



Özgün Araştırma / Original Article

Long-Term Follow-Up Outcomes of Cervical Cancer Patients: A Single Center Experience from the East Anatolian Region of Turkey

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Received: 18.06.2019; Revised: 25.09.2019; Accepted: 07.10.2019

Abstract

Objective: Cervical cancer (CC) is the 4th most common cause of cancer-related deaths in women all over the world. The most important etiologic cause is HPV, and this allows tumor to have high chance of curing with early diagnosis by screening programs. However, information about long-term survival data of CC is limited in our country. In our study; we wanted to reveal the survival times of our patients with CC and the factors that predict these times.

Methods: Seventy-three patients with CC, followed between 2000 and 2017 were analyzed retrospectively. Associations between clinical and histopathological parameters with overall survival (OS) and progression-free survival (PFS) were analyzed using Kaplan- Meier curves and compared by the log-rank test. Univariate and multivariate analysis were used to assess their prognostic values for PFS and OS.

Results: The median age of the patients was 56 years. The most common histological subtype was squamous cell carcinoma (79.5%) followed by adenocarcinoma (16.4%).According to FIGO staging system, 31 (43.8%) of the patients were diagnosed as stage 1-2 and 42 (56.2%) were as stage 3-4.The median PFS and OS are 44 months and 78 months. The 5-year survival rate is 37.5% (12%-75%). Although there was no difference in length of life between histological subtypes, both PFS and OS were longer in patients with good ECOG performance score (0-1), early FIGO stage (1-2), tumor size <4 cm, and without parametrial and lymph node involvement. Multivariate analysis showed that ECOG performance score, parametrial involvement and lymph node involvement were independent prognostic factors for PFS and OS.

Conclusion: The stage at time of diagnosis of CC patients in our region is more advanced and their 5-year survival rates are below the world average, so our women need to be better informed about this subject.

Keywords: Cervical Cancer, HPV DNA, Prognostic Factors

DOI: 10.5798/dicletip.579312

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Servikal Kanser Hastalarının Uzun Dönem Sonuçları: Doğu Anadolu Tek Merkez Deneyimi

Öz

Amaç: Servikal kanser (SK) tüm dünyada kadınlarda kansere bağlı ölümlerin en sık 4. Sebebi iken ülkemizde 12. Sebebidir. En önemli etyolojik neden HPV olması nedeniyle tarama programları ile erken tanı ile kür olma şansı yüksek olan tümörlerdendir. Ancak ülkemizde SK'lerin uzun dönem yaşam verileri ile ilgili bilgiler kısıtlıdır. Bizde çalışmamızda öncelikli olarak SK tanılı hastalarımızın yaşam sürelerini ve bu süreleri predikte eden faktörleri ortaya koymak istedik.

Yöntemler: Erzurum Atatürk Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Anabilim Dalı'nda 2007-2017 yılları arasında SK nedeniyle takip edilen 73 hasta çalışmaya retrospektif olarak dahil edildi. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) ile klinikopatolojik parametreler arasındaki ilişkiler Kaplan-Meier eğrileri kullanılarak analiz edildi ve log-rank testi ile karşılaştırıldı. Tek ve çok değişkenli analiz kriterlerin PFS ve OS için prognostik önemlerini tespit etmek için kullanılmıştır.

Bulgular: Hastaların median yaşı 56'dır. En sık görülen histolojik alttip skuamoz hücreli karsinom (%79,5) ardından adenokarsinom (%16,4) gelmektedir. FIGO evreleme sistemine göre hastaların 31'i (%43,8) evre 1-2, 42'si (%56,2) evre 3-4 olarak tanı almıştır. Median PFS ve OS 44 ay ve 78 aydır. 5 yıllık yaşam oranı %37,5 (%12-%75) dur. Histolojik alttiplerin yaşam süreleri arasında fark olmamakla beraber ECOG performans skoru iyi (0-1) olanların, erken FIGO evresi (1-2) olanların, tumor boyutu <4 cm olanların, parametrial ve lenf nodu tutulumu olmayanların hem PFS hem de OS leri daha uzundur. Multivariate analizler sonucunda ECOG performans skoru, parametrial tutulum ve lenf nodu tutulumu PFS ve OS için bağımsız prognostik faktör olduğu tespit edilmiştir.

