

Original Article

Validation of 2023 FIGO Stage IA1-IIIC2 Endometrial Carcinoma: A Retrospective Analysis of Two Tertiary Centers in South Korea and Taiwan

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Purpose As understanding of the molecular pathogenesis of endometrial carcinoma (EC) advanced, the International Federation of Gynecology and Obstetrics (FIGO) staging system was revised in 2023. This study compared EC survival outcomes using the 2009 and 2023 FIGO staging systems.

Materials and Methods We retrospectively analyzed 3,029 patients diagnosed with 2009 FIGO stage I-III EC between 1985 and 2022 in South Korea, and between 2020 and 2022 in Taiwan. All patients were reclassified using the 2023 FIGO staging, and survival and risk factors were examined under both systems.

Results Transitioning from the 2009 to 2023 FIGO resulted in 549 patients (18.0%) being upstaged and their survival curves being diversified, indicating significant prognostic value of the 2023 FIGO. Re-classification using the 2023 FIGO upstaged the 2009 FIGO stage IA high-risk ECs, allowing more intensive treatment and potentially improving survival outcomes. The most significant changes occurred in the 2009 FIGO stages IA, IB, and IIIA ECs: upstaging in 16.5%, 49.0%, and 2.0% of IA, IB, and IIIA tumors, respectively, and downstaging 0.3% and 40.8% of IB and IIIA tumors, respectively. The risk factors for poor survival included old age (≥ 60 years), menopause, diabetes, substantial lymphovascular space invasion, aberrant p53 expression, and some aggressive histological types (carcinosarcoma, undifferentiated carcinoma, mesonephric-like adenocarcinoma, and neuroendocrine carcinoma).

Conclusion The 2023 FIGO staging provides more refined stratification of early-stage EC than the 2009 version. Thus, the 2023 FIGO may more accurately guide prognosis and therapeutic decision-making.

Key words Endometrium, Endometrial neoplasms, 2023 FIGO staging, Prognosis

Introduction

Endometrial carcinoma (EC) is one of the most common gynecological malignancies worldwide, and its prevalence is increasing due to a declining fertility rate, a rising prevalence of obesity, and an aging population [1,2]. Approximately 75% of patients with EC have International Federation of Gynecology and Obstetrics (FIGO) stage I disease, and the prognosis of early-stage (stage I-II) EC is generally favorable, with 5-year overall survival (OS) rates of 74%-92% [1,3-5]. However, several risk factors have been reported to be associated with a higher risk of recurrence, including older age, larger

tumor size, histological type and grade, depth of myometrial invasion, and lymphovascular space invasion (LVS) [6-8].

Based on significant advances in understanding the molecular pathogenesis of EC, the FIGO revised the staging system for EC in 2023 [9]. The integration of histological type and molecular classification, including pathogenic mutations in *TP53* and *POLE*, into the staging system is the most important feature of this revision. The purpose of this retrospective study was to analyze the frequencies of stage shifts between the 2009 and 2023 FIGO staging systems and to compare the survival outcomes of EC patients under these two staging systems.

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Materials and Methods

1. Patients

During the study periods of 1985-2022 (Samsung Medical Center) and 2020-2022 (National Taiwan University Hospital), we reviewed the electronic medical records of 3,029 patients with pathologically confirmed 2009 FIGO stage IA1-IIIC2 EC. We collected their clinicopathological information, including age, stage, body mass index, medical history, parity, histological type, and p53 expression status.

2. FIGO staging

Patients diagnosed between 2009 and 2023 were reclassified according to the 2023 FIGO staging. Those diagnosed before 2009 were restaged according to both systems. The extent of LVSI was categorized as focal (< 5) or substantial ($\geq$ 5) to classify the cases as stages IB and IIB, respectively. p53 expression status was categorized as wild-type or aberrant (overexpression, complete absence, or cytoplasmic) to identify cases with aberrant p53 expression and designate them as stage IICmp53abn. For 412 cases in which p53 expression status was unavailable, we performed immunostaining for p53 and restaged them as previously described [10-12].

3. Statistical analysis

Data are expressed as the mean with standard deviation for continuous variables and as median and range for categorical variables. Survival rates were estimated using Kaplan-Meier plots. The log-rank test was employed to compare survival among different groups. A Cox proportional hazards regression model was used to identify parameters that independently predict survival. Statistical calculations were performed using IBM SPSS Statistics for Windows ver. 26.0 (IBM Corp.). A p-value < 0.05 was considered statistically significant.

Results

The pathological diagnoses of EC were initially established using the 1988 FIGO staging in 601 patients and the 2009 FIGO staging in 2,446 patients. As shown in Table 1, 2,579 patients (85.1%) were diagnosed with endometrioid EC, and 2,246 (74.3%) tumors were grade 1 or 2 endometrioid EC (non-aggressive histology). Table 2 shows the number of patients in each stage as defined by the 2009 and 2023 FIGO staging systems. Compared to the 2,552 (84.2%) tumors in 2009 FIGO stage I, the number of 2023 FIGO stage I tumors decreased (n=2,154, 69.6%). In contrast, the number of stage II tumors increased from 146 (4.8%) to 564 (18.6%). We observed similar numbers of stage III tumors based on

