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ORIGINAL ARTICLE/ORİJİNAL MAKALE

Prediction of Para-Aortic Lymph Node Metastasis Using Metastatic Pelvic Lymph Node Diameter in Patients With Locally Advanced Cervical Cancer

Lokal ileri evre serviks kanserli hastalarda metastatik pelvik lenf nodu çapı kullanılarak para-aortik lenf nodu metastazının öngörülmesi

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ABSTRACT

Objectives: Investigation of the prediction of para-aortic lymph node (LN) metastasis by metastatic pelvic lymph node diameter in patients with locally advanced cervical cancer.

Methods: Between 28 December 2010 and 30 March 2021, 57 patients with locally advanced cervical cancer (2B-4A 2018 FIGO) at Selcuk University Faculty of Medicine were enrolled in this retrospective analysis. The involvement of pelvic and para-aortic LN in patients with surgical staging and outcomes were assessed.

Results: The average age of 57 patients was 56 (33-78) years. Of patients, 73.7% were stage 2b, 12.3% were stage 3 and 14.0% were stage 4a. Of samples, 91.2% had histological type squamous cells. The mean number of LNs collected was 4 (0-49) and 10 (7-37) in patients with pelvic and para-aortic LN involvement, respectively. Para-aortic LN was positive in 9 patients and negative in 48 patients according to ROC analysis. Para-aortic LN involvement was predicted by metastatic pelvic LN cut-off diameter of 0.75 cm with 100% sensitivity and 89.6% specificity [AUC=0.959, p=0.001 [95% CI, 0.912-1.000].

Conclusion: The cut-off for pelvic LN dissection and metastatic pelvic LN diameter in locally advanced cervical cancer was accepted as 0.75 cm for predicting para-aortic LN involvement.

Keywords: Cervix Cancer, Lymph Node Diameter, Prediction, Surgery

ÖZET

Amaç: Lokal ileri servikal kanserli hastalarda metastatik pelvik lenf nodu (LN) çapına göre para-aortik lenf nodu lenf nodu metastazının tahmininin araştırılması.

Gereç ve Yöntemler: 28 Aralık 2010 ile 30 Mart 2021 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi'nde lokal olarak ilerlemiş servikal kanserli 57 hasta (2B-4A 2018 FIGO) bu retrospektif analize dahil edildi. Cerrahi evreleme ve sonuçları olan hastalarda pelvik ve para-aortik LN tutulumu değerlendirildi.

Bulgular: 57 hastanın ortalama yaşı 56 [33-78] yıldı. Hastaların %73,7'si evre 2b, %12,3'ü evre 3 ve %14,0'ı evre 4a idi. Örneklerin %91,2'sinde histolojik tip skuamöz hücreler vardı. Pelvik ve para-aortik LN tutulumu olan hastalarda toplanan ortalama LN sayısı sırasıyla 4 [0-49] ve 10 [7-37] idi. ROC analizine göre para-aortik LN 9 hastada pozitif, 48 hastada negatifti. Para-aortik LN tutulumu %100 duyarlılık ve %89,6 özgüllük ile 0,75 cm'lik metastatik pelvik LN kesme çapı ile tahmin edildi [AUC=0,959, p=0,001 [95% CI, 0,912-1,000].

Sonuç: Lokal ileri servikal kanserde pelvik LN diseksiyonu ve metastatik pelvik LN çapı için kesme değeri, para-aortik LN tutulumunu tahmin etmek için 0,75 cm olarak kabul edildi.

Anahtar Sözcükler: Serviks Kanseri, Lenf Nodu Çapı, Tahmin, Cerrahi

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INTRODUCTİON

Cervical cancer is the fourth most common female cancer among gynecological cancers in terms of morbidity and mortality (1). The most common histological types are squamous cell types (about 70%), along with adenocarcinoma (25%) and other rare types (5%) (2). The cervical cancer FIGO staging system was recently revised and patients with pelvic and para-aortic lymph node (LN) metastases proven by imaging or histopathology were classified as stage IIIC1 and stage IIIC2, respectively (3). Extended field radiation chemotherapy treatment is applied in cases with para-aortic lymphatic spread (4).

