RESEARCH COMMUNICATION

Preoperative Prognostic Factors and Effects of Adjuvant Therapy on Outcomes of Early Stage Cervical Cancer in Iran

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Abstract

Background: The aim of this study was to investigate the clinical and histopathological characteristics and the pretreatment that might predict prognosis and to evaluate the impact of postoperative adjuvant therapy on the outcomes of patients with early stage cervical carcinoma. Methods: A total of 203 patients with stage IB and stage II cervical cancers treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy were reviewed at the Vali-Asr University Hospital from 1995 to 2002. The median follow-up period was 42 months. Results: The depth of cervical stromal invasion, clinical stage, histology of pure adenocarcinoma and lymph node (LN) status were important histopathological prognostic factors of cervical carcinoma. Patients' prognosis could be stratified into three groups (low, intermediate and high risk), with five-year relapse free survival (RFS) rates of 93.5%, 80.6% and 64.7%, respectively (p=0.002), and overall survival (OS) was 95.3%, 83.1% and 67.2% (p=0.001). Among the patients with pelvic lymph node metastases who were free of parametrial extension, those who received postoperative chemo-radiotherapy had significantly better RFS (p=0.021) and OS (p=0.030) than those who received no adjuvant therapy. Also of the patients without pelvic LN metastases but at a high risk of recurrence, the individuals who received adjuvant radiotherapy had a significantly more favorable RFS (p=0.038) and a marginally improved OS (p=0.064). Conclusion: Depth of cervical stromal invasion, clinical stage and histology are independent predictors of outcome on multivariate analysis using a Cox regression model. RFS is significantly improved with radiotherapy in patients who are without pelvic lymph node metastases but who are in a high risk group for recurrence.

Key Words: Cervical cancer - prognosis - pretreatment variables - radical hysterectomy - adjuvant therapy - survival

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Introduction

Cervical cancer is considered as the major female cancer in developing countries and the second major cause of mortality in gynecologic malignant disease in many parts of the world (Senoussi et al., 1998). The staging of cervical carcinoma has to be preoperative rather than postoperative. However, to treat the malady postoperatively,the histopathologic prognostic factors involved should be investigated (Takeda et al., 2001). As Lai et al (1999) have put it, either primary surgery or radiotherapy is liable to cure about 80% of early cervical carcinoma cases(stage IB or IIB). Zreik et al(1996) and Landoni et al (1997) have noticed a reduction of 30-50% is brought about in 5-years survival rates due to pelvic lymph node metastases.

Although there are a good number clinical variables involved specially in the early stage of the disease,some such as deep cervical stromal invasion,larger tumor size,diffentiation, parametrial extension and lymphatic permeation prove to have a poor prognostic value (Zreik et al.,1996; Landoni et al.,1997; Lai et al., 1999). It is only after surgical intervention,however that many of these features can be diagnosed.An initial treatment plan,if to be clinically useful,calls for a risk group classification that embraces assessable pretreatment factors.

Inspite of the fact that adjuvant radiotherapy(RT) and/or chemotherapy(CT) are common prescription for various high risk groups,one still can not attribute a definite know role to prospective adjuvant therapy in the case of high risk patients at an early stage of the disease (Kenneth.,1996; Lai et al., 1999; Berek and Hacker., 2005; Hoskins et al., 2005). According to Kenneth (1996), Zreik et al(1999), Landoni et al (1997), Lai et al (1999), Bereck and Hacker (2005) and Hoskins et al (2005), it is still a controversy whether to prescribe postsurgery RT for high-risk patients with a lymph node negative disease or treat them after relaps. It should be mentioned that is also a matter of contention as what to do if pelvic lymph node metastases occur.

Lai et al (1998) refers to some previously conducted research indicating the role of chemoradiation in improving RFS in patients with LVSI as well as those with deeply invasive tumors and poor prognoses.

