Radiochemotherapy for patients with locally advanced cervical cancer: early results

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Summary

Purpose: Radiotherapy is the standard treatment for locally advanced cervical cancer. Recent results of the prospective randomized trials have shown an overall survival and local control advantage for cisplatin-based therapy given concurrently with radiation therapy. Thirty-nine patients who received concurrent chemoradiation between October 1999 and December 2000 were evaluated for treatment response, local control and toxicity.

Materials and methods: Thirty-nine patients with Stage IB through IVA cervical carcinoma received weekly cisplatin (40 mg/m^2) concurrent with radiotherapy. Thirty-two patients received both external and intracavitary radiotherapy and seven patients received only external radiotherapy because of insufficient tumor response for intracavitary application. Total external radiotherapy dose was 64.8 Gy with 1.8 Gy daily fractions in patients who received only external radiotherapy. Midline shielding was performed at 50.4 Gy in patients who were going to receive brachytherapy and the total external radiotherapy dose was 54-59.4 Gy. Brachytherapy was performed with a Rotterdam applicator via the microSelectron HDR machine. A total dose of 8.5-18 Gy was applied to point A.

Results: Median age was 55. Distribution by stages were as follows: Stage IB 5.1%, IIA 28.2%, IIB 43.6%, IIIA 7.7%, IIIB 12.8% and IVA 2.6%. Histologically 33 (84.6%) were epidermoid carcinoma, one was adenocarcinoma, two were undifferentiated carcinoma, one was malignant epithelial tumor. In two patients histological type could not be specified. The median duration of follow-up was 20 months. Four patients had local recurrence and three developed distant metastases. Thirty patients (76.9%) had complete response, eight had (20.5%) partial response and one had (2.6%) stable disease. During or after radiochemotherapy 46.2% of the patients developed toxicity due to chemotherapy. Early and late radiation morbidity rates were 66.7% and 71.8%, respectively. No grade III-IV toxicity was observed.

Conclusion: Concurrent chemoradiation for locally advanced cervical cancer is the treatment of choice in suitable patients providing high response rates with acceptable toxicity.

Key words: Cervical cancer; Radiochemotherapy.

Introduction

Carcinoma of the uterine cervix is the second most common malignant neoplasm in women and 25% of the cases present with locally advanced disease (FIGO Stage IIB-IVA) at the time of diagnosis [1]. Radiotherapy is the standard treatment of locally advanced cervical cancer. However treatment results are unsatisfactory particularly for those with bulky disease because the doses required to treat large tumors exceed the limit of toxicity in normal tissue. Different radiation-fractionation schemes, heavy-particle radiotherapy, concurrent use of hyperthermia and chemotherapy are being studied to increase the efficacy of radiotherapy [1-10].

Concurrent use of chemotherapy and radiotherapy could have a synergistic effect. Chemotherapy which is used for systemic disease might increase the sensitivity of the tumor to radiotherapy which is used for local disease. Concurrent chemotherapy inhibits the repair of sublethal damage from radiation and synchronizes cells to a particularly radiosensitive phase of the cell cycle [1, 4, 5, 8, 8-13]. Several prospective randomized studies were performed to test the effect of concurrent chemotherapy and radiotherapy in locally advanced cervical cancer. Hydroxyurea, mitomycin-C, 5-fluorouracil (5-FU) and cisplatin were the most commonly used cytotoxic agents and among these weekly administration of cisplatin was more appropriate providing high response rates with acceptable toxicity [3, 5, 8, 11, 12].

In the present study patients with locally advanced cervical cancer who received weekly cisplatin (40 mg/m^2) concurrent with radiotherapy were evaluated for early treatment response, local control and toxicity.

Materials and Methods

Thirty-nine patients with FIGO Stage IB to IVA cervical carcinoma received weekly cisplatin (40 mg/m^2) concurrent with radiotherapy between January 1999 and December 2000. Two patients with Stage IB disease were medically inoperable and referred for definitive radiotherapy.

Each patient underwent complete physical and pelvic examination, chest X-ray and intravenous pyelography and abdominopelvic computed tomography before treatment, and Karnofsky performance status, complete blood count, liver and kidney function tests were assessed.

External radiotherapy was administered to the whole pelvic region with 6 MV photons with a daily fraction of 1.8 Gy. The superior border of the pelvic portal was at the L4-5 interspace.

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AP/PA portals or a pelvic box technique were used. In patients with lower third of the vagina involvement the treatment portal included the inguinal lymph nodes as well. Total external radiotherapy dose was 54 Gy in patients without parametrial involvement and 59.4 Gy in patients with parametrial involvement. Intracavitary brachytherapy was applied with a Rotterdam applicator set via the microSelectron HDR-Ir 192 remote afterloading machine. The dose delivered to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 2 x 8.5 Gy in nine patients, 3 x 6 Gy in 22 patients and 1 x 8.5 Gy in one. In seven patients the tumor response was insufficient for brachytherapy application so these patients received 64.8 Gy external radiotherapy through shrinking fields after 54 Gy.

