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Topic Discussion

International Federation of Gynecology and Obstetrics Endometrial 2023 Is Better For Radiation Oncology Patients

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Abstract The International Federation of Gynecology and Obstetrics (FIGO) 2023 staging system for endometrial cancer has marked changes from the previous staging system instituted 14 years prior in 2009. The new staging system includes nonanatomic factors for the first time (lymphovascular space invasion and histology) and molecular classification, which impacts the stage in early-stage disease ($IAm_{POLEmut}$ and $IICm_{p53abn}$). The purpose of these changes was to provide (1) high accuracy in the predictive prognosis for patients and (2) identification of distinct treatment-relevant subgroups. Our understanding of the biology and natural history of endometrial cancer has undergone a radical transformation since the Cancer Genome Atlas results in 2013. The 2023 FIGO staging system harmonizes and integrates old and new knowledge on anatomic, histopathologic, and molecular features. Moreover, FIGO 2023 has distinct substages that improve adjuvant treatment decision making. Although the practicality of the new staging system has been debated, we postulate that FIGO 2023 is more useful for radiation oncologists aiming to provide personalized care recommendations. FIGO 2023 requires a change in our perception of a staging system, from a traditional anatomic borders-based system to a staging system integrating anatomy and tumor biology as pivotal prognostic factors for patients while providing important information for treatment decision making.

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) 2023 Endometrial staging system introduces substantial changes compared with the previous FIGO staging system of 2009, which we believe translates into benefits for radiation oncology patients.[1] Both staging systems are shown in Table 1. The new staging system has markedly improved discrimination; that is, it provides statistically significant greater risk stratification,[2-7] yet in some circles, it is controversial because of increased complexity, including nonanatomic factors such as histology and lymphovascular space invasion (LVSI), and optional molecular classification.[8,9] Staging systems should not change frequently because our clinical trial information is based on stage. Fortunately, there have only been 2 FIGO endometrial staging system changes in the past 35 years: new systems were introduced in 1988, 2009, and 2023. FIGO 2023 includes nonanatomic factors such as (optional) molecular classification

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Table 1 FIGO staging by 2009 and 2023. Gravbrot et al[2]

2009 FIGO		2023 FIGO	
I	Tumor confined to uterus	I	Tumor confined to uterus and ovary
IA	<50% myometrial invasion	IA1	Nonaggressive histology limited to endometrium or endometrial polyp
		IA2	Nonaggressive histology with no/focal LVSI with <50% myometrial invasion
		IA3	Low-grade endometrial carcinomas limited to uterus and ovary
IB	≥50% myometrial invasion	IB	Non-aggressive histology with no/focal LVSI with ≥50% myometrial invasion
		IC	Aggressive histologies or grade 3, limited to a polyp or endometrium
II	Tumor invades cervical stroma without extrauterine extension	II	Invasion of cervical stroma without extrauterine extension, substantial LVSI, or aggressive histologies or high-grade with myometrial invasion
		IIA	Invasion of cervical stroma of nonaggressive histology
		IIB	Nonaggressive histology with substantial LVSI
		IIC	Aggressive or high-grade histologies with any myometrial invasion
III	Local or regional spread	III	Local or regional spread of any histologic subtype
IIIA	Serosal or adnexal invasion	IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
		IIIA1	Spread to ovary or fallopian tube, unless meeting IA3 criteria
		IIIA2	Involvement of or spread through uterine serosa
IIIB	Vaginal or parametrial invasion	IIIB	Metastasis or directspread to the vagina, parametria or pelvic peritoneum
		IIIB1	Metastasis or direct spread to vagina or parametria
		IIIB2	Metastasis to pelvic peritoneum
IIIC	Metastasis to pelvic or paraortic lymph node or both	IIIC	Metastasis to pelvic or paraortic lymph node or both
IIIC1	Pelvic lymph node involvement	IIIC1	Pelvic lymph node involvement
		IIIC1i	Micrometastases
		IIIC1ii	Macrometastases
IIIC2	Paraortic lymph node involvement	IIIC2	Paraortic lymph node involvement
		IIIC2i	Micrometastases
		IIIC2ii	Macrometastases
IV	Distant spread	IV	Spread to bladder or intestinal mucosa, or distant metastases
IVA	Extension to pelvic wall, lower 1/3 of vagina, hydronephrosis, or invasion of bladder or bowel mucosa	IVA	Invasion of bladder or intestinal/bowel mucosa
IVB	Distant metatases including within the abdomen, or inguinal lymph node involvement	IVB	Abdominal peritoneal metastases beyond the pelvis
		IVC	Distant metastases to extraabdominal lymph nodes or intraabdominal lymph nodes above the renal vessels, or spread to lungs, liver, brain, or bone

