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Para-aortic lymph node involvement revisited in the light of the revised 2018 FIGO staging system for cervical cancer

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Abstract

Objective This dual-institutional, retrospective study aimed to determine the clinicopathological risk factors for para-aortic lymph node (LN) metastasis among women who underwent radical hysterectomy with systematic pelvic and para-aortic lymphadenectomy for 2009 FIGO stage IB1-IIA2 cervical cancer.

Methods Institutional cervical cancer databases of two high-volume gynecologic cancer centers in Ankara, Turkey were retrospectively analyzed. Women with 2009 FIGO stage IB1-IIA2 cervical cancer that had undergone radical hysterectomy with pelvic and para-aortic lymphadenectomy between January 2006 and December 2018 were included in the study. Patient data were analyzed with respect to para-aortic LN involvement and all potential clinicopathological risk factors for para-aortic LN metastasis were investigated.

Results A total of 522 women met the inclusion criteria. Pelvic LN metastasis was detected in 190 patients (36.4%), para-aortic LN metastasis in 48 patients (9.2%), isolated para-aortic LN metastasis in 4 (0.8%), and both pelvic and para-aortic LN metastasis in 44 (8.4%) women, respectively. The independent risk factors identified for para-aortic LN involvement included parametrial invasion (odds ratio [OR]: 3.57, 95% confidence interval [CI]: 1.65–7.72; $p=0.001$), metastasized pelvic LN size > 1 cm (OR: 4.51, 95% CI: 1.75–11.64; $p=0.002$), multiple pelvic LN metastases (OR: 3.83, 95% CI: 1.46–10.01; $p=0.006$), and common iliac LN metastasis (OR: 2.97, 95% CI: 1.01–8.68; $p=0.04$). A total of 196 (37.5%) patients exhibited at least one risk factor for para-aortic nodal disease.

Conclusion Parametrial invasion, metastasized pelvic LN size > 1 cm, multiple pelvic LN metastases, and common iliac LN metastasis seem to be independent predictors of para-aortic LN involvement.

Keywords Cervical cancer · Para-aortic lymph node · Metastasis · Radical hysterectomy · International Federation of Gynecology and Obstetrics · Staging

Introduction

The assessment of para-aortic nodal status is crucial as para-aortic lymph node (LN) metastasis is a well-known poor prognostic factor in clinically early-stage cervical cancer [1–3]. Although pelvic lymphadenectomy is accepted as an integral component of surgical management among women suffering from stage IB1-IIA1 disease according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, the performance of para-aortic LN dissection is optional with no concrete recommendations for para-aortic lymphadenectomy at the time of radical hysterectomy [4]. On the other hand, the incidence of para-aortic LN metastasis varies widely throughout the literature: ranging from 1.6 to 24.1% in cervical cancer patients undergoing radical hysterectomy [5–12, 3, 13–15]. Despite

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its negative impact on survival outcomes, para-aortic nodal disease tailors adjuvant treatment [16], and chemotherapy with extended-field radiation is indicated in the case of para-aortic lymphatic dissemination [17].

Para-aortic LN involvement generally occurs as a consequence of widespread pelvic LN metastases [16, 10, 14]. Ovarian [15] and/or uterine corpus invasion [18] by the primary tumor have been reported as risk factors for para-aortic lymphatic dissemination. Age > 46 years [3], tumor size > 3.5 cm [3], 2009 FIGO stage IIA disease [3], deep stromal invasion [10, 15], parametrial invasion [15], lymphovascular space invasion (LVSI) [10], and common iliac LN metastasis [19, 14] have been reported as other risk factors for para-aortic LN metastasis among cervical cancer patients who undergo radical hysterectomy.

