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Erken Evre Non-squamoz Hücreli Serviks Kanserli Hastalarda Lenf Nodu Metastazını Belirleyen Faktörler

Factors Determining Lymph Node Metastasis in Patients with Early Stage Non-Squamous Cell Cervical Carcinoma

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ÖZ

Amaç: Erken evre non-squamoz hücreli serviks kanserli hastaların klinikopatolojik özelliklerinin değerlendirilmesi ve lenf nodu metastazını predikte eden faktörlerin tanımlanması amaçlandı.

Gereçler ve Yöntem: Bu çalışmaya, altı jinekolojik onkoloji merkezinde, 1993-2022 yılları arasında, evre IB1-IIA2 non-squamoz hücreli serviks kanseri nedeniyle radikal histerektomi ve lenfadenektomi uygulanan hastalar retrospektif olarak dahil edildi. Risk faktörlerinin lenf nodu metastazı üzerine etkileri tek değişkenli ve çok değişkenli logistik regresyon analizi kullanılarak değerlendirildi.

Bulgular: Çalışmaya 126 hasta dahil edildi ve median yaş 48'di (aralık, 26-77 yıl). FIGO 2009'e göre hastaların 91'i (%72.2) evre IB1, 24'ü (%19), evre IB2, 9'u (%7.1) evre IIA1 ve ikisi (%1.6) evre IIA2'ydi. Tümör subtipi 93 (%73.8) hastada adenokarsinoma, 28 (%22.2) hastada adenosquamoz karsinomdu. Univaryant analizde; yaş, tümör boyutu, stromal invazyon, parametrial

ABSTRACT

Aim: To evaluate the clinical and pathological characteristics of early stage non-squamous cell cervical carcinoma (non-SCCC) patients and identify factors that predict lymph node metastasis.

Materials and method: Patients who underwent radical hysterectomy plus lymphadenectomy for stage IB1-IIA2 non-SCCC between 1993 and 2022 in six gynecologic oncology centers were included in this retrospective study. The effects of the risk factors on lymph node metastasis were evaluated by using univariate and multivariate logistic regression analysis.

Results: The study involved 126 patients with a median age of 48 years (range, 26-77 years). According to FIGO 2009 staging, 91 patients (72.2%) were at stage IB1, 24 (19%) were at stage IB2, 9 (7.1%) were at stage IIA1, and 2 (1.6%) were at stage IIA2. Tumor subtype were adenocarcinoma in 93 (73.8%) patients and adenosquamous carcinoma in 28 (22.2%) patients. In univariate analysis; age, tumor size, stromal invasion, parametrial invasion, uterine involvement,

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invazyon, uterin invazyon, lenfovasküler alan invazyonu (LVAİ), vajinal invazyon ve cerrahi sınır pozitifliği lenf nodu metastazı ile ilişkiliydi. Multivaryant analizde LVAİ (Hazard Ratio; 19.63, 95% Confidence interval: 3.499-110.166; p=0.001) ve uterin invazyon (Hazard Ratio; 4.36, 95% Confidence interval: 1.178-16.165; p=0.027) lenf nodu metastazı için bağımsız prognostik faktörler olarak tanımlandı.

Sonuç: Erken evre non-squamoz hücreli serviks kanserli hastalarda LVAİ ve uterin invazyon lenf nodu metastazının bağımsız belirleyicilerindendi. Bu faktörler preoperatif dönemde biyopsi örneklerinde ve görüntüleme yöntemlerinde yüksek doğruluk oranıyla tanımlanabilir.

Anahtar Kelimeler: Lenf nodu metastazı, lenfovasküler alan invazyonu, non-squamoz hücreli serviks kanseri, uterin invazyon.

lymphovascular space invasion (LVSI), vaginal involvement, and surgical border involvement were associated with lymph node metastasis. In multivariate analysis, LVSI (Hazard Ratio: 19.63, 95% Confidence Interval: 3.499-110.166; p=0.001) and uterine involvement (Hazard Ratio: 4.36, 95% Confidence Interval: 1.178-16.165; p=0.027) were identified as independent prognostic factors for lymph node metastasis.

Conclusion: LVSI and uterine involvement were independent predictors of lymph node metastasis in early-stage non-SCCC patients. These factors can be identified with high accuracy in biopsy specimens and imaging methods in the preoperative period.