All of the patients were administered weekly cisplatin (40 mg/m^2) before radiotherapy. The patients who received cisplatin at least three weeks were included in the present study. Median cisplatin administration was five weeks. Leukocyte, neutrophil and platelet count; serum urea and creatinine concentration were assessed every week before the administration of chemotherapy. Chemotherapy was discontinued if the leukocyte count dropped below 2500/mm^3 and serum creatinine concentration increased to 1.1 mg/dl.

Results

Median age was 55 (range 28-70). Most of the patients were postmenopausal (74.4%). Median number and age of parity were five (range 2-10) and 19 (range 14-29), respectively. Distribution by stage was as follows: Stage IB 5.1%, IIA 28.2%, IIB 43.6%, IIIA 7.7%, IIIB 12.8% and IVA 2.6%. Histologically 33 (84.6%) were epidermoid carcinoma, one was adenocarcinoma, two were undifferentiated carcinoma and one was malignant epithelial tumor. In two patients histological type could not be specified. Karnofsky performance scores were 80 in two patients (5.1%), 90 in nine (23.1%) and 100 in 22 (56.4%). It was not recorded in six patients. Patient characteristics and treatment details are indicated in Tables 1 and 2, respectively.

Table 1. — *Patient characteristics.*

	No. of patients	%
Age		
Median 55 (range 28-70)		
Menopausal status		
Premenopausal	7	17.9
Perimenopausal	3	7.7
Postmenopausal	29	74.4
Histologic type		
Epidermoid carcinoma	33	84.6
Adenocarcinoma	1	2.6
Undifferentiated carcinoma	2	5.1
Malignant epithelial tumor	1	2.6
Unknown	2	5.1
FIGO Stage		
IB	2	5.1
IIA	11	28.2
IIB	17	43.6
IIIA	3	7.7
IIIB	5	12.8
IVA	1	2.6

Table 2. — *Treatment details.*

	No. of patients	%
Radiotherapy		
External RT	11	28.2
External RT and intracavitary Brachytherapy	28	71.8
Treatment field		
AP/PA pelvic	8	20.5
Pelvic box	28	71.8
Whole pelvis and inguinal lymph nodes	3	7.7
Chemotherapy		
3 weeks	6	15.4
4 weeks	7	17.9
5 weeks	21	53.8
6 weeks	5	12.9

Following completion of treatment all patients were monitored the first month, then every three months. Complete and partial response rates were 76.9% and 20.5%, respectively (Table 3).

Median follow-up duration was 20 months (range 5-31). Four patients (10.3%) developed local recurrence and three developed distant metastases (two to lungs, one to bones). One of the patients with local recurrence had Stage IIA, two had Stage IIB and one had Stage IIIA disease. Three of them had partial and one had complete response to treatment. Four patients have since died - one due to lung metastasis, two due to local recurrence and one due to intracranial hemmorhage.

Twenty-one patients developed toxicity due to chemotherapy (Table 4). Emesis was managed with symptomatic treatment in nine patients. Chemotherapy was delayed in 18 patients, seven with hematologic and 11 with nephrologic toxicity. Twenty-six patients developed acute radiation morbidity which were grade 1 or 2 cystitis and diarrhea. None of the patients developed toxicity requring interruption of radiotherapy. Late radiation morbidity was assessed after six months. Five patients (12.8%) had vaginal stenosis, three (7.7%) had urinary incontinence, one (2.6%) had proctitis and three (7.7%) had both vaginal stenosis and proctitis (Table 5).

Table 3. — *Response to treatment.*

	No. of patients	%
Stable disease	1	2.6
Partial response	8	20.5
Complete response	30	76.9

Table 4. — *Toxicity due to chemotherapy.*

	No. of patients	%
Emesis	9	23.1
Hematologic toxicity	9	23.1
Nephrologic toxicity	11	28.2

Table 5. — *Early and late radiation morbidity.*

	No. of patients	%
Early morbidity (Grade I-II)		
Diarrhea	5	12.9
Cystitis and diarrhea	21	53.9
Late morbidity (Grade I-II)		
Vaginal stenosis	5	12.8
Urinary incontinence	3	7.7
Proctitis	1	2.6
Vaginal stenosis and proctitis	3	7.7