The FIGO staging system for cervical cancer has been modified recently [20] and patients suffering from para-aortic LN metastasis proven either by imaging (*r*) or histopathology (*p*) are currently classified as stage IIIC2 disease [20]. In the light of the revised FIGO staging system, accurate information about para-aortic nodal status has become an important clinical issue. Since imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography/computer tomography (PET/CT) have been disappointing in identifying nodal metastases in clinically early-stage cervical cancer [21], histology-proven LN metastasis seems to be the gold standard in assessing nodal status. This dual-institutional, retrospective study aimed to determine clinicopathological risk factors for para-aortic LN metastasis among women undergoing radical hysterectomy with systematic pelvic and para-aortic LN dissection for 2009 FIGO stage IB1-IIA2 cervical cancer.

Materials and methods

Upon receiving approval from the Institutional Review Board (Başkent University Institutional Review Board Approval Number: 604.01.02/9124), patients with cervical cancer who underwent radical hysterectomy and systematic retroperitoneal lymphadenectomy between January 1, 2006 and December 31, 2018 were identified from tumor registries of two high-volume gynecologic oncology departments in Ankara, Turkey. At admission to the hospital, all patients signed an informed consent for allowing the researchers use their medical information for research purposes.

The inclusion criteria included: women with 2009 FIGO stage IB1-IIA2 disease who underwent radical hysterectomy with both pelvic and para-aortic lymphadenectomy, histological type diagnosed as squamous cell carcinoma (SCC), adenocarcinoma (AC), or adenosquamous cell carcinoma (ASC) as well as complete medical records. We excluded women with rare histologies, women who received neoadjuvant chemotherapy, those with synchronous malignancies at diagnosis, as well as women who received inadequate lymphadenectomy (less than 10 pelvic and 5 para-aortic nodes in the final pathology reports) [22, 23].

All operations were performed by a certified gynecologic oncology team. All of the 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. Although intraperitoneal disease detected during surgery was an indication for aborting the procedure; the operation was not abandoned in case of detecting any bulky nodes during surgery. Para-aortic lymphadenectomy was performed using the same method at both centers whereby the lateral aortic, pre-aortic, pre-caval, interaortico-caval, and lateral caval nodes up to the left renal vein were removed.

We extracted the following information from patients' medical records: age, histologic type (SCC,AC, or ASC), primary tumor size in greatest dimension, depth of stromal invasion, LVSI (absent/present), microscopic parametrial invasion (yes/no), vaginal involvement (yes/no), vaginal surgical margins (negative/positive), ovarian metastasis (yes/no), uterine corpus invasion (either myometrial or endometrial) (yes/no), the number of LNs that were removed (total/pelvic/para-aortic), number and location (parametrial, obturator, external iliac, common iliac, presacral) of the pelvic LNs involved, the number of para-aortic LNs involved, common iliac LN metastasis (yes/no), multiple (≥ 2) pelvic LN metastases (yes/no), and metastasized pelvic LN size > 1 cm (yes/no).

Conventional pathology was used for diagnosis in both of the centers. We retrieved all of histological data from the report of the primary pathologist, and we did not centrally review that pathologic data. Ultra-staging was not performed. The depth of cervical stromal invasion was measured in terms of millimeters, and then fractioned into thirds. We defined deep cervical stromal invasion as a tumor that invaded the outer third of the cervical stroma. We considered LVSI to be positive when the tumor cells were noted within endothelium-lined spaces [24]. In patients treated before 2009, stage was determined retrospectively on the basis of clinical information obtained from the medical records of the patients and women were allocated to proper stages according to the 2009 FIGO staging system for cervical cancer.

SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for performing all statistical analyses. Continuous variables were expressed in terms of medians and ranges, whereas binary variables were reported in terms of counts and percentages. Simple logistic regression analysis was performed with the intent of determining the correlation of clinicopathological characteristics with para-aortic LN metastasis. We included those variables with a *p* value less than 0.05 into the multiple logistic regression analysis. A *p*

value < 0.05 was considered in order to indicate statistical significance.

