

Prognostic factors affecting disease-free survival in early-stage cervical cancer patients undergoing radical hysterectomy and pelvic-paraortic lymphadenectomy

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Summary

Objective: This study was performed to identify surgical and histopathologic prognostic factors that could predict 5-year disease-free survival (DFS) after patients underwent radical hysterectomy and pelvic-paraortic lymphadenectomy for FIGO Stage I-II cervical carcinoma.

Methods: A retrospective review was performed for all patients undergoing primary radical hysterectomy and pelvic-paraortic lymphadenectomy for Stage I-II cervical cancer at Ankara Oncology Hospital from 1995 to 2000. Clinical and pathologic variables including age, tumor size (TS), clinical stage, depth of invasion (DI), lymphovascular space involvement (LVSI), cell type, tumor grade, lymph node metastases (LNM), parametrial involvement, surgical margin involvement and pattern of adjuvant therapy were analyzed using univariate analyses. DFS was performed by the Kaplan-Meier method and the log-rank test. Independent prognostic and predictive factors affecting DFS were assessed by the Cox proportional hazard method.

Results: Ninety-three patients underwent primary type III radical hysterectomy and pelvic-paraortic lymphadenectomy. Five-year DFS was 87.1%. LVSI, parametrial involvement and grade were the prognostic factors that independently affected survival. DFS was not significantly different for age, disease status of the surgical margins, tumor size, depth of invasion, cell type, pelvic lymph node metastases and adjuvant radiotherapy.

Conclusions: LVSI, parametrial invasion and histologic grade 2-3 were independent prognostic factors in early-stage cervical cancer patients. Adjuvant radiotherapy in these patients provides no survival advantage.

Key words: Cervix carcinoma; Prognostic factors; Radical hysterectomy; Disease-free survival.

Introduction

Patients with FIGO Stage I and IIa are preferentially treated with radical hysterectomy and pelvic lymph node dissection, achieving 5-year survival rates of approximately 88% [1, 2]. In spite of early disease state, a number of patients will recur, and most of these will eventually die of the disease. Therefore, determination of prognostic factors is required for discrimination between high- and low-risk groups among this population. Individual parameters that predict poor prognosis have been the subject of many publications [1-4]. The prognostic factors that currently have broad clinical usefulness and have been adopted for guidelines for adjuvant therapy are International Federation of Gynecology and Obstetrics (FIGO) stage, tumor grade, tumor size, depth of tumor invasion into the cervical stroma, cell type, lymph-vascular space invasion, lymph node metastases, parametrial invasion and surgical margin involvement [1-4].

It is clear that many of these risk factors are interrelated. Studies have been designed to statistically identify the best combination of these risk factors using multivariate analysis techniques [5-7]. Using Cox's proportional hazards regression model, these studies have produced different sets of combined risk factors for surgically treated patients.

The aim of this study was to identify patients who are at low or high risk by defining the prognostic factors in early-stage cervix carcinomas.

Material and Methods

The study population consisted of 93 patients who were primarily treated by radical hysterectomy and bilateral pelvic and paraortic lymphadenectomy for Stage I or II cervical carcinoma between January 1995 and December 2000 at Ankara Oncology Education and Research Hospital.

We included patients with Stage I-II who were clinically staged as recommended by FIGO and excluded patients with paraortic lymph node involvement. All patients underwent a staging laparotomy, radical hysterectomy, and bilateral pelvic and paraortic lymphadenectomy. All surviving patients were followed-up at least 60 months with a median follow-up of 100 months (range 5-120 months). Pathological and clinical data and follow-up information were retrieved from the medical records. The selection of postoperative adjuvant therapy was at the discretion of the attending gynecologic oncologist in charge of the patient. Generally, patients with lymph node metastases (LNM), parametrial invasion, positive or close surgical margins, and lymphovascular space involvement (LVSI) with deep stromal invasion were considered for adjuvant radiotherapy (RT) or chemoradiotherapy (CT+RT). A total of 76 patients received external beam radiation consisting of pelvic radiotherapy followed by vaginal brachytherapy or chemoradiotherapy. The protocols of postoperative chemotherapy included cisplatin-based regimens for four to six courses. Pelvic radiation

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was given at daily 2 Gy for a total dose of 50 Gy. Remote after-loading of intravaginal iridium-192 brachytherapy was placed one to two weeks after completion of external RT, delivering in 21 Gy/seven fractions within two weeks.

