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Predictors of lymph node metastasis in early-stage cervical cancer
Erken evre serviks kanseri hastalarında lenf nodunu predikte eden faktörler

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ÖZ

Amaç: Serviks kanseri hastalarında lenf nodu metastazının (LNM) değerlendirmesi tedavinin bireyselleştirilmesi için önemli bir konudur. Çalışmamızın amacı, serviks kanserli hastalarda LNM'nin prediktif faktörlerini belirlemektir.

Gereçler ve Yöntem: Bu retrospektif çalışmaya, 2007'den 2019'a kadar Uluslararası Jinekoloji ve Obstetrik Federasyonu (FIGO) evre IB1-IIA2'nin serviks kanseri hastaları dahil edildi. LNM insidanslarıyla beraber tek ve çok değişkenli modellerde pelvik ve paraaortik LNM için risk faktörlerinin prediktif değeri belirlendi.

Bulgular: Çalışmaya dahil edilen 212 hastadan pelvik LNM olan hasta sayısı 81(%38.2), paraaortik LNM'li hasta sayısı 17(%8) idi. Serviks kanseri hastalarında multivariyant analize göre parametriyal tutulum (hazard ratio [HR]: 2.75, 95% confidence interval [CI], 1.18-6.40, p=0.019) ve lenfovasküler tutulum ([HR]: 3.83, 95% [CI], 1.76-8.38, p=0.001) pelvik LNM için bağımsız risk faktörleriydi iken paraaortik LNM için parametriyal tutulum bağımsız risk faktörüydü ([HR]: 3.62, 95% [CI], 1.20-10.98, p=0.023).

Sonuç: Serviks kanseri hastalarında pelvik LNM'nin prediktif faktörleri parametrial tutulum ve LVSI iken paraaortik LNM için prediktif risk faktörü parametrial tutulumdu.

Anahtar Kelimeler: Serviks kanseri, lenf nodu metastazı, risk faktörleri

ABSTRACT

Aim: An accurate assessment of a potential lymph node metastasis (LNM) is an important issue for the individual treatment of cervical cancer. The goal of the current retrospective study was to identify predictive factors of LNM in patients with cervical cancer.

Materials and Methods: In this retrospective study, from 2007 to 2019, patients with cervical cancer of the International Federation of Gynecology and Obstetrics (FIGO) stage IB1-IIA2 were included. Incidences of LNM were described, and the predictive value of the risk factors for pelvic and paraaortic LNM were determined in univariate and multivariate models.

Results: Among 212 patients, the number of patients with pelvic LNM was 81(38.2%), the number of patients with paraaortic LNM was 17(8%). Multivariate analysis revealed that the parametrial involvement (hazard ratio [HR]: 2.75, 95% confidence interval [CI], 1.18-6.40, p=0.019) and LVSI ([HR]: 3.83, 95% [CI], 1.76-8.38, p=0.001) were independent risk factors for pelvic LNM with cervical cancer patients. For paraaortic LNM parametrial involvement was independent risk factor on multivariate analysis ([HR]: 3.62, 95% [CI], 1.20-10.98, p=0.023).

Conclusion: The predictive factors of pelvic LNM in cervical cancer patients were parametrial involvement and LVSI and for paraaortic LNM was parametrial involvement.

Keywords: Cervical cancer, lymph node metastasis, risk factors

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INTRODUCTION

Lymph node metastasis (LNM) in cervical cancers was integrated for the first time in the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification. In this classification, LNM is defined as stage IIIC by imaging and pathological examination. LNM is the most important prognostic factor for cervical cancer patients and directly parallels the clinical stage (1). Risk factors that determine lymph node involvement also determine the prognosis of patients. Although some radiological imaging methods are used to determine lymph node involvement, surgical staging is performed because of their low reliability. The rate of detecting lymph node involvement with radiological imaging in patients with early stage cervical cancer is as low as 10 percent (2). Large meta-analysis concluded that the accuracy for computed tomography (CT), conventional magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in detecting LNM in women with cervical cancer sensitivity of 58%, 56% and 75% respectively (3).