Sonuç: Bölgemizdeki SK'li hastaların tanı anında evreleri daha ileri ve 5 yıllık yaşam oranları dünya ortalamalarının altındadır bu sebeple kadınlarımızın bu konuda daha iyi bilinçlendirilmeleri gerekmektedir.

Anahtar kelimeler: Servikal kanser, HPV, Prognostik faktörler.

INTRODUCTION

Cervical cancer (CC) is the 3rd most common cancer in women all over the world, and it is the 4th most common cancer that causes death and is an important public health problem. The incidence of CC is 9.9/100000 worldwide, and in 2018 around 311365 CC-related deaths were detected, 90% of deaths occurred in least and moderately developed countries¹. In our country, the incidence in women is 4.3 / 100000 and the mortality rate is 1.7/100000, CC is the 12th most common cancer type. In our country, there are better results when compared to world-wide results and at rates close to developed countries². The reason for this is thought to be the effects of traditional sexual life style, pap-smear program implemented by the Ministry of Health for many years and the HPV screening test program that has been implemented in 2014.

CC usually does not show any symptoms at the beginning but postcoital hemorrhage may be the first sign which is rarely seen, and patients with advanced stage disease usually present with intermediate menstrual bleeding. The most common histological subtype is squamous cell carcinoma followed by adenocarcinoma and median age is 47¹. The most important etiological factor for CC is chronic infections caused by high-risk oncogenic human papilloma virus (HPV). Factors that increase this situation are early sexuality, multiple sexual partners, risky sexual partners, immunosuppression, a history of sexually transmitted diseases and a history of HPV related vulvar or vaginal disease³. When planning treatment, International Federation of Gynecology and Obstetrics (FIGO) staging system is taken into consideration most of the time, and in general, radical surgical operations are performed for tumors smaller than 4 cm

and concomitant chemoradiation is used for larger local or locally advanced diseases. Brachytherapy and/or adjuvant chemotherapy may be added to the treatment of selected patients⁴. Palliative chemotherapy is the mainstay of treatment in diseases at metastasis stage. According to The Surveillance, Epidemiology, and End Results (SEER) database, 5-year survival rates were between 91.8% in localized disease and 56.3% in local advanced disease and around 15% in metastatic cases between 2008 and 2014⁵. In addition, in recent years, due to new treatment opportunities life expectancy of cancer patients have increased both in the world and in our country⁶. However, there are very few studies revealing survival times of CC patients and the factors that predict these times in our country. In this study, we aimed to reveal characteristics which may be predictive for survival times and the long-term CC data of our center, which is frequently applied by patients from many provinces of Eastern Anatolia.

METHODS

Between April 2000 and February 2017, 73 patients who were diagnosed as cervical cancer and followed up in the medical oncology department of Erzurum Atatürk University until May 2019, participated in our study, retrospectively. Clinical, demographic and histopathological data such as age, sex, Eastern Cooperative Oncology Group performance status (ECOG) performance status, hormonal status, histological subtype, pathological features, treatment modality and treatment agents were obtained from the patient archive files. Patients were staged according to FIGO 2018 cervix uteri system and divided into two groups: Group I: stage 1 and 2, Group II: stage 3 and 4.

All procedures performed in studies involving human participants 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 comparable ethical standards. Ethics committee approval was obtained from the ethics committee of Erzurum Atatürk University.

