

# The Distribution of Surgical-Pathologic Risk Factors in Relation to Stage in Patients with Early Stage Cervical Carcinoma

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**OBJECTIVE:** The divergence of surgical pathologic risk factors and adjuvant radiotherapy (RT) according to the stage were examined in patients with early stage cervical carcinoma.

**STUDY DESIGN:** 250 patients with adequate pathologic data who had been operated with type III radical hysterectomy were reviewed. Adjuvant RT was given in high-risk patients (tumor positive surgical margin, tumor invasion of parametrium and lymph node metastasis) after RH. Patients were staged according to the 1988 FIGO criteria. Impact of stage on surgical pathologic risk factors and possibility of adjuvant RT was evaluated.

**RESULTS:** The mean age was 53.9 years and tumor size was 30mm. 68.4% of patients was in stage IB1, 12% in IB2 and 19.6% in IIA. Pathological diagnosis was squamous cell carcinoma in 83.2% of patients. A positive correlation was identified between the stage and vaginal metastasis and stromal invasion. However stage didn't effect invasion of parametrium, lymph node metastasis, lymphovascular space invasion, tumor positive surgical margin and ratio of adjuvant RT.

**CONCLUSION:** Stage did not clearly predict surgical pathologic risk factors, a result of uncertainty of clinical staging. Without surgery, it is impossible to determine the actual limits of the disease with the tests available at this time.

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**Key Words:** Cervical carcinoma, Stage, Pathologic risk factors

## Introduction

Cervical cancer is second most common cancer and it is third most common killer in women (after breast and lung cancer).<sup>1</sup> Cervical cancer is staged clinically different from other gynecologic cancer.

In early cervical cancer important prognostic factors are tumor size (cervix size, depth of invasion), lymph node metastasis and lymphovascular space invasion (LVSI)<sup>2</sup>

In this study, the distribution of surgical- pathologic risk factors in relation to stage were evaluated

## Material and Methods

Medical records of patients with stage IB-IIA cervical carcinoma who underwent type III radical hysterectomy between 1993 and 2007 were reviewed retrospectively. The data from

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two hundred fifty patients with adequate pathologic report were assessed

Patients were staged according to the 1988 FIGO staging system by using upper abdominal tomography, pelvic MRI (intravenous pyelography as needed) and recto-vaginal pelvic examination under general anesthesia. The effect of staging on surgical-pathologic risk factors and possibility of receiving postoperative radiotherapy (adjuvant RT) were evaluated.

Patients with high-risk received adjuvant RT. Adjuvant RT criteria; until 2001 one major factor (positive lymph nodes, parametrial invasion, surgical margin invasion and tumor size  $\geq 4$ cm) or two minor factors (lymphovascular space invasion [LVSI], stromal invasion  $>1/2$ , tumor size: 2-4cm and more than two microscopic lymph nodes) exist, since 2001 at least one of these is positive; lymph node, parametrial invasion, and surgical border invasion.

Descriptive statistics were calculated using the SPSS (Statistical Package for Social Sciences) 12.0 package program (SPSS Inc, Chicago IL, USA). Chi-square test was used to evaluate proportions for statistical significance. The cut-off for statistical significance was set at  $P < 0.05$ .

## Results

The mean age was 53.9 years (31-80, median: 52) and

mean tumor size 30mm. (5-70, median: 30). 68.4% of the patients were stage IB1, 12% were stage IB2 and 46.6% were stage IIA. Neoadjuvant chemotherapy (NACT) was applied to

7.2% of the patients. Pathological diagnosis was squamous cell carcinoma in 83.2% of the patients. Surgical pathological results were demonstrated in table 1.

