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A comparative study of intensity-modulated radiotherapy and standard radiation field with concurrent chemotherapy for local advanced cervical cancer

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Summary

Objective: This study aimed to compare three-dimensional conformal radiotherapy (3D CRT) and intensity-modulated radiotherapy (IMRT) combined with concurrent chemotherapy for cervical cancer. *Materials and Methods:* A total of 72 patients with Grades IIa–IIIb cervical cancer were randomly divided into two groups, namely, the IMRT group for IMRT plan (primary lesion, 45 Gy/22; the pelvic wall lymphatic drainage area, 50 Gy/22), and the 3D CRT group (conformal pelvic radiotherapy, 45 Gy/22; subsequent supplement of pelvic wall, 6.0 Gy/3). Both groups received concurrent chemotherapy of nedaplatin 30 mg/m^2 weekly for six cycles, with an after-loading therapy of 6 Gy/6 each time. *Results:* In the IMRT group, the grade III diarrhea rate was 5.6% and the rate in the 3D CRT group was 30.6%; both groups significantly differed. No significant difference was observed between the overall survival and disease-free survival in first, second, and third years in both groups. *Conclusion:* Cervical cancer IMRT can significantly reduce the incidence of acute enteritis. For standard 3D CRT, no significant difference was observed in overall survival and disease-free survival.

Key words: Cervical cancer; Three-dimensional conformal radiotherapy; Intensity-modulated radiotherapy; Efficacy.

Introduction

With the advancements in computer technology, three-dimensional conformal radiotherapy (3D CRT) and intensity-modulated radiotherapy (IMRT) are gaining increased attention because of their dosimetry advantages. Regarding such advantage found by Portelance *et al.* [1] is the reduced prescription dose (45 Gy) in the intestine. Heron *et al.* [2] also believed that IMRT can reduce >30 Gy doses by 52% in the intestine, by 66% in the rectum, and by 36% in the bladder. D'Souza *et al.* [3] found as well that IMRT can reduce the intestinal dose by 33%. By a meta-analysis involving 4,580 cases and 19 trials of IMRT with concurrent chemotherapy, Green *et al.* [4] found improvements in the tumor control rate and overall survival. However, higher incidences of blood and gastrointestinal toxicity occur in patients with concurrent chemoradiotherapy. Beriwal *et al.* [5] reported early results of intensity-modulated and concurrent cisplatin therapy but made no comparison with conventional treatment. Folkert *et al.* [6] used intensity-modulated technology in postoperative patients, and found that the three- and five-year disease-free survival rates were 91.2% and 91.1%, respectively. IMRT has also been found to have certain dosimetry advantages in cervical cancer radiotherapy, with a number of good results observed in postoperative patients. However, based on the positive results of conformal pelvic radiotherapy in previously untreated cervical cancer patients, uncertainties remain on whether intensity-modulated technology can replace traditional treatment for these patients. Using IMRT and concurrent platinum-based chemotherapy may reduce acute radiation reaction. Thus, tolerance to treatment must be promoted, which requires further investigation.

Materials and Methods

In this study, 72 patients were randomly divided into two groups (36 patients each) by the envelope method.

General information

From September 2006 to September 2009, 72 patients with clear pathological diagnosis of Grades IIa–IIIb cervical cancer that met the following criteria were included in the randomized control study: 1) the patient signed and agreed to participate in the study by signing an informed consent form; 2) the patient was 18 to 70 years old; 3) the pathological diagnosis was squamous cell carcinoma, and the clinical stage was within Grades IIa–IIIb; 4) the patient was to undergo treatment for the first time and had no history of cancer or chemoradiotherapy; and 5) the patient had ≥110 g/L hemoglobin, ≥3. 5 × 10^9 /L WBC, ≥100 × 10^9 /L platelets, <1.25 times the normal upper limit of liver and kidney function, and normal blood sugar. Based on the FIGO staging criteria, the patients were randomly divided into two groups by the envelope method. All procedures were approved by the hospital ethics committee. This study was conducted in

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accordance with the declaration of Helsinki and with approval from the Ethics Committee of Huai'an First People's Hospital, Nanjing Medical University. Written informed consent was also obtained from all participants.

Posture

During therapy, the patient was supine with hands clasped and elbows and legs naturally closed.

Computed tomography (CT) scan

A SensationOpen was used for CT simulation. The bladder was emptied 90 minutes before CT scan, and then filled with meglumine diatrizoate injection in order to displace the intestine during scanning. Diatrizoate was taken took before the scan. The scan was started after an injection of iohexol, and the range of sweeping surface was from L1 to five cm under the ischial tuberosity (five mm thickness).

