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2023 FIGO staging system for endometrial cancer: The evolution of the revolution

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HIGHLIGHTS

- 2023 FIGO staging system integrates old and new knowledge on anatomic, histopathologic, and (optional) molecular features.
- 2023 FIGO is superior to 2009 FIGO in the prediction of survival, confirmed by to do date 5 validation studies.
- 2023 FIGO adds prognostic granularity and identifies treatment-relevant subgroups of EC patients.
- 2023 FIGO reinforces molecular testing to EC patients leveraging a strong demand for global access.
- FIGO 2023 system will spur worldwide adoption of molecular classification so more tailored therapy will be adopted.

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ABSTRACT

Introduction. Embracing the complex and diverse nature of the heterogenous group of malignancies that are included under the umbrella of "endometrial cancer" (EC) to better align prognosis with treatment recommendations, requires a more comprehensive staging system. Our goal at the development of the new FIGO staging was to provide 1) high accuracy in the predictive prognosis for a patient with EC, which is the genuine purpose of a staging system, and 2) identification of distinct treatment relevant subgroups. Since the publication of the 2009 staging system by the International Federation of Gynecology and Obstetrics (FIGO) 14 years ago (1, 2), our understanding of the biology and natural history of EC has undergone a radical transformation. The TGCA results in 2013 (3), and the many validation reports published since then (4–9), have taught us that "EC" is composed of at least four distinct molecularly defined diseases. Strong histopathologic markers reflecting tumor biology such as lymph vascular space invasion (LVSI) were identified. Importantly, anatomical borders were shown to lose their prognostic relevance for EC patients in the presence of dominant tumor biology-markers such as molecular subtypes/LVSI (10, 11). This emphasizes the integration of these novel markers into a prognostic staging system that aims to be relevant to patients. The 2023 FIGO staging system for EC harmonizes and integrates old and new knowledge on anatomic, histopathologic, and molecular features (12). It requires a change in our perception of a staging system, from a traditional purely anatomical borders-based system to an integrated staging system integrating anatomical borders and tumor biology as pivotal prognostic factors for EC patients while providing important information for treatment decision making. Therefore, the 2023 FIGO staging

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system demonstrates the logical next step in the evolution of the revolution in a patient-centric staging approach.
Below, we elucidate the rationale for the FIGO 2023 endometrial cancer staging system.

Contents

1. Introduction

Embracing the complex and diverse nature of the heterogenous group of malignancies that are included under the umbrella of "endometrial cancer" (EC) to better align prognosis with treatment recommendations, requires a more comprehensive staging system. Our goal in developing the new FIGO staging was to provide 1) high accuracy in the prognosis for a patient with EC, which is the fundamental purpose of a staging system, and 2) identification of distinct treatment relevant subgroups. Since the publication of the 2009 staging system by the International Federation of Gynecology and Obstetrics (FIGO) [1,2], our understanding of the biology and natural history of EC has undergone a radical transformation. The TGCA results in 2013 [3], and the many validation reports published since then [4–9], have taught us that "EC" is composed of at least four distinct molecularly defined diseases. Strong histopathologic markers reflecting tumor biology such as lymph vascular space invasion (LVSI) were identified. Importantly, anatomical borders were shown to lose their prognostic relevance for EC patients in the presence of dominant tumor biology-markers such as molecular subtypes/LVSI [10,11]. This emphasizes the value of integrating these novel markers into a prognostic staging system that aims to be relevant to patients. The 2023 FIGO staging system for EC harmonizes and integrates old and new knowledge on anatomic, histopathologic, and molecular features [12]. It requires a change in our perception and definition of a staging system, from a traditional purely anatomical borders-based system to an integrated staging system incorporating anatomical borders and tumor biology as pivotal prognostic factors for EC patients while providing important information for treatment decision making. Therefore, the 2023 FIGO staging system demonstrates the logical next step in the evolution of the revolution in a patient-centric staging approach.

Below, we elucidate the rationale for the FIGO 2023 endometrial cancer staging system.

2. Do we need a new staging system?

The new FIGO 2023 system is shown in Table 1 as adapted from the FIGO publication [12]. The incidence of EC has ubiquitously increased worldwide during the past 3 decades with >40 countries experiencing increasing mortality [13]. A more nuanced FIGO staging system that integrates the tremendous amount of new evidence published in the past 14 years will provide an improved and more differentiated prognostication of EC patients. Furthermore, the new FIGO staging system is likely to accelerate the use of new therapeutics to optimize care as it integrates tumor biology makers and identifies treatment-relevant subgroups.

