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Predictive factors of lymph node metastasis in patients with 2014 figo stage Ib1-IIa2 cervical squamous cell cancer: A multicentric study

Okan Aytekin[1], Necim Yalcin[2], Hande Esra Koca Yildirim[3], Mehmet Unsal[1], Okan Oktar[3], Fatih Celik[1], Abdurrahman Alp Tokalioglu[1], Mustafa Gokkaya[2], Dilek Yuksel[3], Caner Cakir[3], Cigdem Kilic[3], Ilker Selcuk[1], Gunsu Kimyon Comert[1], Tayfun Toptas[2], Vakkas Korkmaz[3], Isin Ureyen[2], Alper Karalok[4], Derman Basaran[5] Sevgi Koc[3], Tolga Tasci[6], Taner Turan[1]

[1] Department of Gynecologic Oncology, Faculty of Medicine, University of Health Sciences, Ankara Bilkent City Hospital, Ankara
[2] Department of Gynecologic Oncology, Faculty of Medicine, University of Health Sciences, Antalya Training and Research Hospital, Antalya
[3] Department of Gynecologic Oncology, Faculty of Medicine, University of Health Sciences, Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Ankara
[4] Department of Gynecologic Oncology, Ulus Lıv Hospital, Istanbul
[5] Department of Gynecologic Oncology, Faculty of Medicine, Hacettepe University, Ankara
[6] Department of Gynecologic Oncology, Faculty of Medicine, Bahcesehir University, Istanbul, Turkey

Abstract

Aim: The objective of this study is to identify the risk variables associated with lymph node metastasis (LNM) in individuals diagnosed with cervical squamous cell carcinoma (SCC).

Material and Methods: Cervical cancer patients who underwent type II/III radical hysterectomy and pelvic lymphadenectomy +/- para-aortic lymphadenectomy were analyzed.

Results: In total, 422 SCC patients were included in the cohort. Three hundred-twenty-three (76.5%) patients were stage IB1, 59 (14%) were stage IB2, 33 (7.8%) were stage IIA1, and 7 (1.7%) were stage IIA2. Eighty-seven (20.6%) patients had LNM only in the pelvic region, 2 (0.5%) patients in the paraaortic region, and 8 (1.9%) patients in both regions. In the multivariate logistic analysis, parametrial invasion (hazard ratio [HR]: 2.182, 95% confidence interval [CI]: 1.090–4.366, p=0.027), lymphovascular space invasion (LVSI) (HR: 6.300, 95% CI: 2.968–13.370, p<0.001) and deep stromal invasion (HR: 2.122, 95% CI: 1.088–4.139, p=0.027) were identified as significant risk factors for LNM.

Discussion: In summary, age, FIGO stage, tumor size, vaginal invasion, surgical border involvement, and uterine involvement were not identified as independent risk factors for LNM. However, parametrial invasion, LVSI, and deep stromal invasion are independent risk factors for LNM in stage IB1-IIA2 cervical SCC patients.

Keywords

Cervical Cancer, Lymph Node Metastasis, Parametrial Invasion, Deep Stromal Invasion, Lymphovascular Space Invasion

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Corresponding Author: Okan Aytekin, Department of Gynecologic Oncology, Faculty of Medicine, Ankara Bilkent City Hospital, University of Health Sciences, 06800, Ankara, Turkey.
E-mail: okanaytekin13@hotmail.com P: +90 536 662 49 59
Corresponding Author ORCID ID: https://orcid.org/0000-0002-6430-4607
Other Authors ORCID ID: Necim Yalcin, https://orcid.org/0000-0001-5980-3244 · Hande Esra Koca Yildirim, https://orcid.org/0000-0002-3715-9424
Mehmet Unsal, https://orcid.org/0000-0002-9920-6804 · Okan Oktar, https://orcid.org/0000-0002-9696-7886 · Fatih Celik, https://orcid.org/0000-0002-9523-180X
Abdurrahman Alp Tokalioglu, https://orcid.org/0000-0002-1776-2744 · Mustafa Gokkaya, https://orcid.org/0000-0002-0477-157X
Dilek Yuksel, https://orcid.org/0000-0002-2366-8412 · Caner Cakir, https://orcid.org/0000-0003-2559-9104 · Cigdem Kilic, https://orcid.org/0000-0002-4433-8068
Ilker Selcuk, https://orcid.org/0000-0003-0499-5722 · Gunsu Kimyon Comert, https://orcid.org/0000-0003-0178-4196 · Tayfun Toptas, https://orcid.org/0000-0002-6706-6915
Vakkas Korkmaz, https://orcid.org/0000-0001-8895-6864 · Isin Ureyen, https://orcid.org/0000-0002-3491-4682 · Alper Karalok, https://orcid.org/0000-0002-0059-8773
Derman Basaran, https://orcid.org/0000-0002-2689-1417 · Sevgi Koc, https://orcid.org/0000-0002-1703-0690 · Tolga Tasci, https://orcid.org/0000-0001-8645-4385
Taner Turan, https://orcid.org/0000-0001-8120-1143
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Introduction