Keywords: Lymph node metastasis, lymphovascular space invasion, non-squamous cell cervical carcinoma, uterine involvement

INTRODUCTION

Cervical carcinoma (CC) is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths in women worldwide. According to the 2020 GLOBOCAN data, there were approximately 600,000 new cases diagnosed annually, resulting in 340,000 deaths (1). Although high-income countries have been able to reduce the incidence and mortality rates of CC through vaccination and screening programs, it remains a significant health problem in low to middle-income countries (2).

In the early stages of cervical carcinoma, excellent survival outcomes are achieved with surgical and/or chemoradiotherapy. However, survival rates in local advanced stages are low. The most important prognostic factors determining survival are the stage of the disease and lymph node involvement (3-5). The FIGO has recently updated the clinical staging guidelines for cervical carcinoma in 2018, highlighting the importance of including the lymph node status in the staging process (6). Accurate identification of lymph node metastasis is essential in managing patients and selecting appropriate treatment modalities.

Squamous cell cervical carcinoma (SCCC) is the most prevalent histological subtype, accounting for approximately 70-80% of all cases (7). Non-squamous cell cervical carcinoma (non-SCCC) represents a group of diseases with different morphologies and prognoses. Its clinicopathological characteristics, oncological outcomes, and behavioral patterns differ from SCCC. In comparison with SCCC, non-SCCC is partially resistant to radiotherapy and more frequently leads to distant metastasis, resulting in a more unfavorable prognosis (8).

Our comprehensive knowledge about cervical carcinoma originates mainly from studies on SCCC patients, but there is limited data available specifically about pure non-SCCC patients. In this study, our primary aim was to evaluate the clinicopathological characteristics of non-SCCC patients. Subsequently, we aimed to identify the factors that predict lymph node metastasis in this patient group.

MATERIALS AND METHOD

This study included patients who underwent abdominal radical hysterectomy and bilateral systematic pelvic±para-aortic lymphadenectomy for 2009 FIGO stage IB1-IIA2 cervical carcinoma between 1993 and 2022 in six gynecologic oncology centers. Clinicopathological data of the patients were retrieved retrospectively from patient files or electronic databases. All patients were staged by bimanual examination under general anesthesia according to FIGO 2009 criteria before surgical treatment. Magnetic resonance imaging and/or computerized tomography were used when necessary. This study was approved by local ethical committee by the file number of E2-23-4901.

Patients with squamous cell cancer, mixed type cancer, non-e-

pithelial cervical cancer, synchronized cancer, micro-invasive cervical cancer, received neoadjuvant chemotherapy, didn't undergo pelvic lymphadenectomy and advanced cervical cancer (2009 FIGO stage IIB-IVB) were excluded. Histopathological evaluation was carried out according to 2020 World Health Organization (WHO) criteria (9). Cervical tumors were classified as; squamous cell carcinomas, adenocarcinomas, other epithelial tumors (carcinosarcoma, adenosquamous, undifferentiated and adenoid basal), mixed epithelial and mesenchymal tumors, and germ cell tumors. Tumor size was considered as the largest diameter of the tumor. Deep stromal invasion was defined as the stromal invasion of a tumor invading the outer half of the cervical stroma. Lymphovascular space invasion (LVSI) was defined as the tumoral cells or cell clusters holding on vessels' walls that were stained with hematoxylin and eosin in the pathologic sections containing both the tumor and the surrounding healthy tissue. Uterine involvement is defined as the spread of the disease above the internal os, involving endometrial and/or myometrial areas. Surgical border involvement is defined as when the tumor is located ≤0.5 cm from the distal end of the specimen. Vaginal involvement is defined as the presence of a tumor in any part of the vagina.

All operations were performed by gynecologic oncologists. Bilateral pelvic lymphadenectomy was performed to complete skeletonization, with all lymphatic tissue of the common, external and internal iliac vessels and the obturator fossa removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was the aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. The presacral lymphatic tissue was harvested separately. Each of common iliac, external iliac, internal iliac, obturator and presacral regions was included in the pelvic region. Para-aortic lymphadenectomy was added to the surgical procedure depending on the presence of suspicious lymph nodes in the paraaortic region and at the discretion of the senior surgeon, often performed up to the level of the inferior mesenteric artery. Bilateral salpingo-oophorectomy (BSO) was performed according to the patient's age and attending surgeon's discretion.

