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ORIGINAL PAPER

Factors affecting prognosis in high-intermediate risk endometrial cancer in according to ESMO/ESGO/ESTRO risk classification – FIGO 2023 analysis of survival outcomes and staging dynamics compared to the FIGO 2009 system

Eren Can Guleryuz [1,2], Busra Korpe [2], Vakkas Korkmaz [3]

[1] Ankara Etlik Zubeyde Hanim Women's Health and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Türkiye
[2] Ankara Etlik City Hospital, Department of Obstetrics and Gynecology, Ankara, Türkiye
[3] Ankara Etlik City Hospital, Department of Gynecologic Oncology, Ankara, Türkiye

ABSTRACT

Introduction and aim. Accurate staging is essential for determining treatment strategies and predicting outcomes in endometrial cancer (EC). The FIGO staging system was updated in 2023 to incorporate histological and molecular features. This study evaluates the impact of the FIGO 2023 system on high-intermediate risk endometrioid EC cases and compares its prognostic value with the FIGO 2009 system.

Material and methods. A retrospective analysis of 140 high-intermediate risk endometrial cancer cases from two tertiary hospitals was conducted. Patients were reclassified using FIGO 2023, and staging shifts were analyzed. Survival outcomes, including overall survival (OS) and progression-free survival (PFS), were assessed using Kaplan-Meier analysis and log-rank tests. Univariate and multivariate regression analyses were performed to identify prognostic factors.

Results. Within this high-intermediate risk group, patients were stratified into three groups: group 1 (n=79) consisted of those with LVSI (+) Stage I, group 2 (n=17) included patients with LVSI (-) Stage IB grade 3, and group 3 (n=44) comprised individuals with Stage II. Based on age, a statistically significant difference was identified between group 1 and group 3 ($p<0.05$), while no statistically significant difference in BMI was observed among the groups ($p>0.05$). Additionally, there was a statistically significant difference among the groups concerning the type of surgery performed ($p<0.05$) Although no statistically significant difference in survival outcomes was observed, a trend toward improved risk stratification in OS was noted. Positive lymphovascular space invasion emerged as a key factor influencing upstaging.

Conclusion. FIGO 2023 provides a refined staging approach that better aligns with clinical outcomes. Larger prospective studies incorporating molecular profiling are needed to confirm its prognostic utility.

Keywords. endometrial cancer, FIGO, high-intermediate risk, lymphovascular space invasion, staging system

Introduction

Accurate staging and risk stratification are crucial for determining optimal treatment strategies and predicting patient outcomes in endometrial cancer (EC).[1,2] In this context, the staging systems developed by the International Federation of Gynecology and Obstetrics

Corresponding author: Busra Korpe, e-mail: busraejderoglu@yahoo.com

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(FIGO) serve as critical tools for clinicians, enabling standardized assessment and facilitating communication about disease extent and prognosis.[3]

However, the field of gynecologic oncology is constantly evolving, and as our understanding of EC improves, periodic updates to staging and risk stratification systems become necessary.[4] The growing recognition of molecular characteristics and lymphovascular space invasion (LVSI) as key prognostic indicators has demonstrated that the FIGO 2009 staging criteria are increasingly insufficient in reflecting disease biology and guiding optimal adjuvant therapy.[5-7] As a result, the FIGO 2023 staging system was introduced to incorporate these advancements and improve prognostic accuracy.[8]

The updated 2023 FIGO system integrates various histological types, tumor patterns, LVSI and molecular classifications to better reflect the improved understanding of the complex nature of several types of EC and their underlying biological behavior.[9,10] In addition to improving prognostic alignment, these changes aim to enhance clinical usability and facilitate precise risk stratification for treatment planning. Given that LVSI has been identified as a key factor in disease progression and recurrence, its inclusion in the FIGO 2023 staging criteria represents a fundamental shift in EC classification. However, the practical implications of these modifications, particularly their effect on stage migration and survival outcomes, remain unclear.

