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ORIGINAL ARTICLE

Restaging of Cervical Cancer Patients Treated with Adjuvant Radiotherapy According to FIGO 2018 and Suggestions for the Next Staging: Turkish Society for Radiation Oncology Gynecologic Group Study (TROD 04-004)

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OBJECTIVE

The objective of this study was to compare Federation of Gynecology and Obstetrics (FIGO) 2009 and 2018 staging systems in patients with uterine cervical cancer.

METHODS

Medical records of 571 patients who were treated with adjuvant radiotherapy or radiochemotherapy between 2001 and 2018 were retrospectively reviewed. Differences in overall survival (OS) and progression-free survival (PFS) rates according to FIGO 2009 and FIGO 2018 staging systems were compared using the log-rank test. Cox regression model was used to identify independent prognostic factors for survival.

RESULTS

The median follow-up was 59 months. Five-year OS and PFS rates were 81.1% and 77.7%, respectively. Stage migration was recorded in 401 patients (70.2%) and the most remarkable stage migration was detected in stage I patients (60%). A total of 157 (27.5%) patients upstaged to stage IIIC disease. According to FIGO 2009, 5-year OS rates were 87.3%, 80.5% (p=0.076), and PFS rates were 82.8%, 77.5% (p=0.036) for stage IB1 and IB2, respectively. According to FIGO 2018, the 5-year OS rates for stage IB1, IB2, and IB3 were 89.8%, 87.1%, and 81.4% (p=0.310), and PFS rates were 90.2%, 80.5%, and 80.1% (p=0.189), respectively. Patients with ≥2 pelvic lymph node (LN) metastases had worse 5-year OS and PFS rates than patients with one metastasis (p=0.015 and p=0.006). Number of para-aortic LN metastasis and metastatic LN ratio (MLNR) were also correlated with 5-year OS and PFS.

CONCLUSION

Current FIGO staging system better discriminates patients with cervical cancer. However, integration of metastatic LN number and/or MLNR to the upcoming FIGO staging system may improve the prognostic value of the staging.

Keywords: Cervical cancer; FIGO staging; lymph node metastasis; radiotherapy.

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INTRODUCTION

According to the latest data from the Global Cancer Observatory, cervical cancer is the fourth most common cancer in women worldwide, strongly linked to high-risk human papillomavirus (HPV) infection.[1] Cervical cancer is still an important cause of death despite screening programs and HPV vaccination, especially in developing countries. Clinical trials are underway to improve treatment outcomes.

Staging often plays a critical role in the assessment of cancer spread and the development of treatment strategies. The most widely accepted staging system for cervical cancer is the International Federation of Gynecology and Obstetrics (FIGO) staging system. FIGO was originally founded in 1954, and the cervical cancer stage classification was developed shortly thereafter.[2]

The staging has undergone multiple modifications since that time, the former staging system was published in 2009.[3] According to the FIGO 2009 staging system, stage IA disease included tumors with largest extention ≤7 mm, that cannot be evaluated macroscopically and stage IB disease was defined as clinically and macroscopically visible lesions limited to the uterine cervix, or microscopic lesions greater in size than stage IA disease. Tumors measuring ≤4 cm were classified as stage IB1, while those >4 cm were classified as stage IB2. Many studies found that the recurrence rates after surgery were dramatically lower in patients with tumors ≤2.0 cm compared to those with tumors 2.1–4.0 cm in greatest dimension.[4–8] The revised staging system was presented at the FIGO XXII World Congress of Gynecology and Obstetrics in 2018.[9] Thereafter, lateral extent was not considered in stage IA disease. Major changes have been made for stages IB and IIIC disease (Table 1).

The main goal of this study was to restage cervical cancer patients treated with radical hysterectomy (RH), followed by adjuvant radiotherapy (RT) or radiochemotherapy (RCT) and demonstrate stage migration according to the current FIGO 2018 staging system. We also aimed to analyze the basic prognostic factors and their impact on survival outcomes.

MATERIALS AND METHODS

The medical records of 571 patients treated with adjuvant RT or RCT between January 1, 2001, and December 30, 2018, from seven centers in Türkiye were retrospectively evaluated. This retrospective study was conducted in compliance with the principles of the Helsinki Declaration.

Staging

In the former FIGO 2009 staging system, the patient's stage was mainly based on gynecologic examination by the clinician. The current FIGO 2018 staging system integrated the data from imaging modalities and pathologic evaluation in addition to the gynecologic examinations as well. In this study, all patients were staged according to both FIGO 2009 and 2018 staging systems. Patients with metastatic disease, recurrent disease, synchronous malignancy, and who were lost to follow-up were excluded from this study.

Surgery

All patients underwent radical surgery before RT. The surgical procedure was performed in the form of RH plus bilateral salpingo-oophorectomy, with pelvic and/or para-aortic LN surgery (sampling or dissection-LND). Less than 10 dissected LN was considered as sampling.

All dissected LNs were pathologically evaluated. Isolated tumor cells were defined as cells or masses of cells measuring ≤0.2 mm; micrometastases were defined as tumors larger than 0.2 mm but ≤2 mm; and macrometastases were defined as tumors >2 mm.

Nodal Staging

The patients with pathological stage IIIC disease were categorized according to the number of LN metastasis (1 vs. ≥2) and metastatic LN ratio (MLNR) (1–5%, 6–9% and ≥10%). MLNR was determined as [number of metastatic LNs/the total number of dissected LNs] ×100. Although published studies used 10% as cutoff value for MLNR (1–9% and ≥10%), we used three-tier system using a cutoff value of 5% (1–5%, 6–9% and ≥10%).[10,11] For the stage IIIC subgroup, the number of pelvic LN metastasis (PLN 1 vs. ≥2) and para-aortic LN metastasis (PALN 1 vs. ≥2) were also analyzed.

