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FIGO Staging Update

FIGO staging of endometrial cancer: 2023

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ABSTRACT

Introduction: Many advances in the understanding of the pathologic and molecular features of endometrial cancer have occurred since the FIGO staging was last updated in 2009. Substantially more outcome and biological behavior data are now available regarding the several histological types. Molecular and genetic findings have accelerated since the publication of The Cancer Genome Atlas (TCGA) data and provide improved clarity on the diverse biological nature of this collection of endometrial cancers and their differing prognostic outcomes. The goals of the new staging system are to better define these prognostic groups and create substages that indicate more appropriate surgical, radiation, and systemic therapies.

Methods: The FIGO Women's Cancer Committee appointed a Subcommittee on Endometrial Cancer Staging in October 2021, represented by the authors. Since then, the committee members have met frequently and reviewed new and established evidence on the treatment, prognosis, and survival of endometrial cancer. Based on these data, opportunities for improvements in the categorization and stratification of these factors were identified in each of the four stages. Data and analyses from the molecular and histological classifications performed and published in the recently developed ESGO/ESTRO/ESP guidelines were used as a template for adding the new subclassifications to the proposed molecular and histological staging system.

Results: Based on the existing evidence, the substages were defined as follows:
Stage I (IA1): non-aggressive histological type of endometrial carcinoma limited to a polyp or confined to the endometrium; (IA2) non-aggressive histological types of endometrium involving less than 50% of the myometrium with no or focal lymphovascular space invasion (LVSI) as defined by WHO criteria; (IA3) low-grade endometrioid carcinomas limited to the uterus with simultaneous low-grade endometrioid ovarian involvement; (IB) non-aggressive histological types involving 50% or more of the myometrium with no LVSI or focal LVSI; (IC)

Conflict of Interest

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aggressive histological types, i.e. serous, high-grade endometrioid, clear cell, carcinosarcomas, undifferentiated, mixed, and other unusual types without any myometrial invasion.

Stage II (IIA): non-aggressive histological types that infiltrate the cervical stroma; (IIB) non-aggressive histological types that have substantial LVSI; or (IIC) aggressive histological types with any myometrial invasion.

Stage III (IIIA): differentiating between adnexal versus uterine serosa infiltration; (IIIB) infiltration of vagina/parametria and pelvic peritoneal metastasis; and (IIIC) refinements for lymph node metastasis to pelvic and para-aortic lymph nodes, including micrometastasis and macrometastasis.

Stage IV (IVA): locally advanced disease infiltrating the bladder or rectal mucosa; (IVB) extrapelvic peritoneal metastasis; and (IVC) distant metastasis. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all endometrial cancers. If the molecular subtype is known, this is recorded in the FIGO stage by the addition of "m" for molecular classification, and a subscript indicating the specific molecular subtype. When molecular classification reveals p53abn or *POLEmut* status in Stages I and II, this results in upstaging or downstaging of the disease ($IICm_{p53abn}$ or $IAm_{POLEmut}$).

Summary: The updated 2023 staging of endometrial cancer includes the various histological types, tumor patterns, and molecular classification to better reflect the improved understanding of the complex nature of the several types of endometrial carcinoma and their underlying biologic behavior. The changes incorporated in the 2023 staging system should provide a more evidence-based context for treatment recommendations and for the more refined future collection of outcome and survival data.

Keywords: Cancer Staging; Endometrial Cancer; Endometrial Cancer Molecular Staging; FIGO Cancer Staging; FIGO Endometrial Cancer Staging

INTRODUCTION

Since the publication of the last International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer in 2009, a considerable amount of new information has emerged that better defines the pathology and molecular findings as they relate to the type of endometrial carcinoma. In addition, new treatments, results of clinical trials, and prognostic and survival data that correlate with pathologic and surgical findings have been reported. Therefore, the FIGO Committee on Women's Cancer determined that modifications and updates in the staging system were warranted to reflect these new findings and data (**Tables 1** and **2**).

PATHOLOGY

1. Histological type

Histopathological findings are central features of the 2023 revision of the FIGO staging of endometrial carcinoma.