To define prognosis and estimate the risk of nodal metastasis in EC, multiple risk models have been created based on pathological information. In Europe, adjuvant treatment and surgical planning are commonly guided by the classification system established by European Society of Medical Oncology, the European Society of Gynecologic Oncology, and the European Society of Radiotherapy (ESMO, ESGO, ESTRO).[11,12]

According to this guideline, cases of EC are categorized as low, intermediate, high-intermediate, high and advanced metastatic groups. The high–intermediate group is described as: (1) stage I EC, grade 3, less than 50% myometrial invasion regardless of LVSI; (2) stage I EC, grade 1–2, positive LVSI, irrespective of myometrial invasion; or (3) stage 2 EC in the ESMO/ESGO/ESTRO risk classification.[13] Since high-intermediate risk cases include early-stage tumors with LVSI positivity, the integration of LVSI into the FIGO 2023 system is expected to significantly impact patient stratification and treatment decisions. This inclusion, along with the lack of treatment consensus, prompted our interest in evaluating changes in this risk group.

Aim

Despite advancements, the optimal management of high-intermediate risk EC remains unclear. With LVSI now a formal staging component, assessing FIGO 2023's impact on survival and stage distribution is crucial. This study evaluates the real-world effects of these revisions, analyzing stage migration and survival outcomes to determine if FIGO 2023 improves prognostic accuracy over FIGO 2009.

Material and methods

A retrospective cohort analysis was conducted on 1163 EC patients who underwent primary treatment at the Gynecologic Oncology Clinics of two tertiary hospitals between March 2011 and August 2023. The study design was approved by the institutional research ethics committee (Approval number: 08.06.2022-2022/78).

A total of 140 patients who met specific criteria, focusing on individuals with endometrioid-type EC classified as high-intermediate risk based on the ESMO/ESGO/ESTRO risk classification.[12] Patients categorized as low, intermediate, high, and advanced metastatic risk, those with non-endometrioid histology, individuals with irregular follow-up, and those with limited data accessibility were excluded from the study. Additionally, patients undergoing fertility-sparing treatment were excluded to maintain uniformity in treatment strategies (Fig. 1).

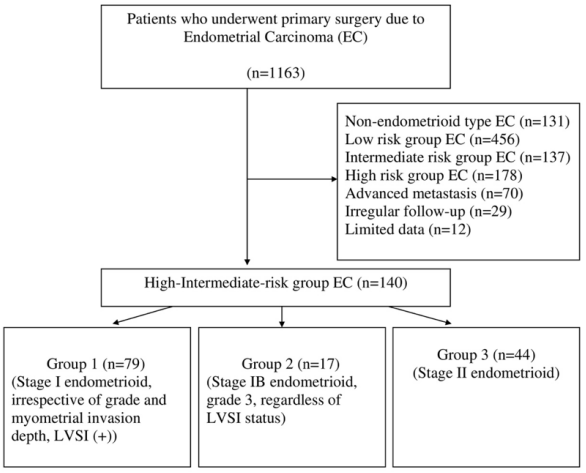

Fig. 1. Flow chart of the study

Cancer staging for EC was initially classified based on the 2009 FIGO staging system, and all cases were subsequently reclassified according to the 2023 FIGO system. In early stages, surgical procedures included hysterectomy, bilateral salpingo-oophorectomy (based on the age of the patient), infracolic omental biopsy and peritoneal washings tailored to specific histological subtypes. Lymph node staging, primarily was performed in the majority of cases, with some cases involving a systematic pelvic +/- paraaortic lymphadenectomy. During the study period, lymphadenectomy in our institution was guided by intraoperative frozen section, and no sentinel lymph node procedures were performed for EC cases. The decision for lymph node dissection followed the criteria established by Mariani et al.[14] Patients with a tumor diameter ≤2 cm,

myometrial invasion ≤50%, and no intraoperative evidence of macroscopic disease were classified as low risk and underwent hysterectomy without lymph node dissection. In cases that did not meet these criteria, lymph node dissection was performed. All surgeries were conducted by gynecologic oncologists.

