Cumhuriyet Tıp Derg 2010; 32: 303-314
Cumhuriyet Med J 2010; 32: 303-314

Original research-Orijinal araştırma

Multivariate analysis of prognostic factors in patients with stage IB cervical cancer who underwent radical hysterectomy

Radikal histerektomi yapılan evre IB serviks kanserli hastalarda prognostik faktörlerin çok değişkenli analizi

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Abstract

Aim. The aim of this study was to assess the effects of prognostic factors on survival of cervical cancer patients. **Methods.** Data obtained from 193 patients who had been diagnosed as stage IB cervical cancer and underwent a type III radical hysterectomy and a systematic bilateral pelvic plus para-aortic lymphadenectomy between 1993 and 2007 were reviewed. **Results.** Twenty-three were excluded from the study as they have lost to follow-up immediately after surgery. Mean age was 53 years and median follow up was 62 months. During follow-up, recurrence was developed in 27 patients, while 26 died. In univariate analysis, the presence of metastasis in any lymph node, involvement of pelvic or para-aortic lymph nodes and adjuvant radiotherapy were significant factors in terms of disease free survival (DFS) and overall survival (OS) rate. Age and the lymphovascular space invasion were significant factors only for OS rate, whereas the depth of stromal invasion only for DFS rate. Tumor size, stage, cell type, grade, parametrial involvement, and positive surgical margins had no prognostic value. In multivariate analysis, presence of metastasis in any lymph node, pelvic lymph node involvement and age were found as independent prognostic factors for both DFS and OS. Stromal invasion was found as an independent prognostic factor only for DFS. However, no significance was found for para-aortic lymph node involvement, lymphovascular space invasion and adjuvant therapy. **Conclusion.** In the present study, only the lymph node status was an important factor among those determining patients with a high risk after early stage radical hysterectomy. Furthermore, it was found that age also had an important effect on survival rate as much as lymph node status had.

Key words: Cervical cancer, prognostic factors.

Özet

Amaç. Bu çalışmada serviks kanserinde prognostik etkisi olduğu düşünülen faktörlerin yaşam oranları üzerindeki etkisi değerlendirildi. **Yöntem.** 1993-2007 tarihleri arasında evre IB serviks kanseri tanısı alan, tip III radikal histerektomi ve sistematik bilateral pelvik+para-aortik lenfadenektomi geçiren 193 hastanın verileri gözden geçirildi. **Bulgular.** 23 hasta cerrahiden hemen sonra kontrollere gelmediğinden çalışma dışı bırakıldı. Değerlendirilen 170 hastanın yaş ortalaması 53 yıldı, ortanca takip süresi 62 aydı. Bu süre içinde 27 hastada nüks geliştiği ve 26 hastanın öldüğü belirlendi. Univaryant analizde herhangi bir lenf nodunda metastaz varlığı, pelvik veya para-aortik lenf nodu tutulumu ve adjuvan radyoterapi hastalıksız yaşam oranı (DFS) ve sağ kalım oranı (OS) için anlamlıydı. Yaş ve lenfovasküler alan invazyonu sadece OS için, stromal invazyon derinliğiyse sadece DFS için anlam taşımaktaydı. Tümör boyutu, evre, hücre tipi, grade , parametrial tutulum ve cerrahi sınır pozitifliğinin prognostik değerinin olmadığı görüldü.

Multivaryant analizde ise herhangi bir lenf nodunda metastaz varlığı, pelvik lenf nodu tutulumu ve yaşın, hem DFS hemde OS için bağımsız prognostik faktörler olduğu saptandı. Stromal invazyon sadece DFS için bağımsız prognostik faktördü. Buna karşın para-aortik lenf nodu tutulumu, lenfovasküler alan invazyonu ve adjuvan radyoterapinin anlamlı olmadığı belirlendi. **Sonuç.** Bu çalışmada erken evrede radikal histerektomi sonrası yüksek-riskli grubu belirleyen faktörlerden sadece lenf nodu durumunun önemli olduğu görüldü. Bunun yanı sıra yaşın lenf nodu durumu kadar yaşam oranları üzerine etkili olduğu saptandı.