Results

A total of 522 women fulfilled the inclusion criteria. Clinicopathological characteristics of the study population are shown in Table 1. The median age of the patients at surgery was 50.0 years (range, 23–81 years). All of the patients went through a radical hysterectomy ± bilateral/unilateral salphingo-oophorectomy with pelvic and para-aortic lymphadenectomy. The median number of total LNs harvested was 41.0 (range, 16–138). The median number of pelvic and para-aortic LNs removed was 30.0 (range, 10–97), and 11.0 (range, 5–52), respectively. Retroperitoneal LN metastases were detected in 194 patients (37.1%). There were 190 patients who had pelvic nodal involvement (36.4%), and 48 patients who had para-aortic lymphatic dissemination (9.2%). Pelvic LN metastasis only was found in 146 women (28.0%). Four patients had isolated para-aortic nodal involvement (0.8%). Among 190 women with pelvic LN metastasis, 44 (23.1%) had concurrent para-aortic nodal involvement.

Squamous, adenocarcinoma, and adenosquamous histologies represented 79.1%, 11.9, and 9.0% of tumors, respectively. The median tumor size was 3.5 cm (range, 0.8–11 cm). There were 75 (14.4%) women with microscopic parametrial invasion while the primary tumor involved vagina in 93 (17.8%) patients. Fourteen (4.6%) of 302 women with 2009 FIGO stage IB1 disease, 21 (16.0%) of 131 cases with 2009 FIGO stage IB2 disease, 5 (9.4%) of 53 patients with 2009 FIGO stage IIA1 disease, and 8 (22.2%) of 36 women with 2009 FIGO stage IIA2 disease were upstaged to 2018 FIGO stage IIIC2. We observed no significant difference in terms of median para-aortic LNs removed between women with and without para-aortic nodal disease (11.0 [range, 5–45] vs. 13.0 [range, 5–52], respectively; $p = 0.12$).

Univariate analysis revealed that deep stromal invasion ($p = 0.02$), the presence of LVSI ($p < 0.0001$), parametrial invasion ($p < 0.0001$), ovarian metastasis ($p < 0.0001$), pelvic LN metastasis ($p < 0.0001$), common iliac LN metastasis ($p < 0.0001$), metastasized pelvic LN size > 1 cm ($p < 0.0001$), and multiple (≥ 2) pelvic LN metastases were associated with para-aortic LN metastasis (Table 2). We examined multicollinearity for the pelvic nodal factors, and removed "pelvic LN metastasis" from the multivariate analysis as its association to para-aortic nodal involvement was smaller when compared to "multiple pelvic LN metastases". In multivariate analysis, parametrial invasion (odds ratio [OR]: 3.57, 95% confidence interval [CI]: 1.65–7.72; $p = 0.001$), metastatic pelvic LN size > 1 cm (OR: 4.51, 95% CI: 1.75–11.64; $p = 0.002$),

Table 1 Clinicopathological characteristics of 522 cervical cancer patients undergoing radical hysterectomy with systematic pelvic and para-aortic lymphadenectomy

Characteristic	Values
Age, years (median, range)	50 (23–81)
Histopathology	
Squamous cell carcinoma	413 (79.1%)
Adenocarcinoma	62 (11.9%)
Adenosquaamous carcinoma	47 (9.0%)
2018 FIGO stage, *n* (%)	
IB1	52 (10.0%)
IB2	131 (25.1%)
IB3	97 (18.6%)
IIA1	34 (6.5%)
IIA2	15 (2.9%)
IIIC1	145 (27.8%)
IIIC2	48 (9.2%)
2009 FIGO Stage, *n* (%)	
IB1	302 (57.9%)
IB2	131 (25.1%)
IIA1	53 (10.1%)
IIA2	36 (6.9%)
Lymphovascular space involvement	
Negative	129 (24.7%)
Positive	393 (75.3%)
Stromal invasion	
< 2/3	91 (17.4%)
≥ 2/3	431 (82.6%)
Vaginal involvement	
Yes	93 (17.8%)
No	429 (82.2%)
Microscopic parametrial involvement	
Yes	75 (14.4%)
No	447 (85.6%)
Tumor size, cm (median, range)	3.5 (0.8–11)
Positive vaginal surgical margin	
Yes	60 (11.5%)
No	462 (88.5%)
Number of LNs removed (median, range)	41.0 (16–138)
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	146 (28.0%)
Positive pelvic and para-aortic LNs	44 (8.2%)
Positive para-aortic LNs only	4 (0.8%)
Ovarian metastasis	
Yes	12 (2.3%)
No	489 (93.7%)
Uterine corpus invasion	
Yes	111 (21.3%)
No	411(78.7%)

