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Prognostic Factors and Treatment Outcome in 178 Locally Advanced Cervical Cancer Patients

Ozlem Yetmen Dogan[1*], Makbule Dogan Eren[1], Sedef Ozdemir Dag[2], Alparsalan Mayadağli[3]

[1]Radiation Oncology Department, Kartal Dr Lutfi Kırdar Training and Research Hospital, Saglik Bilimleri University, Istanbul, Turkey
[2]Radiation Oncology Department, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey
[3]Radiation Oncology Department, Bezmialem Vakıf University, Istanbul, Turkey
Email: *dryetmen@gmail.com

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Abstract

Background: To evaluate local control, survival, radiation side effects and treatment outcome in locally advanced cervical cancer patients. **Materials and Methods:** Among 2006-2011, 178 patients with locally advanced cervical cancer were treated with chemoradiotherapy +/− radiotherapy and high dose rate (HDR) brachytherapy. Follow-up was complete for all patients. Concomitant chemotherapy was not administered in 44 patients due to renal impairments and ECOG of 2 - 3. **Results:** The median follow-up period was 34.5 months (range, 5 to 93) and 42 months (range, 14 to 93 months) for alive patients. Five years local-regional control, progression-free survival and overall survival rates were 87.8%, 58.9% and 67.3% in all patients, respectively. In this retrospective study young age, tumor diameter, stage, presence of residual tumor and administration of chemotherapy were effected in survival analysis. The parameters which affected the complete response of patients were defined as presence of concomitant chemotherapy and number of courses <5. Central region recurrence rate was defined higher in the group with treatment duration of 9 weeks and higher ($p = 0.044$). **Conclusion:** Primary chemoradiotherapy +/− radiotherapy achieved a satisfactory rate of local control and survival rates with acceptable complications in locally advanced cervical cancer. Concomitant chemotherapy and treatment duration were the important prognostic factors for completed response locally advanced cervical cancers.

Keywords

Locally Advanced Cervix Cancer, Chemo-Radiotherapy, Cervix Cancer

1. Introduction

Cervical cancer is among the cancers, in which the mortality rates are decreased

as the result of intense studies on its diagnosis and treatment [1]. The most important prognostic factors for cervical cancer have been defined as the stage, cell type, lesion size, presence of deep invasion, lymphovascular invasion and regional lymph node involvement. Lymph node involvement is the most important among these factors. Surgery or radiotherapy provides the recovery rate of 90% - 95% in the early disease. The primary treatment of locally advanced cervical cancer is the radical radiotherapy applied concomitantly with cisplatin based chemotherapy. The control rates of large tumors are increased by the use of brachytherapy in the cervical cancer [2] [3].

In the five randomized, phase III studies published until February 1999, the general survival rate was increased by 30% and the toxicity was reported within the accepted limits by the help of cisplatinium based chemotherapy concomitantly administered with radiotherapy [4] [5] [6] [7] [8]. Although there were differences in the stage, radiotherapy dose, radiotherapy and cisplatin administration protocols between the studies, the statistically significant increase in the survival rate was observed in five studies with concomitant administration of radiotherapy and chemotherapy. According to the obtained results, it is accepted currently that concomitant administration of cisplatinium based chemotherapy is the standard treatment in cervical cancer patients who are being treated by radiotherapy [9] [10].

In this retrospective study, we evaluate the long term follow up for locally advanced cervical cancer who had chemo-radiotherapy in our hospital. In the literature there are a lot of factors in the treatment for locally advanced cervical cancer, in that study we searched the prognostic factors for treatment. This study shows that prognostic factors, which are tumor size, age, presence of residual tumor, number of chemotherapy treatments, are important for treatment options. A total of 178 patients with FIGO Stage IB2-IV cervical cancer, who applied to the Radiation Oncology Clinic at the Dr. Lutfi Kırdar Kartal Research and Training Hospital between years 2006 and 2011, and received radiotherapy and/or concomitant chemotherapy, were evaluated.