Histopathological evaluations were performed by specialized gynecologic pathologists. LVSI was identified as the detection of tumor cells or clusters on the vessel wall through hematoxylin-eosin staining.[15] Focal LVSI was defined by the presence of a single focus around the tumor, substantial is described by a multifocal or diffuse distribution of LVSI or the detection of tumor cells within five or more lymphovascular space.16 Adjuvant treatment decisions followed ESMO/ESGO/ESTRO guidelines, including radiotherapy, chemotherapy, or combined therapies, depending on the patient's risk profile.[17]

Disease-free survival (DFS) was measured from the initiation of treatment until recurrence in patients who experienced recurrence, the date of the final follow-up for those without recurrence, or the date of death from any cause. Overall survival (OS) was calculated from the time of diagnosis to either the date of death or last hospital visit. Stage and substage-specific 5-year and 10-year DFS and OS rates were calculated and compared.

Patient follow-up records included detailed information such as age, body mass index (BMI), type of surgery (laparoscopy or laparotomy), surgery dates, LVSI status based on postoperative pathological evaluations, cancer stage, grade, myometrial invasion, risk group classification, lymph node involvement, adjuvant therapy, specifics of administered adjuvant treatments, recurrence during follow-up (if any) including location and timing, and information regarding any deaths during the follow-up period.

Statistical analysis

Statistical analyses were performed using the SPSS version 26.0 software package (IBM, Armonk, NY, USA). Descriptive statistics were presented in terms of number, percentage, mean, and standard deviation, as well as median. The normal distribution of variables was assessed visually (histograms and probability plots) and analytically (Kolmogorov–Smirnov, Shapiro-Wilk tests). Numeric variables that did not show normal distribution among the three groups were analyzed by using the Kruskal-Wallis test. Chi-square analysis and Fisher's Exact test were preferred for comparing nominal data. Survival analyses were conducted using Kaplan-Meier survival analysis and the Log Rank test. Univariate analyses were performed using Linear Regression analysis, and multivariate analyses were conducted using Cox Regression analysis. In the statistical analyses of the study, comparisons with a p-value below 0.05 were considered statistically significant.

Results

A total of 140 patients from the high-intermediate risk group of EC were included in the study. Within this high-intermediate risk group, patients were stratified into three groups: group 1 (n=79) consisted of those with LVSI (+) Stage I, group 2 (n=17) included patients with LVSI (-) Stage IB grade 3, and group 3 (n=44) comprised individuals with Stage II. All cases in Group 1 had substantial LVSI (+).

Upon comparing the groups based on age, a statistically significant difference was identified between group 1 and group 3 ($p<0.05$), while no statistically significant difference in BMI was observed among the groups ($p>0.05$). Additionally, there was a statistically significant difference among the groups concerning the type of surgery performed ($p<0.05$) (Table 1).

Table 1. Comparison of demographic parameters, treatment modalities, recurrence and mortality of high-intermediate risk groups*

