GOCM Gynecology and Obstetrics Clinical Medicine

Rationality of the FIGO2023 staging for early-stage endometrial cancer, compared with the FIGO2009 staging

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To cite: Zhu A, Dong Y, Li X, *et al*. Rationality of the FIGO2023 staging for early-stage endometrial cancer, compared with the FIGO2009 staging. *Gynecology and Obstetrics Clinical Medicine* 2024;**4**:e000016. doi:10.1136/gocm-2024-000016

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gocm-2024-000016).

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Received 10 March 2024
Accepted 14 March 2024

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ABSTRACT

Objective The International Federation of Gynecology and Obstetrics (FIGO) released a new staging for endometrial cancer (EC), which revised the FIGO2009 staging to include histopathological and molecular features. The purpose of this study was to validate the prognostic accuracy of the new staging and discuss its clinical applicability.

Methods In this single-centre retrospective study, 540 patients with primary surgically treated early-stage EC were enrolled and staged according to FIGO2009/2023. Kaplan-Meier survival analysis was used to compare for prognostic differentiation. Cox regression was used to identify potential prognostic indicators.

Results A total of 81 patients underwent staging shifts, all stage elevation. The prognosis difference between new stages I and II was more significant. The new staging was more predictive of death postoperatively. Lesion maximum diameter (LMD) was one of the independent risk factors associated with prognosis. Taking LMD=5.70 cm as the cut-off value could further differentiate patients with divergent prognoses within FIGO2023 stage IIC.

Conclusion FIGO2023 staging demonstrated greater prognostic accuracy. In addition, LMD may be another critical factor affecting prognosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many factors have been incorporated into the new staging system. Its prognostic accuracy and clinical applicability ought to be discussed.

WHAT THIS STUDY ADDS

⇒ The new staging was more predictive of death post-operatively. Lesion size could further differentiate patients with divergent prognoses.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a reference for clinical practice of new staging, while also suggesting that there are still shortcomings in the new staging.

INTRODUCTION

Endometrial cancer (EC) is a common malignant tumour of the female reproductive system,[1] and its incidence has been growing globally in recent years.[2 3] Since the release of International Federation of Gynecology and Obstetrics (FIGO) 2009 staging, extensive research evidence has led to noteworthy headway in understanding EC's histopathological and molecular features. At the same time, the FIGO2009 staging has gradually revealed its shortcomings in usage, including neglect of histological types, overly crude staging and poor prognostic accuracy, which cannot meet clinical needs. In 2023, the FIGO Women's Cancer Committee formally released an updated staging system for EC,[4] which is significantly different from the FIGO2009 staging. Based on the anatomical extent of the tumour, the FIGO2023 staging introduces non-anatomical parameters in stage I/II, including histological type, lymphovascular space invasion (LVSI) and molecular staging. For stage III/IV, the staging was divided in more detail based on the anatomical and histological distribution of the tumour, such as distinguishing between intra/extrapelvic peritoneal metastases and lymph node ultrastaging. Another change is to categorise low-grade endometrioid carcinomas that meet specific criteria in patients with both uterine and ovarian involvement as stage IA3, which is considered to have a good overall prognosis. This comprehensive staging approach aims to reflect prognosis better and guide clinical decision-making.

However, the prognostic accuracy of the new FIGO2023 staging system lacks validation, and its clinical applicability ought to be discussed. This study focuses on the stage shifts of early-stage EC (stage I/II) between the old and new staging, evaluates the predictive ability of the FIGO2023 staging for recurrence or death, and discusses the clinical impact of the updates.

METHODS

Study population and data collection

Inclusion criteria: consultation at the Gynecology Department, Peking University People's Hospital (PKUPH), Beijing, China,

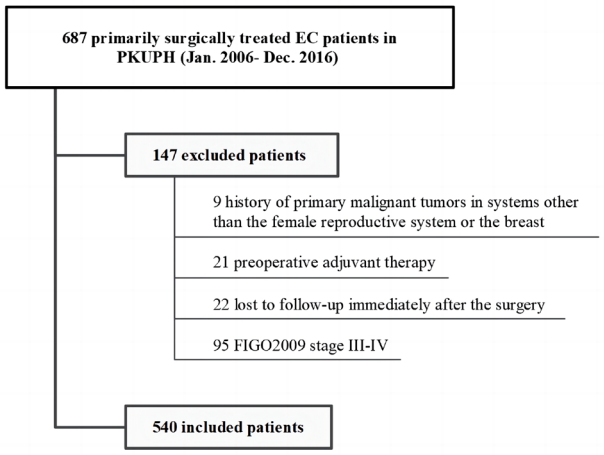


Figure 1 Consolidated Standards of Reporting Trials diagram. EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; PKUPH, Peking University People's Hospital.

from January 2006 to December 2016; EC diagnosed by surgical pathology; FIGO2009 stages I–II. Exclusion criteria: history of primary malignant tumours in systems other than the female reproductive system or the breast; treatment prior to surgery; loss to follow-up immediately after surgery.

Baseline information about each patient was collected, including age, height, weight, pregnancy, delivery, comorbidities, family history of cancer and CA125. All included patients underwent total hysterectomy, bilateral adnexectomy, selective pelvic and para-aortic lymph node dissection and pelvic lavage. Pathological information, including Bokhman classification, histological grade, myometrial invasion, cervical stromal invasion, LVSI, peritoneal cytology, oestrogen receptor (ER), progesterone receptor (PR), p53, Ki67 and lesion maximum diameter (LMD), was extracted from the original surgery pathology reports. Two independent gynaecological pathologists reviewed the pathology slides, and any disputes were submitted to an expert committee for final decision. A positive immunohistochemical result for ER, PR or p53 was defined as over 10% of tumour cells being moderately or strongly stained in one slide. The determination of the Ki67 index was based on the proportion of tumour cells showing positive staining.