Table 1. Patients' characteristics and histopathologic results

Parameter		Mean (range)/n(%)
Age		53.9 (31-80) (median:52)
Tumor size (mm)		30 (5-70) (median:30)
Stage	B1	171 (68.4)
	IB2	30 (12)
	IIA	49 (19.6)
Histopathology	Squamous	208 (83.2)
	Adenocancer	33 (13.2)
	Adenosquamous	9 (3.6)
NACT	Negative	232 (92.8)
	Positive	18 (7.2)
BSO	Negative	45 (18)
	Positive	205 (82)
Parametrial invasion	Negative	207 (82.8)
	Positive	43 (17.2)
Surgical border invasion	Negative	226 (90.4)
	Positive	24 (9.6)
LVSI	Negative	109 (43.6)
	Positive	141 (56.4)
Stromal invasion	<1/2	93 (37.2)
	>1/2	157 (62.8)
Ovarian metastasis	Negative	247 (98.8)
	Positive	3 (1.2)
Vaginal metastasis	Negative	199 (79.6)
	Positive	51 (20.4)
Lymph node metastasis	Negative	165 (66)
	Positive	85 (34)
Number of removed lymph nodes		53.4 (13-160) (median:52)
Number of positive lymph nodes		4.1 (1-39) (median:2)
Site of positive lymph nodes	Pelvic	72 (28.8)
	Paraortic	2 (0.8)
	Pelvic-Paraortic	11 (4.4)
Postoperative RT	Negative	83 (33.2)
	Positive	167 (66.8)

BSO: Bilateral salpingo-oophorectomy,  
NACT: Neoadjuvant chemotherapy

LVSI: Lymphovascular space invasion,  
RT: Radiotherapy

Parametrial invasion, lymph node metastasis, paraaortic lymph node metastasis, surgical border invasion, LVSI and ovarian metastasis didn't change according to the stage (Table 2, Table 3). However, while lymph node invasion was 29.8 % in stage IB1, it was 43.3 % in IB2 and 42.9% in IIA. Surgical border invasion was more common in stage IIA ( $p=0.188$ ). Parametrial invasion in stage IB2 was higher than others

There was a positive correlation between stage and vaginal metastasis and depth of invasion. While the vaginal metastasis

was 14.6% in stage IB1, it was 23.3 % in stage IB2 and 38.8% in stage IIA. Deep stromal invasion ratio was higher in stage IIA (Table 3).

Stage didn't affect the possibility of adjuvant RT ( $p=0.059$ ). However 62% of patients with stage IB1 received adjuvant. This rate was 76.7% in IB2 and 78.8% in stage IIA (Table 4)

**Table 2: The distribution of parametrial invasion, lymph node metastasis, paraaortic lymph node invasion and surgical border invasion in relation to stage**

Stage	Parametrial invasion		Lymph node <sup>1</sup> metastasis		Paraaortic LN		Surgical border invasion	
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
IB1	146 (%85.4)	25 (%14.6)	120 (%70.2)	51 (%29.8)	162 (%94.7)	9 (%5.3)	158 (%92.4)	13 (%7.6)
IB2	21 (%70)	9 (%30)	17 (%56.7)	13 (%43.3)	28 (%93.3)	2 (%6.7)	27 (%90)	3 (%10)
IIA	40 (%81.6)	9 (%18.4)	28 (%57.1)	21 (%42.9)	47 (%95.9)	2 (%4.1)	41 (%83.7)	8 (%16.3)
P	0.117		0.122		0.880		0.188	

<sup>1</sup> Pelvic + Paraaortic lymph node metastasis

LN: Lymph node

**Table 3: The effects of stage on LVSI, ovarian metastasis, vaginal metastasis and stromal invasion**

Stage	LVSI		Ovarian metastasis		Vaginal metastasis		Stromal invasion	
	Negative	Positive	Negative	Positive	Negative	Positive	< 1/2	> 1/2
IB1	74 (%43.3)	97 (%56.7)	169 (%98.8)	2 (%1.2)	146 (%85.4)	25 (%14.6)	70 (%40.9)	101 (%59.1)
IB2	16 (%53.3)	14 (%46.7)	29 (%96.7)	1 (%3.3)	23 (%76.7)	7 (%23.3)	13 (%43.3)	17 (%56.7)
IIA	19 (%38.8)	30 (%61.2)	49 (%100)	-	30 (%61.2)	19 (%38.8)	10 (%20.4)	39 (%79.6)
P	0.443		0.417		0.001		0.024	