Statistics

Overall survival (OS) was calculated from the date of diagnosis to the date of death, and censored at the date of last follow-up for survivors. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of recurrence or death and censored at the date of last follow-up for survivors without recurrence. Associations between clinical and histopathological parameters with OS and PFS were analyzed using Kaplan-Meier curves and compared by the log-rank test. Univariate and multivariate cox-regression analyses were performed to determine effects of probable prognostic factors, including gage, hormonal status, Eastern Cooperative Oncology Group (ECOG) performance status, FIGO stage groups, tumor size, parametrial involvement, lymph node involvement, surgery for OS and PFS. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95 % confidence intervals (CIs). All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0). $P < 0.05$ was considered as statistically significant.

RESULTS

Detailed demographic data of 73 patients included in our study are shown in Table 1. The median age of the patients was 56 (34-83) and there were 14 patients (19.2%) under the age of 45, 45 patients (61.6%) between the ages of 45-65 and 14 patients (19.2%) over 65 years of age. 18 (24.7%) patients were in the premenopausal period and 55 (75.3%) were in the postmenopausal period. According to ECOG performance score, the score of 19 (26%) patients is 0, the score of 28 (38.4%) is 1, the score of 20 (27.4%) is 2 and the score of 6

Table I: Baseline Clinic and Demographic Characteristics of 73 Patients with Cervical Cancer

		N (%)
Age	Median (range)	56 ± 11,3 (34-83)
	<45	14 (19.2)
	45-65	45 (61.6)
	≥65	14 (19.2)
Menopausal status	Pre	18 (24.7)
	Post	55 (75.3)
ECOG performance score	0	19 (26)
	1	28 (38.4)
	2	20 (27.4)
	3	6 (8.2)
Histological subtype	Squamous	58 (79.5)
	Adenocarcinoma	15 (20.5)
FIGO stage	1A	4 (5.5)
	1B	7 (9.6)
	2A	10 (13.7)
	2B	11 (15.1)
	3A	2 (2.7)
	3B	1 (1.4)
	3C	22 (30.1)
	4A	7 (9.6)
	4B	9 (12.3)
Tumor size	<4 cm	22 (30.1)
	≥4 cm	51 (69.9)
Parametrial involvement	No	25 (34.2)
	Yes	48 (65.8)
Lymph node involvement	No	37 (50.7)
	Yes	36 (49.3)
Surgery	No	48 (65.8)
	Yes	25 (34.2)
Treatment	Only surgery	11 (15.1)
	CRT	37 (50.7)
	CRT+Brachiaterapy	3 (4.1)
	CRT+Chemoterapy	12 (16.4)
	Carboplatin+Paclitaxel	10 (13.7)
Progression	No	28 (38.4)
	Yes	45 (61.6)
Status	Alive	33 (45.2)
	Death	40 (54.8)

ECOG; Eastern Cooperative Oncology Group performance status. FIGO; International Federation of Gynecology and Obstetrics

(8.2%) is 3. Tumors of 58 (79.5%) patients had squamous carcinoma histology and 15 (20.5%) patients had adenocarcinoma histology. According to FIGO staging system, 4 (5.5%) patients were stage 1A, 7 (9.6%) patients were stage 1B, 10 (13.7%) patients were stage 2A, 11 (15.1%) patients were 2B, 2 (2.7%) patients were 3A, 1 (1.7%) patients were 3B, 22 (30.1%) patients were 3C, 7 (9.6%) patients were 4A and 9 (12.3%) patients were staged as 4B. According to FIGO groups, 32 (43.8%) patients were group I and 41 (56.2%) patients were group II. Tumor size of 51 (69.9%) patients was greater than 4 cm, 48 (65.8%) patients had parametrial involvement and 36 (49.3%) patients had lymph node involvement. 25 (34.2%) of our patients underwent curative radical surgery, and 14 of these patients received simultaneous chemo-radiotherapy (CCRT). In addition, 37 (50.7%) patients had simultaneous CCRT, 3 (4.1%) patients had CCRT + brachytherapy, 12 (16.4%) patients had CCRT + chemotherapy, and 10 (13.7%) patients had palliative standard chemotherapy (carboplatin + paclitaxel). At the end of the median follow-up period of 45 months (3-180 months), progression was detected in 45 (61.6%) of our patients and 40 (54.8%) patients died. The 5-year survival rate was 37.5% for all patients, 75% for FIGO group I, and 12% for group II.

