

MINI-REVIEW

Aligning the treatment of endometrial cancer to FIGO stage based on European and American guidelines

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Abstract

In 2023 the International Federation of Gynecology and Obstetrics (FIGO) updated the endometrial cancer staging to better align with prognosis and therapy. We present an approach to treatment of patients with endometrial cancer based on their FIGO stage utilizing the European and American evidence-based treatment guidelines. The major difference between the American and European guidelines is that the American guidelines still utilize anatomic stage and histologic type, while the European guidelines have incorporated tumor molecular profile in their risk stratification. Another major difference is that for FIGO stage IC, the American guidelines recommend vaginal brachytherapy with or without chemotherapy, while the European guidelines recommend no adjuvant therapy.

Keywords

FIGO; Staging; Endometrial cancer; Treatment guidelines

In 2023, the International Federation of Gynecology and Obstetrics (FIGO) updated the staging for endometrial carcinoma (Table 1) [1]. This updated classification better aligns with prognosis. It also permits enhanced tailoring of adjuvant therapy for any given stage.

The most significant changes occurred in early-stage disease, *i.e.*, stage I and II. Histology is now considered part of the staging assignment. Low-grade (LG) carcinomas include grade 1 and 2 endometrioid tumors. High-grade carcinomas (*i.e.*, aggressive histology) include grade 3 endometrioid adenocarcinoma, serous carcinoma, clear cell carcinoma, mixed carcinomas, carcinosarcoma, gastrointestinal type mucinous carcinoma, mesonephric-like carcinoma, and undifferentiated carcinoma. Molecular profiling (*i.e.*, evaluation for the presence of polymerase epsilon (POLE) mutations (POLEmut), abnormal expression of p53 (p53abn), and mismatch repair (MMR) gene mutations) is also now recommended and included as part of the staging, especially for aggressive histologic types, since it will aid in prognostication and facilitate treatment planning. Absent or focal lymphovascular space invasion (LVSI) versus substantial/extensive LVSI (defined as 5 or more involved vessels) is now also part of certain staging definitions.

Patients with low-grade endometrioid adenocarcinoma of the endometrium and ovary are considered to have stage IA3 endometrial cancer if the following criteria are met: no more than 50% myometrial invasion, no substantial/extensive LVSI, unilateral ovarian involvement without rupture or involvement of the capsule, and no other sites are involved. Patients with stage IA3 disease are considered to have good prognosis.

In 2021, the European Society of Gynaecological Oncology

(ESGO), European Society for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP) provided updated guidelines for the treatment of patients with endometrial carcinoma based on prognostic groups [2]. The groups were stratified based on five prognostic risk levels: low, intermediate, high-intermediate, high, and advanced/metastatic. The low-risk group corresponds to FIGO 2023 stages IA1, IA2, IA3, and IA_{POLEmut} (any histology confined to the uterine corpus or with cervical invasion with any degree of LVSI that exhibits a POLE mutation). The intermediate risk group corresponds to FIGO 2023 stages IB and IC. The high-intermediate group corresponds to FIGO 2023 stages IIA and IIB. The high-risk group corresponds to FIGO 2023 stages IIC, IIC_{p53abn} (any histology with p53abn confined to the uterine body with any degree of myometrial invasion, with or without cervical invasion with any degree of LVSI), as well as stages III and IVA with no residual disease. Patients with grade 3 endometrioid adenocarcinoma with <50% myometrial invasion and none or focal LVSI are in the intermediate risk group. The advanced metastatic disease group corresponds to patients with FIGO 2023 stages III or IVA with residual disease, as well as those with stage IVB or IVC disease. Notably, as the 2021 ESGO/ESTRO/ESP guidelines reflect the most recent synthesis of histologic and molecular data, based on pertinent studies, these guidelines occasionally recommend treatments more or less aggressive, stage for stage, than those proscribed in the corresponding National Comprehensive Cancer Network (NCCN) and American Society of Radiation Oncology (ASTRO) guidelines [2, 3].

We review here our approach to the treatment of patients with endometrial cancer according to the FIGO 2023 stag-

TABLE 1. Crosswalk between FIGO staging and the European classification.