<sup>1</sup> Pelvic + Paraaortic lymph node metastasis

LN: Lymph node

**Table 4: The effects of stage on the possibility of receiving adjuvant RT**

Stage	Adjuvant RT	
	Negative	Positive
IB1	65 (%38)	106 (%62)
IB2	7 (%23.3)	23 (%76.7)
IIA	11 (%22.4)	38 (%78.8)
P	0.059	

RT: Radiotherapy

## Discussion

The importance of early stage cervical cancer is increasing from point of view of gynecologic oncologists for the rate of the patients gets increased in this stage. Despite early cervical cancer was cured with radical hysterectomy and pelvic lymphadenectomy and/or radiotherapy in last two decades, the mortality rate of the patients didn't change.<sup>3-4</sup>

Lymph node metastasis is an important prognostic factor for cervical cancer. Patients with stage IB-IIB cervical cancer who have pelvic lymph node metastasis have 5-years survival rate of 64-68.2%. This rate falls to 33.3-35% in paraaortic invasion.<sup>5-8</sup> The cervical cancer stages according to 1988 Federation of Gynecology and Obstetrics (FIGO) staging system. Because of this cancer staged as a clinically (with imaging modalities and pelvic examination), it differs from other gynecologic cancer. The management of cervical cancer principally depends on stage. Despite the status of retroperitoneal lymph nodes is one of the main prognostic factors and it determines the treatment modality, it is ignored in FIGO staging system.<sup>9</sup>

In this study, the rate of lymph node metastasis was 29.8% in stage IB1 and 43.3% in stage IB2 and 42.9% in stage IIA. Stage didn't effect lymph node metastasis ( $p=0.122$ ). Sakuragi et al. reported that pelvic lymph node metastasis was 11.5% in stage IB and 26.4% in stage IIA (10). The rate of lymph node metastasis changed 0.3 % to 1.4 % in stage IA1 and 0% to 5% in stage IA2 in the studies carried out depending on FIGO 1995 classification. The results of other studies are supporting our studies and it has been reported that pelvic lymph node metastasis is 12-22% for stage IB patients and 10-27% for stage IIA .<sup>11-14</sup>

In early cervical cancer the effects of LVSI is not clear on survival. While some authors state that LVSI is a risk factor for survival, others don't accept this. In studies carried out by Ho et al. lymph node metastasis was determined in 38% of patients with LVSI and 15% of patients without LVSI.<sup>15</sup> These results support the invasion of tumor cells along with lymphovascular invasion to lymph nodes. In the studies carried out depending on FIGO 1995 classification, it was determined that lymphovascular invasion was 17% in stage IA1 and 21.5-25% in stage IA2.<sup>11-16</sup> Burghandt et al. found out that, LVSI was 39% in stage IA and it was 46% in stage IB-IIB. Lymph node invasion was determined in %40 of cases.<sup>17</sup> In the study published from Turkey, the result of 200 patients who were diagnosed to have early stage cervical cancer (33 of them were stage IA, 18 were IIA, 149 were IB) and who had abdominal hysterectomy and bilateral salphingo-oophorectomy were evaluated.<sup>18</sup> In 83% of all patients, LVSI was determined %77 of those who had LVSI were IB. 21% of the patients who were in stage IB had lymph node metastasis. In this study, LVSI was

56.7% of patients in stage IB1, 46.7% of patients in stage IB2 and 61.2% of them stage in IIA. The possibility of LVSI didn't change in relation to stage.