48 (65.7%) of our patients were diagnosed as CC between 2000 and 2013 and 25 (34.3%) were diagnosed between 2014 and 2017. Of the 25 patients diagnosed after 2014, 14 (56%) were stage 3-4 and 11 (44%) were stage 1-2. However, among patients diagnosed before 2014, 27 (56.25%) were FIGO stage 3-4, 21 (43.75%) were stage 1-2. According to chi-square analysis, no relationship was found between FIGO stage groups and year of diagnosis (p: 0.984).

The life expectancy according to clinical and pathological parameters is shown in Table 2. Median PFS and OS times were 44 months and

Table II: Overall and Progression-free survival times according to clinical and pathological parameters

	Total (n)	Total (%)	PFS			OS		
			Mean	Median	p	Mean	Median	p
Age								
<45	14	19.2	72.2	30	0,426	83.2	56	0.546
45-65	45	61.6	81.9	52		90.9	80	
≥65	14	19.2	47.6	38		66.6	45	
Hormonal status								
Premenapaus	18	24.7	82.9	36	0,573	92.8	107	0.624
Post	55	75.3	68.1	44		80.9	78	
ECOG groups								
0-1	47	64.4	99.9	108	0,000	115.9	129	0,000
2-3	26	35.6	24.3	13		28.8	20	
Histologic Subtype								
Squamous	58	79.5	70.5	38	0,990	80.9	56	0.704
Adenocarcinoma	15	20.5	72.8	72		90.8	107	
FIGO groups								
I (stage 1-2)	32	43.8	126.9	129	0,000	135.5	129	0,000
II (stage 3-4)	41	56.2	25.2	19		43.3	24	
Tumor size								
<4 cm	22	30.1	135.5	129	0,000	141.2	129	0,000
≥4 cm	51	69.9	37.5	19		57.5	32	
Parametrial involvement								
No	25	34.2	148.5	NR	0,000	161.4	NR	0,000
Yes	48	65.8	40.2	19		54.4	30	
Lymph node involvement								
No	37	50.7	116.5	129	0,000	132.1	129	0,000
Yes	36	49.3	22.5	16		36.5	22	
Surgery								
No	48	65.8	52.7	25	0,002	65.2	43	0,002
Yes	25	34.2	111.1	129		124.1	129	
Overall	73	100	71.9	44		84.2	78	

ECOG; Eastern Cooperative Oncology Group performance status, FIGO; International Federation of Gynecology and Obstetrics

78 months at the time of analysis. There was no statistically significant difference in PFS (p: 0.426, p: 0.573, p: 0.896, respectively) and OS times (p: 0.546, p: 0.624, p: 0.915, respectively) in terms of age groups, hormonal status and histological subtypes. The median PFS / OS times of patients with ECOG performance score 0-1 was longer than those with a score of 2-3 (PFS: 108 vs. 13 months, p: 0,000, OS: 129 vs 20 months, p: 0,000). The median PFS / OS of FIGO group 1 was 129/129 months, and of group 2 was 19/24 months, and survival times of group I was statistically longer (p: 0,000, p: 0,000, respectively). Although the median PFS / OS times of the patients without parametrial

