Treatment results and prognostic factors for cervical cancer patients treated by radiochemotherapy with weekly cisplatin

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Summary

Objective: This retrospective trial aims to report the treatment results of patients with locally advanced cervical cancer treated by concomitant radiochemotherapy with weekly cisplatin.

Methods: Between October 1999 and December 2003, 81 patients with FIGO Stages IB-IVA were treated at Ege University Faculty of Medicine Department of Radiation Oncology by radiochemotherapy with weekly cisplatin (40 mg/m^2). Intracavitary high-dose rate brachytherapy was applied to 76 patients (93.8%) and five patients (6.2%) were treated with external radiotherapy alone. Early and late side-effects of the treatment were analyzed according to RTOG-EORTC criteria.

Results: Median age was 55 years and the most frequent histology was epidermoid carcinoma. Median follow-up time was 42 months. Five-year overall, disease-free and local relapse-free survival rates were 69%, 77%, and 82%, respectively. The presence of low Hgb level (< 12g/dl), bulky tumor (> 4 cm), poor performance status, pelvic nodal involvement and limited early response to treatment had a significant impact on the local failure rate. Prognostic factors influencing disease-free survival were bulky tumor, performance status, pelvic nodal status, pretreatment Hgb level and limited early response to treatment. A significantly higher 5-year overall survival rate was observed in patients with good performance status, without pelvic nodal involvement, normal pre-treatment Hgb level and complete response to treatment. Grade 3-4 side-effects were not observed in any patients. The most frequent acute side-effects were leukopenia, anemia, nausea and vomiting. Long-term side-effects were observed in 54% of patients.

Conclusion: This series suggests that radiochemotherapy with weekly cisplatin is an effective and a safe treatment in locally advanced cervical cancer.

Key words: Cervical cancer; Radiochemotherapy; Prognostic factors.

Introduction

In developing countries such as Turkey, uterine cervix carcinoma is one of the most common cancers among women [1]. Despite the availability of effective screening programs, most of these cancers are still diagnosed in locally advanced stages. The standard treatment for patients with cervical carcinoma of FIGO Stage IB2 to IVA regardless of the histological type is cisplatin-based concomitant chemoradiotherapy [2, 3]. The advantage of concomitant chemoradiotherapy over radiotherapy alone in locally advanced cervical cancer has now been well documented in a series of prospective randomized trials [4-9]. Although these trials differed with respect to disease stage, chemotherapy regimens and chemoradiotherapy schedules, all of them demonstrated a 30%-50% improvement in survival when cisplatin-based chemotherapy was administered concurrently with radiation therapy. Based on this observation the U.S. National Cancer Institute released a clinical alert in February 1999 recommending that "strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer" [10]. Although the side-effects of chemoradiotherapy are tolerable for most patients, the addition of concurrent chemotherapy to radiotherapy markedly increases hematological and gastrointestinal toxicity and adds to the overall complexity of the treatment. Even though early publication of some trials precluded mature analysis of late radiation effects, available data suggest that the addition of concurrent chemotherapy did not markedly increase the risk of major late complications. Most women with locally advanced cervical cancer that is confined to the pelvis are candidates for radiochemotherapy. However, the benefit of adding concurrent chemotherapy to radiotherapy should always be weighed against the risk of serious acute side-effects.

Our previously published, interim results have shown promising efficacy and acceptable toxicity with radiochemotherapy in locally advanced cervical cancer [11]. Nevertheless, the small number of enrolled patients (39 patients) and a short median follow-up duration (20 months) have been the major points of scientific questions. To strengthen our data, we have decided to publish the data with more patients enrolled and longer follow-up time.

The objectives of the present study were to assess the outcomes associated with treatment including treatment toxicity and to evaluate the prognostic factors.

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Materials and Methods

Eighty-one patients were treated at Ege University Faculty of Medicine Department of Radiation Oncology between October 1999 and December 2003. The initial evaluation included complete physical and pelvic examination, abdominopelvic computed tomography (CT), chest radiography, complete blood count (CBC), and liver and kidney function tests. Patients had to have biopsy-proven uterine cervical carcinoma, Stage IB2 to Stage IVA according to FIGO criteria without distant metastasis, with a Karnofsky performance status ≥ 70 (KPS), and sufficient blood count, liver and kidney function test results.

