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Is the revised 2018 FIGO staging system for cervical cancer more prognostic than the 2009 FIGO staging system for women previously staged as IB disease?

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ABSTRACT

Objective: The purpose of this study was to compare the prognostic value of the revised FIGO staging system with that of the 2009 FIGO staging system for women previously staged as IB disease.
Methods: Institutional cervical cancer databases of two high-volume gynecologic cancer centers in Ankara, Turkey, were retrospectively analyzed. Only women with 2009 FIGO stage IB1 or IB2 disease who underwent primary surgery were included. Survival curves were generated using Kaplan-Meier plots, and the log-rank test was used for survival comparisons. The Cox proportional hazards regression model was used to obtain hazard ratios (HRs) and 95% confidence interval (CI).
Results: Data from 425 women were analyzed. The 2009 FIGO stage IB2 (n = 131) disease was associated with a nearly three-fold increased risk of mortality when compared to the 2009 FIGO stage IB1 (n = 294) disease (HR: 2.72, 95% CI: 1.69–4.37; $p < 0.001$). Stage migration was observed in 372 (87.5%) patients, according to the revised FIGO staging system, leading to no significant difference in five-year overall survival rates between stage IB1 (n=53) and IB2 (n=127) disease (95.2% vs. 89.3%, respectively; $p = 0.23$),or between stage IB2 (n=127) and IB3 (n=95) disease (89.3% vs. 84.2%, respectively; $p = 0.12$). Similarly, there was no significant difference in five-year overall survival rates between stage IIIC1 (n=114) and IIIC2 (n=36) disease (79.0% vs. 67.2%, respectively; $p = 0.34$).
Conclusion: When compared to the 2009 FIGO staging system, the revised staging system has more sub-stages, which leads to fewer patients in each sub-stage, resulting in diminished statistical power.
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Introduction

Validity, reliability, and practicality are crucial for a good staging system for cancer [1]. An optimal staging system should be capable of easily assigning women to obvious prognostic categories, as well as referring patients to individualized treatments [1–3]. Universal terminology provided by any staging system should allow comparison of therapeutic outcomes between different centers worldwide [1,3]. Particularly, the stage should reflect survival with the aid of stratifying prognostic factors and guiding adjuvant treatment [2,4].

Cancer staging systems are not static [5], and the International Federation of Gynecology and Obstetrics (FIGO) has recently revised the staging classification for cervical cancer [6].The main changes in the revised FIGO staging system compared to the previous one [7] are: (a) For microinvasive disease, the horizontal dimension is no longer considered in the 2018 revision, as it is subject to many artefactual errors; (b) For stage IB disease, the sub-stages have been revised with respect to 2-cm increments in tumor size (stage IB1: invasive carcinoma≥5 mm depth of stromal invasion and <2 cm in greatest dimension, stage IB2: invasive carcinoma ≥2 cm and <4 cm in greatest dimension, stage IB3: invasive carcinoma ≥4 cm in greatest dimension);and (c) The involvement of lymph nodes (LNs) according to either imaging (r) or pathology (p) has been described as a new sub-stage (stage IIIC)

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(stage IIIC1: pelvic LN metastasis only, stage IIIC2: para-aortic LN metastasis) [6]. With the introduction of the 2018 FIGO staging system for cervical cancer, the number of sub-stages has increased from 10 to 13 [6,7].

The former clinical staging system has been called into question for under-staging patients, particularly for women with nodal involvement [8], as the five-year survival rate drops from 85% to 50% if nodal metastases are present [9]. The purpose of this dual-institutional, retrospective study was to compare the prognostic value of the revised FIGO staging system with that of the 2009 FIGO staging system in women who were uniformly treated with radical hysterectomy and pelvic and para-aortic lymphadenectomy.