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion.

Table 2 Suggested treatment by 2023 FIGO stage

Stage	Suggested Treatment	Rationale
IA1-IA3, IAmPOLEmut	Observation ± VCB	ASTRO, EEE
IB	VCB	ASTRO, EEE, PORTEC 2
IC	VCB ± Chemo	ASTRO, EEE
IIA-IIB	EBRT	ASTRO, EEE, PORTEC 1/2, GOG 249
IIC, IICmp53ABN	EBRT and Chemo	ASTRO, EEE, PORTEC III
IIIA-IVA	EBRT and Chemo, or Chemo alone	ASTRO, EEE, PORTEC III
IVB-IVC	Chemo	ASTRO, EEE

Abbreviations: ASTRO = American Society for Radiation Oncology; Chemo = chemotherapy; EEE = ESGO-ESTRO-ESP (Concin et al) and ESMO (Oaknin et al) guidelines for endometrial cancer EBRT = external beam radiation therapy; VCB = vaginal cuff brachytherapy.

for *POLE* and P53 mutant cases in stages I and II, substantial (LVSI; 5 or more foci), and histology. The Cancer Genome Atlas (TCGA) endometrial study was published 11 years ago and identifies P53 and *POLE* mutant cases, for which therapy can be escalated and de-escalated, respectively (Table 2).[10,11] The TCGA data inform our decision making on a daily basis for delivery of adjuvant therapies, both radiation and chemotherapy. The sentinel hallmark of FIGO 2023 is the creation of improved prognostic and treatment-relevant subgroups, following suit of multiple other FIGO and American Joint Committee on Cancer staging systems that employ nonanatomic factors, such as head and neck, breast, skin, melanoma, testis, and prostate. This report will describe some of the major changes of FIGO 2023 and the aspects that are relevant to radiation oncology related patient care.

FIGO 2023 does not mandate suggested treatment, because it is not a guideline, but it permits the physician to identify treatment-relevant subgroups, and hence, selection of adjuvant therapies. Our suggested preference for adjuvant therapies is shown in Table 2. Already, multiple reports have identified statistically significant greater discrimination with the new staging system.[2-7] We believe that this will improve treatment decision making and enable greater precision and personalization in choice of adjuvant therapies.

Stage I

Stage I designation will be used less frequently in the new staging system because of "upstaging" of cases to stage IIB owing to substantial LVSI, and aggressive histologies now designated as stage IIC. Population data indicate that tumors now classified as stage I have a significant difference in 10 year overall survival (OS) ranging from 86% for substage IA_1 to 68% for substage IA_3 which result in different recommended treatments (Fig. 1 and Table 2).[2]

Stage IA1-IA3 require no adjuvant therapy and is consistent with European guidelines and mostly consistent with American Society for Radiation Oncology (ASTRO) recommendations.[12-14] ASTRO guidelines do permit vaginal cuff brachytherapy (VCB) in stage I, grade 1 and 2 cases with <50% myometrial invasion when adverse features are present such as age >60 years and LVSI. Stage IA3 includes synchronous tumors of the endometrium and ovary that share a clonal relationship and have a favorable prognosis. The tumors must be: (1) low grade and have no more than superficial myometrial invasion; (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). Low-grade tumors are specifically defined in FIGO 2023 as grade 1 and 2. Gravbrot et al[2] reported on >134,000 patients with endometrial cancer evaluated over a decade from the National Cancer Database and documented that IA3 (low-grade synchronous tumors of the endometrium and ovary) cases have a 10-year OS of 73% compared with 43% previously in FIGO 2009 stage IIIA1 (endometrial cancers with spread to the adnexa) (Fig. 2).[2] Our recommendation for the new stage IA3 is observation in most cases (Table 2).