Table 1. Characteristics of 3,029 patients with EC

Characteristic	No. of patients (%)
Age (yr), median (range)	53 (17-91)
Body mass index (kg/m ²), mean $\pm$ SD	25.05 $\pm$ 4.56
Parity	
0	594 (19.6)
1	430 (14.2)
2	1,388 (45.7)
3	411 (13.7)
$\geq$ 4	202 (6.6)
Unknown	6 (0.2)
Medical history	
Hypertension	674 (22.3)
Diabetes	312 (10.3)
Hyperlipidemia	173 (5.7)
Histological type	
Endometrioid carcinoma	2,579 (85.1)
Serous carcinoma	132 (4.4)
Carcinosarcoma	113 (3.7)
Mixed carcinoma	94 (3.1)
Clear cell carcinoma	64 (2.1)
Undifferentiated carcinoma	18 (0.6)
Mesonephric-like adenocarcinoma	17 (0.6)
Neuroendocrine carcinoma	7 (0.2)
Mucinous adenocarcinoma	2 (0.1)
Unclassifiable	3 (0.1)
FIGO grade of endometrioid carcinoma	
1	1,546 (50.8)
2	700 (23.5)
3	333 (10.9)
p53 expression	
Aberrant (mutation) pattern	234 (7.7)
Wild-type pattern	2,230 (73.6)
Unknown	565 (18.7)
Adjuvant chemotherapy	
Doxorubicin plus platinum	31 (1.0)
Paclitaxel plus platinum	252 (8.3)
Platinum only	92 (3.0)
Others	61 (2.0)

EC, endometrial carcinoma; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.

the 2009 (n=331, 10.8%) and 2023 FIGO (n=311, 10.3%) staging systems.

Table 3 and Fig. 1 show Kaplan-Meier curves for progression-free survival (PFS) and OS of EC patients according to the 2009 and 2023 FIGO staging. The 5-year PFS rates of 2009 FIGO stage IA, IB, and II tumors were 94.7%, 81.2%, and 77.5%, respectively. The 5-year OS rates of 2009 FIGO stage IA, IB, and II tumors were 96.0%, 89.3%, and 83.8%, respectively, with median OS of 246.17, 192.03, and 232.23 months,

Table 2. EC stage distribution according to the 2009 and 2023 FIGO staging systems

Stage	2009 FIGO	2023 FIGO
I	2,552 (84.2)	2,154 (71.1)
	IA: 2,160 (71.3)	IA1: 975 (32.2)
	IB: 392 (12.9)	IA2: 822 (27.1)
		IA3: 28 (0.9)
		IB: 215 (7.1)
II	146 (4.8)	564 (18.6)
		IIA: 71 (2.3)
		IIB: 45 (1.5)
		IIC: 448 (14.8)
III	331 (10.8)	311 (10.3)
	IIIA: 49 (1.6)	IIIA1: 19 (0.6)
	IIIB: 12 (0.4)	IIIA2: 9 (0.3)
	IIIC1: 145 (4.8)	IIIB1: 10 (0.3)
	IIIC2: 125 (4.1)	IIIB2: 2 (0.1)
		IIIC1: 146 (4.8)
		IIIC2: 125 (4.1)

Values are presented as number of patients (%). EC, endometrial carcinoma; FIGO, International Federation of Gynecology and Obstetrics.

respectively. The difference in OS among these stages was significant ($p < 0.001$). Median OS for the 2023 FIGO stages could not be calculated because cases with long-term survival were censored without death.

Table 4 and Fig. 2 summarize the frequency of transitions from the 2009 to 2023 FIGO staging for each stage. Among the 2,160 2009 FIGO stage IA tumors, 1,804 (83.2%) were restaged as 2023 FIGO stage IA1-3 tumors, including IA1 ($n=975$, 45.1%), IA2 ($n=821$, 38.0%), and IA3 ($n=8$, 0.4%). The remaining 356 tumors (16.5%) were restaged as IB ($n=16$, 0.7%), IC ($n=111$, 5.1%), IIB ($n=26$, 1.2%), and IIC ($n=203$, 9.4%). Among the 392 2009 FIGO stage IB tumors, 199 (50.8%) were not stage-shifted, but the remaining 193 (49.2%) were restaged as IIC ($n=172$, 43.9%), followed by IIB ($n=17$, 4.3%), IC ($n=3$, 0.8%), and IA2 ($n=1$, 0.3%). Of the 146 2009 FIGO stage II tumors, 71 (48.6%) were restaged as IIA, two (1.4%) as IIB, and 73 (50.0%) as IIC. Fig. 3 shows Kaplan-Meier survival curves according to 2023 FIGO staging in patients initially diagnosed with 2009 FIGO stage IA, IB, II, and IIIA ECs.

Tables 5 and 6 present the risk factors for poor PFS and OS in EC patients, respectively. Patients aged 60 years or older demonstrated a significantly higher risk of poor outcomes than those under 60 years in both univariate (for PFS: hazard ratio [HR], 2.619; $p < 0.001$ and for OS: HR, 3.279; $p < 0.001$) and multivariate (for PFS: HR, 1.731; $p < 0.001$ and for OS: HR, 1.859; $p < 0.001$) analyses. Diabetes was also associated with poor outcomes in both univariate (for PFS: HR, 1.551; $p=0.008$ and for OS: HR, 2.177; $p < 0.001$) and multivariate (for OS: HR, 1.561; $p=0.014$) analyses. Postmenopausal status at the time of EC diagnosis was a significant unfavorable prognostic factor in both univariate (for PFS: HR, 2.188; $p < 0.001$ and for OS: HR, 2.976; $p < 0.001$) and multivariate

Table 3. PFS and OS of patients with EC according to the FIGO 2009 and 2023 staging

PFS					OS				
2009 FIGO			2023 FIGO		2009 FIGO			2023 FIGO	
Stage	Median (mo)	5YSR (%)	Stage	5YSR (%)	Stage	Median (mo)	5YSR (%)	Stage	5YSR (%)
IA	242.50	94.7	IA1	97.5	IA	246.17	96.0	IA1	98.6
IB	NA	81.2	IA2	96.2	IB	192.03	89.3	IA2	97.5
			IA3	92.3				IA3	100
			IB	89.1				IB	95.4
			IC	93.4				IC	93.5
II	NA	77.5	IIA	92.0	II	232.23	83.8	IIA	93.8
			IIB	80.7				IIB	82.7
			IIC	73.5				IIC	80.6
IIIA	NA	76.7	IIIA1	82.4	IIIA	NA	80.7	IIIA1	82.1
IIIB	NA	54.5	IIIA2	37.5	IIIB	NA	53.9	IIIA2	50.0
IIIC1	109.47	73.7	IIIB1	38.9	IIIC1	141.57	74.5	IIIB1	38.1
IIIC2	101.30	61.3	IIIC1	73.7	IIIC2	163.33	61.6	IIIC1	74.5
			IIIC2	61.3				IIIC2	61.6

EC, endometrial carcinoma; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; OS, overall survival; PFS, progression-free survival; 5YSR, 5-year survival rate.