	Group 1 (n=79)	Group 2 (n=17)	Group 3 (n=44)	p
Age (y)	60.89±8.76[a]	60.29±10.94[a,b]	54.61±8.50[b,c]	0.001
BMI (kg/m^2)	31.72±3.57	32.64±6.03	31.41±4.88	0.858
Type of operation n (%)				
Hysterectomy	7 (8.9)	1 (5.9)	1 (2.3)	
TAH+BSO+Pelvic LND+Obx	9 (11.4)	0 (0)	4 (9.1)	<0.001
TAH+BSO+Pelvic LND+Paraaortic LND+Obx	63 (79.7)	16 (94.1)	24 (54.5)	
Radical Hysterectomy (Type2-Type3) + Pelvic LND+ Paraaortic LND+ Obx	0 (0)	0 (0)	15 (34.1)	
Adjuvant treatment n(%)				
Yes	41 (51.9)[a]	13 (76.5)[b]	34 (77.3)[b,c]	0.009
No	38 (48.1)	4 (23.5)	10 (22.7)	
Type of adjuvant treatment n(%)				0.234
CT	5 (8.8)	2 (11.8)	2 (5.6)	
Sandwich	0 (0)	0 (0)	2 (5.6)	
Hormone treatment	0 (0)	1 (5.9)	0 (0)	
RT after CT	2 (3.5)	1 (5.9)	2 (5.6)	
CT after RT	1 (1.8)	1 (5.9)	0 (0)	
Cuff brachytheraphy	18 (31.6)	1 (5.9)	8 (22.2)	
External pelvic RT	9 (15.8)	4 (23.5)	8 (22.2)	
EBRT	6 (10.5)	3 (17.6)	12 (33.3)	
Recurrence				
Yes	16 (20.3)	1 (5.9)	7 (15.9)	0.364
No	63 (79.7)	16 (94.1)	37 (81.4)	
Mortality				
Yes	14 (17.7)	0 (0)	6 (13.6)	0.177
No	65 (82.3)	17 (100)	38 (86.4)	

* different letters shows statistical significance, groups that share the same letter are not significantly different from each other, BMI – body mass index, BSO – bilateral salphingoopherectomy, CT – chemotherapy, EBRT – external beam radiation therapy, LND – lymph node dissection, Obx – omental biopsy, TAH – total abdominal hysterectomy, RT – radiotherapy

A statistically significant difference in adjuvant treatment was observed (p<0.05), specifically between group 1 and other groups (Table 1). However, there was no statistically significant difference in terms of disease recurrence and mortality (p>0.05).

Table 2. Stage shifts between FIGO 2009 and FIGO 2023 surgical staging systems

FIGO 2009	FIGO 2023	FIGO 2009	FIGO 2023	FIGO 2009	FIGO 2023
Stage IA (n=41, 29.3%)	IA1 (n=0)	Stage IB (n=55, 39.3%)	IA1 (n=0)	Stage II (n=44, 31.4%)	IA1 (n=0)
	IA2 (n=0)		IA2 (n=0)		IA2 (n=0)
	IA3 (n=0)		IA3 (n=0)		IA3 (n=0)
	IB (n=0)		IB (n=0)		IB (n=0)
	IC (n=1, 0.2%)		IC (n=0)		IC (n=0)
	IIA (n=0)		IIA (n=0)		IIA (n=21, 47.7%)
	IIB (n=34, 82.9%)		IIB (n=30, 54.5%)		IIB (n=14, 31.8%)
	IIC (n=6, 14.6%)		IIC (n=25, 45.5%)		IIC (n=9, 20.5%)

Table 2 presented the stage shifts between the FIGO 2009 and 2023 surgical staging systems. Among the 24 patients who experienced recurrence, after restaging according to FIGO 2023, all were upstaged into Stage IIA (n=3), IIB (n=8), and IIC (n=9). In univariate regression analysis, age, type of surgery, myometrial invasion, and the number of pelvic lymph nodes were identified as risk factors for DFS and OS in all patients (p<0.05). However, in the multivariate regression analyses, statistical significance was not observed (p>0.05).

In the survival analyses, no statistically significant difference was observed in DFS and OS among the groups in both the FIGO 2009 and 2023 surgical staging systems (p>0.05) (Fig. 2A and 2B, Fig. 3A and 3B). The p-values were determined as p=0.160 and p=0.074 for DFS and OS, respectively, according to the FIGO 2023 staging.

Discussion

Accurate staging is fundamental for tailoring treatment strategies and predicting outcomes in EC.[1] The 2023 FIGO staging system represents a significant advancement, incorporating histological types, tumor patterns, and molecular classifications to better capture the complexities of EC.[8] It is important to assess how updated staging systems impact the classification and management of EC, with a focus on enhancing patient care and outcomes.[17] Studies examining the effects of updated guidelines on disease diagnosis and management play a pivotal role in advancing our understanding.[19]

In this study we assessed the impact of the FIGO 2023 system on 140 endometrioid EC cases in high-intermediate risk group compared to the 2009 FIGO system. Our results revealed that most of the cases progressed into a more advanced stage under the new FIGO 2023 staging system. Notably, all recurrent and deceased patients were among those upstaged, suggesting that the revised classification better aligns with actual disease progression. This highlights the potential of the FIGO 2023 system to more accurately stratify high-risk patients, potentially guiding more appropriate therapeutic decisions.