A recent survey of 135 clinicians from the International Gynecologic Cancer Society, and 172 pathologists from the International Society of Gynaecological Pathologists was generated to determine the adequacy of the previous 2009 staging system, and to identify areas for improvement [14]. The highest priority issues were the need to determine 1) whether stage IIIA patients (ovarian/fallopian tube involvement) can be reliably separated into favorable versus unfavorable outcome groups to avoid over-treatment of the former group and 2) whether stage IIIC patients (lymph node metastases) can be separated into favorable versus unfavorable outcome groups based on the size of lymph node metastases. Additionally, the majority of pathologists (76%) and clinicians (84%) viewed LVSI as an independent prognostic variable and favored incorporating LVSI into staging. The majority of clinicians (65%) indicated a preference for incorporating tumor histotype and 63% favored incorporation of molecular classification into staging. When queried about adoption of staging rules for distinguishing favorable versus unfavorable prognoses for "synchronous" involvement of endometrium and ovaries by endometrial cancer more than two-thirds concurred. This survey presents new and relevant data that identify the shortcomings of the 2009 staging system and offers a strategy for prioritizing and designing outcome-

Table 1
2023 FIGO Staging.

2009 FIGO Staging		
Stage		
I*		**Tumor confined to the corpus uteri**
IA*		No or less than half myometrial invasion
IB*		Invasion equal to more than half of the myometrium
II*		**Tumor invades cervical stroma, but does not extend beyond the uterus****
III*		**Local and/or regional spread of the tumor**
IIIA*		Tumor invades the serosa of the corpus uteri and/or adnexae#
IIIB*		Vaginal and/or parametrial involvement#
IIIC*		Metastases to pelvic and/or para-aortic lymph nodes#
	IIIC1*	Positive pelvic nodes
	IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV*		**Tumor invades bladder and/or bowel mucosa, and/or distant metastases**
IVA*		Tumor invasion of bladder and/or bowel muscosa
IVB*		Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

2023 FIGO Staging		
Stage		
I		**Confined to uterine corpus**
IA		Stage IAmPOLEm: POLEmut confined to uterine corpus +/− cervical invasion, regardless of LVSI or histotype
	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI
IC		Aggressive histologies, limited to polyp/endometrium
II		**Confined to the uterus**
IIA		Low-grade endometrioid, invasion of the cervical stroma
IIB		Low-grade endometrioid, substantial LVSI
IIC		Aggressive histologies, myoinvasion
		Stage IICmp53abn: p53abn confined to uterus +/− cervical invasion + myoinvasion, regardless of LVSI or histotype
III		**Local and/or regional spread**
IIIA	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	IIIB1	Metastasis or direct spread to the vagina and/or the parametria
	IIIB2	Metastasis to the pelvic peritoneum
IIIC	IIIC1	Pelvic lymph node metastasis
	IIIC1i	Micrometastasis (0.2–2 mm and/or >200 cells)
	IIIC1ii	Macrometastasis (>2 mm in size)
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)
	IIIC2i	Micrometastasis (0.2–2 mm and/or >200 cells)
	IIIC2ii	Macrometastasis (>2 mm in size)
IV		**Advanced or metastatic disease**
IVA		Invasion of the bladder mucosa and/or the intestinal mucosa
IVB		Peritoneal metastasis beyond the pelvis
IVC		Distant metastasis

*Either G1, G2, or G3.
**Endocervical glandular involvement only should be considered as Stage I and not as Stage II.
#Positive cytology has to be reported separately without changing the stage.
Some definitions:
Aggressive histotypes are composed of high-grade endometrioid (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.
LVSI: extensive/substantial, ≥5 vessels involved.
#myoinvasion <50% + no/focal LVSI + ovarian tumor pT1a. macrometastases are >2 mm in size, micrometastases are 0.2–2 mm and/or >200 cells, a.

based studies specifically targeted to resolving controversial and unresolved issues. These topics have now been integrated in the FIGO 2023 staging system.

3. Outcomes of new staging system

To date, five validation studies of new FIGO 2023 staging system have been published and more are forthcoming [15–21]. These studies consistently confirm the greater prognostic precision of the FIGO 2023 staging system compared to the previous one. Furthermore, the changes made have significant implications regarding the systemic and radiotherapy treatment choices and the accurate selection of patients for surgery at both the primary diagnosis and at relapse [4,8,10,11].

4. Major changes and their rationale

4.1. EARLY STAGE DISEASE (stages I/II)

4.1.1. LVSI in endometrioid EC

FIGO 2023 stages IA and IB include low-grade endometrioid ECs with *no or focal LVSI* only, while the presence of *substantial LVSI*, as defined by the WHO definition (5 or more foci), in low-grade endometrioid ECs confined to the uterus automatically upshifts these cases to a stage IIB disease. Extensive literature has documented LVSI as a powerful prognostic factor. In fact, Bosse et al. in evaluating data from the PORTEC I and II trials stated, "Substantial LVSI, in contrast to focal or no LVSI, was the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis

and overall survival. Therapeutic decisions should be based on the presence of substantial, not 'any' LVSI" [22]. The NCCN has adopted lymph vascular space involvement as a clear prognostic category [23,24]. Post hoc analysis of randomized trials, prospective cohort studies, large database series, and single-institution reports consistently demonstrate that LVSI is an independent and strong prognostic factor for recurrence and overall survival in EC [24–26]. A registry study of >1500 patients from Sweden with Stage I–III endometrioid EC identified LVSI as the strongest independent risk factor for lymph node metastases. Moreover, this study demonstrated an independent association of LVSI with overall survival even in patients with negative lymph node status after systematic lymphadenectomy (pTN0 disease), indicating that hematogenous dissemination might be important in patients with LVSI in their tumors [26]. Importantly, a study of the Danish Gynaecological Cancer Database in high-grade, stage I-III EC demonstrated that in the presence of strong biological factors such as LVSI/molecular subtypes, anatomical tumor stage loses its relevance for recurrence and survival, while the biological factors remain significant for the outcome of patients [27].

4.1.2. Histological subtypes

Knowledge of the histological subtype and grade is a prerequisite for treatment decision making in EC, and thus is routinely performed. The 2023 FIGO staging system reflects the substantially different prognosis of high-grade (aggressive) histological subtypes compared to low-grade (G1/G2) endometrioid (non-aggressive) histological subtypes. The high-grade, aggressive histological subtypes with myometrial invasion are now classified as FIGO IIC in the 2023 FIGO staging system, which is comprised of serous, clear cell, high-grade endometrioid, mesonephric-like, gastrointestinal-type mucinous endometrial, undifferentiated carcinomas, and carcinosarcomas. A validation study based on three ESGO (European Society of Gynaecological Oncology) accredited centers by Schwameis et al. [19] showed that patients with high-grade EC with myometrial invasion (now 2023 FIGO stage IIC) have a 5-year progression-free survival (76.4%) similar to the old 2009 FIGO stage II (71.2%) and similar to the new overall stage II patients (70.2%). Moreover, the 5-year overall survival rate for this group of high-grade EC with myometrial invasion is lower (86.8%) than that of low-grade EC with cervical involvement (91.7%). For serous carcinomas the high-grade component drives prognosis [28]. In the case of clear cell carcinomas, the clear cell component must be substantial before the cancer takes on the prognosis of the clear cell component [29]. We want to underline that histological subtype and grading are particularly useful predictors of prognosis when molecular classification is not available but nevertheless have clear limitations [30]. A more accurate allocation to a distinct prognostic group is achieved by molecular classification, which is therefore encouraged in all endometrial carcinomas [31,32]. This is particularly important in high-grade histologies to allow proper allocation into the correct prognostic group [22,32,33].

4.2. Molecular subtypes, if accessible (new molecularly defined FIGO stages IAm$_{POLEmut}$ and IICm$_{p53abn}$)

Molecular classification has revolutionized our understanding of EC and of its management and has been integrated into international European Guidelines for >3 years [31,32]. Multiple studies have repeatedly shown the pivotal impact of molecular subtypes on prognosis (and the decreased significance of anatomical borders in their presence; [4,8,10,11]. Now, a new era has begun in which new level I evidence is arising that demonstrates the pivotal predictive value of the molecular subtypes. Their predictive impact is already guiding our treatment decisions and will increasingly do so [10,34–36]. Of note, we stress that molecular classification is not mandatory in 2023 FIGO system. We provided 2 options, one with and one without molecular classification. Both options provide improved prognostication based on the integrated new knowledge of anatomical and histopathologic parameters and on molecular subtypes, in cases where they are known [15–21]. There are significant differences in outcomes by molecular subtypes. In a study of 75 stage I, grade 3 (FIGO 2009) patients from MSKCC 3 year PFS was 95.8% for the POLE group and 60% for the p53 mutated group [11]. The new FIGO system includes two molecularly defined substages in two clearly defined scenarios, both concerning early stage disease only: 1) Uterus confined (corpus+/−cervical invasion) disease with a pathogenic *POLE* mutation is defined as 2023 FIGO IAm$_{POLEmut}$, and 2) Uterus confined (corpus+/−cervical invasion) disease with myometrial invasion with a p53 abnormality that is defined as 2023 FIGO IICm$_{p53abn}$. It is well established that *POLE*mut early stage disease has an excellent prognosis even in the absence of adjuvant treatment [4,8,10,27], and thus European Guidelines suggest omitting adjuvant treatment in uterus confined *POLE*mut cases [31,32]. On the other hand, it is well known that p53 abnormal cases with myometrial invasion have a particularly poor prognosis, even in fully lymph node staged, previously defined stage I disease (thus unrelated to occult lymph node disease) [10,11,27]. PORTEC III demonstrated that p53 mutated patients who receive chemotherapy have a markedly superior survival [4].

The ESGO study by Schwameis et al. and a second Japanese validation study by Kabayashi-Kato et al. confirmed the superiority of the 2023 FIGO staging system to predict PFS and OS compared to the 2009 FIGO system with the best discriminatory ability for the molecularly defined substages [16,19] (see Fig. 1).