Histological tumor type is an important prognostic predictor in endometrial carcinoma. All endometrial carcinomas should be classified according to the 5th edition of *WHO Classification of Tumors, Female Genital Tumors* [3]. The following different histological types have been recognized: 1) endometrioid carcinoma (EEC), of low grade (grades 1 and 2) or high grade

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Table 1. 2023 FIGO staging of cancer of the endometrium*,†

Stage	Description
Stage I	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 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 II	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 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)‡
	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 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

EEC, endometrioid carcinoma; ESGO, European Society of Gynecological Oncology; ESP, European Society of Pathology; ESTRO, European Society for Therapeutic Radiology and Oncology; FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumor cell; LVSI, lymphovascular space involvement; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; SLN, sentinel lymph node; WHO, World Health Organization.

*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 (**Table 2**).

†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. 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 identify disease truly confined to the uterus. Thus, the ESGO-ESTRO-ESP guidelines allow an approach of SLN in all patients with endometrial carcinoma, which is endorsed by FIGO. 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 thorough (ultrastaging) staging as it will increase the detection of low-volume disease in lymph nodes.

‡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. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (Stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1), by the following criteria: 1) no more than superficial myometrial invasion is present (<50%); 2) absence of extensive/substantial LVSI; 3) absence of additional metastases; and 4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

§LVSI as defined in WHO 2021: extensive/substantial, ≥5 vessels involved.

‖Grade and histological type

- Serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are considered high-grade by definition. For EECs, grade is based on the proportion of solid areas: low grade = grade 1 (≤5%) and grade 2 (6%–50%); and high grade = grade 3 (>50%). Nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumor by one. The presence of unusual nuclear atypia in an architecturally low-grade tumor should prompt the evaluation of p53 and consideration of serous carcinoma. Adenocarcinomas with squamous differentiation are graded according to the microscopic features of the glandular component.
- Non-aggressive histological types are composed of low-grade (grade 1 and 2) EECs. Aggressive histological types are composed of high-grade EECs (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.
- It should be noted that high-grade EECs (grade 3) are a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making [1]. Without molecular classification, high-grade EECs cannot appropriately be allocated to a risk group and thus molecular profiling is particularly recommended in these patients. For practical purposes and to avoid undertreatment of patients, if the molecular classification is unknown, high-grade EECs were grouped together with the aggressive histological types in the actual FIGO classification.

¶Micrometastases are considered to be metastatic involvement (pN1[mi]). The prognostic significance of ITCs is unclear. The presence of ITCs should be documented and is regarded as pN0(i+). According to TNM8, macrometastases are >2 mm in size, micrometastases are 0.2–2 mm and/or >200 cells, and isolated tumor cells are ≥0.2 mm and ≤200 cells [2]. Based on staging established by FIGO and the American Joint Committee on Cancer (AJCC). *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

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Table 2. FIGO endometrial cancer stage with molecular classification*

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

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space involvement; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal.
*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 *POLEmut*
- Intermediate prognosis: MMRd/microsatellite instability and NSMP
- Poor prognosis: 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}.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

Conceptualization: B.J.S., M.G.X., C.C., F.C., G.D., K.S., L.K., M.D., C.N.; Investigation: B.J.S., M.G.X., C.C., F.C., G.D., K.S., L.K., M.D., C.N.; Methodology: B.J.S., M.G.X., C.C., F.C., G.D., K.S., L.K., M.D., C.N.; Project administration: B.J.S.; Supervision: B.J.S.; Visualization: B.J.S.; Writing - original draft: B.J.S., M.G.X., C.C., F.C., G.D., K.S., L.K., M.D., C.N.; Writing - review & editing: B.J.S., M.G.X., C.C., F.C., G.D., K.S., L.K., M.D., C.N.