It is known that cervical cancer invades parametrial tissues directly or by means of lymphatic embolization. In spite of the improvements in the imaging techniques like MRI, preoperative parametrial invasion still can not be determined clearly. For this reason the only way to reveal the invasion of parametrium is histological examination.<sup>19</sup> Stage IA and IB1 has been successfully treated by removing a part of parametrium or the whole. After radical hysterectomy among the patients who have cervical cancer in stage IA-IB1, the survival rates of 5-years reached to 90-95%.<sup>20</sup>

In the study of Steed et al., parametrial invasion was determined as 5% in patients with stage IA and IB1 in correlation with the literature.<sup>19</sup> In our study, parametrial invasion was determined in 14.6% of stage IB1 cases, 30% of stage IB2 cases and 18.4% of stage IIA cases. Parametrial invasion that are important prognostic risk factors like LVSI and lymph node metastasis in early cervical cancer were not affected by stage.

After radical hysterectomy, radiotherapy and/or chemotherapy are used in patients who have high-risk of relapse to eradicate microscopic and residual tumor.<sup>21</sup> In this study, it was determined that stage didn't affect the possibility of postoperative radiotherapy. While 62% of those with stage IB1 received adjuvant radiotherapy, this rate increased to 78.8% in stage IIA ( $p=0.059$ ).

In this study a positive correlation was identified between the stage and vaginal metastasis and stromal invasion. Vaginal metastasis was determined in 14.6% of stage IB1 patients, 23.3% of stage IB2 patients and 38.8% of stage IIA patients. The rate of deep stromal invasion was 59.1% in stage IB1, 56.7% in stage IB2 and 79.6% in stage IIA.

It was observed that surgical margin invasion, parametrial invasion, lymph node metastasis and paraaortic lymph node invasion that are accepted as important prognostic factors in early cervical cancer didn't change in relation to stages. It was stated that the result of uncertainty caused by clinically staging of cervical cancer. We can not show the invasion of disease clearly with current imaging methods. For this reason survival rates reported especially for early cervical cancer have been changing.

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## Erken Evre Serviks Kanserli Hastalarda Cerrahi Patolojik Risk Faktörlerinin Evreye Göre Dağılımı

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Erken evre serviks kanserinde cerrahi patolojik risk faktörlerinin ve adjuvant radyoterapinin (RT) evreye göre değişimi incelendi. Evre IB-IIA olup tip III radikal histerektomi (RH) yapılan ve patoloji kaydı yeterli olan 250 hastanın verileri gözden geçirildi. RH sonrası yüksek-riskli hasta grubuna (cerrahi sınır pozitifliği, parametriumda tümör varlığı ve lenf nodu metastazı) adjuvant RT verildi. Hastalar 1988 FIGO kriterleri kullanılarak klinik olarak evrelendirildi. Evrenin cerrahi prognostik faktörler ve adjuvant RT alma olasılığı üzerindeki etkisi değerlendirildi.

Yaşı ortalama 53.9 yıl, ortalama tümör boyutu 30mm'yd. Hastaların %68.4'ü evre IB1, %12'si IB2 ve %19.6'sı IIA idi. Patolojik tanı %83.2 hastada yassı hücreli kanserdi. Vajen metastazı ve stromal invazyon derinliği evreyle doğru orantılı olarak artmaktaydı. Ancak parametrium tutulumu, lenf nodu metastazı, lenfovasküler alan invazyonun, over metastazı, cerrahi sınır tutulumu ve adjuvant RT evreden etkilememekteydi. Evre serviks kanserinde cerrahi patolojik risk faktörlerini net olarak predikte etmemektedir. Bu durum klinik olarak evrelenmesinin yarattığı belirsizliğin sonucudur. Cerrahi uygulamadan, olanaklarımız dâhilindeki tetkiklerle hastalığın ne ölçüde yayıldığını kesin olarak gösterememekteyiz.

**Anahtar Kelimeler:** Serviks kanseri, Evre, Patolojik risk faktörleri

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