Table 1 (continued)

Characteristic	Values
Common iliac LN metastasis	
Yes	21 (4.0%)
No	501 (96.0%)
Multiple pelvic LN metastases	
Yes	131 (25.1%)
No	391 (74.9%)
Metastasized pelvic LN size > 1 cm	
Yes	132 (25.3%)
No	390 (74.7%)

n number, *LN* lymph node

multiple pelvic LN metastases (OR: 3.83, 95% CI: 1.46–10.01; $p=0.006$), and common iliac LN metastasis (OR: 2.97, 95% CI: 1.01–8.68; $p=0.04$) appeared to be independent risk factors for para-aortic LN involvement (Table 2).

The patients were scored according to the risk factors they exhibited for para-aortic LN metastasis. Patients with no risk factors were scored as "0" whereas women exhibiting only one risk factor were scored as 1. We scored women with two, three, and four risk factors as 2, 3, and 4 respectively. When no risk factor was present, the incidence of para-aortic LN metastasis was 0.9% (3/326). The rate of para-aortic LN involvement was 7.1% (6/85), 22.7% (15/66), 50% (19/38), and 71.4% (5/7) among women with one, two, three and four risk factors, respectively (Table 3).

Within a subgroup analysis of women with documented pelvic LN metastasis ($n=190$), we tried to determine the relationship between the involved pelvic LN station and para-aortic LN metastasis. The most common form of pelvic lymphatic dissemination among women with both pelvic and para-aortic nodal involvement ($n=44$) was the concurrent involvement of obturator and external iliac node stations ($n=8$, 18.2%), followed by "external iliac LN metastasis only" ($n=7$, 15.9%) and "obturator LN metastasis only" ($n=6$, 13.6%). Concurrent involvement of obturator, external iliac, and common iliac LN stations was detected in four (9.1%) women. Surprisingly, two (4.5%) women with para-aortic nodal disease had "parametrial LN involvement only" as pelvic LN metastasis. Involvement of external iliac ($p=0.005$), common iliac ($p=0.002$), and presacral ($p=0.03$) node bundles were associated with para-aortic nodal disease among women with documented pelvic LN metastasis (Table 4).

Discussion

This retrospective study investigated the relationship between clinicopathological characteristics and para-aortic LN metastasis in a cohort of 522 women that had undergone radical hysterectomy for 2009 FIGO stage IB1-IIA2 cervical cancer. The para-aortic LN metastasis rate was 9.2%. Our findings indicated that parametrial invasion, metastasized pelvic LN size > 1 cm, common iliac LN involvement, and multiple pelvic LN metastases were significant risk factors for para-aortic lymphatic dissemination.

The reader should note some limitations associated with the current study. As all retrospective reviews, our study is inherent to selection and referral bias due to its nature. The lack of pre-operative work-up with routine use of PET/CT and/or MRI, and the lack of labeling the para-aortic LNs excised as "supramesenteric" and "inframesenteric" seem to be methodological shortcomings. Additionally, the lack of ultrastaging might have caused underestimation of nodal disease since micrometastases are identifiable in histologically negative LNs in 15% of clinically early-stage cervical cancer patients [25, 26]. Nonetheless, some of our findings are prominent and seem to contribute to the body of knowledge on this topic.