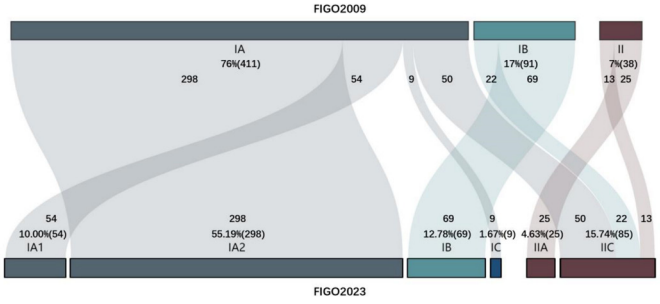


Figure 2 Stage shifts of cases after restaging according to FIGO2023 staging. FIGO, International Federation of Gynecology and Obstetrics.

Follow-up and definitions

All patients were followed up through the outpatient clinic or by phone after surgery. Information collected included patients' symptoms, laboratory test results and postoperative adjuvant therapy. Recurrence and death from any cause during the follow-up were recorded. If any abnormality was detected during the follow-up, the patient was required to come to our centre for further testing, and the diagnosis of recurrence would be made if new lesions were found in pathology or were highly suggestive on imaging. Reasons for termination of follow-up included death from any cause, loss of contact and arrival at the final follow-up date (28 September 2021). Overall survival (OS) was defined as the time interval from the surgery date to death from any cause. Disease-free survival (DFS) was defined as the time interval from the surgery date to confirmation of EC recurrence.

Statistical analysis

Student's t-test and χ^2 test were used for comparing continuous and categorical variables, respectively. OS and DFS were assessed using the Kaplan-Meier (K-M) survival analysis and the log-rank test. Univariate and multivariate Cox regression analyses were used to identify potential prognostic indicators, with HR and its 95% CI provided. Receiver operating characteristic (ROC) curve was drawn to show the efficiency of LMD for predicting death and recurrence. All statistical analyses were done using SPSS software (IBM Corp Released 2017. IBM SPSS Statistics for Windows, V.25.0). P<0.05 was considered statistically significant.

RESULTS

Data screening and stage shifts

All 687 patients were primarily surgically treated and diagnosed with EC by surgical pathology at the Gynecology Department of PKUPH from January 2006 to December 2016. We excluded patients who had a history of primary malignant tumours in systems other than the female reproductive system or the breast (n=9), who received treatment earlier than the surgery (n=21), who had been lost to follow-up immediately after the surgery (n=22) and who belonged to FIGO2009 stages III–IV (n=95). Finally, 540 patients were selected for further research (figure 1).

The 540 patients were restaged according to the FIGO2023 staging. Due to data limitations, we failed to classify 'substantial' versus 'focal' LVSI according to '≥5 vessels involved'. Instead, we relied on the diagnosis strings given by pathologists, such as 'massive', 'extensive' and 'numerous' in the description of LVSI. The cases considered 'substantial' LVSI in this study were all of the aggressive histological type and shifted from FIGO2009 stage IA/IB to FIGO2023 stage IIC, resulting in 0 patients categorised as FIGO2023 stage IIB. There were no cases

Table 1 Baseline clinical and pathological characteristics of each FIGO2009/FIGO2023 substage (n=540)

