Preoperative prediction of retroperitoneal lymph node involvement in clinical stage IB and IIA cervical cancer

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Abstract

Objective:

Lymph node metastasis (LNM) is the most important factor affecting survival in early-stage cervical cancer (CC). International Federation of Gynecology and Obstetrics revised the staging of CC in 2018 and reported LNM as a staging criterion. We investigated the preoperatively assessable risk factors associated with LNM in surgically treated stage IB1-IIA2 CC patients.

Materials and Methods:

This was a retrospective cohort study of women who underwent radical hysterectomy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy for CC stage IB1–IIA2 from 2004 to 2019. All patients included in this study were examined with speculum inspection, parametrial assessment by rectovaginal palpation under general anesthesia, transvaginal ultrasonography,

magnetic resonance imaging (MRI), and chest radiography. Clinical staging was done according to the preoperative findings. MRI was used to measure tumor and lymph node dimensions.

Results:

Out of the 149 women included in the study, 29 (19.4%) had LNM. Univariate analysis revealed that larger tumor size (≥30 mm), lymphovascular space invasion (LVSI) detected with diagnostic biopsy, parametrial involvement, and deep stromal invasion status were significantly different between the group with LNM and the group without LNM. In multivariate analysis, specific preoperative risk factors such as MRI based tumor diameter ≥30 mm and LVSI (+) on the diagnostic biopsy were found to be independent risk factors for LNM in the multivariate analysis.

Conclusion:

The rate of LNM is high in patients with CC with a tumor size ≥30 mm and preoperative biopsy LVSI status even if they are clinically in early stages. Surgeons can take this into account while deciding between primary surgery and chemoradiotherapy in the treatment of CC.

INTRODUCTION

Cervical cancer (CC) is the second most common cancer type that affects women worldwide and is the main cause of cancer-related mortality in women in the developing countries.[12] The International Federation of Gynecology and Obstetrics (FIGO) system used for staging CC is based on clinical examination. The standard surgical management for FIGO stage IB and IIA CC is radical hysterectomy and bilateral pelvic and para-aortic lymph node (LN) dissection. CC usually spreads in a lateral direction along the parametrium and vagina, uterine corpus, and LNs through straight local spread or permeation of tumor emboli into the lymphovascular space.[1]

The staging of this disease has been modified 10 times since the 1950s.[34] In the last modification in 2018, the FIGO clinical staging system includes the assessment of LN status. Furthermore, LN metastases (LNMs) are considered high-risk factors associated with an increased recurrence rate and decreased survival rate.[56] Therefore, it is necessary to evaluate the LNs to determine the stage of the disease accurately. Due to this modification, a need for further examination to determine the status of LNs in clinical practice has arisen.[4]

The main purpose of this study was to predict LNM preoperatively in patients with clinical stage IB and IIA CC who underwent radical hysterectomy.

MATERIALS AND METHODS

This study included 149 patients who underwent surgical treatment for FIGO stage IB–IIA CC between January 2004 and January 2019 in Istanbul Kanuni Sultan Suleyman Research and Training Hospital in the Department of Gynecological Oncology. Patients underwent radical hysterectomy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy. All operations were performed by expert gynecological oncologists. Patients receiving neoadjuvant chemotherapy, patients with second primary gynecologic malignancy, patients with stage IIB and higher CC, patients in stage IA1–IA2, patients who were incidentally diagnosed as having CC after simple hysterectomy, and patients with insufficient records were excluded from the study. The study was approved by the local ethics committee of the participating institution and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

All patients were diagnosed with invasive CC and the diagnosis was confirmed by biopsy. FIGO 2009 staging for cervical carcinoma was used for all patients.[7] Although FIGO cervical staging

classification was revised on January 1, 2018, we used previous staging classification during 2018 as well to maintain consistency among our data.

