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Risk factors for lymph node involvement in early-stage cervical cancer: A retrospective cohort study

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Abstract

One of the most important prognostic factors in cervical cancer is lymph node involvement that affects disease-free survival and plays an important role in the treatment. This study aimed to determine the factors affecting lymph node involvement in early stage cervical cancer. A total of 169 cervical cancer patients with stage IA2-IIA2 were enrolled. Age, histologic subtype, deep stromal invasion (DSI), largest tumor diameter (LTD), lymphovascular space invasion (LVSI), vaginal surgical margin, ovarian metastasis status, parametrial involvement, lymph node count and presence of metastasis were retrospectively reviewed. All of these parameters are divided into two groups: LNM positive (group 1) and negative (group 2). The median age of the patients was 52 (26-77) years. In the univariate regression analysis; LVSI ($p < 0.001$), DSI ($p=0.018$), parametrial involvement ($p = 0.001$), and vaginal surgical margin positivity ($p = 0.020$) were in statistically significant correlations with lymph node involvement. In multivariate regression analysis, LVSI [51/118 (43.2%) vs 7/51 (13.7%), OR = 3.9, $p = 0.003$] and parametrial involvement [(16/24 (66.6%) vs 42/145 (28.9%), OR = 3.9, $p = 0.009$] were the independent risk factors for lymph node metastasis. LVSI and parametrial involvement are two crucial risk factors for lymph node metastasis in patients diagnosed with early-stage cervical cancer.

Keywords: cervical cancer, lymph-vascular space invasion, lymph node metastasis, risk factors

1. Introduction

Cervical cancer is an important public health issue, ranking fourth leading cause of cancer-related deaths among women globally (1). The treatment options for cervical cancer vary based on the stage of the cancer, with radical hysterectomy and pelvic lymph node dissection serving as the standard approach in early-stage cases (2).

Lymph node involvement emerges as a critical prognostic factor in early-stage cervical cancer that affects disease-free and overall survival. Lymph node metastasis (LNM) is a vital determinant of survival (3). The incidence of LNM ranges between 4.3% and 19.6% in early-stage cervical cancer (4). Surgical staging of lymph nodes represents the preferred method both for management and prognostication in early-stage cervical cancer (5). Debates persist on whether lymphadenectomy should be done for all patients and the extent of the radicality of the surgery (6,7). The therapeutic benefit of lymphadenectomy in early-stage cervical cancer remains controversial (8).

Sentinel Lymph Node (SLN) mapping and biopsy have recently gained popularity in gynecological oncology, particularly in vulvar cancer and cervical cancer, as an alternative method to identify the status of lymph node metastasis (9). However, this technique requires specific equipment and trained personnel making it unfeasible in various settings, particularly in developing nations with high cervical cancer prevalence.

This study aims to identify factors influencing lymph node involvement in early-stage cervical cancer and to propose avenues for future research to identify low-risk cervical cancer cases that may not require lymphadenectomy.

2. Materials and Methods

This retrospective cohort study was carried out between September 2008 and January 2018, on 169 patients with stage IA2-IIA2 cervical cancer who underwent radical hysterectomy and systematic bilateral pelvic-paraaortic lymph node dissection at a tertiary hospital. The study was approved by the

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Board of Medical Speciality Education at the University of Health Sciences, Zekai Tahir Burak Women's Research and Training Hospital and was in agreement with Declaration of Helsinki (Approval number:8, date:05.12.2017). This study included patients who had complete medical records and regular post-operative follow-up Patients who did not have systematic lymph node dissection, those with incomplete medical records, those without regular follow-up, those who underwent only simple hysterectomy (stage IA1), and those with advanced cervical cancer (IIB-IVB) were excluded.

In order to determine the factors that influence lymph node metastasis, an analysis was conducted on the demographic and clinicopathological characteristics of patients. We classified patients into two groups: group 1 had lymph node metastasis, while group 2 did not. The study analyzed parameters such as age, histology, International Federation of Gynecology and Obstetrics (FIGO) stage (2009), deep stromal invasion (DSI), largest tumor diameter (LTD), lymphovascular space invasion (LVSI), positive surgical margins in the vagina, status of ovarian metastasis, parametrial involvement, quantity of lymph nodes, and the status of metastasis. The clinical stage and histological classification of the patients were assessed according to the FIGO 2009 guidelines (10). All procedures were conducted by surgeons specializing in gynecological oncology. The pelvic lymphadenectomy involved extracting the lymph nodes of iliac and obturator arteries. Similarly, the para-aortic lymphadenectomy involved eliminating lymph nodes above the inferior vena cava and aorta up to renal vein. Systematic lymphadenectomy was characterized by the removal of a minimum of 15 lymph nodes. For a thorough pelvic and para-aortic lymph node dissections, the removal of at least 10 and 5 lymph nodes were considered adequate. The study accounted for the largest of the three diameters of the tumor observed macroscopically by the gynecopathologist. The presence of tumor cells in the endothelium of lymphatic or vascular structures supplying the tumor defined LVSI, while DSI was described as tumor invasion into the outer third of the cervical stroma.