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Materials and Methods

This study included a total of 203 cases of stage IB and II cervical carcinoma treated with radical hysterectomy and bilateral pelvic lymphadenectomy(RH-PLND) at Vali-Asr University hospital between 1995 and 2002 (table 1). The FIGO clinical stage of the patients was as follows: 131 stage IB and 72 stage IIA. The patient's age ranged from 23 to 78(mean: 49.8) years. The median follow-up periods were 42(range: 2-120) months. Systematic pelvic and Para aortic lymphadenectomy, not sampling, were employed as described previously (Takeda et al., 2001). Para aortic lymphadenectomy was performed at least up to the level of the inferior mesenteric artery. In this series, all of the potential prognostic variables, including the clinicopathologic parameters and the use of adjuvant therapy were studied for those patients who were treated between 1995 and 2002.

A complete pathological review was performed for these cases. Deep cervical stromal invasion was defined as a tumor invading the outer third of the cervical stroma. The distribution of the patient's age, FIGO stage and the histopathologic factors are shown in table 1.

The selection of postoperative adjuvant therapy was at the discretion of the responsible attending gynecologic oncologist. Generally, the adjuvant RT prescribed for the patients with parametrial extension involved surgical margins and deep (>2 of 3+ lymphatic permeation or full thickness) cervical stromal invasion. Adjuvant CT and/or RT was proposed when pelvic lymph node metastasis was noted. The protocols of postoperative CT and RT were described before (Landoni et al; Lai et al., 1998; Lai et al.,1993). Cisplatin-based regimens were used for 3 courses. Adjuvant RT consisted of external radiation by 10 MEV photons to the whole pelvis of 44 grays (GY) with or without a parametrial boost of 14 GY, followed by intravaginal high- dose-rate brachytherapy, 5-10 GY/ fraction, for one to two times. Computed tomography (CT) imaging available in our hospital was performed when pelvic examination showed the tumor size was >2 cm by or when deep cervical stromal invasion was suspected clinically. In our experience, CT imaging could not demonstrate Parametrial involvement and depth of cervical stromal invasion accurately (unpublished observation).

Patient age (<50 years vs. >50 years or <35 years vs. >35 years), clinical stage, depth of cervical stromal invasion (≤2/3 vs> 2/3), tumor size (<2 cm vs. >2 cm) and histological type (squamous vs. pure adenocarcinoma vs. adenosquamous) were considered assessable before definitive treatment. Analyses of pretreatment variables in predicting histologic findings at surgery (lymph node metastases and parametrial extension) were performed on all the patients (n=203) regardless of the follow-up time.

Statistical analysis

Survival analysis was performed using Kaplan- Meier curves and the log-rank test. The difference in survival function was compared with the generalized Wilicoxon test. Independent prognostic factors were determined by the multivariate Cox regression model. Adequacy of Cox model was investigated by examining the generalized residuals. Pearson's chi-square or Fisher exact test was used to compare the differences of proportions.

Student's t test was used to compare the means in population of normal distribution, whereas nonparametric analysis by Mann-Whitney U test was used when the distribution was not normal. A probability value of $p<0.05$ was considered significant.

Table 1. Clinicopathologic Variables in Patients with Early Stage Cervical Cancer

Factor	Category	Number (%)
Age	≥50	111 (55)
	>50	92 (45)
Histology	SCC	183 (90)
	Pure AD	16 (8)
	AS	4 (2)
Stage	IB	131 (65)
	II	72 (35)
Tumor size	<2cm	69 (34)
	>2cm	134 (66)
Lymph node	Negative	163 (80)
	Positive	40 (20)
Depth of stromal invasion		
	2/3≤	78 (39)
	>2/3	125 (61)
Vaginal margin Involvement		
	No	196 (97)
	Yes	7 (3)
Parameterial extension		
	Yes	25 (12)
	No	178 (88)
Lymph-vascular space invasion		
	Negative	129 (64)
	Positive	74 (36)
Adjuvant therapy	CT	25 (13)
	RT	68 (33)
	CT+RT	6 (3)
	NA	104 (51)

SCC, squamous cell carcinoma; Pure AD, pure adeno-carcinoma; CT, Chemotherapy; RT, radiotherapy; NA, no adjuvant therapy

Results

Incidences of pelvic lymph node metastasis at stages IB and II were 2% and 5.2% respectively. A summary of the 5-year relapse-free survival (RFS) and overall survival (OS) rates according to clinicopathologic variables by univariate analysis among the whole series is presented in Table 2. Histology of pure adenocarcinoma, clinical stage II, pelvic lymph node metastases, depth of cervical stromal invasion>2/3, parametrial extension, and Lymph-vascular space invasion (LVSI) were significant adverse prognostic factors.