All data were obtained from the patients' charts retrospectively. Patient age, menopausal status, and type of surgery were investigated. The staging was performed according to the FIGO 2009 clinical staging system by examination under general anesthesia, and patients were evaluated using imaging modalities (transvaginal ultrasonography, magnetic resonance imaging [MRI], and chest radiography). Clinical examination included speculum inspection and parametrial assessment by rectovaginal palpation under general anesthesia. Parametrial involvement evaluation was performed by examination under general anesthesia and using MRI. All of the patients received MRI scans in the preoperative period and all MRI scans were reviewed by two radiologists. Tumor diameter was defined as the greatest tumor diameter measured on T2-weighted images in the sagittal, coronal, and transverse axial planes. MRI-reported LNM was defined as larger than 10 mm in the maximal short-axis diameter that was measured on T2 weighted in transverse axial planes. All surgical and diagnostic biopsy specimens were evaluated by specialized gynecological pathologists. Vertical and horizontal tumor dimensions, lymphovascular space invasion (LVSI) status, depth of stromal invasion (DOI), the presence of parametrial invasion, histological type of the tumor, number of LNs, and status were recorded. The longest dimension of tumor diameter was analyzed. DOI was defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. LVSI was defined as the presence of tumor cells inside the capillary lumens of either the lymphatic or microvascular drainage systems within the primary tumor.

Radical hysterectomy consisted of removal of the uterus and adjacent parametrium to its most lateral extent along the paracolpium and the upper portion of the vagina and the proximal uterosacral ligaments. Pelvic lymphadenectomy included common iliac, external iliac, internal iliac, obturator, presacral, and parametrial LNs. Para-aortic LN dissection was performed by removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the bifurcation and proceeding to the inferior mesenteric artery if necessary.[8] Pelvic LN dissection was performed for all patients. Para-aortic LN dissection was performed in 130 patients (90.7%). The indication for para-aortic LN dissection was a bulky LN and/or suspicious appearance in the para-aortic LN area.

Statistical analysis was performed using SPSS version 20.0 software (IBM Corporation, Armonk, NY, USA) in the evaluation of the obtained results. Descriptive statistical methods such as frequency, percentage, mean, standard deviation (SD), and median were used in the evaluation of the data. Pearson's Chi-squared test and Fisher's exact test were used to evaluate the risk factors for positive LN in univariate analysis. In the logistic regression analysis, variables were selected through the enter method and the risk ratios were calculated by taking the first categories as references. The results were evaluated at a 95% confidence interval. $P < 0.05$ was considered statistically significant.

RESULTS

The general characteristics of the 149 patients included in the study are shown in Table 1. The median age of the patients was 48 (29–70) years and median parity was 3 (0–13). About 83.8% of the patients were in clinical stage IB1. In 29 patients (19.4%), LNM was found. Of the patients with LNM, 23 (79.3%) had only pelvic LNM and 6 (20.7%) patients had pelvic and para-aortic LNM. Isolated para-aortic LNM was not observed.

	Patients (n=149)
Age (year), median (minimum-maximum)	48 (29-70)
Parity, median (minimum-maximum)	3 (0-13)
Tobacco use, *n* (%)	48 (32.2)
Stage, *n* (%)	
Ib1	125 (83.8)
Ib2	18 (12)
IIa1	4 (2.6)
IIa2	2 (1.3)
Hystology, *n* (%)	
Squamous	125 (83.8)
Adenocarsinoma	22 (14.7)
Myxed	2 (1.3)
Tumor diameter (mm) ± SD (MR based)	29.3±15.6
Tumor diameter (mm) ± SD (pathology based)	29.4±13.4
LVSI (+) (on the surgical specimen), *n* (%)	75 (50.3)
LVSI (+) (on the diagnostic biopsy), *n* (%)	22 (14.7)
Parametrial involvement, *n* (%)	36 (24.2)
Vaginal involvement, *n* (%)	9 (6.0)
Lymphadenectomy, *n* (%)	
Pelvic	14 (9.3)
Pelvic + para-aortic	135 (90.7)
Lymph node count, median (minimum-maximum)	28 (11-96)
Pelvic	18 (11-42)
Pelvic + para-aortic	29 (22-96)
Lymph node metastasis, *n* (%)	29 (19.4)
Pelvic metastasis	23 (79.3)
Pelvic + para-aortic metastasis	6 (20.7)