Numerous factors for LNM in patients with cervical cancer have been studied over the years, including age, tumor size, stage, parametrial involvement, lymphovascular space invasion (LVSI), stromal invasion, vaginal involvement (4-6). Identification of pelvic and paraaortic lymph nodes involvement are crucial in its management, as it impacts not only prognosis but also choice for initial treatment after surgery and surgical approach as well (7).

The aim of the study was to identify rate of LNM in patients with pelvic and paraaortic lymph node involvement in cases operated for cervical cancer and the factors determining them.

MATERIALS AND METHODS

The cervical cancer patients who underwent radical hysterectomy according to the Wertheim-Okabayashi with bilateral pelvic and paraaortic lymphadenectomy evaluated between 2007-2019 at single gynecologic oncology center and permitted assessment of the nodal status. Women with stage IB1–IIA2 cervical cancer who underwent a radical hysterectomy with available results for pelvic and paraaortic lymph node status, epithelial and non-epithelial types and received any neoadjuvant chemotherapy as well as no synchronous malignancies at diagnosis were eligible for this study. In patients who received neoadjuvant chemotherapy (NACT) or underwent extraperitoneal or transperitoneal lymphadenectomy without hysterectomy were not included in the study. While those with unknown lymph nodes status were excluded.

This study was approved by the local ethics committee (2021/24). Demographic and clinicopathologic characteristics collected from medical records included age, FIGO stage, histologic type, depth of stromal invasion, tumor size (cm), LVSI (absent/present), parametrial involvement (absent/present), vaginal involvement (absent/present), lymph node status. Clinical stage and histological classification were based on the criteria established by the revised FIGO 2009. FIGO 2018 staging was not used because the patients could not be evaluated with preoperative imaging methods. Histopathologic evaluations were performed according to 2014 World Health Organization (WHO) criteria (8). Uterine cervical tumors were classified as squamous cell cancer (keratinizing, nonkeratinizing, papillary, warty, verrucous, basaloid, lymphoepithelial), adenocarcinoma (endocervical, mucinous, endometrioid, clear cell, serous, mesonephric, and villoglandular) and other types (adenosquamous, neuroendocrine, undifferentiated, adenoid basal and adenoid cystic). All patients had a complete bilateral pelvic lymphadenectomy along the common, the external and the obturator fossae. In addition, paraaortic lymphadenectomy was performed to determine the extent of the field for chemoradiation. The depth of cervical stromal invasion was measured in millimeters and then bisected. We defined deep cervical stromal invasion as a tumor invading the outer half of the cervical stroma. Risk factors of LNM were determined by univariate and multivariate analyses.

Data recording and statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Inc, Chicago, IL, USA) version 20.0. The normality of continuous variable distributions was evaluated using the Kolmogorov-Smirnov test. Categorical variables are expressed as number and percentage and were analyzed using Pearson's Chi-square ($\chi 2$) test or Fisher's exact test, as appropriate. The Mann-Whitney U test was used to analyze the difference between samples that were from non-normal distributions. Multivariate analysis was performed using Cox proportional hazards models. A multivariate analysis model was created with variables that were statistically significant or clinically significant in univariate analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. A P value of less than 0.05 was considered statistically significant.

RESULTS

During the study period 212 patients with cervical cancer stages IB1-IIA2 included. The mean age of patients at diagnosis was 52.3 years (range, 26-81). Demographic and clinicopathological characteristics of the patients are presented in Table 1.

Table 1. Demographic and clinicopathological characteristics of patients (n:212)

Factors		Mean ± SD	Median (range)
Age (year)		52.30±11.29	52 (26-81)
Tumor size (cm)		3.54±1.57	3.5 (0.5-9.0)
Number of removed pelvic lymph node		40.47±14.00	39 (10-81)
Number of removed paraaortic lymph node		15.82±9.01	14 (2-53)
Number of total lymph node		56.29±20.81	52 (12-119)
		n	%
FIGO 2009 stage	IB1	141	66.5
	IB2	34	16.0
	IIA1	28	13.2
	IIA2	9	4.2
Tumor type	Squamous cell carcinoma	161	74.5
	Glandular tumors and precursors	48	22.2
	Other types	3	1.4
Parametrial involvement	Negative	178	84.6
	Positive	34	15.4
Lymphovascular space invasion	Negative	67	32.9
	Positive	145	67.1
Stromal invasion	≤1/2	47	24.1
	>1/2	164	75.9
Vaginal involvement	Negative	157	74.5
	Positive	55	25.5
Metastatic lymph nodes sites	Pelvic	81	38.2
	Pelvic and paraaortic	17	8.0