Anahtar sözcükler: Serviks kanseri, Prognostik faktörler

Geliş tarihi/Received: November 11 2009; **Kabul tarihi/Accepted:** September 24 2010

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Introduction

Cervical cancer is clinically staged according to FIGO criteria. In 1995, a revision was made in this staging system and stage IB divided into two subgroups by using 4cm as cut-off value: IB1 ≤4cm and IB2 >4cm [1]. As one cannot say extent of invasion by the clinical staging system used in the cervical cancer, it also does not reflect a homogenous patient group. Thus, the treatment planned according to this clinical stage can be inadequate in some patients, while it can cause unnecessary therapies in some others.

In cervical cancers, the treatment plan relies on stage and surgical-pathological risk factors. Adjuvant chemoradiotherapy is given to the patients who are at high risk after surgery in terms of recurrence. However, prognostic values of the factors which are considered as high risk including lymph node metastasis [2-4], positive surgical margins [5,6] and parametrial invasion [7-10] are controversial. On the other hand, there is also an ongoing debate on factors which are not considered as high risk including depth of stromal invasion [7], cell grade [7, 8], tumor size [9, 12], lymphovascular space invasion [11-13], cell type [14, 15] and age [16]. In the present study, it was aimed to determine prognostic factors in stage IB cervical cancer.

Materials and methods

Data obtained from 193 patients with sufficient pathological records who had been diagnosed as stage IB cervical cancer and underwent type III radical hysterectomy and systematic bilateral pelvic plus para-aortic lymphadenectomy between 1993 and 2007 with pathology diagnosis including squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma were reviewed. As it is used in stage IB tumors and is thought to improve surgical-pathological risk factors, patients receiving neo-adjuvant therapy excluded from the study. Patients were clinically staged according to FIGO staging system by examining under general anesthesia and using computerized tomography, magnetic resonance imaging and intravenous pyelogram, when needed. Patients who were treated before 1995 were re-staged as IB1 and IB2 upon patients' records. Post-operative radiotherapy (adjuvant radiotherapy) was given to high risk group (positive surgical margin, presence of tumor in parametrium and tumor invasion at lymph node) after radical surgery. Effects of age, stage, surgical-pathological factors (cell type, parametrial invasion, lymph node involvement, depth of cervical stromal invasion, tumor size, tumor grade, positive surgical margin and LVSI) and adjuvant radiotherapy on survival were investigated. Numeric values and differences in rate were assessed by chi-square test and ANOVA table. Univariate analysis was performed by using Log Rank test. Statistical power of factors those were found as significant in univariate analysis were assessed in multivariate analysis by using Cox regression model. Kaplan-Meier

method was used for survival analysis. $p<0.05$ was considered as significant.

Results

Twenty-three patients were excluded from the study as they have lost to follow-up immediately after surgery. Furthermore, there was no data regarding final status of 19 patients; but they were included in analysis as they had follow-up period ranging from 13 to 124 months. In 170 patients included in analysis, mean age 53 years (range: 34-80) and median tumor size was 30mm (range: 5-70). Tumor size was ≤20 mm in 35.9%, 21-30 mm in 28.8%, 31-40 mm in 25.9% and ≥40 mm in 9.4% of the patients. Cell type was squamous cell carcinoma in 90% of patient group. A lymph node metastasis was present in any of lymph nodes (at least one lymph node metastasis regardless of region) in 32.4% of the patients. Average number of removed lymph node was 53 (range: 13-113, median: 50). Number of removed lymph node was ≤20 in 4.7% and ≤25 in 8.8% of the patients. General characteristics and surgical-pathological outcomes of study group were shown in Table 1.