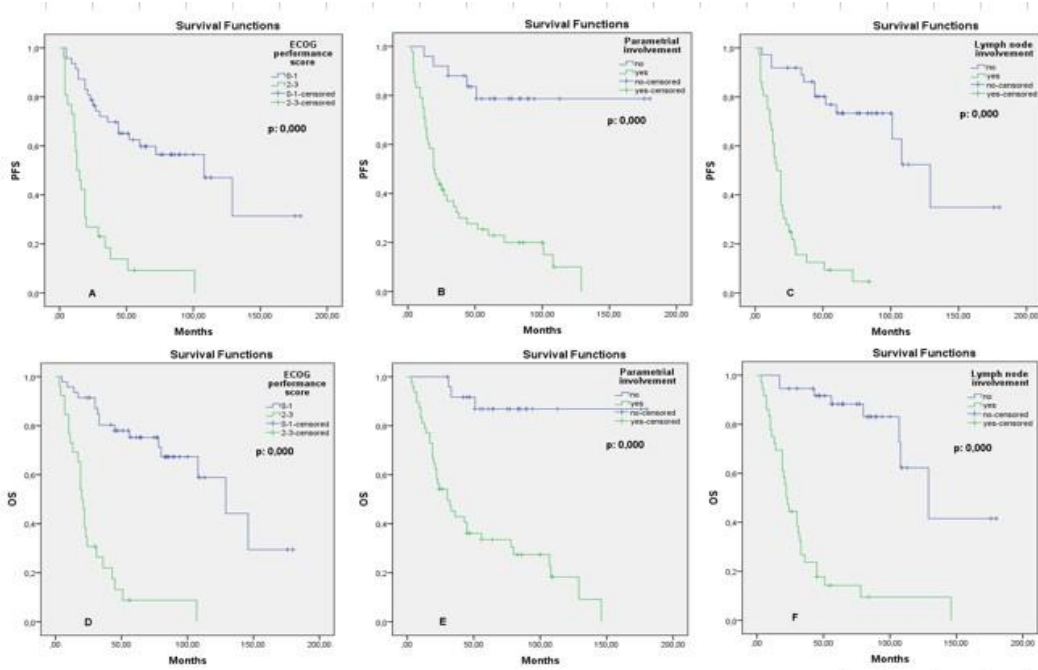
involvement were not reached, they were longer than those with involvement (p: 0,000, p: 0,000, respectively). Patients with lymph node involvement had statistically shorter PFS and OS than those without lymph node involvement (PFS: 16 vs. 129 months, p: 0,000, OS: 22 vs 129 months, p: 0,000) (Figure 1). Cases who undergone surgery had longer PFS and OS (PFS: 129 vs 25 months, p: 0.002, OS: 129 vs. 43 months, p: 0.002).

The prognostic significance of clinicopathological data for PFS and OS is shown in Table 3; According to univariate analysis, ECOG performance status, FIGO stage, tumor size, parametrial involvement, lymph node involvement and surgery have prognostic significance for both PFS and OS. However, in multivariate analysis, ECOG performance status, parametrial involvement, and lymph node involvement were independent prognostic factors for both PFS (p:0,006, p:0,004, p:0,023, respectively) and OS (p:0,000, p:0,012, p:0,017, respectively).

DISCUSSION

Although incidence and mortality rates have started to decrease especially in developed countries due to HPV screenings for CC, it is still an important cause of death for women worldwide⁷. Therefore, we wanted to reveal the survival rates of CC patients in our country and clinicopathological features that can predict this. In our study group, patients with good ECOG performance, in FIGO group I, and those without parametrial and lymph node involvement had both longer PFS and OS. According to multivariate analyzes, ECOG performance status, parametrial involvement and lymph node involvement are independent prognostic factors for both PFS and OS.

Figure 1: PFS and OS times according to clinicopathologic characteristics.