Cervical cancer is a prominent malignancy affecting women globally, occupying the fourth position in terms of prevalence [1]. Squamous cell carcinoma (SCC) is the most prevalent histologic subtype of cervical cancer. Radical hysterectomy with pelvic lymphadenectomy is the standard approach for early-stage disease, while chemoradiotherapy is the standard treatment for advanced stages of the disease [2]. The addition of pelvic lymphadenectomy in the surgical management of early-stage cervical cancer is widely accepted. However, the appropriateness of para-aortic lymphadenectomy remains a subject of debate due to the associated risk of severe complications and the requirement for a high degree of surgical proficiency [3, 4].

Table 1. Clinical Features

Features		Mean±SD	Median (range)
Age at initial diagnosis		52±10.2	51 (26-80)
Tumor size (mm)		30.9±13	30 (6-80)
Number of removed lymph nodes		47±20.2	44 (10-128)
Number of metastatic lymph node		3±4.1	2 (1-31)
		n	%
FIGO 2014 stage	IB1	323	76.5
	IB2	59	14
	IIA1	33	7.8
	IIA2	7	1.7
Tumor size	≤20 mm	114	27
	>20 mm - ≤40 mm	248	58.8
	>40 mm	60	14.2
Parametrial invasion	Negative	357	84.6
	Positive	64	15.2
	Not reported	1	0.2
Surgical border involvement	Negative	398	94.3
	Positive	24	5.7
Vaginal invasion	Negative	352	83.4
	Positive	70	16.6
Lymphovascular space invasion	Negative	163	38.6
	Positive	241	57.1
	Not reported	18	4.3
Stromal invasion	<%50	137	32.5
	≥%50	265	62.8
	Not reported	20	4.7
Bilateral salpingo-oophorectomy	Not performed 1	83	19.7
	Performed	339	80.3
Adnexal metastasis 2	Negative	341	98
	Positive	2	0.6
	Not reported	5	1.4
Uterine invasion	Negative	341	80.8
	Positive	57	13.5
	Not reported	24	5.7
Lymph node metastasis	Negative	325	77
	Positive	97	23
Site of metastatic lymph node	Only pelvic	87	20.6
	Only paraaortic	2	0.5
	Pelvic and paraaortic	8	1.9

SD: Standard Deviation
1: Seventy-four patients received bilateral ovarian transposition and 9 patients had unilateral salpingo-oophorectomy and unilateral ovarian transposition
2: Seventy-four patients who underwent bilateral ovarian transposition were excluded and 348 patients were evaluated

Cervical cancer can spread directly to the vagina, parametrium, uterus, and nearby organs, such as the rectum and bladder. Furthermore, it disseminates through the lymphatic vessels to the nearby lymph nodes, such as the obturator, external iliac, and internal iliac nodes, and subsequently to the common iliac and paraaortic nodes. A late manifestation of the disease is hematogenous metastasis to the lungs, liver, and skeleton [5].

The presence of lymph node metastasis (LNM) is an important factor of prognosis in patients with cervical cancer [6]. The occurrence of pelvic LNM in individuals diagnosed with early-stage cervical cancer (stages IA1-IB1) has been documented to be approximately 15-20% [7, 8]. These patients have a poorer prognosis, and their 5-year survival rates are lower than those of patients without LNM [9, 10]. LNM is associated with the histological subtype, tumor size, parametrial invasion, deep stromal invasion, and lymphovascular space invasion (LVSI) [10, 11]. LNM was not included in the International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging system until 2018. In the latest classification, evaluation of lymph nodes by imaging and/or pathology is incorporated as stage IIIC disease. Stage IIIC1 is defined if LNM is in the pelvic lymph nodes, and stage IIIC2 if LNM is in the para-aortic lymph nodes [12].

In the present study, patients with stages IB1, IB2, IIA1 and IIA2 SCC had radical hysterectomy and pelvic ± paraaortic lymphadenectomy. Our objective was to identify the prognostic markers associated with lymph node metastasis in patients with cervical SCC.