The tumor type was squamous cell carcinoma in 161 (74.5%) patients, adenocarcinoma in 48 (22.2%) and other types in 3 (1.4%). The mean tumor size was 3.54 cm (range, 0.5-9 cm). Tumor size was greater than 2 cm in 93.8% of patients with pelvic lymph node metastasis and 88.2 percent of those with paraaortic LNM. One hundred and forty-one (66.5 %) patients were stage IB1, 34 (16.0 %) were stage IB2, 28 were stage IIA1 (13.2 %) and nine (4.2%) were stage IIA2 according to FIGO 2009 criteria. Median number of removed lymph nodes was 52 and ranged between 12 and 119.

Patients with metastatic lymph nodes in pelvic region was 81 (38.2 %), in only para-aortic region was 17 (8.0%). In all patients with paraaortic lymph node metastasis, pelvic lymph node metastasis was also observed. Univariate analysis indicated that parametrial involvement, vaginal involvement, DSI, LVSI, tumour size>2 cm were predictive factors for pelvic lymph node metastasis. However, multivariate analysis revealed that the parametrial involvement (hazard ratio [HR]: 2.75, 95% confidence interval [CI],

1.18-6.40, p=0.019) and LVSI ([HR]: 3.83, 95% [CI], 1.76-8.38, p=0.001) were independent risk factors for pelvic LNM with cervical cancer patients The univariate and multivariate analysis comparing the pelvic lymph nodes status are shown in Table 2.

Table 2. Independent risk factors for pelvic lymph node metastasis (n:212)

	PLND (+) n: 81	PLND (-) n:131	*p*	95% CI	*p*
Age	50.14±9.69	53.63±12.02	*0.058*		
Number of removed pelvic lymph node	41.19±13.55	40.36±14.11	*0.797*		
Number of removed paraaortic lymph node	14.82±6.12	15.95±9.34	*0.628*		
Parametrial involvement	23 (28.4)	11 (8.4)	***<0.001***	2.75 (1.18-6.40)	***0.019***
Stromal invasion >1/2	74 (91.4)	90 (68.7)	***<0.001***	2.07 (0.72-5.94)	*0.179*
Vaginal involvement	28 (34.6)	27 (20.6)	***0.024***	1.15 (0.57-2.32)	*0.702*
Vaginal surgical margin positivity	9 (11.1)	10 (7.6)	*0.389*		
Pathology (non-SCC)	20 (24.7)	31 (23.7)	*0.865*		
LVSI	71 (87.7)	74 (56.5)	***<0.001***	3.83 (1.76-8.38)	***0.001***
Tumor size≥2cm	76 (93.8)	100 (76.3)	***0.001***	1.94 (0.58-6.54)	*0.283*

Univariate analysis indicated that parametrial involvement, vaginal involvement, LVSI were predictive factors for paraaortic LNM. After adjusting for other variables only parametrial involvement ([HR]: 3.62, 95% [CI], 1.20-10.98, p=0.023) was found to be independent risk factor for paraaortic LNM in patients with cervical cancer. The univariate and multivariate analysis comparing the paraaortic lymph nodes status are shown in Table 3.

Table 3. Independent risk factors for paraaortic lymph node metastasis (n:212)

	PaLND (+) n: 17	PaLND (-) n: 195	*p*	95% CI	*p*
Age	50.94±8.68	52.42±11.50	*0.607*		
Number of removed pelvic lymph node	43.33±22.03	40.41±13.91	*0.722*		
Number of removed paraaortic lymph node	18.33±5.51	15.77±9.08	*0.722*		
Parametrial involvement	8 (47.1)	26 (13.3)	***<0.001***	3.62 (1.20-10.98)	***0.023***
Stromal invasion >1/2	16 (94.1)	148 (75.9)	*0.085*		
Vaginal involvement	9 (52.9)	46 (23.6)	***0.008***	2.17 (0.73-6.44)	*0.164*
Vaginal surgical margin positivity	3 (17.6)	16 (8.2)	*0.191*		
Pathology (non-SCC)	7 (41.2)	44 (22.6)	*0.085*		
LVSI	16 (94.1)	129 (66.2)	***0.017***	5.44 (0.68-43.42)	*0.110*
Tumor size≥2cm	15 (88.2)	16 (82.6)	*0.550*		