Pathology was reviewed for histologic type, grade, depth of invasion, surgical margin status, retroperitoneal node status, LVSI, and parametrial involvement. Histological type, depth of stromal invasion, LVSI, and grade were reviewed by one of the authors (GB). Deep cervical stromal invasion was defined as a tumor invading the outer one-third of the cervical stroma. LVSI was considered to be present when tumor cells were noted within a vascular or lymphatic space lined by flattened endothelial cells. For tumor size, the surgical specimen was measured and recorded in the pathological report. Parametrial involvement was determined on pathological review. A chart review was performed to determine clinical outcomes including time to recurrence, salvage therapies, and survival.

The removed lymph node numbers corresponding to the 25th, 50th, and 75th quartiles were 15, 20 and 30 lymph nodes, respectively. Therefore, removed nodes were categorized as ≤ 30 and > 30 .

Potential prognostic, predictive and treatment factors included in this study were age (≤ 50 , > 50), FIGO stage (I, II), histological type, grade [1-3], LVSI (absent, present), pathologic tumor size (< 2 cm, 2-4 cm, > 4 cm), removed pelvic and periaortic nodes (≤ 30 , > 30), parametrial involvement (absent, present), depth of tumor invasion into the cervical stroma, lymph node metastases, surgical margin involvement (absent, present), and adjuvant radiotherapy (Table 1).

Statistics

Statistical analysis was performed using the SPSS 10.05 for Windows computer program. The follow-up interval was calculated in months and defined as the time between the date of surgery and date of the event (death, distant or local recurrence) or last follow-up. When disease-free survival (DFS) is used as an endpoint, an event includes the first documented recurrence of disease. DFS rates were calculated by the Kaplan-Meier method and the log-rank test was used for comparison. The stepwise Cox proportional hazard model was used to assess the independent prognostic and predictive factors affecting DFS; *p* values less than 0.05 derived from two-tailed tests were considered significant.

Results

Median age was 48 (19-74) years. Five-year survival was 87.1%. Characteristics of patients are shown in Table 1. Eighty-two percent had squamous cell carcinoma, 48% grade 2-3 lesions, and 17% had lesions 4 cm or greater in diameter. Pelvic lymph node metastases occurred in 21/93 (23%).

Patient characteristics and univariate analysis of factors predicting 5-year DFS are presented in Table 1. The 5-year DFS was 61% for patients with LVSI and 96% for those without LVSI ($p < 0.001$). The 5-year DFS was 54% for patients with parametrial involvement and 94% for those without parametrial involvement ($p < 0.001$). The 5-year DFS was 94% for patients with grade 1 tumor and 80% for those with grade 2-3 tumor ($p = 0.03$)

Among the prognostic variables entered into the univariate analysis LVSI (Figure 1), grade (Figure 2) and parametrial involvement (Figure 3) correlated with DFS.

When the variables were entered into the multivariate analysis, grade, presence of LVSI and parametrial involvement were significantly associated with lower disease-free survival (Table 2).

Among 21 patients with positive pelvic nodes, 18 received adjuvant radiotherapy, two received adjuvant chemoradiation and one received no further treatment.

Table 1. — Characteristics of the patients and univariate analysis of possible prognostic, predictive variables for 5-year disease-free survival.

	Number (%)	5-year DFS (%)	<i>p</i> (log rank)
Age			
≤ 50	58 (62)	86	
> 50	35 (38)	89	N.S.
FIGO			
Stage I	65 (70)	91	
Stage II	28 (30)	79	N.S.
Histologic subtype			
Squamous	77 (82)	88	
Adenocarcinoma	10 (11)	90	N.S.
Adenosquamous	4 (4)	50	
Clear cell	2 (2)	100	
Tumor diameter (cm)			
< 2	17 (18)	88	
2-4	60 (65)	90	N.S.
> 4	16 (17)	75	
Grade			
1	48 (52)	94	
2-3	45 (48)	80	0.039
Lymphovascular invasion			
No	70 (75)	96	
Yes	23 (25)	61	< 0.001
Parametrial involvement			
No	79 (85)	94	
Yes	14 (15)	54	< 0.001
Pelvic nodes			
Negative	72 (77)	89	
Positive	21 (23)	81	N.S.
Number of nodes			
≤ 30	67 (72)	87	
> 30	26 (28)	88	N.S.
Surgical margins			
Negative	87 (94)	87	
Positive	6 (6)	83	N.S.
Outer 1/3 stromal invasion			
No	62 (67)	90	
Yes	31 (33)	81	N.S.
Radiotherapy			
Yes	76 (82)	84	
No	17 (18)	100	N.S.

DFS - disease-free survival.

Table 2. — Prognostic factors for disease-free survival in multivariate analysis.

