification reveals *POLEmut* or p53abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of "m" for molecular classification, and a subscript is added to denote *POLEmut* or p53abn status, as shown below. MMRd or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. When molecular classification reveals MMRd or NSMP, it should be recorded as Stage Im_{MMRd} or Stage Im_{NSMP} and Stage IIm_{MMRd} or Stage IIm_{NSMP}.
- FIGO Stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known. When the molecular classification is known, it should be recorded as Stage IIIm or Stage IVm with the appropriate subscript for the purpose of data collection. For example, when molecular classification reveals p53abn, it should be recorded as Stage $IIIm_{p53abn}$ or Stage IVm_{p53abn}.

2023 FIGO staging of endometrial cancer

Stage	Description
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c]
	IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria
	IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes
	IIIC1i Micrometastasis
	IIICii Macrometastasis
	IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	IIIC2i Micrometastasis
	IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

The presence of **ITCs** should be documented, not considered metastatic, and is regarded as pN0(i+)

Verification of the prognostic precision of the new 2023 FIGO staging system

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com

Original Research

Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients – An international pooled analysis of three ESGO accredited centres

Richard Schwameis [a], Francesco Fanfani [b,c], Christoph Ebner [d], Naomi Zimmermann [a], Inge Peters [b,c], Camilla Nero [b,c], Christian Marth [d], Robin Ristl [e], Katharina Leitner [d], Christoph Grimm [a], Felicitas Oberndorfer [f], Ilaria Capasso [b,c], Alain G. Zeimet [d], Stephan Polterauer [a], Giovanni Scambia [b,c], Anna Fagotti [b,c], Nicole Concin [d,*]

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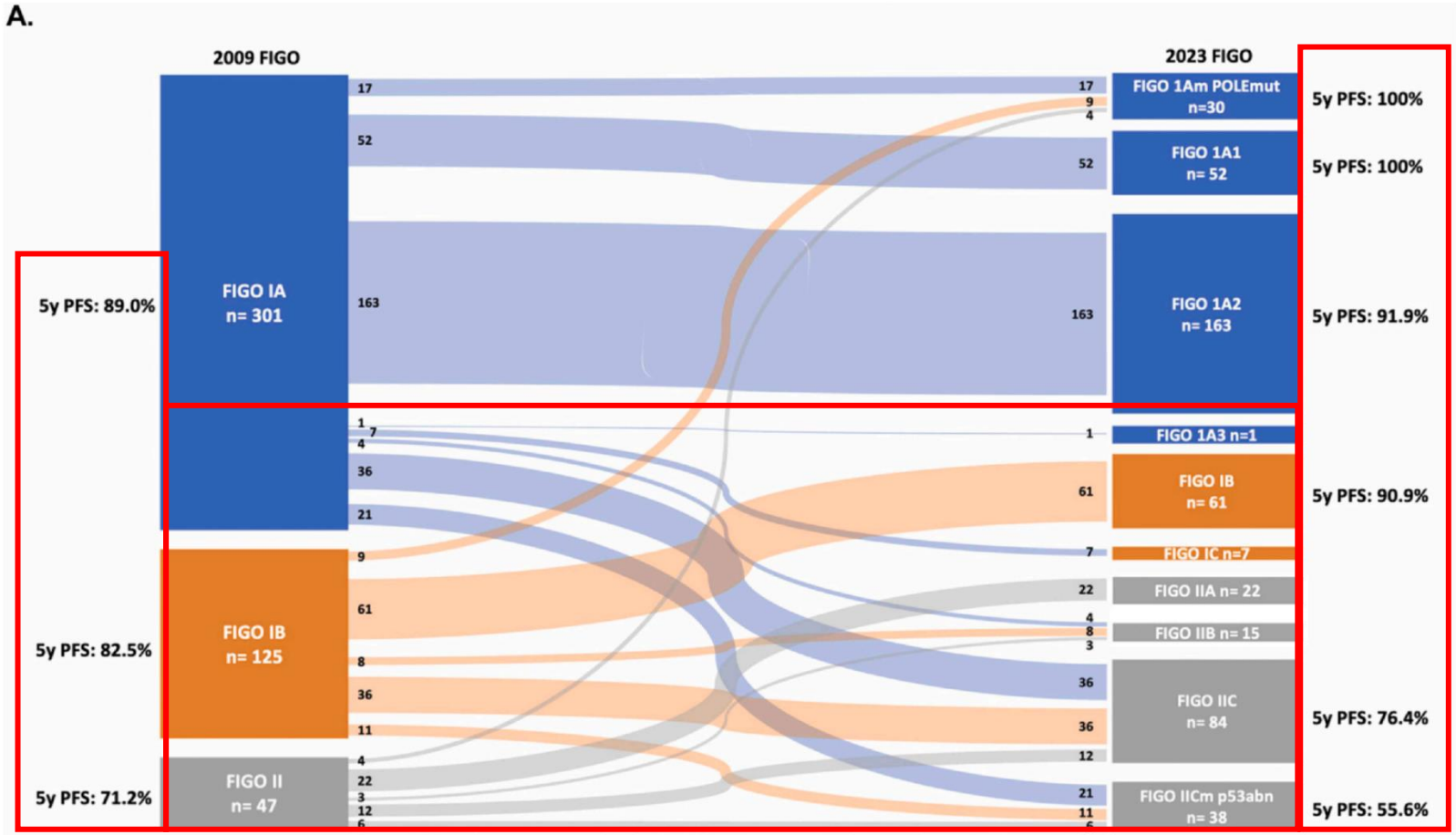
N = 519