External-beam radiotherapy was delivered using a 6 MV linear accelerator with a daily fraction dose of 1.8 Gy through the pelvic box or AP-PA portals. Brachytherapy was applied via a microSelectron high-dose rate remote afterloader Ir-192. A median of five cycles (range: 3-7) of cisplatin (40 mg/m²/weekly) was administered to all patients concurrent with radiotherapy. Complete blood count, kidney and liver function tests and pelvic examination were repeated before each chemotherapy cycle. Following completion of the whole treatment all patients were assessed by gynecological examination, abdominopelvic CT, CBC and liver and kidney function tests during the first month, and then every three months. Toxicity was assessed using the RTOG-EORTC early and late radiation morbidity criteria [12]. Since many of the patients had vaginal morbidity and this morbidity was not included in the RTOG-EORTC system, vaginal morbidity was graded according to the Franco-Italian glossary [13].

Statistical analysis

All statistical analyses were performed by the software program SPSS 10.0. Survival analysis was done using the Kaplan-Meier method. Overall survival was defined as the time from the first day of treatment to death or last follow-up. Patient age, tumor stage and size, nodal status, pretreatment hemoglobin level, early treatment response and performance status were the probable prognostic factors analyzed for actuarial overall survival and local control. The log-rank test was used for univariate analysis and the Cox regression model for multivariate analysis. Statistical significance was considered for p values of less than 0.05.

Results

Patients

The median age was 55 (range 28–74) years. Squamous cell carcinoma was the most common histologic type (70%). Distribution by stage was as follows: Stage IB 2.5%, IIA 23.5%, IIB 55.6%, IIIA 9.9%, IIIB 7.4%, IVA 1.2%. Most of the patients were (64.2%) postmenopausal. Median number of parity was five (range: 1-14). Median age of parity was 18 (range 14-32). Pelvic nodal involvement was determined in 14 (17.3%) patients. Tumor size was larger than 4 cm in 52 patients (64.2%). Patient characteristics are shown in Table 1.

Table 1. — *Patient characteristics.*

	No. of patients	%
Age	Median 55 (28-74)	
KPS		
90-100	40	50
70-80	3	4
ND	38	46
Menopausal status		
Premenopausal	20	24.7
Perimenopausal	9	11.1
Postmenopausal	52	64.2
Histopathology		
Epidermoid	70	86.4
Non-epidermoid	11	13.6
Tumor Size		
< 4 cm	29	35.8
> 4 cm	52	64.2
Pelvic nodal involvement		
Present	14	17.3
Absent	67	82.7
Stage		
IB	2	2.5
IIA-IIB	64	79.1
IIIA-IIIB	14	17.3
IVA	1	1.2
Early treatment response		
No response	2	2.5
Partial response	10	12.3
Complete response	60	74.1
N.D.	9	10.1

KPS: Karnofsky performance status; ND: not defined.

Treatment

Median number of chemotherapy cycles was five (range: 3-7) and 85% of the patients received more than five cycles. Twelve patients received only three cycles, 19 patients received four cycles, 31 patients received five cycles, 16 received six cycles and three patients were administered seven cycles as scheduled. Chemotherapy toxicity was managed by dose delays rather than by dose reduction. External radiotherapy was combined with intracavitary high-dose rate brachytherapy in 76 patients (93.8%) and five patients (6.2%) were treated with external radiotherapy alone.

Treatment results

Median follow-up duration was 42 months (range: 6-81 months). Five-year overall, disease-free and local recurrence-free survival rates were 69%, 73% and 82%, respectively (Figure 1). Eleven patients (13.6%) developed local recurrence and ten patients developed distant metastasis. Median time for local failure and distant metastasis was 23 months (range: 0-49) and 22 months (range: 7-69), respectively. The lung was the most common site of distant metastases, followed by bone and liver. Early complete and partial response rates were 74.5% and 13.5%, respectively.

Patterns of failure

Of the 81 patients local recurrence was significantly more frequent in the following groups of patients with bulky tumors (> 4 cm) (p = 0.02), poor performance status (KPS < 80) (p = 0.00), initial low Hgb level (< 12 g/dl) (p = 0.00), pelvic nodal involvement (p = 0.04) and limited early response (p = 0.00). In multivariate analysis, KPS was the only significant factor (p = 0.02).