2.1. Statistical Analysis

To determine the distribution of data, the Kolmogorov-Smirnov normality test was conducted. Descriptive statistics were used to obtain the median, minimum, and maximum values. The categorical variables were compared between groups via the $\chi 2$ test. The Independent T test was utilized to examine parametric data. For pairwise comparisons, numerical variables were evaluated using the Mann-Whitney U test. Univariate and multivariate regression analyses identified risk factors for LNM and to calculate relative risks. All variables were expressed with 95% confidence intervals (CI). Data were processed using the Statistical Package for Social Sciences (SPSS) version 21 (IBM Corp., Armonk, N.Y.; USA). A p value of less than 0.05 was accepted as statistically significant.

3. Results

A total of 169 patients were involved in the research and were split into two groups: non-LNM (group 2, n: 111, 65.7%) and LNM (group 1, n: 58, 34.3%). Age, the number of lymph nodes, stage, and histological subtype did not differ between the groups (p>0.05) (Table 1).

Table 1. Comparison of patients according to the lymph node metastasis

		LNM (+) *n*: 58	LNM (-) *n*: 111	*p-value*
Age		49.5 (32-70)	52 (26-77)	0.120*
Number of pelvic lymph nodes		43 (14-97)	39 (14-92)	0.471*
Number of paraaortic lymph nodes		12.5 (5-41)	12 (5-45)	0.130*
Total number of lymph nodes		58 (20-138)	51 (24-119)	0.252*
Pelvic lymph node metastasis		2 (1-43)	NA	NA
Paraaortic lymph node metastasis		0 (0-33)	NA	NA
Total number of lymph node metastases		2 (1-73)	NA	NA
Histology	SCC	44	0.306**	0.306
	Adenocarcinoma	7	20	
	Adenosquamous carcinoma	7	7	

SCC: Squamous cell carcinoma LNM: Lymph node metastasis NA: Not applicable, *:Mann-Whitney U, **:$\chi 2$ test
P<0.05 was considered statistically significant.

In univariate analysis, tumor size (*OR*=1.02, 95% *CI*: 1.01–1.04, P=0.004), LVSI (*OR*=8.3, 95% *CI*: 3.3–20.6, P=0.001), DSI (*OR*=3.6, 95% *CI*: 1.4–9.2, P=0.007), LTD ≥4 cm (*OR*=4.3, 95% *CI*: 1.5–12.2, P=0.007), parametrial involvement (*OR*=1.06, 95% *CI*: 1.00–1.12, P=0.021), and positive vaginal margins (*OR*=3.6, 95% *CI*: 1.7–7.8, P=0.0001) were significantly associated with lymph node metastases (Table 2).

In binary multivariate logistic regression analysis, LVSI (*OR*=6.3, 95% *CI*: 2.4–16.5, P=0.0001) and parametrial involvement (*OR*=2.6, 95% *CI*: 1.6–6.0, P=0.020) were significantly associated with lymph node metastases (Table 3).

4. Discussion

Our study sought to identify risk factors for lymph node metastasis in stage IA2-IIA2 cervical cancer. We found that LVSI and parametrial involvement were significant factors linked to lymph node metastasis.

Lymph node metastasis had prognostic significance in

early-stage cervical cancer. Several clinicopathological parameters, including advanced stage (11), large tumor size (3, 11), LVSI (3,11,12), DSI (13-15) and parametrial involvement (3), have been identified as potential indicators of LNM in cervical cancer. Our analysis found that LVSI and parametrial involvement were significantly related to LNM. However, we observed a higher rate of LNM than previously reported in the literature. One possible explanation is that most of our patients had tumors larger than 2 cm. Moreover, the FIGO staging system was revised in 2018, taking into account any imaging modality or pathological findings to allocate the stage. As a result, some of our patients previously classified in lower stages have now been upstaged to stage IIIC.