Materials and methods

After Institutional Review Board approval (Başkent University Institutional Review Board Approval Number: 604.01.02/ 9125), patients with biopsy-proven cervical cancer undergoing radical hysterectomy and systematic lymphadenectomy between January 1, 2006, and September 30, 2018, were identified from the tumor registries of two high-volume gynecologic oncology departments in Ankara, Turkey. The inclusion criteria were: women with 2009 FIGO stage IB1 or IB2 disease who underwent radical hysterectomy with pelvic and para-aortic lymphadenectomy, no neoadjuvant chemotherapy, no synchronous malignancies, and complete medical records. The stage was determined retrospectively according to the new 2018 FIGO staging system, based on the final pathologic assessment. We excluded those who had received inadequate lymphadenectomy (fewer than 10 pelvic and 5 para-aortic nodes on the final pathology reports). Women who received pelvic lymphadenectomy only, those who did not complete standard adjuvant treatment, and those with intraperitoneal disease detected during surgery were also excluded.

All patients underwent open surgery consisting of radical hysterectomy with pelvic and para-aortic lymphadenectomy. Radical hysterectomy was performed in accordance with Piver's type III hysterectomy. The surgical procedure was terminated if intraperitoneal disease was detected during surgery. However, the operation was not abandoned if any bulky lymph nodes were detected during surgical exploration. During the study period, pelvic and para-aortic lymphadenectomy was conducted routinely in both centers; following the institutional policy for patients undergoing radical hysterectomy with 2009 FIGO stage IB1 or IB2 disease.

The following data were abstracted from the patients' medical records: age, histologic type, tumor size in greatest dimension, depth of stromal invasion, lymphovascular space invasion (LVSI) (absent/present), microscopic parametrial invasion (yes/no), vaginal surgical margins (negative/positive), number of LNs removed (total/pelvic/para-aortic), adjuvant treatment (none/chemoradiation/external beam radiation therapy/extended field irradiation plus concurrent chemotherapy), recurrence (yes/no), death (yes/no), and follow-up.

Tumor size was obtained from pelvic magnetic resonance imaging (MRI) in most of the patients (n = 331), whereas it was determined macroscopically in women who did not receive pelvic MRI (n = 94). Conventional pathology was used for diagnosis in both centers. In cases of rare histologic subtypes, immunohistochemical staining was performed. All histological data were retrieved from the primary pathologist's report and were not reviewed centrally. Ultra-staging was not performed. Depth of cervical stromal invasion was measured in millimeters and then divided into thirds. Deep cervical stromal invasion was defined as tumor invading the outer third of the cervical stroma. LVSI was considered positive when tumor cells were noted within endothelium-lined spaces [10].

The decision about the need for adjuvant therapy was made at the discretion of a multidisciplinary team at each institution. Adjuvant radiotherapy with whole-pelvic external beam radiation therapy was administered when any two of these four adverse pathological features were present: adenocarcinoma histology, tumor size>4 cm, LVSI, or stromal invasion >2/3 [11]. Women with either positive surgical margins, positive nodal status, or microscopic parametrial invasion were treated with chemo-radiation. All patients with documented para-aortic nodal metastasis received extended-field radiotherapy plus concurrent chemotherapy. Vaginal brachytherapy was added when the vaginal margin was insufficient or positive.

Disease-free survival (DFS) was defined as the duration in months between the date of surgery and the date of first recurrence or the date of death from any cause, whichever occurred first, or the date of last visit for patients who remained alive without recurrence. Patients who were alive with no evidence of disease were censored on the date they were last known to be alive in disease-free survival analyses. Overall survival (OS) was defined as the duration in months between the date of surgery and the date of death from any cause or the date of last contact. Surviving patients were censored at their last known follow-up. The date of the last follow-up entry was November 30, 2018.

The Statistical Package for the Social Sciences (SPSS) software version 23.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. Continuous variables were expressed as medians and ranges; binary variables were reported as counts and percentages. Survival curves were generated using the Kaplan-Meier plots, and the log-rank test was used for survival comparisons. The Cox proportional hazards regression model was used to obtain hazard ratios (HRs) and a 95% confidence interval (CI). All p-values were two-sided, with significance set at $p < 0.05$.