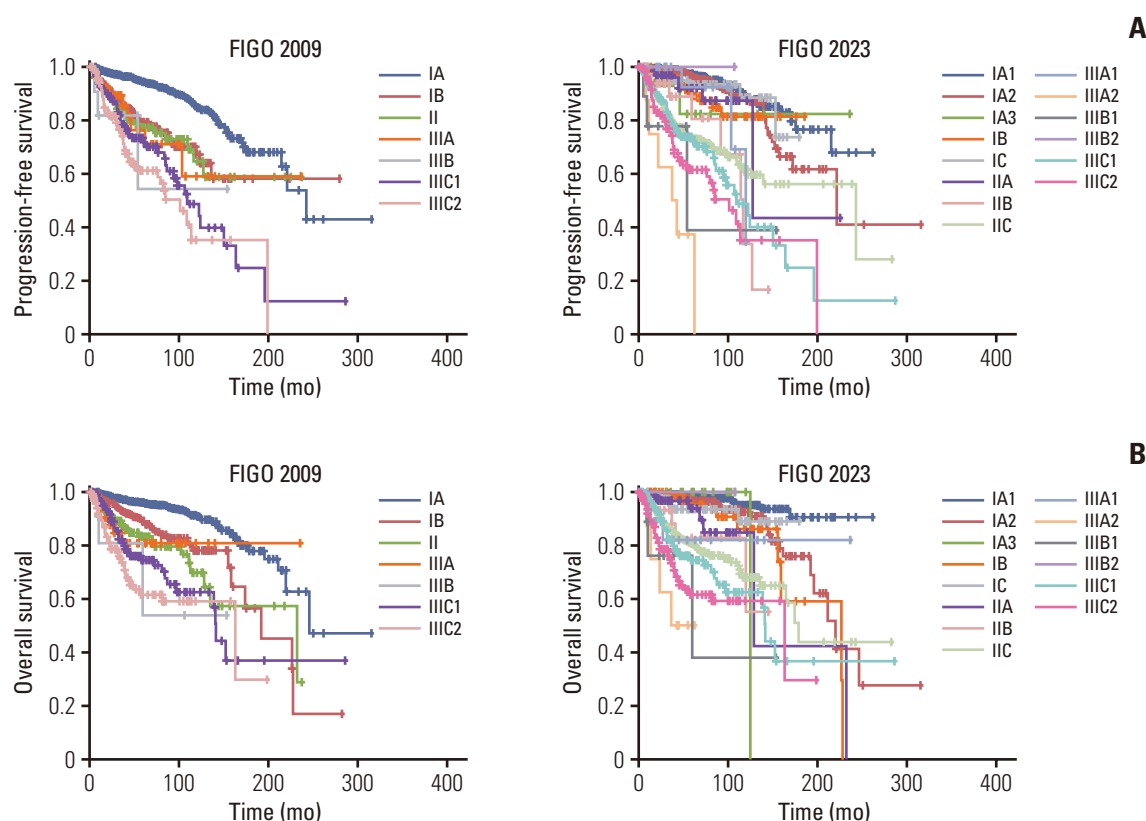


Fig. 1. Kaplan-Meier survival curves of progression-free survival (A) and overall survival (B) by International Federation of Gynecology and Obstetrics (FIGO) 2009 and 2023 staging.

(for OS: HR, 1.501; $p=0.020$) analyses. In contrast, a history of hyperlipidemia was associated with a significantly lower risk of poor outcomes in the multivariate analysis (for OS: HR, 0.461; $p=0.036$).

Regarding histological type, serous carcinoma (for PFS: HR, 4.842; $p < 0.001$ and for OS: HR, 5.457; $p < 0.001$), mixed carcinoma (for PFS: HR, 1.926; $p=0.010$ and for OS: HR, 2.722; $p < 0.001$), clear cell carcinoma (for PFS: HR, 3.564; $p < 0.001$ and for OS: HR=3.577; $p < 0.001$), mesonephric-like adenocarcinoma (for PFS: HR=10.119; $p < 0.001$ and for OS: HR, 3.108; $p=0.259$), carcinosarcoma (for PFS: HR, 6.489; $p < 0.001$ and for OS: HR, 6.355; $p < 0.001$), undifferentiated carcinoma (for PFS: HR, 4.744; $p < 0.001$ and for OS: HR, 5.368; $p < 0.001$), and neuroendocrine carcinoma (for PFS: HR, 18.061; $p < 0.001$ and for OS: HR, 21.382; $p < 0.001$) were associated with poor outcomes in univariate analysis. The latter three types had independent prognostic value in the multivariate analysis (carcinosarcoma—for PFS: HR, 1.769; $p=0.010$ and for OS: HR, 2.024; $p=0.005$; undifferentiated carcinoma—for PFS: HR, 2.815; $p=0.017$ and for OS: HR, 8.038; $p < 0.001$; neuroendocrine carcinoma—for PFS, HR, 9.445; $p < 0.001$ and for OS: HR, 2.557; $p=0.049$). Regarding p53 expression status,

aberrant p53 expression predicted significantly worse outcomes in both univariate (HR, 6.944; $p < 0.001$) and multivariate (HR, 3.577; $p < 0.001$) analyses.