Stage IB now comprises low-grade (nonaggressive histologies) that penetrate >50% of the myometrium. In an elegant study of the combined Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) 1 and 2 studies with molecular classification, Horeweg et al[10] showed that these cases are consistent with the No Specific Molecular Pathology group and that VCB is preferred with no advantage for external beam radiation (EBRT). For No Specific Molecular Pathology, both EBRT (98.3%) and vaginal brachytherapy (96.2%) yielded better locoregional control than no adjuvant therapy (87.7%; $P < .0001$). Stage IC is a novel entity and includes nonmyoinvasive aggressive histologic lesions including lesions confined to polyps. Gravbrot et al[2] demonstrated that this group has

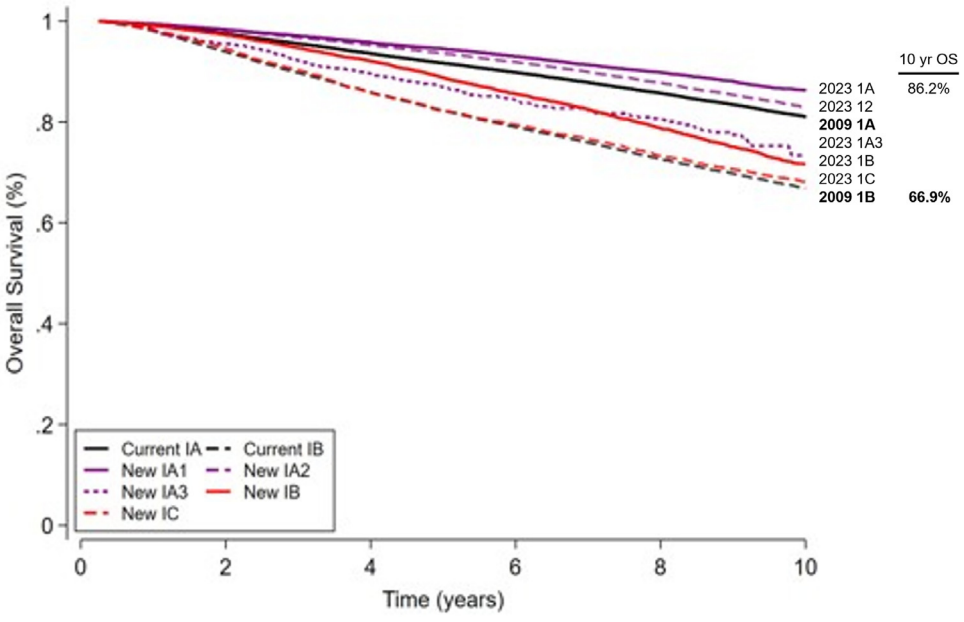

Figure 1 Overall survival in stage 1 patients in FIGO 2009 and 2023. Gravbrot et al.[2]

worse outcomes than patients with low-grade histology (formerly grade 1 and 2) with deep myometrial invasion (≥50%). Consistent with ASTRO and European guidelines, we advocate VCB ± chemotherapy for stage IC (Table 2).[12-14] Stage I also includes IAm$_{POLE\text{mut}}$ cases that are *POLE*mut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histologic type. These cases have been found in a meta-analysis of 11 studies to have a very favorable prognosis, low incidence of lymph node metastasis, and limited myometrial invasion, thus, we typically recommend observation (Table 2).[15]

Stage II

FIGO 2023 Stage IIA are low-grade endometrioid cases with cervical stromal involvement. Stage IIB refers to early-stage disease with 5 or more foci of LVSI, which is