Results

Six hundred and forty-seven women underwent radical hysterectomy and systematic lymphadenectomy at the two gynecologic cancer centers during the study period. We excluded 78 patients who had received neoadjuvant chemotherapy, 31 patients who did not complete the recommended adjuvant treatment, 11 women with radical hysterectomy abandoned because of intraperitoneal disease detected during surgery, three patients with synchronous malignancy, and nine with incomplete medical records. Nineteen women with inadequate lymphadenectomy and 27 patients receiving only pelvic lymphadenectomy were also excluded. Finally, there were 469 women with cervical cancer undergoing radical hysterectomy and systematic lymphadenectomy. Of those, 37 had stage IIA1 disease, and seven had stage IIA2 disease. Since the current study focused on only women with 2009 FIGO stage IB disease, women with stage II disease were also excluded. Therefore, the present analysis addresses the remaining 425 women with 2019 FIGO stage IB cervical cancer.

The clinicopathological characteristics of the study population are shown in Table 1. The median age at surgery was 50.0 years (range: 23–81 years), and the median duration of follow-up for the survivors was 47.0 months (range: 3–149 months). For the entire cohort, the five-year disease-free survival rate was 75.1% (Standard error [SE]: 2.92), whereas the five-year overall survival rate was 84.4% (SE: 2.82).

According to the 2009 FIGO staging system, 294 (69.2%) women had stage IB1 disease, and 131 (30.8%) had stage IB2 disease. A total of 372 (87.5%) patients were assigned to a new stage with the revised FIGO staging system. Table 2 represents the cross-tabulation of the distribution of patients according to the 2009 and 2018 staging systems. Of 294 women formerly staged as IB1

Table 1
Clinicopathological characteristics of 425 cervical cancer patients formerly staged as IB1 and B2 undergoing radical hysterectomy with pelvic and para-aortic lymphadenectomy.

Characteristic	Values
Age, years (median, [range])	50 (23-81)
Histopathology	
Squamous cell carcinoma	326 (76.7 %)
Adenocarcinoma	50 (11.8 %)
Adenosquamous carcinoma	38 (8.9 %)
Others*	11 (2.6%)
2009 FIGO Stage, n (%)	
IB1	294 (69.2 %)
IB2	131 (30.8 %)
2018 FIGO Stage, n (%)	
IB1	53 (12.5%)
IB2 IB3	127 (29.9%)
IIIC1	95 (22.4%)
IIIC2	114 (26.8%)
	36(8.5%)
Lymphovascular space involvement	
Negative	113 (26.6%)
Positive	312 (73.4%)
Stromal invasion	
<2/3	116 (27.3%)
≥2/3	331 (72.7%)
Positive vaginal surgical margin	
Yes	41(9.6%)
No	384 (90.4%)
Microscopic parametrial involvement	
Yes	44(10.4%)
No	381(89.6%)
Tumor size, cm (median, [range])	3.5 (0.8-9.5)
<2cm	63 (14.8%)
2.0-3.9cm	183 (43.1%)
≥4 cm	179 (42.1%)
Adjuvant therapy	
None	137 (32.2%)
Radiotherapy alone	109 (25.6%)
Chemoradiation	179(42.2%)
Number of LNs removed (median, [range])	41.0 (17-138)
Number of pelvic LNs removed	30.0 (10-97)
Number of para-aortic LNs removed	11.0 (5-52)
Nodal Status	
Positive pelvic LNs only	114 (26.8%)
Positive pelvic and para-aortic LNs	32 (7.5%)
Positive para-aortic LNs only	4 (0.9%)
Recurrence	
Yes	80 (18.8%)
No	345 (81.2%)
Status	
Alive	369 (86.8%)
Dead	56 (13.2%)

Abbreviations: nnumber; LNlymph node.
* Others include clear cell carcinoma (n = 4), small cell neuroendocrine carcinoma of the cervix (n = 3), glassy cell carcinoma (n = 2), basaloid cell carcinoma (n = 1), and lymphoepithelioma-like carcinoma (n = 1).

Table 2
Cross table demonstrating the distribution of patients according to the 2009 FIGO and the revised 2018 FIGO staging systems.

	2018 Stage					
	IB1	IB2	IB3	IIIC1	IIIC2	Total
2009 Stage IB1	53	127	29	70	15	294
2009 Stage IB2	0	0	66	44	21	131
Total	53	127	95	114	36	425

disease, 127 (43.2%), 29 (9.9%), 70 (23.8%), and 15 (5.1%) were upstaged to sub-stages IB2, IB3, IIIC1, and IIIC2, respectively. Only 53 (18.0%) women remained as stage IB1 according to the new 2018 FIGO staging system. Of 131 patients formerly staged as IB2 disease, 66 (50.4%), 44 (33.6%), and 21 (16.0%) were upstaged to sub-stages IB3, IIIC1, and IIIC2, respectively. All the patients previously staged as IB2 disease had stage migration.