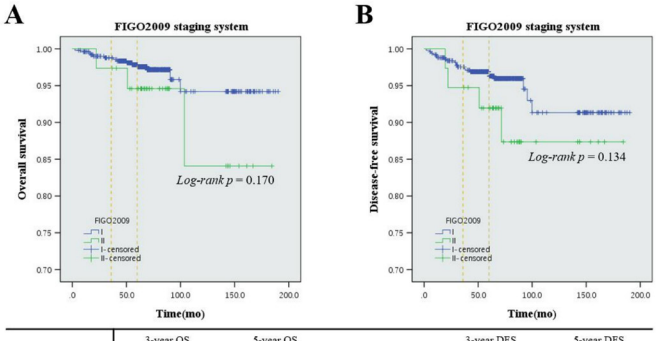
Characteristic	Total (n=540)	FIGO2009				FIGO2023						
		IA (n=411)	IB (n=91)	II (n=38)	P value	IA1 (n=54)	IA2 (n=298)	IB (n=69)	IC (n=9)	IIA (n=25)	IIC (n=85)	P value
Clinical characteristics												
Age, year (mean±SD)	55.5±9.3	54.6±9.3	60.3±8.0	53.4±9.3	0.000**	50.9±9.6	54.3±8.9	60.2±8.2	57.6±8.3	51.7±9.6	59.7±8.5	0.000**
BMI, kg/m^2 (mean±SD)	26.2±4.6	26.4±4.7	26.3±4.5	24.5±3.7	0.051	26.8±5.1	26.4±4.4	26.9±4.7	22.5±3.5	25.4±3.8	25.4±5.1	0.033*
Gravida (mean±SD)	2.5±1.5	2.5±1.4	2.8±1.6	2.5±1.5	0.228	2.6±1.3	2.4±1.4	2.8±1.5	2.6±1.3	2.4±1.4	2.8±1.6	0.156
Para (mean±SD)	1.5±1.0	1.4±1.0	1.6±1.1	1.4±1.1	0.125	1.2±0.7	1.4±1.0	1.6±1.0	1.8±1.0	1.2±0.8	1.8±1.3	0.011*
CA125, U/mL, median (Q1, Q3)	19.6 (12.0, 31.7)	17.6 (11.8, 28.0)	24.9 (14.3, 42.4)	31.3 (13.1, 44.4)	0.000**	16.7 (11.8, 29.2)	17.8 (11.8, 27.5)	29.3 (14.6, 58.0)	21.0 (9.6, 35.9)	30.9 (14.0, 80.3)	19.7 (11.3, 31.9)	0.001**
Breast cancer history, n (%)					0.158							0.001**
Positive	13 (2.4)	11 (2.7)	0 (0.0)	2 (5.3)		2 (3.7)	4 (1.3)	0 (0.0)	2 (22.2)	1 (4.0)	4 (4.7)	
Negative	527 (97.6)	400 (97.3)	91 (100.0)	36 (94.7)		52 (96.3)	294 (98.7)	69 (100.0)	7 (77.8)	24 (96.0)	81 (95.3)	
Diabetes history, n (%)					0.366							0.443
Positive	121 (22.4)	95 (23.1)	21 (23.1)	5 (13.2)		9 (16.7)	71 (23.8)	16 (23.2)	4 (44.4)	4 (16.0)	17 (20.0)	
Negative	419 (77.6)	316 (76.9)	70 (76.9)	33 (86.8)		45 (83.3)	227 (76.2)	53 (76.8)	5 (55.6)	21 (84.0)	68 (80.0)	
Hypertension history, n (%)					0.192							0.196
Positive	226 (41.9)	173 (42.1)	42 (46.2)	11 (28.9)		19 (35.2)	126 (42.3)	34 (49.3)	1 (11.1)	8 (32.0)	38 (44.7)	
Negative	314 (58.1)	238 (57.9)	49 (53.8)	27 (71.1)		35 (64.8)	172 (57.7)	35 (50.7)	8 (88.9)	17 (68.0)	47 (55.3)	
Familial tumour history, n (%)					0.095							0.199
Positive	79 (14.6)	55 (13.4)	14 (15.4)	10 (26.3)		4 (7.4)	41 (13.8)	10 (14.5)	1 (11.1)	7 (28.0)	16 (18.8)	
Negative	461 (85.4)	356 (86.6)	77 (84.6)	28 (73.7)		50 (92.6)	257 (86.2)	59 (85.5)	8 (88.9)	18 (72.0)	69 (81.2)	
Postoperative adjuvant treatment, n (%)					0.000**							0.000**
Use	231 (42.8)	136 (33.1)	69 (75.8)	26 (68.4)		8 (14.8)	82 (27.5)	48 (69.6)	7 (77.8)	16 (64.0)	70 (82.4)	
Non-use	309 (57.2)	275 (66.9)	22 (24.2)	12 (31.6)		46 (85.2)	216 (72.5)	21 (30.4)	2 (22.2)	9 (36.0)	15 (17.6)	
Pathological characteristics												
Bokhman classification, n (%)					0.552							0.000**
Type 1	505 (93.5)	385 (93.7)	86 (94.5)	34 (89.5)		54 (100.0)	298 (100.0)	69 (100.0)	2 (22.2)	25 (100.0)	57 (67.1)	
Type 2	35 (6.5)	26 (6.3)	5 (5.5)	4 (10.5)		0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)	0 (0.0)	28 (32.9)	
Histological grade, n (%)					0.000**							0.000**
G1	200 (37.0)	181 (44.0)	12 (13.2)	7 (18.4)		37 (68.5)	144 (48.3)	12 (17.4)	0 (0.0)	7 (28.0)	0 (0.0)	
G2	246 (45.6)	171 (41.6)	57 (62.6)	18 (47.4)		17 (31.5)	154 (51.7)	57 (82.6)	0 (0.0)	18 (72.0)	0 (0.0)	
G3	94 (17.4)	59 (14.4)	22 (24.2)	13 (34.2)		0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)	0 (0.0)	85 (100.0)	
Myometrial invasion, n (%)					0.000**							0.000**
<1/2	438 (81.1)	411 (100.0)	1 (1.1)	26 (68.4)		54 (100.0)	298 (100.0)	1 (1.4)	9 (100.0)	19 (76.0)	57 (67.1)	
≥1/2	102 (18.9)	0 (0.0)	90 (98.9)	12 (31.6)		0 (0.0)	0 (0.0)	68 (98.6)	0 (0.0)	6 (24.0)	28 (32.9)	