A stepwise variable selection was initially performed by the multivariate Cox regression with all of 10 clinicopathologic variable . Five variables (stage, histology, parametrial extension, pelvic lymph node metastases and depth of cervical stromal invasion) were selected as significant prognostic factors .

The purpose of the current study was to select variables that could be assessable in pretreatment settings. Variables

Table 2. Univariate Analysis of Clinicopathologic Variables (n=203)

Factor	Category	No .of patients	5-year (%) OS	RFS	p values OS	RFS
Age	≥35	17	78.5	73.7	0.38	0.30
	>35	186	83.8	75.4		
	≥50	111	84.0	82.1	0.18	0.34
	>50	92	86.5	78.7		
Histology	S	183	82.5	80.2	0.002	0.048
	Pure AD	16	71.4	64.8		
	AS	4	75.0	79.1		
Stage	IB	131	82.6	80.8	0.004	0.03
	II	72	75.1	69.3		
Tumor size	<2cm	69	82.0	87.2	0.08	0.15
	<2cm	134	78.0	76.1		
Pelvic lymph node metastasis	Neg	163	89.3	86.8	0.005	0.001
	Pos	40	64.5	56.1		
Depth of stromal invasion	≤2/3	78	93.5	89.2	0.002	0.002
	>2/3	125	78.1	74.6		
Vaginal margin involvement	Yes	7	86.0	84.6	0.68	0.42
	No	196	82.0	80.3		
Parametrial extension	Yes	25	62.8	56.4	0.042	0.021
	No	178	83.2	86.1		
Lymph-vascular space invasion	Neg	129	84.5	81.7	0.010	0.012
	Pos	74	72.3	69.8		
Adjuvant therapy	CT	25	74.6	72.8	0.004	0.002
	RT	68	73.1	76.2		
	CT+RT	6	51.2	50.5		
	NA	104	87.2	84.3		

SCC, squamous cell carcinoma; Pure AD, Pure adeno-carcinoma; CT, Chemotherapy; RT, radiotherapy; NA, no adjuvant therapy

that could not be estimated accurately before surgery, such as parametrial extension, pelvic lymph node metastases, and lymphatic permeation, were then excluded. Among the remaining variables that were considered assessable before treatment, depth of cervical stromal invasion, clinical stage and histological subtype were independent predictors of outcome in a multivariate analysis.The regression coefficients and prognostic scores (PS) are presented in Table 3.

We could stratify the patients into three prognostic risk groups by integrating the histopathologic factors relating to the extent of tumor(parametrial invasion and LN status) and those relating to biological characteristics of the tumor(histologic type and LVSI), i.e. low risk(patients with a tumor confined to the uterus not associated with LVSI: n=90), intermediate risk(patients with a tumor confined to the uterus associated with positive LVSI and

Table 3. Multivariate Analysis and Prognostic Scores of Pretreatment Variables (n = 203)

Factor	Coefficient/Relative risk	95% CI	P value/PS
Depth of stromal invasion	0.5041		0.02
2/3	1		0
>2/3	2.44	1.33-2.97	5
Stage	0.4028		0.03
IB	1		0
II	1.58	1.34-2.12	4
Histological subtype	0.3431		0.038
SCC	1		0
Pure AD	1.98	1.05-2.49	5
AS	1.83	1.46-2.57	3

patients with squamous/adenosquamous carcinoma associated with parametrial invasion or pelvic lymph node metastasis: n=98) and high risk(patients with pure adenocarcinoma associated with parametrial invasion or pelvic lymph node metastasis and patients with common iliac/Para aortic node metastasis; n=25) .The five-year relapse free survival (RFS) rates for the low, intermediate and high-risk groups were 93.5%, 80.6% and 64.7% respectively (p=0.002), and the overall survival (OS) rates were 95.3%, 83.1% and 67.2% respectively (p=0.001).