RT/RCT

While adjuvant RCT was applied to patients with high-risk factors (LN metastases, positive/close surgical margins, and/or parametrial involvement), adjuvant RT was applied to patients with intermediate-risk factors (lymphovascular space involvement [LVSI], tumor ≥4 cm, and deep stromal invasion [DSI]).[12–14]

RT was administered as external RT±vaginal cuff brachytherapy (VCB). External RT was in the form of external pelvic RT with conventional daily doses to a total dose of 45–59.4 Gy (median 45 Gy). Para-aortic fields were added when there were para-aortic LN metastases and lower para-aortic lymphatics were included when there were common iliac LN metastases. VCB when used was applied to the proximal 3–5 cm of the

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Table 1 Summary of the changes in uterine cervical cancer staging

Stage	Former (2009) FIGO system	Current (2018) FIGO system
IA1	Measured stromal invasion ≤3 mm, largest extention ≤7 mm	Measured stromal invasion ≤3 mm
IA2	Measured stromal invasion >3 mm and ≤5 mm, largest extention ≤7 mm	Measured stromal invasion >3 mm and ≤5 mm
IB1	Tumors with ≤4 cm size	Tumors with ≤2 cm size
IB2	Tumors with >4 cm size	Tumors with >2 and ≤4 cm size
IB3	-	Tumors with >4 cm size
IIIC1	-	Only the patients with pelvic LN metastasis (either radiographic or pathologic)
IIIC2	-	The patients with paraaortic LN metastasis (either radiographic or pathologic)

FIGO: International Federation of Gynecology and Obstetrics; LN: Lymph node

vagina and the dose was prescribed to the vaginal mucosa or 5 mm depth from the vaginal surface according to the American Brachytherapy Society recommendations.[15] Concomitant cisplatin at a dose of 40 mg/m2 was administered weekly to patients with high-risk factors during external RT.

Follow-up

The key components of follow-up included gynecological examination and laboratory tests every 3 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter. Imaging modalities and PAP smear were performed when needed. Local and distant recurrences were evaluated using computed tomography, magnetic resonance, or positron-emission tomography imaging.

Statistical Methods

The statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 24. Kaplan–Meier method was used for survival analysis. Overall survival (OS), progression-free survival (PFS), local recurrence-free survival (LRFS), disease-specific survival (DSS), and distant metastasis-free survival (DMFS) were calculated. All time related events were calculated from the date of surgery to the past follow-up, death, or recurrence, whichever came first. Differences in survival rates according to FIGO 2009 and FIGO 2018 staging systems were compared using the log-rank test. Multivariate cox regression model was used to identify independent prognostic factors for survival outcomes. P-value of <0.05 was considered as statistically significant.

The primary endpoints were identifying stage migration between FIGO 2009 and 2018 staging systems in cervical cancer patients and their impact on survival outcomes. The secondary endpoints were identifying prognostic factors for survival. This retrospective study was conducted in compliance with the principles of Helsinki Declaration and informed consent was obtained from each patient. Ethical approval was not obtained from the Institutional Review Board for this retrospective study.

RESULTS

The median age was 50 years (range, 24–78 years). Squamous cell carcinoma was the most common histopathological type constituting 77.7% of all patients. Patient and treatment characteristics are listed in Table 2. The most commonly used surgical procedure was Wertheim hysterectomy in 466 (81.6%) patients.

Pelvic and para-aortic LND, pelvic LND alone, and pelvic sampling were performed in 328 (57.4%), 138 (24.2%), and 34 (6%) patients, respectively. The mean number of dissected pelvic and para-aortic LN (sampling/LND) was 23 (range, 1–101) and 6 (range, 1–54), respectively.

RT consisted of external RT and VCB in 387 (67.8%), external RT alone in 179 (31.3%), and VCB alone in 5 (0.9%) patients. Three hundred and twenty-two (56.4%) patients received concomittant cisplatin and 72% of them received at least four cycles. The median total dose of external RT was 45 Gy (range, 45–59.4 Gy). Doses and fractionations of VCB varied based on institutional preferences and from most frequent to the lesser were as follows: 3×500 cGy, 3×600 cGy, 2×650 cGy, 5×500 cGy, and 4×700 cGy.

FIGO Stage Migration

Stage migration was recorded in 401 (70.2%) patients. The most remarkable stage migration was detected in 343 (60%) stage I patients. Migration to stage I was de-

Table 2 Patient and treatment characteristics

Characteristics	n	%	Characteristics	n	%
Age (year)			Surgery		
Median, Range	50 (24–78)		Wertheim	466	81.6
Menopausal status			TAH+BSO	34	6
Premenopausal	277	48.5	Other	71	12.4
Postmenopausal	294	51.5	Surgical margin		
Histopathology			Negative	358	62.7
Squamous cell carcinoma	444	77.7	Positive	128	22.4
Adenocarcinoma	90	15.8	Close (<5 mm)	73	12.8
Adenosquamous	37	6.5	CIS	3	0.5
Tumor size			VAIN	4	0.7
<2 cm	81	14.2	Unknown	5	0.9
≥2 and <4 cm	244	42.7	Lymph node surgery		
≥4 cm	238	41.7	None	71	12.4
Unknown	8	1.4	Sampling	34	6
Lymphovascular Space Involvement			Pelvic LND	138	24.2
(+)	407	71.3	Pelvic+Para-aortic LND	328	57.4
(-)	139	24.3	Nodal status		
Unknown	25	4.4	Negative	414	72.5
Deep Stromal Invasion			Pelvic positive	135	23.6
(+)	480	84.1	Paraaortic positive	4	0.7
(-)	80	14	Pelvic+paraaortic positive	18	3.2
Unknown	11	1.9	Radiotherapy		
Parametrial Invasion			External RT and VCB	387	67.8
(+)	87	15.2	External RT	179	31.3
(-)	479	83.9	VCB	5	0.9
Unknown	5	0.9	Concomitant chemotherapy		
Vaginal Involvement			(+)	322	56.4
(+)	81	14.2	(-)	249	43.6
(-)	483	84.6			
Unknown	7	1.2			