Verification of the prognostic precision of the new 2023 FIGO staging system

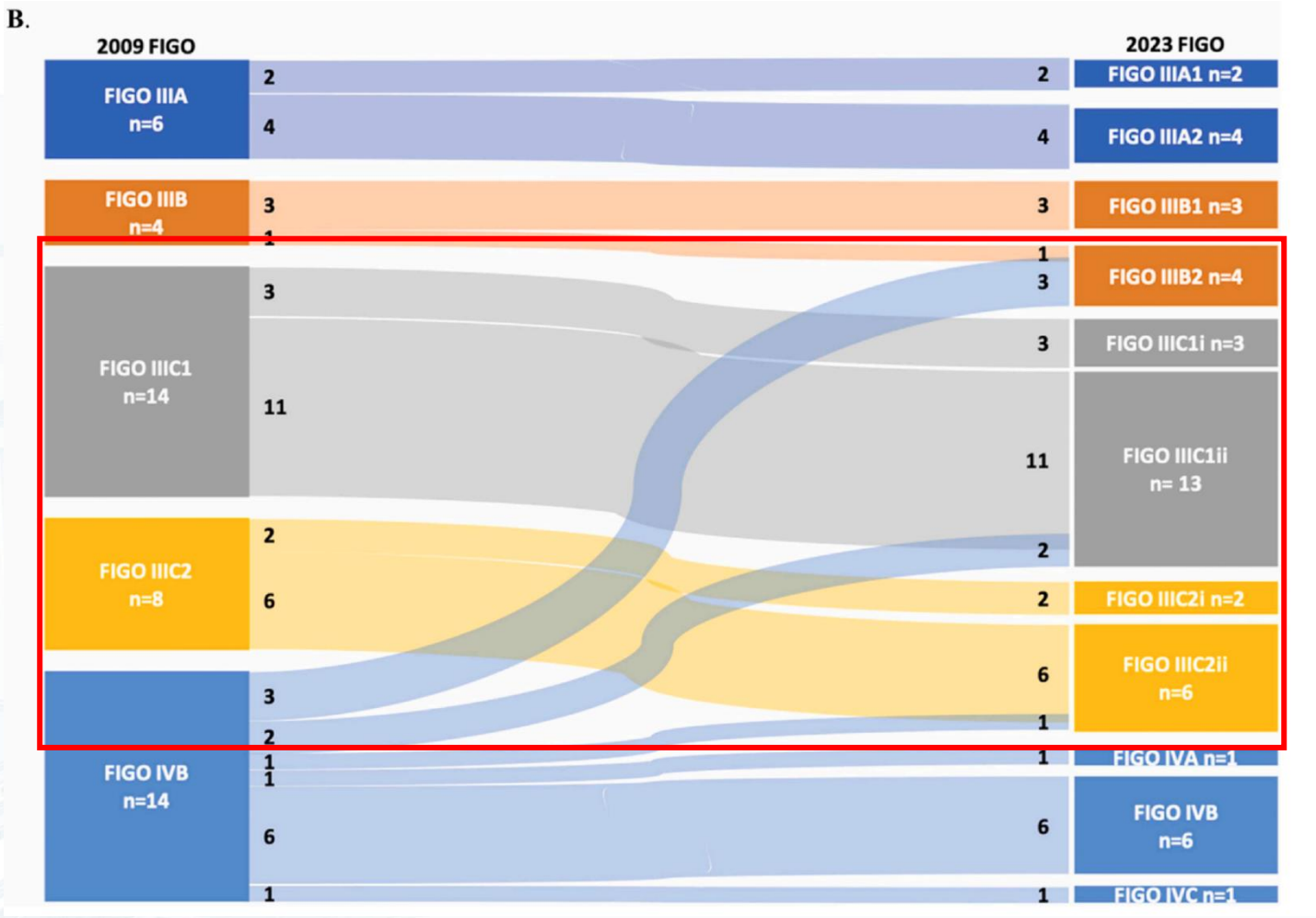
- New substages added further prognostic granularity in early-stage disease
- Substantial stage shift in anout one quarter of patients to a higher prognostic precision



Schwameis et al (2023)

Verification of the prognostic precision of the new 2023 FIGO staging system

- Substantial stage shift in anout one quarter of patients to a higher prognostic precision



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Verification of the prognostic precision of the new 2023 FIGO staging system

Table 3
Stage distribution and 5-year progression-free (PFS) and overall survival (OS) rates in 232 endometrial cancer patients (Austrian cohort) according to the 2009 and 2023 FIGO staging system.