DİSCUSSION

In an attempt to prevent unnecessary morbidity of surgical staging in the cervical cancer, the factors that affect the LNM have been investigated in this study. There are several treatment approaches for cervical cancer treatment consisting of surgery and radiotherapy (with or without concurrent chemotherapy). Patients with positive lymph node involvement after surgery and patients with predicted lymph node positivity are referred to adjuvant treatments. In our study, Parametrial involvement and LVSI for pelvic LNM and Parametrial involvement for paraaortic LNM were predictors in patients with cervical cancer patients.

Parametrial involvement was found to be the only significant clinicopathological predictor for the presence of both pelvic and paraaortic LNM, which are associated with a particularly poor prognosis (9). Parametrial involvement has already been described as risk factors in other studies and is part of risk identification (10). Du et al. identified parametrial involvement as the only related factor of LNM in cervical cancer patients (10). This result was similar to the reports of Liu et al. that parametrial involvement, LVSI and the depth of cervical stromal invasion are independent risk factors for pelvic LNM. Patients with parametrial involvement had a 9 times higher risk of pelvic LNM than patients without parametrial involvement (11). However, Narayan et al. found that only uterine invasion appeared to be associated with an increased risk of LNM in cervical cancer (12). Kılıç et al. concluded that LNM, LVSI and vaginal involvement are risk factors for parametrial involvement. Therefore, less radical surgical approaches can be applied to patients with early-stage cervical cancer patients such as negative LNM and LVSI (13). In our study, we have shown that Parametrial involvement is an independent predictor for the pelvic and paraaortic LNM. Therefore, if parametrial involvement is preoperatively suspected and intraoperatively confirmed, systematic lymph node dissection would not be highly recommended.

It is clearly evident that the presence of LVSI were independent risk factor for LNM with cervical cancer patients (14). There are several studies that are in agreement with our findings. Li et al. demonstrated in a group of 665 patients that presence of LVSI increased the risk of LNM (15). Gulseren et al. reported that LVSI and tumor size (≥2 cm) were significant predictor for pelvic LNM (16). Our results suggested that independent prognostic factors for LNM include LVSI in cervical cancer patients. However, we did not find a significant association between pelvic lymph node involvement and the size of tumor when 20 mm is determined as a cut-off.

The presence of pelvic LNM for the entire cohort was 38%. This rate was higher when compared to previous studies. Batista et al. reported the incidence of PLN metastasis in early stage cervical cancer patients ranges from 3.7% to 21.7% (17). Sakuragi et al. evaluated 208 patients with stage IB–IIB cervical cancer who underwent radical hysterectomy and systematic pelvic and paraaortic lymph node dissection. They detected LNM at a rate of 25.5% (18). The higher incidence of LNM in our study is of great importance in terms of evaluating risk factors.

Several studies have suggested that the tumor size might be more impact in predicting pelvic and paraaortic LNM (19, 20). Horn et al. reported that patients with a tumor size of ≤2.0 cm represent a low risk of pelvic lymph node involvement (21). On the other hand, Yuksel et al. analyzed 384 patients with FIGO 2014 stage IB cervical cancer. Although the possibility of lymph node involvement increases in tumors larger than 4 cm, it is not associated with survival (22). In our study, the tumor size was above 2 cm in the majority of patients with pelvic and paraaortic LNM (93.8% and 88.2% respectively). Despite of this, tumor size above 2 cm was not statistically significant for both pelvic and paraaortic LNM.

The diagnostic accuracy of the intraoperative frozen section these criteria play an important role in their practical application. In a Surveillance Epidemiology and End Results (SEER) analysis, Richard et al. included 218 stage IB cervical cancer patients with positive LNM and compared the radical hysterectomy completed and abandoned groups. In that study they found similar 5-year survival rates (69% vs. 71%, respectively, p=0.46) (23). Additionally, Phanedra et al. evaluated the value of intraoperative frozen section of LN in cervical cancer patients and showed high sensitivity and specificity (86.7% vs. 100%, respectively) (24). In spite of the mentioned studies, routine frozen examination is not recommended in cervical cancer patients.