Besides the molecularly defined substages in the two well defined situations outlined above, the molecular subtype, if known, should be *recorded* in all other situations. This is done by the addition of "m" (for "molecular subtype") after the regular FIGO stage (defined by anatomical and histopathological parameters) and the denotation of the specific molecular subtype as a subscript, e.g. for a low-grade (G2) endometrioid carcinoma with >50% myometrial invasion, that is MMRd, i.e. 2023 FIGO stage Ibm$_{MMRd.}$

4.3. ADVANCED STAGE DISEASE (stages III/IV)

4.3.1. Metastasis to the ovary: Low-grade endometrioid carcinoma of the endometrium and the ovary (disaggregation of 2009 FIGO stage IIIA to new 2023 FIGO stages IA3 and IIIA1)

Previously (2009 FIGO), all metastases of EC to the ovary were clustered as stage IIIA, while the new FIGO 2023 differentiates low-grade endometrioid carcinoma of the endometrium and the ovary (if specific criteria are met; new 2023 FIGO IA3) from other metastatic patterns to the ovary (2023 FIGO IIIA1). This new differentiation is based on the favorable biological behavior and good prognosis of low-grade endometroid carcinoma of the endometrium and ovary, if specific, well defined, criteria are met (according to World Health Organization <50% myometrial invasion, absence of LVSI, no other metastases and according to ESGO-ESTRO-ESP guidelines if the ovarian tumor is equivalent to pT1a) [31,37]. Several studies have demonstrated that these tumors are clonally related and hence are not "simultaneous" separate primaries but true metastases [38–42] (see Fig. 2). Importantly, this differentiation of metastatic spread to the ovary is informative for treatment. The ESGO-ESTRO-ESP Guidelines for the management of patients with EC do not recommend adjuvant treatment in these cases [31].

4.3.2. Refinement of lymph node metastasis (new 2023 FIGO stages IIIIC1i/ii and IIIC2i/ii)

With the broad adoption of sentinel lymph node biopsy in clinical routine and pathological ultrastaging, small volume disease (micrometastases and isolated tumor cells, ITCs) is increasingly detected. While micrometastases (0.2-2 mm in size) and macrometastases (>2 mm)

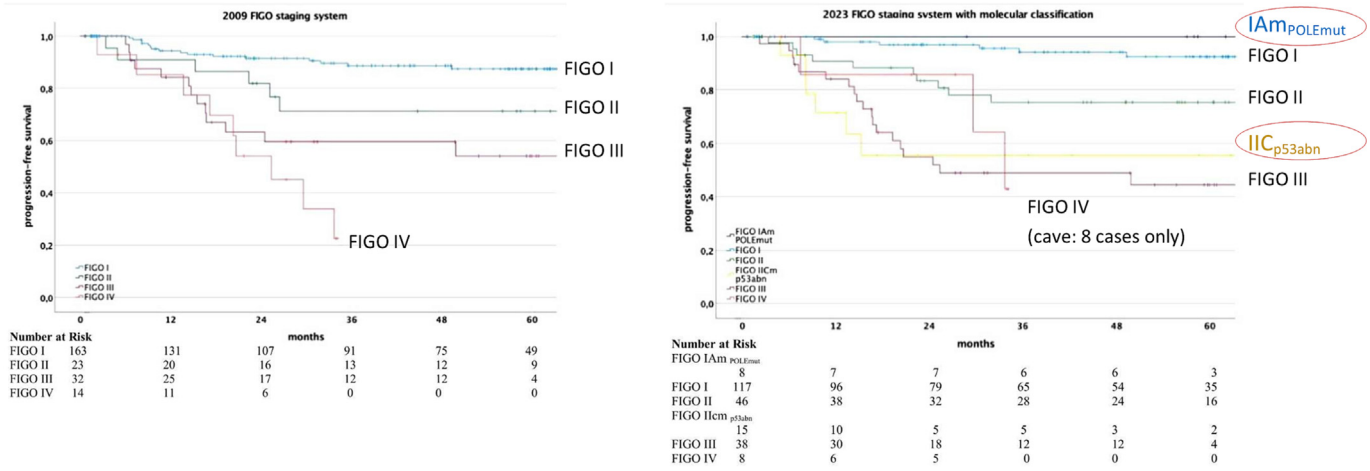

Fig. 1. The validation study of Schwameis et al. demonstrated that the molecularly defined stages $IAm_{POLEmut}$ and $IICm_{p53abn}$ groups had a 100% 5-year PFS, and 56% 5-year PFS, respectively. Thus, these 2 molecularly defined FIGO stages demonstrated the most favorable and the worst prognostic subgroups among early stage disease, added prognostic granularity and improved prognostic precision of 2023 FIGO staging system (right graph) in comparison to 2009 (left graph).

are considered as lymph-node positive disease (pN1), the clinical relevance of ITCs is currently not completely understood and is therefore regarded as lymph-node negative disease (pN0). The new 2023 FIGO stage discriminates between micro- and macrometastases among pelvic (IIIC1) and para-aortic (IIIC2) lymph node metastases by the addition of "i" for micro, and "ii" for macrometastases. Matsuo et al. confirmed the clinical relevance of this refinement. Consistent with other staging systems, the size of nodal metastases was found to be significant for the patients` prognosis, with pelvic and para-aortic lymph node metastases being associated with a worse prognosis compared to micrometastatic lymph node disease ($p = 0.041$) [17].