2. Material Method

In this present study, our gynecology oncology clinic evaluate all the patients every week for treatment options. That clinic refers locally advanced cervical cancer patients to our radiation department for treatment.178 patients with locally advanced cervical cancer, who applied to the Radiation Oncology Clinic at the Dr. Lutfi Kırdar Kartal Research and Training Hospital between January 2006 and December 2011, and received radiotherapy or chemoradiotherapy treatments with complete follow ups, were retrospectively investigated.

FIGO (International Federation of Gynecology and Obstetrics) 2009 system was used for the staging. Patients who were treated before that date were re-staged according to this staging system. Anamnesis, systemic and gynecological examinations, whole blood count, biochemistry and PA chest radiographic

examinations were performed in all patients. Although clinical staging was performed, MRI and PET-CT were used for the staging. Rectoscopy and cystoscopy were performed in patients with the suspect of rectum or bladder involvement. Patient characteristics are summarized in Table 1.

Table 1. Patients characteristics.

	RADIOTHERAPY		CHEMO-RADIOTHERAPY	
	N (44)	24.7%	N (134)	75.3%
Age				
≤60	25	56.8	97	72.4
60<	19	43.2	37	27.6
Histology				
Squmous	40	90.9	119	88.8
Adenocarsinoma	4	9.1	9	6.7
Adenosquamous	-	-	3	2.2
Others	-	-	3	2.3
Stage				
IB2	3	6.8	6	4.5
IIA	3	6.8	9	6.7
IIB	25	56.8	87	64.9
IIIA	3	6.8	5	3.7
IIIB	6	13.6	13	9.7
IV	4	9.1	14	10.4
Tm diameter				
≤4 cm	14	31.8	31	23.1
>4 cm	30	68.2	103	76.9
Menapousal status				
Pre-menapause	21	47.7	57	42.5
Post-menapause	23	52.3	77	57.5
First symptom				
Vaginal bleeding	28	64.6	93	69.4
Vaginal bleeding + pain	11	25	29	21.6
Pain	4	9.1	8	6
Asymptomatic	1	2.3	4	3
Nodal status				
Nod (−)	8	18.2	37	27.6
Pelvic nod (+)	12	27.3	28	20.9
Para-aortic nod (+)	0	0	2	1.5
Pelvic +para-aortic (+)	0	0	3	2.2
Unknown	24	54.5	64	47.8

Conventional or conformal external radiotherapy was administered in the pelvic region with fractions of 1.8 - 2 Gy with a total of 45 - 50.4 Gy. Standard pelvic areas were used as the treatment volumes. Intracavitary treatment was performed in 157 (88.2%) patients after the external radiotherapy. External boost therapy was administered in 21 (11.8%) patients, who did not have intracavitary treatment. Cisplatin 40 mg/m^2 week chemotherapy was administered concomitantly with radiotherapy in 134 patients as the standard regimen. Concomitant chemoradiotherapy was administered with 6 courses in 2 (1.5%) patients; with 5 courses in 78 (43.8%) patients; with 4 courses in 51 (28.7%) patients; with 3 courses in 2 (1.1%) patients; and 2 courses in 1 (0.6%) patient. Concomitant chemotherapy was not administered in 44 patients because they had renal impairments and/or ECOG of 2 - 3.

Among patients with adequate responses to the external radiotherapy, the point A was administered in 87 patients with 4 fractions of 26 Gy; in 40 patients with 3 fractions of 21 Gy; in 16 patients with 5 fractions of 27.5 Gy; in 5 patients with 4 fractions of 24 Gy; in 3 patients with 3 fractions of 18 Gy; in 3 patients with 5 fractions of 30 Gy; and in 3 patients with 3 fractions of 15 Gy by using intracavitary radiotherapy Cs^{137} sourced, high velocity rate Curietron device.