Continued

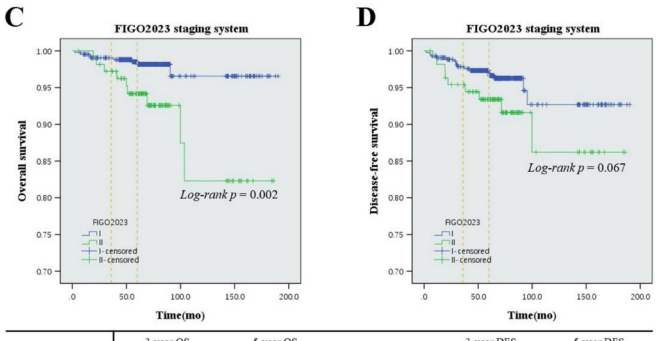
Table 1 Continued

Characteristic	Total (n=540)	FIGO2009				FIGO2023						
		IA (n=411)	IB (n=91)	II (n=38)	P value	IA1 (n=54)	IA2 (n=298)	IB (n=69)	IC (n=9)	IIA (n=25)	IIC (n=85)	P value
Cervical stromal invasion, n (%)					0.000**							0.000**
Positive	38 (7.0)	0 (0.0)	0 (0.0)	38 (100.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	25 (100.0)	13 (15.3)	
Negative	502 (93.0)	411 (100.0)	91 (100.0)	0 (0.0)		54 (100.0)	298 (100.0)	69 (100.0)	9 (100.0)	0 (0.0)	72 (84.7)	
LVSI, n (%)					0.000**							0.000**
Positive	53 (9.8)	24 (5.8)	21 (23.1)	8 (21.1)		0 (0.0)	12 (4.0)	11 (15.9)	0 (0.0)	3 (12.0)	27 (31.8)	
Negative	487 (90.2)	387 (94.2)	70 (76.9)	30 (78.9)		54 (100.0)	286 (96.0)	58 (84.1)	9 (100.0)	22 (88.0)	58 (68.2)	
Peritoneal cytology, n (%)					0.002**							0.239
Positive	22 (5.1)	14 (4.3)	2 (2.7)	6 (18.2)		0 (0.0)	13 (5.4)	2 (3.7)	0 (0.0)	3 (15.0)	4 (5.5)	
Negative	409 (94.9)	311 (95.7)	71 (97.3)	27 (81.8)		39 (100.0)	226 (94.6)	52 (96.3)	6 (100.0)	17 (85.0)	69 (94.5)	
ER, n (%)					0.555							0.000**
Positive	478 (93.4)	364 (93.8)	81 (93.1)	33 (89.2)		44 (95.7)	280 (96.9)	64 (98.5)	4 (57.1)	23 (95.8)	63 (77.8)	
Negative	34 (6.6)	24 (6.2)	6 (6.9)	4 (10.8)		2 (4.3)	9 (3.1)	1 (1.5)	3 (42.9)	1 (4.2)	18 (22.2)	
PR, n (%)					0.465							0.000**
Positive	464 (90.6)	355 (91.5)	76 (87.4)	33 (89.2)		44 (95.7)	278 (96.2)	62 (95.4)	1 (14.3)	24 (100.0)	55 (67.9)	
Negative	48 (9.4)	33 (8.5)	11 (12.6)	4 (10.8)		2 (4.3)	11 (3.8)	3 (4.6)	6 (85.7)	0 (0.0)	26 (32.1)	
p53, n (%)					0.724							0.000**
Positive	157 (31.8)	116 (30.9)	28 (34.1)	13 (36.1)		13 (28.9)	71 (25.6)	17 (27.9)	5 (71.4)	7 (30.4)	44 (55.0)	
Negative	336 (68.2)	259 (69.1)	54 (65.9)	23 (63.9)		32 (71.1)	206 (74.4)	44 (72.1)	2 (28.6)	16 (69.6)	36 (45.0)	
Ki67, % (mean±SD)	34.9±21.7	33.3±21.2	40.3±22.1	39.7±23.6	0.016*	31.3±23.9	29.8±18.5	33.2±19.2	52.9±22.3	38.1±26.1	53.3±20.4	0.000**
LMD, cm (mean±SD)	3.2±1.9	2.8±1.7	4.3±2.3	3.8±1.8	0.000**	2.0±1.2	2.8±1.6	4.3±2.5	1.9±0.4	3.8±1.8	3.6±2.0	0.000**

*P<0.05; **p<0.01.
BMI, body mass index; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; LMD, lesion maximum diameter; LVSI, lymphovascular space invasion; PR, progesterone receptor.



	3-year OS	5-year OS	3-year DFS	5-year DFS
FIGO2009 I	0.988	0.976	0.975	0.963
FIGO2009 II	0.974	0.946	0.947	0.920



	3-year OS	5-year OS	3-year DFS	5-year DFS
FIGO2023 I	0.991	0.982	0.978	0.967
FIGO2023 II	0.972	0.942	0.954	0.934

Figure 3 Kaplan-Meier analysis of OS and DFS of old and new staging systems (n=540). OS (A) and DFS (B) in the study cohort according to FIGO2009 staging; OS (C) and DFS (D) in the study cohort according to FIGO2023 staging. DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival.

in this study that qualified as low-grade endometrioid carcinomas confined to the uterus and ovaries, and therefore, 0 patients were categorised as FIGO2023 stage IA3. The staging was not adjusted to $IAm_{POLEmut}$ or $IICm_{p53abn}$ because the molecular typing of the cases was unknown.

A total of 81 stage shifts occurred (figure 2), all of which were stage elevations, including IA–IC (n=9), IA–IIC (n=50) and IB–IIC (n=22). The main shifting trends: cases of FIGO2009 IA stage diverged into FIGO2023 stages IA, IC and IIC; cases of FIGO2009 IA, IB and II stages converged into FIGO2023 IIC stage. According to the FIGO2023 staging, more patients were categorised as stage II (7%→20.37%). As shown in the baseline characteristics (table 1), body mass index, para, breast cancer history, the expression of ER/PR/p53 and Bokhman classification showed significant differences among different substages of FIGO2023, but not of FIGO2009. However, peritoneal cytology showed significant differences among different substages of FIGO2009, but not of FIGO2023.

Comparing oncological outcomes of stage I/II under two staging systems

The median follow-up time for all 540 patients was 75 months (ranging from 3 to 190 months). In total, there were 25 recurrences and 17 deaths (including 10 cancer-specific deaths). The difference of OS between new stages I and II was more significant (figure 3 and online supplemental table 1).