Analysis of pretreatment variables in predicting histologic findings at surgery was performed on the 203 patients. The incidence of pelvic lymph node metastases, the common iliac lymph node metastases and parametrial extension according to the pretreatment risk group classification are presented in Table 4.There were 4.4% pelvic lymph node metastases, 1.1% common iliac lymph node metastases, and 3.3% parametrial extension in the low-risk group, whereas in the high-risk group, there were 44% pelvic lymph node metastases, 20% common iliac lymph node metastases, and 30% parametrial extension. Including all the patients with pelvic lymph node metastases, adjuvant therapy did not appear to significantly influence RFS or OS. Among the patients with pelvic lymph node metastases who were free from parametrial extension , those who received postoperative chemotherapy(CT) or CT +RT had significantly better RFS (p=0.021) and OS(p=0.03) than those who received no adjuvant therapy . Five-year RFS and OS rates of the former were 73.8% and 75.1%, respectively, and the latter rates were 61.4% and 59.5%, respectively.

The outcome for the lymph node negative patients was excellent: the 5-years RFS and OS rates were 86.8% and 89.3% respectively (Table 2).

Table 4. Literature Review of Multivariate Analysis of Prognostic Factors in Early Stage Cervical Cancer Cases

Authors	Age	Stage	Grade	HT	LNM	LVSI	PM	PI	TS	DI	RTb	CTb
Takeda	-*	-	-	(+)**	(+)	(+)	-	-	-	-	-	-
Lai	-	(+)	(+)	-	-	-	-	-	(+)	(+)	(+)	(+)
Ho	-	-	-	-	(+)	(+)	-	-	-	(+)	(+)	(+)
Metindir	-	-	(+)	-	-	(+)	-	(+)	-	-	-	-
Trattner	-	-	-	(+)	(+)	-	-	-	-	-	-	-
Ayhan	-	-	-	-	-	(+)	(+)	-	(+)	-	-	-
Current study[a]	-	(+)	-	(+)	-	-	-	-	-	(+)	(+)	(+)

HT, Histological type; LNM, Lymph node metastasis; LVSI, lymph-vascular space invasion; PM,Positive margin; PI, Parametrial invasion; TS, Tumor size; DI, Depth of invasion; RT, adjuvant radiotherapy; CT, adjuvant chemotherapy; (+)**, with positive effect: in patients that had this prognostic factors had poorer prognosis; -* without any effect in multivariate analysis; [a]In this study only variables that were assessable as pretreatments for predicting the prognoses of patients were evaluated; [b]These factor effects on outcome were evaluated after surgical treatment .

We selected lymph node negative high-risk patients according to our model(clinical stage II, depth of stromal invasion>2/3 and hystologic subtype of pure adenocarcinoma). The RFS and OS rates for patients with and without adjuvant RT were 88.7% and 95.4% versus 52.4% and 66.1% (RFS, p=0.063; OS, p=0.041). Although a significant difference could be demonstrated in OS, this narrow criterion would not be clinically useful, because only 7 of 203 (3.4%) patients had this characteristic. Subsequently, we added other indications such as parametrial extension, full-thickness cervical stromal invasion, tumor size >2 cm and positive vaginal margin, to the definition of high risk lymph node negative subsets (n=67). Those who received adjuvant RT had significantly better RFS(p=0.038) and improved OS rates (p=0.067) than those who did not receive adjuvant therapy. Five – year RFS and OS rates of the former group were 79.8% and 84% respectively, but the rates for the latter were 58.7% and 65.9% respectively.

The percentages of the lymph node negative patients with high-risk characteristics who required postoperative radiation to reduce the probability of relapse in the low, intermediate ,and high-risk groups were 1.1%, 16.3% and 52%, respectively. If common iliac and para aortic lymph node metastases or parametrial extension were used as indications for postoperative RT in lymph node positive patients, the overall ratio of patients requiring RT in the whole series would be the summation of the lymph node negative and lymph node positive groups, i.e., 3.5% for the low risk group, 31.4% for the intermediate-risk group, and 72.6% for the high-risk group.