4.3.3. New evaluation of peritoneal carcinomatosis (disaggregation of 2009 FIGO stage IVB to new 2023 FIGO stages IIIB, IVB and IVC)

The previous 2009 FIGO stage IVB was composed of a heterogeneous group of patients clustering any peritoneal carcinomatosis (pelvic or extrapelvic), organ-specific distant metastases, and lymph node metastases beyond pelvic/paraaortic region into one group. A SEER Database study from 2020 including >900 patients with 2009 IVB disease clearly demonstrated that the metastatic site affects prognosis and that patients with peritoneal metastasis have significantly better survival compared to patients with organ-specific metastasis [43]. In the new 2023 FIGO staging system we distinguished peritoneal carcinomatosis from distant metastases. Peritoneal carcinomatosis limited to the pelvis only has now become 2023 FIGO stage IIIB2 (downstaged from previous 2009 stage IVB), and peritoneal carcinomatosis beyond the pelvis remains in the stage IV category but now forms a separate substage (2023 stage IVB) discriminating it from other distant intra- and extra-abdominal metastases (2023 stage IVC) [15].

A validation study by Haight et al. has confirmed the prognostic relevance of the new differentiation of peritoneal carcinomatosis (pelvic versus extrapelvic) from distant metastasis in the new 2023 FIGO staging system (see Fig. 3). Furthermore, the study by Matsuo et al. has confirmed the distinct prognosis of the new substages of 2023 FIGO stage IV

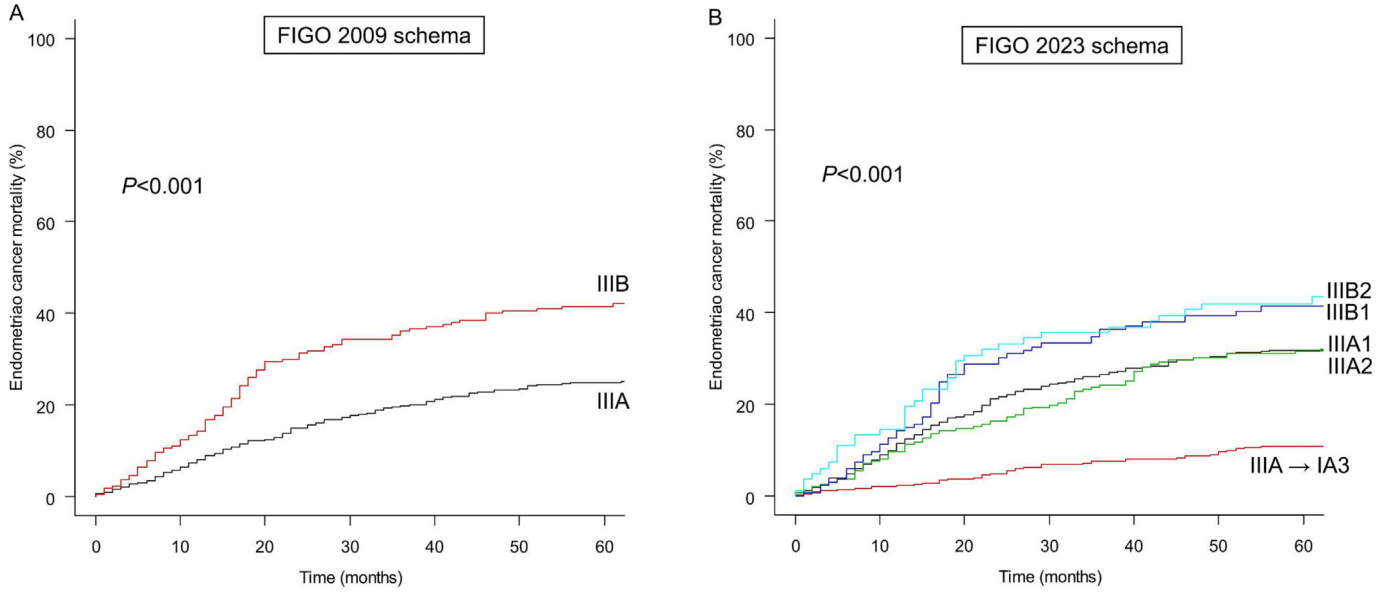

Fig. 2. The validation study of Matsuo et al. based on the Surveillance, Epidemiology, and End Results (SEER) Database confirmed the higher prognostic precision of the new FIGO staging system by the differentiation of low-grade endometrioid EC and OC from "other" metastatic spread to the ovary. The 5-year EC-specific mortality rate of the overall 2009 FIGO IIIA group was 24.9%, while 2023 FIGO splits this overall group into the prognostically favorable low-grade endometrioid EC and OC group (new IA3) with a 5-year EC-specific mortality rate of 11.0% and the other ovarian metastasis group (new IIIA1) with a 5-year EC-specific mortality rate of 31.6% ($P < 0.001$).