Statistics

Categorical variables are expressed as number and percentage and were analyzed using Pearson's Chi-square ($\chi 2$) test or Fisher's exact test for univariate analysis, as appropriate determine whether they had statistically significant effects on lymph node metastasis. Multivariate analysis was performed using a Cox proportional hazards model. Variables identified as risk factors in univariate analysis (p value <0.05) were used to create an exact logistic regression model. Hazard ratios with 95% confidence intervals were calculated. p value <0.05 was considered statistically significant for the results. Data analyses were performed by using Statistical Package for Social Sciences (IBM SPSS Inc, Chicago, IL, USA) version 20.0.

RESULTS

A total of 126 patients were enrolled in the study, with a median age of 48 years (range, 26-77 years). According to the FIGO 2009 classification, 91(72.2%) patients were staged as IB1, 24 (19%) as IB2, 9 (7.1%) as IIA1, and 2 (1.6%) as IIA2. Tumor subtypes were identified as adenocarcinoma in 93 (73.8%) patients and adenosquamous carcinoma in 28 (22.2%) patients. The median tumor size was 30 mm (range, 8-72 mm). Forty-five (35.7%) patients presented tumors ≤20 mm and 26 (20.6%) patients had tumors >40 mm.

The parametrial invasion was detected in 23 (18.3%) patients, surgical border involvement in 14 (11.1%) patients, vaginal involvement in 20 (15.9%) patients, lymphovascular space invasion (LVSI) in 57 (45.2%) patients, deep stromal invasion in 83 (65.9%) patients, and uterine involvement in 27 (21.4%) patients. Bilateral salpingo-oophorectomy was performed on 113 patients and 6 (5.2%) patients had .ovarian metastasis.

While pelvic lymphadenectomy was conducted in all patients, para-aortic lymphadenectomy was additionally performed in 121 (96%) patients. The median number of lymph nodes removed was 37 and ranged from 11 to 113. Lymph node metastasis was observed in 32 (25.4%)patients. Twenty-two (17.5%) patients showed metastasis solely in the pelvic region and 10 (7.9%) patients had metastasis in both the pelvic and para-aortic regions. Detailed information regarding clinical, surgical, and pathological factors is presented in Table 1.

Table 1. Clinical and surgico-pathological features

Characteristics		**Mean±SD**	**Median (range)**
Age at initial diagnosis		51.4±11.34	48 (26-77)
Tumor size (mm)		29.9±14.69	30 (8-72)
Number of removed lymph nodes		49.5±24.06	37 (11-113)
Number of metastatic lymph node		5.7±7.32	1 (1-37)
		n	**%**
FIGO 2009 stage	IB1	91	72.2
	IB2	24	19
	IIA1	9	7.1
	IIA2	2	1.6
Tumor type	Adenocarcinoma	93	73.8
	Others [1]	33	26.2
Tumor size	≤20 mm	45	35.7
	>20 mm - ≤40 mm	55	43.7
	>40 mm	26	20.6
Parametrial invasion	Negative	103	81.7
	Positive	23	18.3
Surgical border involvement	Negative	112	88.9
	Positive	14	11.1
Vaginal involvement	Negative	106	84.1
	Positive	20	15.9
Lymphovascular space invasion	Negative	59	46.8
	Positive	57	45.2
	Not reported	10	7.9
Stromal invasion	≤ %50	42	33.3
	> %50	83	65.9
	Not reported	1	0.8
Bilateral salpingo-oophorectomy	Not performed [2]	13	10.6
	Performed	113	89.7
Ovarian metastasis [3]	Negative	110	94.8
	Positive	6	5.2
Uterine involvement	Negative	94	74.6
	Positive	27	21.4
	Not reported	5	4
Lymph node metastasis	Negative	94	74.6
	Positive	32	25.4
Site of metastatic lymph node	Only pelvic	22	17.5
	Only paraaortic	-	-
	Pelvic and paraaortic	10	7.9

In univariate analysis, various factors were defined as statistically predictive of lymph node metastasis, including age, tumor size, stromal invasion, parametrial invasion, uterine involvement, LVSI, vaginal involvement, and surgical border involvement (Table 2).