n: Number; TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy; CIS: Carcinoma in situ; VAIN: Vaginal intraepithelial neoplasia; LND: Lymph node dissection; RT: Radiotherapy; VCB: Vaginal cuff brachytherapy

tected in 244 (42.7%) patients: 2 (0.4%) patients from stage IA2 to IB1, 134 (23.4%) patients from stage IB1 to IB2, and 108 (18.9%) patients from stage IB2 to IB3.

Migration to stage IIIC1 due to the presence of pelvic LN metastases was observed in 1 patient in stage IA2, 54 patients in stage IB1, 33 patients in stage IB2, 23 patients in stage IIA, 15 patients in stage IIB, one patient in stage IIIA, and eight patients in stage IIIB according to FIGO 2009. Overall, 88 (15.4%) patients from stage I, 38 (6.6%) patients from stage II, and 9 (1.6%) patients from stage IIIA/B were upstaged to stage IIIC1 (Fig. 1).

Migration to stage IIIC2 due to the presence of the para-aortic LN metastasis was recorded in six patients in stage IB1, five patients in stage IB2, one patient in stage IIA, nine patients in stage IIB, and one patient in stage IIIB. Overall, 11 (1.9%) patients from stage I, 10 (1.8%) patients from stage II, and 1 (0.2%) patient from stage IIIB were upstaged to stage IIIC2 (Fig. 1).

Due to the incompatibility of staging systems, stages of patients with stage IA1 and IVA did not change.

Follow-up and Survival Outcomes

The median follow-up time was 59 months (range, 3–228 months). Four hundred and fifty-four (79.5%) patients were alive, and 430 (75.3%) of these were free of disease at the time of analysis. While 89 (15.6%) patients died due to cervix cancer, 28 (4.9%) died due to other reasons during follow-up. Twenty-four patients were alive with disease at their last follow-up: Eight with pelvic wall recurrences, four with vaginal cuff recurrence, and nine with distant metastasis, in whom three of these had also local recurrence. The median time to locoregional failure and distant metastasis

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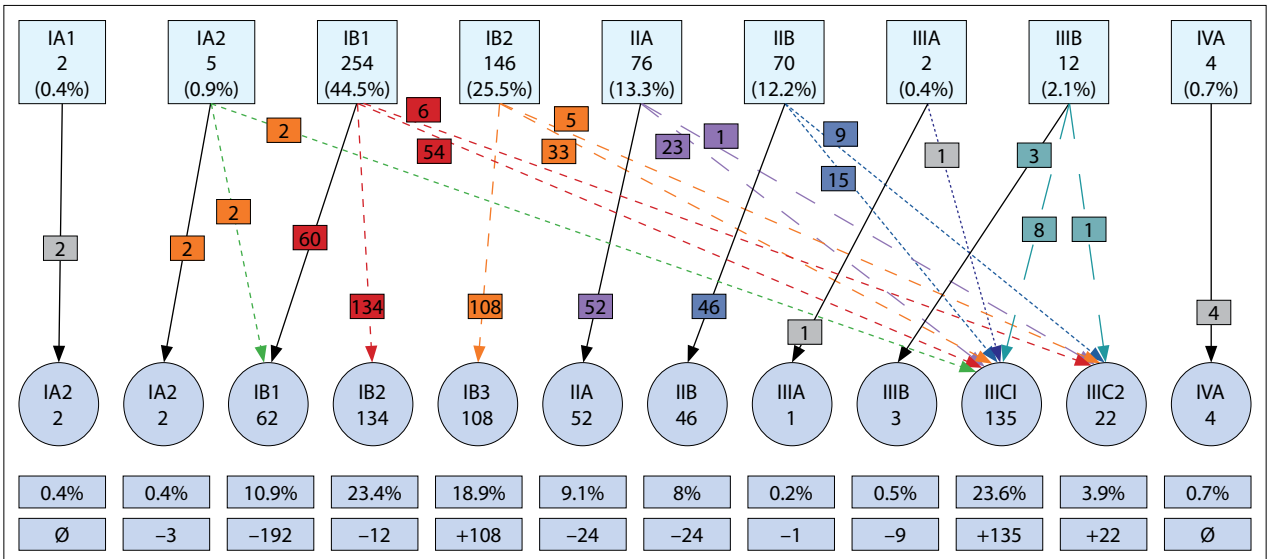

Fig. 1. Stage distribution of the patients according to the former FIGO 2009 and current FIGO 2018 staging systems.
FIGO: Federation of Gynecology and Obstetrics.

was 15 months (range, 1–152 months) and 18 months (range, 1–152 months), respectively.

Five-year OS, PFS, LRFS, DSS, and DMFS rates were 81.1%, 77.7%, 87.9%, 84.3%, and 84.8%, respectively. Survival rates of each stage according to both FIGO 2009 and 2018 are shown in Table 3. For patients staged according to FIGO 2009, 5-year OS rates were 87.3% for IB1, and 80.5% for IB2 (p=0.076), and according to FIGO 2018, 5-year OS rates were 89.8% for IB1, 87.1% for IB2, and 81.4% for IB3 (p=0.310).