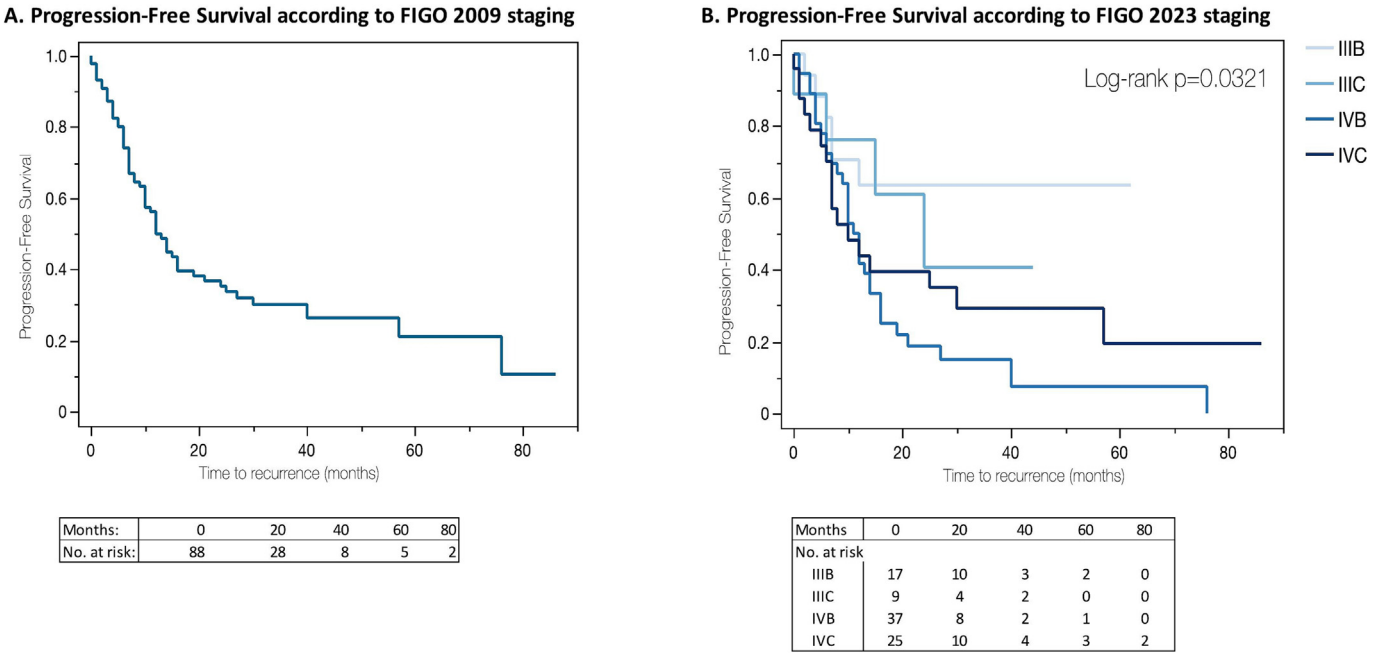

Fig. 3. The validation study by Haight et al. focused on the heterogenous cohort of 2009 FIGO stage IVb and its new disaggregation in 2023 FIGO staging system. The study confirmed the significantly improved ability of the 2023 FIGO system to properly prognosticate patients. EC patients had a significantly different prognosis depending on the presence of pelvic peritoneal carcinomatosis only (2023 FIGO stage IIIB), extrapelvic peritoneal carcinomatosis (2023 FIGO stage IVB) or distant intra-and extraabdominal disease (including lymph nodes beyond the pelvic/paraaortic region and parenchymal metastases, 2023 FIGO stage IVC). 5-year PFS rates ranged from >60% for stage IIIB and <10% for stage IVC.

demonstrating 5-year EC-specific mortality rates of 56.3% at bowel- and bladder mucosa infiltration alone (2023 FIGO stage IVA), 62.7% at the presence of extrapelvic peritoneal carcinomatosis (stage IVB), and 71.4% in distant intra- and extra-abdominal disease (stage IVC, $p < 0.001$) [17]. The improved discrimination of previous heterogenous 2009 FIGO stage IV disease is clinically important. Treatment decision making in terms of surgical versus non-surgical first line treatment and/or extent and type of surgery varies significantly in cases with limited pelvic versus extensive/extrapelvic peritoneal carcinomatosis [17], especially in view of our markedly more effective novel therapeutic modalities [31,32]. A National Cancer Database analysis between FIGO 2009 and 2023 of >130,000 patients also supports the above findings (Gravbot, personal communication). The Ten-year OS for 2023 FIGO stage IIIB2 (pelvic peritoneal carcinomatosis only), was 49.4%, compared to 18.7% for 2009 stage IVB patients. In general, substage hazard ratios for death spanned a wider range across stages in the 2023 FIGO staging system compared to the 2009 system (1.21–16.88 versus 2.08–11.58).