The results of the Cox regression and Kaplan Meier analyses according to the previous and revised FIGO stages are shown in Tables 3 and 4. The five-year DFS rate of the 2009 FIGO stage IB2 disease was significantly lower than that of the 2009 FIGO stage IB1 disease (61.7% vs. 81.0%, respectively; $p < 0.001$), leading to a nearly two-fold increased risk of recurrence (HR: 2.12, 95% CI: 1.42–3.16; $p < 0.001$). Under the revised FIGO staging system, the five-year DFS rates were not significantly different between stages IB1and IB2 (91.5% vs. 81.9%, respectively; $p = 0.11$). However, the five-year DFS rate for stage IB3 disease was significantly lower than that of stage IB2 disease (67.6% vs. 81.9%, respectively; $p = 0.01$ [log-rank test]) (Fig. 1). Similarly, stage IB3 disease was significantly associated with lower five-year DFS when compared to stage IB1 disease (HR: 4.77, 95% CI: 1.68–13.53; $p = 0.003$) (Fig. 1). When stage IIIC2 disease was compared to stage IIIC1 in terms of five-year DFS, stage IIIC2 disease was associated with a nearly two-fold increased risk of recurrence (HR: 2.48, 95% CI: 1.32–4.65; $p = 0.005$) (Fig. 1).

The five-year OS rate of the 2009 FIGO stage IB2 disease was significantly lower than that of the 2009 FIGO stage IB1 disease (73.5% vs. 88.0%, respectively; $p < 0.001$), leading to a nearly three-fold increased risk of mortality (HR: 2.72, 95% CI: 1.63–4.37; $p < 0.001$). According to the 2018 FIGO staging system, there was no significant difference in five-year OS rates between stages IB1 and IB2 (95.2% vs. 89.3%, respectively; $p = 0.23$), nor between stages IB2 and IB3 (89.3% vs. 84.2%, respectively; $p = 0.12$) (Fig. 2). Similarly, no significant difference was found in five-year OS rates between stages IIIC1 and IIIC2 (79.0% vs. 67.2%, respectively; $p = 0.34$) (Fig. 2). However, the five-year OS rates seemed to drop as stages increased (Table 4).

When lymph node-positive patients were removed from the FIGO 2009 staging data, we identified 209 women with stage IB1 disease and 66 with stage IB2 disease. The five-year DFS rate for node-negative stage IB1 women was 82.5%, compared to 66.7% for node-negative women with stage IB2 disease ($p = 0.004$) (Fig. 3). However, we were unable to demonstrate a significant difference in terms of five-year OS rates between node-negative women with stage IB1 disease and stage IB2 disease (89.9% vs. 85.0%, respectively; $p = 0.093$) (Fig. 4).

Discussion

The current study aimed to compare the prognostic value of the revised FIGO staging system with that of the 2009 FIGO staging system in women undergoing radical hysterectomy and systematic retroperitoneal lymphadenectomy in the light of histology-proven LN involvement. Our study revealed that 87.5% of patients formerly staged as IB1 or IB2 disease were assigned to a new stage with the revised 2018 FIGO staging system. The new staging system seemed to be prognostic across sub-stages of IB2 and IB3, as well as across sub-stages IIIC1 and IIIC2, in terms of five-year DFS. However, we were unable to demonstrate its prognostic significance in terms of five-year OS. In contrast, the five-year OS rate of the 2009 FIGO stage IB2 disease was significantly lower than that of the 2009 FIGO stage IB1 disease (73.5% vs. 88.0%, respectively; $p < 0.001$), leading to a nearly three-fold increased risk of mortality (HR: 2.72, 95% CI: 1.63–4.37; $p < 0.001$).

The current study has some limitations. Its retrospective nature is inherently susceptible to selection and referral bias. The lack of central pathology review and the limited number of patients are further limitations. Nonetheless, our study contributes to current knowledge on this topic.

