

Long term outcomes of patients who underwent radical hysterectomy for cervical cancer

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ABSTRACT

Introduction: We aimed to examine the parameters affecting long-term prognosis and survival in patients diagnosed with early stage cervical cancer and undergoing radical hysterectomy in our Gynecology and Obstetrics Clinic.

Material and Method: The files of 86 cervical cancer patients who underwent radical hysterectomy and pelvic paraaortic lymph node dissection for cervical cancer between 2010 and 2021 were retrospectively reviewed. Tumor size, FIGO stage, vagina, endometrium, ovary, parametrium, pelvic lymph node, paraaortic lymph node and deep stromal involvement were examined by examining the files and pathology reports of the patients. Then, the effects of these parameters on pelvic and paraaortic lymph node involvement, postoperative prognosis and survival of the patients were tried to be revealed.

Results: The 86 patients included in the analysis had a mean age of 55.2 (range: 38-72) and a median tumor size of 35 mm (range: 2-74). Cell type was squamous cell carcinoma in 81.4% and adenocarcinoma in 18.6% of the patient group. During the follow-ups, recurrence was detected in 22 (25.6%) patients. During the follow-up period, it was found that 18 (20.9%) patients died. In univariate analysis, the presence of metastases in any lymph node was found to reduce DFS and OS. The mean follow-up period of the cases examined was 66 (min:12-max:132) months; The mean OS and DFS of the patients were 111.84 (95% CI:103.26-120.43) and 105.72 (95% CI:95.87-115.57) months, respectively.

Conclusion: Pelvic and paraaortic lymph node involvement was found to be the most important prognostic factor regardless of histological type in cervical cancers. Survival was found to be significantly lower in patients with any lymph node involvement.

Keywords: Cervical cancer, radiotherapy, radical hysterectomy, prognostic factor, survival

INTRODUCTION

According to 2018 GLOBOCAN data, cervical cancer ranks fourth worldwide after breast, colorectal and lung cancers. The frequency order rises to the second rank in socioeconomically backward countries (such as South America and Africa) (1). Cervical cancer death rates have decreased in the last few decades due to the widespread application of cytology screening, advances in classical surgical methods, the introduction of new instruments and medical technologies, and the spread of chemoradiotherapy. However, more than 265,000 women die from cervical cancer each year (2). Cervical cancer staging was classically determined by clinical examination according to the International Federation of Gynecology and Obstetrics (FIGO) (3). However, FIGO proposed a modification in 2018 that included the use of imaging methods and postoperative pathological examination in order to perform more detailed staging (4). Cervical cancer

treatment plan varies according to the stage at diagnosis. Cure can be achieved with surgery (alone or by adding radiotherapy) in early stage cervical cancers (Stage I-IIa) (5). In the Surveillance, Epidemiology, and End Results (SEER) database, 5-year survival rates for cervical cancer were reported as 91.8% for localized disease and 56.3% for locally advanced disease and 15% for metastatic cases between 2008 and 2014 (6). Life expectancy of cancer patients has increased both in the world and in our country, thanks to new treatment opportunities (7). In recent years, numerous studies have investigated the relationship between 5-year survival rates of women with cervical cancer and various treatment modalities, including radical hysterectomy (8, 9). Most of these studies have focused on general trends in survival rates without investigating the clinical and pathological aspects and only a few reports have discussed the long-term observation of these patients. In this study, we aimed to examine the clinical

and pathological aspects of the parameters affecting the prognosis and 10-year disease-free survival (DFS)-overall survival (OS) in patients diagnosed with cervical cancer and undergoing radical hysterectomy in our Gynecology and Obstetrics Clinic.