Material and Methods

The study was designed retrospectively. Cervical cancer patients who underwent type II/III radical hysterectomy and pelvic lymphadenectomy +/- para-aortic lymphadenectomy were analyzed at 6 gynecologic oncology centers between 1993 and 2022. The electronic database system, medical files, and pathology reports were utilized to obtain patient information. Patients who were not treated with a radical hysterectomy, those with microinvasive cancer, a non-squamous cell component in their tumors, synchronous primary tumors, and those receiving neo-adjuvant chemotherapy were excluded.

The following clinical data were collected: age, FIGO stage, the pathologic data (parametrial invasion, vaginal invasion, surgical border involvement, depth of stromal invasion, LVSI, uterine invasion, size of the tumor, lymph node status, adnexal metastasis). The tumor size was determined by the greatest tumor diameters. The clinical stage was evaluated in accordance with the FIGO 2014 criteria. Deep stromal invasion was defined as ≥½ stromal invasion. In hematoxylin and eosin stained pathologic sections, LVSI was described as tumor cells or cell clusters adhering to vascular walls containing both tumor and surrounding healthy tissue. The spread of the disease to the endometrium and/or myometrium above the level of the internal ostium has been defined as uterine invasion. The criterion for surgical border involvement was established as a measurement of less than 0.5 cm between the tumor and the termination point of the specimen. In contrast, vaginal metastasis was defined as the detection of the tumor in any

location within the vagina. The decision to include a bilateral salpingo-oophorectomy in the surgical procedure was based on factors such as the patient's age, the state of the ovaries, and the professional judgment of the surgeon. Depending on the presence of suspicious lymph nodes in the paraaortic region and the preference of the senior surgeon, paraaortic lymphadenectomy was added to the surgical procedure and was performed up to the level of the inferior mesenteric artery or left renal vein. All surgical procedures were performed by gynecological oncologists.

The effects of categorical variables on LNM were evaluated using Fisher's exact test or Pearson's Chi-square test, as applicable, to see whether they were statistically significant. With factors that were statistically significant in univariate analysis, a model for multivariate analysis was developed. Backward stepwise multivariate Cox proportional hazard regression analysis was utilized to identify the effects of LNM-influencing variables. A p-value less than 0.05 was determined to be statistically significant for the obtained results. Statistical Package for the Social Sciences (SPSS) for Windows version 22.0 was used to conduct statistical analyses.

Ethical Approval

This study was approved by the Ethics Committee of Ankara City Hospital (Date: 2022-11-09, No: E2-22-2777).

Results

In total, 422 SCC patients were included in the cohort. The size of the median tumor was 30 mm (range, 6-80) and the mean age of the patients was 52±10.2 years (range, 26-80). Three hundred twenty-three (76.5%) patients were stage IB1, 59 (14%) were stage IB2, 33 (7.8%) were stage IIA1, and 7 (1.7%) were stage IIA2. All patients underwent pelvic lymphadenectomy, while 389 patients (92.2%) underwent paraaortic lymphadenectomy. The median number of lymph nodes excised was 44. Ninety-seven (23%) patients had metastatic lymph nodes. The mean number of metastatic lymph nodes was 3±4.1 (range, 1-31). Eighty-seven (20.6%) patients had LNM only in the pelvic region, 2 (0.5%) patients in the paraaortic region, and 8 (1.9%) patients in both regions. Bilateral salpingo-oophorectomy was performed in 339 (80.3%) patients. There were 64 (15.2%) cases with positive parametrial invasion, 24 (5.7%) with surgical border involvement, 70 (16.6%) with vaginal invasion, 57 (13.5%) uterine invasion, 241 (57.1%) with LVSI, and 265 (62.8%) with deep stromal invasion. The clinical characteristics and surgical pathological outcomes of the patients were detailed in Table 1. In the univariate analysis, parametrial invasion, surgical border involvement, uterine invasion, deep stromal invasion, and positive LVSI were found to be associated with LNM (Table 2). However, age, tumor size, FIGO stage, and vaginal involvement were not associated with LNM. In the multivariate logistic analysis, parametrial invasion (hazard ratio [HR]: 2.182, 95% confidence interval [CI]: 1.090–4.366, p=0.027), LVSI (HR: 6.300, 95% CI: 2.968–13.370, p<0.001) and deep stromal invasion (HR: 2.122, 95% CI: 1.088–4.139, p=0.027) were identified as