Table 2. Univariate regression analysis for Lymph node metastasis (LNM)

	Estimate	SE	Z	OR (95% CI)	P-value
Age	-0.0157	0.0130	-1.204	0.98 (0.96-1.01)	0.229
Tumor size	0.0250	0.00879	2.84	1.02 (1.01-1.04)	**0.004***
Total number of lymph nodes	0.00231	0.00665	0.347	1.0 (0.99-1.0)	0.729
Age >52	-	-	-	0.674 (0.421-1.08)	0.101
LVSI (+)	-	-	-	8.3 (3.3-20.6)	**0.0001***
DSI (+)	-	-	-	3.6 (1.4-9.2)	**0.007***
LTD ≥2 <4 cm ≥4 cm	-	-	-	 2.5 (0.8-7.3) 4.3 (1.5-12.2)	 0.094 **0.007***
Parametrial Involvement (+)	-	-	-	3.6 (1.7-7.8)	**0.0001***
Vaginal Surgical Margin	-	-	-	2.0 (0.8-5.2)	0.156

*LTD: Largest tumour diameter. DSI: Deep stromal invasion. LVSI: Lymphovascular space invasion. OR: Odds Ratio SE: Standart Error (SE), CI:C*onfidence Interval, **:P<0.05 was considered statistically significant*

Table 3. Multivariate regression analysis for Lymph node metastasis (LNM)

Independent variables	OR (95% CI)	P-value
Age >52	0.84 (0.42-1.67)	0.617
LVSI (+)	6.3 (2.4-16.5)	**0.0001***
DSI (+)	0.6 (0.2-1.9)	0.421
LTD ≥2 <4 cm ≥4 cm	 1.7 (0.5-5.7) 3.0 (0.9-10.0)	 0.407 0.078
Parametrial Involvement (+)	2.6 (1.6-6.0)	**0.020***
Vaginal Surgical Margin	1.2 (0.4-3.6)	0.681

SE: Standart Error (SE), OR:Odds Ratio, CI:Confidence Interval, LTD: Largest tumour diameter. DSI: Deep stromal invasion. LVSI: Lymphovascular space invasion, +: positive;
*Reference for age : ≤52, reference for LTD: <2 cm, reference for LVSI, DSI, Parametrial Involvement, and Surgical margin: negative; *:P<0.05*

Roman et al. conducted a study that revealed none of the patients with negative LVSI had pelvic LNM, indicating a significant correlation (p=0.0001) (16). Similarly, Sakuragi et al. analyzed LVSI and LNM correlation in their study and found that lymphatic and blood vessel invasion separately caused an increase in LNM positivity from 9.4% when LVSI was negative to 43% when LVSI was positive (p<0.0001) (17). Our findings align with those of Sakuragi et al., with 43.2% (51/118) LNM in LVSI-positive and 13.7% (7/51) in LVSI-negative patients.

In a study of 399 cases of early cervical cancer, 32 patients (12.4%) were found to have parametrial invasion, the majority of which were squamous cell carcinoma (18). This finding is consistent with our study, in which 14.2% (24/169) of patients were found to have parametrial invasion.

Although this study has a few drawbacks, including its retrospective design, limited sample size, and absence of central histopathological examination, it has several strengths. All patients underwent surgery by a gynecological oncologist, and all pathological examinations were conducted by an experienced gynecopathologist.

Our study found that LVSI and parametrial invasion are significant risk factors for lymph node metastasis in early-stage cervical cancer.

Conflict of interest

The authors have no conflicts of interest.

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Authors' contributions

Concept: U.E., V.K., B.Ö., Design: U.E., V.K., K.A., B.Ö., Data Collection or Processing: U.E., V.K., K.A., B.Ö., Analysis or Interpretation: U.E., V.K., E.K., K.A., B.Ö., A.B., Literature Search: U.E., V.K., E.K., K.A., B.Ö., Writing: U.E., V.K., E.K., K.A., B.Ö.

Ethical Statement

The database management in accordance with privacy legislation and the presented study in accordance with the ethical principle of the Declaration of Helsinki. Ethical approval for this study was obtained by the the Board of Medical Speciality Education at the University of Health Sciences, Zekai Tahir Burak Women's Research and Training Hospital (Approval number:8, 05.12.2017). The work has not been published previously and it is not under consideration for publication elsewhere.

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