MATERIAL AND METHOD

Ethics committee approval for the study was obtained from Ethics Committee of Selçuk University (Date: 21.04.2021, Meeting no: 2021/08, Decision no: 2021/214). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The records of 86 patients who were diagnosed with cervical cancer and underwent surgical treatment in the Gynecology Oncology Clinic of our university between January 2010 and February 2021 were reviewed retrospectively. Exclusion criteria from the study were: not attending follow-ups, going to another center for treatment after diagnosis, and having other accompanying gynecological or non-gynecological malignancies. The data of the patients were analyzed retrospectively. The preoperative diagnosis was based on the histopathologic examination of tissue obtained from cervical biopsy and fractionated abrasion. Patients were staged using the FIGO 2018 clinical staging system based on vaginal speculum examination, bimanual examination, and rectal examination. Early-stage cervical cancer refers to FIGO stage IA, IB1, and IB2 disease. The patients were evaluated with imaging methods (computed tomography, magnetic resonance imaging) at the time of diagnosis. All patients underwent radical hysterectomy and pelvic + paraaortic lymphadenectomy. By examining the demographic data and pathology reports of the patients, tumor size, FIGO stage, vagina, endometrium, ovary, parametrium, pelvic lymph node, paraaortic lymph node, deep stromal involvement were examined. After the operation, the patients were surgically staged. After the postoperative recovery period, radiotherapy was applied to 47 patients (54.7%). Then, the effects of these parameters on pelvic and paraaortic lymph node involvement and the postoperative prognosis and survival of the patients were tried to be revealed. Relapse development and its treatment, 10-year DFS, and OS were analyzed. The patients were checked every 3 months for the first 2 years, every 6 months for the next 2 years, and annually in the following years. Pelvic examination, whole abdomen ultrasonography imaging and complete blood count were performed at each control. Abdominal and thorax tomography was performed annually for scanned metastasis. DFS was taken as the time interval from the time of diagnosis to recurrence or to the last follow-up visit. OS was taken as the time interval from the time of diagnosis to the date of the last examination or the date of death.

Statistical Evaluation

Survival analyzes were performed using the Kaplan-Meier method and the results were compared with the log-rank test. Cox regression analysis was used to evaluate risk factors. Chi-square and Fisher tests were used to compare proportions. Student-t test was used to compare parametric continuous variables. All statistical analyzes were performed with the Statistical Package for the Social Sciences (SPSS) program. $p < 0.05$ was considered statistically significant.

RESULTS

The 86 patients included in the analysis had a mean age of 55.2 (range: 38-72) and a median tumor size of 35 mm (range: 2-74). Tumor size was ≤ 20 mm in 53.5%, $>20 - \leq 40$ mm in 32.6%, and >40 mm in 14% of patients. Cell type was squamous cell carcinoma in 81.4% and adenocarcinoma in 18.6% of the patient group. General characteristics study group were shown in **Table 1**. Mean follow-up was 66.84 (SD 37.16) months (range: 12-132). During the follow-ups, recurrence was detected in 22 (25.6%) patients. It was observed that 60.8% of these recurrences developed in the first year, and 78.9% within 3 years. Only pelvic recurrence was observed in all of the patients, and no long-distance recurrence was observed. The mean time from radical surgery to recurrence was 20.3 months (range: 4-72; median: 11). During the follow-up period, it was found that 18 (20.9%) patients died. All deaths occurred within 3 years. Mean duration from radical surgery to death was 28.1 months (range: 12-32; median:18).

In univariate analysis, the presence of metastases in any lymph node was found to reduce DFS and OS (**Table 3** and **Table 4**). In multivariate analysis, factors that were found to be significant in univariate analysis were evaluated and it was determined that although the presence of metastases in any lymph node reduced both DFS and OS times, there were no statistically independent prognostic factors. This situation contradicts the literature and is associated with the low number of cases (**Table 3** and **Table 4**).