According to univariate analysis prognostic factors influencing disease-free survival were tumor size (p =

0.03), performance status (p = 0.00), tumor size (p = 0.03), initial Hgb level (p = 0.00), pelvic nodal involvement (p = 0.01) and early treatment response (p = 0.00).

A significantly higher 5-year overall survival rate was observed among patients with good performance status compared to those with poor performance status (79% vs 0%; p = 0.00), and in those with a Hgb level > 12 g/dl compared to those with a lower Hgb level (53.1% vs 25.0%; p = 0.00). Pelvic nodal involvement and limited early response to treatment had an adverse effect on overall survival (p < 0.00). These factors were not confirmed in the multivariate analysis.

The results of the univariate analysis are shown in Table 2.

Table 2. — *Prognostic factors.*

	5-year overall survival (p value)		5-year disease-free survival (p value)		5-year local failure still survival (p value)	
Age						
< 45	58%		66%		66%	
≥ 45	69%	(0.61)	74%	(0.52)	73%	(0.14)
KPS						
90-100	79%		71%		79%	
70-80	50%	(0.00)	0%	(0.00)	0%	(0.00)
Hgb level						
< 12 g/dl	50%		49%		61%	
> 12 g/dl	86%	(0.00)	77%	(0.00)	94%	(0.00)
Tumor size						
< 4 cm	78%		89%		100%	
> 4 cm	62%	(0.21)	63%	(0.03)	78%	(0.00)
Pelvic nodal involvement						
(+)	57%		45%		58%	
(-)	80%	(0.00)	78%	(0.01)	86%	(0.04)
Histology						
Epidermoid	69%		76%		84%	
Non-epidermoid	63%	(0.08)	59%	(0.14)	70%	(0.07)
Early treatment response						
No response	0%		0%		0%	
Partial response	50%		40%		40%	
Complete response	76%	(0.00)	85%	(0.00)	95%	(0.00)

KPS: Karnofsky performance status.

Side-effects

The treatment was generally well tolerated and relatively easy to administer. There were no treatment-related deaths. Late radiation morbidity was evaluated at least six months after the treatment. None of the patients developed grade 3 or 4 late toxicity. The most frequent acute side-effects of chemotherapy were leukopenia, anemia, nausea and vomiting. Fifty-nine patients developed toxicity due to radiotherapy. Cystitis, diarrhea and radiodermitis were the most common acute side-effects related to radiotherapy. According to the RTOG/EORTC late radiation morbidity criteria all of them had grade 1-2 toxicity and two patients had urinary incontinence, two proctitis, 11 soft tissue fibrosis, and 11 had multiple side-effects. According to the Franco-Italian glossary 18 patients had vaginal stenosis. Treatment-related acute and long-term side effects are indicated in Tables 3 and 4, respectively.

Table 3. — *Early toxicity related to radiochemotherapy.*

	No. of patients	%
Nausea and vomiting	21	25.9
Diarrhea	5	6.2
Dermatitis	5	6.2
Cystitis	36	44.4

Table 4. — *Long-term morbidity related to radiochemotherapy.*

	No. of patients	%
Vaginal stenosis	18	22.2
Urinary incontinence	2	2.4
Proctitis	2	2.4
Soft tissue fibrosis	11	13.5
Multiple	11	13.5

Discussion

It has been stated that concurrent radiochemotherapy reduces the risk of recurrence by up to 50% in patients with locally advanced cervical cancer [10]. Five randomized studies as well as a meta-analysis have demonstrated that chemotherapy administered concurrently with radiotherapy improves overall survival in comparison with radiotherapy alone [14]. After 1999, the percentage of published papers about radiochemotherapy in cervical cancer increased from 30% to 80%. This observation shows that radiochemotherapy is a well accepted treatment modality worldwide. Various cytotoxic drugs have been used in addition to radiotherapy including cisplatin, 5-fluorouracil, mitomycin C, hydroxyurea, or carboplatin. The optimal combination and schedule have not been determined yet, but cisplatin is accepted as the most effective drug.

Four prospective randomized trials of weekly cisplatin combined with radiotherapy showed significantly better progression-free and overall survival rates in the cisplatin group [4-7].

Rose *et al.* noted a 67% disease-free and a 66% overall survival at two years with weekly cisplatin in the randomized trial of RTOG [4]. Four-year disease-free and overall survival rates were 79% and 83%, respectively, in a series by Keys *et al.* [5]. In the current study local-failure free, progression-free and overall survival rates were 82%, 73% and 68% at five years, respectively, and the results are comparable with the published literature.