	2009 FIGO			2023 FIGO		
Stage	Patients n (%)	5-year PFS rate in % (95% CI)	5-year OSrate in % (95% CI)	Patients n (%)	5-year PFSrate in % (95% CI)	5-year OSrate in % (95% CI)
I	**163 (70.3)**	**87.4 (80.1–92.2)**	**96.2 (89.5–98.7)**	**125 (53.9)**	**93.0 (84.9–96.8)**	**97.8 (91.0–99.5)**
IA	123 (53.0)	89.0 (80.8–93.4)	95.0 (86.4–98.2)	98 (42.2)	94.6 (84.1–97.0)	97.1 (89.0–99.3)
$IAm_{POLEmut}$				8 (3.4)	100	100
IA1				8 (3.4)	100	100
IA2				81 (34.9)	91.9 (81.5–96.5)	96.7 (87.4–99.2)
IA3				1 (0.4)	100	100
IB	40 (17.2)	82.5 (61.9–92.6)	100	25 (10.8)	90.9 (50.6–98.6)	100
IC				2 (0.9)	100	100
II	**23 (9.9)**	**71.2 (46.6–86.0)**	**79.4 (53.5–91.8)**	**61 (26.3)**	**70.2 (55.9–80.6)**	**86.0 (70.7–93.6)**
IIA				12 (5.2)	71.4 (33.7–90.1)	91.7 (53.6–98.8)
IIB				0 (0.0)	-	-
IIC				34 (14.6)	76.4 (56.7–87.9)	86.8 (63.1–95.7)
$IICm_{p53abn}$				15 (6.5)	55.6 (26.5–77.2)	79.6 (37.1–94.8)
III	**32 (13.8)**	**54.1 (33.5–70.8)**	**64.3 (41.5–80.1)**	**38 (16.4)**	**44.4 (27.0–60.5)**	**64.3 (43.9–78.9)**
IIIA	6 (2.6)	83.3 (27.4–97.5)	83.3 (27.4–97.5)	6 (2.6)	83.3 (27.4–97.5)	83.3 (27.4–97.5)
IIIA1				2 (0.9)	100	100
IIIA2				4 (1.7)	75.0 (12.7–96.1)	75.0 (12.7–96.1)
IIIB	4 (1.7)	66.7 (5.4–94.5)	66.7 (5.4–94.5)	7 (3.0)	35.7 (5.2–69.9)	57.1 (11.1–80.4)
IIIB1				3 (1.3)	50.0 (1.0–91.1)	50.0 (1.0–91.1)
IIIB2				4 (1.7)	25.0 (1.0–66.6)	50.0 (5.8–84.4)
IIIC				25 (10.8)	36.6 (16.9–56.6)	61.4 (33.8–80.3)
IIIC1	14 (6.0)	52.6 (22.9–75.6)	53.8 (17.3–80.3)	16 (6.9)	44.9 (19.1–67.9)	60.0 (23.7–83.4)
IIIC1i				3 (1.3)	50.0 (1.0–91.1)	66.6
IIIC1ii				13 (5.6)	42.3 (15.6–67.1)	65.5 (25.1–87.8)
IIIC2	8 (3.4)	30.0 (4.5–62.7)	58.3 (17.9–84.4)	9 (3.9)	25.9 (3.9–57.1)	63.5 (23.9–86.6)
IIIC2i				2 (0.9)	50.0 (1.0–91.1)	100
IIIC2ii				7 (3.0)	17.9 (1.0–53.7)	51.4 (11.7–81.3)
IV	**14 (6.0)**	**22.6 (3.9–50.4)**	**43.5 (8.3–75.7)**	**8 (3.4)**	**42.9 (5.9–77.7)**	**64.3 (15.3–90.2)**
IVA	0 (0)			1 (0.4)	n.e.	n.e.
IVB	14 (6.0)	22.6 (3.9–50.4)	43.5 (8.3–75.7)	6 (2.6)	n.e.	n.e.
IVC				1 (0.4)	n.e.	n.e.

CI, Confidence Interval; *POLE*mut, *POLE* mutated; p53abn, p53 abnormal
* n.e. not evaluated: for substages of 2023 FIGO IV disease no statistical prognostic evaluation was done due to small case number in the overall stage IV category (n = 8).
Results of main stages are written in bold letters.

Remarkably lower 5-year PFS for stage III patients in 2023 FIGO staging system (44.4% vs. 54.1%)