Discussion

One of the most important features of the 2023 revision of the EC FIGO staging system is the addition of histological type as one of the determining factors. This change is based on previous data indicating that histological type has a significant predictive ability beyond what is provided by the 2009 FIGO staging alone [9,13]. Notably, “non-aggressive histologic type,” defined as low-grade (grades 1 or 2) endometrioid carcinoma (EEC), is an important factor in the 2023 FIGO stage I classification, whereas in the 2009 FIGO staging, only the depth of myometrial invasion mattered for stage I. Furthermore, in addition to serous and clear cell carcinomas—which generally show worse prognoses than EEC [14,15]—the 2023 FIGO staging classifies grade 3 EEC, undifferentiated carcinoma, mixed carcinoma, carcinosarcoma, and mesonephric-like adenocarcinoma as aggressive

Table 4. Shifts in stage from the 2009 to 2023 FIGO staging

Stage	2009 FIGO						
	IA (n=2,160)	IB (n=392)	II (n=146)	IIIA (n=49)	IIIB (n=12)	IIIC1 (n=145)	IIIC2 (n=125)
2023 FIGO							
IA1	975 (45.1)	-	-	-	-	-	-
IA2	821 (38.0)	1 (0.3)	-	-	-	-	-
IA3	8 (0.4)	-	-	20 (40.8)	-	-	-
IB	16 (0.7)	199 (50.8)	-	-	-	-	-
IC	111 (5.1)	3 (0.8)	-	-	-	-	-
IIA	-	-	71 (48.6)	-	-	-	-
IIB	26 (1.2)	17 (4.3)	2 (1.4)	-	-	-	-
IIC	203 (9.4)	172 (43.9)	73 (50.0)	-	-	-	-
IIIA1	-	-	-	19 (38.8)	-	-	-
IIIA2	-	-	-	9 (18.4)	-	-	-
IIIB1	-	-	-	-	10 (83.3)	-	-
IIIB2	-	-	-	-	2 (16.7)	-	-
IIIC1	-	-	-	1 (2.0)	-	145 (100)	-
IIIC2	-	-	-	-	-	-	125 (100)

Values are presented as number of patients (%). FIGO, International Federation of Gynecology and Obstetrics.

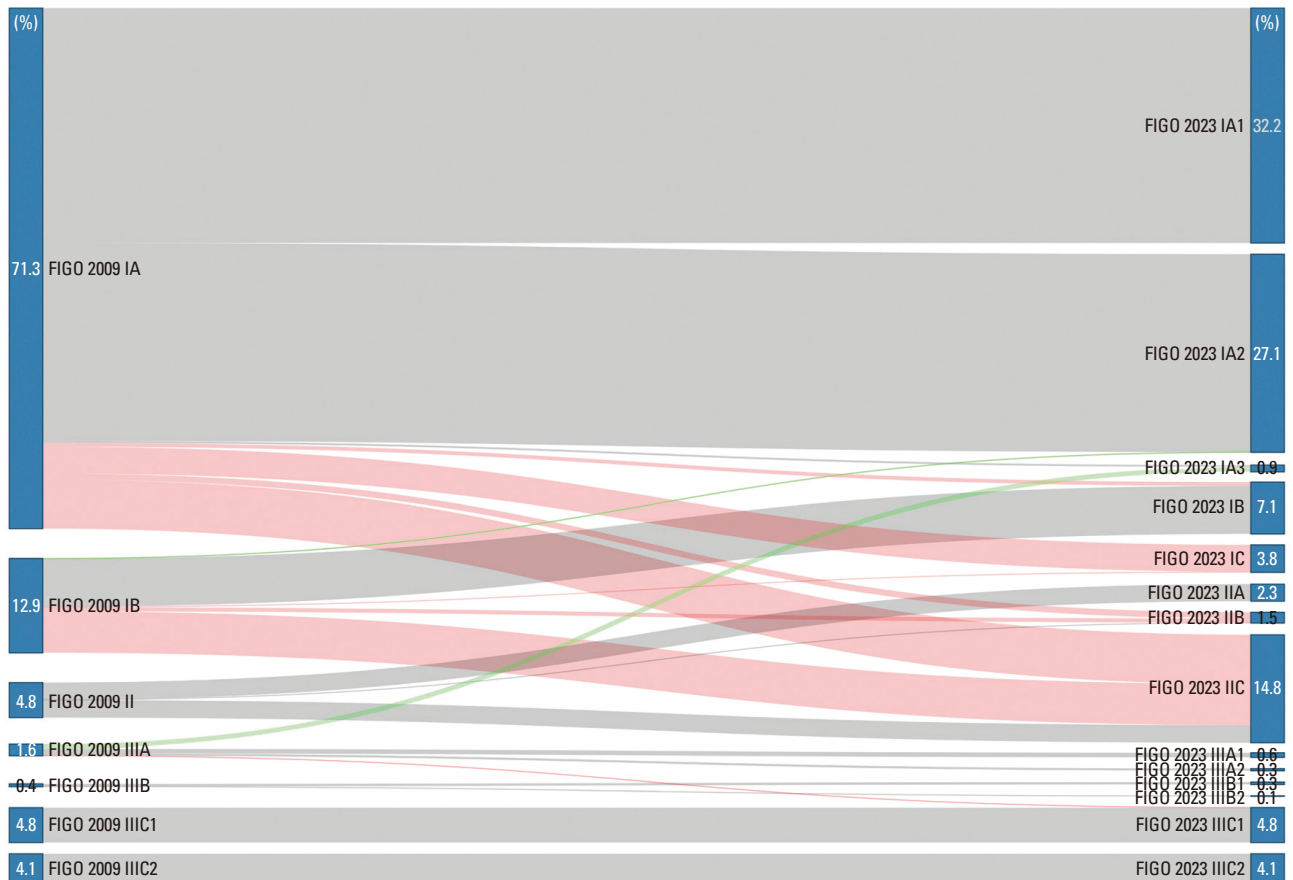


Fig. 2. Sankey diagram showing the shift of each stage from International Federation of Gynecology and Obstetrics (FIGO) 2009 to FIGO 2023. Red indicates upstage, green indicates downstage, and gray indicates transition to the same stage.