Table 1. Characteristics and surgico-pathological risk factors

Parameter		Mean (min-max) / n (%)
Age		53 (34-80, median:52)
Tumor size (mm)		29 (5-70, median:30)
Tumor size (mm)	≤20	61 (35.9)
	21-30	49 (28.8)
	31-40	44 (25.9)
	>40	16 (9.4)
Stage	IB1	154 (90.6)
	IB2	16 (9,4)
Cell type	Squamous	134 (78.8)
	Adenocancer	26 (15.3)
	Adenosquamous	10 (5.9)
Grade	1	22 (12.9)
	2	128 (75.3)
	3	20 (11.8)
Ovarian status	Ovarian transposition	29 (17.1)
	Bilateral oophorectomy	141 (82.9)
Parametrial invasion	Negative	142 (83.5)
	Positive	28 (16.5)
Surgical border invasion	Negative	156 (91.8)
	Positive	14 (8.2)
Lymphovascular space invasion	Negative	72 (42.4)
	Positive	98 (57.6)
Stromal invasion	≤1/2	65 (38.2)
	>1/2	105 (61.8)
Lymph node metastasis[a]	Negative	115 (67.6)
	Positive	55 (32.4)
Number of removed lymph node		53 (13-113, median:50)
Number of metastatic lymph node		4 (1-19, median:2)
Site of metastatic lymph node	Pelvic	47 (27.6)
	Para-aortic	2 (1.2)
	Pelvik and para-aortic	6 (3.5)
Adjuvant radiotherapy	Not received	58 (34.1)
	Received	112 (65.9)

Median follow-up was 62 months (range: 1-182). During follow-up, recurrence was detected in 27 (15.9%) patients. It was seen that, of these recurrences, 51.9% was developed within first year and 77.8% was developed within 3 years. It was found that pelvic only recurrence occurred in 9,4% and distance only recurrence in 5.3% of patients, while both pelvic and distance recurrence occurred in 1.2% of the patients. Mean duration

from radical surgery to recurrence was 21.6 months (range:3-66; median:12). During follow-up period, it was found that 26 (15.3%) patients died. 30.8% of deaths occurred within first year, whereas 76.9% within 3 years. Mean duration from radical surgery to death was 26.9 months (range: 1-83; median:18).

In univariate analysis, presence of metastasis in any lymph node, pelvic lymph node involvement, para-aortic lymph node involvement and adjuvant radiotherapy decreased disease free survival (DFS) and overall survival rate (OS) (Table 2). LVSI and younger age solely worsened OS rate, while depth of stromal invasion solely worsened DFS rate. OS decreased from 91% to 81% in the presence of stromal invasion (p=0.080). It was seen that stage, tumor size, cell type, grade, parametrial involvement and positive surgical margin had no prognostic value.

In multivariate analysis, factors found to be significant in univariate analysis were assessed and it was found that presence of metastasis in any lymph node, pelvic lymph node involvement, para-aortic lymph node involvement and age were found as independent prognostic factors for both DFS and OS rate (Table 3).

Table 2. Prognostic factors and survival; univariate analysis

Parameter		DFS	p	OS	p
Age	≤50	%79	0.113	%78	0.028
	>50	%88		%90	
Stage	IB1	%85	0.363	%86	0.326
	IB2	%77		%77	
Cell type	Squamous	%82	0.163	%83	0.186
	Other[a]	%92		%92	
Grade	1	%77	0.523	%82	0.744
	2	%84		%84	
	3	%90		%90	
Tumor size (mm)	≤20	%92	0.237	%92	0.279
	21-30	%80		%81	
	31-40	%80		%80	
	>40	%81		%81	
Lymph node metastasis[b]	Negative	%90	0.005	%91	0.0001
	Positive	%73		%71	
Pelvic lymph node metastasis	Negative	%88	0.038	%90	0.007
	Positive	%76		%74	
Para-aortic lymph node metastasis	Negative	%86	0.000	%87	0.000
	Positive	%38		%38	
Parametrial invasion	Negative	%85	0.754	%85	0.691
	Positive	%82		%82	
Surgical border invasion	Negative	%85	0.175	%85	0.513
	Positive	%71		%79	
Lymphovascular space invasion	Negative	%89	0.145	%92	0.029
	Positive	%81		%79	
Stromal invasion	≤1/2	%92	0.022	%91	0.080
	>1/2	%79		%81	
Adjuvant radiotherapy	Negative	%95	0.006	%95	0.008
	Positive	%79		%79	

[a]Adenocancer or adenosquamous cancer. [b]Pelvic and/or para-aortic.