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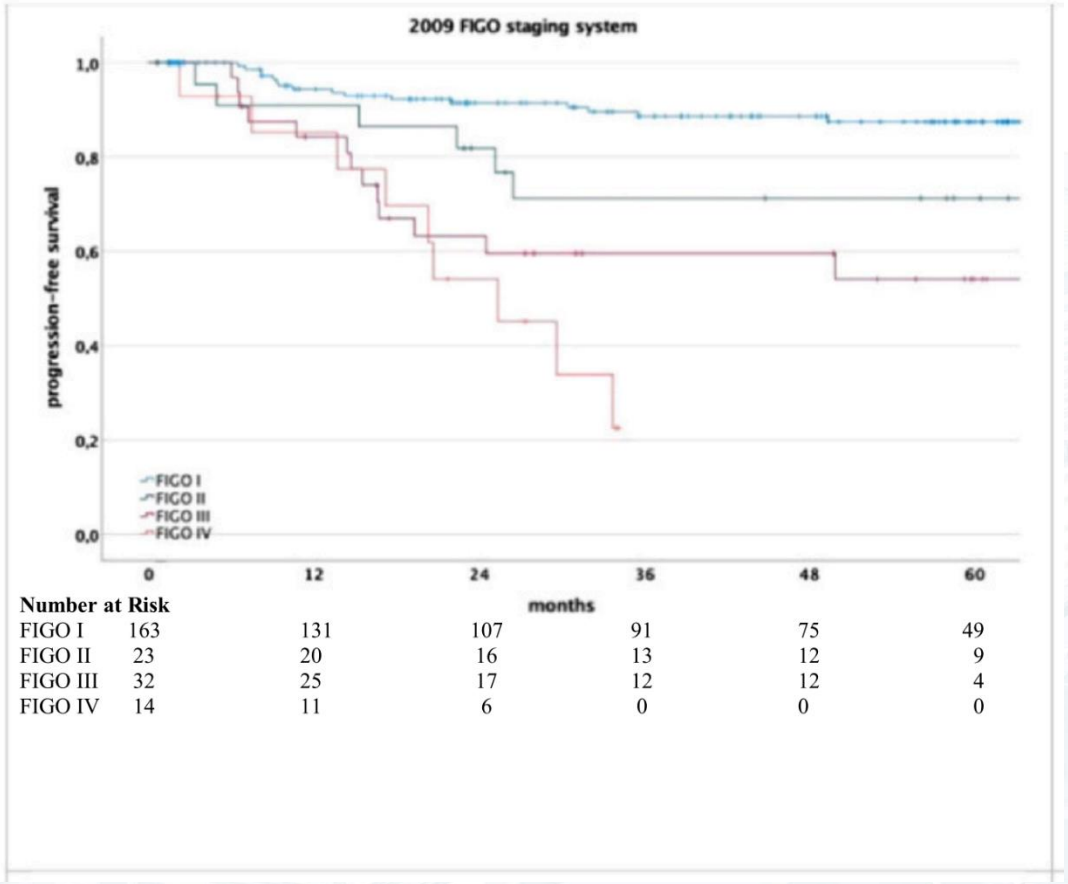
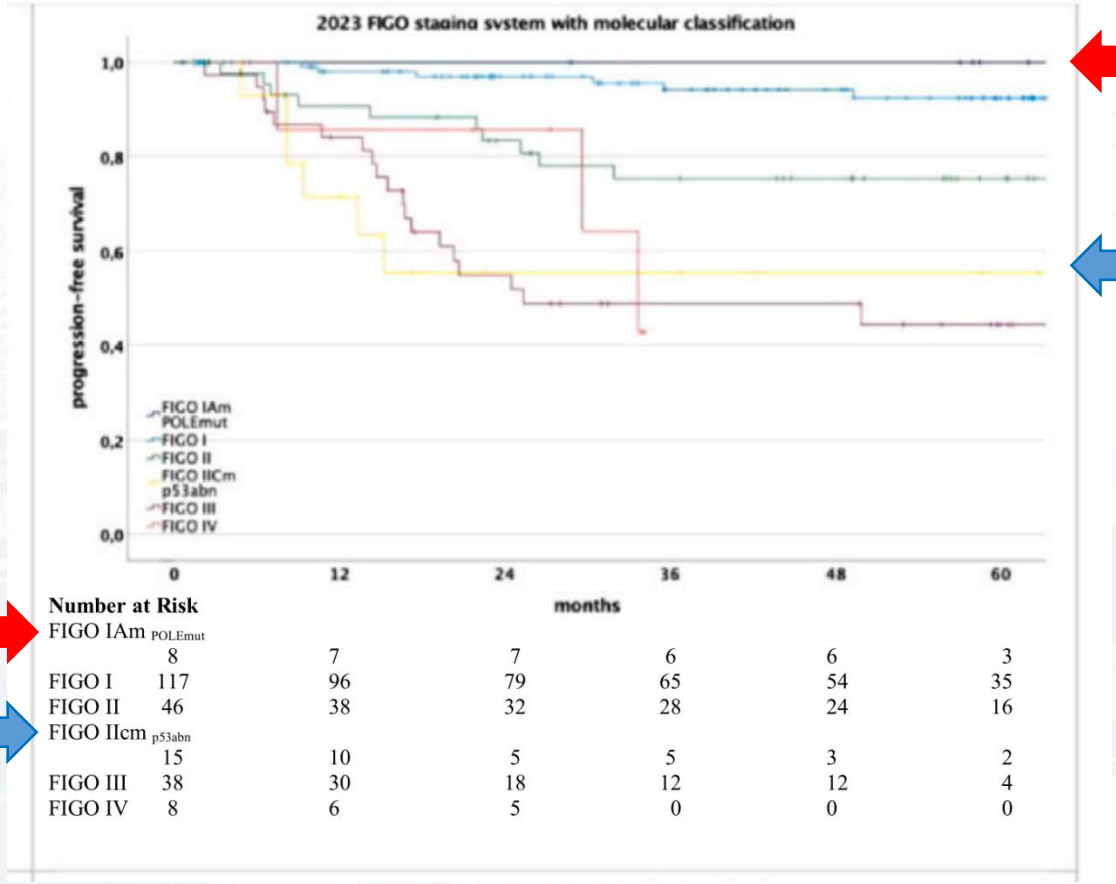
Verification of the prognostic precision of the new 2023 FIGO staging system