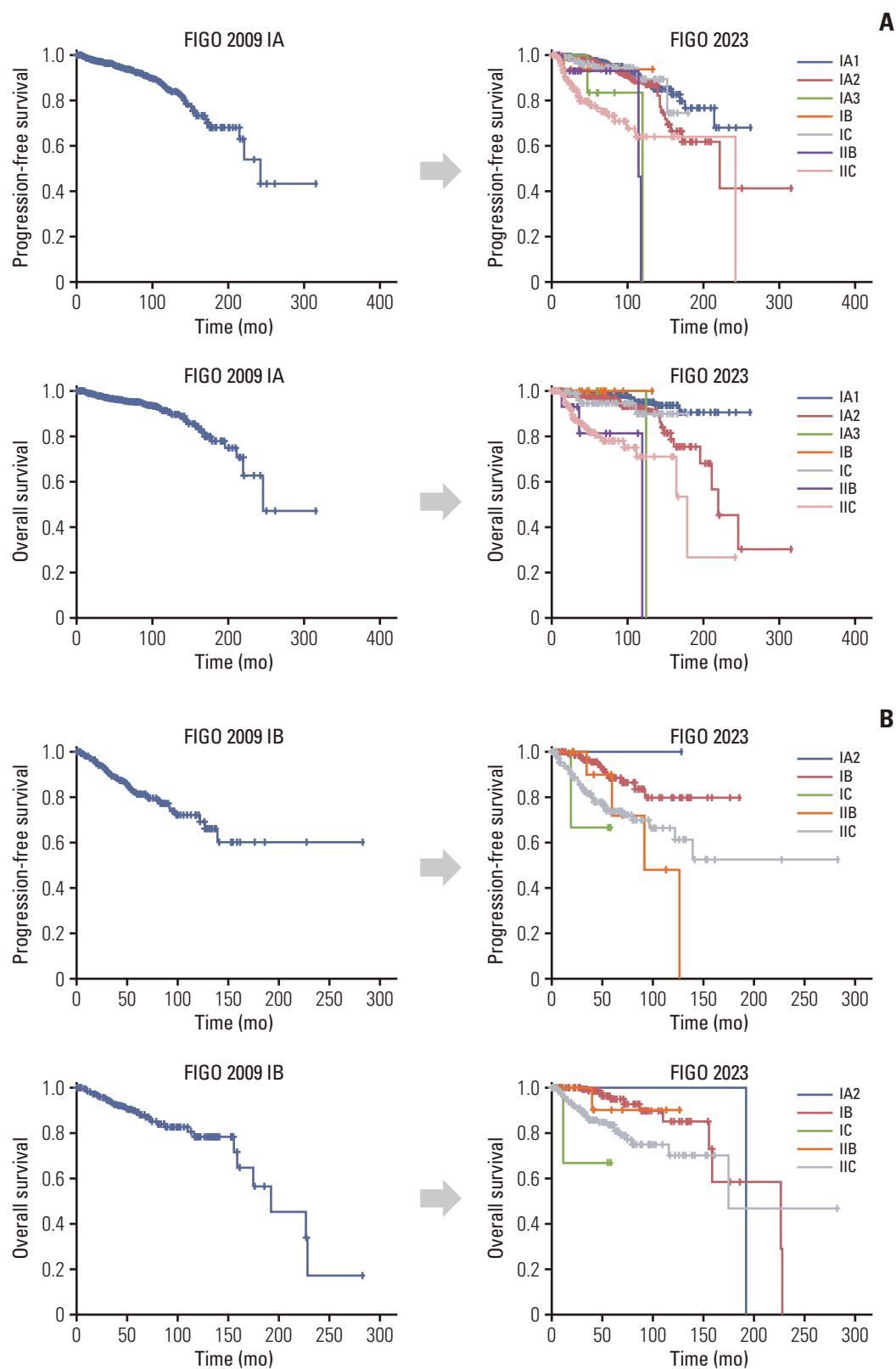


Fig. 3. Shift of International Federation of Gynecology and Obstetrics (FIGO) 2009 to 2023 staging. It shows restaged 2023 FIGO survival curves for the same patient cohort by each FIGO 2009 stages IA (A), IB (B), II (C), and IIIA (D). (Continued to the next page)