The mean follow-up period of the cases examined was 66 (min:12-max:132) months; The mean OS and DFS of the patients were 111.84 (SD 16.12) (95% CI:103.26-120.43) and 105.72 (SD 17.09) (95% CI:95.87-115.57) months, respectively. (**Figure 1** and **Figure 2**). When 10-years OS according to the histology results of the patients examined within the scope of the study is considered, the average OS time of those with squamous cell cancer was 112.6 (SD 4.88) (95% CI:102.62-132.47) months, while the average survival time in other histological types was 104.25 (SD 9.27) (95% CI:97.78-124.71) months. There was no statistically significant difference in terms of DFS and OS between those with squamous cell cancer and other histological types ($p=0.631$, $p=0.868$) (**Table 2**).

Table 1. Characteristics of the study population	
	N (%)
Age; years, mean ± standard deviation	55.2±10.7
Menopausal status	
Premenopause	27 (31.4)
Postmenopause	59 (68.6)
Histological subtype	
Squamous	70 (81.4)
Adenocarcinoma	16 (18.6)
FIGO STAGE (2018)	
Stage IA1	13 (15.1)
Stage IA2	4 (4.7)
Stage IB1	15 (17.4)
Stage IB2	22 (25.6)
Stage IB3	14 (16.3)
Stage IIA1	5 (5.8)
Stage IIA2	-
Stage IIB	2 (2.3)
Stage IIIA	-
Stage IIIB	-
Stage IIIC1	7 (8.1)
Stage IIIC2	4 (4.7)
Stage IVA	-
Stage IVB	-
Tumor size	
≤ 2 cm	46 (53.5)
>2 - ≤ 4 cm	28 (32.6)
> 4 cm	12 (14)
Depth of invasion	
<%50	77 (89.5)
≥%50	3 (3.5)
Full thickness invasion	6 (7)
LVSI	
No	72 (83.7)
Yes	14 (16.3)
Parametrial involvement	
No	82 (95.3)
Yes	4 (4.7)
Vaginal involvement	
No	79 (91.4)
Yes	7 (8.1)
Perineural invasion	
No	81 (94.2)
Yes	5 (5.8)
Lymph node involvement	
No	84 (97.7)
Yes	2 (2.3)
Surgery	
Type 1 Hysterectomy	12 (14)
Type 2 Hysterectomy	62 (72.1)
Type 3 Hysterectomy	12 (14)
Treatment	
Only surgery	39 (45.3)
RT	35 (40.7)
RT+Brachiatery	12 (14)
Recurrence	
No	64 (74.4)
Yes	22 (25.6)
Status	
Alive	68 (79.1)
Death	18 (20.9)