Number at Risk						
FIGO I	163	131	107	91	75	49
FIGO II	23	20	16	13	12	9
FIGO III	32	25	17	12	12	4
FIGO IV	14	11	6	0	0	0



Number at Risk						
FIGO IAm $_{POLEmut}$	8	7	7	6	6	3
FIGO I	117	96	79	65	54	35
FIGO II	46	38	32	28	24	16
FIGO IIcm $_{p53abn}$	15	10	5	5	3	2
FIGO III	38	30	18	12	12	4
FIGO IV	8	6	5	0	0	0

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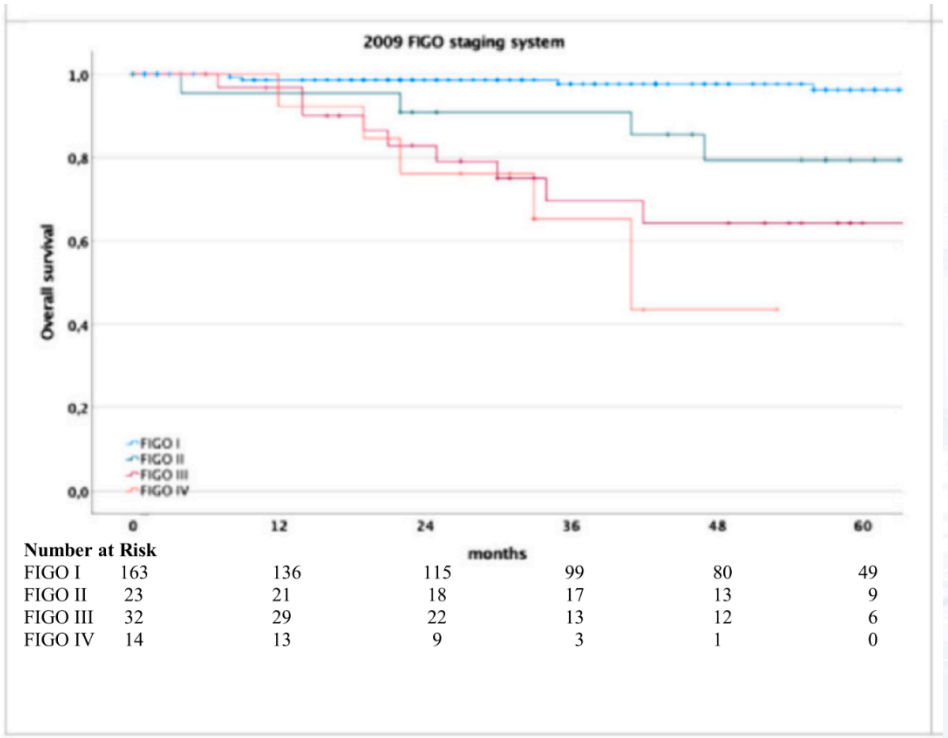
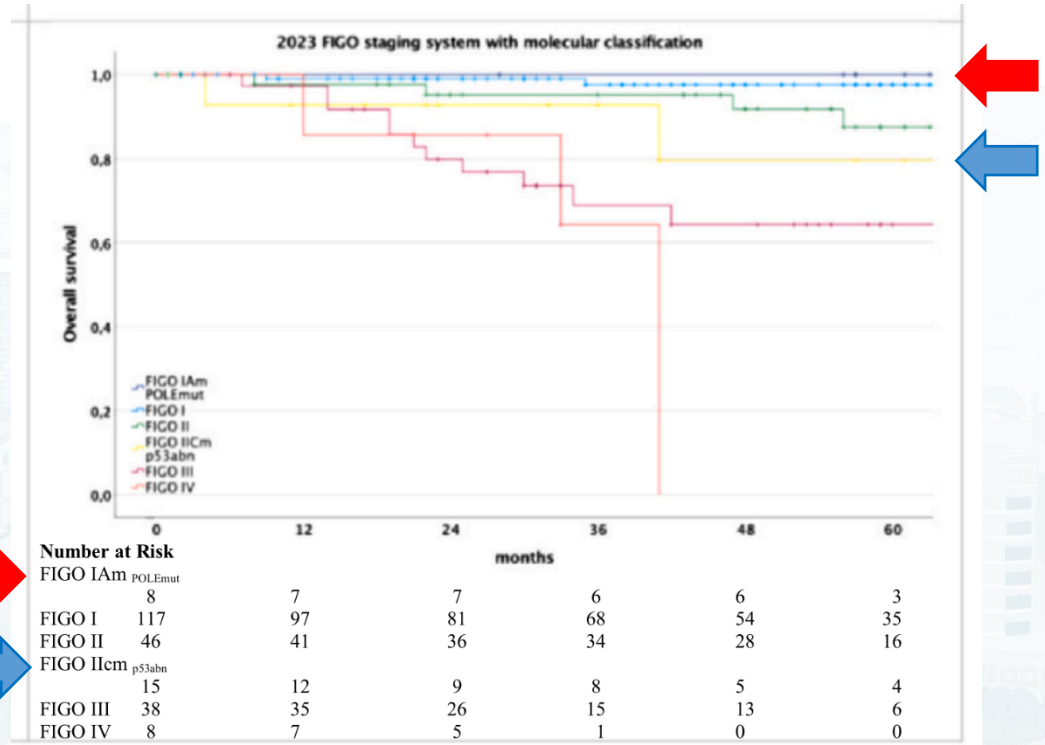