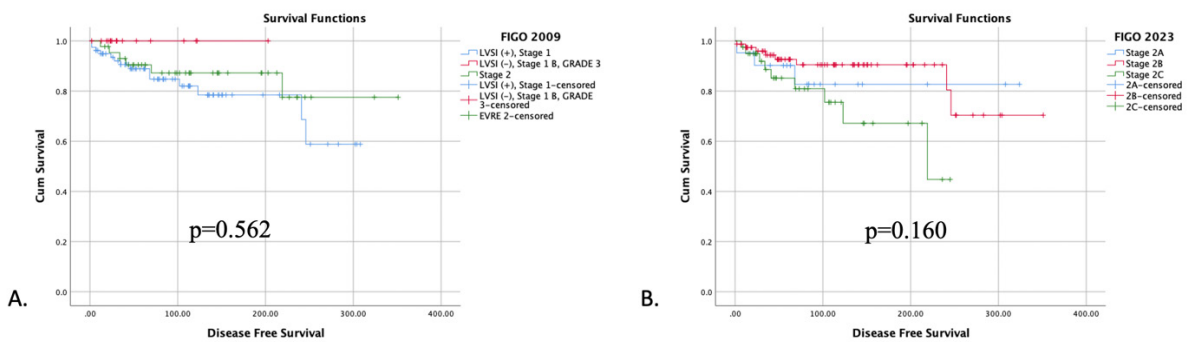

Fig. 2. A: Disease-free survival analysis of high intermediate risk groups according to FIGO 2009 vs. 2023, B: staging system

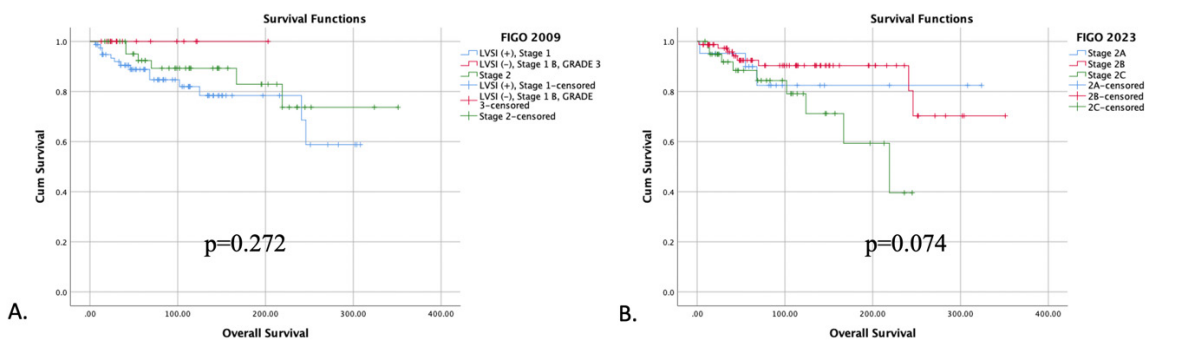

Fig. 3. A: Overall survival analysis of high intermediate risk groups according to FIGO 2009 vs. 2023, B: staging system

The high-intermediate risk group has consistently been associated with a significantly poorer prognosis in prior studies.[19,21] A key factor contributing to adverse outcomes is the higher prevalence of lymph node metastases, reinforcing the need for precise staging to guide management.[22-25] While our univariate analysis identified certain factors as potential risk factors for disease-free and overall survival, the multivariate analyses did not confirm statistical significance. This discrepancy suggests a need for larger, prospective studies to clarify the prognostic value of these factors.