ECOG performance score (A-D), Parametrial involvement (B-E), Lymph node involvement (C-F)

Table III: Univariate and Multivariate Analysis of Potential Prognostic Factors for OS and PFS

OS	Univariate		Multivariate	
	HR	p	HR	p
Age	1,180 (0,714-1,949)	0,518	-	-
Menopausal status	1,203 (0,572-2,728)	0,626	-	-
ECOG performance status	7,907 (3,887-16,083)	0,000	4,662 (2,204-9,859)	0,000
Histologic subtype	0,858 (0,388-1,898)	0,705	-	-
FIGO stage	9,514 (3,925-23,058)	0,000	0,822 (0,155-4,370)	0,818
Tumor size (<4 cm vs ≥4 cm)	7,444 (2,615-21,188)	0,000	2,090 (0,688-6,347)	0,194
Parametrial involvement (No vs Yes)	10,466 (3,212-34,10)	0,000	4,826 (1,413-16,486)	0,012
Lymph node involvement (No vs Yes)	9,972 (4,460-22,299)	0,000	6,069 (1,379-26,719)	0,017
Surgery (No vs Yes)	0,290 (0,128-0,658)	0,003	0,877 (0,369-6,347)	0,765
PFS	Univariate		Multivariate	
	HR	p	HR	p
Age	1,174 (0,722-1,908)	0,517	-	-
Menopausal status	1,222 (0,604-2,472)	0,577	-	-
ECOG performance status	5,090 (2,713-9,550)	0,000	2,476 (1,298-4,723)	0,006
Histologic subtype	0,995 (0,477-2,077)	0,990	-	-
FIGO stage	14,055 (5,346-36,656)	0,000	2,195 (0,541-8,908)	0,271
Tumor size (<4 cm vs ≥4 cm)	9,334 (3,274-26,614)	0,000	2,541 (0,820-7,875)	0,106
Parametrial involvement (No vs Yes)	7,453 (2,922-19,007)	0,000	4,425 (1,626-12,046)	0,004
Lymph node involvement(No vs Yes)	9,872 (4,548-21,429)	0,000	3,682 (1,201-11,295)	0,023
Surgery (No vs Yes)	0,330 (0,158-0,689)	0,003	1,051 (0,476-2,316)	0,903

ECOG; Eastern Cooperative Oncology Group performance status, FIGO; International Federation of Gynecology and Obstetrics

Most of cervical carcinomas originate from the junction of endocervical primary columnar epithelium and ectocervical squamous epithelium. HPV-related chronic infection in this region transform into invasive carcinoma

period approximately in 8-15 years. Therefore, although cervical- squamosal -carcinoma decreased a little with the spread of screening programs and HPV vaccination, it is still constitutes 70-80% of all CCs⁸. In addition, approximately 20% of CCs is composed by adenocarcinoma and an increase detected in last 3 decades. The reason for this condition is attributed to the inability of screening methods to detect adenocarcinomas effectively⁹. Although some investigators have found no difference in survival according to histological subtype, both early and advanced stage adenocarcinomas have a shorter survival than the same stage squamous-carcinomas according to the SEER database which includes 24562 CC patients (39% and 21% higher risk of death for early and advanced-stage carcinomas, respectively)^{10,11}. In our study, although histological subtype rates were in accordance with the literature, findings of our study were incompatible with SEER database and no difference was found between the survival time and histological subtype. We think that primarily this may be due to the small number of patients in our study. In addition, in our study, 5-year survival rates were lower than the world-wide (37.5% vs. 66%, respectively). In our study group, the patients had more advanced FIGO stage (43.8% vs. 56.2, respectively) and the higher median age (56 vs. 47, respectively) than the literature and these may be the factors causing these results.