Number at Risk

FIGO I	163	136	115	99	80	49
FIGO II	23	21	18	17	13	9
FIGO III	32	29	22	13	12	6
FIGO IV	14	13	9	3	1	0



Number at Risk

FIGO IAm $_{POLEmut}$	8	7	7	6	6	3
FIGO I	117	97	81	68	54	35
FIGO II	46	41	36	34	28	16
FIGO IIcm $_{p53abn}$	15	12	9	8	5	4
FIGO III	38	35	26	15	13	6
FIGO IV	8	7	5	1	0	0

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Verification of the prognostic precision of the new 2023 FIGO staging system

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Letter to the Editor

Validation of the 2023 FIGO staging schema for advanced endometrial cancer

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IIIA-B: N = 1,295
IIIC: N = 1,365
IV: N = 2,813

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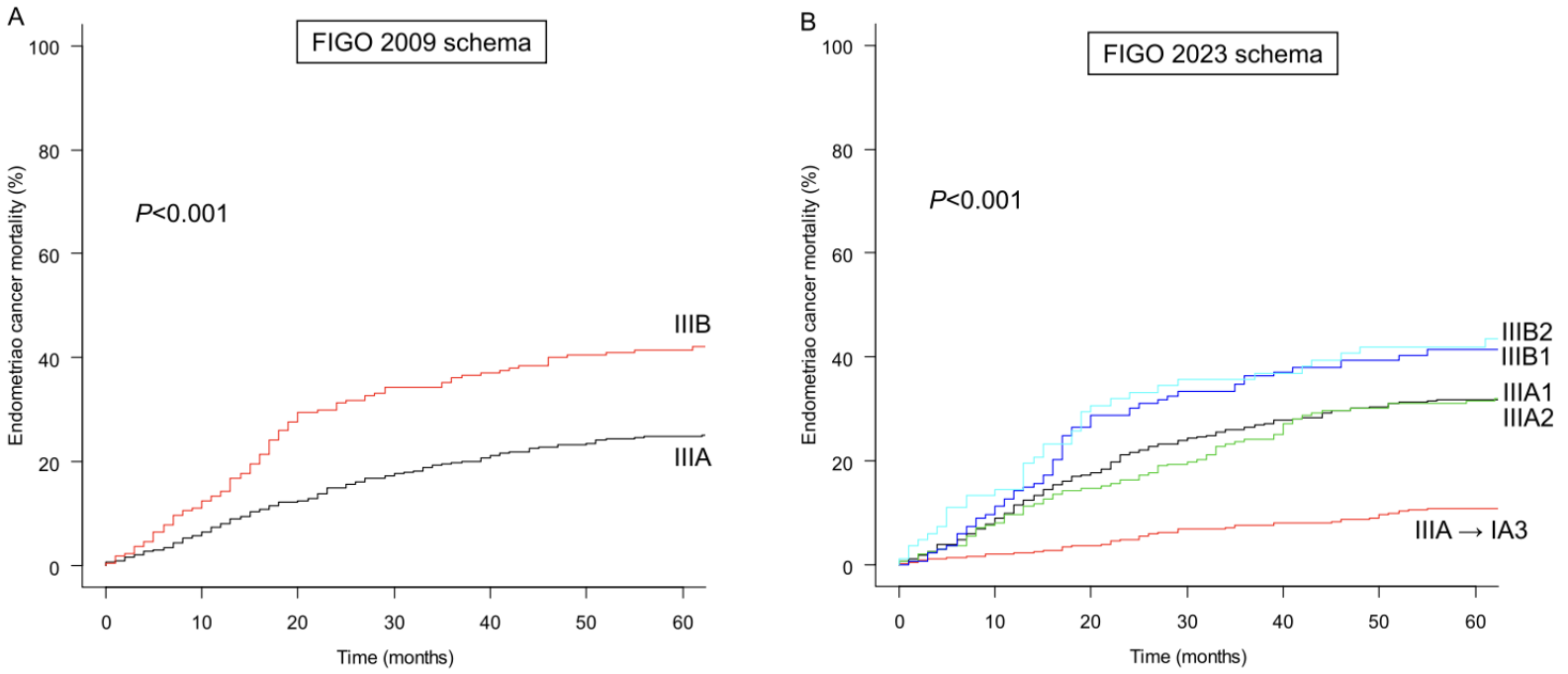