Five-year PFS rates according to FIGO 2009 were 82.8% for IB1 and 77.5% for IB2 (p=0.036). The corresponding PFS rates in FIGO 2018 were 90.2% for IB1, 80.5% for IB2, and 80.1% for IB3 (p=0.189). Although FIGO 2009 staging system significantly discriminates stage IB1 from IB2 in terms of PFS, we could not find any statistical difference among FIGO 2018 stage IB subgroups in terms of both PFS and OS rates. However, the 5-year OS and PFS rates for stage IB1 were better than stage IB2 and IB3 in the current FIGO 2018 staging system (Fig. 2).

The major difference between the two staging systems in terms of determining the prognosis was for stage IIB disease. The 5-year OS, PFS, and DMFS rates in stage IIB

Table 3 Five-year overall, local recurrence-free, progression-free, and distant metastasis-free survival rates of patients according to both FIGO 2009 and FIGO 2018 staging systems

Stage	FIGO 2009						FIGO 2018					
	n	%	5-y OS (%)	5-y LRFS (%)	5-y PFS (%)	5-y DMFS (%)	n	%	5-y OS (%)	5-y LRFS (%)	5-y PFS (%)	5-y DMFS (%)
IB1	254	44.5	87.3	92.1	82.8	86.6	62	10.9	89.8	95.1	90.2	91.6
IB2	146	25.5	80.5	85.9	77.5	86.9	134	23.4	87.1	90.1	80.5	86.4
IB3	–	–	–	–	–	–	108	18.9	81.4	87.7	80.1	88.3
IIA	76	13.3	74.1	83.3	71.5	82	52	9.1	76.2	83.5	70.6	82.3
IIB	70	12.2	72.4	80.5	70.9	81.2	46	8	81.7	83.2	79	89.7
IIIB	12	2.1	37	81.5	38.9	48.6	3	0.5	50	–	66.7	66.7
IIIC1	–	–	–	–	–	–	135	23.6	77.2	85	73.8	81.3
IIIC2							22	3.9	46.5	89.8	48.8	52.5

FIGO: International Federation of Gynecology and Obstetrics; n: Number; y: year; OS: Overall survival; LRFS: Local recurrence-free survival; PFS: Progression-free survival; DMFS: Distant metastasis-free survival

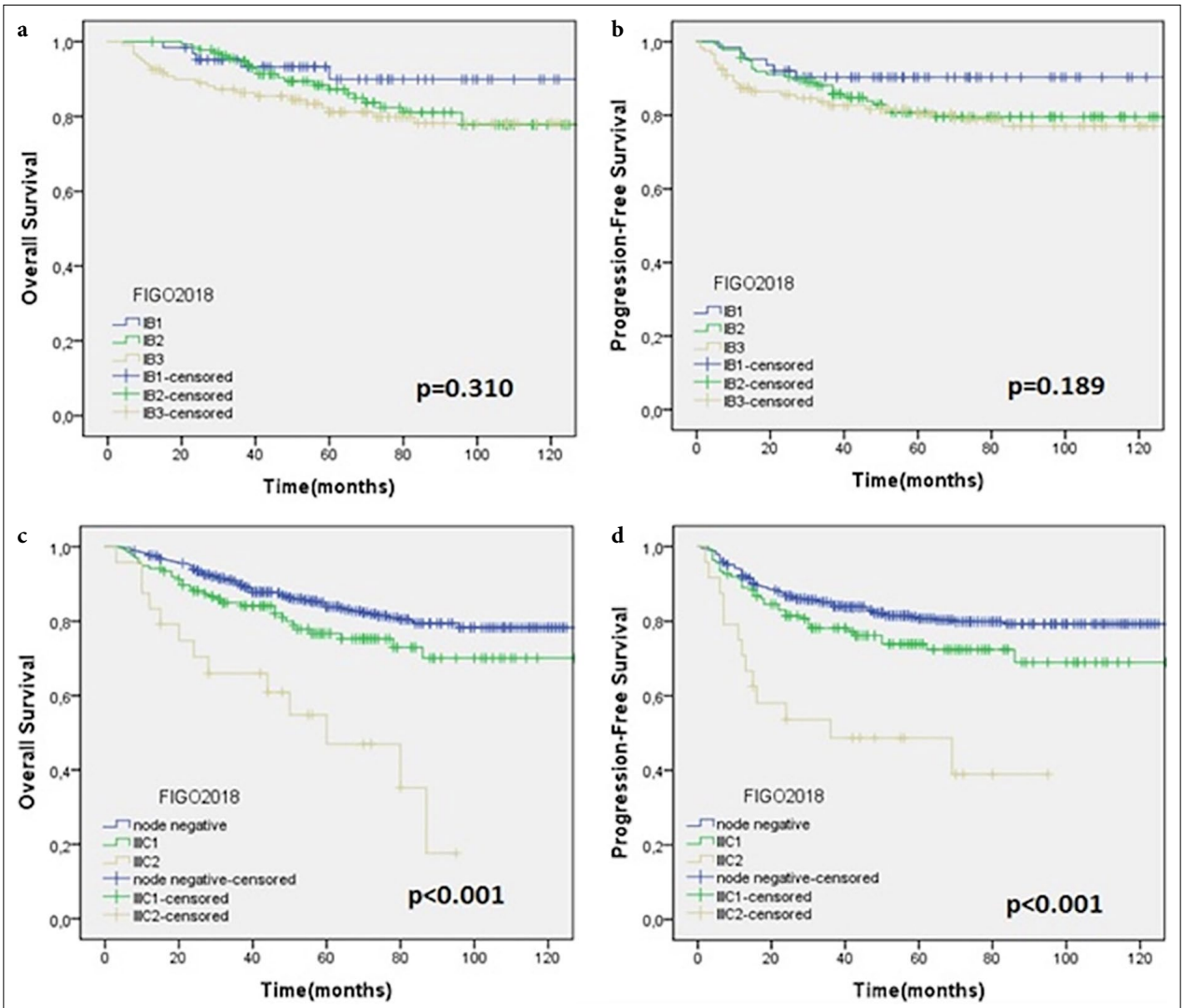

Fig. 2. Kaplan–Meier overall survival and progression-free survival curves regarding stage IB (IB1, IB2, and IB3) subgroups (a, b) and lymph node status (c, d) in FIGO 2018.
FIGO: Federation of Gynecology and Obstetrics.

disease according to the former 2009 staging system were 72.4%, 70.9%, and 81.2%, and it was 81.7%, 79%, and 89.7%, respectively, in the recent 2018 staging system.