Treatment responses (complete response, partial response, stationary disease, and progressive disease) were evaluated according to criteria of the World Health Organization. Early and late side effects were defined according to RTOG/EORTC acute and late radiation morbidity scoring criteria. During the follow up, control was planned in every 3 months in the first year; in every 6 months up to 5 years; and once in a year after the year 5. Gynecological examination and vaginal smear were performed at every control visit. Routine biochemistry teats, chest radiography, and radiological examinations were performed in every 6 months. If there was any suspect of recurrence or metastasis, additional examinations were performed.

SPSS (Statistical Package for the Social Sciences) for Windows 17.0 program was used for statistical analyses. Local-regional control, progression-free survival, and overall survival curves were obtained by using Kaplan-Meier method; log-rank test was used for the significance. Time to progression was noted as recurrence at the time of diagnosis, metastasis or time to death, which was developed due to any reason other than the recurrence. The overall survival was defined as time between the diagnosis and death. Significant factors in the single variable analysis were included in the multiple variable analysis. Chi square test was used for local-regional recurrences, and parameters affecting the distance metastasis and treatment response. Cox regression method was used in the multiple variable analysis.

Age, stage, tumor diameter, tumor response at the end of external pelvic radiation, concomitant chemotherapy and number of courses, menopausal status, local recurrence area, total treatment duration, and external radiotherapy dose were selected as the prognostic factors. Results were accepted significant within the 95% confidence interval, and at $p < 0.05$.

3. Results

Locally advanced cervical cancer patients, who applied to our clinic between the years 2006 and 2011, and had concomitant chemoradiotherapy or radical radiotherapy, were retrospectively evaluated. Median age was 54 (30 - 85) years; the application symptom of majority of our patients was abnormal vaginal bleeding (67.4%). Patients were followed up with the median of 34.5 (5 - 93) months and 42 (14 - 93) months for alive patients.

When patients were evaluated according to their stages; 9 (5.1%) were at the stage IB2; 12 (6.7%) were at the stage IIA; 112 (62.9%) were at the stage IIB; 8 (4.5%) were at the stage IIIA; 19 (10.7%) were at the stage IIIB; and 18 (10.1%) at the stage IV. Majority of our patients had squamous cell carcinoma (89.3%). Pelvic node involvement was determined in 40 (22.4%) patients; paraaortic lymph node involvement was observed in 2 (1.1%) patients; and both pelvic and paraaortic lymph nodes were determined in 3 (1.6%) patients.

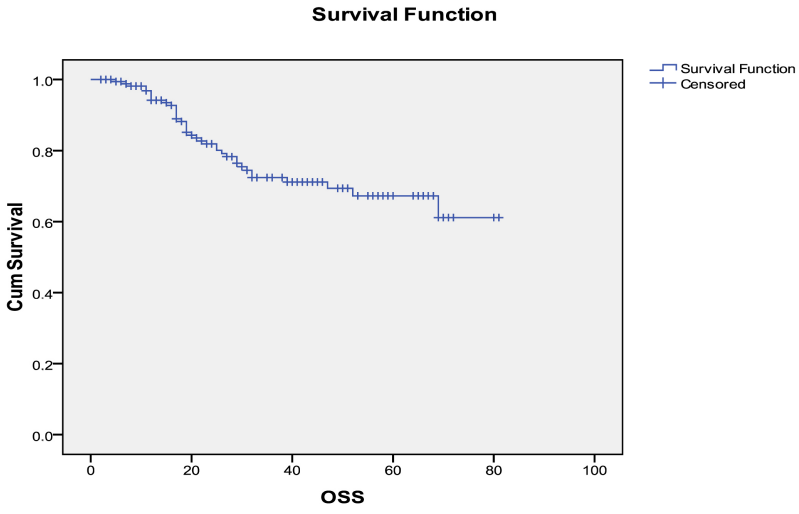
Median radiotherapy dose was 4600 cGy (range: 4500 – 5040 cGy). During post-radiotherapy or post-chemoradiotherapy evaluations, 146 out of 178 patients (82%) had complete response, whereas 19 (10.7%) patients had partial response. During the post-treatment follow up, local recurrence was detected in 17 (9.5%) patients, and distance metastasis was detected in 49 (27.5%) patients. The highest rates of distant and regional recurrences were the Stage IIB in those patients.