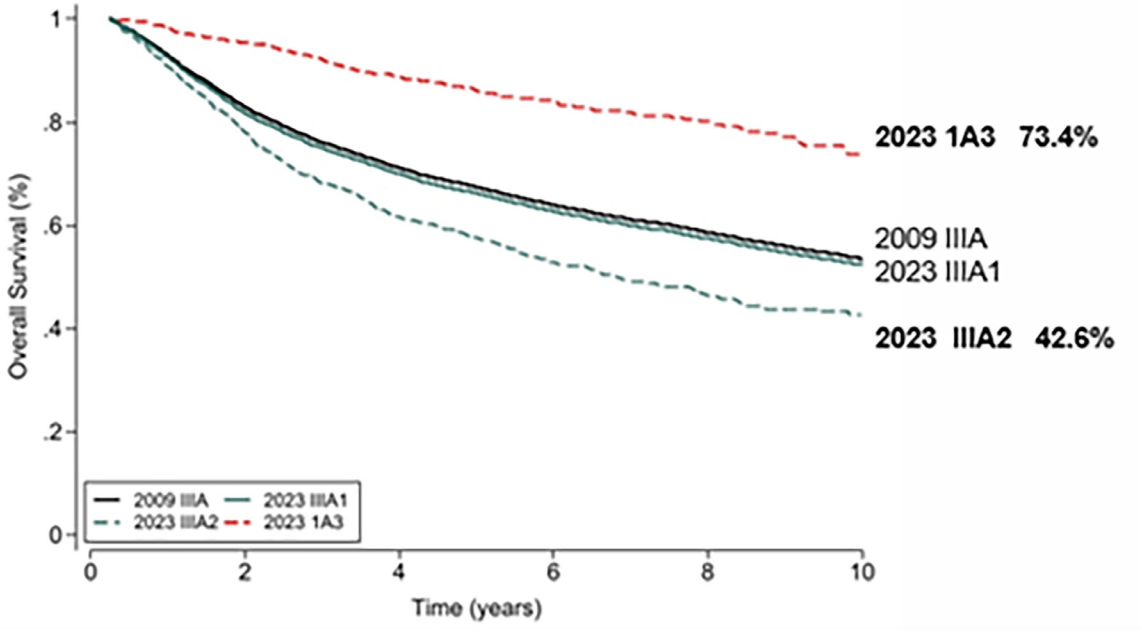

Figure 2 Overall survival in stage IIIA patients in FIGO 2009 and 2023 (including FIGO 2023 stage IA3). Gravbrot et al.[2]

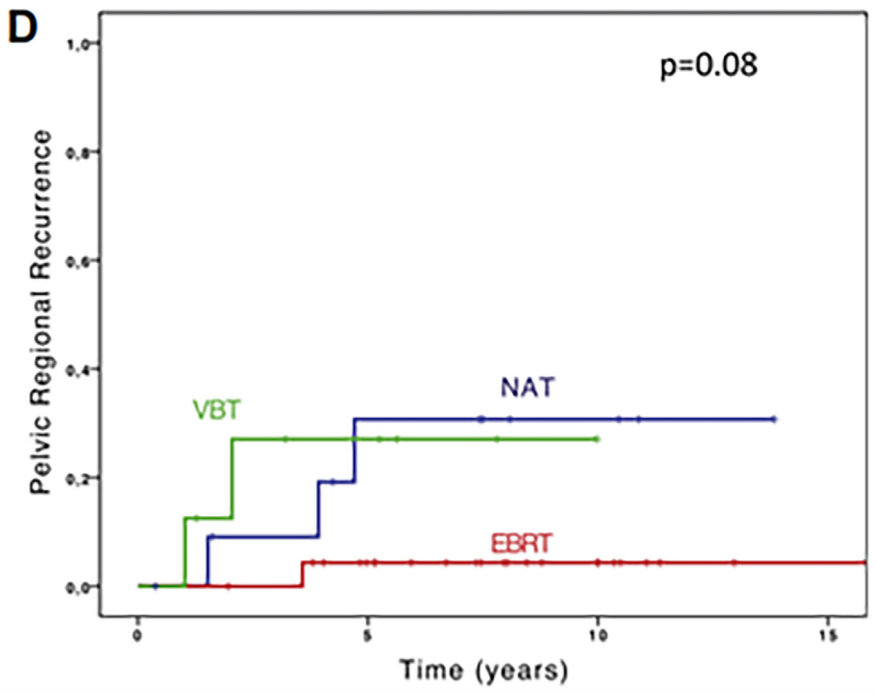

Figure 3 Local regional control in 44 patients with substantial LVSI from PORTEC 1 and 2 receiving no adjuvant therapy (NAT), vagina brachytherapy (VBT), and EBRT. Bosse et al.[16]