(grade 3); 2) serous carcinoma (SC); 3) clear cell carcinoma (CCC); 4) mixed carcinoma (MC); 5) undifferentiated carcinoma (UC); 6) carcinosarcoma (CS); 7) other unusual types, such as mesonephric-like; and 8) gastrointestinal mucinous type carcinomas. These different histological types have different molecular features, microscopic appearance, precursor lesions, and natural history. Previous studies have shown that histological typing may be essential in staging [4]. In this revised FIGO staging, non-aggressive histological types are composed of low-grade (grades 1 and 2) EECs, while aggressive histological types are composed of high-grade EECs (grade 3), SC, CCC, MC, UC, CS, and mesonephric-like and gastrointestinal type mucinous carcinomas. Importantly, high-grade EEC (grade 3) is a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification [1]. Molecular profiling within this high-grade EEC group is able to discriminate an excellent prognosis group (*POLEmut* in early-stage disease) from a bad prognosis group (p53 abnormal [p53abn]). It should be noted that recent data have demonstrated that high-grade EECs falling into the non-specific molecular profile (NSMP) group, especially when estrogen receptor (ER)-negative, also have a bad prognosis [5,6]. Furthermore, it is well established that in the mismatch repair deficient (MMRd) molecular subtype, grading does not matter. Thus, without molecular classification, high-grade EECs cannot be appropriately allocated to a risk group. Molecular profiling is of particular importance and highly recommended in high-grade EECs. 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.

The 2020 World Health Organization (WHO) classification [3] incorporates mucinous carcinoma as a variant of low-grade EECs because of its shared molecular features and natural history. It is distinguished from gastrointestinal type mucinous endometrial carcinoma, a rare type of tumor with different features and worse prognosis, which should be considered high-grade and included in the group of aggressive histological types.

2. Tumor grade

Characterization of histological grade is very important in both the initial biopsy/curettage and the final hysterectomy specimen, especially in EEC and in NSMP [1]. SC, CCC, MC, UC, CS, and mesonephric-like and gastrointestinal mucinous type carcinomas are considered high-grade by definition.

For EECs, grading is prognostically significant [7,8]. The grading criteria for EECs are primarily based on architectural features [9]. In this revised FIGO staging scheme, the binary approach of *WHO Classification of Tumors, Female Genital Tumors* [3] has been adopted. In brief, low-grade EECs are subdivided into grade 1 and 2 tumors, which exhibit up to 5% and 6%–50% solid non-glandular growth, respectively [9]. In contrast, high-grade EECs (grade 3) are characterized by 50% or more solid component. This binary grading system allows easier clinical decision-making and has improved reproducibility [10], but it is prudent to remember that the three-tiered system is still of value in patients requesting fertility-preserving strategies. It is important to consider that nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumor by one. Nuclear atypia in an architecturally low-grade EEC should be taken as an indication to rule out CS. EECs with squamous differentiation are graded according to the microscopic features of the glandular component. The International Society of Gynecological Pathologists (ISGYP) guidelines endorse the interpretation of a confluent microacinar pattern as solid growth, although there is no definitive scientific evidence in support of this [10]. Grading is especially important in NSMP endometrioid cancers. MMRd and *POLEmut* endometrioid cancers can seem high-grade because of their frequent mutations.

3. Myometrial invasion

The extent of myometrial invasion has long been recognized as an essential prognostic risk factor [11]. 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% [12-15]. The assessment of tumor invasion from adenomyosis is a controversial issue without strong scientific evidence [16].

4. Lymphovascular space invasion (LVSI)

LVSI should be assessed at the invasive front of the tumor [16,17]. It is crucial to distinguish LVSI from mimickers, such as a microcystic elongated and fragmented (MELF) pattern of myometrial invasion and retraction artifacts [18-20] that may occur in the setting of minimally invasive surgery. It is very important to distinguish "substantial" or "extensive" LVSI from "focal" or "no" LVSI [21-23]. Although determination of the precise number of involved vessels to discriminate between focal and extensive/substantial requires additional scientific evidence, for staging purposes the recommendation by WHO 2020 (≥5 vessels) is adopted [3].

The recognition of myometrial invasion and identification of LVSI in tumor tissue is dependent on appropriate sampling. Therefore, it is important to consider ISGYP recommendations, which state that one section per centimeter of the largest tumor dimension will suffice [24].