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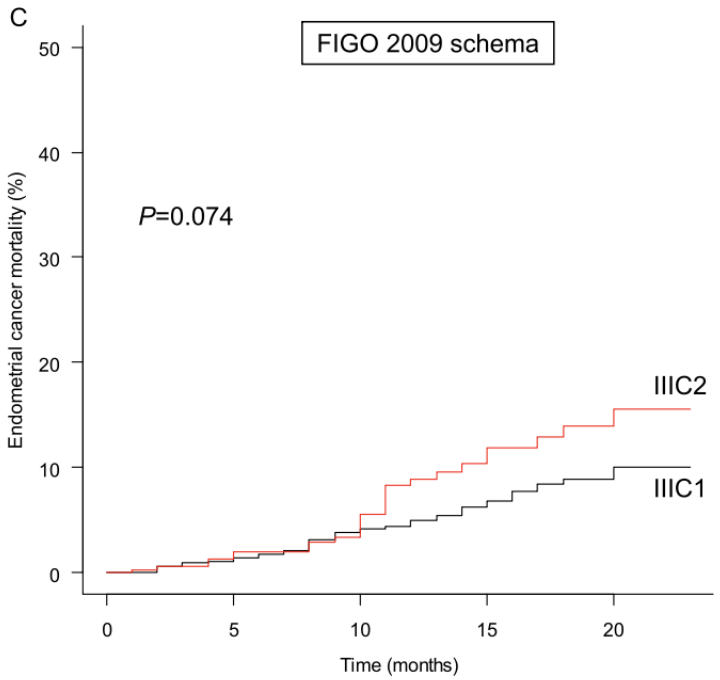
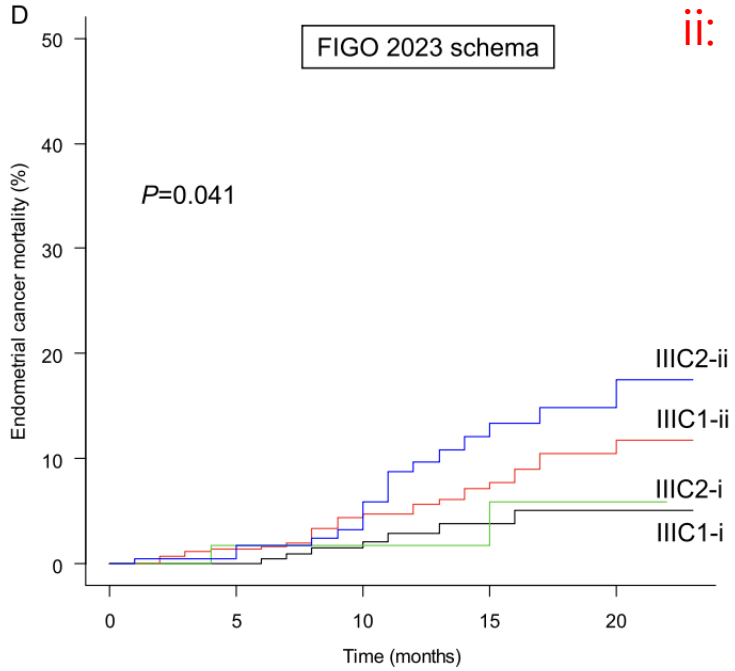
i: micrometastasis
ii: macrometastasis





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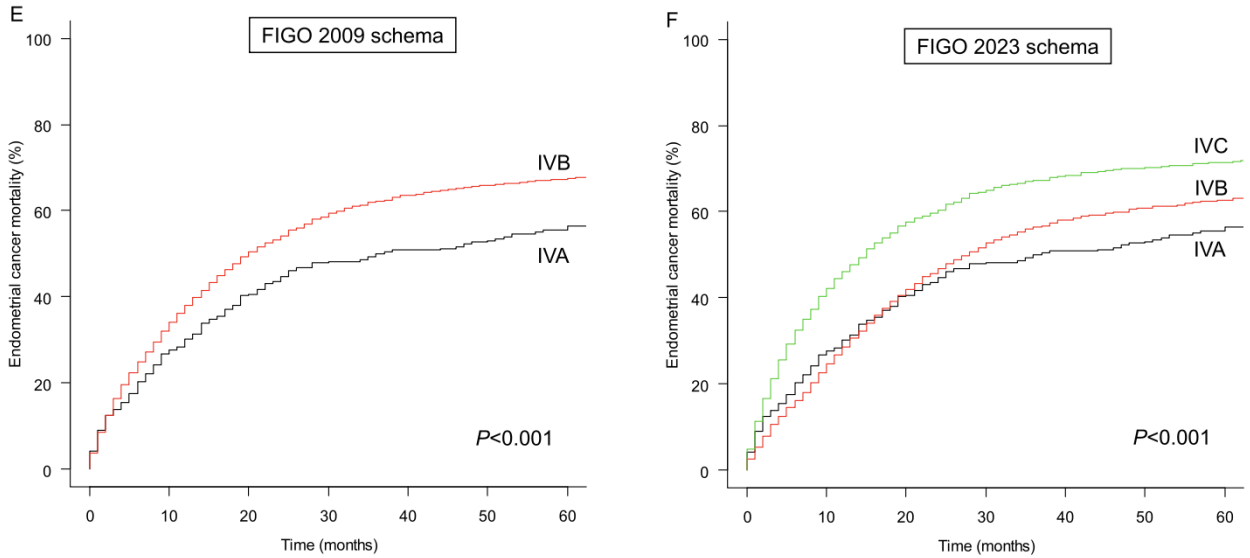

Fig. 1. Endometrial cancer-specific mortality. Cumulative incidence curves for endometrial cancer-specific mortality are shown for stage IIIA-IIIB based on 2009 the International Federation of Gynecology and Obstetrics (FIGO) schema (panel A) and the 2023 FIGO schema (panel B), for stage IIIC based on the 2009 FIGO schema (panel C) and the 2023 FIGO schema (panel D), and for stage IV disease based on the 2009 FIGO schema (panel E) and the 2023 FIGO schema (panel F). Competing risk analysis with the Gray test for *P*-value. Meta-data are shown in Table S2.