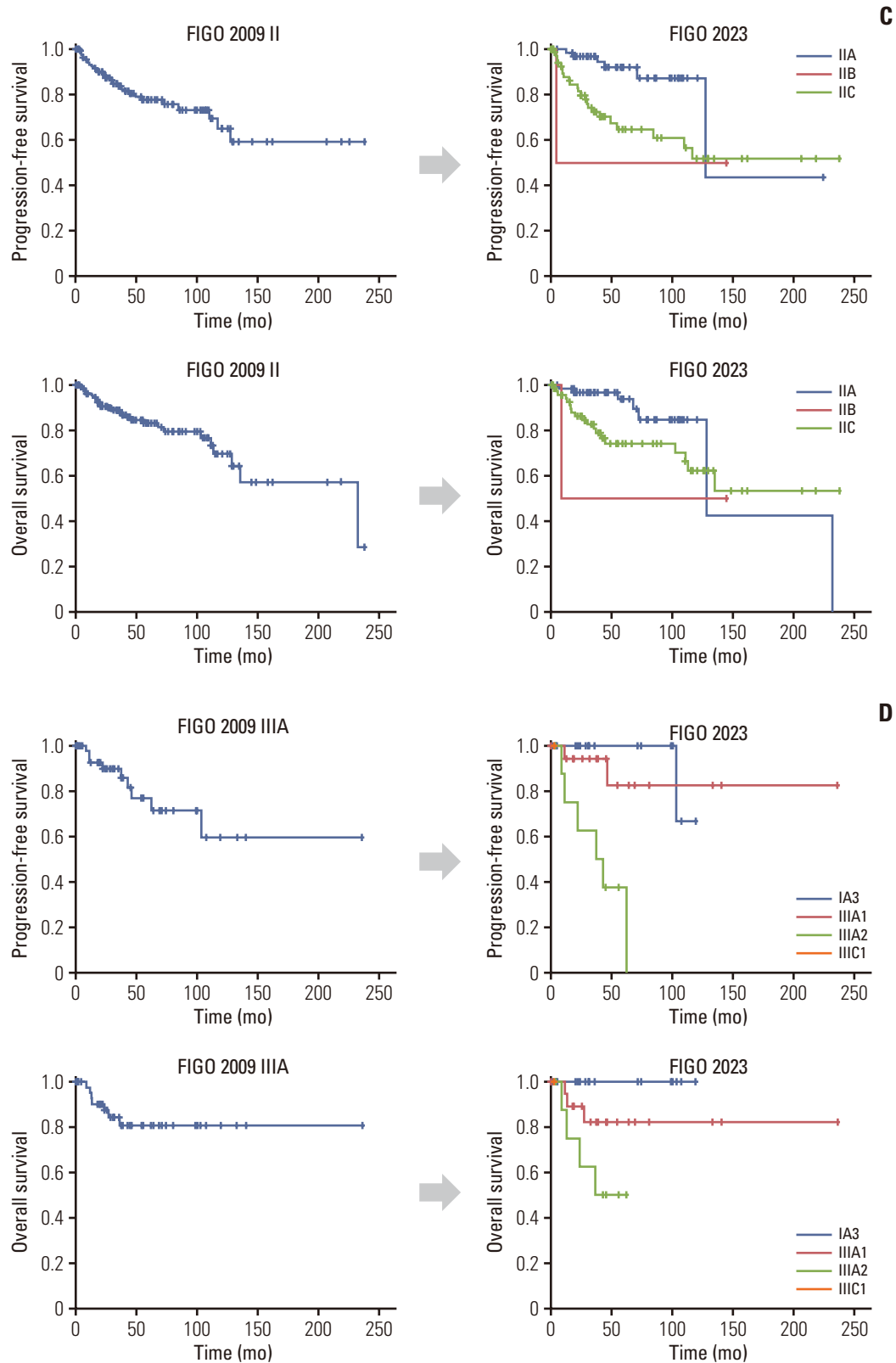


Fig. 3. (Continued from the previous page)

Table 5. Results of survival analysis for progression-free survival of patients with EC

Characteristic	Univariable		Multivariable	
	Hazard ratio	p-value	Hazard ratio	p-value
Age (yr)				
< 60	1.000	NA	1.000	NA
≥ 60	2.619	< 0.001	1.731	< 0.001
Body mass index (kg/m²)				
< 35	1.000	NA	1.000	NA
≥ 35	1.073	0.835	1.378	0.354
Medical history				
Diabetes	1.551	0.008	1.104	0.593
Hypertension	1.691	< 0.001	1.177	0.273
Hyperlipidemia	1.067	0.820	0.619	0.118
Postmenopausal status at diagnosis	2.188	< 0.001	1.281	0.099
Parity				
0	1.000	NA	1.000	NA
1	0.579	0.018	0.459	0.002
2	0.762	0.091	0.528	< 0.001
3	1.368	0.085	0.714	0.107
≥ 4	2.350	< 0.001	0.945	0.816
Histological type				
Endometrioid carcinoma	1.000	NA	1.000	NA
Serous carcinoma	4.842	< 0.001	1.341	0.164
Carcinosarcoma	6.489	< 0.001	1.769	0.010
Mixed carcinoma	1.926	0.010	0.892	0.674
Clear cell carcinoma	3.564	< 0.001	1.435	0.233
Undifferentiated carcinoma	4.744	< 0.001	2.815	0.017
Mesonephric-like adenocarcinoma	10.119	< 0.001	2.151	0.174
Neuroendocrine carcinoma	18.061	< 0.001	9.445	< 0.001
LVSI				
Substantial	4.844	< 0.001	2.545	< 0.001
Absent/Focal	1.000	NA	1.000	NA
p53 expression				
Aberrant (mutation)	5.235	< 0.001	2.710	< 0.001
Wild type	1.000	NA	1.000	NA
Adjuvant chemotherapy				
No chemotherapy	1.000	NA	1.000	NA
Doxorubicin plus platinum	4.721	< 0.001	2.266	0.012
Paclitaxel plus platinum	4.918	< 0.001	1.819	0.002
Platinum only	3.450	< 0.001	2.265	0.001
Others	8.495	< 0.001	3.050	< 0.001

EC, endometrial carcinoma; LVSI, lymphovascular space invasion; NA, not applicable (It indicates that the p-value cannot be applied to the reference group for the hazard ratio).

histological types. As a result, IA1 tumors are now upstaged to IC if they exhibit an aggressive histological type limited to the endometrium or an endometrial polyp, and IA2 or IB tumors are upstaged to IIC if an aggressive histological type is present with any myometrial invasion. For example, a serous carcinoma invading less than half of the myometrium was formerly classified as 2009 FIGO stage IA [16], but

is now classified as stage IIC under the 2023 FIGO staging [9]. For the conversion from the 2009 to the 2023 FIGO staging, the stages most affected were IA, IB, II, and IIIA. Due to the classification of aggressive histological types, the shift from 2009 FIGO stage IA and IB tumors to 2023 FIGO IC and IIC, respectively, was particularly notable. Of the 114 2023 FIGO IC tumors, 111 (97.4%) derived from 2009 FIGO stage