Lymph Node (LN) Status and Survival Outcomes

In the recent FIGO 2018 staging system, 157 (27.5%) patients were up-staged to stage IIIC; 135 (23.6%) patients in stage IIIC1, 22 (3.9%) patients in stage IIIC2 including 4 (0.7%) patients with only para-aortic LN metastasis, and 18 (3.2%) patients with pelvic and para-aortic LN metastases.

When the patients without LN metastasis (n=414, 72.5%) were compared with patients in stage IIIC1 (n=135, 23.6%) and IIIC2 (n=22, 3.9%) disease, there were significant differences in OS and PFS rates according to LN status (Table 4 and Fig. 2).

Nodal Staging

The median number of metastatic LNs was 2 (range, 1–73). Five-year OS and PFS rates were higher in patients with one LN metastasis than those with ≥2 LN metastases (85.5% versus 61.4%, p=0.015 and 81.3% versus 59.5%, p=0.006, respectively) (Fig. 3).

The median number of pelvic LN metastasis in patients with stage IIIC1 disease was 2. Patients with pelvic LN metastastes were divided into two groups according to the number of LN metastases (PLN 1 and PLN ≥2).

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Table 4 Lymph node status and 5-year overall survival and progression-free survival rates in stage IIIC disease according to the FIGO 2018 staging system

Variable	n	%	5-y OS		5-y PFS	
			%	p	%	p
FIGO 2018 stage						
LN negative	414	72.5	84	<0.001	80.5	<0.001
IIIC1	135	23.6	77.2		73.8	
IIIC2	22	3.9	46.5		48.8	
Stage IIIC with sampling/LND						
Number of metastatic LNs (pelvic/paraaortic)						
1	72	12.6	85.5	0.015	81.3	0.006
≥2 LN	82	14.4	61.4		59.5	
MLNR (%)						
1–5	74	13	82.8	0.027	78.7	0.022
6–9	27	4.7	75.7		72	
≥10	53	9.3	56.1		56.5	
Stage IIIC1 with sampling/LND						
PLN						
1	69	12.1	86.3	0.144	81.9	0.049
≥2	64	11.2	67.4		64.7	
Stage IIIC2 with sampling/LND						
PALN						
1	10	1.8	78.8	0.020	70	0.041
≥2	11	1.9	–		24.2	

FIGO: International Federation of Gynecology and Obstetrics; n: Number; y: Year; OS: Overall survival; PFS: Progression-free survival; LN: Lymph node; LND: Lymph node dissection; MLNR: Metastatic lymph node ratio; PLN: The number of pelvic lymph node metastasis; PALN: The number of paraaortic lymph node metastasis

Five-year OS rates were similar between two groups; however, 5-year PFS rates were lower in patients with PLN ≥2 compared to those with PLN1 (Fig. 3).

The median number of metastatic LN in patients with stage IIIC2 disease was 2. The patients with para-aortic LN metastasis were divided into two groups according to the number of LN metastases (PALN 1 and PALN ≥2). Five-year OS and PFS rates were significantly lower in patients with PALN ≥2 compared to those with PALN 1 (Fig. 3).

The median value of MLNR in stage IIIC was 6%. Five-year OS and PFS rates were significantly lower in patients with a MLNR of ≥10% compared to those with a MLNR of <10% (Table 4 and Fig. 3).

When survival curves of FIGO 2009 and FIGO 2018 staging systems were visually compared, the difference among the survival curves of all stages observed more clearly in the FIGO 2018 staging system (Fig. 4).

Other Prognostic Variables

Univariate analysis revealed that large tumor size (both ≥2 cm and ≥4 cm), presence of LVSI, and para-aortic LN metastases were unfavorable prognostic factors for both OS and PFS. The presence of parametrial invasion was also poor prognostic factor for OS. DSI also affected PFS unfavorably (Tables 5, 6).

In multivariate analysis, the presence of LVSI and LN status was independent poor prognostic factors for both OS and PFS (Tables 5 and 6).

DISCUSSION

The goal of this study was to evaluate the current FIGO 2018 staging system and to analyze the prognostic factors and survival outcomes in patients with cervical cancer treated with adjuvant RCT or RT. There are several publications in the literature about the most recent FIGO 2018 staging system. In a validation study by Matsuo et al.[16] using the National Cancer Institute's Surveillance, Epidemiology, and End Results program between 1988–2014, the authors stated that the current FIGO staging system for cervical cancer is useful to distinguish survival groups, and