	Hazard ratio (confidence interval)	<i>p</i> value
Lymphovascular invasion	10.76 (2.71-42.62)	0.001
Grade 2-3	5.11 (1.24-20.96)	0.023
Parametrial invasion	10.34 (2.97-35.97)	< 0.001

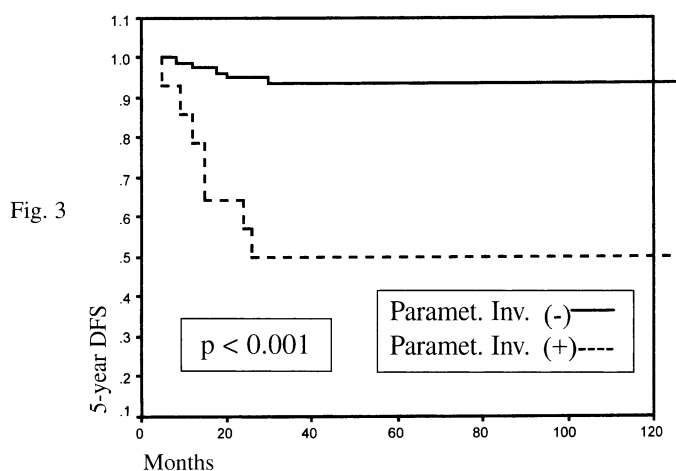
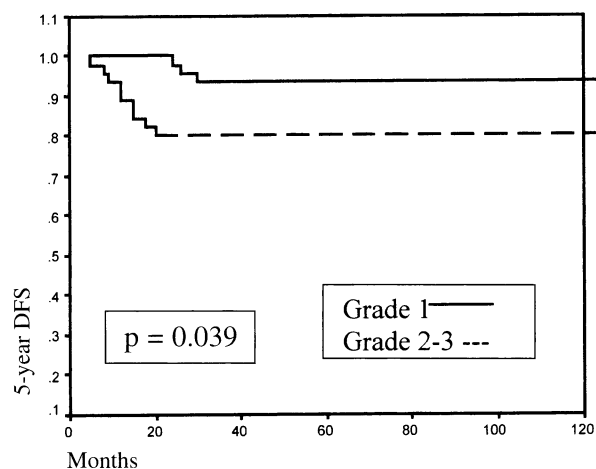
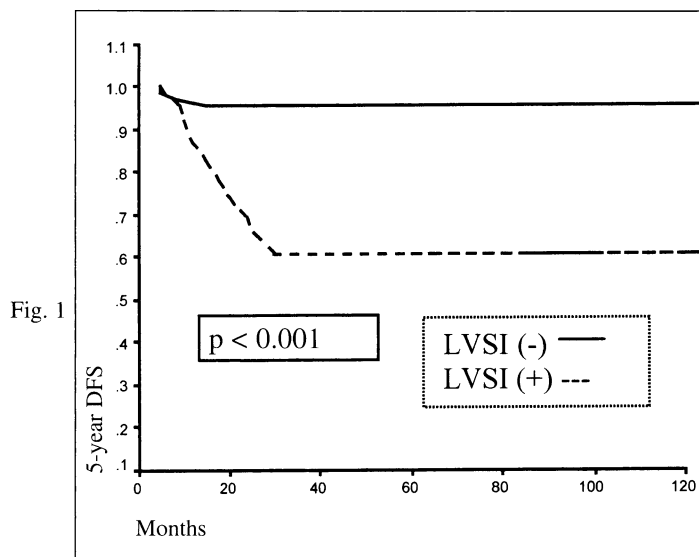


Figure 1. — Five-year disease-free survival rates by LVSI.

Figure 2. — Five-year disease-free survival rates by grade.

Figure 3. — Five-year disease-free survival rates by parametrial involvement.

The survival of patients receiving radiotherapy was not significantly different than that of patients who did not receive radiotherapy. Adjuvant chemotherapy was given to five patients. These patients had positive pelvic lymph nodes, and/or outer one-third cervical stromal invasion, and/or a tumor with size greater than 4 cm.

Twelve patients (13%) had a recurrence. Sites of recurrence were pelvic, in ten (83%) and distant, in two (17%). Six patients with recurrence received chemotherapy. All 12 patients with recurrence died of their disease within five and 30 months.

Discussion

There are many factors predicting DFS among early-stage patients with cervical cancer. TS, LVSI, DI, LNM, parametrial invasion, surgical margin involvement, age and stage all influence survival [5, 6, 8, 9]. In our study, LVSI, parametrial involvement and grade were independent risk factors. In our multivariate Cox regression

model, we used three variables including LVSI, grade, and parametrial involvement.