LN involvement is one of the primary prognostic factors in locally advanced cervical cancer (5,6). Five-year event-free survival is approximately 57% in LN-negative patients, whereas it decreases to 34% and 12% in pelvic-positive and para-aortic LN-positive patients, respectively (7). Para-aortic LN involvement is found in 17-24% of locally advanced cervical cancer patients (8). Para-aortic LN metastases are present in 15% [1B2/2B FIGO 2009] and 40% [3B/4 FIGO 2009] patients with locally advanced cervical cancer (9). The major challenge in locally advanced cervical cancer is identifying patients with para-aortic LN metastases who may be candidates for ancillary therapy with extended field radiotherapy or chemotherapy or immunotherapy after standard chemoradiation (10).

Cervical cancer spreads primarily to regional pelvic LNs. Pelvic LN involvement is a known risk factor for para-aortic LN metastasis. Para-aortic LN involvement generally occurs as a result of extensive pelvic LN metastases (11-14) . Rarely, para-aortic LN metastasis can occur without pelvic LN metastasis. The possible route of spread may be the posterior cervical trunk, which drains into sacral LNs, common iliac LNs, and para-aortic LNs, but cervical cancer cells spread primarily with pelvic lymphatics before reaching the para-aortic LNs (15). We aimed to investigate histopathological metastatic pelvic lymph node diameter for predicting para-aortic lymph node metastasis in patients with locally advanced cervical cancer.

METHODS

In this retrospective study, 57 patients diagnosed with locally advanced cervical cancer [IIB-IVA 2018 FIGO] between 28 December 2010 and 30 March 2021 in our clinic were included in the study (16). Pelvic and para-aortic LN involvement of all the patients with surgical staging and outcomes were evaluated. This study was approved by Selçuk University Faculty Of Medicine, Ethics Committee with protocol number 2022/337.

The cases were evaluated according to age, surgical stage, histological type [squamous and non-squamous] and lymph node status [number of pelvic and para-aortic lymph nodes, metastasis and diameter]. Inclusion criteria were histological diagnosis of stage IIB-IVA and squamous and non-squamous type carcinoma according to the FIGO 2018 system (17). Exclusion criteria were non-surgical staging and without pelvic and para-aortic lymph node dissection. Signed values are not taken into account. The histopathological results were evaluated according to pelvic and para-aortic LN involvement after extraperitoneal LN dissection. The short-axis diameter of metastatic pelvic LNs was measured in mm.

2.1 Pelvic and para-aortic lymph node surgical staging

Extraperitoneal LN dissection with a laparotomic J incision was performed in all patients. When

entering the abdomen, pelvic lymphadenectomy was performed in both external iliac, obturator and bilateral common iliac lymph nodes. Para-aortic lymphadenectomy was performed in the aortacaval space, vena cava and left and right para-aortic area, up to the left renal vein, and caudally up to both common iliac bifurcation and both psoas muscles.

2.1.1 Statistical analysis

SPSS version 21 [IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA] was used for all statistical computations. Categorical variables are presented as frequencies and percentages, while quantitative variables are given as median and minimum-maximum. ROC analysis was performed for the cut-off, sensitivity and specificity of the data. Statistical significance was accepted as $p<0.05$.

RESULTS

The median age of 57 patients included in the study was 56 [33-78] years (Table 1). Of patients, 73.7% were evaluated as stage 2b, 12.5% as stage 3 and 13.3% as stage 4a. Squamous cell histological type was detected in 91.2%. Pelvic and para-aortic LN involvements were detected in 10 [17.5%] and 9 [15.8%] patients, while the median number of LNs collected was 4 [0-49] and 9 [0-35], respectively. Metastatic LN involvements were detected only in the pelvic area in 5 [8.8%] patients, only in the para-aortic area in 4 [7,0%] patients, and in the pelvic and para-aortic areas in 5 [8.8%] patients.

In the ROC analysis, para-aortic LN was positive in 9 patients and negative in 48 patients (Figure 1). When the metastatic pelvic LN diameter cut-off was accepted as 0.75 cm, the sensitivity was 100% and specificity was 89.6% for predicting para-aortic LN involvement [AUC=0.959, p=0.001 [95% CI, 0.912 1.000]. If the metastatic pelvic LN diameter cut-off was assumed to be 1.55 cm, sensitivity of 88.9% and specificity of 91.7% were found. If the diameter cut-off was 2.1 cm, the sensitivity was 77.8% and the specificity was 93.8%, and if the diameter cut-off was 3.1 cm, the sensitivity was 44.4% and the specificity was 97.9% for predicting para-aortic LN metastasis.