RT: radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

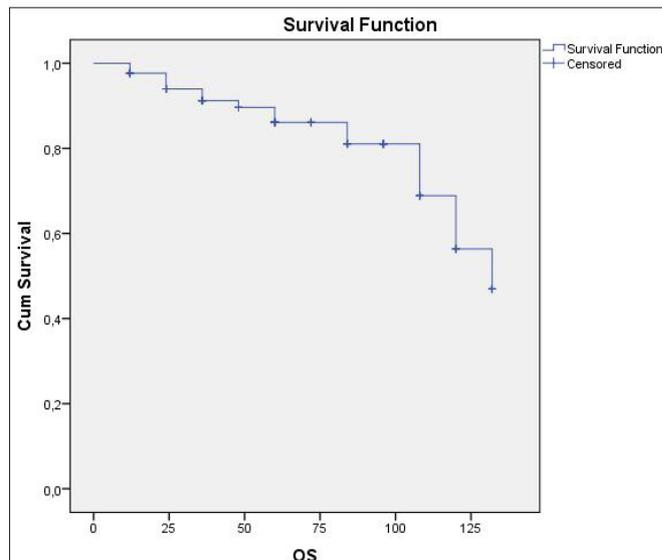


Figure 1. OS for all patients

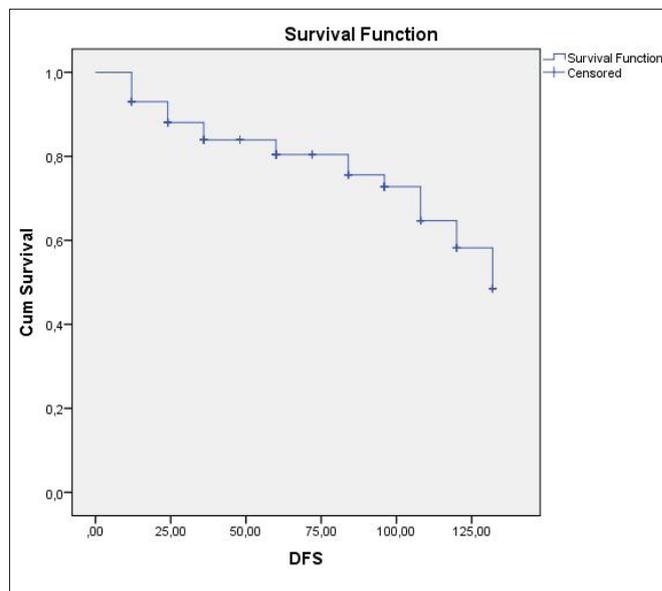


Figure 2. DFS for all patients

The mean OS of those without parametrial involvement was 113.15 (SD 4.44) (95% CI:108.66-132.47) months, and the mean DFS was 108.23 (SD 5.01) (95% CI:97.58-119.01) months. In those with parametrial involvement, the same parameters were 90 (SD 22.04) (95% CI:89.0-108.0), 60 (SD 22.65) (95% CI:59.35-86.64) months, respectively (Table 2). A statistically significant difference was found between 10-year DFS and OS rates according to parametrial involvement (p=0.007, p=0.05). A statistically significant difference was found between 10-year OS and DFS rates according to lymph node involvement (p<0.05, p<0.05, respectively). The 10-year OS and DFS rate of patients without lymph node involvement was significantly higher than those with lymph node involvement. (Figure 3-6).

Table 2. Result of Kaplan-Meier survival analysis					
	N (%)	DFS (Mean)	p	OS (Mean)	p
Menopausal status					
Premenopause	27 (31.4)	94.83±8.71	0.725	94.83±8.71	0.149
Postmenopause	59 (68.6)	106.83±5.86		115.93±4.51	
Histological subtype					
Squamous	70 (81.4)	104.89±5.78	0.868	112.6±4.88	0.631
Adenocarcinoma	16 (18.6)	104.25±9.27		104.25±9.27	
FIGO STAGE (2018)					
Stage I	54 (62.8)	116.52±5.69	0.005	122.73±4.51	0.001
Stage II	19 (22)	100.92±11.9		108.63±10.36	
Stage III	13 (15.1)	78.31±11.94		80.54±11.81	
Stage IV	-				
Depth of invasion					
<%50	77 (89.5)				0.767
≥%50	3 (3.5)	censored		censored	
Full thickness invasion	6 (7)	censored		censored	
LVSI					
No	72 (83.7)	106.34±5.29	0.57	111.81±4.63	0.767
Yes	14.8(16.3)	100.45±14.73		108.55±13.02	
Vaginal involvement					
No	79 (91.9)	105.28±5.33	0.737	110.3±4.79	0.312
Yes	7 (8.1)	98.68±15.9		96±5.19	
Perineural invasion					
No	81 (94.2)	107.9±5.06	0.097	113.04±4.43	0.334
Yes	5 (5.8)	70.8±19.02		88.5±15.09	
Parametrial involvement					
No	82 (95.3)	108.23±5.01	0.007	113.15±4.44	0.05
Yes	4 (4.7)	60±22.65		90±22.04	
Pelvic lymph node involvement					
No	78 (90.7)	109.09.21±5.19	0.05	115.75±4.37	0.02
Yes	8 (9.3)	83.5±11.85		86.5±11.45	
Paraortic lymph node involvement					
No	84 (97.7)	113.74±4.23	0.01	127.96±2.28	0.03
Yes	2 (2.3)	42±6		48±0	
Surgery					
Type 1 Hysterectomy	12 (13.9)	122.4±8.58	0.207	122.4±8.58	0.449
Type 2 Hysterectomy	62 (72.2)	99.97±6.48		108.65±5.61	
Type 3 Hysterectomy	12(13.9)	102.37±3.34		105±3.96	
Treatment					
Only surgery	39 (45.3)	124.96±3.99	0.01	censored	0.01
ERT	35 (40.7)	91.54±8.55		-	
ERT+Brachiatery	12 (14)	70±10.52		censored	