Treatment planning

The clinical target volume (CTV) contained the primary tumors of the uterus, cervix, vagina, and other regions such as below the lymphatic drainage area (L4, iliac, internal iliac, external iliac, obturator, parametrial, paracervical, and presacral lymph nodes from L5 to L3). The CTV did not include pelvic tissue. Based on the actual situation, the planning target volume (PTV) was formed by the CTV boundary out-expansion of 1.0 cm. The sensitive tissues including the rectum, bladder, small intestine, and femoral head were sketched. After target delineation CMS radiation treatment planning system, the authors designed IMRT plans for the patients based on the reverse design principle. Seven field irradiations and six MV X-ray were used as follows: 1) 50 Gy for the pelvic wall lymph drainage (excluding the presacral lymphatic drainage area); 2) 45 Gy/22 for the uterus, cervix, vagina, and other primary tumor areas; 3) the dose gradient PTV was ≤ 10%; and 4) 40 Gy irradiated volume (V_{40}) of rectum and bladder were less than 40%, and V_{40} of intestine was < 30%. The priorities for PTV were the rectum, bladder, small intestine, femoral head, and spinal cord. To the patients, a conformal conformal pelvic radiotherapy of 45 Gy/22F was given, and then, another 6.0 Gy/3 F was subsequently supplied by the radiation field to the center while sheltering the pelvic wall. An oncor linear accelerator was used.

Chemotherapy and detection

Two groups were treated with nedaplatin 30 mg/m^2 weekly for six cycles. During treatment, routine blood analysis was conducted twice a week to monitor the liver and kidney function, once a week for blood biochemistry, and once a month for ECG (monthly review). If needed, the granulocyte colony-stimulating factor was used for symptomatic treatment.

Toxicity evaluation

Acute toxicity was evaluated by the Common Terminology Criteria for Adverse Events v3.0 [7].

Table 1. — *Clinical data.*

Group	Conventional (n=36)	Intensity-modulated (n=36)
Age (years)		
Range	24-73	22-75
Median	56	57
Pathological type		
Squamous carcinoma	35	34
Adenocarcinoma	1	2
PS grade		
0-1	36	36
FIGO staging		
IIa	11	10
IIb	16	17
IIIa	6	7
IIIb	3	2

Statistical analysis

The primary endpoint for the treatment was toxic reaction. The secondary endpoint was the overall survival rate and tumor-free survival rate. SPSS17.0 statistical software was used, and the Kaplan–Meier method and line Log-rank test were used for survival analysis. Count data were analyzed by the χ^2 test, and $p < 0.05$ was considered significant.

Results

Follow-up observations were conducted every three months in the first year, every six months in the second year, and then once a year starting from the third year. The follow-up rate was 100%. The patients' characteristics were similar (Table 1).

Toxicity

Nausea, vomiting, hemoglobin, and neutrophils decreased in the two groups, but were not significantly different. In the grades I and II IMRT group, the diarrhea rate was 55.6% (20/36); in the grade III and above group, the rate was 5.6% (2/36). In the grades I and II 3D CRT group, the diarrhea rate was 69.4% (25/36); in the grade III and above group, the rate was 30.6% (11/36). For grades III and above, significant differences were observed between the two groups (Table 2).

Survival

In the IMRT group, the one-, two-, and three-year overall survival rates were 94.4%, 86.1%, and 77.8%, respectively.

Table 2. — *Adverse reactions.*

Toxicity	Control group (n=36)					Study group (n=36)				
	0	1	2	3	4	0	1	2	3	4
Nausea, vomiting	9	20	5	2	0	15	16	3	2	0
Hemoglobin deduction	22	12	2	0	0	24	10	2	0	0
Neutrophils deduction	0	5	20	9	2	1	6	18	10	2
Platelet deduction	17	9	8	2	0	20	8	7	1	0
Diarrhea	0	10	15	10	1	14	12	8	2	0

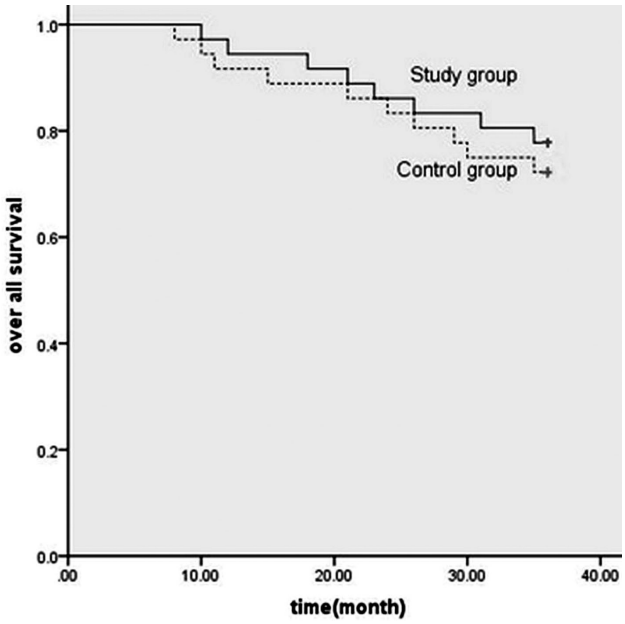

Figure 1. — Overall survivals of patients (p = 0.575).