Randomized controlled trials, such as GOG-99[26], PORTEC-1[27] have established the effectiveness of adjuvant radiation therapy in addressing intermediate and high-intermediate risk early-stage EC. Within our study, patients in group 1 received notably less adjuvant treatment. The reclassification of LVSI-positive cases to Stage IIC under the 2023 system suggests a more refined risk stratification, leading to increased eligibility for adjuvant therapy. This observation underscores the evolving role of staging systems in shaping treatment strategies and highlights the importance of periodically reassessing clinical guidelines to reflect emerging evidence.

The FIGO 2023 system remains relatively underexplored in the literature, with limited studies evaluating its clinical impact. In a recent publication by Schwameis et al.[19], it was noted that there are significant stage shifts in approximately one-quarter of patients, with prognostic implications that may influence treatment decisions. The introduction of new substages in early-stage EC has enhanced prognostic stratification, allowing for better identification of treatment-relevant subgroups. However, Schwameis et al.'s study did not specifically analyze the high-intermediate risk group, leaving a critical gap in the literature. Similarly, another recent study comparing the FIGO 2009 and 2023 systems, with and without molecular classification, demonstrated that 47% of FIGO 2009 Stage I patients were upstaged based on histopathological findings alone. Notably, in the molecular-informed FIGO 2023 system, 85% of p53-abnormal tumors were upstaged, highlighting the critical role of molecular markers in refining risk stratification. Moreover, POLE-mutated cases were frequently downstaged, suggesting that molecular data significantly influence staging accuracy and prognostic assessment.[20] However, while these findings underscore the relevance of integrating molecular markers into staging algorithms, our study was limited in this aspect, as we could not assess key molecular features such as p53 abnormalities, POLE mutations, and mismatch repair status.

In our study, although no statistically significant difference was observed between groups in the survival analyses based on this updated system, the decreasing trend in the p-value of OS and its proximity to the significance level are noteworthy. This underscores the importance of considering the FIGO 2023 staging for women monitored due to high-intermediate risk EC, urging a revision of their stages and a review of treatment plans accordingly. This observation highlights the potential significance of the evolving staging criteria in refining patient management strategies.

Study limitations

Despite its contributions, our study has several limitations. Its retrospective design limits control over confounding variables and prevents causal inferences. Additionally, the relatively small sample size may reduce statistical power and limit the generalizability of our findings to broader EC populations, highlighting the need for validation in larger, multicenter cohorts. The absence of molecular data further restricts our ability to assess the full impact of the FIGO 2023 system, given the growing role of molecular profiling in EC classification. Future prospective studies with extended follow-up are essential to determine whether upstaging translates into improved patient outcomes. Nonetheless, our study contributes to the literature by evaluating the new staging system in a highly homogenized cohort and providing valuable insights into its prognostic impact, an area where published data remain limited.

Conclusion

The FIGO 2023 staging system has led to significant upstaging in high-intermediate risk endometrioid EC, with all recurrent and deceased cases being among those reclassified. The primary factor influencing upstaging was LVSI positivity, suggesting improved identification of high-risk patients. While our survival analysis did not demonstrate a statistically significant difference between FIGO 2009 and 2023 staging systems, trend toward to a lower p-value in OS analysis is noteworthy. This emphasizes the potential clinical relevance of the new staging system. In this regard, larger-scale further multicenter prospective studies, including molecular profiling, are needed.

Declarations

Funding

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Author contributions

Conceptualization, V.K. and E.G.; Methodology, V.K. and B.K.; Software, B.K..; Validation, V.K., B.K. and E.G.; Formal Analysis, B.K.; Investigation, E.G.; Resources, X.X.; Data Curation, E.G.; Writing – Original Draft Preparation, B.K. and E.G.; Writing – Review & Editing, V.K.; Visualization, B.K.; Supervision, V.K.; Project Administration, E.G.

Conflicts of interest

The author(s) declare no competing interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study design was approved by the instutional research ethics committee (Approval number: 08.06.2022-2022/78).

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