In univariate analyses, age ≥60 years, histological grade G3, LVSI, negative ER, negative PR, positive p53, LMD and FIGO2023 stage II were associated with OS. Among them, the HR of FIGO2023 stage II relative to FIGO2023 stage I is 4.133, while the HR is 2.344 for FIGO2009. All the factors that demonstrated statistical significance above were incorporated into the multivariate analysis. The independent risk factors influencing OS were obtained to be age ≥60 years, negative ER and LMD. As for DFS, age ≥60 years, histological grade G3, negative ER, negative PR and LMD were incorporated into the multivariate analysis, and the independent risk factors were also age ≥60 years, negative ER and LMD (table 2).

Comparing oncological outcomes of shifting subgroups at FIGO2009 stage IA and FIGO2023 stage IIC

411 patients were enrolled in FIGO2009 stage IA, of which 352 remained in FIGO2023 stage IA, 9 shifted to FIGO2023 stage IC and 50 shifted to FIGO2023 stage IIC. 85 patients were enrolled in FIGO2023 stage IIC, with 13 from FIGO2009 stage II, 50 from FIGO2009 stage IA and 22 from FIGO2009 stage IB. The K-M curves of OS in different shifting subgroups of FIGO2009 stage IA tended to separate, whereas OS and DFS of FIGO2023 stage IIC tended to overlap (figure 4).

For cases of FIGO2023 stage IIC, age ≥60 years and LMD were associated with OS in univariate analyses. LMD was the independent risk factor influencing OS, and also the only risk factor influencing DFS (table 3).

Association between prognosis and lesion size

Lesion size was closely related to prognosis in all 540 patients and in 85 FIGO2023 stage IIC patients. Using LMD as a stratification factor, we compared the OS and DFS of FIGO2023 stage I/II patients at different cut-off values (2, 3, 4, 5 and 6 cm) (online supplemental table 2). The difference between OS/DFS was statistically significant when the cut-off value was 4/5/6 cm in FIGO2023 stage II patients, suggesting that the LMD may further indicate prognosis. The ROC curves showed that the LMD=5.70 cm was the optimal cut-off value for predicting death and recurrence (online supplemental figure 1). The cut-off value of LMD=5.70 cm successfully further distinguished the OS and DFS of FIGO2023 stage IIC patients (figure 5).

DISCUSSION

Histopathology

Histopathology is a central feature of the new staging system. Tumour histological type is a significant predictor of prognosis in EC.[5] In our study cohort, the main factor contributing to elevated staging in patients with early-stage EC was the aggressive histological type. Patients with early-stage EC of an aggressive histological type will be classified as stage IC if there is no myometrial invasion

Table 2 Univariate and multivariate Cox regression analyses of factors influencing OS/DFS (n=540)

	OS						DFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Characteristic	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI
Age ≥60 years	0.000**	7.658	2.492 to 23.537	0.013*	10.607	1.637 to 68.747	0.020*	2.536	1.156 to 5.562	0.017*	0.242	0.076 to 0.772
BMI ≥28 kg/m^2	0.538	0.703	0.229 to 2.158				0.846	1.087	0.469 to 2.520			
Gravida=0	0.488	1.686	0.385 to 7.380				0.874	1.124	0.265 to 4.770			
Para=0	0.988	1.011	0.231 to 4.427				0.913	1.070	0.320 to 3.575			
CA125 ≥35 U/mL	0.869	1.099	0.358 to 3.371				0.689	0.801	0.271 to 2.368			
Positive breast cancer history	0.392	2.420	0.320 to 18.286				0.081	3.622	0.853 to 15.384			
Positive diabetes history	0.493	1.441	0.508 to 4.090				0.098	1.995	0.881 to 4.517			
Positive hypertension history	0.055	2.648	0.979 to 7.163				0.264	1.564	0.714 to 3.429			
Positive familial tumour history	0.847	1.130	0.324 to 3.941				0.607	0.728	0.218 to 2.438			
Postoperative adjuvant treatment use	0.872	1.083	0.410 to 2.859				0.213	1.649	0.750 to 3.626			
Bokhman type 2	0.059	3.352	0.957 to 11.735				0.220	2.130	0.636 to 7.140			
Histological grade G3	0.001**	5.342	2.061 to 13.848	0.145	8.001	0.489 to 130.905	0.018*	2.686	1.186 to 6.081	0.630	1.365	0.384 to 4.845
Myometrial invasion ≥1/2	0.089	2.373	0.878 to 6.418				0.089	2.073	0.895 to 4.805			
Positive cervical stromal invasion	0.183	2.344	0.670 to 8.207				0.144	2.222	0.761 to 6.491			
Positive LVSI	0.023*	3.769	1.203 to 11.813	0.812	1.241	0.209 to 7.377	0.516	1.495	0.445 to 5.026			
Positive peritoneal cytology	0.137	3.115	0.697 to 13.925				0.052	3.406	0.991 to 11.707			
Negative ER	0.003**	5.374	1.740 to 16.597	0.018*	26.831	1.751 to 411.085	0.000**	6.922	2.877 to 16.653	0.001**	0.027	0.004 to 0.208
Negative PR	0.028*	3.531	1.142 to 10.920	0.441	0.354	0.025 to 4.960	0.007**	3.579	1.423 to 9.001	0.502	1.953	0.277 to 13.782
Positive p53	0.010*	3.705	1.366 to 10.050	0.205	2.657	0.586 to 12.047	0.470	1.344	0.602 to 3.002			
Ki67	0.056	8.692	0.943 to 80.073				0.086	4.969	0.797 to 30.989			