5. Cervical stromal invasion

Cervical stromal invasion is subjected to significant inter-observer variation [25,26] and strict criteria are recommended. Any invasion of the cervical stroma, identified at the level of or deeper than a benign endocervical crypt, should be considered cervical stromal invasion. Cervical glandular extension is not considered for staging.

6. Adnexal involvement

Adnexal involvement has an impact on overall survival [27,28]. In the past, it was considered necessary to distinguish between endometrial carcinoma with ovarian metastasis and synchronous primary tumors of the endometrium and the ovary. In the case of high-grade

tumors, ovarian involvement is almost always categorized as metastatic. However, 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 [29,30]. This clonal relationship is not always concordant with the clinical outcomes expected of metastatic endometrial carcinoma.

Accordingly, the 2020 edition of the WHO classification [3] and the European Society of Gynecological Oncology (ESGO), European Society for Therapeutic Radiology and Oncology (ESTRO), and European Society of Pathology (ESP) guidelines [31] suggest conservative management (as if they were 2 independent primaries) for the group of patients with simultaneous low-grade carcinomas of the endometrium and the ovary if specific criteria are present, showing a good prognosis [32]. This revised 2023 FIGO staging for endometrial carcinoma endorses this view and establishes 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; and 4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/breach (equivalent to pT1a). The cases not fulfilling these criteria should be interpreted as extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1).

Tumor involvement of the fallopian tube should also be recorded and staged as IIIA1. Tubal involvement by endometrial carcinoma in the form of intramucosal spread has controversial prognostic significance, without strong scientific evidence. Pathologists should be careful in distinguishing tubal involvement by serous carcinoma from the coincidental presence of an independent serous tubal intraepithelial carcinoma; in these cases, appropriate sampling (SEE-FIM protocol) [33], as well as ancillary diagnostic techniques, such as immunohistochemistry and molecular pathology, are required. The presence of intraluminal tubal floating tumor fragments is a controversial issue, particularly in serous carcinoma, but is not considered for staging purposes. The same applies for positive washing cytology.

7. Uterine serosal involvement

By following ISGYP recommendations [16], uterine serosal involvement is 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.

8. Lymph node status

Lymph node status is an important prognostic factor for endometrial carcinoma. According to TNM8 [2], macrometastases are larger than 2 mm, micrometastases are 0.2–2 mm 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. A finding of isolated tumor cells does not upstage a carcinoma [2,34]. Ultrastaging is recommended for the analysis of sentinel lymph nodes [35-37].

9. Molecular classification

One of the major advances in the diagnosis and treatment of endometrial carcinoma during the past decade has been the ability to molecularly segregate and classify these carcinomas. Molecular features can be used to estimate risk of recurrence and hence survival [38-41].

Perhaps the most impactful molecular classification is that proposed by The Cancer Genome Atlas (TCGA) [33], which classifies endometrial carcinomas into 4 categories: 1) *POLE*/

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ultramutated, with somatic inactivating hotspot mutations in the *POLE* exonuclease domain and a very high mutational burden (ultramutated). Irrespective of grade, *POLE* mutated tumors have an excellent prognosis; 2) microsatellite instability-high/hypermutated, characterized by EECs or undifferentiated carcinomas with MMRd/microsatellite instability, have an intermediate prognosis; 3) somatic copy-number alteration high/serous like (SCNA-high) with a low mutation rate, nearly universal (95%) *TP53* mutations, and a highly unfavorable prognosis. Most of these tumors are serous carcinomas, but up to 25% are endometrioid (mostly high-grade) and carcinosarcomas; and 4) somatic copy-number alteration low (SCNA-low), which includes EECs and CCCs with low copy-number alterations and low mutational burden. In this intermediate group, ER expression and histological grade impact the prognosis [5,6].

TCGA molecular-based classification can be applied to clinical practice, by using a simplified surrogate that includes three immunohistochemical markers (p53, MSH6, and PMS2) and one molecular test (analysis for pathogenic *POLE* mutations). This surrogate approach classifies endometrial carcinoma into 4 groups: *POLEmut*; MMRd; p53abn; and NSMP. According to the 2020 edition of the WHO classification [3], abnormal p53 (mutation-type) staining is characterized by either strong nuclear expression in tumor cells (>80%), the complete absence of expression in tumor cells with retained internal control, or, rarely, unequivocal cytoplasmic expression.