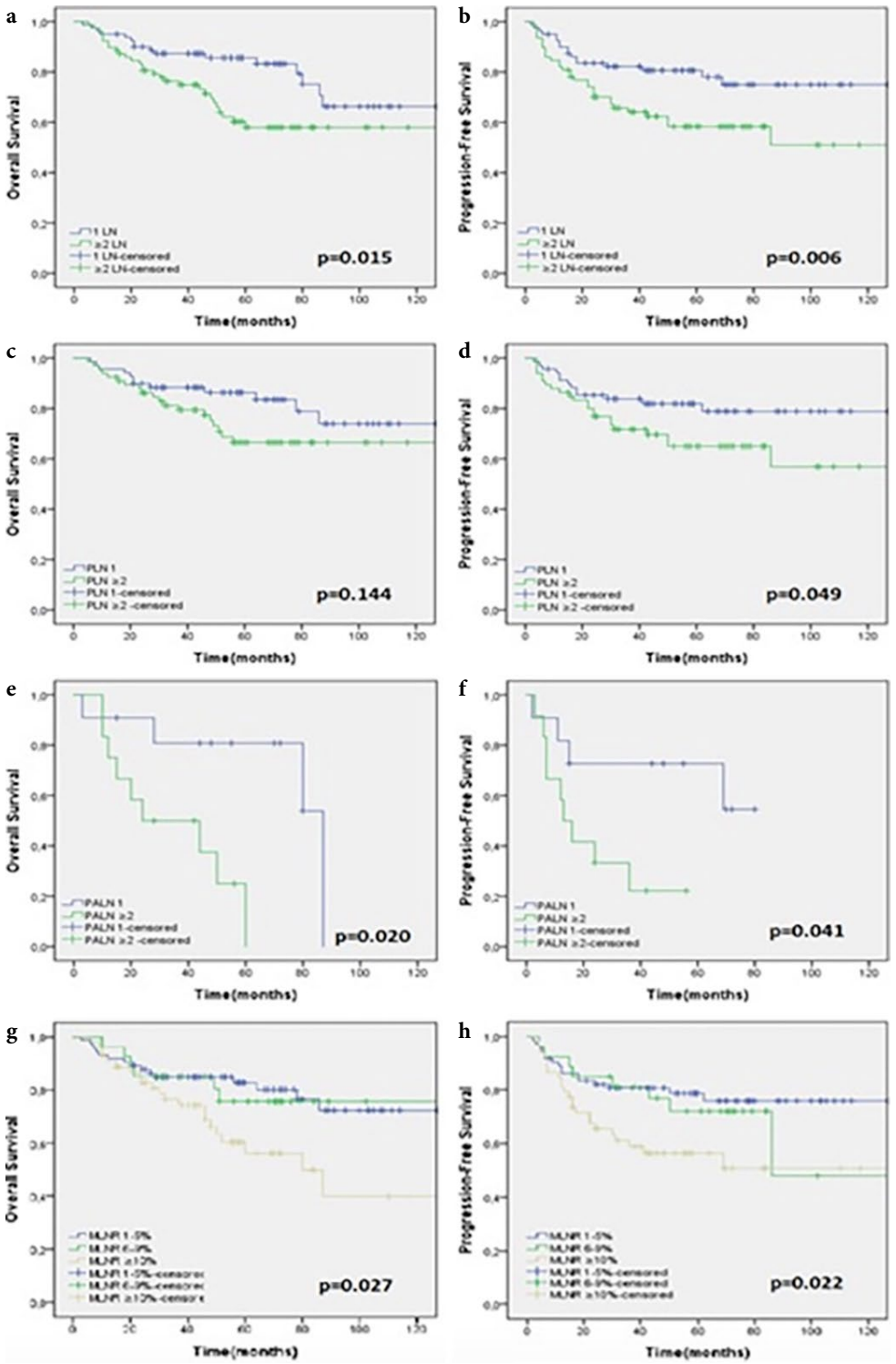

Fig. 3. Kaplan–Meier overall survival and progression-free survival curves regarding number of metastatic lymph nodes (a, b) in stage IIIC, pelvic lymph nodes (c, d) in stage IIIC1, para-aortic lymph nodes (e, f) in stage IIIC2, and metastatic lymph node ratio (1–5%, 6–9%, and ≥10%) (g, h) in stage IIIC according to FIGO 2018.

FIGO: Federation of Gynecology and Obstetrics; LN: Lymph node; PLN: The number of pelvic lymph node metastasis; PALN: The number of paraaortic lymph node metastasis; MLNR: Metastatic lymph node ratio.

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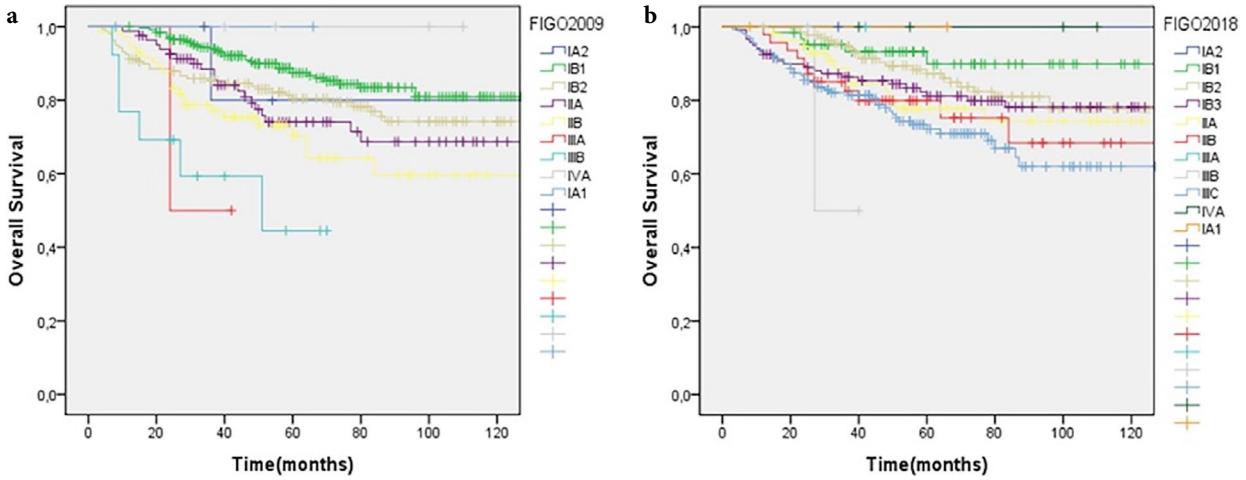