Continued

Table 2 Continued

Characteristic	OS						DFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI
LMD	0.034*	1.194	1.013 to 1.406	0.012*	1.311	1.061 to 1.619	0.006**	1.238	1.063 to 1.442	0.001**	1.344	1.132 to 1.597
FIGO2009 stage II	0.183	2.344	0.670 to 8.207				0.144	2.222	0.761 to 6.491			
FIGO2023 stage II	0.004**	4.133	1.593 to 10.726	0.345	0.268	0.018 to 4.111	0.074	2.109	0.931 to 4.776			

*P<0.05; **p<0.01.
BMI, body mass index; DFS, disease-free survival; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; LMD, lesion maximum diameter; LVSI, lymphovascular space invasion; OS, overall survival; PR, progesterone receptor.

Figure 4 Kaplan-Meier analysis of shifting subgroups of FIGO2009 stage IA cases and FIGO2023 stage IIC cases. OS (A) and DFS (B) of patients shifting from FIGO2009 stage IA to FIGO2023 stage IA, IC and IIC (n=411); OS (C) and DFS (D) of patients shifting from FIGO2009 stage IA, IB and II to FIGO2023 stage IIC (n=85). DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival.

and stage IIC if there is. These patients were previously classified as FIGO2009 stage IA/IB. As can be seen in figure 4, patients of IA–IIC migration had significantly worse OS/DFS compared with those of IA–IA, reflecting the rationale for adding histological type into the new staging, whereas the K-M curves failed to reflect a significant trend in patients of IA–IC due to the small number (n=9). The new staging also emphasises the importance of evaluating LVSI and adopts 'substantial' LVSI (≥5 vessels involved) defined by the WHO 2020 report.[6] Absent or focal LVSI is associated with a better prognosis, whereas substantial LVSI is associated with a worse prognosis.[7] In this study, due to data limitations, the determination of whether LVSI was 'substantial' relied on the pathologist's diagnosis strings, which may have resulted in staging bias. The new staging requires pathologists to record LVSI accurately. However, the interpretation of LVSI is inherently tricky. Surgical manipulation, poor fixation, tumour necrosis and mesenchymal retraction may cause misinterpretation of LVSI.[8 9] More rigorous definitions and more specific interpretation criteria are urgently needed. Meanwhile, the amount of vascular involvement used to define 'substantial' LVSI needs further discussion.[10–12] Therefore, adding LVSI in the FIGO2023 staging, which has not yet matured in pathological diagnosis, may bring limitations in clinical application.

Molecular typing

The new staging recommends complete molecular typing of all. Using biopsy specimens is sufficient; repeating

Table 3 Univariate and multivariate Cox regression analyses of factors influencing OS/DFS in FIGO2023 stage IIC (n=85)

	OS			DFS		
Characteristic	P value	HR	95% CI	P value	HR	95% CI
Univariate analysis						
Age ≥60 years	0.025*	11.174	1.354 to 92.226	0.062	4.673	0.927 to 23.555
BMI ≥28 kg/m^2	0.880	1.132	0.227 to 5.638	0.509	0.493	0.061 to 4.021
Gravida=0	0.996	0.000	0.000 to null	0.996	0.000	0.000 to null
Para=0	0.996	0.000	0.000 to null	0.996	0.000	0.000 to null
CA125 ≥35 U/mL	0.714	0.674	0.082 to 5.530	0.795	0.754	0.090 to 6.320
Positive breast cancer history	0.995	0.000	0.000 to null	0.342	2.772	0.339 to 22.673
Positive diabetes history	0.707	1.360	0.274 to 6.746	0.196	2.573	0.614 to 10.785
Positive hypertension history	0.095	3.943	0.789 to 19.696	0.255	2.304	0.547 to 9.701
Positive familial tumour history	0.994	0.000	0.000 to null	0.658	0.623	0.077 to 5.067
Postoperative adjuvant treatment use	0.074	0.278	0.068 to 1.132	0.272	0.443	0.104 to 1.894
Bokhman type 2	0.677	0.710	0.142 to 3.557	0.698	0.727	0.145 to 3.641
Myometrial invasion ≥1/2	0.066	3.854	0.916 to 16.219	0.075	3.691	0.878 to 15.517
Positive cervical stromal invasion	0.585	1.569	0.311 to 7.907	0.151	2.889	0.680 to 12.279
Positive LVSI	0.459	1.737	0.403 to 7.495	0.832	0.839	0.166 to 4.247
Positive peritoneal cytology	0.244	3.580	0.419 to 30.581	0.256	3.449	0.407 to 29.232
Negative ER	0.754	1.291	0.260 to 6.407	0.260	2.279	0.544 to 9.554
Negative PR	0.331	0.352	0.043 to 2.893	0.796	0.808	0.160 to 4.082
Positive p53	0.995	51125111.842	0.000 to null	0.109	5.561	0.683 to 45.277
Ki67	0.569	2.988	0.069 to 129.626	0.954	1.123	0.022 to 58.116
LMD	0.016*	1.671	1.099 to 2.542	0.020*	1.622	1.080 to 2.438
Multivariate analysis						
Age ≥60 years	0.137	5.302	0.588 to 47.839			
LMD	0.012*	1.615	1.113 to 2.345			

*P<0.05; **p<0.01.
BMI, body mass index; DFS, disease-free survival; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; LMD, lesion maximum diameter; LVSI, lymphovascular space invasion; OS, overall survival; PR, progesterone receptor.