Two years and 5 years local control rate, progression-free survival, and overall survival were determined as 89% and 87.8%; 68.4% and 58.9%; 81.9% and 67.3% in all patients, respectively (**Figure 1**).

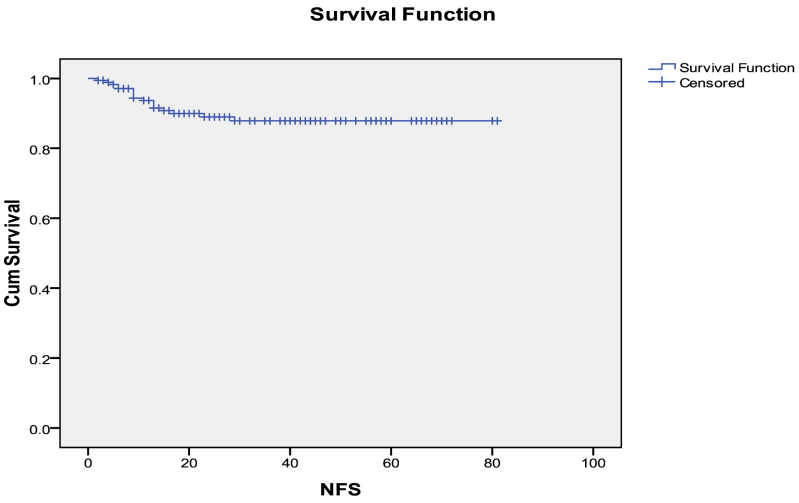
In the univariate analysis, young age (≤60 years) was affected negative factor for local control in all patients ($p = 0.026$). Tumor diameter over 4cm was defined as an unfavorable factor for only progression-free survival ($p = 0.021$). Presence of residual tumor affected the overall, progression-free survival and the local control after the treatment ($p \leq 0.001$). It was observed that concomitant administration of chemoradiotherapy were favorable factors on the overall and progression-free survivals ($p = 0.005$). Number of chemotherapy courses <5 had negative effect on the overall survival, but it was not statistically significant ($p = 0.7$) (**Table 2**).

The parameters which affected the complete response of patients were defined as presence of concomitant chemotherapy and number of courses <5 (**Table 3**). Also, when the correlation between treatment duration and local recurrence region was investigated, central region recurrence rate was defined higher in the group with treatment duration of 9 weeks and higher ($p = 0.044$).

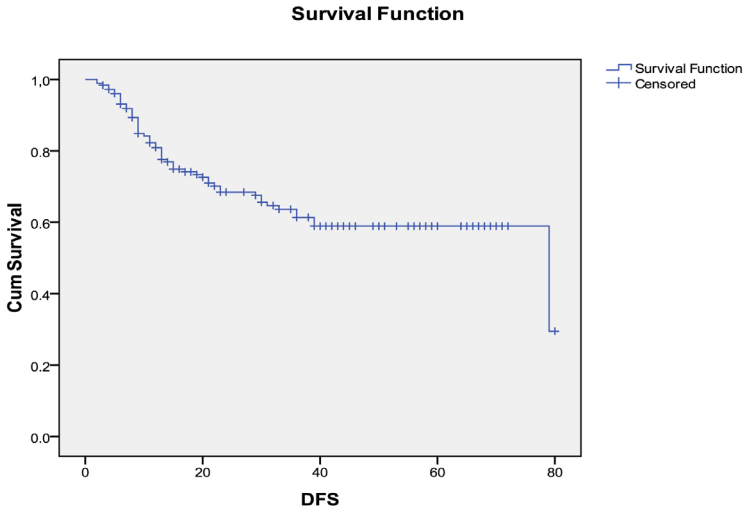
In the multivariate analysis performed on all patients, residual tumor presence was defined as an independent prognostic factor affecting the progression-free survival and overall survival. The tumor diameter more than 4cm had an unfavorable effect on the progression-free survival and overall survival. Concomitant cisplatin-based chemotherapy administration had favorable effects on progression-free survival and overall survival (**Table 4**).