Recurrence and mortality rate markedly impaired in the presence of these factors. Stromal invasion was an independent prognostic factor for only DFS and predicted recurrence rate. However, it was seen that LVSI and adjuvant radiotherapy had no significance. Furthermore, in multivariate analysis, presence of metastasis in para-aortic lymph node alone had no significance effect on survival rate, when compared to absence of metastasis in same nodes.

Table 3. Prognostic factors and survival; multivariate analysis

Parameter	DFS p	OS p
Age (≤50 vs >50)	0.036	0.015
Lymph node metastasis[a]	0.017	0.016
Pelvic lymph node metastasis	0.030	0.036
Para-aortic lymph node metastasis	0.062	0.097
Stromal invazyon (≤1/2 vs >1/2)	0.027	0.085
Lymphovascular space invasion	0.381	0.899
Adjuvant radiotherapy	0.350	0.629

[a]Pelvic and/or para-aortic.

Discussion

Ambiguity caused by clinical staging in cervical cancers impedes homogenization of patient groups in studies and causes differential outcomes between studies. Notably, this situation and abundance of factors those can affect prognosis increase value of multivariate analysis in cervical cancer. Results of univariate analysis have limited value and, in fact, factors which show prognostic value in univariate analysis should have no prognostic implication on survival. Results of univariate and multivariate analysis which were performed in other centers were shown in Table 4 and 5.

Table 4. Prognostic factors for cervical cancer in the other studies; results of univariate analysis

References	Stage	Therapy	Tm size	Tm volume	SBI	LN met	LVSI	PI	DSI	Age	Grd	CT	NACT
Rutledge L. (2)	IB1-2	RH	+			+	+	+	+	-	-	-	-
Lee JM (11)	IB	RH	-			+	-	-	+			-	
Kamelle SA (8)	IB2	RH	+			+	+	+	+	-	-	-	-
Trimbos JB (15)	IB-IIB	RH	+		+	+	+	+	+				
Finan MA (4)	IB1-2	RH	+			+	-	+	-	-	-	-	
Trattner M (9)	IB-IIB	RH		+	+	+	+	+	+	-	-	-	
Burghardt E (13)	IB-IIA	RH		+		+	+	+					
Kovalic JJ (10)	IIB-IIIB	RT	+					+		-			
Sevin BU (5)	I-II	RH	+	+	+	+	+		+	-	-	-	
Kawagoe T (6)	IB-II	RH	+		-	+		+		-		-	
Kristensen G (7)	IB	RH	+			+	+	+	+		-		
Comerci G (12)	IB-IIB	RH	+		-		+			-	-	-	

Tm: Tumor, LN met: Lymph node metastasis, SBI: Surgical border invasion, LVSI: Lymphovascular space invasion, PI: Parametrial invasion, DSI: Deep stromal invasion, Grd: Grade, CT: Cell type, NACT: Neoadjuvant chemotherapy, RH: Radical hysterectomy, RT: Radiotherapy,

Disease stage has poor prognostic value in cervical cancer and implies uncertainty. In a study by Finan et al. [4], stage was an independent prognostic factor and 5-year OS rate was 90% and 72.8% (RR:7.65, CI: 2.81) in stage IB1 and IB2, respectively (p=0.0001). This was supported by other studies [3, 5, 17]. On the other hand, in a study (IB1 and IB2; median follow-up: 35 months) by Rutledge et al. [2], prognostic value (DFS rate: 92.5% for IB1 and 74.3% for IB2; p=0.012) which was detected in univariate analysis have no longer seen in multivariate analysis and it was found that stage was not an independent prognostic factor. In the present study (with 62 months median follow-up), stage had no effect on survival rate. However, DFS rate was 8% higher, whereas OS rate was 9% higher in stage IB1. Lymph node status is ignored in FIGO staging system, although lymphatic system is the main way of tumor spread in cervical cancer. However, lymph node metastasis more clearly shows extent of tumor spread than stage. In the present study, rate of metastasis in any lymph node was 32.4%, whereas rate of pelvic lymph node metastasis was 27.6%. DFS rate decreased from 90% to73%, while OS rate from 91% to 71% in the presence of metastasis in any lymph node. In pelvic lymph node metastasis, DFS rate decreased by 12%, while OS rate by 16%.