Fig. 4. Kaplan–Meier overall survival curves regarding FIGO 2009 (a) and FIGO 2018 (b) staging system.
FIGO: International Federation of Gynecology and Obstetrics.

a significant DSS difference was detected in stage I disease (5-year DSS 97.0% in stage IB1, 92.1% in stage IB2, and 83.1% in stage IB3 disease [p<0.001]). They concluded that patients with stage IB2 disease have a nearly 2-fold increased risk of cervical cancer death compared to those with stage IB1 disease. Yan et al. [17] have also reported that survival rates in stage IB disease decreased gradually with increase in stage, especially that of stage IB3, although it did not reach statistically significance and they also found that survival rates were higher in patients with stage IIA1 compared to those with stage IB3 disease. Similarly, Zeng et al.[18] found no significant difference in 5-year OS rates between stages IB1 and IB2 disease (97.9% vs. 92.7%, respectively; p=0.079). However, the 5-year OS rate for stage IB3 disease was lower than that of stage IB2 disease (78.6% vs. 92.7%, respectively; p=0.049). In other studies, recurrence rates were significantly lower in patients with a primary tumor size <2.0 cm compared to those who have tumors measuring 2.1–4.0 cm in greatest dimension.[9,19] Furthermore, the current data supported that 2 cm as a cutoff value for tumor size was an independent prognostic factor for both OS and PFS. We thought that the addition of a 2 cm cutoff value for the tumor size may be an appropriate parameter for the staging of patients with the early-stage cervical cancer. Although survival rates decrease with increase in stage I disease, no statistical difference was shown for 5-year OS and PFS rates among stage I subgroups in the present study.

We also showed prognostic importance of well known factors such as LVSI, ≥4 cm tumor size related to PFS and OS in our analysis similar to the other studies in the literature [12–14,20,21]. Bhatla et al.[9] suggested that the presence of pelvic or para-aortic LN metastases assigned the case to stage IIIC regardless of other findings, as they had poorer survival compared to those who did not have LN metastases. With the addition of stage IIIC to the current staging system, the survival difference between stage IB itself appeared more prominent. In our data, 99 (17.3%) out of 400 patients with stage IB disease in the former FIGO 2009 with LN metastasis upstaged to stage IIIC and a clear distinction of the survival curves within the stage IB subgroups was observed.

With the addition of LN metastasis to the current staging system, so called early-stage patients with LN metastasis in the former staging are defined as stage IIIC now and RCT is the standard of care in these patients. The prognosis of patients with metastatic LN was poor due to higher rates of local recurrence and distant metastases.[22,23] FIGO reported that the 5-year survival rates of patients with LN positive cervical carcinoma diagnosed with stages IA–IV (n=953) were 64.1% compared with 94.1% for LN negative patients (n=3364).[24] Similarly, Dai et al.[25] demonstrated that the 5-year OS rates of patients in the LN positive and LN negative groups differed significantly (54.2% vs. 87.8%, respectively [p<0.001]). In our data, in accordance with the literature, patients without LN metastases had better survival rates compared to patients with pelvic and/or para-aortic LN involvement. Furthermore, we found that 5-year LRFS rates (stage IIIC1 85% and stage IIIC2 89.8%) of patients with stage

Table 5 Univariate long-rank and multivariate Cox regression analyses regarding overall survival

Variable	Classification	Univariate analysis		Multivariate analysis	
		5-y OS (%)	p	HR (95% CI)	p
Age (year)	<50 versus ≥50	83 versus 79.3	0.234	2.313	
Tumor size (cm)	<2 versus ≥2	89.9 versus 80.2	**0.019**	(0.914–5.854)	0.077
	<4 versus ≥4	83.9 versus 78.2	**0.020**	1.412	0.088
				(0.950–2.099)	
	<2	89.9	**0.017**		
	2–3.9	82			
	≥4	78.2			
Surgical margin	Negative/close (<5 mm) vs. Positive	85.1 versus 78.7	0.667		
LVSI	No versus Yes	88.2 versus 78.5	**0.021**	1.678	**0.046**
				(1.010–2790)	
DSI	<1/2 versus ≥1/2	87.8 versus 80.5	0.136		
Parametrial invasion	No versus Yes	82.4 versus 74.1	**0.012**	1.536	0.075
				(0.958–2.462)	
Histology	SCC versus non-SCC	81.7 versus 78.6	0.244	1.620	**0.002**
LN status	Negative	84	**<0.001**	(1.187–2.211)	
	Pelvic positive	77.2			
	Para-aortic positive	46.5			

Y: Year; OS: Overall survival; HR: Hazard ratio, CI: Confidence interval; LVSI: Lymphovascular space invasion; DSI: Deep stromal invasion; SCC: Squamous cell carcinoma; LN: Lymph node

IIIC were higher than DMFS rates (stage IIIC1 81.3% and stage IIIC2 52.5%) according to current FIGO 2018 staging system (Table 3). We think that these patients with lower DMFS rates definitively need for other consolidation strategies either as effective chemotherapy agents or immunotherapy or targeting agents after RCT to increase the systemic control.