the World Health Organization definition of substantial LVSI. In the PORTEC-1 and 2 studies, for patients with substantial LVSI, the risk of pelvic regional recurrence at 5 years after EBRT was 4.3%, compared with VCB 27.1% and no adjuvant therapy 30.7%; hence, we recommend EBRT (Table 2, Fig. 3).[16] In one study of 959 patients from Sweden LVSI was the most important prognostic factor for OS in staged patients, and in fact, LVSI remained significant for OS in staged patients even with no lymph node metastases.[17] In Gynecologic Oncology Group (GOG) 249, 46% of patients were high grade and OS was similar between VCB and 3 cycles of chemotherapy and pelvic EBRT, local control was improved by 9% in the pelvis, 4% in the paraortic region , late toxicity was similar, and acute toxicity was improved with EBRT. Some have questioned the validity of these data because only 3 cycles for chemotherapy were given. However, in GOG 157, the recurrence risk was 24% lower with 6 versus 3 cycles of chemotherapy, but this was not statistically significant (HR, 0.76; CI, 0.51-1.13), and the authors concluded that the 3 additional cycles of chemotherapy added toxicity without significantly reducing the risk of cancer recurrence.[18] Stage IIC includes aggressive histologies and p53abn cases. In the molecular analysis of the PORTEC III study, 57% of patients were stage I and II, and OS was improved only in the p53abn cohort.[11] Consistent with ASTRO and European guidelines in most cases we recommend EBRT and chemotherapy (Table 2). In one study from Duke University, 5-year OS was 56% for serous and clear cell cancers compared with 92% for grade 1 endometrioid EC, demonstrating the importance of histology. P53 mutant early-stage cases are designated as IICm-$_{p53abn}$. The combined PORTEC study by Horeweg et al[10] showed that for p53 abnormal cases, EBRT (96.9%) had a substantial benefit over vaginal brachytherapy (64.3%) and no adjuvant therapy (72.2%; p = .048, Fig. 4). Consistent with other guidelines we favor EBRT and chemotherapy in this substage.[12-14]

Stage III and IV

For stage IIIA-IVA, we generally recommend EBRT and chemotherapy (Table 2). Chemotherapy alone is a treatment option because in GOG 258 there was no improvement in OS with EBRT and chemotherapy versus chemotherapy alone; however, vaginal recurrence was 5% lower and pelvic and paraortic was 9% lower with the addition of EBRT.[19] Stage IIIA1 is involvement of the adnexa, and stage IIIA2 is a new stage with uterine serosal involvement. Stage IIIA2 has a 10% reduction in OS at 10 years compared with stage IIIA1.[2] Stage IIIB1 is the same as previous, with metastasis or direct spread to the vagina or parametria, while IIIB2 is a new substage representing pelvic peritoneal involvement. This is a crucial change for radiation oncologists since in the FIGO 2009 system these cases were designated as stage IVB and may not have received adjuvant EBRT. FIGO 2023 stage IIIB2 had a 10-year OS of 49% compared with 19% for FIGO