Table 5. Prognostic factors for cervical cancer in the other studies; results of multivariate analysis

References	Stage	Therapy	Tm size	Tm volume	SBI	LN met	LVSI	PI	DSI	Age	Grd	CT	Stage
Rutledge L. (2)	IB1-2	RH					+		+				
Lee JM (11)	IB	RH											+
Kamelle SA (8)	IB2	RH					+						
Trimbos JB (15)	IB-IIB	RH			+	+		+					
Finan MA (4)	IB1-2	RH	+			+							
Trattner M (9)	IB-IIB	RH				+							+
Stehman FB (16)	I-IVA	RT	+			+				+			+
Burghardt E (13)	IB-IIA	RH		+		+	+	+					
Kovalic JJ (10)	IIB-IIIB	RT	+					+					+
Horn LC (3)	IIA-B	RH	+			+							+
Kawagoe T (6)	IB-II	RH	+			+							
Kristensen G (7)	IB	RH	+						+				
Fyles AW (14)	IA-IVA	RT	+			+				+	+	+	
Comerci G (12)	IB-IIB	RH	+				+						
Takeda N (31)	IB-IIB	RH				+	+	+				+	

Tm: Tumor, LN met: Lymph node metastasis, SBI: Surgical border invasion, LVSI: Lymphovascular space invasion, PI: Parametrial invasion, DSİ: Deep stromal invasion, Grd: Grade, CT: Cell type, NACT: Neoadjuvant chemotherapy, RH:Radicalhysterectomy, RT: Radiotherapy,

In univariate analysis, survival rate markedly decreased in the presence of para-aortic lymph node metastasis (DFS rate from 86% to 38% and OS rate from 87% to 38%). However, in multivariate analysis, it was seen that presence of lymph node metastasis and pelvic lymph node metastasis were independent prognostic factors, while para-aortic lymph node metastasis had no prognostic value.

This was caused by small number of patients with para-aortic lymph node metastasis (n=8). Thus, results of univariate analysis had no clear value. Relationship between lymph node metastasis and survival was demonstrated in many studies (Table 4 and 5). In a study (Stage IB-IIIB) by Trattner et al. [9], lymph node metastasis observed as a prognostic factor and OS rate decreased from 85% to 45% in the presence of lymph node metastasis (p<0.0001). Prognostic value of lymph node metastasis was demonstrated by

multivariate analysis in majority of other studies [3, 4, 6, 8, 13, 16]. On the other hand, in a study by Rutledge et al. [2], although 2-year DFS rate decreased from 89% to 63% with involvement of lymph node in univariate analysis, they failed to detect this prognostic effect in multivariate analysis. In a study by Metindir et al. [18], it was also shown that lymph node involvement had no effect on 5-year DFS rate. It is thought that tumor size affects surgical-pathological risk factors and survival in cervical cancer. In a study (Stage 1-IV), Wagenaar et al. [19], showed that cut-off value of 40mm is an important factor for stromal invasion>10mm (19% vs. 30%; p<0,01) and lymph node metastasis (10% vs. 16%; p=0.01). In a study (Stage I-II), Sevin et al. [5], showed that rate of lymph node metastasis increased from 3.2% in patients with tumor size ≤10mm to 11.5% in patients with tumor size between 11-20mm, to 23.6% in those with tumor size 21-30mm and to 31.5% in those with tumor size>30mm (p<0.001. However, in a study (Stage IB2) Rettenmaier et al. [20], detected that there was no relationship between tumor size and surgical-pathological risk factors. But patient group of this study was consisting of patients with tumor size ≥40mm. In a study of Gynecologic Oncology Group (GOG) (Stage IB, squamous cell carcinoma) by Delgado et al. [21], it was detected that cut-off values of 20mm and 30mm had no significance in predicting pelvic lymph node metastasis in patients without macroscopic disease or para-aortic extension. In the same study, rate of pelvic lymph node metastasis was 14.8% in patients with tumor size ≤20mm, whereas 19.9% in those with tumor size >20mm (p>0.05). These values were 15.4% and 23.0% for 30mm cut-off value (p>0.05). No clear relationship between tumor size and recurrence or survival. In the present study, tumor size had no prognostic value in terms of survival. There are some studies which are indicating tumor size as a significant factor for survival [2, 5-10, 19, 22-26], while there is some other studies which are showing such relationship in univariate analysis [11, 12, 17]. However, important one is the multivariate analysis. There is also some studies indicating tumor size as an independent prognostic factor [3, 6, 7, 10, 12-14, 20, 25-30], while there is others indicating opposite in multivariate analysis [2, 8, 9, 11, 15, 17, 31, 32].