Several studies have demonstrated the prognostic value of this TCGA-surrogate approach. *POLEmut* denotes a favorable prognosis. MMRd and NSMP indicate an intermediate prognosis, while p53abn indicates a poor prognosis. Most notably, data suggest that carcinomas falling into the *POLEmut* group may benefit from de-escalation of postoperative adjuvant therapy because of the consistently better outcome in these cases. In contrast, p53abn has a much worse prognosis, suggesting that some form of increased intensive therapy may be of benefit. Improved risk assessment by integrating molecular and clinicopathological factors in endometrial carcinoma has been demonstrated by many studies [42-50]. Furthermore, the TCGA surrogate approach has been verified by the molecular portion of PORTEC 3 [38].

There is a small subset of tumors (approximately 5%) that combine more than one molecular feature (e.g., *POLEmut* and p53abn or MMRd and p53abn), and they are referred to as "multiple classifiers." In the case of multiple classifiers with *POLEmut* or MMRd and secondary p53 abnormality, the available scientific evidence indicates that they should not be classified as p53abn, because they retain the favorable prognosis of *POLEmut* or MMRd tumors; however, this is still an evolving field. Patients with both *POLEmut* and p53abn should be considered *POLEmut*; patients with both MMRd and p53abn should be considered MMRd [40]. For tumors with both a pathogenic *POLEmut* and MMRd, data are limited, and therefore screening for Lynch syndrome should be considered.

Integrating all currently available evidence, FIGO has taken the position that, when feasible, the addition of molecular subtype evaluation to the staging criteria should be performed as it allows a better prediction of prognosis in a staging/prognosis scheme (**Table 2**). The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial carcinoma for prognostic risk-group stratification and as potential influencing factors for adjuvant or systemic treatment decisions. Molecular subtype assignment can be conducted on a biopsy specimen, in which

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appropriate handling and control of fixation conditions may allow for a better performance of immunohistochemical and molecular techniques than on the final hysterectomy specimen.

The molecular characterization of endometrial cancer and its clinical relevance is a rapidly evolving field and changes can continue to occur based on incoming data. As noted, several groups have shown that molecular subtypes of endometrial cancer have a substantial impact on prognosis, recurrence, and survival outcomes in various cohorts of patients [30]. Depending on the molecular profile, adjuvant strategies that would de-escalate or intensify treatments after surgery are being defined. With respect to systemic treatment in primary advanced and recurrent endometrial cancer, 2 randomized Phase III trials (ENGOT-en6/GOG-3031/RUBY and NRG-GY018/Keynote-868) have demonstrated a statistically significant and unprecedented PFS advantage with the addition of an immune checkpoint inhibitor (ICI) (dostarlimab or pembolizumab, respectively) to standard carboplatin/paclitaxel chemotherapy followed by ICI maintenance therapy in MMRd patients with a hazard ratio (HR) of 0.28 (95% confidence interval [CI], 0.16–0.5) and 0.30 (95% CI, 0.19–0.48), respectively [51,52]. Several clinical trials investigating adapted adjuvant treatment after surgery or different systemic treatment options in patients with advanced/recurrent endometrial carcinoma based on molecular profiles are in progress.

FIGO STAGING OF ENDOMETRIAL CANCER

1. Stage I

The 2023 revised FIGO staging system includes major changes to Stage I. In most cases, Stage I is restricted to tumors confined to the uterine corpus, characterized by non-aggressive histological types (i.e., low-grade EEC), the absence of substantial/extensive LVSI, or aggressive histological types without myometrial invasion.