The prognosis of CC is particularly related to many other tumoral characteristics not included in staging systems. Prognostic significance of various factors in CC such as age, peritoneal cytology, hemoglobin level, platelet count, cyclooxygenase expression, galectin expression, PIKC3A mutation and PET-CT

volumetric parameters have been demonstrated in various studies. However, lymph node involvement is still one of the most important prognostic factors^{12,13}. Delgado et al. in their study of 732 operated CC patients, found 5-year survival rates of patients with negative lymph node as 85-95% and patients with positive lymph node as 45-55%¹⁴. In another study, tumor size greater than 6 cm, presence of pelvic lymph node involvement and presence of distant metastasis were found as independent factors for OS in 85 patients treated with CCRT¹⁵. In their study of 163 early stage (stage 1-2) CC patients, Park et al. found that tumor stage and lymph node involvement were independent prognostic factors¹⁶. In the study of Shinohara et al., they found 6 histopathologic factors as prognostic. They found that in 130 stage 1-2 CC patients who underwent radical hysterectomy and radiotherapy, those with parametrial invasion, venous infiltration, pelvic lymph node metastases, thickness of the residual muscular layer (<5 mm), tumor depth (≥ 13 mm), and invasive tumor growth pattern had shorter life expectancy¹⁷. In our study, we found that ECOG performance status, parametrial involvement and lymph node involvement were independent prognostic factors for both PFS and OS in multivariate analyzes in accordance with the literature. In addition, we showed that the most predictive parameter for PFS was parametrial involvement and lymph node involvement was the most predictive factor for OS. However, contrary to expectations, FIGO groups were prognostic for PFS/OS in univariate analyzes but not independent factors in multivariate analyzes. We attributed this situation to the fact that parametrial and lymph node involvement within the criteria of the FIGO stage is more prognostic than other criteria or because of the small number of our patients. Therefore, we think that FIGO staging system still has serious prognostic importance in CC and should be taken into consideration when planning the treatment.

The pap-smear test is on the use for CC screening worldwide and is based on microscopic examination of cells from the cervical region and has been used in our country since 2004. However, under the leadership of our Ministry of Health, HPV DNA screening has been started in primary health care institutions since 2014 in our country. With HPV DNA screening test, HPV nucleic acids from peripheral blood can be detected without the need for colposcopic examination and more sensitive (94.6% vs. 55.4%, respectively) and similar specific (94.1% vs. 96.8%, respectively) results can be obtained (94.1% vs. 96.8%, respectively)¹⁸. The first results of this screening program launched in Turkey were reported in 2018¹⁹. Above one million women aged between 30 and 65 years have been reached in approximately one and a half years, HPV DNA positivity was found in 3.5% (n: 37515) and CC was detected in 85 of these patients. However, in that study, there was no information about the stages and treatments of patients with cancer. Although the rate of early stage disease is expected to increase in patients diagnosed after 2014 due to the increased number of patients screened, in our study the effects of this could not be seen. There was no difference in terms of FIGO stage groups of patients between diagnosed before and after 2014 (p: 0.984). Our clinic serves patients coming from many cities and rural areas around Erzurum province where our clinic is located, and the Eastern Anatolia region is one of the regions which are more backward socio-culturally and have more closed lifestyles. Because of this, women more likely to hide their gynecological diseases, avoid gynecological examinations and do not show adequate participation in screening programs so, we think that this may be the reason. However, as the screening program continues, positive effects are expected to occur eventually.

Our study has certain limitations such as being retrospective and low number of patients. Therefore, it is useful to confirm our results with prospective, multicentric and more patient-numbered studies.

CONCLUSION

Despite the ongoing screening methods, CC is still an important public health problem. Although there is a significant decrease in CC-related mortality rates in developed countries, CC is still one of the major causes of cancer-related mortality in women in developing countries. In our country, the studies that determine the life expectancy and predict the characteristics of CC patients are very limited. For this reason, we wanted to present the follow-up results of CC patients in our clinic and we found that the patients in our study group had lower five-year survival rates than the world average. We detected that ECOG performance status, parametrial involvement, and lymph node involvement were independent prognostic factors for both PFS and OS, and although HPV DNA screening began, there was still no improvement in the stage of presentation at the time of admission. These results show us that all women in our country should be made more aware about this issue, especially in our eastern regions.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare that they have no conflict of interest.

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