OS: overall survival, DFS: disease free survival, ERT:External radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

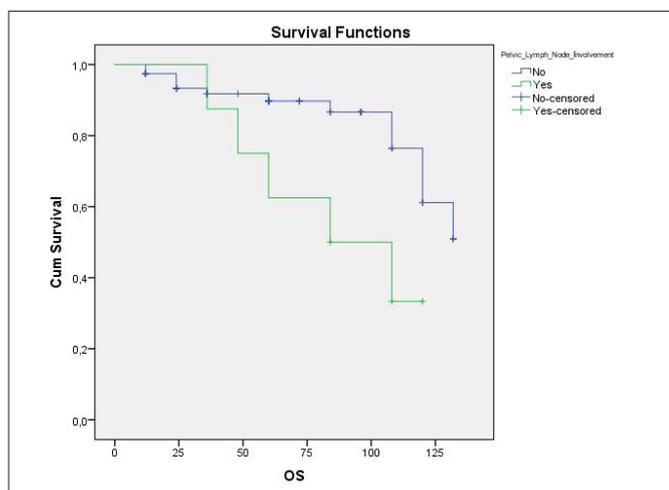


Figure 3. OS according to pelvic lymph node involvement

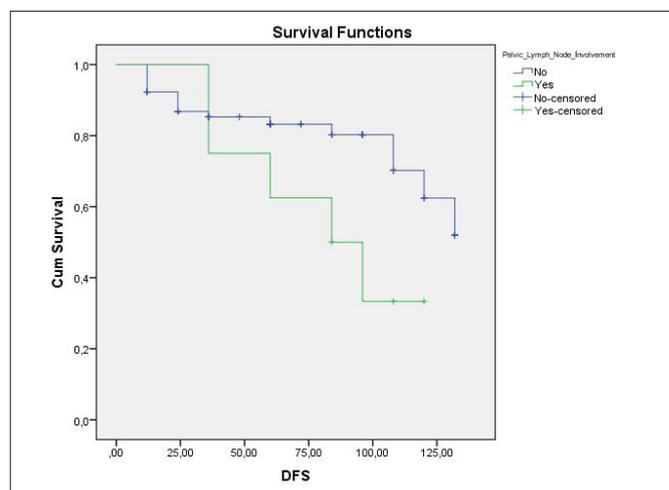


Figure 4. DFS according to pelvic lymph node involvement

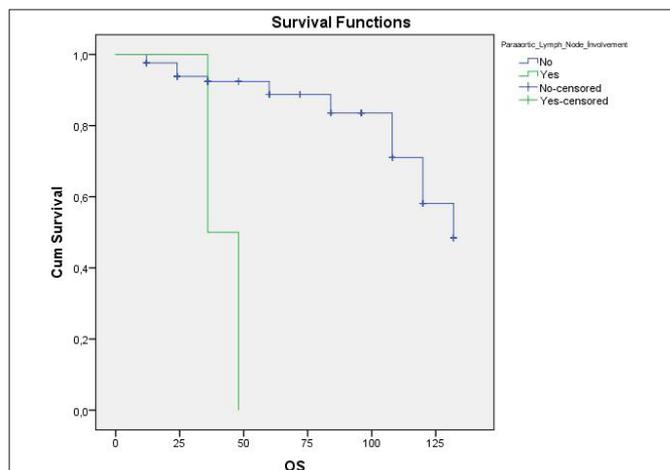


Figure 5. OS according to paraaortic lymph node involvement

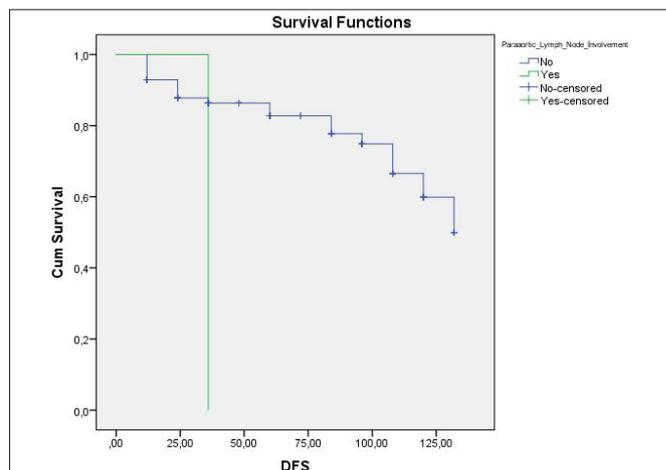


Figure 6. DFS according to paraaortic lymph node involvement

	UNIVARIATE			MULTIVARIATE		
	HR	95% CI	P	HR	95% CI	P
Age (years)	0.969	0.927-1.014	0.175			
Hystologic type						
Squamous			Reference			
Adenocarcinoma	1.311	0.423-4.058	0.639			
Menopausal status						
Premenopause			Reference			
Postmenopause	0.486	0.175-1.344	0.164			
Tumor diameter						
≤ 2 cm			Reference			
> 2 cm	0.896	0.355-2.26	0.815			
FIGO Stage						
I			Reference			
II	1.58	0.405-6.171	0.05	2.77	0.689-11.14	0.151
III	6.19	2.047-18.74	0.04	7.68	1.98-29.74	0.003
IV	-	-	-			