Stage IA1 tumors include those that are limited to an endometrial polyp or confined to the endometrium of non-aggressive histological types (i.e., low-grade EECs). Stage IA2 includes tumors of non-aggressive histological type involving up to 50% of the myometrium, with no LVSI or focal LVSI. Stage IA3 tumors are low-grade endometrioid carcinomas limited to the uterus with simultaneous low-grade endometrioid ovarian involvement, if the following criteria are met: 1) no more than superficial myometrial invasion is present (<50%); 2) the absence of substantial/extensive LVSI; 3) the absence of additional metastases; and 4) unilateral ovarian tumors, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

Stage IB tumors represent non-aggressive histological types (i.e., low-grade EECs) with invasion of 50% or more of the myometrium, and with no or focal LVSI.

Stage IC tumors are aggressive tumor types within a polyp or confined to the endometrium without myometrial invasion.

The rationale for establishing these categories is evidence-based. Endometrial carcinomas limited to endometrial polyps or confined to the endometrium (any histology subtypes) are associated with a good prognosis [53,54]. A staging operation is necessary to establish this category. A significant proportion (≥40%) of high-grade tumors (particularly serous carcinomas) assumed to be limited to a polyp or the endometrium have occult lymph node and/or peritoneal involvement when appropriately staged and hence are actually Stage III disease [55-57].

Low-grade EECs are associated with a good prognosis when they are limited to the uterine corpus and there is no LVSI or focal LVSI [4,23,58-62].

There is a subset of patients with low-grade endometrioid carcinomas involving the endometrium and the ovaries, which are associated with a good prognosis [63-65]. They were previously described as synchronous independent tumors, but molecular analysis has established a common clonal origin [29,30]. FIGO endorsed the criteria by WHO and ESGO-ESTRO-ESP guidelines to identify this group of tumors that are categorized as Stage IA3 [3,31].

The absence of LVSI and focal LVSI have been related to a good prognosis in opposition to substantial/extensive LVSI in low-grade EECs restricted to the uterus [23,60-62]. The criteria for LVSI follow the rules of WHO [3]. Accordingly, LVSI should fall into one of the following three categories: "LVSI negative" (0 vessels); "LVSI focal" (<5 vessels); or "LVSI substantial/extensive" (≥5 vessels).

2. Stage II

The revised staging system includes major changes to Stage II. The number of women with Stage II tumors will markedly increase under the new staging system. Stage IIA tumors include non-aggressive histotlogical that have invasion of the cervical stroma. Stage IIB now represents cases that include non-aggressive histological types with substantial LVSI as defined by the WHO 2021 report, regardless of local tumor spread. An extensive body of literature supports these findings. Randomized trials, prospective cohort studies, large database series, and single-institution reports consistently demonstrate that LVSI is an independent and strong prognostic factor for the recurrence of endometrial carcinoma [66-69]. A retrospective registry study of more than 1,500 patients from Sweden with Stage I–III identified LVSI as the strongest independent risk factor for lymph node metastases and decreased survival, even in the absence of lymph node metastases in patients with endometrioid adenocarcinomas [67].

Stage IIC tumors represent aggressive histological types with any myometrial involvement, while aggressive histological types without myometrial involvement are Stage IC. Aggressive histological types include high-grade endometrioid, serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas. Once again, randomized trials, prospective cohort studies, large database series, and retrospective reports consistently demonstrate that aggressive histological types have a markedly higher rate of relapse [70,71].

Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial carcinoma has been demonstrated by many studies [38,39,41-47,72].

3. Stage III

In Stage III, the tumor has spread locally or regionally. The revised subclassifications aim to better reflect the clinical picture and prognosis and enable a more appropriate treatment decision-making process. The differences from the previous staging system are summarized below.

First, differentiation between adnexal (IIIA1) versus uterine serosa infiltration (IIIA2) in Stage IIIA is defined to better reflect tumor behavior, especially in high-grade and non-endometrioid carcinomas.

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Second, Stage IIIB is now divided into 2 substages. Stage IIIB1 aligns with the previous Stage IIIB disease and is characterized by involvement of the vagina and/or the parametria. Involvement of the pelvic peritoneum is now classified as IIIB2 (previous Stage IV) to better reflect clinical treatment decisions in terms of indication for surgery versus non-surgical first-line treatments for patients with advanced stage disease. These treatment decisions vary significantly in cases with limited pelvic versus extensive/extrapelvic peritoneal carcinomatosis. The anatomical landmark of the pelvis is the line between the anterior superior iliac spines.