As the major determinant of nodal involvement is the patient sample selected for reporting, the exact prevalence of para-aortic nodal disease is hard to determine in cervical cancer patients undergoing radical hysterectomy [27]. Hence, the rate of para-aortic nodal disease reported in the literature varies widely; ranging from 1.6% [6] to 24.1% [14]. Our finding of 9.2% is nearly identical to the 9.6% of para-aortic LN involvement rate reported by Tsuraga et al. [2]. Additionally, our finding of 9.2% of para-aortic nodal disease is comparable to the figures reported as 8.0% by Michel et al. [9], and 8.5% by Ouldamer et al. [28].

We found the isolated para-aortic LN involvement rate to be 0.8% in this study. The skip metastasis rate has been reported to be lower than 4.0% [29], even lower than 1.5% in most of the previous studies including women with clinically early-stage cervical cancer [5–7, 10–12, 28, 13]. Our finding of 0.8% supports previously reported low rates of isolated para-aortic LN metastasis.

Positive pelvic LN status strongly correlates with para-aortic nodal disease among women undergoing radical hysterectomy for cervical cancer [7, 10, 3]. Matsuo et al. [14] and Ditto et al. [30] reported that all patients with para-aortic LN involvement had concurrent pelvic LN metastasis. Huang et al. [12] reported that among 19 women with para-aortic nodal disease, 18 (94.7%) had pelvic LN metastasis. Tsuraga et al. [2] reported the same figure as 92.3% (12/13) in a series of 302 women undergoing radical hysterectomy. In the current study, among 48 women with para-aortic LN involvement, 44 (91.6%) were found to have documented pelvic LN metastasis.

Apart from the previous studies, we tried to determine the relationship between all of the involved pelvic LN stations and para-aortic LN involvement among women with positive pelvic LNs. Although previous studies emphasized only the

Table 2 Univariate and multivariate analyses of women with cervical cancer undergoing radical hysterectomy with regard to para-aortic lymph node metastasis

	Cases	Univariate analyses *p*	Multivariate analyses		
			OR	95% CI	*p*
Age, years					
≥ 50	22/273 (8.0%)	0.36			
< 50	26/249 (10.4%)				
Histopathology					
SCC	35/413 (8.5%)	0.26			
AC or ASC	13/109 (11.9%)				
Cervical stromal invasion					
< 2/3	6/138 (4.3%)	**0.02**			
≥ 2/3	42/384 (10.9%)				
Parametrial invasion					
Absent	24/447 (5.3%)	**< 0.0001**	**3.57**	**1.65–7.72**	**0.001**
Present	24/75 (32.0%)				
Primary tumor size					
< 2 cm	4/69 (5.8%)	0.37			
≥ 2 cm	44/453 (9.7%)				
Vaginal involvement					
Absent	36/429 (8.4%)	0.17			
Present	12/93 (12.9%)				
LVSI					
Absent	1/129 (0.8%)	**< 0.0001**			
Present	47/393 (11.9%)				
Number of metastatic pelvic LNs					
0–1	9/391 (2.3%)	**< 0.0001**	**3.83**	**1.46–10.01**	**0.006**
≥ 2	39/131 (29.8%)				
Ovarian metastasis					
Absent	41/489 (8.4%)	**< 0.0001**			
Present	5/12 (41.6%)				
BSO/USO not performed	2/21 (9.5%)				
Uterine corpus invasion					
Absent	34/371 (9.2%)	0.19			
Present	14/111 (12.6%)				
Pelvic LN metastasis					
Absent	4/333 (1.2%)	**< 0.0001**			
Present	44/189 (23.2%)				
Common iliac LN metastasis					
Absent	37/501 (7.4%)	**< 0.0001**	**2.97**	**1.01–8.68**	**0.04**
Present	11/21 (52.4%)				
Pelvic LN metastasized size > 1 cm					
Absent	9/390 (2.3%)	**< 0.0001**	**4.51**	**1.75–11.64**	**0.002**
Present	39/132 (29.5%)				

Bold characters indicate statistical significance

SCC squamous cell carcinoma, *AD* adenocarcinoma, *ASC* adenosquamous carcinoma, *LVSI* lymphovascular space invasion, *LN* lymph node, *BSO* bilateral salphingo-oopherectomy, *USO* unilateral salphingo-oopherectomy

importance of the common iliac LN station for para-aortic nodal disease [31, 2, 3, 19, 14], the usual suspect pelvic node stations for para-aortic LN involvement were external iliac, common iliac, and presacral node bundles in the present study (Table 4).