Parametrial involvement						
No			Reference			
Yes	2.97	0.668-13.2	0.21			
Depth of invasion						
<%50			Reference			
≥%50	0.001	0.001-0.001	0.985			
Full thickness invasion	0.678	0.9-5.12	0.706			
LVSI						
No			Reference			
Yes	1.18	0.385-3.61	0.772			
Vaginal involvement						
No			Reference			
Yes	2.354	0.237-23.411	0.465			
Perineural invasion						
No			Reference			
Yes	2.01	0.458-8.81	0.355			
Pelvic lymph node involvement						
No			Reference			
Yes	3.137	1.1-8.49	0.03	1.198	0.043-0.922	0.03
Paraortic lymph node involvement						
No			Reference			
Yes	13.16	2.64-65.47	0.002	6.562	0.366-128.269	0.215
Surgery						
Type 1 Hysterectomy			Reference			
Type 2 Hysterectomy	3.02	0.399-22.92	0.284			
Type 3 Hysterectomy	1.89	0.169-21.22	0.604			
Adjuvan Therapy						
Only surgery			Reference			
ERT	7.138	2.01-25.27	0.002			
ERT+Brachiaterapy	0.001	0.001-0.001	0.979			

OS: overall survival, HR: hazard ratio, CI: confidence interval, ERT: External radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