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]	<48 years	14.3	***0.014***	1 (Reference)	0.732-9.721	*0.137*
	≥48 years	33.3		2.667		
Histopathology	Adenocarcinoma	26.9	*0.520*			
	Others	21.2				
FIGO 2009 stage	Stage I	23.5	*0.110*			
	Stage II	45.5				
Tumor size	≤20 mm	22.2	***0.022***			
	>20 mm - ≤40 mm	18.2				
	>40 mm	46.2				
Tumor size [1]	≤30 mm	21.8	*0.236*			
	>30 mm	31.2				
Tumor size	≤40 mm	20.6	***0.006***	1 (Reference)	0.601-10.942	*0.204*
	>40 mm	46.2		2.564		

Stromal invasion	≤%50	9.5	***0.003***	1 (Reference)	0.348-8.033	*0.520*
	>%50	33.7		1.673		
Parametrial invasion	Negative	18.4	***<0.001***	1 (Reference)	0.262-5.099	*0.848*
	Positive	56.5		1.156		
Uterine involvement	Negative	13.8	***<0.001***	1 (Reference)	1.178-16.165	***0.027***
	Positive	55.6		4.364		
Lymphovascular space invasion	Negative	3.4	***<0.001***	1 (Reference)	3.499-110.166	***0.001***
	Positive	45.6		19.633		
Vaginal involvement	Negative	20.8	***0.006***	1 (Reference)	0.610-14.088	*0.180*
	Positive	50		2.931		
Surgical border involvement	Negative	20.5	***<0.001***			
	Positive	64.3				

Three different categorizations were used for tumor size: (i) the cohort's median value (>30 mm), (ii) values stratified according to FIGO 2018 (≤20 mm, >20 mm - ≤40 mm, and >40 mm), and (iii) values stratified according to FIGO 2009 (>40 mm).

Correlations were examined among the factors found significant in univariate analysis. A high correlation was observed between surgical border involvement and vaginal involvement. Therefore, surgical border involvement was not included in the multivariate analysis model. Age (<48 years vs. ≥48 years), tumor size (>40 mm vs. ≤40 mm), parametrial invasion (positive vs. negative), uterine involvement (positive vs. negative), LVSI (positive vs. negative), vaginal involvement (positive vs. negative), and stromal invasion (>%50 vs. ≤%50) were used to create a model for multivariate analysis. According to this model, only LVSI (Hazard Ratio: 19.63, 95% Confidence Interval: 3.499-110.166; p=0.001) and uterine involvement (Hazard Ratio: 4.36, 95% Confidence Interval: 1.178-16.165; p=0.027) were identified as independent prognostic factors for lymph node metastasis in non-SCCC (Table 2).

DISCUSSION

One of the most important routes of spread in CC is lymph node metastasis. Lymph node metastasis plays a crucial role in determining the stage and management of the disease, as a significant prognostic factor. The 5-year overall survival (OS) rate is around 90% when there is no lymph node metastasis and it drops to 30-60% in the presence of lymph node involvement (10,11). Due to the prognostic importance of lymph node metastases, accurate identification of metastases before treatment allows the identification of CC patients who will not undergo surgery or who may benefit from adjuvant treatment (expanded field radiotherapy). In our study, we retrospectively examined the clinical and pathological characteristics of surgically treated stage IB-IIA non- SCCC patients and assessed factors predicting lymph node metastasis. The lymph node metastasis rate in our study was 25.4%. LVSI and uterine involvement were identified as independent factors predicting lymph node metastasis.

In early-stage CC, the standard surgical treatment is radical hysterectomy plus lymph node dissection. The goal of this surgical approach is to remove both macroscopic and potential microscopic metastases, identifying the patients that have metastasis and might benefit from postoperative adjuvant therapy. Studies report that lymph node metastasis rates in surgically treated stage IB-IIA CC patients range from 12% to 51% (2,3,11,12). However, the majority of removed lymph nodes are non-metastatic and due to the questionable contribution of lymphadenectomy in early stages to overall survival, unnecessary lymph node dissection can lead to complications like infections, nerve damage, lymphatic cyst formation, vascular injury, venous thromboembolism, and lower limb lymphedema. Accurate preoperative and intraoperative identification of lymph node status will prevent complications.

