



# Does the Radiotherapy Technique Have an Impact on the Survival of Patients with Cervical Cancer?

Beyza ŞİRİN ÖZDEMİR,<sup>1</sup> Gamze Melek AKSU,<sup>1</sup> Aylin Fidan KORCUM,<sup>1</sup> Taylan BÜKÜLMEZ,<sup>2</sup> Mine GENÇ,<sup>1</sup> Melek Nur YAVUZ<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology, Akdeniz University, Antalya-Turkey

<sup>2</sup>Department of Radiation Oncology, Van Regional Training and Research Hospital, Van-Turkey

## OBJECTIVE

Concurrent chemoradiotherapy is the primary treatment for patients with locally advanced cervical cancer. We evaluated the treatment results and prognostic factors in patients treated with chemoradiation.

## METHODS

We retrospectively reviewed the records of 150 patients with locally advanced cervical cancer treated with curative chemoradiotherapy between 1999 and 2014 at our hospital.

## RESULTS

The median follow-up period was 37.5 months (range: 5.6–186 months). All patients received both external beam radiation therapy (EBRT) and intracavitary brachytherapy. EBRT was delivered with conventional 2-dimensional radiotherapy or 3-dimensional conformal radiotherapy (3DCRT). Eighty-seven percent of patients received cisplatin-based chemotherapy during EBRT. Total or nearly total remission was achieved in 72% of patients. With a median follow-up duration of 37.5 months, 29% of patients died, 13% of patients had local-regional recurrence, and 25% of patients had distant metastasis. The 2-, 5-, and 10-year overall survival rates were 76%, 62%, and 47%, respectively, and the progression-free survival rates were 68%, 62%, and 58%, respectively. We evaluated prognostic factors for overall survival and progression-free survival. The most important prognostic factor was the radiotherapy technique. The survival curves were estimated by the Kaplan–Meier method, and differences were assessed using the log-rank test; a p-value<0.05 was considered significant.

## CONCLUSION

Chemoradiotherapy is an effective and tolerable treatment method for patients with cervical cancer. These patients treated with 3DCRT have a better overall survival.

**Keywords:** Prognostic factors; Radiotherapy; Radiotherapy technique; Cervical cancer.

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## Introduction

Cervical cancer is the 4th most commonly diagnosed cancer in women worldwide and one of the best-known

malignancies.[1] The accepted etiological factors are early first intercourse, multiple partners, high parity, and infections.[2-3] Case-control studies and prevalence surveys have shown that human papilloma virus

DNA can be detected in patients with cervical cancer in 90%–100% of cases.[4]

While the standard treatment for patients with LACC (stages IB2–IVA ) is concomitant chemoradiotherapy, radical hysterectomy is used as the primary therapy for patients with early-stage carcinoma (stages IA–IB1) of the cervix.[5,6] Today, the 2DRT technique has been replaced by the 3DCRT technique and intensity-modulated radiotherapy (IMRT), thus aiming to reduce the complication rates.

Here, we evaluated the treatment results and prognostic factors in patients treated with chemoradiotherapy and compared 2 different treatment techniques .

## Materials and Methods

We retrospectively reviewed the records from a single institution of 150 patients with LACC treated with curative chemoradiotherapy between 1999 and 2014. Pretreatment evaluation comprising gynecological examination, magnetic resonance imaging, computed tomography (CT), and/or 18F-fluorodeoxyglucose positron emission tomography (beginning in 2008) was performed for all patients for staging. All patients received pelvic external beam radiation therapy (EBRT), followed by intracavitary brachytherapy. Ten patients with metastatic para-aortic lymph nodes were irradiated with extended field. Pelvic EBRT was delivered at a total dose of 45–50.4 Gy (median: 50.4 Gy) in 1.8-Gy fraction doses using 18–25 MV X-rays. However, extended-field EBRT was delivered at a total dose of 45 Gy in 1.8-Gy fraction doses. Until June 2009, 2DRT with a 4-field box technique [anterior-posterior (AP)-posterior-anterior (PA) and 2 lateral] was used; subsequently, 3DCRT (AP-PA and 2 lateral plus 3 or 4 segments) was performed. For planning 2DRT, X-Ray (conventional) simulator was used, and the edges of fields were determined with standardized simulator planning guided by bony landmarks for the pelvic irradiation of primary cervical carcinoma (the superior border of the AP-PA field at the inferior edge of L4, the inferior border at the inferior edge of the ischium, the lateral borders placed 2 cm outside of the bony pelvis rim, the anterior border of the lateral field over the anterior edge of the pubic symphysis, and the posterior border at the S2–S3 interspace). For para-aortic nodes, the superior border of the AP-PA field was at the T12-L1 interspace, and the width of the AP-PA field was approximately 10 cm (encompass tips of the transverse processes).