The number of LNs retrieved generally represents the thoroughness of LN dissection [30]. Variations in the rate

Table 3 Number of women with documented para-aortic lymph node metastasis among patients exhibiting null (0), one, two, three, or four risk factors for para-aortic lymph node involvement

Risk score	*n* (%)	Para-aortic lymph node negative, *n* (%)	Para-aortic lymph node positive, *n* (%)
0	326 (62.5%)	323 (99.1%)	3 (0.9%)
1	85 (16.3%)	79 (92.9%)	6 (7.1%)
2	66 (12.6%)	51 (77.3%)	15 (22.7%)
3	38 (7.3%)	19 (50.0%)	19 (50.0%)
4	7 (1.3%)	2 (28.6%)	5 (71.4%)

Table 4 The relationship between the involved pelvic lymph node station and para-aortic lymph node metastasis among 190 women with documented pelvic lymph node metastasis

Pelvic lymph node station	Para-aortic lymph node negative ($n=146$)	Para-aortic lymph node positive ($n=44$)	*p*
Parametrial lymph node metastasis			
Yes	38 (26.0%)	15 (34.1%)	
No	108 (74.0%)	29 (65.9%)	0.33
Obturator lymph node metastasis			
Yes	88 (60.2%)	31(70.5%)	
No	58 (39.8%)	13 (29.5%)	0.28
External iliac lymph node metastasis			
Yes	74 (50.7%)	33 (75.0%)	
No	72 (49.3%)	11 (25.0%)	0.005
Common iliac lymph node metastasis			
Yes	10 (6.8%)	11 (25.0%)	
No	136 (93.2%)	33 (75.0%)	0.002
Presacral lymph node metastasis			
Yes	4 (2.7%)	5 (11.4%)	
No	142 (97.3%)	39 (88.6%)	0.03

of para-aortic LN metastasis may be a consequence of inadequate nodal dissection [26], inaccuracies of pathological examination [26], and the features of the patient sample selected for reporting [27]. However, timely and accurate information about LN status has become an important clinical issue for candidates of radical hysterectomy in the light of the revised FIGO staging system [20]. Despite the widely application of PET/CT for the assessment of nodal status in patients with cervical cancer, high false-negative rates have been reported for para-aortic LN involvement even among women with locally-advanced disease [32–34]. The threshold of PET-CT imaging is nearly 5 mm in order to detect tumor tissue accurately [35]. Failure to detect micrometastasis by imaging techniques is the principle reason for false-negative diagnoses of nodal disease [36]. Hence, in 12% of the patients with locally-advanced cervical cancer, false-negative results have been reported associated with para-aortic nodal disease [37, 38]. In this background, histology-proven LN involvement seems to be the gold standard for assessing para-aortic nodal status when indicated [26].

Although a large part of the gynecologic oncology community is moving towards sentinel lymph node (SLN) biopsy only, it should be reminded that SLN mapping is not currently recommended for cervical cancer patients with a primary tumor diameter > 2 cm [4]. On the other hand, it should be emphasized that the rate of para-aortic LN metastases has been reported as only 2% in women with a tumor size < 2 cm [9]. The corresponding figure was 5.8% in the current study (Table 2). In this background, it is hard to present SLN navigation surgery as an important clinical tool in the management of cervical cancer patients those would have an apparent risk of para-aortic LN involvement.