Discussion

In the current study, we investigated the prognostic impact of various histopathological factors and the therapeutic impact of postoperative adjuvant therapy. In a previously published prospective, randomized study Landoni et al showed that stages IB to stages IIA of cervical cancer can be cured equally well by either a radical surgery or a radiation. However, 46 of 55(84%) patients with tumor size of >4 cm received adjuvant RT after RH-PLND, and 62 of 114(54%) patients with a tumor size < 4 cm received adjuvant RT in that study (Landoni et al.,1997).

Due to the increase in the number of patients with early-stage invasive cervical cancer,gynecological oncologists tend to stick increasing importance to this disease.Despite the fact that the majority of those who have the disease can be traeted with radical hysterectomy and pelvic lymphadenectomy,there is no reduction over the last two decades in the 20% mortality rate of thease patients (Lai et al.,1993; HO et al.,2004).

Surgery when combined with radiation can lead to unignorable complications.Having made such an observation Lai et al(1999) and Landoni et al(1997) refer to a number of these complications that adversely affect ones quality of life(QOL).They include intestinal adhesion and obstruction,lymphedema of the legs,radiation entritis,radiation cystitis and sexual dysfunction resulting from fibrosis and stenosis of vaginal vault.So ,it is advisable to limit postoperative therapy only to those patients who would really benefit from it without having to incur those complications.It is quite obvious that to avoid a combination of both modalities ,that is surgery and radiation, as a treatment for early-stage disease necessitable a careful ,wise pretreatment assessment.

The points of focus in the present study are similar to a number of other works in the literature. We have reported our analysis on the incidence and risk factors of pelvic and paraaortic lymph node metastasis like Takeda et al(2001) and Sakuragi et al(1999) parametrial invasion like Zreik et al(1996), Sevin et al(1996), Wright et al(2007) and Steed et al(2007) and the prognostic significance of LVSI like Sakuragi et al(2000), Metindir et al(2007) and Trattner et al(2001).

We found that the depth of cervical stromal invasion, clinical stage, histology of pure adenocarcinoma and Lymph node (LN) status are important histopathological prognostic factors of cervical carcinoma treated with radical hysterectomy and systematic lymphadenectomy. Among the variables that could be assessed before treatment, depth of cervical stromal invasion, clinical stage and histology were independent predictors of outcome in a multivariate analysis using a Cox regression model. Some authors reported that lymph node metastasis, LVSI, stage, grade, parametrial invasion and other factors had a critical effect on survival it is shown in Table 4.

Adjuvant treatment modalities with radiation employed after radical hysterectomy have been used in an attempt to eradicate microscopic residual tumors in patients at a high risk of relapse. Our study shows adjuvant radiotherapy in patients who were without pelvic lymph node metastases but are in a high risk group for recurrence, significantly improves RFS this is like to Lai et al study .But in many studies (table 4) it is not yet proved that adjuvant pelvic radiation therapy improves the survival of patients with lymph node metastasis(Takeda et al., 2001; Metindir et al.,2007; Trattner et al.,2001; Ayhan et al.,2004), nor is it clear whether adjuvant therapy is necessary for patients who have no evidence of metastasis or LVSI .The Gynecologic Oncology group conducted a study (protocol 92) that showed adjuvant pelvic pelvic radiotherapy after radical surgery significantly reduces the number of recurrences in women with node negative stage IB cervical cancer with at least two of the following risk factors: >1/3 stromal invasion, capillary lymphatic space invasion ,and large clinical tumor diameter(Takeda et al., 2001).

Also as shown by Buekers et al(2007) ,the stage of cervical cancer and a combination of tumor diameter and patients age may serve as factors to help stratify early-stage cervical cancer patients and determine the rate of success for adjuvant radiotherapy.Regarding GOG 92 our study shows that tumor volume is not likely to confer additional prognostic information if the histopathological extent of tumor and lymph node status are confirmed. This is like what Takeda et al.(2001) found out.

In conclusion, among the variables that could be assessed before treatment, depth of cervical stromal invasion, clinical stage and histology were independent predictors of outcome in multivariate analysis using a Cox

regression model. Adjuvant radiotherapy in patients who were without pelvic lymph node metastases but who were in high risk group for recurrence, significantly improved RFS.

Patients for whom postoperative CT or RT might be beneficial are identifiable. The data from this retrospective review may be useful only when feature prospective trials for the treatment of patients with early stage cervical cancer are designed.

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