Table 4. Univariate and Multivariate Analysis of Potential Prognostic Factors for DFS						
	UNIVARIATE			MULTIVARIATE		
	HR	95% CI	P	HR	95% CI	P
Age (years)	0.988	0.95-1.028	0.543			
Hystologic type						
Squamous			Reference			
Adenocarcinoma	0.913	0.306-2.72	0.871			
Menopausal status						
Premenopause			Reference			
Postmenopause	0.845	0.323-2.208	0.731			
Tumor diameter						
≤ 2 cm			Reference			
> 2 cm	1.024	0.255-4.116	0.973			
FIGO Stage						
I			Reference			
II	1.463	0.461-4.638	0.518	1.433	0.428-4.799	0.559
III	4.117	1.577-10.752	0.004	5.233	1.469-18.639	0.01
IV	-	-	-			
Parametrial involvement						
No			Reference			
Yes	4.543	1.313-15.715	0.017	1.751	0.383-8.01	0.47
Depth of invasion						
<%50			Reference			
≥%50	0.001	0.001-0.001	0.981			
Full thickness invasion	0.541	0.0072-4.041	0.549			
LVSI						
No			Reference			
Yes	1.33	0.486-3.635	0.579			
Vaginal Involvement						
No			Reference			
Yes	1.526	0.188-12.422	0.693			
Perineural invasion						
No			Reference			
Yes	2.655	0.78-9.035	0.04	1.107	0.26-4.707	0.89
Pelvic lymph node involvement						
No			Reference			
Yes	2.494	0.911-6.827	0.05	1.687	0.041-1.182	0.01
Paraaortic lymph node involvement						
No			Reference			
Yes	6.784	1.502-30.653	0.013	3.793	0.534-26.945	0.183
Surgery						
Type 1 Hysterectomy			Reference			
Type 2 Hysterectomy	4.054	0.542-30.308	0.173			
Type 3 Hysterectomy	1.911	0.172-21.21	0.598			
Adjuvan Therapy						
Only surgery			Reference			
ERT	7.557	2.132-26.781	0.002	6.689	1.174-27.215	0.006
ERT+Brachiatery	9.216	1.925-44.128	0.005	10.477	1.848-59.405	0.008

DFS: disease free survival, HR: hazard ratio, CI: confidence interval ERT: External radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

As a result of the cox regression analysis performed to determine the factors affecting DFS and OS, lymph node involvement and FIGO stage were found to be risk factors affecting OS and DFS. Variables that were found to be effective in univariate analysis were included in multivariate analysis. Accordingly, when the effect of other variables was controlled, lymph node involvement and FIGO stage were found to be important prognostic factors in determining OS and DFS. It was found that the risk of death is 3.13 times higher when there is pelvic lymph node involvement, and 13.16 times higher when there is paraaortic lymph node involvement. (Table 3 and Table 4).

DISCUSSION

Cervical cancer is gaining more importance day by day due to its increasing incidence among patients. Generally, these patients are treated with radical hysterectomy and pelvic lymphadenectomy. However, very different prognoses are observed in patients at the same FIGO stage. Therefore, it is important to determine the prognostic factors affecting the survival rate in these cases. Few studies focus on overall trends in survival rates and discuss long-term observation of these patients.

The life expectancy of patients after radical hysterectomy and pelvic lymphadenectomy in cervical cancer depends on many factors. Treatment-related factors as well as the stage of cervical cancer are important prognostic factors (10). As the stage progresses, the response to treatment decreases. According to SEER data, 5-year survival after treatment in stage 1 cervical cancer is around 91.8%, while the same rate is around 15% in stage 4 cancer (6). Consistent with the literature, in our study, stage was the most significant predictor of both DFS and OS. According to the results of the presented study, 10-year OS after treatment in cervical cancer is 83.6%, 76.6% and 15.2% in Stage 1, stage 2, and stage 3 respectively. In addition, the probability of regional lymphatic metastasis increases as the stage progresses. This negatively affects the prognosis in cervical cancer. In many studies, it has been stated that lymph node involvement reduces survival statistically significantly (11). In a Japanese study involving 117 patients, patients were divided into two groups according to lymph node involvement, and 5-year survival was found to be 52% in the group with lymph node involvement and 89% in the group without lymph node involvement (p value=0.0005) (12). Presence of lymph node involvement is accepted as an independent risk factor for cervical cancer prognosis in the literature (13). In the study of Monaghan et al. (14) published in 1990 covering 498 cases, they found 5-year survival as 91% in lymph node-negative cases and 51% in cases with positive lymph node involvement. In a study by Kim et al. (15) published in 2000, involving 366 patients, 5-year survival was found to be 95% in lymph node-negative cases and 78% in cases with positive lymph node involvement. Similar results were found in this study, which supports the literature. Survival is reduced in patients with pelvic lymph node involvement. While the 10-year OS rate was 76.4% in patients with negative pelvic lymph nodes, this rate was 33.3% in patients with positive pelvic lymph nodes. Therefore, we believe that extraperitoneal lymph node sampling before surgery in cervical cancers will be beneficial.