Table 1: Characteristics of cases according to 2018 cervical cancer staging

Variables		[n=57] Median	[%]
Age, years		56 [33-78]	
Stage			
	IIb	42	73.7
	III	7	12.3
	IVA	8	14.0
Histologic type			
	Squamous	52	91.2
	Non-squamous	5	8.8
Pelvic lymph node involvement, n		10	17.5
Total pelvic lymph node count		5 [0-49]	
Para-aortic lymph node involvement, n		9	15.8
Total para-aortic lymph node count		10 [7-37]	
Lymph node involvement, n			
	Pelvic	5	8.8
	Para-aortic	4	7.0
	Pelvic and para-aortic	5	8.8

n=number of patients

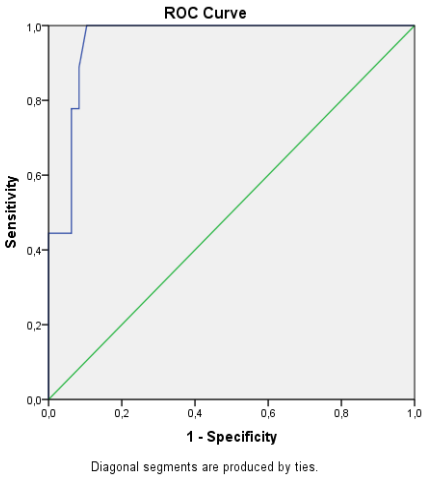


Figure 1: *ROC analysis of metastatic lymph node diameter in predicting para-aortic lymph node involvement*

DISCUSSION

Currently, since LN involvement is accepted as a prognostic factor in cervical cancer, treatment of cervical cancer is planned according to LN involvement. However, pelvic and para-aortic LN involvement is detected by imaging methods or surgically by pathological diagnosis (16). When evaluating LN involvement, studies evaluating para-aortic LN metastasis according to metastatic pelvic LN diameter surgically and giving a metastatic pelvic LN cut-off value are limited. In this study, the prediction of para-aortic lymph node involvement by metastatic pelvic lymph node diameter after extraperitoneal LN dissection was investigated in locally advanced cervical cancer. 9 patients must have had paln due to the rarity of the cases.

While para-aortic LN metastasis is thought to be correlated with pelvic LN metastasis, the skip LN metastasis rate is reported to be below 4% in studies (18,19). The study by Ayhan et al. (20) 522 patients, 2009 FIGO stage IB1-IIA2] included cases with aver age of 50 years med[23-81], 79.1% squamous cell histological type, and 37% stage 3c. They collected median pelvic LN number of 30.0 [10–97] and median para-aortic LN 11.0 [5–52] and identified pelvic LN metastasis in 190 patients [36.4%], para-aortic LN metastasis in 48 patients [9.2%], isolated para-aortic LN metastasis in 4 patients [0.8%] and both pelvic and para-aortic LN metastases in 44 patients [8.4%]. In this study, the median of the patients was 56 med [33-78] years, 12.3% of the patients were stage 3, 91.2% squamous cell histological type with pelvic and para-aortic LN involvement in 10 [16.7%] and 9 [15.0%] patients, respectively. The median number of LNs collected was 4 [0-49] and 9 [0-35], respectively. Metastatic LN involvement was detected only in the pelvic area in 5 [8.8%] patients, only in the para-aortic area in 4 [7.0%] patients, and in the pelvic and para-aortic areas in 5 [8.8%] patients. The significant difference between these studies is due to including locally advanced cervical cancer patients and the low number of patients in our study.

Because of the higher incidence of para-aortic LN metastases in the case of pelvic LNs, para-aortic lymphadenectomy or sampling is recommended when suspicious enlargement of the pelvic LNs is found by intraoperative palpation (21). Tsuruga et al. observed a positive effect of para-aortic lymphadenectomy on the surgical treatment of cervical cancer with extensive iliac LN metastases. Intraoperative frozen analysis can be a useful method to identify diffuse iliac LN metastases during surgery (22) . In the study by Matsuo et al., (11) the incidence of intraoperative ≥1 cm metastasized LN or multiple pelvic LN metastases and para-aortic LN was 16.7% and 18.2%, respectively. Likewise, Ayhan et al. [20] reported that metastatic pelvic LN size >1 cm [OR: 4.51, 95% CI: 1.75–11.64; p = 0.002] was among the independent risk factors identified for para-aortic LN involvement. Moreover, this