Adjuvant radiotherapy or concomitant chemoradiotherapy was applied to cervical cancer patients with high risk factors such as lymph node metastasis, surgical margin positivity, and parametric invasion (25). When patients with cervical cancer who received primary chemoradiotherapy and those who received adjuvant therapy after surgery were compared, recurrence and survival rates were similar, while complication rates were higher in the surgical group (26).

The limitation of this study is its retrospective design. Main strength of our study is performing systematic lymph node dis-

section in all patients greatly contributed to the homogenization of the group.

Primary chemoradiotheraphy may be preferred over surgery in the treatment of cervical cancer patients with suspected parametrial and lymph node involvement. Due to the high incidence of postoperative complications, such as, lymphedema, lymphocysts, infections, nerve and vascular injury, systematic lymph node dissection is not recommended routinely (27).

The presented study was conducted to evaluate the risk factors which have considerable value to predict pelvic and para-aortic LNM in cervical cancer. In the last decade, several clinicopathological factors including tumor size, LVSI, DSI, parametrial involvement have been reported as predictors of LNM in cervical cancer. Our data demonstrated a statistically significant difference between Parametrial involvement and frequency of pelvic and paraaortic LNM in cervical cancer patients. Moreover, LVSI was significant risk factor for pelvic LNM.

REFERENCES

Takekuma M, Kasamatsu Y, Kado N, Kuji S, Tanaka A, Takahashi N, et al. The issues regarding postoperative adjuvant therapy and prognostic risk factors for patients with stage I–II cervical cancer: a review. Journal of Obstetrics and Gynaecology Research. 2017;43(4):617-26.

2. Scheidler J, Hricak H, Kyle KY, Subak L, Segal MR. Radiological evaluation of lymph node metastases in patients with cervical cancer: a meta-analysis. Jama. 1997;278(13):1096-101.

3. Selman TJ, Mann C, Zamora J, Appleyard T-L, Khan K. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. Cmaj. 2008;178(7):855-62.

4. Kodama J, Seki N, Ojima Y, Nakamura K, Hongo A, Hiramatsu Y. Prognostic factors in node-positive patients with stage IB-IIB cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy. International Journal of Gynecology & Obstetrics. 2006;93(2):130-

5. Takeda N, Sakuragi N, Takeda M, Okamoto K, Kuwabara M, Negishi H, et al. Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. Acta obstetricia et gynecologica Scandinavica. 2002;81(12):1144-51.

6. Trattner M, Graf A-H, Lax S, Forstner R, Dandachi N, Haas J, et al. Prognostic factors in surgically treated stage Ib–IIb cervical carcinomas with special emphasis on the importance of tumor volume. Gynecologic oncology. 2001;82(1):11-6.

7. Kim PY, Monk BJ, Chabra S, Burger RA, Vasilev SA, Manetta A, et al. Cervical cancer with paraaortic metastases: significance of residual paraaortic disease after surgical staging. Gynecologic oncology. 1998;69(3):243-7.

8. Cree IA, White VA, Indave BI, Lokuhetty D. Revising the WHO classification: female genital tract tumours. Histopathology. 2020;76(1):151-6.

9. De Foucher T, Bendifallah S, Ouldamer L, Bricou A, Lavoué V, Varinot J, et al. Patterns of recurrence and prognosis in locally advanced FIGO stage IB2 to IIB cervical cancer: Retrospective multicentre study from the FRANCOGYN group. European Journal of Surgical Oncology. 2019;45(4):659-65.

10. Du R, Li L, Ma S, Tan X, Zhong S, Wu M. Lymph nodes metastasis in cervical cancer: incidences, risk factors, consequences and imaging evaluations. Asia□Pacific Journal of Clinical Oncology. 2018;14(5):e380-e5.

11. Liu Y, Zhao L-J, Li M-Z, Li M-X, Wang J-L, Wei L-H. The number of positive pelvic lymph nodes and multiple groups of pelvic lymph node metastasis influence prognosis in stage IA–IIB cervical squamous cell carcinoma. Chinese Medical Journal. 2015;128(15):2084-9.