Tumor size has been recognized as a prognostic factor in stage I cervical cancer for a long time [12], with larger tumor sizes

Table 3
Disease-free survival details according to the 2009 FIGO and the revised 2018 FIGO staging systems.

Stage	2009 FIGO	n	Number Of events	5-year DFS,%, (SE)	HR (95% CI)	p	2018 FIGO	n	Number of events	5-year DFS,%, (SE)	HR (95%CI)	p
I	IB1	294	46	81.0 (3.29)	1		IB1	53	4	91.5 (4.80)	1	
	IB2	131	41	61.7 (5.82)	2.12 (1.42-3.16)	<0.001	IB2	127	18	81.9 (4.72)	2.33 (0.79-6.82)	0.12
							IB3	95	27	67.6 (6.06)	4.77 (1.68-13.53)	0.003
III							IIIC1	114	23	75.2 (5.61)	1	
							IIIC2	36	15	45.3 (9.16)	2.48 (1.32-4.65)	0.005

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics, n: number, DFS: Disease-free survival, SE: Standard error, HR: Hazard ratio, CI: Confidence interval.

Table 4
Overall survival details according to the 2009 FIGO and the revised 2018 FIGO staging systems.

Stage	2009 FIGO	n	Number Of events	5-year OS,%, (SE)	HR (95% CI)	p	2018 FIGO	n	Number of events	5-year OS,%, (SE)	HR (95%CI)	p
I	IB1	320	28	88.0 (2.82)	1		IB1	53	2	95.2 (3.68)	1	
	IB2	157	32	73.5 (4.83)	2.72 (1.69-4.37)	<0.001	IB2	127	9	89.3 (3.86)	2.33 (0.51-10.67)	0.27
							IB3	95	12	84.2 (5.90)	4.45 (1.02-19.37)	0.04
III							IIIC1	114	18	79.0 (5.22)	1	
							IIIC2	36	8	67.2 (8.40)	1.48 (0.65-3.37)	0.35

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics, n: number, OS: Overall survival, SE: Standard error, HR: Hazard ratio, CI: Confidence interval.

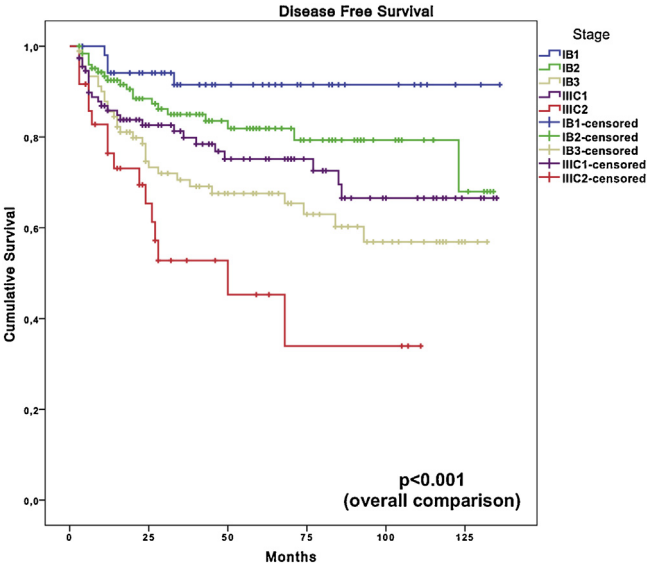

Fig. 1. Disease-free survival curves of women allocated to new stages according to the 2018 FIGO staging system for cervical cancer (stage IB1 vs. stage IB2, $p = 0.11$; stage IB2 vs. stage IB3, $p = 0.01$; stage IIIC1 vs. stage IIIC2, $p = 0.003$).