For planning 3DCRT, CT simulation images of the patients were taken (adjacent axial slice spacing, 2.5

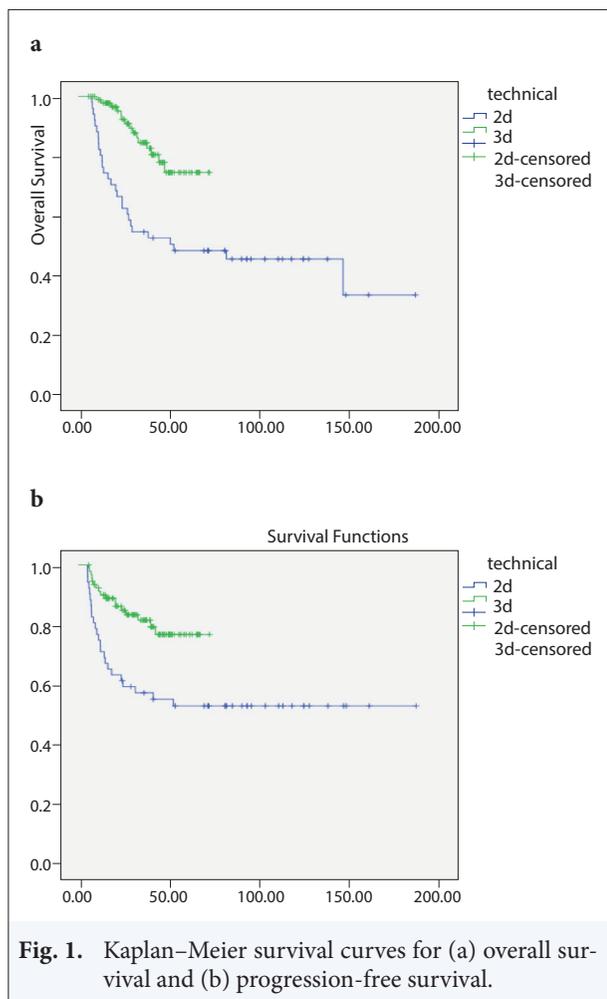
mm; GE-Lightspeed64<sup>®</sup> computed tomography simulator; GE, Fairfield, USA). The target volumes and critical normal tissues (bowel, bladder, and rectum) were outlined on each CT slice.

Following EBRT, all patients underwent “Nucletron Microselectron IR-192” high-dose-rate brachytherapy, which was applied at a total dose of 28–30 Gy in 6-7-Gy fraction doses. Concurrent weekly cisplatin at 35–40 mg/m<sup>2</sup> was administered intravenously during EBRT. The survival curves were estimated by the Kaplan–Meier method, and differences were assessed using the log-rank test; p-values<0.05 were considered significant. Prognostic factors studied were age, tumor size (>4 cm, ≤4 cm), stage, vaginal extension, pelvic wall

**Table 1** Patient characteristics according to 2DRT and 3DCRT techniques

	2DRT n (%)	3DCRT n (%)	P value
Patient number	52 (35)	98 (65)	
Mean age	56.5	54	0.2
FIGO			0.08
Ib	2 (3.8)	7 (7.1)	
Ila	0 (0)	10 (10.2)	
Ilb	33 (63.5)	64 (65.3)	
IIla	3 (5.8)	2 (2.0)	
IIlb	9 (17.3)	9 (9.2)	
IVa	5 (9.6)	6 (6.1)	
Lymphadenopathy			0.1
Yes	5 (12.8)	23 (24.0)	
No	34 (87.2)	73 (76.0)	
Histologic type			0.7
Squamous	42 (80.8)	86 (87.8)	
Adenocarcinoma	3 (5.8)	4 (4.1)	
Adenosquamous	6 (11.5)	7 (7.1)	
Other	1 (1.9)	1 (1.0)	
Tumor size			0.5
≤4cm	22 (43.1)	46 (48.9)	
>4 cm	29 (56.9)	48 (51.1)	
Vaginal extension			0.001
Yes	33 (63.5)	27 (27.6)	
No	19 (36.5)	71 (72.4)	
Parametrial extension			0.006
Yes	49 (94.2)	75 (76.5)	
No	3 (5.8)	23 (23.5)	
Pelvic wall involvement			0.006
Yes	11 (21.2)	6 (6.1)	
No	41 (78.8)	92 (93.9)	
Extended field (Pelvic+Paraaortic RT)	4 (7.7)	6 (6.1)	0.7

2DRT: conventional 2-dimensional radiotherapy, 3DCRT: 3-dimensional conformal radiotherapy.



involvement, parametrial extension, and radiotherapy technique (2DRT or 3DCRT). The level of significance was set at  $p < 0.05$ . In addition, “stepwise cox regression analysis” was performed.