Many authors have reported that LNM has a critical effect on survival [10, 11]. However, some reports showed that LNM was not an independent prognostic factor in multivariate analysis [6]. Our study revealed that 5-year DFS for patients with positive lymph nodes was 81%, compared to 88% for patients with no positive nodes. We did not find that LNM was an independent prognostic factor in univariate analysis. In our protocol, patients with LNM received postoperative adjuvant radiotherapy or chemoradiotherapy, and therefore, additional adjuvant therapy might have improved the prognosis of these patients.

Delgado *et al.* reported on 645 patients with squamous cell carcinoma and found clinical tumor size, LVSI, and depth of invasion (DI) to be the best combined prognostic factors for the disease-free interval [6]. Using these parameters, they proposed a scoring system that identifies three separate risk groups for recurrence. In contrast,

Kamura *et al.* found LNM, histologic subtype, and tumor diameter to be the best combined risk factors for survival [5]. They also created a system of three prognostic groups with significantly different survival curves. In patients with high-risk early-stage cervical carcinoma, postoperative CT+RT seems to improve survival compared to RT alone [12]. Sevin *et al.* reported on 370 patients and created a new scoring system. With this scoring system, patient groups are defined naturally from the data instead of using artificial cut-off points and based on measurable pathologic and clinical manifestations rather than a mathematic equation. The clinician can assess the risk of an individual patient to develop a recurrence and potentially die from cancer simply by this model [8].

The reported incidence of LVSI ranges from less than 30% to greater than 50% [11,13]. We found LVSI in 25% of our specimens and recorded that 47.6% of lesions with LVSI had LNM in contrast to 14.3% of those without LVSI. This supports the theory that primary tumors with LVSI represent tumor cells in transit to the pelvic nodes. The influence of LVSI on survival in patients with early-stage cervical cancer is still controversial. Some authors have stated that LVSI is a risk factor for predicting survival, while others did not support this notion [8, 14, 15]. Our findings support that LVSI is an important and independent prognostic factor.

The influence of parametrial involvement on survival in patients with early-stage cervical cancer is also still controversial [14, 16]. Yuan *et al.* and Inoue *et al.* reported that nodal metastasis rate increases significantly when tumor extends to the parametrium [10, 17]. They reported that parametrial involvement with positive lymph nodes worsens the recurrence rate more than parametrial involvement alone. Winter *et al.* reported a series of 556 Stage IB-IIA patients who were treated primarily with radical surgery [18]. Parametrial involvement did not affect the survival rate of patients when stratified according to lymph node metastases. However, in contrast to these reports, there are findings that parametrial extension was an independent prognostic factor independent of lymph node status [19]. Our findings support that parametrial involvement is an independent prognostic factor.

Delgado *et al.* found that DFS correlated with grade but not with keratinization [6]. Grading is clearly the most controversial of all of the histopathologic prognostic factors. The major reason for this is the lack of standard criteria. We used the Reagan classification [20]. This classification divided tumors into large cell keratinizing, large cell nonkeratinizing, and small cell nonkeratinizing. Our findings showed that grade is an independent prognostic factor.

We found that the removed nodes were not correlated with DFS. Thus, our results do not confirm the opinion that removal of more nodes decreases or improves survival.

A prospective randomized GOG trial investigated the benefits and risks of adjuvant pelvic radiotherapy: 277 patients with high-risk, node-negative Stage IB cervical cancer were randomized to radiotherapy or observation (137 vs 140) [21]. The eligibility criterion included at

least two of the following factors: > 1/3 stromal invasion, large tumor size and LVSI. It has been reported that the crude estimate in the reduction in risk for patients receiving radiotherapy was 47%. Despite the radiotherapy, pelvic recurrence was the most common site of relapse. In another study [22], a total of 69 patients of whom 25 (36.2%) had only one pathological risk factor and 44 had (63.8%) two or more risk factors received radiotherapy. In their analysis, although pelvic recurrence rates showed lower ratios in patients who received RT than in patients treated by surgery alone, RT neither reduced pelvic recurrence rates nor improved DFS of patients and caused significant morbidity.

In our study, the survival of patients receiving radiotherapy was not significantly different than that of patients who did not receive radiotherapy.

Our limited series does suggest that tumor with grade 2 and 3, LVSI and parametrial involvement are independent prognostic factors in early-stage cervical cancer patients. Adjuvant radiotherapy in these patients provides no survival advantage. Clearly, the relatively small number of patients seen in this study limits the power of our calculations.

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