Low Risk	
Stage IA	Low-grade (LG) endometrial carcinoma (<i>i.e.</i> , grade 1 or 2 endometrioid adenocarcinoma) with <50% myometrial invasion and absent or focal (<5 involved vessels) lymphovascular space invasion (LVSI). It also includes patients with both endometrial and unilateral ovarian involvement, so long as the histology is LG endometrioid adenocarcinoma with <50% myometrial invasion, there is absent or only focal LVSI, there is no ovarian capsular involvement or rupture, and there are no other metastatic sites
Stage IA _{POLEmut}	Any histologic type with polymerase epsilon (POLE) mutation confined to the uterine corpus or with cervical extension with any degree of LVSI
Intermediate Risk	
Stage IB	LG endometrial carcinoma with ≥50% myometrial invasion and absent or focal (<5 involved vessels) LVSI
Stage IC	Aggressive histology limited to a polyp or confined to the endometrium
Stage IIC	Grade 3 endometrioid adenocarcinoma with <50% myometrial invasion and none or focal LVSI
High-intermediate Risk	
Stage IIA	LG endometrial carcinoma with cervical stromal involvement, with absent or focal (<5 involved vessels) LVSI
Stage IIB	LG endometrial carcinoma with substantial/extensive (≥5 involved vessels) LVSI, with or without cervical stromal involvement
High Risk	
Stage IIC	Aggressive histology with any myometrial invasion
Stage IIC _{m^{p53abn}}	Any histology that is p53 abnormal confined to the uterine corpus with any myometrial invasion, with or without cervical invasion with any degree of LVSI
Stage III (no residual disease)	Any histology with local or regional spread: adnexa and/or uterine serosa (IIIA), vagina, parametrium and/or pelvic peritoneum (IIIB), pelvic lymph nodes (IIIC1) or para-aortic lymph nodes (IIIC2)
Stage IVA (no residual disease)	Invasion of bladder and/or bowel mucosa
Advanced Metastatic	
Stage III or IVA (with residual disease)	Any histology with local or regional spread: adnexa and/or uterine serosa (IIIA), vagina, parametrium and/or pelvic peritoneum (IIIB), pelvic lymph nodes (IIIC1) or para-aortic lymph nodes (IIIC2), Invasion of bladder and/or bowel mucosa (IVA)
Stage IVB	Peritoneal metastasis above the pelvic brim
Stage IVC	Abdominal parenchymal metastases and/or metastases to intra-abdominal lymph nodes above the renal vessels, as well as extra-abdominal metastatic disease

ing system using the evidence-based European and American guidelines [2, 4]. We also indicate notable differences in ESGO/ESTRO/ESP guidelines and those of NCCN and ASTRO.

Patients with stage IA, including IA_{POLEmut}, are at low risk of recurrence. These patients can undergo surveillance and do not need adjuvant therapy.

Patients with stage IB or IC disease are at intermediate risk of recurrence and vaginal brachytherapy should be considered, especially if they are older than 60 years. FIGO IC disease is notably treated as lower overall risk in the European guidelines, favoring observation, even for p53-mutated tumors, whereas ASTRO and NCCN guidelines still recommend vaginal brachytherapy with or without chemotherapy.

Observation is an alternative in patients younger than 60 years if the cancer is estrogen receptor positive (ER+) and has a non-specific molecular profile (NSMP), *i.e.*, both p53 wild type (p53wt) and mismatch repair gene proficient (MMRp) without POLE mutations. Of note, patients with FIGO stage IIC grade 3 endometrioid adenocarcinoma with <50% myometrial invasion and none or focal LVSI are included in the intermediate risk category.

Patients with stage IIA or IIB endometrial cancer are considered at a high-intermediate risk of recurrence. Whole pelvis external beam radiation is recommended for these patients. However, observation can be considered in cases of stage IIA, NSMP, ER+ cancers. Vaginal brachytherapy boost is conditionally recommended in the NCCN and ASTRO guidelines.

Patients with stage IIC, including IICm_{p53abn}, and those with stage III–IVA with no residual disease are treated with concomitant external beam radiation and chemotherapy (e.g., cisplatin every three weeks) followed by four cycles adjuvant chemotherapy (e.g., carboplatin and paclitaxel). Alternatively, they may also be treated with sequential chemotherapy and radiation therapy or chemotherapy only, based on the patient's overall clinical status (e.g., performance status) and a synthesis of all pathological findings. The NCCN and ASTRO guidelines are more permissive to various combinations and sequencing of chemotherapy with or without external beam radiation therapy, with or without vaginal brachytherapy compared to the European guidelines.

The NCCN 2024 guidelines recommend adding trastuzumab to carboplatin and paclitaxel in cases of stage III or IV human epithelial growth factor receptor 2 (HER2)-positive uterine serous carcinoma and HER2-positive carcinosarcomas [4, 5]. The recommended adjuvant therapy for patients with stage IIIC1 with carcinosarcoma, clear-cell, serous or mixed histology or stage IIIC2 or IV (any histologic type) is carboplatin, paclitaxel, and dostarlimab-gxly regardless of the presence of measurable disease [4, 6]. These patients also have the option to receive consolidative radiotherapy with whole pelvic radiation or vaginal brachytherapy following systemic therapy per both European and American guidelines.

Patients with advanced/metastatic disease include those with FIGO 2023 stage IVB and IVC, and those with stage III and IVA with residual disease. In these cases, treatment should be individualized. Systemic therapy can be used if primary debulking surgery is considered not feasible or advisable. If there is a good response to systemic therapy, interval debulking surgery can be considered. Only enlarged lymph nodes should be removed. Residual lymph node disease can be treated with systemic therapy, radiation therapy or both. For cases of stage III or IVA with measurable disease, as well as stage IVB and IVC (except carcinosarcoma) the combination of carboplatin, paclitaxel, and pembrolizumab is suggested [4, 5]. An alternative for patients with stages IIIA, IIIB, IIIC1 (with measurable disease), or IV is carboplatin, paclitaxel and dostarlimab-gxly [4, 6].