Various factors such as age, tumor size, LVSI, parametrial invasion, deep stromal invasion, histological type, and grade have been reported as independent prognostic factors for the risk of nodal metastasis, although there are inconsistencies in studies (2,3). Yanaranop et al. identified a lymph node metastasis rate as 11.9% in 251 stage IB1-IIA cervical adenocarcinoma patients. Authors defined in their multivariate analysis that lymphovascular space invasion (LVSI) and a tumor size larger than 2 cm were independent prognostic factors (13).

Recently, Cao et al. conducted a study that involved 975 stage IA-IIA CC patients and lymph node metastasis rate was 14.8%

(14). In their multivariate analysis, tumor size (>4 cm), LVSI, deep stromal invasion, and deep uterine involvement were identified as independent prognostic factors associated with lymph node metastasis. The authors noted that 74.3% of patients with lymph node metastasis had LVSI positivity in biopsy material, while in 5.3% of cases, LVSI was detected in subsequent pathology despite being falsely negative in the initial biopsy material. In a cohort study of stage IB CC patients, Zhao et al. found that parametrial invasion, LVSI and tumor size were associated with lymph node metastasis in multivariate analysis (15).

The number of studies showing an association between uterine involvement and lymph node metastasis, which was not given enough importance in the management of CC patients in the past and was not among the staging criteria, has increased in recent years. In our study, uterine involvement was defined as an independent factor predicting lymph node metastasis in multivariate analysis. Cao et al. categorized uterine involvement into three categories (endometrial, <50% myometrial invasion, ≥50% myometrial invasion). The authors reported that only deep myometrial invasion was an independent prognostic factor for predicting lymph node metastasis (14).

He et al. observed a 30.0% rate of lymph node metastasis in a group of 2212 stage IA-IIB CC patients (16). The rate of lymph node metastasis was 37. 7% in patients with uterine involvement and 27. 7% in those without (p<0. 001). The authors reported in their multivariate analysis that the presence of uterine involvement increased the likelihood of lymph node metastasis by approximately 1.6 times and by 2.3 times in adenocarcinoma histology. Yang et al. determined a lymph node metastasis rate of 15.8% in stage IA-IIA CC patients (17). The authors reported that lymph node metastasis was 44. 3% in the presence of uterine involvement and 5. 8% in the absence of uterine involvement (p<0. 001). Uterine involvement was defined as an independent prognostic factor in their multivariate analysis.

Due to the use of a clinical staging system instead of surgical staging in the staging and treatment of CC patients, pathologic confirmation of lymph node metastases in every patient is not acceptable. This method may delay a patient's adjuvant treatment and can lead to unnecessary morbidity, adversely affecting the oncological outcome. With the technological advances in recent years, preoperative evaluation of lymph nodes with imaging methods help to predict lymph node metastasis . However, imaging methods can lead to both false positive and false negative results and cause over- or under-treatment. Studies have reported 58%, 56% and 75% sensitivity and 92%, 93% and 98% specificity for CT, conventional MRI and PET-CT to detect lymph node metastasis in CC, respectively (3). Imaging methods have some limitations due to their moderate sensitivity.

The main limitation of our study is its retrospective design. Since the study cohort consisted of pure non-SCCC patients, it is more valuable in terms of outcomes in non-SCCC patients compared to heterogeneous patient groups in the literature. Other advantages of our study are that all surgical procedures were performed by expert gyneco-oncologists, lymphadenectomy was performed as complete pelvic plus paraaortic lymphadenectomy in almost all patients and pathology results were reported by experienced gynecopathologists.

In conclusion, LVSI and uterine involvement were independent predictors of lymph node metastasis in early stage non-SCCC patients undergoing surgery. These factors can be identified with high accuracy in biopsy specimens and imaging methods in the preoperative period. Due to the subjective nature of clinical staging in CC and limitations in imaging methods, in order to identify lymph node metastasis with a higher accuracy rate in the preoperative period, it would be useful to create models that include clinicopathologic factors and imaging methods. In this way, patients at high risk for lymph node metastasis can be directed to chemoradiotherapy, avoiding unnecessary surgical treatment and possible complications.

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