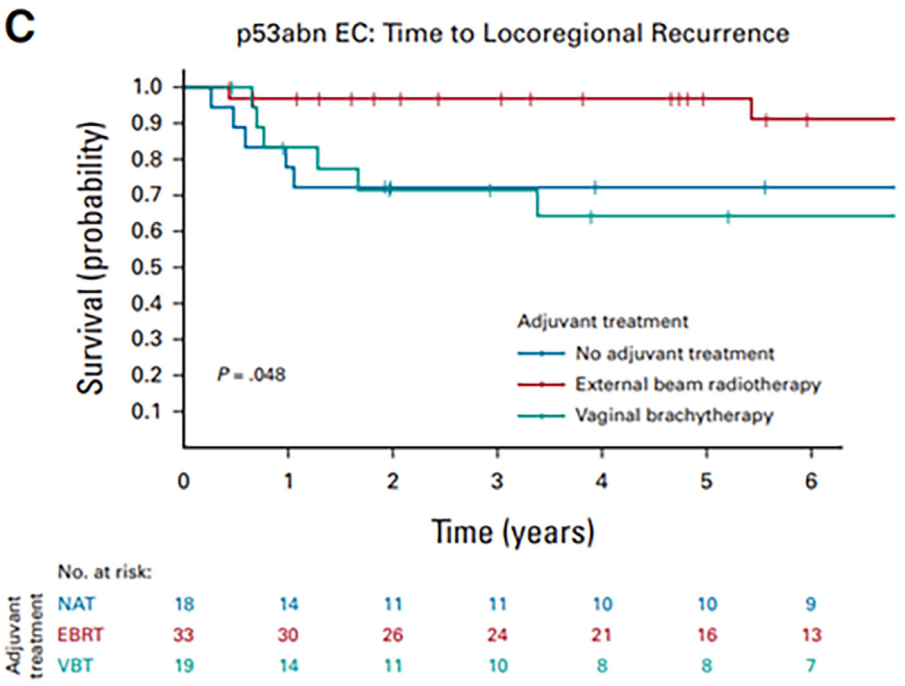

Figure 4 Time to locoregional recurrence in PORTEC 1 and 2 in p53 abnormal endometrial cancer. Horeweg et al.[10]

2009 stage IVB (Fig. 5).[2] Interdisciplinary communication will be crucial to accurately identify pelvic peritoneal involvement (stage IIIB2) compared to abdominal peritoneal involvement (stage IVB). The new staging system employs micro (<2 mm) and macro (≥2 mm) involvement of lymph nodes which significantly affects OS, and stage IV has been demonstrated to show improved discrimination.[3,6] ASTRO and European guidelines indicate that chemotherapy radiation is conditionally recommended for stage III and IVA. Many physicians advocate for chemotherapy first largely to prevent bone marrow suppression from EBRT. There is a paucity of prospective data to guide us. A recent trial compared concurrent chemotherapy and EBRT, as given in Radiation Therapy Onclogy Group 9708, PORTEC III, and GOG 258, to sandwich therapy (3 cycles of chemotherapy, EBRT, and 3 more cycles) and showed no difference in survival.[20] Clear cell carcinomas are high grade by definition and may behave heterogeneously.[13] Some clear cell carcinomas have a relatively good prognosis (eg, Mismatch Repair deficient cases) and may be managed with radiation therapy alone.[13]