4.3.4. Relevance of the 2023 FIGO staging for the development and implementation of clinical trials

Beyond prognosis, 3 randomized controlled trials (RTCs) have delivered level I evidence this year for the predictive value of MMRd status for IO treatment in addition to chemotherapy in advanced and recurrent EC and lead to molecular-subgroup specific approvals in Europe and the US [34–36]. RTC trials evaluating IO monotherapy in the biomarker selected MMRd patient population are ongoing. Multiple clinical trials have demonstrated the impressive clinical benefit of molecularly targeted agents in specific biomarker positive EC patient populations, e.g. Selinexor in p53 wild-type patients [44] or Trastuzumab-deruxtecan in HER2 positive patients [45]. Adjuvant treatment trials assigning specific treatment according to specific molecular subtypes are ongoing, e.g. the RAINBO trial [46] and PORTEC-4a [47]. Surgical trials prospectively evaluating the incidence and pattern of extrauterine spread in EC according to molecular subtypes in fully surgically staged patients are on the way and may provide a starting point for investigating differential surgical approaches per molecular subtype in future trials [48]. The 2023 FIGO staging system integrates information on molecular subtypes, improves prognostication and identifies treatment-relevant subgroups, and thus will facilitate more clinically relevant trial design and support individualized treatment approaches.

4.4. Health equity

We believe the FIGO 2023 staging of EC can facilitate more equitable health care for all women. We stress the new system encourages molecular testing for the benefit of EC patients but does not mandate it. The (optional) integration of molecular subtypes into the new FIGO staging system emphasizes the pivotal clinical impact of molecular testing for improved prognostication and crucially for treatment decision making in EC patients and consequently leverages global accessibility to molecular testing for all patients with EC. Optimal delivery of care to EC patients is hampered when molecular testing is not readily accessible and thus all efforts in support of equitable global access must be undertaken. Whelan et al. and others have documented that Black patients were more likely than White patients to have p53-abnormal EC ($N = 362$, 71.1% vs 53.2%, $p = 0.003$) [49]. This is consistent with previous findings that showed the prognostically unfavorable TCGC molecular subtypes to be more common in Black EC patients [50]. The higher frequency of these adverse molecular subtypes among Black patients may contribute to survival disparities. Attention to this important fact in the new staging system will influence adjuvant therapy choices and encourage trial design for and inclusion of disadvantaged populations. The 2023 FIGO staging prompts stakeholders and health care regulators to recognize the significance of broad implementation and availability of molecular testing. Significant costs will be saved with the adoption of FIGO 2023 through facilitation of individualized effective treatments [51]. Systemic treatments including chemotherapy and immunotherapy as well as radiotherapy are expensive treatment modalities. The new FIGO staging system guides a more precise prognostic evaluation and identifies relevant patient subgroups for treatment de-escalation, escalation, and individualized approaches, respectively. This includes

patients in whom adjuvant treatment can be spared, e.g. in the new FIGO stages IA3 and $IAm_{POLEmut}$. The higher prognostic granularity of new FIGO staging system allows a more tailored therapy for individual patients and thus is more personalized in a diverse patient population. This is particularly important for women from rural settings who may travel many hours to a cancer therapy location for their adjuvant therapy.

4.5. Critiques

The new FIGO has been criticized for no longer being a staging system, but rather a combined prognostic/staging system. It is important to note that the FIGO staging systems have always been prognostic systems. Actually, the prognostic significance is fundamental to the nature of the FIGO staging system. A prognostic system has greater relevance and utility for the patient and the physician who treats her. Initially, the only prognostic parameters available were the anatomic borders of disease spread. This has substantially changed. A myriad of studies has demonstrated the pivotal prognostic relevance of markers reflecting tumor biology, such as molecular subtypes, extend of LVSI, grading and histological subtypes [3–11,22,24–30,40–42]. Moreover, purely anatomic borders have been shown to lose their prognostic relevance in the presence of these dominant tumor biology markers [3–11,25–27]. Thus, integration of these biological markers into the prognostic FIGO staging system is crucial. Any prognostic system that is exclusively limited to the evaluation of anatomic spread would be inherently handicapped. Therefore, (the new 2023 FIGO does not substitute an anatomical staging system for a prognostic staging system,) the new 2023 FIGO improves and advances the prognostic FIGO system with the integration of tumor biology into the description of anatomic spread. The new FIGO staging system requires a change in our perception of a staging system (paradigm shift), from a traditional purely anatomic border-based system to an integrated staging system respecting anatomic borders AND tumor biology as pivotal prognostic factors for EC patients.