result suggests that patients with pelvic LN metastases may be best suited for para-aortic LN dissection as a diagnostic procedure, given that the benefits of staging surgery should outweigh any possible morbidity[23]. It is worth noting that while a positive common iliac LN strongly suggests para-aortic LN status, negative common iliac LN does not necessarily guarantee negative para-aortic LN. Likewise, in the study by Gouy et al.(13) , para-aortic LN involvement was observed in the histological analysis of 22 patients [9%] in LACC, while PET/CT results in false negatives. The false negative rate in the para-aortic LN region was 18% [16/90] and 4% [6/150] in PET/CT in patients with and without pelvic LN involvement, respectively. Likewise, Benedetti-Panic et al. found 80% of metastatic LNs were <1.0 cm in greatest dimension in LN-positive cervical carcinoma patients[24]. Belhocine et al. (25) found 80% [8 LN] of their metastatic LNs were micrometastatic LN and only 2 LN >1.0 cm. In addition, in the systematic review and meta-analysis by Thelissen et al.(26) , in the absence of suspicious para-aortic LNs on PET-CT or MRI, para-aortic LN dissection occurred in 11-12% of all patients with LACC and 21% of patients with pelvic LN metastases. They concluded that patients with pelvic LN metastases had significantly higher staging rate after para-aortic LN dissection than an unselected cervical cancer case group [21% vs 11-12%], confirming the predictive power of pelvic LN involvement for para-aortic LN involvement. In the light of the literature, pelvic LN dissection may be chosen under suitable conditions, because it has high predictive value for para-aortic LN involvement. In this study, para-aortic LN was positive in 9 patients and LN was negative in 48 patients. When the cut-off diameter of the metastatic pelvic LN was accepted as 0.75 cm, the sensitivity was 100% and the specificity was 89.6% for predicting para-aortic LN involvement. The significant difference in the studies is related to the surgical evaluation of LNs. Evaluation of pelvic lymph node metastasis to predict peroperative para-aortic lymph node metastasis may provide inspiration for further studies.

The limitations of this study are that it is retrospective, included a small number of patients, the diameter of lymph nodes was measured on the formalin-fixed paraffin-embedded samples and not fresh or frozen, and it included a single center. The strengths of the study are that all patients had surgical dissection of locally advanced LN, and metastatic LN diameters were examined with ROC analysis to predict para-aortic LN involvement. As a result, the cut-off value of metastatic pelvic LN diameter for the prediction of paraaortic LN metastasis in locally advanced cervical cancer can be accepted as 0.75 cm.

The findings of this study demonstrate that setting the metastatic pelvic lymph node (LN) diameter threshold at 0.75 cm provides a highly valuable clinical marker for predicting the risk of para-aortic LN metastasis in patients with locally advanced cervical cancer. Based on ROC analysis, this cut-off value yielded a sensitivity of 100% and a specificity of 89.6% in identifying para-aortic LN involvement, indicating that it is both a reliable and balanced predictor—capable of detecting all true positive cases while keeping the false positive rate low. This suggests that the 0.75 cm threshold can serve as a key criterion in determining which patients may benefit from surgical evaluation of the para-aortic region during staging procedures.

From a clinical perspective, the 0.75 cm metastatic pelvic LN cut-off has the potential to play a critical role in standard treatment planning. In particular, in cases where

suspicious enlargement of pelvic LNs is detected intraoperatively, this measurement can help guide the decision to perform para-aortic lymphadenectomy or sampling. By applying this criterion, unnecessary surgical interventions—and the associated risk of morbidity—can be minimized, while ensuring that patients with para-aortic metastases are correctly identified and directed toward the appropriate treatment field. Furthermore, this finding highlights that histopathological measurements can serve as a valuable complement to imaging modalities, especially in situations where imaging alone may not provide sufficient accuracy for decision-making.

CONCLUSİON

In conclusion, adopting the 0.75 cm metastatic pelvic LN diameter as a threshold offers a practical, evidence-based, and highly accurate parameter for guiding both surgical staging and diagnostic para-aortic lymphadenectomy. This measure represents a simple yet effective prognostic tool that clinicians can confidently integrate into individualized patient management strategies.

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