Third, Stage IIIC is further divided into micrometastasis (IIIC1i, IIIC2i) and macrometastasis to the lymph nodes (IIIC1ii, IIIC2ii), while isolated tumor cells are not considered metastatic and regarded as pN0(i+). The substaging is based on the better prognosis in those patients who have micrometastasis to the lymph nodes [73-77]. This subcategorization also reflects the increasing utilization of the sentinel lymph node technique and ultrastaging, which allows improved identification of small volume disease, including micrometastasis. A reasonable approach for the surgical designation of Stage III versus Stage IV is the upper limit of the para-aortic lymph node metastasis to the renal vessels bilaterally.

Finally, low-grade EECs involving both the endometrium and ovary and matching specific criteria are no longer classified as Stage III but as Stage IA3 tumors, because they show evidence of a clonal relationship and can be considered to have an overall good prognosis [29]. For those cases, no adjuvant treatment is recommended. Stage IA3 excludes cases with adnexal involvement and more than 50% myometrial invasion, presence of substantial LVSI, bilateral ovarian involvement, capsule breech, and presence of additional metastatic lesions. These cases remain as Stage III and require adjuvant treatment as before.

4. Stage IV

The main change to this part of the FIGO staging system is the addition of an extra substage for those presenting with extrapelvic peritoneal metastasis, what is now classified as Stage IVB, and is distinguished from those with peritoneal involvement that does not extend beyond the pelvis, which is Stage IIIB2. Local invasion of bladder mucosa and/or intestinal/bowel mucosa remains Stage IVA, while distant metastases, including to any extra-abdominal lymph nodes or intra-abdominal lymph nodes above the renal vessels to the lungs, liver, brain, or bone, have now become Stage IVC.

Peritoneal carcinomatosis is overall rare (detected in approximately 2% of all patients with endometrial carcinomas) and these patients should be distinguished from those with distant metastases [78,79].

5. FIGO staging with molecular classification

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 a complete molecular classification surrogate (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial carcinoma for prognostic risk-group stratification and as potential influencing factors for adjuvant and systemic treatment decisions.

POLEmut denotes a favorable prognosis. MMRd and NSMP indicate an intermediate prognosis and therefore do not alter the stage, while p53abn indicates a poor prognosis.

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In early endometrial cancer, the presence of pathogenic *POLE* mutations or of p53 abnormalities now modifies the FIGO stage. For Stage I and II tumors based on surgical/anatomical and histological findings, a *POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type, is now classified as Stage $IAm_{POLEmut}$, whereas a p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion and regardless of the degree of LVSI, is classified as Stage $IICm_{p53abn}$. Although scientific evidence is limited, in the unusual situation when a low-grade EEC confined to the uterus is p53abn, the tumor is upstaged to $IIC2m_{p53abn}$. In the case of multiple classifiers with *POLEmut* or MMRd and secondary p53 abnormality, tumors should be considered as *POLEmut* or MMRd, and staged accordingly. The RAINBO program is a platform of four international clinical trials and an overarching research program that will address refining adjuvant treatment in endometrial cancer based on molecular features (ClinicalTrials.gov NCT05255653).

Advanced endometrial cancer stage based on surgical and/or clinicopathological features is not altered after additional molecular characterization, although more prognostic information and treatment directions are obtained by knowledge of the molecular classification. Thus, Stage III and IV tumors, for which molecular classification reveals p53abn, should be recorded as Stage $IIIm_{p53abn}$ or Stage IVm_{p53abn}, respectively, for the purposes of data collection. Furthermore, Stage III and IV tumors, for which molecular classification reveals MMRd, should be recorded as Stage $IIIm_{MMRd}$ or Stage IVm_{MMRd}, respectively, for the purpose of data collection and in view of its predictive value for ICI treatment and the demonstrated substantial progression-free survival and preliminary overall survival benefit. Advanced stage *POLEmut* endometrial carcinomas are a very rare category and although the clinical behavior seems favorable, this is based on anecdotal evidence, and for now these are classified as Stage $IIIm_{POLEmut}$ or Stage $IVm_{POLEmut}$.