The immediate and distant future will bring greater precision in prognosis (and treatment) with thorough staging systems for other malignancies that include pathologic and molecular parameters alongside the anatomic extension of the tumors. FIGO and AJCC started this process by integrating biomarkers, such as estrogen receptor (ER) and progesterone receptor (PR) expression and HER2 expression and/or amplification into the prognostic staging system of breast cancer patients 6 years ago [52]. The TNM staging system for patients with oropharyngeal carcinoma incorporates the finding of human papillomavirus (HPV) into that system [53]. Perineural invasion is incorporated into the TNM staging system as a criterion for T3 tumors in squamous cell carcinoma of the skin. For melanoma, ulceration is also considered [54,55].

The FIGO 2023 system is clearly more complex than its predecessor. An increased reporting workload is required by our pathology colleagues. Additionally, the objective determination of LVSI can be difficult and may require shorter processing times of the surgical specimens to prevent artifact. IHC is widely available for determination of MMR and p53 status. In many countries, adoption of POLE testing is currently limited. Like most new technologies, costs will likely be reduced over time. The highest incident cancer in the world is non-small cell lung cancer and mutational testing is performed now in both adenocarcinomas and squamous cell carcinomas. We anticipate that the FIGO 2023 system will spur worldwide adoption of molecular classification so more tailored and effective therapy will be available for our EC patients. Going forward, we continue to support alignment with AJCC, UICC, patient advocates and other stakeholders.

5. Conclusion

The FIGO 2023 system provides improved prognostic precision for patients with EC and identifies distinct treatment relevant subgroups. We anticipate this will facilitate more tailored therapy for patients and aid in clinical trial design. FIGO 2023 provides relevant and actionable information for disadvantaged populations by the (optional) integrations of molecular subgroups. It reinforces the pivotal role of molecular testing to deliver optimal care to EC patients leveraging a strong demand for global access. Hence, we anticipate it results in more equitable therapy choices. The differentiation level of FIGO 2023 reflects the diversity of the disease with distinct prognostic subgroups and the increasing complexity of our treatment algorithms as we enter the 2nd decade following publication of The Cancer Genome Atlas which heralded the molecular era. The pivotal role of tumor biology factors, such as LVSI and molecular subtypes, for both improved prognostication and treatment decision making processes, led to their integration in major international guidelines a couple of years ago and to their wide adoption in clinical practice. Their integration in the 2023 FIGO staging system is the natural next step in the evolution of the revolution.

CRediT authorship contribution statement

David Gaffney: Writing – original draft, Visualization, Investigation, Conceptualization. **Xavier Matias-Guiu:** Writing – review & editing, Visualization, Investigation. **David Mutch:** Writing – review & editing, Visualization, Investigation. **Giovanni Scambia:** Writing – review & editing, Visualization, Investigation. **Carien Creutzberg:** Writing – review & editing, Visualization, Investigation. **Christina Fotopoulou:** Writing – review & editing, Visualization, Investigation. **Jonathan S. Berek:** Writing – review & editing, Visualization, Investigation. **Nicole Concin:** Writing – original draft, Visualization, Investigation, Conceptualization.

Declaration of competing interest

David Gaffney: DSMC Chair of Merck trial, co-Chair Gyn Committee NRG Oncology, member Board of Directors for International Gyn Cancer Society, PI of NCI LAPS grant to Huntsman Cancer Institute.

Xavier Matias-Guiu: Advisory Boards: Astra-Zeneca, Lilly, Amgen, GSK, Janssen, Illumina, MSD.

David Mutch: PI of the Endometrial Cancer SPORE.

Giovanni Scambia: No conflicts of interest to declare at this time.

Carien Creutzberg: DSMC member of a Merck trial, chair of GCIG Endometrial Committee, member of ESGO Guidelines Committee, Dutch Cancer Society grants for PORTEC trials.

Christina Fotopoulou: Honoraria received from AZ, MSD, Roche, GSK, Oncoinvent.

Jonathan S. Berek: Research grants from Immunogen and Eisai.

Nicole Concin: Consulting/Advisory activities for ImmunoGen, Seagen, Akesobio, EISAI, GSK, AZ, Mersana, Seattle Genetics, eTheRNA immunotherapies NV, Kartos; Travel Expenses from Roche, Genmab, Amgen; Educational fees from Kartos, MSD, Medscape Oncology, TouchIME; functions in societies: President of the ESGO, Co-Chair of ENGOT Early Drug Development Network, FIGO committee for women's cancer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.02.002.

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