In a study by Rutledge et al. [2], it was detected that survival rate of 92.5% in stage IB1 (≤40mm) decreased to 74.3% in stage IB2 (40mm) in univariate analysis (p=0.004). However, they failed to demonstrate this relationship in multivariate analysis. Finan et al. [4], reported 5-year OS rate as 90% in stage IB1 (≤40mm) and 72.3% in stage IB2 (>40mm) (p<0.0265). This difference had no significance in multivariate analysis, but tumor size was an independent prognostic factor for survival. This implies a linear relationship between tumor size and survival. In a study (Stage IIA-IIB, median follow-up: 54 months) by Horn et al. [3], it was shown that cut-off value of 40mm predict 5-year OS rate in univariate analysis (49.5% vs.67.4%; p=0.0015) and tumor size was an independent prognostic factor in this study. Stehman et al. [16], evaluated data of GOG#24, GOG#56 and GOG#59 by using multivariate analysis and demonstrated that tumor size is an independent prognostic factor. Recurrence rate and mortality rate was 3.9 and 2.5 fold higher in patient with 100mm tumor size than those with 20mm tumor size, respectively. Kovalic et al. [10], demonstrated that pelvic recurrence rate of 21% in tumor size<50mm increased to 30% when tumor size became 50mm or higher in stage IIB in their study (IIB, IIIB; median follow-up:10.7 years). Grigsby et al. [17], evaluated a patient group (IIB and IIA; median follow-up: 11 years) which was undergone surgery following radiotherapy and found pelvic recurrence rate as 16% in those with a stage IB tumor<30mm and 9% in those with a stage IB tumor>30mm. These rates were 21% and %21 for distance metastasis. The difference didn't reach statistical significance. Similar results were detected in stage IIA tumors. Tumor can spread to parametrial area by either lymphatic system or direct invasion. Clinical stage considers parametrial involvement. However, prognostic value is not as prominent as lymph node invasion. Trimbos et al. [15], demonstrated that parametrial invasion is an independent prognostic factor in locally advanced early stage (IB-IIB) bulky tumors (RR: 2.33, CI: 1.23-4.42, p=0.009). There are studies supporting results of Trimbos et al. in the literature [10, 13]. In a study (Stage