in hysterectomy specimens is unnecessary.[13] Since the groundbreaking introduction of molecular typing of EC by The Cancer Genome Atlas (TCGA) project in 2013,[14] simplified alternatives to TCGA molecular typing have been used in clinical practice, and the prognostic value has been well documented.[4 15–18] This study retrospectively included patients with no data on molecular typing, so there was no stage elevation due to p53abn and no stage reduction due to POLEmut, which is another limitation of this study. However, reporting molecular typing remains a severe challenge. Alternative immunohistochemistry markers are readily available, whereas POLE mutation analysis can be challenging for many centres. Differentiating pathogenic mutations from non-pathogenic mutations is another hurdle.[19] It may be possible to skip POLE mutation analysis for histologically low-grade, low/intermediate-risk EC, but complete molecular typing can be highly advantageous for aggressive histological subtypes.[15] When p53abn or MMRd are present, it is especially recommended undergoing POLE mutation analysis to avoid incorrect typing and overtreatment.[20 21] Therefore, simpler and easier reporting protocols are needed to promote molecular typing globally.

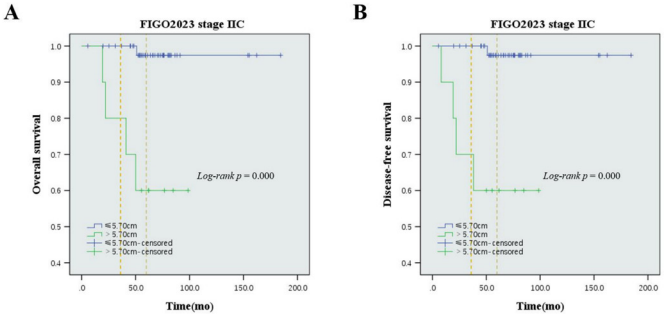


Figure 5 Kaplan-Meier analysis of OS/DFS in FIGO2023 stage II cases with LMD=5.70 cm as the cut-off value. OS (A) and DFS (B) in FIGO2023 stage IIC patients with LMD=5.70 cm as the cut-off value. DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; LMD, lesion maximum diameter; OS, overall survival.

Lesion size

In addition, our results suggest that LMD is also an important factor influencing the prognosis. The ROC curve analysis showed that 5.70 cm is the optimal cut-off value for predicting death and recurrence. Patients with different prognoses can be differentiated within FIGO2023 stage IIC when the cut-off value is 5.70 cm. Although neither of the FIGO 2009/2023 staging systems incorporates lesion size, several studies support the association of lesion size with prognosis. The Mayo criteria classify patients with endometrioid carcinoma, histological grades 1–2, myometrial infiltration <50%, tumour diameter ≤2 cm and no evidence of tumour outside of the uterine corpus as a low-risk group for those who do not require lymphadenectomy.[22] Sozzi *et al* analysed data from 1166 patients and found that tumour size was an independent prognostic factor for local recurrence in low-risk EC and used the LMD ≥2.5 cm as the cut-off value for predicting local recurrence in patients with low-risk EC.[23] Our centre conducted a study using the ultrasound results before hysteroscopy or curettage to determine the initial lesion size, then analysed its correlation with lymph node metastasis and recurrence in patients with EC. The study found that the initial lesion size ≥4.25 cm was significantly associated with the prognosis of EC.[24] The staging system could also include the lesion size as a prognostic factor. However, the method and threshold for determining the lesion size still need to be discussed.

This study has several limitations. Due to small number of cases and lack of data such as lymph node ultrastaging, we did not discuss stage III/IV. Lack of molecular typing data prevented staging adjustment. LVSI evaluation criteria inconsistent with WHO 2021 may have caused staging bias. Results may be flawed due to retrospective nature. Data from a single centre may limit generalisability to other countries/regions.

In conclusion, compared with the traditional FIGO2009 staging based on tumour extent, the FIGO2023 staging incorporates complementary histopathological and molecular features to improve the prognostic value and help achieve precision medicine.[25 26] However, the excessive changes and complicated factors of the new staging system pose challenges to clinicians, pathologists and epidemiologists, which may affect its global dissemination. A prudent discussion with current evidence and local medical resources is needed before adopting the new staging as an alternative to the old one.

Contributors AZ performed the formal analysis, visualisation and original draft. YD performed the data curation and methodology. YW performed the conceptualisation. XL performed the review and editing. JW performed the supervision and project administration as the guarantor. All authors approved the final manuscript and the submission to this journal.

Funding National Key Research and Development Program of China (2022YFC2704405).

Competing interests JW is the editor-in-chief of *Gynecology and Obstetrics Clinical Medicine* and was not involved in the editorial review or the decision to publish this article.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of PKUPH (2016PHB054-01). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used during this study are available from the corresponding author on reasonable request.