12. Narayan K, Fisher R, Bernshaw D. Significance of tumor volume and corpus uteri invasion in cervical cancer patients treated by radiotherapy. International Journal of Gynecologic Cancer. 2006;16(2).

13. Kilic C, Cakir C, Yuksel D, Tokgozoglu N, Comert GK, Karalok A, et al. Which factors predict parametrial involvement in early stage cervical cancer? A Turkish multicenter study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2019;243:63-6.

14. Zhou J, Ran J, He Z-Y, Quan S, Chen Q-H, Wu S-G, et al. Tailoring pelvic lymphadenectomy for patients with stage IA2, IB1, and IIA1 uterine cervical cancer. Journal of Cancer. 2015;6(4):377.

15. Li X, Yin Y, Sheng X, Han X, Sun L, Lu C, et al. Distribution pattern of lymph node metastases and its implication in individualized radiotherapeutic clinical target volume delineation of regional lymph nodes in patients with stage IA to IIA cervical cancer. Radiation Oncology. 2015;10(1):1-7.

16. Gulseren V, Kocaer M, Gungorduk O, Ozdemir IA, Gokcu M, Mart EM, et al. Preoperative predictors of pelvic and

para-aortic lymph node metastases in cervical cancer. Journal of Cancer Research and Therapeutics. 2019;15(6):1231.

17. Batista TP, Bezerra ALR, Martins MR, Carneiro VCG. How important is the number of pelvic lymph node retrieved to locorregional staging of cervix cancer? Einstein (Sao Paulo). 2013;11:451-5.

18. Sakuragi N, Satoh C, Takeda N, Hareyama H, Takeda M, Yamamoto R, et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1999;85(7):1547-54.

19. Hawnaur J, Johnson RJ, Buckley C, Tindall V, Isherwood I. Staging, volume estimation and assessment of nodal status in carcinoma of the cervix: comparison of magnetic resonance imaging with surgical findings. Clin Radiol. 1994;49(7):443-52.

20. Park J-Y, Kim D-Y, Kim J-H, Kim Y-M, Kim Y-T, Nam J-H. Outcomes after radical hysterectomy according to tumor size divided by 2-cm interval in patients with early cervical cancer. Ann Oncol. 2011;22(1):59-67.

21. Horn L-C, Fischer U, Raptis G, Bilek K, Hentschel B. Tumor size is of prognostic value in surgically treated FIGO stage II cervical cancer. Gynecol Oncol. 2007;107(2):310-5.

22. Yüksel D, Şahin EK, Ünsal M, Çakır C, Kılıç Ç, Cömert GK, et al. The prognostic factors in 384 patients with FIGO 2014 stage IB cervical cancer: What is the role of tumor size on prognosis? European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021;266:126-32.

23. Richard SD, Krivak TC, Castleberry A, Beriwal S, Kelley III JL, Edwards RP, et al. Survival for stage IB cervical cancer with positive lymph node involvement: a comparison of completed vs. abandoned radical hysterectomy. Gynecologic oncology. 2008;109(1):43-8.

24. Gubbala PK, Laios A, Wang Z, Dhar S, Pathiraja PJ, Haldar K, et al. Routine intraoperative frozen section examination to minimize bimodal treatment in early-stage cervical cancer. International Journal of Gynecologic Cancer. 2016;26(6).

25. Kilic F, Cakir C, Yuksel D, Korkmaz V, Kimyon Comert G, Boran N, Koc S, Turan T, Turkmen O. Analysis of the prognostic factors determining the oncological outcomes in patients with high-risk early-stage cervical cancer. J Obstet Gynaecol. 2022 Feb;42(2):281-8.

26. Fanfani F, Vizza E, Landoni F, De Iaco P, Ferrandina G, Corrado G, et al. Radical hysterectomy after chemoradiation in FIGO stage III cervical cancer patients versus chemoradiation and brachytherapy: Complications and 3-years survival. European Journal of Surgical Oncology (EJSO). 2016;42(10):1519-25.

27. Sivanesaratnam V, Sen D, Jayalakshmi P, Ong G. Radical hysterectomy and pelvic lymphadenectomy for early invasive cancer of the cervix—14-year experience. International Journal of Gynecologic Cancer. 1993;3(4).