Table 6. Results of survival analysis for overall survival of patients with EC

Characteristic	Univariable		Multivariable	
	Hazard ratio	p-value	Hazard ratio	p-value
Age (yr)				
< 60	1.000	NA	1.000	NA
≥ 60	3.279	< 0.001	1.859	< 0.001
Body mass index (kg/m²)				
< 35	1.000	NA	1.000	NA
≥ 35	0.752	0.529	0.909	0.835
Medical history				
Diabetes	2.177	< 0.001	1.561	0.014
Hypertension	2.388	< 0.001	1.359	0.055
Hyperlipidemia	0.824	0.592	0.461	0.036
Postmenopausal status at diagnosis	2.976	< 0.001	1.501	0.020
Parity				
0	1.000	NA	1.000	NA
1	1.582	0.090	1.156	0.602
2	1.282	0.282	0.729	0.192
3	2.574	< 0.001	0.915	0.741
≥ 4	5.129	< 0.001	1.417	0.220
Histological type				
Endometrioid carcinoma	1.000	NA	1.000	NA
Serous carcinoma	5.457	< 0.001	1.338	0.200
Carcinosarcoma	6.355	< 0.001	2.024	0.005
Mixed carcinoma	2.722	< 0.001	1.151	0.601
Clear cell carcinoma	3.577	< 0.001	1.067	0.846
Undifferentiated carcinoma	5.368	< 0.001	2.557	0.049
Mesonephric-like adenocarcinoma	3.108	0.259	1.837	0.571
Neuroendocrine carcinoma	21.382	< 0.001	8.038	< 0.001
LVSI				
Substantial	4.023	< 0.001	2.288	< 0.001
Absent/Focal	1.000	NA	1.000	NA
p53 expression				
Aberrant (mutation)	6.944	< 0.001	3.577	< 0.001
Wild type	1.000	NA	1.000	NA
Adjuvant chemotherapy				
No chemotherapy	1.000	NA	1.000	NA
Doxorubicin plus platinum	5.994	< 0.001	2.332	0.009
Paclitaxel plus platinum	3.406	< 0.001	1.497	0.082
Platinum only	3.205	< 0.001	2.008	0.011
Others	9.282	< 0.001	3.629	< 0.001

EC, endometrial carcinoma; LVSI, lymphovascular space invasion; NA, not applicable (It indicates that the p-value cannot be applied to the reference group for the hazard ratio).

IA tumors, and 375 (83.7%) of the 448 2023 FIGO IIC tumors were upstaged from 2009 FIGO IA and IB tumors. The introduction of molecular classification for EC is also important in the 2023 FIGO staging. *POLE* mutations have been associated with a good prognosis in EC [17-20], whereas aberrant p53 expression is related to poor outcomes [20-22]. We confirmed that aberrant p53 expression is a significant predic-

tive factor associated with lower PFS and OS, demonstrating independent prognostic value. Additionally, substantial LVSI was adopted as a factor in determining stage IIB. Substantial LVSI has been reported as an independent prognostic factor for pelvic and distant recurrences, lymph node metastasis, and OS in patients with early-stage EC [23-26]. As a result, substantial LVSI was included in the 2023 FIGO staging to

distinguish stage IIB from stage IB or IIA.

It is well known that high-risk factors for EC recurrence include histological type, LVSI, age, and other variables [27]. We assessed HRs for OS using both univariate and multivariate survival analyses. We found that age over 60 years, hypertension, and certain aggressive histological types (serous carcinoma, clear cell carcinoma, neuroendocrine carcinoma, and undifferentiated carcinoma) exhibited high HRs.

Based on the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines [28], 2009 FIGO stage I ECs can be classified into three risk groups: (1) intermediate risk (stage IA, grade 3 EEC with non-substantial LVSI or stage IA, non-endometrioid EC without myometrial invasion), (2) high-intermediate risk (stage IB, grade 3 EEC regardless of LVSI status or stage I EEC with substantial LVSI regardless of histological grade or depth of myometrial invasion), and (3) high risk (stage I, non-endometrioid EC with any myometrial invasion) groups. Since the 2023 FIGO staging integrates these risk factors, adjuvant treatment can now be implemented according to the 2023 FIGO stages.

In the 2009 FIGO staging system for endometrial cancer, stage I was simplified into only two substages (IA and IB), and stage II had only one substage. This simplicity made it convenient for clinical use, but it required additional considerations for high-risk factors such as histological type, LVSI, and age [27]. As shown in Table 2, when comparing the 2009 FIGO to the 2023 FIGO staging, the percentage of patients with stage I disease decreased from 84.2% to 69.6%, while 2023 FIGO stage II increased from 4.9% (in 2009 FIGO) to 18.6%. Also, as shown in Fig. 2, when each 2009 FIGO stage was converted to 2023 FIGO, a single survival curve in the 2009 FIGO system was subdivided into multiple curves in the 2023 FIGO system. This suggests that each 2009 FIGO stage contained more heterogeneous patient groups than the corresponding 2023 FIGO stages. Despite the favorable prognosis for early-stage EC [1,3-5], the survival curve of 2009 FIGO stage IA in Fig. 1B showed a downward trend. However, under the 2023 FIGO staging, stage IA1 shows a survival curve closer to a straight line, indicating a more homogeneous patient group. As a result, high-risk patients included in 2009 FIGO stage IA would be assigned higher stages in the 2023 FIGO system based on histological type or LVSI, potentially receiving more intensive treatment, which may positively impact survival. The most significant changes when converting from 2009 FIGO to 2023 FIGO staging occurred in FIGO 2009 IA, IB, and II tumors.