Several factors related with outcome have been identified. In our analysis, tumor size was identified as an independent prognostic factor for local control and disease free survival (p < 0.05). Similar results were documented in both stage-limited [15], and non-stage-limited [16-19] analysis. Two large trials reported that tumor size was a strong prognostic factor for treatment outcome in stage III disease [19, 20]. The patients with large tumors had many pelvic and distant failures and poor survival. In addition, Eifel *et al.* [15] noted that tumor size had a strong relation to central and pelvic control and disease-free survival in patients with Stage IB disease.

The 5-year overall and disease-free survival rates of patients with epidermoid histology were significantly

higher than those of the patients with non-epidermoid histology in some studies [18, 21, 22]. Fyles and Mitsuhashi compared a group of patients with epidermoid histology to a group with non-epidermoid histology and reported that survival, local and distant control was worse in patients with non-epidermoid histology [21, 22]. Non-epidermoid histology was not an adverse prognostic factor in the present study which may be due to the small number of patients with non-epidermoid histology (11 patients).

Hgb level had a significant effect on the therapeutic outcome with higher survival and locoregional control rates in patients with high Hgb levels. Similar results were also reported in various studies [18, 19, 21, 23, 24]. Pederson *et al.* [18] analyzed the data for four subgroups classed by Hgb value and found a strong influence on survival and both local and distant failure. Serkiesi *et al.* [23] noted that Hgb level was an independent parameter of poor overall and disease-free survival in cervical cancer patients treated by definitive irradiation and this effect was mainly due to increased risk of distant metastases. The prognostic impact of pelvic nodal involvement in cervical cancer is well established. Patients with positive pelvic lymph nodes were considered as a high-risk group in the Gynecologic Oncology Group (GOG) study [25]. Pelvic lymph node metastasis had a significant impact on both overall and disease-free survival [26]. In the current study the presence of pelvic nodal involvement had an adverse effect on overall and disease-free survival and local control.

Early treatment response was a strong prognostic factor for survival and local control in our analysis. Radiation-induced tumor regression as a prognostic factor in cervical cancer has been evaluated by a number of investigators [19, 20, 27, 28]. Takheshi and co-workers indicated that the early treatment response significantly affected the overall survival but not the local control [19]. Early treatment response is also important for bulky tumors for the delivery of intracavitary brachytherapy.

The addition of chemotherapy to radiotherapy increases toxicity rate. Although the incidence and severity of hematologic and gastrointestinal complications are markedly increased [4, 5, 8, 23], good tolerance to concurrent cisplatin and RT has also been reported. In the present study administration of cisplatin at 40 mg/m^2/weekly combined with RT was accompanied by hematologic, gastrointestinal and genitourinary toxicity in 35%, 32%, and 20% of the patients, respectively. Adverse effects were almost exclusively transient. These results are comparable to those reported in randomized trials and retrospective series. In the study by Keys *et al.* [5], hematologic, gastrointestinal and genitourinary toxicity rates were 42%, 39% and 18%, respectively. In the trial by Serkiesi *et al.* [23] using concurrent weekly cisplatin and RT, hematologic toxicity was observed in 43% of the patients, gastrointestinal toxicity in 33% and genitourinary toxicity in 16%. Likewise, Pearcey *et al.* reported that gastrointestinal, hematologic, and genitourinary toxicity were more frequent in the combined modality arm but this has not caused clinically important treatment delays [8]. Although few detailed analyses of late complications of chemoradiotherapy have been reported, available data suggest that concurrent cisplatin-based chemotherapy does not increase the risk of serious late effects of radiation. Rakovitch *et al.* reported an increased rate of late side-effects related to radiochemotherapy when mitomycin was included in the regimen [29]. Vaginal stenosis was the most common late morbidity in the present study. Yalman noted a 94% grade 1-3 vaginal morbidity due to external radiotherapy and intracavitary HDR brachytherapy in 771 patients with gynecologic malignancy [30] .

Radiochemotherapy has been the standard treatment for locally advanced cervical cancer providing significantly higher overall and disease-free survival rates than radiotherapy alone. Although the present study is retrospective the results were consistent with the literature indicating that this standard treatment approach is effective for locally advanced cervical cancer with acceptable early and late toxicity.

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