(a)



(b)



(c)

Figure 1. 5 years Overall Survival (OSS), Local Control Rates (NFS), Disease-free Survival (DFS).

Table 2. Univariate analysis of overall survival, progression free survival and local control rates.

		Overall survival		Progression Free Survival		Local Control Rates	
	N	2 years OS (%)	*P*	2 years PFS (%)	*P*	2 years LCR (%)	*P*
Age							
60≥	122	85.9	0.322	68.1	0.435	85.3	0.026
60<	56	73.2		69.3		97.8	
Stage							
IB2-IIA	21	100	0.027	83.9	0.072	90.9	0.446
IIB-IV	157	79.8		66.5		88.6	
Tm diameter							
4≥	45	90.9	0.5	79.4	0.021	93.9	0.207
4<	133	79.1		65		87.3	
Residual tm							
Positive	32	63.5	<0.0005	32.1	<0.0005	69.4	0.001
Negative	146	85.2		74.8		91.9	
Presence of residual tumor							
Central	13	80.8	0.386	7.7	0.201	7.7	0.580
Peripheral	4	33.3		25		25	
Menopausal st.							
Pre-	78	84.7	0.864	69.2	0.544	88.5	0.198
Post-	100	79.8		67.8		90.7	
Chemotherapy (CHT)							
Positive	134	85.3	0.005	90.1	0.040	92.8	0.375
Negative	44	69.1		51.3		91.6	
Number of CHT							
5≤	80	89	0.759	76	0.588	89.1	0.656
5>	54	77.5		67.8		86.9	

Table 3. The parameters which affected the treatment responses.

	Complete response (n)	Not-complete response (n)	*P*
Chemotherapy (CHT)			
Positive	115	19	0.039
Negative	31	13	
Tm diameter			
4≥	107	26	0.5
4<	39	6	
Number of CHT			
5≤	75	5	0.002

Continued

5>	40	14	
Total treatment time (EBRT + ICRT)			
9 weeks<	125	27	0.788
8 weeks>	21	5	
Age			
60≥	45	11	0.68
60<	101	21	
Stage			
IB2-IIA	17	4	1.000
IIB-IV	129	28	

Table 4. Multivariate analysis performed on all patients (n: 178).

	Local control rates (*p*)	Progression free survival (*p*)	Overall survival (*p*)
Age	0.095	0.617	0.451
Stage	0.345	0.048	0.972
Tumor	0.554	0.041	0.057
Residuel	0.006	<0.0005	0.001
Treatment	0.984	0.760	0.237
Chemotherapy	0.687	0.039	0.002

Side Effects

The most commonly encountered early side effects in our patients were grade 1 - 2 cystitis (21.8%), and grade 1 - 2 diarrhea (11.3%). No grade IV side effect was observed in any patiens. Side effects were evaluated statistically by using Chi square test, but no significant result was obtained. When the late side effects were evaluated, they were defined as grade 3 proctitis (12.7%) and grade 3 genitourinary side effects (6%).

4. Discussion

In locally advanced cervical cancer local control rates are 70% - 90% in the standard radiotherapy treatment and 2/3 of recurrences are observed within the radiotherapy region [2] [4] [5] [11]. The results of five randomized studies, in which concomitant chemoradiotherapy was administered to increase the efficacy of radiotherapy, were published, and it was shown that chemotherapy administration, especially the cisplatin based chemotherapy, provided survival advantage [4] [5] [6] [7] [8] [12] [13].