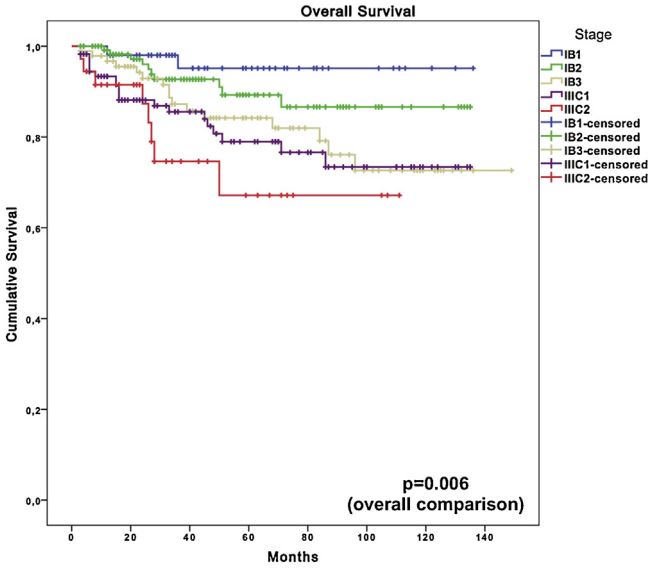

Fig. 2. Overall survival curves of women allocated to new stages according to the 2018 FIGO staging system for cervical cancer (stage IB1 vs. stage IB2, $p = 0.23$; stage IB2 vs. stage IB3, $p = 0.12$; stage IIIC1 vs. stage IIIC2, $p = 0.34$).

displaying higher rates of nodal involvement, more recurrences, and decreased survival rates [13–15]. Matsuo et al. [16] recently reported five-year survival rates as 97.0%, 92.1%, and 83.1% for women with 2018 FIGO stages IB1, IB2, and IB3, respectively. Similarly, the corresponding figures were 95.2%, 89.3%, and 84.2%, respectively, in the current study. In the same study [16], survival rates were significantly different between 2018 FIGO stage IB1 and stage IB2 disease, with a nearly two-fold increased risk in cervical cancer mortality in stage IB2 compared to stage IB1 disease. However, we were unable to demonstrate a significant difference in five-year OS between 2018 FIGO stage IB1 and IB2 disease. This might be due to the limited number of patients in each 2018 FIGO sub-stage (stage IB1[n = 53], stage IB2 [n = 127]) in our study.

However, tumor size, a predictor of disease recurrence for cervical cancer [12,17], worked well in our cohort for discriminating outcome in terms of disease-free survival across sub-stages IB2 and IB3. In the current study, the five-year DFS rate for stage IB3 disease was significantly lower than that of stage IB2 disease (67.6% vs. 81.9%, respectively).Similarly, stage IIIC2 disease had significantly lower DFS than stage IIIC1disease, with a nearly two-fold increased risk of recurrence in the former.

Stage has long been reported to be more advanced when staging is performed surgically [18]. Although spread to the regional LNs is the major route of metastasis in cervical cancer [19], nodal status has recently been included in the FIGO staging system as well [6]. Lymph node metastasis is indeed a major prognostic factor associated with decreased survival in clinically early-stage disease [20]. However, it should be kept in mind that histology-proven LN metastasis is an absolute parameter in assessing nodal status when compared to radiographic data [21]. We should emphasize that all

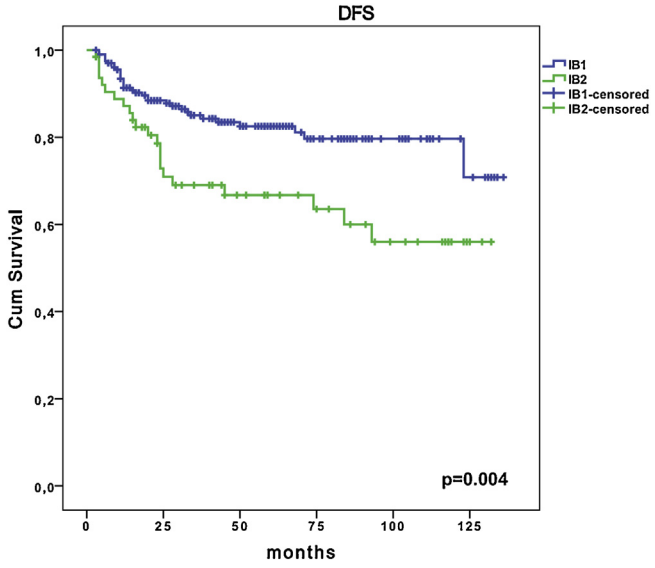

Fig. 3. Disease-free survival curves of the patients with FIGO 2009 stage IB1 (n = 209) and IB2 (n = 66) when women with lymph node metastases are removed from 2009 staging data.