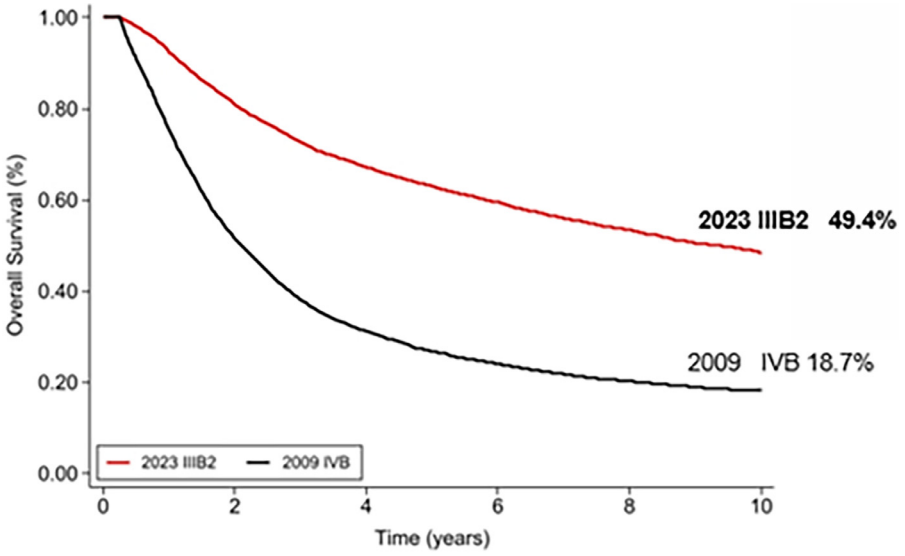

Figure 5 Overall survival in stage IIIB2 patients (pelvic peritoneal involvement) in FIGO 2023 compared with stage IVB patients from FIGO 2009. Gravbrot et al.[2]

Cost-effectiveness and Equity

Molecular testing represents an initial cost upfront; however, cost savings may be realized by avoiding costly and unnecessary adjuvant treatment as well as costs associated with treatment toxicity for patients with POLEmut cancers. Indeed, reports in early-stage endometrial cancer (EC) and in stage III EC have indicated the cost-effectiveness of molecular testing. [21,22] The authors conclude in their reports that molecular classification in EC can guide treatment and should be routine practice for all stages. The frequency of POLEmut EC is 10%, and adjuvant treatment is not associated with outcome.[23] We strongly support payers to adopt the inclusion of *POLE* testing for patients with EC. The cost of POLE testing will continue to decline as novel technologies are developed,[24,25] including machine learning-based detection of the molecular group using digitized pathology slides.[26]

Health equity, or the ability for each patient to attain their full health potential, cannot be realized when molecular testing is not readily accessible.[27] Survival disparities in ECs are well-documented, particularly for Black patients who have nearly twice the mortality of White patients. Although underlying reasons for the disparity are multifactorial, lack of recognition of these adverse molecular subtypes may contribute. Whelan et al[28] 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 = .003). Additionally, Black patients with EC are more likely to have unfavorable TCGA subtypes. The incorporation of molecular subtyping into the new staging system will allow for more appropriate provision of adjuvant therapy, which could mitigate survival disparities in the future. Additionally, improved risk stratification will encourage more appropriate clinical trial design and facilitate inclusion of patients historically excluded from trial participation (eg, early stage but high risk for recurrence by molecular subtype).

Conclusion

Alignment of American Joint Committee on Cancer and FIGO staging is critical for gynecologic cancers. Standard operating procedures, public comment period, and involvement of all stakeholders are a priority to promote harmonization. FIGO 2023 staging for EC represents a marked change from prior FIGO endometrial staging systems. The number of subsites has increased from 9 in 2009 to 19 in 2023. The new staging system includes nonanatomic factors for the first time (LVSI and histology) and molecular classification in early-stage disease (IAm$_{POLE\text{mut}}$ and IICm$_{p53abn}$). These changes have led to significantly increased prognostic discrimination and description of treatment-relevant subgroups.[2-7] For radiation oncology, stages IA1-IA3 and IAm$_{POLE\text{mut}}$ require no adjuvant therapy; however, stage IIIB2 (pelvic peritoneal involvement) clearly warrants EBRT, where these patients were previously designated stage IVB and not receiving definitive EBRT. With a greater emphasis on molecular tumor characteristics and improved prognostic discrimination, we believe that FIGO 2023 will lead to a better and more personalized approach to patient care.

Disclosures

David K. Gaffney received PI LAPS grant, UG1 to HCI; serves as Chair DSMC Merck; serves on the Board of Directors IGCS and is the Associate Editor Gyn Oncol. Gita Suneja received grants - NIH, 5 for the Fight; travel expense from American Brachytherapy Society, Binaytara Foundation; leadership - Radiation Oncology Institute. Carien Creutzberg received research support Varian paid to institution (outside this work); DSMC − MSD compensation to institution for time spent on DSMB; leadership - GCIG immediate past chair of endometrial committee and chair of endometrial consensus conference; ESGO-ESTRO member of guidelines committee for endometrial cancer; equipment − Elekta oncentra research platform (to institution, outside this work). Chris Weil declares no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2024.05.010.

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