DISCUSSION

The purpose of this revision of the FIGO endometrial cancer staging system is to incorporate the essential new published evidence as summarized above. The goal is to improve the clarity of the diverse biological nature of endometrial carcinomas with differing prognostic outcomes, better define these prognostic groups, and create substages that yield more appropriate surgical, radiation, and systemic therapies. As with all staging systems, the evolution of the updated classification must be based on the results of clinical studies.

The committee felt that the risk stratification, including the molecular classification that has recently been developed by ESGO, ESTRO, and ESP helps to better define the prognosis and therapeutic approaches for these diseases [80,81]. Therefore, it was determined that notation of the molecular classification, when performed, should be included to stage the patient's disease. Notwithstanding the fact that these tests may not be available in some settings, the molecular findings are sufficiently prognostic that treatment might be modified in those patients for whom this information is obtained.

The inclusion of molecular measures for endometrial cancer follows the work done with breast cancer staging in 2018, when, along with tumor grade, several molecular assays results—ER status, progesterone receptor status, and Her2*neu*—were added to the staging system to reflect the impact on prognosis of these significant molecular parameters [34].

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In summary, 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. The following changes have been incorporated into the updated endometrial cancer staging system:

- Stage I: (IA1) non-aggressive histological type limited to an endometrial polyp or confined to the endometrium; (IA2) non-aggressive histological types involving less than half the myometrium with no or focal LVSI as defined by the WHO criteria; (IA3) low-grade endometrioid carcinomas limited to the uterus with simultaneous low-grade endometrioid ovarian involvement; (IB) non-aggressive histological types involving one half or more of the myometrium with no or focal LVSI; and (IC) aggressive histological types limited to a polyp or confined to the endometrium.
- Stage II: (IIA) tumors that infiltrate the endocervical stroma, or (IIB) have substantial LVSI or (IIC) aggressive histological types, i.e., serous, clear cell, carcinosarcomas, undifferentiated, mixed, gastrointestinal-type mucinous endometrial carcinoma, and mesonephric-like carcinomas with any myometrial invasion.
- Stage III: (IIIA1) differentiation between adnexal versus (IIIA2) uterine serosa involvement; (IIIB1) vaginal and/or parametrial involvement and (IIIB2) pelvic peritoneal carcinomatosis; refinements are defined within Stage IIIC to reflect the extent of pelvic and abdominal lymph node metastases with (IIIC1i) micrometastasis and (IIIC2ii) macrometastasis.
- Stage IV: (IVA) reflects locally infiltrative, (IVB) extrapelvic peritoneal metastasis, and (IVC) distant metastatic disease.

When performed, the *POLEmut* and p53abn molecular groups can increase or decrease the stage of endometrial cancer in Stages I and II. No changes occur through the molecular staging in Stages III and IV. Stage III and IV cases, for which the molecular classification is known, should be recorded as Stage IIIm and Stage IVm with the specification of the molecular class for the purpose of data collection. Based on these molecular assays, an "m" notation is always required to indicate that the stage is modified in case of early stages or recorded in case of advanced stages.

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Appendix 1. Member list

Members and Associate Members of the FIGO Women's Cancer Committee, 2021–2023

Jonathan S. Berek (Chair), Sarikapan Wilailak (Vice Chair), Sean Kehoe (Past Chair), Rose Anorlu, Joanna Cain, Carien Creutzberg, Christina Fotopoulou, Gerhard Lindeque, Xavier Matias-Guiu, Orla McNally, David Mutch, Aikou Okamoto, Rene Pareja, Tali Pomerantz, Giovanni Scambia, Barbara Schmalfeld, Muna Addulrazak Tahlak.

Members of the FIGO Endometrial Cancer Staging Subcommittee, 2021–2023

Jonathan S. Berek (Chair), Nicole Concin, Carien Creutzberg, Christina Fotopoulou, David Gaffney, Sean Kehoe, Kristina Lindemann, Xavier Matias-Guiu, David Mutch.