The 2023 FIGO staging system provides a more refined stratification of early-stage disease than the 2009 FIGO system. As a result, the 2023 FIGO staging system is both more prognostic and therapeutic, allowing for adjuvant treatment

decisions to be guided directly by the stage. Further research is needed to investigate treatments according to the new 2023 FIGO staging system and the corresponding survival outcomes.

Ethical Statement

The study protocol was approved by the Institutional Review Boards of Samsung Medical Center (SMC; Seoul, South Korea; approval number: 2021-06-070) and National Taiwan University Hospital (NTUH; Taipei City, Taiwan; approval number: 202108087RINC). Owing to the retrospective nature of this study, the Institutional Review Boards waived the requirement for the investigators to obtain signed informed consent.

Author Contributions

Conceived and designed the analysis: Kim MS, Lai YL, Lee Y, Kim HS, Chen YL, Lee YY.

Collected the data: Kim MS, Lai YL, Lee Y, Chen YL, Lee YY.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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References

- Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. *Lancet*. 2022;399:1412-28.
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-49.
- Lu KH, Broaddus RR. Endometrial cancer. *N Engl J Med*. 2020;383:2053-64.
- Tejerizo-Garcia A, Jimenez-Lopez JS, Munoz-Gonzalez JL, Bartolome-Sotillos S, Marqueta-Marques L, Lopez-Gonzalez G, et al. Overall survival and disease-free survival in endometrial cancer: prognostic factors in 276 patients. *Onco Targets Ther*. 2013;9:1305-13.
- Lajer H, Elnegaard S, Christensen RD, Ortoft G, Schledermann DE, Mogensen O. Survival after stage IA endometrial cancer; can follow-up be altered? A prospective nationwide Danish survey. *Acta Obstet Gynecol Scand*. 2012;91:976-82.
- Veade AE, Foote J, Ehrisman J, Broadwater G, Davidson BA, Lee PS, et al. Associations between lymphovascular space invasion, nodal recurrence, and survival in patients with surgical stage I endometrioid endometrial adenocarcinoma. *World J Surg Oncol*. 2019;17:80.
- Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer*. 1987;60:2035-41.
- Johnson AL, Medina HN, Schlumbrecht MP, Reis I, Kobetz EN, Pinheiro PS. The role of histology on endometrial cancer survival disparities in diverse Florida. *PLoS One*. 2020;15:e0236402.
- Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. *Int J Gynaecol Obstet*. 2023;162:383-94.
- Kim H, Na K, Bae GE, Kim HS. Mesonephric-like adenocarcinoma of the uterine corpus: comprehensive immunohistochemical analyses using markers for mesonephric, endometrioid and serous tumors. *Diagnostics (Basel)*. 2021;11:2042.
- Koh HH, Park E, Kim HS. Mesonephric-like adenocarcinoma of the ovary: clinicopathological and molecular characteristics. *Diagnostics (Basel)*. 2022;12:326.
- Lee Y, Choi S, Kim HS. Comprehensive immunohistochemical analysis of mesonephric marker expression in low-grade endometrial endometrioid carcinoma. *Int J Gynecol Pathol*. 2024;43:221-32.
- Barlin JN, Soslow RA, Lutz M, Zhou QC, St Clair CM, Leitao MM Jr, et al. Redefining stage I endometrial cancer: incorporating histology, a binary grading system, myometrial invasion, and lymph node assessment. *Int J Gynecol Cancer*. 2013;23:1620-8.
- Sakuragi N, Hareyama H, Todo Y, Yamada H, Yamamoto R, Fujino T, et al. Prognostic significance of serous and clear cell adenocarcinoma in surgically staged endometrial carcinoma. *Acta Obstet Gynecol Scand*. 2000;79:311-6.
- Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. *Br J Cancer*. 2006;94:642-6.
- Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009;105:103-4.
- Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, ter Haar N, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. *J Natl Cancer Inst*. 2015;107:402.
- Leon-Castillo A, Britton H, McConechy MK, McAlpine JN, Nout R, Kommoss S, et al. Interpretation of somatic POLE mutations in endometrial carcinoma. *J Pathol*. 2020;250:323-35.
- Van Gool IC, Rayner E, Osse EM, Nout RA, Creutzberg CL, Tomlinson IP, et al. Adjuvant treatment for POLE proofreading domain-mutant cancers: sensitivity to radiotherapy, chemotherapy, and nucleoside analogues. *Clin Cancer Res*. 2018;24:3197-203.
- Vermij L, Smit V, Nout R, Bosse T. Incorporation of molecular characteristics into endometrial cancer management. *Histopathology*. 2020;76:52-63.
- Stelloo E, Nout RA, Osse EM, Jurgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts. *Clin Cancer Res*. 2016;22:4215-24.
- Leon-Castillo A, Gilvazquez E, Nout R, Smit VT, McAlpine JN, McConechy M, et al. Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. *J Pathol*. 2020;250:312-22.
- Bosse T, Peters EE, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Mens JW, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer: a pooled analysis of PORTEC 1 and 2 trials. *Eur J Cancer*. 2015;51:1742-50.
- Guntupalli SR, Zigelboim I, Kizer NT, Zhang Q, Powell MA, Thaker PH, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. *Gynecol Oncol*. 2012;124: 31-5.
- Benedetti Panici P, Basile S, Salerno MG, Di Donato V, Marchetti C, Perniola G, et al. Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. *Am J Obstet Gynecol*. 2014;210:363.
- Wang J, Xu P, Yang X, Yu Q, Xu X, Zou G, et al. Association of myometrial invasion with lymphovascular space invasion, lymph node metastasis, recurrence, and overall survival in endometrial cancer: a meta-analysis of 79 studies with 68,870 patients. *Front Oncol*. 2021;11:762329.
- Abu-Rustum N, Yashar C, Arend R, Barber E, Bradley K, Brooks R, et al. Uterine neoplasms, version 1.2023, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2023;21:181-209.
- Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer*. 2021;31:12-39.