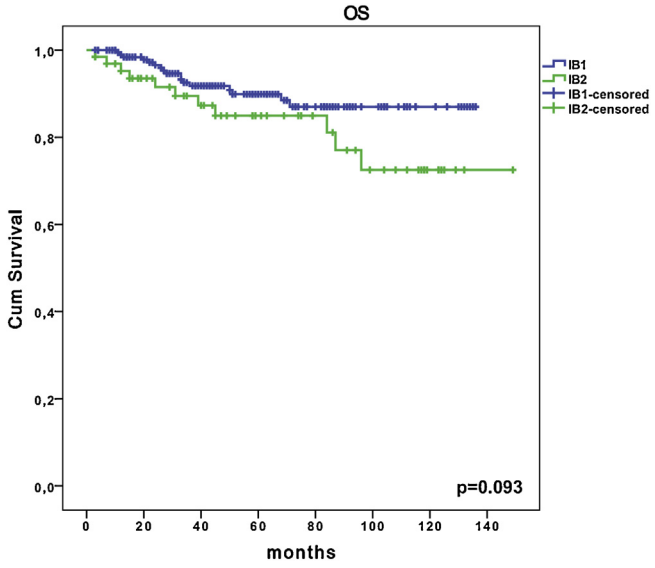

Fig. 4. Overall survival curves of the patients with FIGO 2009 stage IB1 (n = 209) and IB2 (n = 66) when women with lymph node metastases are removed from 2009 staging data.

the documented LN metastases were histology-proven in the current study.

Matsuo et al. [16] reported the five-year survival rate as 62.1% in 2018 FIGO stage IIIC1 disease; in our study, the corresponding figure was 79.0%. It should be noted that evidence of LN metastasis was not retrievable in the Matsuo study, and it is not known if documented nodal metastasis was based on radiographic data alone or histology proven. The relatively higher rate of five-year overall survival in stage IIIC1 disease in the current study might be explained by the removal of bulky nodes, as well as the performance of systematic lymphadenectomy in all cases.

The Matsuo et al. study [16] was unable to assess the survival outcomes of women with stage IIIC2 disease since information about para-aortic lymphadenectomy was not available in their database. The five-year DFS and OS rates for stage IIIC2 disease were 45.3% and 67.2%, respectively, in our study. The similar OS rates in stages IIIC1 and IIIC2 in the current study might be due to the limited number of patients assigned to each sub-stage (stage IIIC1[n = 114], stage IIIC2 [n = 36]). Further research is needed for the prognostic discrimination of the revised FIGO staging system across sub-stages IIIC1 and IIIC2.

An increase in the number of sub-stages, from 10 to 13, is an important consequence of the revised FIGO staging system, as it results in fewer patients in each sub-stage. Although the FIGO 2018 staging system divides stage IB disease by 2-cm increments in tumor size to clarify the disease demonstrated by this patient population (stages IB1, IB2, and IB3), only extracting node-positive women from this category might also be an option for the new FIGO staging system. In this scenario, node-positive patients would be removed from stage IB disease and would be allocated to stage IIIC, while no changes due to tumor size in stages IB1 and IB2 would have taken place. Such a classification might be more prognostic than the current 2018 FIGO staging system, as more patients would be allocated to each sub-stage (no stage IB3 disease would exist). This would probably result in increased statistical power in terms of the revised staging system's prognostic discrimination.

The revised 2018 FIGO staging system is based on a clinical rationale that relies principally on tumor size and LN involvement. Division of stage IB disease by 2-cm increments in tumor size helped to delineate the wide spectrum of disease demonstrated by this patient population, whereas extracting node-positive women from this category and classifying them as stage IIIC disease led to more realistic survival outcomes when compared to the former staging system.

In conclusion, the revised FIGO staging system seemed to reflect OS adequately, as there was a clear statistical tendency for poorer five-year OS rates with increasing stage. However, we were unable to observe its prognostic discrimination across sub-stages IB1 and IB2or IB2 and IB3. This might be due to the limited number of patients assigned to each sub-stage in our study. The increased number of sub-stages may be a disadvantage of the revised FIGO staging system.

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