IB2, median follow up: 25 months) by Kamelle et al. [8], it was shown that parametrial involvement decreased 25 month-DFS from 82% to 53% in univariate analysis (p=0.007). Although presence of parametrial invasion increases recurrence in univariate analysis, it is also shown that it is not an independent prognostic factor in other studies [2, 4, 8]. In the present study, it was found that presence of parametrial invasion has no prognostic value. Depth of stromal invasion was an independent prognostic factor in terms of recurrence in the present study. It was seen that stromal invasion depth higher than 1/2 decreased DFS rate from 92% to 79% (p=0.027). However, depth of stromal invasion didn't predict survival. Similar to our study, Ho et al. [33], demonstrated that stromal invasion is an independent prognostic factor but has no value regarding survival. In a study with a patient group in stage IB and IIA without pelvic lymph node, Samial et al. [34], stromal invasion>10mm was found as an independent prognostic factor that predicts survival. Kriestensen et al. [7], identified stromal invasion as an independent prognostic factor in their study (IB, squamous cell carcinoma) in which they showed that DFS rate decreased as stromal invasion depth increased. Although presence of tumor in surgical margin is an indication for adjuvant radiotherapy, prognostic value of this factor have not been shown clearly. Trimbos et al. [15], (IB2-IIB, tumor size>4 cm) accepted positive surgical margin as an independent factor that predicts survival (RR:4.39, CI:2.4-0.2, p<0.001). In a study (n=113) by Trattner et al. [9], positive surgical margin was detected in 8 patients and it was found that 5-year survival rate decreased from 91% to 28% in the presence of this factor (p=0.0202). But they failed to show this effect in multivariate analysis. Similar results were also reported by Sevin et al. [5]. In our study, it was seen that positive surgical margin had no prognostic value. This finding has been supported by other studies [6, 12, 30, 34]. Data regarding incidence and prognostic value of LVSI display discrepancy. This could be explained by failure in standardization of LSVI definition. In the present study, despite no increase in recurrence rate, survival decreased from 92% to 79% in presence of LSVI (p=0.029). However, it was found that this had no prognostic value in multivariate analysis. In a study (IB2, median follow up: 25 months) by Kamelle et al. [8], it was seen that LSVI was an independent prognostic factor and DFS decreased from 93% to 62% in its' presence (p=0.0002). Similar results were reported in other studies [2, 4, 12, 13, 31, 33]. However, Lee et al. [11], showed that LSVI had no prognostic value in stage IB. Similarly, Samial et al. [34], identified that LSVI had no prognostic value in stage IB and IIA patient groups with negative lymph node. Patient age can be predictive factor in prognosis, although it isn't a pathological factor. In the present study, age was seen as an independent prognostic factor. Recurrence decreases and survival increases by advanced age. A study on stage I-IVA patient group which received radiotherapy as primary treatment by Stehman et al. [16], appears to support this conclusion. Results of Kawagoe et al.[6], Prempree et al.[35], and Stenhopoe et al.[36] were also in this way, but van der Graaf et al.[37], Meanweel et al.[38], and Sigurdsson et al. [40], suggest that young age has advantage in terms of survival. There is also, however, studies indicating that age has no prognostic value. Ho et al. [33], found that age had no significance for recurrence and survival in early stages (IB-II). In their study, 5 year survival which was 88% in patients 50 years old or elder decreased to 77% in patient younger than 50 years old, but this difference had no statistical significance (p=0,348). Similar results were reported by other studies [8, 10, 12, 30, 40, 41]. In the present study, adjuvant radiotherapy indicates poor prognosis. DFS and OS which was 95% in patients who received no adjuvant radiotherapy decreased to 79% in those who received radiotherapy (p=0.006 and p=0.008, respectively). In multivariate analysis, radiotherapy was predicting survival. However, given that adjuvant radiotherapy is given to high risk group, poor prognosis associated to this factor could be comprehensible. Thus, prognostic value of adjuvant radiotherapy alone is controversial. In a study by Sevin et al. [5], five year survival rate was found as 79% in patient who didn't need adjuvant radiotherapy, while 54% in those who received radiotherapy (p>0.0001). However, it was also shown that this factor didn't affect survival [2, 8, 9, 34]. In the present study, pathological diagnosis was squamous cell carcinoma in 78.8 of patients

and cell type (squamous, adenosquamous and adenocarcinoma) had no effect on prognosis. Similar results were shown by other studies [1, 11, 12]. However, in a study in which radical surgery was performed, Takeda et al. [31], detected that cell type, adenocarcinoma, decreased survival in stage IB-IIB patient group and they also found that it was an independent prognostic factor. Similarly, Fyles et al. [14], identified that cell type was an independent prognostic factor in their patients with stage I-IV tumor who received radiotherapy with a median follow-up of 10.1 years.

Additionally, prognostic value of factors such as cell grade, perineural invasion and hemoglobin level was attempted to be identified. However, data about their prognostic value is not as strong as above-mentioned factors. Clinical staging that was not reflecting a homogenous patient group complicates standardization of cervical cancer treatment. Treatment has to be individualized. Therefore, pre-operative and surgical-pathological risk factors have to be identified precisely regarding recurrence and, treatment has to be planned according to this. For this purpose, it is important to identify independent prognostic factors in cervical cancer.

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