Table 2. Factors predicting the lymph node metastasis

Factors		Univariate Analysis		Multivariate Analysis		
		Positive Lymph Node		Risk of Lymph Node Metastasis		
		Percentage	P value	Hazard Ratio	95% Confidence Interval	P value
Age 1	≤51 years	23.7	0.715			
	≥51 years	22.2				
Tumor size	≤20 mm	18.4	0.398			
	>20 mm - ≤40 mm	24.6				
	>40 mm	25				
Tumor size 1	≤30 mm	22	0.573			
	>30 mm	24.4				
FIGO 2014 stage	IB1	22.3	0.705			
	IB2	23.7				
	IIA1	30.3				
	IIA2	14.3				
FIGO 2014 stage	Stage I	22.5	0.476			
	Stage II	27.5				
Parametrial invasion	Negative	19.3	<0.001	1 (Reference)	1.090-4.366	0.027
	Positive	42.2		2.182		
Uterine involvement	Negative	21.1	0.042	1 (Reference)	0.506-2.120	0.924
	Positive	33.3		1.035		
Lymphovascular space invasion	Negative	6.1	<0.001	1 (Reference)	2.968-13.370	<0.001
	Positive	34.4		6.300		
Surgical border involvement	Negative	21.4	0.001	1 (Reference)	0.882-6.644	0.086
	Positive	50		2.421		
Vaginal involvement	Negative	21.6	0.127			
	Positive	30				
Stromal invasion	<%50	10.9	<0.001	1 (Reference)	1.088-4.139	0.027
	≥%50	29.8		2.122		

1: Median Value

significant risk factors for LNM (Table 2).

Discussion

This investigation analyzes the clinical and pathological characteristics of 422 patients diagnosed with stage IB1-IIA2 cervical SCC who underwent radical hysterectomy and lymphadenectomy. Additionally, the study investigates the relationship between LNM and these parameters. Deep stromal invasion, LVSI, and parametrial invasion were independent factors for LNM. Deep stromal invasion, LVSI, and parametrial invasion increased the incidence of LNM by more than twofold, sixfold, and twofold, respectively.

As predictors of LNM in cervical cancer, the following have been identified: The advanced stage [8, 13, 14], histology [8], larger tumor size [8, 13-17], LVSI [8, 13-18], deep stromal invasion [13-16, 18], parametrial invasion [13, 15, 18], older age [13, 17] and high level serum squamous cell carcinoma antigens (SCC-Ag) [13, 16]. In contrast, our study found no association between age, tumor size or FIGO stage and LNM.

The present study examined the prevalence of lymph node metastasis (LNM) in patients diagnosed with stage IB1, IB2, IIA1, and IIA2 cervical squamous cell carcinoma (SCC). The findings revealed LNM rates of 22.3%, 23.7%, 30.3%, and 14.3% for each stage. In the cervical SCC study presented by Yang et al., LNM metastases rates in stage IB1-2 and IIA1-2 were similar to our study [13]. In contrast to previous studies [8, 13, 14], stage was not found to be associated with LNM in our study. This may be explained by the fact that the stage IA2 group, where LNM is rarely seen, was not included in our study. Tumors larger than 2 cm were associated with an increased risk of LNM in a study by Togami et al. of patients with stages IA2-IIB cervical cancer [19]. Yang et al. found that a tumor diameter greater than 2 cm was statistically significant in the univariate analysis for LNM but not in the multivariate analysis [13]. In our study, however, tumor diameter was not found to be significant. In accordance with our study, Wang et al. reported that deep stromal invasion and LVSI were significantly associated with LNM in a multivariate analysis of cervical SCC [16]. Similarly, Zhou et al. demonstrated in a multivariate study of stages IA2, IB1, and IIA1 epithelial cervical carcinoma that deep stromal invasion and LVSI had a significant association with LNM [14].

In a multivariate analysis of cervical cancer, Nanthamongkolkul et al. and Togami et al. also reported that parametrial invasion was significantly associated with LNM [15, 19]. According to the study by Benedetti-Panici et al.[20], the parametrium is the initial location of extracervical spread, which could explain these results.

Limitation

The main limitation of this study is its retrospective design. In addition, the locations of lymph node involvement (external iliac, internal iliac, obturator, common iliac, and paraaortic nodes) are not specified. However, the study's strengths are its multicentric design and large patient population. Secondly, patients with only squamous cell types were included, whereas microinvasive patients were excluded. Thirdly, all surgical procedures were conducted by gynecological oncology specialists, and pathologic assessments were performed by expert gyneco-pathologists.

Conclusion

In summary, age, FIGO stage, tumor size, vaginal invasion, surgical border involvement, and uterine involvement were not identified as independent risk factors for LNM. However, parametrial invasion, LVSI, and deep stromal invasion are independent risk factors for LNM in stage IB1-IIA2 cervical SCC patients. Further clinical research can help to strengthen these results.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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