LVSI=Lymphovascular space invasion, SD=Standard deviation, MR=Magnetic resonance

Table 1:
General charecteristics of the patients

The mean tumor size was 29.3 ± 15.6 (mean ± SD) mm according to the MRI reports. When the cutoff value for the tumor diameter was 30 mm, the sensitivity was 83.3% and the specificity was 55.8% (area under the curve: 0.787) [Figure 1]. Furthermore, the mean size tumor was 29.4 ± 13.4 (mean ± SD) mm according to pathology reports. A κ statistic was calculated to measure excellent agreement between MRI-based tumor diameter and pathology reports (κ: 0.85). LNM was significantly increased in patients with tumor diameter greater than 30 mm (*P*: 0.012) [Table 2]. LNM ratios were similar in squamous cell carcinomas and adenocarcinomas. The presence of vaginal metastasis did not increase the risk of LNM. LNM rates were similar in low-grade tumors and high-grade tumors. The results of the univariate analysis, which was performed on the factors affecting LNM, are shown in Table 2. LN involvement was significantly higher in patients with LVSI (+) on the diagnostic specimen (*P*: <0.01) and DOI (*P*: 0.001). The age of the patient, histological type of CC, grade, and vaginal involvement were not statistically significant in determining LNM.

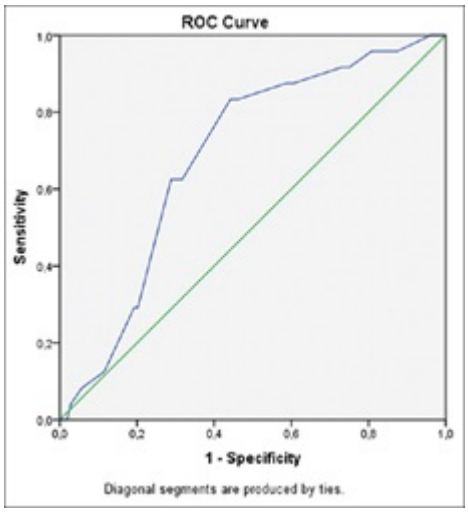

Figure 1:
Cut-off value for the tumor diameter according to receiver operating characteristic. Area under the curve: 0.787

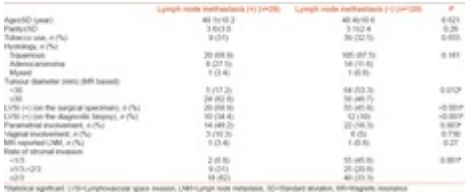

Table 2:
Factors affecting lymph node methastasis

The results of the specific preoperative multivariate analysis performed in accordance with MRI-based tumor diameter, LVSI (on the diagnostic biopsy), DOI, and parametrial involvement on the surgical specimen which can be evaluated are shown in [Table 3]. Tumor diameter and LVSI (+) were calculated as an independent preoperative risk factor for LNM (*P*: 0.008 and *P*: 0.042).

Variable	OR (95 CI)	*P*
Tumour diameter (mm) (MR based) ≥30 mm	2.1 (1.9-2.3)	0.008*
LVSI (+) (on the diagnostic biopsy)	2.5 (1.8-3.4)	0.042*

*Statistical significant. LVSI=Lymphovascular space invasion, MR=Magnetic resonance, OR=Odds ratio, CI=Confidence interval

Table 3:
Multivariate analysis of specific preoperative risk factors for lymph node involvement

DISCUSSION

LN involvement is an important criterion for survival in patients with early-stage CC.[56] This retrospective study shows that MRI-based tumor diameter determination and LVSI (+) on the diagnostic biopsy are independent risk factors for patients with early clinical stage CC. We believe that preoperative evaluation is the most important step for these patients.

National Comprehensive Cancer Network Guideline presents LNM as a criterion for inoperability and recommends primary chemoradiotherapy in patients with CC.[4] The new FIGO modification emphasizes the need to assess the LN in the preoperative period.

In this study, we examined factors that could be associated with LNM and we attempted to determine an MRI based cutoff value for tumor size. LNM was found in 19.4% of patients who were clinically operable. However, for this group of patients, operation should not be the choice of treatment. According to the 2018 revised FIGO staging system, this group of patients with LNM should be determined preoperatively. In the last modification of FIGO, it was suggested that LNM should be evaluated by imaging techniques and pathologically. Due to the fact that most patients with operable CC did not have LNM, it would be advantageous to examine the presence of LNM in a defined group. According to the results of this study, the LNM ratio was 6.4% in patients with tumor size below 30 mm, while it was 30.3% in patients with tumor size above 30 mm. The sensitivity and specificity of tumor size at 30 mm were 83.3% and 55.8%, respectively. Sensitivity was reported to be high for the prediction of LNM presence. However, specificity seemed to be low in the prediction of an absence of LNM. Additional tests would be needed for patients with tumor size <30 mm to determine the presence of LNM. Positron-emission tomography could be used as an additional imaging technique.[7] However, histopathological evaluation has been accepted as the gold standard for showing nodal involvement.