### Results

The median age at diagnosis was 55 years (range: 23–91 years). According to the International Federation of Gynecology and Obstetrics staging system, 6% of patients were in stage I, 71% were in stage II, 16% were in stage III, and 7% were in stage IV. Histopathologically, 85% of the patients had squamous cell carcinoma. Mean clinical and radiological tumor diameter was 4.9 cm. Vaginal extension was seen in 60 patients (40%): 2/3 upper in 82% and 1/3 lower part of the vagina in 18% of the 60 patients. Sixty-nine patients (46%) underwent lymph node dissection, and 35 patients (23%) had pathological lymph node metastasis. Ten patients had para-aortic lymph node metastasis by radiology or pathology.

<b>Table 2</b> Survival outcomes of patients receiving 2DRT and 3DCRT		
	<b>2DRT</b>	<b>3DCRT</b>
2 year OS-DFS rates	56%-58%	85%-82%
5 year OS-DFS rates	50%-53%	76%-77%
10 year OS-DFS rates	47%-53%	-

Whereas 2DRT was performed in 52 patients (35%), 3DCRT was performed in 98 patients (65%). Table 1 shows the characteristics of the patients according to the technique. All patients completed EBRT and brachytherapy as planned. The mean total equivalent dose in 2 Gy/fraction dose was calculated as 89.2 Gy (range: 80–91.7 Gy). The para-aortic fields were also treated in 10 patients due to positive para-aortic lymph nodes by radiology or pathology.

In total, 130 patients (87%) received cisplatin-based concomitant chemotherapy (35–40 mg/m<sup>2</sup> once per week), whereas 10 patients did not receive concomitant chemotherapy because of extended field for the external irradiation of para-aortic lymph nodes, it was not evident whether 10 patients received chemotherapy.

With a median follow-up duration of 37.5 months (range: 5.6–186 months), 99 patients (66%) had no evidence of disease at the last follow-up. During follow-up, 43 patients (29%) had recurrence by imaging and clinical examination, 19 patients had loco-regional relapse, 37 patients had distant metastases, and 13 patients had both loco-regional and distant metastases. It was detected that the loco-regional relapse rate of 3DCRT was lower than that of 2DRT (2% and 33%, respectively) ( $p = 0.001$ ). Distant metastasis rates of 3DCRT and 2DRT were 19% and 38%, respectively (0.01).

The 2-, 5-, and 10-year overall survival (OS) and DFS rates were 76%, 62%, and 47% and 68%, 62%, and 58%, respectively.

Age ( $p = 0.01$ ), stage ( $p = 0.001$ ), vaginal extension ( $p = 0.02$ ), pelvic wall involvement ( $p = 0.001$ ), and radiotherapy technique ( $p < 0.001$ ) were found to be significant prognostic factors in terms of OS.

The radiotherapy technique was found to be the only significant prognostic factor for DFS ( $p < 0.001$ ). The radiotherapy technique was the most important factor according to stepwise cox regression analysis.

Survival rates were superior in patients receiving 3DCRT (Table 2). Figure 1 shows the survival curves of 2DRT and 3DCRT.

In the follow-up period, after the completion of radiotherapy, rectovaginal fistula and small bowel adhesion were observed in 2 patients, both of whom were

treated with 3DCRT. Serious side effects were not observed in the other patients during or after radiotherapy.