The FIGO 2023 staging of endometrial carcinoma is certainly more complex than the previous staging classification [7]. It more than doubles the number of substages compared to the previous (2009) classification. However, in contrast to the previous staging system that used anatomic extent of the cancer, the FIGO 2023 staging classification adds biologically relevant parameters such as molecular subtype, extent of LVSI, histologic subtype and grade. Some have challenged some of the prognostic criteria that are part of the FIGO 2023 staging [8]. For example, one point of contest is whether the degree of LVSI (focal versus substantial) carries any more prognostic significance than the mere presence of LVSI. Moreover, something that additionally complicates the prognostic significance of this LVSI metric is that practices for counting vessel involvement are not rigidly defined. Some institutions may report the degree of vessel involvement within one tissue section, while others may sum the number of involved vessels in the aggregate collection of tissue sections being reviewed. There is also the inter- and intra-observer variability in diagnosing

histologic subtype and grade. Molecular profiling is not readily available, except in resource-rich institutions and countries. Even in the United States, testing for POLE mutations is not widely available.

In August 2025 the European societies provided an update to the 2021 guidelines (Table 2) [9]. In this update they address the use of immune checkpoint inhibitors and trastuzumab in patients with FIGO stage III or IV disease similar to the American guidelines. Different from the American guidelines, the European guidelines consider adding a poly (ADP-ribose) polymerase (PARP)-inhibitor to maintenance immune checkpoint inhibitor. The European guidelines also suggest that hormonal therapy is preferred in cases of low-grade estrogen receptor-positive, low volume or asymptomatic advanced disease, and for patients with recurrent slow-growing tumors. The updated European guidelines also state that although there is limited data suggesting that the risk of recurrence of FIGO 2023 stage IC is greater than for low grade endometrioid carcinomas, adjuvant therapy is “generally not recommended”. In contrast, the NCCN guidelines state that vaginal brachytherapy is preferred in this situation. In cases of stage IC serous or clear cell carcinoma, the American guidelines also suggest considering adding systemic therapy to brachytherapy. The 2025 European guidelines consider the risk of stage IA1 LG endometrial cancer NSMP estrogen receptor negative or p53abn to be uncertain. Furthermore, they point out that there is not enough data to assign a risk category to POLE mutated stage III to IVA cases. The 2025 updated European guidelines risk stratification has become more complex for FIGO stages I and II, and now consider cases of stage IA2, IA3 and IB that are NSMP estrogen receptor negative or p53abn to be in the high-risk category. Patients with stage IIA NSMP estrogen receptor positive tumors and Stage IIC with none or focal LVSI and MMR deficient (MMRd) are considered intermediate risk, while stage IIA, IIB, and IIC NSMP estrogen receptor negative are considered high-risk (Table 2).

We already consider estrogen receptor status in our approach to the management of early-stage (I and II) endometrial cancer. The tumor MMR status is not part of the FIGO staging system and is not considered in the American guidelines. As suggested by the Europeans, MMR status is another factor to consider in patients with FIGO stage IB or subsets of stage IIC together with the full clinical picture (e.g., patient's age, performance status, co-morbid conditions).

Molecular profiling of endometrial cancer is constantly evolving. New markers reflecting tumor biology will be identified and added to the staging classification with or without replacing others. We are certain that endometrial cancer staging will continue to be refined. The FIGO 2023 staging better aligns with prognosis and allows us to recommend adjuvant therapy based on risk stratification and currently available evidence. There are differences in the European and American treatment recommendations. We presented here an approach to the treatment of women diagnosed with endometrial cancer based on the FIGO 2023 staging and currently available medical societies' guidelines.

TABLE 2. European guidelines 2025 update.

Risk level	FIGO stage	Main treatment recommendation
Uncertain	• IA1 NSMP ER negative	No adjuvant therapy
	• IC NSMP ER negative or p53abn	No adjuvant therapy
	• III–IVA POLEmut	Consider de-escalation from high-risk treatment
Low	• I or II POLEmut	No adjuvant therapy
	• IA MMRd or NSMP ER positive	
	• IC MMRd	
Intermediate	• IB MMRd or NSMP ER positive	Vaginal brachytherapy
	• IIA NSMP ER positive	
	• IIC with any myometrial invasion and none or focal LVSI, no cervix invasion MMRd	
High-intermediate	• IIA NSMP ER positive	External beam radiation therapy to pelvis
	• IIA MMRd	
	• IIB MMRd or NSMP ER positive	
High	• IIC cervical stromal invasion or with substantial LVSI MMRd	Radiotherapy and chemotherapy
	• IIC _{p53abn}	
	• IA2, IA3, IB NSMP ER negative	
	• IIA, IIB, IIC NSMP ER negative	
	• All III to IVA except POLEmut	

NSMP: nonspecific molecular profile; ER: estrogen receptor; p53abn: p53 abnormal; POLEmut: POLE mutated; MMRd: mismatch repair deficient; LVSI: lymphovascular space invasion; FIGO: International Federation of Gynecology and Obstetrics.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

EH—conceptualization; writing—original draft; writing—review & editing. BF, JGP—writing—review & editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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