It was published in the meta-analysis, which included 18 randomized studies in 2008, that cisplatin-based chemoradiotherapy decreased the local and distant recurrences; and increased progression-free and overall survival more than the

non-cisplatin based chemoradiotherapy regimens [8]. Gynecological Oncology Group analyzed 642 patients, who had definitive radiotherapy because of locally advanced disease in 3 prospective, clinical trials. The group reported in this multivariate analysis that the most important independent predictor was para-aortic lymph node involvement among other risk factors related to survival and relapse. The most important two prognostic factors were reported as pelvic lymph node involvement and tumor size in cases without para-aortic lymph node involvement. The other weak risk factors were clinical stage, patient age, and performance status. In this analysis, it was shown that cell type, histological grade, pre-treatment hematocrit level, and peritoneal cytology signs did not have any significant prognostic importance in the locally advanced disease.

In the literature, the prevalence of pelvic failure depends on several factors, which according to the studies are age, cancer stage, initial tumor stage, lymph node invasion and residual tumor volume after chemoradiotherapy [14] [15]. The rate of residual cervical tumor after hysterectomy is estimated at 40% - 50% [5]-[17]. In a multicenter series of 175 patients who underwent surgery after chemoradiotherapy and brachytherapy for advanced cervical cancer, Classe *et al.* showed that patients with a complete histological response had a better survival rate at five years than patients who had residual tumor (88.9% vs 54.7%, p = 0.0001) [17]. Houvenaeghel *et al.* Showed that the presence of residual tumor of the uterine cervix was associated with a higher rate of pelvic lymph node involvement (p = 0.0031) and that the rate of pelvic lymph node metastases after chemoradiotherapy was 16% [18].

In the present study, it was observed that early age onset of the disease had unfavorable effects on local control of the disease in all patients. Tumor size > 4 cm had negative effects on the progression-free survival; and Stage IIB-IV of patients had negative effects on the overall survival. It was observed in the post-treatment, control MRI examinations that the presence of residual tumor was a worse prognostic factor for the survival and local-regional control. The pelvic nodal involvement, which was reported among the most important prognostic factors in many studies, was not determined as significant in this present study [19] [20] [21]. It was thought that this was caused because nodal condition of the majority of patients was unknown. Cisplatin is the preferred systemic agent for concomitant use with radiotherapy, because of its low bone marrow toxicity. The leading side effects in concomitant chemoradiotherapy studies were hematological toxicities. As it was in the study of Gynecologic Oncology Group, drug toxicity rates were increased and grade III and IV toxicities might be observed in administrations of two or more drug combinations [22].

In the study by Keys *et al.* in which 183 cases with Stage IB2 cervical cancer were randomized to radiotherapy only and concomitant cisplatin (40 mg/m^2) administration with radiotherapy. The hematological toxicity was determined in 3 cases in the first arm, and 39 cases in the second arm. The gastrointestinal toxicity was determined in 26 cases in the first arm, and in 9 cases in the second

arm. The genitourinary side effects of grade I and II were determined higher in the combined treatment group, whereas no difference was determined in late side effects between the groups [5]. When this present study is evaluated for side effects, the most commonly encountered side effects were related to the genitourinary system, and there was no difference in late side effects between the groups. The results were similar to toxicity results of the study conducted by Keys *et al.*

Given its retrospective design, this study has a number of limitations. A multidisciplinary approach to the treatment of cervical cancer has led to marked improvement in outcome. The combination of EBRT and HDR BRT together with concomitant chemotherapy in the treatment of locally advanced carcinoma of cervix is safe and well tolerated with acceptable morbidity.

5. Conclusion

This study is prospective and it has limitations but it shows us that prognostic factors for locally advanced cervical cancer are very important. We have to be careful when the patient has young age, more than 4 cm tumor, presence of residual tumor after treatment and we have to try to give more than 5 times concomitant chemotherapy with radiotherapy. Also pelvic nodal involvement is important factor for cervical cancer treatment but in our study we couldn't determined. Multidisciplinary approach is needed for locally advanced cervical cancer because survival is much better than the other cancer types.

Conflict of Interest

This article has no conflict of interest.

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