The relationship between LNM and tumor size has been shown in some studies.[79] In a study by Sakuragi *et al*., the incidence of LNM was reported to increase in accordance with the FIGO stage and tumor size. They found out that the incidence of pelvic LN involvement was 11.5% in stage IB, 26.7% in stage IIA, 39.2% in stage IIB, pelvic LN involvement was 11.1% in those with a tumor size of ≤2 cm, it was 26.9% in those with tumor size of 2–4 cm, and it was 48% in patients whose tumor size was >4 cm.[10] In a study by Kato *et al*., increased tumor size was reported to increase the rate of LNM. In patients with tumors <2 cm, the LN involvement rate was reported to be 7.4%, while this rate was 22.2% in patients with tumors >2 cm. The LNM rate was reported as 5.9% for tumor volume of ≤1 cm, 9.9% for tumor volume of 1 cm, and 27.4% for tumor volume between 2 and 2.5 cm.[11] Kinney *et al*. reported that tumor size affected LN and parametrial involvement. They also showed that parametrial invasion was not observed in patients with the stage IB squamous cell, of which tumor size was ≤2 cm, and 5 years disease-free survival rate was 97.6%.[12]

Conventionally, morphological evaluations with imaging techniques were considered unsatisfactory, especially because of low sensitivity. The connection between LNM and LN size has

been evaluated in some studies.[1314] Gong *et al.* wrote about different imaging techniques for the detection of pelvic LNM of gynecological malignancies,[13] and the results of their meta-analysis showed that the sensitivity of morphological evaluations with imaging was <50%. Later, Yu *et al.* have reported that MRI-based LNM was an independent risk factor in early clinical stage CC.[14] This finding was different from our result. One reason may be that only two patients have MR-reported LNM in present study.

Our study showed that the presence of LVSI on the diagnostic specimen was related to LNM. The correlation between LNM and LVSI on the surgical specimen has been assessed in many studies, but differently, to these studies, we evaluated LVSI status preoperatively diagnostic biopsy and LNM. Finally, we showed that LVSI status on preoperatively specimen was an independent risk factor for LNM in early clinical stage CC. We believe that preoperatively specimen evaluation period was a very important step for the management of CC.

Further analysis of our results revealed that the presence of vaginal metastasis was not related to LNM. The rates of LNM in adenocarcinoma or squamous cells were similar. Low-grade tumors had a similar LNM ratio to high-grade tumors. The histologic grade reflected the degree of differentiation of the tumor cells.

This study had several limitations. First, it was retrospective in design. Second, information on the treatment of recurrent disease and the clinical outcomes of patients with recurrent disease could not be objectively evaluated. Third, we did not evaluate the overall survival rates and disease-free survival rates. Moreover, we evaluated only preoperatively LVSI status because we focused only preoperative period, and sentinel LN procedure was not used in our clinics. Finally, we reported 36 patients with parametrial involvement in postoperative hysterectomy specimens which is high for the patient group early clinically staged, but most of them were reported as microscopical involvement of parametrium. Despite these limitations, strengths of the study were the relatively large number of patients included, the similarity of their demographic characteristics, uniform standards in decision-making, and operation techniques which were applied by the same surgical team. Furthermore, all MRI scans were reviewed by the same expert team of radiologists. All of these aspects increased the validity of the results and mitigated the weaknesses of the study.

In our study, LN involvement was found to be increased with the increase in tumor size and LVSI status on the diagnostic biopsy which was compatible with the literature. This study also offered a cutoff value of 30 mm. The rate of LNM was observed to be high in patients with CC with a tumor size >30 mm and LVSI (+) even if they were clinically in early stages. The maximum diameter of resectable CC and LVSI status on preoperative specimens were helpful in quantitatively predicting the presence of LNM. We believe that preoperative assessments, especially tumor diameter and LVSI status on the diagnostic specimen, are important in formulating an individualized treatment plan for the individual cases.