In addition, not only the presence but also the prognostic significance of the number of metastatic LNs in cervical cancer has been investigated in several studies.[20,26,27] Liu et al. recently reported that ≥2 pelvic LN metastases were associated with poorer survival.[28] In the other studies evaluating pelvic LN involvement, Li et al. found that the presence of ≥3 LN metastases was associated with worse OS and DMFS similar to Okazawa et al.[29–31] who found worse PFS outcomes in patients with ≥3 LN metastases than those with 1 or 2 LN metastases. In the present study, the presence of ≥2 LN metastases in stage IIIC patients had worse OS and PFS rates compared to those with one LN metastasis and there was a decreasing trend in OS in stage IIIC1 patients with ≥2 LN metastases compared to patients with only one LN metastasis. Since it is a multi-institutional retrospective study, we could not include location, sites, and size of the metastatic LNs in this analysis which was reported to be significant predictors for the prognosis by Hosaka et al.[32]

There are few articles in the literature regarding prognostic importance of the number of metastatic para-aortic LNs. Takeda et al. showed that presence of common iliac or para-aortic LN metastasis was related with poor survival.[33] Recently, Raut et al. found that the presence of ≥3 para-aortic LN metastases was associated with a worse DFS rates compared to those with <3 para-aortic LN metastases (13.6% vs. 56.3%, p=0.001).[34] In the present study, patients with ≥2 para-aortic LN metastasis had worse survival rates compared to patients with only one para-aortic LN metastasis. We think that the number of metastatic LNs should be evaluated separately in stage IIIC1 and IIIC2 disease. Like the other staging systems such as breast cancer and colon cancer adding the number of LN metastases to the staging system for the next revision of the FIGO staging system would be beneficial.

MLNR is associated with tumor burden of nodal disease and previous studies showed that MLNR had

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Table 6 Univariate long-rank and multivariate Cox regression analyses regarding progression-free survival

Variable	Classification	Univariate analysis		Multivariate analysis	
		5-y PFS (%)	p	HR (95% CI)	p
Age (year)	<50 versus ≥50	76.8 versus 78.5	0.449		
Tumor size (cm)	<2 versus ≥2	89.9 versus 76.1	**0.009**	1968	0.126
	<4 versus ≥4	80.9 versus 74.3	**0.015**	(0.827–4.682)	0.090
				1.392	
				(0.949–2.042)	
	<2	89.9	**0.009**		
	2–3.9	78			
	≥4	74.3			
Surgical margin	Negative/close (<5 mm) versus Positive	78.1 versus 76.2	0.631		
LVSI	No versus Yes	87.8 versus 74.8	**0.004**	2.028	**0.009**
				(1.191–3.451)	
DSI	<1/2 versus ≥1/2	87.7 versus 76.1	**0.036**	1.875	0.116
				(0.857–4.104)	
Parametrial invasion	No versus Yes	79 versus 70.5	0.087		
Histology	SCC versus non-SCC	78.8 versus 73.7	0.206		
LN status	Negative	80.5	**<0.001**	1.626	**0.001**
	Pelvic positive	73.8		(1.207–2.191)	
	Para-aortic positive	48.8			

Y: Year; PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval; LVSI: Lymphovascular space invasion; DSI: Deep stromal invasion; SCC: Squamous cell carcinoma; LN: Lymph node

prognostic value for many types of cancer such as rectal cancer, breast cancer, and esophageal carcinoma.[10,35–37] The total number of dissected LNs depends on surgical procedure, pathological examination, and patient anatomy. Fleming et al.[38] reported that a MLNR of >6.6% was associated with a worse PFS (p=0.01) and a MLNR of >7.6% with a worse OS rates (p=0.01). Polterauer et al.[11] reported that LN positive patients with a MLNR of ≥10% had worse PFS and OS rates compared with patients with a MLNR of <10%. Chen et al.[39] used cutoff values of 0%, 5% and 20% for analysis and higher MLNR values were found to be correlated with lower 5-year OS rates. Aslan et al.[40] also observed MLNR of 5% as an independent prognostic factor for both DFS and OS in LN positive cervical cancer patients. In our analysis, based on MLNR subgroups (1–5%, 6–9% and ≥10%), 5-year OS rates were 82.8%, 75.7%, and 56.1% (p=0.027) and 5-year PFS rates were 78.7%, 72, and 56.5% (p=0.022), respectively. We showed that MLNR was a significant prognostic factor for both OS and PFS and we think that a cutoff value of ≥10% could be a strong predictor for considering both OS and PFS rates. We suggest the FIGO committee consider adding MLNR in the next revision of the FIGO staging system and two different staging groups can be formed such as pathologically and clinically, and the MLNR status for operated cervical cancer patients can be added.

The comparison between FIGO 2009 and FIGO 2018 staging systems revealed a significant difference in OS and PFS rates in the early stages due to upstaging of patients with LN metastasis to stage IIIC. There was no significant difference between stages according to 2009 staging system and survival curves were close to each other. As determined in the survival graph, the difference between whole stages becomes clearer in the current FIGO 2018 staging system. Furthermore, the certain result is that all stages will have improved outcomes. This could be interpreted as Will Rogers phenomenon.

Despite having achieved prognostic accuracy, our study has some limitations. With combining data from seven institutions, the contribution of multiple sur-

geons, pathologists, and different surgical approaches could be accepted as a limitation of the study. However, this limitation could also be seen as strength, as it makes our conclusions more general and increases the available sample size. Second limitation of this study is that the size of metastatic LNs. We also did not include the presence of extracapsulary invasion in patients with stage IIIC2 disease in this analysis. We are planning to put these details in our further study and will try to evaluate if these paramaters have prognostic value in terms of OS, PFS, LRFS, and DMFS rates.

In conclusion, although FIGO 2018 staging system includes main factors such as LN status and tumor size, it still needs further prognostic factors that predict both OS and DFS rates. As shown in our analysis, we think that including the number of metastatic LNs and MLNR in the next version of the FIGO staging system will improve the accuracy of the staging system.

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