Discussion

Pelvic radiotherapy alone fails to control the progression of cervical cancer in 35% to 90% of patients with locally advanced disease and in approximately two-thirds of the cases progression occurs within the irradiated volume [1, 5, 8]. Recent results from each of five randomized trials showed an overall survival advantage for cisplatin-based chemotherapy [3, 5, 8, 11, 12]. Theoretically by the administration of chemotherapy concurrent with radiotherapy the two treatments may interact to increase the killing of tumor cells without delaying the course of radiotherapy or protracting the overall treatment time which may accelerate the proliferation of tumor cells. Chemotherapy inhibits the repair of radiation-induced DNA damage, promotes the redistribution of cells into a radiosensitive phase of the cell cycle, and reduces the fraction of hypoxic cells that are radioresistant [1, 4, 9, 13, 14]. In chemoradiotherapy trials cisplatin, 5-FU, mitomycin C and hydroxyurea are the agents investigated most frequently and cisplatin is considered the most active agent in cervix cancer. In a study by Rose *et al.* [5] (Gynecologic Oncology Group) 526 women with cervix carcinoma of Stage IIB to IVA were randomized to receive 40 mg/m^2 cisplatin per week for six weeks (group 1), 50 mg/m^2 cisplatin on days 1 and 29 followed by 4g/m2 5-FU given as a 96-hour infusion on days 1 and 29 and 2 g/m^2 oral hydroxyurea twice weekly for six weeks (group 2) and 3 g/m^2 oral hydroxyurea twice weekly for six weeks (group 3). Median duration of follow-up was 35 months. Both groups that received cisplatin had a higher rate of progression-free survival than the group that received hydroxyurea alone. In Morris *et al*'s study [12] 403 women with advanced cervical cancer (Stage IB through IVA) were randomly assigned to receive either 45 Gy of radiation to the pelvis and paraaortic nodes or 45 Gy of radiation to the pelvis alone plus two cycles of 5-FU and cisplatin (days 1 through 5 and days 22 through 26 of radiation). Overall and disease-free survival rates were significantly higher for the combination therapy group. In Wong *et al.*'s [9] three-arm study with the use of concurrent cisplatin in patients with Stage IIB and III disease patients were randomized to receive pelvic radiotherapy alone or pelvic radiotherapy in combination with either weekly or twice-weekly cisplatin (25 mg/m^2). At the completion of radiotherapy the response rate was significantly higher in those patients who received radiotherapy and twice-weekly cisplatin than in those patients who received radiotherapy alone. However with follow-up ranging from 42 to 72 months there was no difference in the rate of loco-regional recurrence or survival among the three groups and it was concluded that cisplatin in the dose used (25 mg/m^2) failed to improve long-term tumor control.

Pearcey *et al.* [15] compared radical radiotherapy with and without weekly cisplatin chemotherapy (40 mg/m^2) in 259 patients with FIGO Stage IB to IVA cervical cancer. Median follow-up was 82 months and no significant difference was found in progression-free survival and in 3- and 5-year survival rates between two groups. However the preliminary results of this study, which was presented in the year 2000, were criticized in a review by Lehman and Thomas regarding patient selection and randomization criteria, dose of radiotherapy, hemoglobin levels of the combined modality group and the statistical errors [1].

Green and associates [16] did a systematic review of all known randomized controlled trials of chemoradiation for cervical cancer done between 1981 and 2000 (19 trials including 4,580 patients). Cisplatin was the most common agent used and the findings suggest that chemoradiation improves overall- and progression-free survival, and a significant benefit on both local control and distant recurrence was also recorded. In our study objective response rate was 97.4%. It is too early to draw a conclusion about overall- and progression-free survival.

The most frequent toxic effect of concurrent chemoradiotherapy is myelosuppression. Cisplatin is less myelosuppressive and can be given weekly during radiotherapy with acceptable levels of toxicity. When a combination of two or three drugs are used – as in the Gynecologic Oncology Group study – the frequency of grade 3 and grade 4 toxicity increases [5]. Souhami *et al.* [17] used concurrent cisplatin and radiotherapy followed by high-dose brachytherapy to treat 50 patients with cervical cancer. The response rate was high, but 28% of the patients had severe late gastrointestinal complications. It was shown that this effect was due to high-dose brachytherapy. Sundfer *et al.* [6] used neoadjuvant cisplatin and 5-FU in 47 patients and radiotherapy alone in 47 patients. Eight patients experienced a mucosal toxicity of grade 3 or 4 in the chemotherapy group and one patient refused further chemotherapy. Late gastrointestinal toxicity was observed in four patients in the radiotherapy alone group and in two patients in the combined modality group. Three patients have died due to treatment-related toxicity, one in the radiotherapy alone group and two in the combined modality group. In Keys *et al.*'s study 374 women with bulky Stage IB cervical cancer were randomly assigned to receive radiotherapy alone or in combination with weekly cisplatin (40 mg/m^2) followed by adjuvant hysterectomy [8]. In the combined-therapy group 39 patients had grade 3 or grade 4 hematologic toxicity as compared with three patients in the radiotherapy alone group. Grade 3 or grade 4 gastrointestinal toxicity was seen in 26 patients in the combined-

therapy group as compared with nine patients in the radiotherapy alone group. The frequency of grade 1 and grade 2 genitourinary and neurologic adverse effects was higher in the combined-therapy group. In our study gastrointestinal toxicity was the most frequent and none of the patients had grade 3 or 4 early or late radiation morbidity.

Concurrent chemoradiation for locally advanced cervical cancer is the treatment of choice in suitable patients providing high response rates with acceptable toxicity.

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