## Discussion

The standard treatment for patients with early-stage cervical cancer is surgery. Chemoradiotherapy has an essential role in curative treatment in patients with LACC. After 5 randomized trials published between 1999 and 2000, the survival advantage of curative chemoradiotherapy has been proven, and it has been accepted as the standard treatment for LACC.[5-9] Based on a meta-analysis, a potential absolute OS and DFS benefit of 12% and 16%, respectively, has been attributed to the use of chemoradiotherapy.[10] Cochrane's meta-analysis analyzed and compared the results of 13 studies on chemoradiotherapy versus radiotherapy.[11] The meta-analysis showed a 6% improvement in the 5-year survival with chemoradiotherapy. Chemoradiotherapy was also found to reduce progression and improve DFS. Five retrospective studies have demonstrated that the 5-year OS with chemoradiotherapy ranges from 55% to 73% in patients with LACC.[12-16] In our series, the 5-year OS of 150 patients was 62%. According to the techniques, the 5-year OS of 3DCRT and 2DRT were 76% and 50%, respectively. In our study, despite the high rate of patients with stage IV and para-aortic nodal metastases and the fact that 13% of our patients did not receive concurrent chemotherapy, our results are consistent with those reported in the literature.

The benefit of brachytherapy in terms of survival and local control has been reported by Coia et al.[17] In their study, the use of brachytherapy and the number of intracavitary insertions were significantly associated with survival. At 4 years, local failure was significantly reduced (29% versus 17%) with 2 or more intracavitary applications and the survival rate was improved (60% versus 73%). In our study, all patients received brachytherapy.

Previous studies have confirmed age, performance status, tumor diameter, and lymph node status as prognostic factors of the progression-free rate for patients with LACC.[18,19] All these factors in addition to clinical stage and bilateral parametrial or bilateral pelvic wall extension were significant for survival. Pelvic nodal status and tumor diameter have been reported to be significant independent prognostic factors for survival and recurrence. In our study, age, stage, vaginal extension, pelvic wall involvement, and radiotherapy technique were found to be significant prognostic factors in terms of OS.

To the best of our knowledge, our study is one of the few studies in the literature that has compared 3DCRT and 2DRT techniques regarding survival in the long-term follow-up period. In a study, the 5-year survival rate for 2DRT and 3DCRT was found to be significantly different (73.0% and 82.3%, respectively). Accompanying comorbidities of these patients were also examined, and patients with cervical cancer with more comorbidities were found to have poorer survival rates.[20] In our study, the survival results were better in the patients receiving 3DCRT, as expected. However, a limitation of our study was the heterogeneity between the 2 groups.

In 2013, a study compared conformal and conventional radiotherapy techniques in 5 patients dosimetrically.[21] Dose homogeneity and doses of the organs at risk (rectum, bladder, and small bowel) were not significantly improved. However, 3DCRT provided a significantly better target coverage. In addition, the use of CT simulation allowed superior visualization of the pelvic lymph nodes and reduced the chances of geographical miss. Therefore, they reported that it might be better in local control and survival. Gulia et al. performed a dosimetric comparison between the conventional 4-field based on bony landmarks and the target volume delineated on CT in 50 patients.[22] They showed that DFS is lower in patients with inadequate target volume coverage. They recommended the routine use of CT-based planning for the 4-field technique.

In our study, the radiotherapy technique was the most important prognostic factor. Patients receiving 3DCRT had superior survival rates and treatment responses. The primary reason for this was that the error risks arising from a potential geographic miss or individual anatomical variations were reduced because the target volume and critical normal tissues were determined based on CT-simulation images. The other reason was that 3DCRT demonstrated a better coverage and dose homogeneity inside the CTV because of the added segments to lateral fields.

Throughout pelvic radiotherapy or after the completion of treatment, genitourinary or gastrointestinal side effects have been shown.[23,24] In our study, severe complications were observed in only 2 patients. Nutrition education was important to reduce gastrointestinal complications. Furthermore, prior abdominal and pelvic surgery was also a high-risk factor for toxicities; this was not performed in our patients. It was also important in reducing the risk of developing complications. Chemoradiotherapy was well tolerated by our patients.

Modern technologies in radiotherapy delivery, such as IMRT, allow greater sparing of normal tissues and

provide highly conformal dose distributions. Although advantages of EBRT in patients with LACC treated with IMRT have been shown in terms of survival and side effects, it may have disadvantages, such as motion or filling of organs, and inhomogeneity within target volumes may affect local control.[25-28]

Although the application of IMRT in patients with definitive cervical cancer is not yet a standard approach, prospective clinical studies are needed to evaluate the comparative efficacy of IMRT and conventional or 3DCRT techniques.

## Conclusion

In stages IB–IV cervical cancer, chemoradiotherapy is effective and acceptable with regard to local control and survival advantage, and a reasonable rate of complications is observed. Furthermore, the conformal radiotherapy technique has been shown to be superior to the conventional radiotherapy technique. Further studies are needed to define the rate of toxicities and factors affecting the management of patients with LACC.

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