In the light of the revised FIGO staging system [20], it is of paramount importance to have information about the predictors of para-aortic LN metastasis among women undergoing radical hysterectomy. Matsuo et al. [15] reported parametrial involvement (OR = 1.90) and pelvic LN metastasis (single node OR = 4.99, and multiple-node OR = 28.1) as being risk factors for para-aortic LN involvement among 957 women who had undergone a histological para-aortic LN evaluation. Han et al. [3] reported that age > 46 years, tumor size > 3.5 cm and 2009 FIGO stage IIA disease were independently associated with para-aortic LN metastasis in a cohort of 723 women with 2009 FIGO stage IB1-IIIA2 disease. In a study of 112 women surgically treated for 2009 FIGO stage IB-IIB cervical cancer, Matsuo et al. [14] identified the presence of common iliac LN metastasis (OR = 4.03), multiple pelvic LN metastases (OR = 7.35), and metastasized pelvic LN size ≥ 1 cm (OR = 8.92) as independent predictors for para-aortic LN involvement. The current study revealed parametrial involvement (OR = 3.57), common iliac LN metastasis (OR = 2.97), metastasized pelvic LN size > 1 cm (OR = 4.51), and multiple pelvic LN metastases (OR = 3.83) as significant risk factors for para-aortic LN metastasis. Although our findings do not seem to add any new key information on what is already known regarding para-aortic LN involvement due to cervical cancer, we have confirmed the findings of Matsuo et al. [14, 15] in the current study of 522 women who uniformly received systematic retroperitoneal LN dissection with a median of 11 para-aortic LNs removed.

The risk of para-aortic nodal disease is not uncommon among women undergoing radical hysterectomy for cervical cancer. In a Japanese nation-wide study [15], a significant proportion of women (nearly 1 in 5) with 2009 FIGO stage IB-IIB cervical cancer were found to be at risk for para-aortic lymphatic dissemination. We found out that among 522 women undergoing radical hysterectomy for 2009 FIGO stage IB1-IIA2 cervical cancer, 196 (37.5%)

exhibited at least one independent risk factor for para-aortic nodal disease (Table 3).

A sufficient number of patients with detailed clinicopathological characteristics, performance of para-aortic lymphadenectomy in a standard fashion in both of the centers, a satisfactory median number of LNs removed, and an average prevalence of para-aortic LN involvement that does not result in diminished statistical power seem to be the major strengths of the present study.

Finally, we conclude that parametrial involvement and metastatic pelvic LN size > 1 cm appears to be independent risk factors for para-aortic LN involvement in women undergoing radical hysterectomy. These features should be explored via PET-CT and/or MRI in the pre-operative work-up of radical hysterectomy candidates since these imaging techniques are able to detect parametrial involvement and metastatic pelvic LN size > 1 cm with a high accuracy rate [25, 35]. In the case of detecting either clinically evident common iliac LN metastasis or multiple pelvic LN metastases intra-operatively, a thorough para-aortic lymphadenectomy should be performed. According to our findings, external iliac, common iliac, and presacral node stations seem to be the common suspects for para-aortic LN involvement among women with documented pelvic LN metastasis. Particular attention should be paid for those LN bundles during surgery in order to exclude para-aortic LN metastasis. However, clinicians should be aware of the fact that determination of para-aortic LN status timely and accurately is crucial in the light of the modified FIGO staging system for reporting realistic survival outcomes.

Author contributions AA: conceptualized and designed the study, prepared the draft manuscript. MMM: conceptualized and designed the study, analyzed and interpreted the data, prepared the draft manuscript. KA: collected the data, performed statistical analyses, edited and reviewed the manuscript. YAT: collected the data, edited and reviewed the manuscript. EK: controlled the quality of the data, analyzed and interpreted the data, edited and reviewed the manuscript. MÖ: controlled the quality of the data, analyzed and interpreted the data, performed statistical analyses, edited and reviewed the manuscript. All co-authors revised the manuscript critically and approved the final version to be published. MÖ accepts full responsibility for the work and/or the conduct of the study, had access to the data, and oversaw the decision to publish.

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