In a study by Shinohara et al. (16) parametrial invasion, venous infiltration, pelvic lymph node metastasis, residual muscle layer thickness (<5 mm), tumor depth (≥ 13 mm) and invasive tumor growth pattern was examined as prognostic factors and shorter survival were found in patients with any of these factors in early stage cervical cancer patients who underwent radical hysterectomy and radiotherapy. In the study conducted by Burghardt et al. (17) which examined 1,004 cases covering 3 centers, 5-year survival was found to be 62.4% in cases with parametrial involvement, and this rate was 85.8% in cases without parametrial involvement. The results of this study were close to the literature in terms of parametrial involvement. Although parametrial

involvement increased the risk of death 2.97 times in this study, it was not statistically significant ($p=0.21$). In the present study, consistent with the literature, lymph node involvement were found to be independent prognostic factors for both DFS and OS in multivariate analyzes. The most predictive parameters for PFS and OS were pelvic and paraaortic lymph nodes involvement, respectively.

Literature studies have stated that adenocarcinoma histological type is a poor prognostic factor by many centers (15,18). Many studies found no difference in survival by histologic subtype, but in the SEER database, which included 24562 cervical cancer patients, adenocarcinomas were reported to have shorter survival than same-stage squamous carcinomas (39% and 21% higher risk of death for early and advanced carcinomas, respectively) (18,19). In the study of the American Society of Surgeons, which included 157 cases treated between 1984 and 1990, 9,351 (83.8%) squamous cell cervical cancer, 1,405 (12.6%) adenocarcinoma and 401 adenosquamous cell cervical cancer were examined. No effect of histological type on overall survival could be demonstrated in clinically staged 1B cases (13). In our study, the histological subtype rates were consistent with the literature and our findings supported the SEER database. In this study, the 10-year survival rate for squamous cell cancers was 59.9%, while it was 43.8 for adenocancers.

In a study conducted in our country, examining a total of 70 cases diagnosed with stage 1B2 and 2A2 cervical cancer, comparing radical hysterectomy+adjuvant chemoradiotherapy, primary chemoradiotherapy, neoadjuvant chemotherapy followed by radical hysterectomy, neoadjuvant chemoradiotherapy followed by radical hysterectomy, there was no statistically significant difference in OS and DFS between these 4 different treatment modalities. In the present study, it was determined that radical hysterectomy followed by adjuvant radiotherapy did not differ statistically in terms of OS and DFS

The most important limitations of our study are its retrospective nature and the small number of patients. The development of surgical techniques and the fact that there are some changes in the methods used with the following years prevent our study from being homogeneous. However, since all patients are operated and followed up by the same team, it is thought that homogeneity is achieved in this regard. The most important strength of this study is that it includes long-term results. It would be beneficial to confirm our results with prospective, multicenter studies with a larger number of patients.

CONCLUSION

Although the number of cases is limited, pelvic and paraaortic lymph node involvement and FIGO stage were found to be the most important prognostic factor regardless of histological type in cervical cancers. Survival was found to be significantly lower in patients with lymph node involvement. Except for lymph node involvement and FIGO stage, no effect of other prognostic factors on survival was found.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval for the study was obtained from Ethics Committee of Selçuk University (Date: 21.04.2021, Meeting no: 2021/08, Decision no: 2021/214).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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