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How Applicable is the 2023 Staging System for Endometrial Cancer?

Mini review
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Author Details

*M Faruk Kose**

Private Department of Gynecologic Oncology, Acibadem University School of Medicine, Turkey

*Corresponding author

M Faruk Kose, Department of Gynecologic Oncology, Acibadem University School of Medicine, Turkey

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Abbreviations

FIGO: International Federation of Gynecology and Obstetrics; NCCN: National Comprehensive Cancer Network; MSKCC: Memorial Sloan Kettering Cancer Center; ESMO/ESGO/ESP: European Society for Medical Oncology/ European Society of Gynaecological Oncology/ European Society of Pathology; MMR: Mismatch Repair; MMRd or dMMR: Mismatch Repair Deficient; NSMP: No Specific Molecular Profile; p53mut; p53mutant; P53wt; p53wild Type; MMRp or pMMR: Mismatch Repair Proficient; MSS, Microsatellite Stable; MSI: Microsatellite Instable; POLE: Polymerase Epsilon; POLEmut: Polymerase Epsilon-Ultramutated

Mini Review

Since the molecular pathological classification in The Cancer Genom Atlas (TCGA) in 2013, numerous studies have been conducted to determine prognostic factors for endometrial cancer [1-4]. The results of robust randomized controlled trials (RCTs), particularly PORTEC III, have shown that the prognostic significance of the 2009 staging system diminishes as more data emerge. RCTs such as GOG 99, PORTEC I, II, III, GOG 249, and GOG 258 have demonstrated that while radiotherapy (especially brachytherapy) provides around a 10% benefit in local control for intermediate and high-intermediate-risk groups, it does not contribute to overall survival (OS) [5]. Subsequent to the 4-year patient outcomes of the GOG 99 study, low-risk, intermediate-risk, high-intermediate-risk, and high-risk groups were identified. Although radiotherapy showed no survival benefit at 2 years, subgroup analyses led to the identification of risk groups [6]. The indication for adjuvant radiotherapy in these risk groups, especially in the intermediate-risk group, has always been subject to debate [7].

In the new staging system, changes have been made to stage IA, II, and III particularly based on lymphovascular space invasion (LVSI), microscopic or macroscopic lymph node involvement, and metastases to adjacent organs according to histopathological type [8]. For instance, if low-risk endometrioid adenocarcinoma has metastasized to the ovary, it is considered stage IA3; whereas, if there is ovarian metastasis (except when meeting stage IA3 criteria), it is evaluated as stage IIIA1. The extent of LVSI also alters the stage based on whether it is focal or diffuse [8]. Some studies consider fewer areas then four and others five of LVSI as focal, or more areas as diffuse.

Furthermore, in endometrial cancer patients, four subgroups have been identified through immunohistochemical (IHC) staining and molecular pathological evaluations. These groups-POLE ultramutated, MSI hypermutated, copy number (CN) low endometrioid, and CN-high serous-like groups-have been clearly defined, and genetic alterations have been identified in these groups [9]. To identify patients belonging to these four groups, it is recommended to start with POLE mutation analysis independent of histopathological type, followed by MMR IHC or MSI testing in the non-POLE mutation group, and if MMR is normal, then p53 IHC analysis [10]. The PROMISE study suggests that the evaluation of MMR proteins by IHC is recommended as the first step, followed by POLE sequencing in the MMRp group and p53 IHC in cases without a POLE mutation [9].

Ultimately, four risk groups have been established: the POLE mutation group with low risk, the MMRd or MSI-H group with intermediate risk, the NSMP high-intermediate risk group with normal or wild-type p53, and the p53 aberrant group with high risk6. While IHC is good for determining p53 mutations, it is not perfect. It may not detect p53 mutations in some CN-high cases; therefore, molecular tests should be performed in cases where p53 mutation is suspected [10].

In early-stage endometrial cancer patients (stage I-II), there is a demand to incorporate molecular changes into staging [8]. For example, the IAmPOLEmut group is defined as "POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type," while the IICmp53abn

group is defined as "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."[6] In advanced-stage cases (stage III-IV), although molecular evaluation does not change the stage, it has been suggested that data should be collected for future reference [8].

The role of lymphadenectomy in the surgery of endometrial cancer patients has always been debatable [10]. In the GOG 99 trial, where systematic lymphadenectomy was performed, the average number of harvested lymph nodes was found to be 10 [11]. However, in PORTEC studies, lymphadenectomy was not performed [12]. Following RCT studies by MSKCC and Mayo Clinics, sentinel lymph node mapping has become a standard surgical practice not only in endometrioid cancer patients but also in high-risk histopathologies [13].

Game-changing developments for endometrial cancer patients occurred in 2023. Initially, with the importance of prognostic evaluations in subgroup analyses, the 2023 staging system was introduced, and joint guidelines from ESMO/ESG/ESP were published. These guidelines outlined the four risk groups mentioned above (POLE, MMRd or MSI-H, NSMP, p53 aberrant) and corresponding treatment modalities based on risk groups. Of course, the publication of these guidelines was facilitated by the evident survival benefits of chemotherapy and immunotherapies in the treatment arms of mentioned RCTs.

In the validation study of the 2023 FIGO staging system, it was shown to lead to a significant stage shift in approximately one-quarter of patients, resulting in higher prognostic sensitivity [14]. In early-stage diseases, the new substages provided more prognostic details and identified treatment-relevant subgroups.

Excellent clinical outcomes have been demonstrated in the early-stage POLE mutant group even without adjuvant treatment. However, the necessity of adjuvant treatment in advanced-stage POLE mutant groups remains controversial [10]. The p53abn groups have been shown to have the worst prognosis, but also derive the most benefit from chemotherapy. However, adjuvant brachytherapy is not recommended in cases of intermediate risk with no MI or limited to polyps and with p53 abnormalities [7].

Another significant change is the addition of chemotherapy in cases where radiotherapy is recommended in intermediate and high-risk groups. Chemotherapy can be used concurrently or sequentially [15]. The most significant game-changing studies in treatment have been the RUBY and Keynote 868 trials, demonstrating statistically significant benefits of immunotherapy in advanced or recurrent endometrial cancer patients across all groups [16]. The most important two immunotherapy agents have been shown to be dostarlimab in the RUBY study and pembrolizumab in the Keynote 868 study [17]. Trastuzumab is recommended in the NCCN guidelines for HER2-positive uterine serous carcinoma and carcinosarcoma (stage III/IV).

Ongoing studies such as PORTEC IVa, RAINBO, TAPER, CAN-STAMP, NRG-GY018, DOMENICA, Keynote C93, LEAP-001, NRG_GY020, and NRG-GY026 will shed light on some unanswered treatment modalities through RCTs.

In conclusion, the game has changed for endometrial cancer patients. Molecular-based evaluations have gained importance, akin to the VAR system in football. POLE mutant groups are managed with the blue guideline, MMRd or MSI-H groups with the green guideline, NSMP group with the orange guideline, and p53abn group with the red guideline. Centers capable of detecting POLE mutations can follow the NCCN guidelines. In centers where POLE mutations cannot be detected, cases other than the classic low-risk group should undergo MMR protein IHC, and treatment should be planned accordingly.

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