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Supplement

Table S1 3-year and 5-year OS/DFS for each sub-stage of old and new staging systems (n=540)

Sub-stage		OS			DFS		
		3-year OS/%	5-year OS/%	*Log-rank p*	3-year DFS/%	5-year DFS/%	*Log-rank p*
FIGO2009	IA	99.3	97.8	0.254	98.3	96.7	0.266
	IB	96.6	96.6		94.3	94.3	
	II	97.4	94.6		94.7	92.0	
FIGO2023	IA1	100.0	100.0	0.007**	98.1	98.1	0.252
	IA2	99.0	97.7		98.3	97.1	
	IB	98.5	98.5		95.4	95.4	
	IC	100.0	100.0		100.0	80.0	
	IIA	100.0	100.0		100.0	100.0	
	IIC	96.4	92.4		94.0	91.4	

* p<0.05 ** p<0.01

Table S2 Comparison of OS/DFS in patients with different LMDs

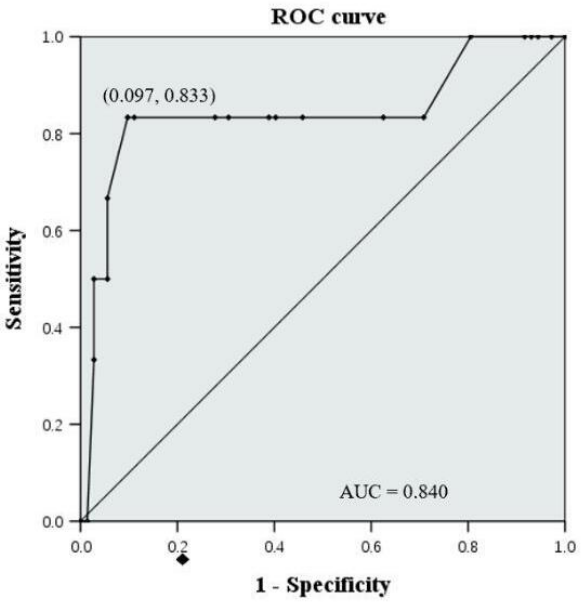
cut-off values		OS						DFS					
		FIGO2023 stage I			FIGO2023 stage II			FIGO2023 stage I			FIGO2023 stage II		
		Survival	Death	P-value	Survival	Death	P-value	no	recurrence	P-value	no	recurrence	P-value
2cm	≤2cm	102(40.96)	2(40.00)	0.965	21(29.17)	1(16.67)	0.513	101(41.39)	3(30.00)	0.473	21(28.77)	1(20.00)	0.673
	>2cm	147(59.04)	3(60.00)		51(70.83)	5(83.33)		143(58.61)	7(70.00)		52(71.23)	4(80.00)	
3cm	≤3cm	167(67.07)	3(60.00)	0.739	39(54.17)	1(16.67)	0.077	165(67.62)	5(50.00)	0.246	39(53.42)	1(20.00)	0.148
	>3cm	82(32.93)	2(40.00)		33(45.83)	5(83.33)		79(32.38)	5(50.00)		34(46.58)	4(80.00)	
4cm	≤4cm	201(80.72)	4(80.00)	0.968	50(69.44)	1(16.67)	0.009**	198(81.15)	7(70.00)	0.381	50(68.49)	1(20.00)	0.027*
	>4cm	48(19.28)	1(20.00)		22(30.56)	5(83.33)		46(18.85)	3(30.00)		23(31.51)	4(80.00)	
5cm	≤5cm	222(89.16)	4(80.00)	0.517	64(88.89)	1(16.67)	0.000**	219(89.75)	7(70.00)	0.051	64(87.67)	1(20.00)	0.000**
	>5cm	27(10.84)	1(20.00)		8(11.11)	5(83.33)		25(10.25)	3(30.00)		9(12.33)	4(80.00)	
6cm	≤6cm	237(95.18)	5(100.00)	0.615	68(94.44)	2(33.33)	0.000**	234(95.90)	8(80.00)	0.020*	68(93.15)	2(40.00)	0.000**
	>6cm	12(4.82)	0(0.00)		4(5.56)	4(66.67)		10(4.10)	2(20.00)		5(6.85)	3(60.00)	

* p<0.05 ** p<0.01

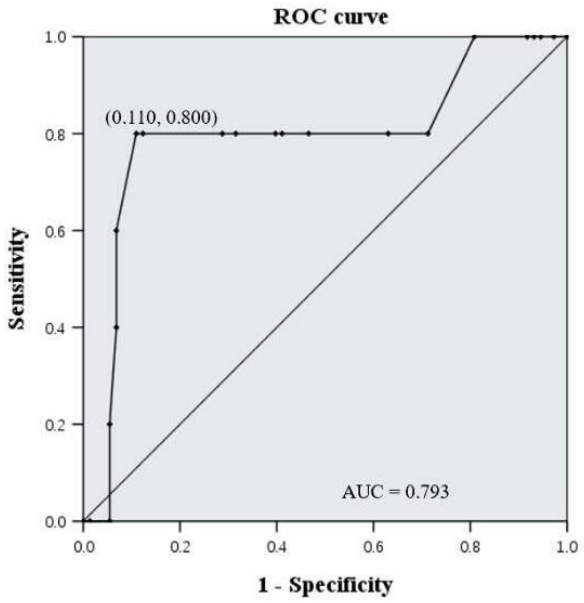
Figure S1 ROC curves of LMD in FIGO2023 stage II cases

ROC curves for predicting death (A) and recurrence (B) based on the LMD.

A


ROC curve
(0.097, 0.833)
AUC = 0.840
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

B


ROC curve
(0.110, 0.800)
AUC = 0.793
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	#3	State specific objectives, including any prespecified hypotheses	2
Methods			

Study design	#4	Present key elements of study design early in the paper	3
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	3
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	3
Bias	#9	Describe any efforts to address potential sources of bias	3
Study size	#10	Explain how the study size was arrived at	N/A
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	3
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	3
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	3
Statistical methods	#12c	Explain how missing data were addressed	3
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	N/A
Statistical methods	#12e	Describe any sensitivity analyses	4
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	4

		eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	4
Participants	#13c	Consider use of a flow diagram	5
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	6
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	4
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
Main results	#16b	Report category boundaries when continuous variables were categorized	8
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12

Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12