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Verification of the prognostic precision of the new 2023 FIGO staging system

Based on these data together with the increasing number of historical stage IVB endometrial cancers in the United States (Fig. S3), the revised staging schema for stage IVB-IVC diseases appears to provide important discriminatory data on survival and may be useful for informing both treatment and prognostication. Together with the fact that this group has dismal prognosis almost similar to advanced epithelial ovarian cancer [[10]], this calls for special attention and more investigations to improve the oncologic outcome.

Similarly, the removal of patients with low-grade endometrioid tumours with isolated adnexal disease from stage III appears to be warranted based on the favourable outcome of this group. However, the re-classification of patients with stage III tumours may be of more limited value as the new criteria have resulted in sub-groups with very similar endometrial cancer mortality and, in the case of patients with nodal metastasis either to pelvic or para-aortic region, the size of metastasis was prognostic but not the anatomical site.

In conclusion, the 2023 FIGO endometrial cancer staging schema is a major revision from the 2009 FIGO schema. Almost doubled enriched sub-stages based on detailed anatomical metastatic sites and incorporation of histological information enable more robust prognostication in advanced disease.

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Conclusion

- The current modifications to the endometrial staging system have been made **to further define the differences in prognosis and survival** that have been reported since the 2009 system was published.

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 involvement
IIIC1	Pelvic node involvement
IIIC2	Paraaortic node involvement
IVA	Tumor invasion into bladder or bowel mucosa
IVB	Distant metastases (including abdominal metastases) or inguinal lymph node involvement

2009 FIGO Staging **Grade, Mn invs**

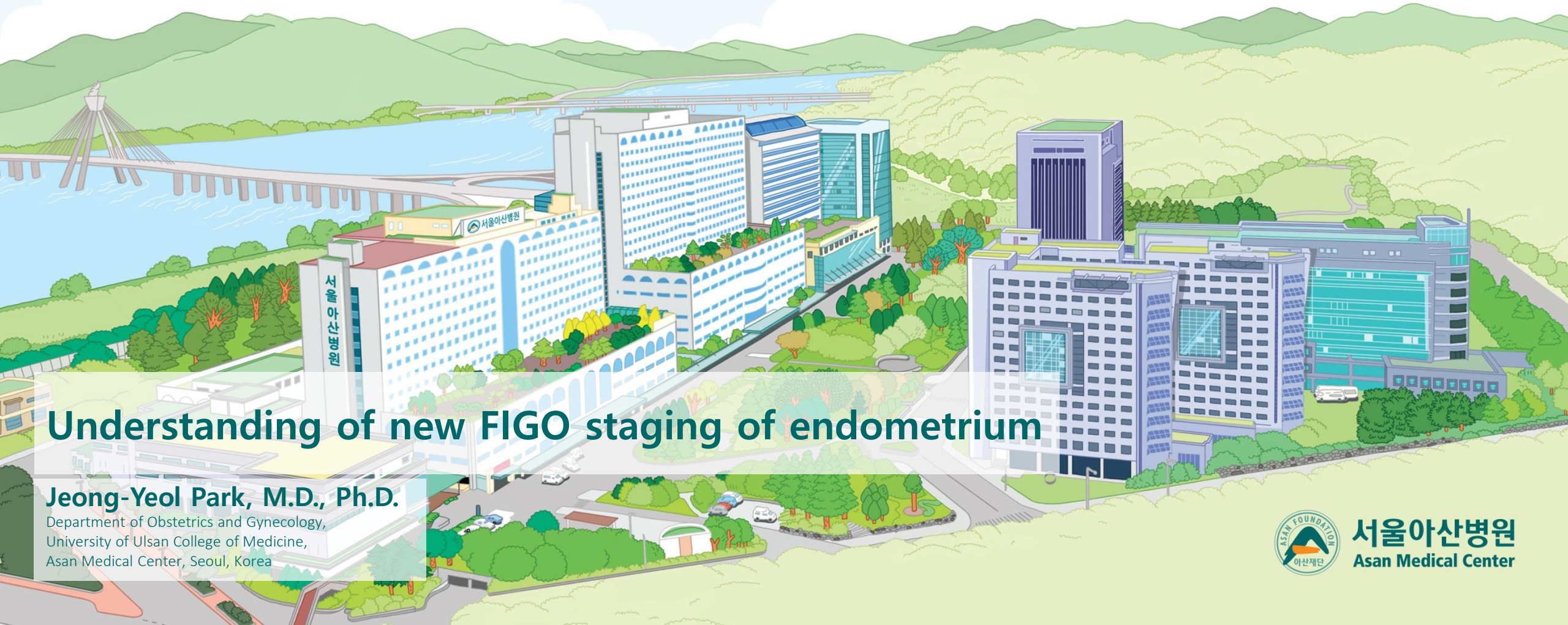
Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

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

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage IAm$_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICm$_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

2023 FIGO Staging **Grade, Mm invs, Histologic type, LVSI, Mol classification, actual prognosis**

Thank you for Kind attention !!!



Understanding of new FIGO staging of endometrium

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