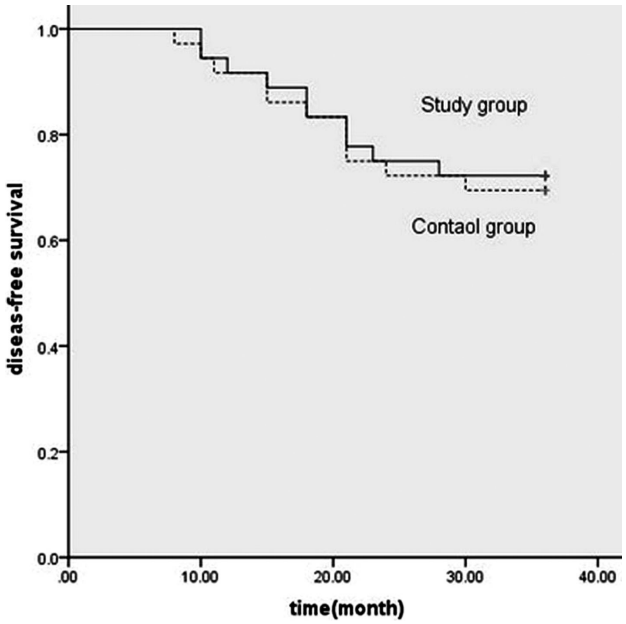

Figure 2. — Tumor-free survivals of the two groups (p = 0.800).

The one-, two-, and three-year disease-free survival rates were 91.7%, 75.0%, and 72.2%, respectively. In the 3D CRT group, the one-, two-, and three-year overall survival rates were 91.7%, 86.1%, and 75.0%, respectively. The one-, two- and three-year disease-free survival rates were 91.7%, 72.2%, and 69.4%, respectively, and no significant difference was observed (Figures 1 and 2).

Discussion

Concurrent platinum-containing chemoradiotherapy is opted for patients with Grade IIb and above cervical cancer [8]. In this study, 70.8% of the patients met this standard. Traditional external radiation is a combination of conformal pelvic radiotherapy and intracavitary radiotherapy. However, traditional technology affects large amounts of normal tissue, especially sensitive ones such as intestinal, rectal, and bladder tissues. IMRT optimizes the 3-D coverage of the conformal area of the target, improves the target dose, and reduces the irradiation of normal tissue surrounding the target area [1-3]. Song *et al.* [9] compared IMRT with 3-DCRT and determined the optimal dose distribution for the treatment of cervical cancer. They found that the small bowel and bladder average V_{10} and V_{20} decreased by 10.8% and 7.4% (p = 0.001 and 0.04), respectively.

Chen *et al.* [10] conducted a study on early cervical cancer treated by IMRT with concurrent chemotherapy. They found that the local control and disease-free survival rates were 93% and 78%, respectively, in three years. However, no clear conclusion was drawn for patients with late-stage cancer. Kavanagh *et al.* [11] suggested that cervical cancer patients unsuitable for brachytherapy can be subjected to IMRT for primary tumor. Guerrero *et al.* [12] proposed intensity-modulated integrated dosage (SIB) technology to replace traditional total pelvic irradiation. In SIB, 25 splits are performed for each 3.1 Gy. Salama *et al.* [13] applied intensity-modulated treatment with concurrent chemotherapy to 12 cases of cervical cancer, endometrial cancer, and other gynecological tumors, and found high tolerability. These studies suggested that intensity-modulated treatment can partly exert a positive effect on cervical cancer, and can be regarded as an alternative to endovascular treatment in some patients. However, no conclusion was drawn regarding concurrent chemoradiotherapy under the conventional fractionation mode in the initial treatment.

To examine the positive results of the traditional radiation mode (conformal pelvic radiotherapy and intracavitary brachytherapy) in the treatment of cervical cancer, the dose-administration mode in this study was made to be consistent with that of the traditional cassette mode. Conventional technique and IMRT treatment gave 45 Gy at point A and 50 Gy at the pelvic wall point B. The start time and dose of endovascular treatment were the same, i.e., the physical and biological doses for patients were the same as the traditional method. This result differed from the improvement in tumor physical and biological doses in nasopharyngeal intensity-modulated therapy [14]. The problems that remain to be solved are as follows. First, can the physical advantage produce increased amounts of minor radiation reac-

tions? Second, is the survival rate the same as traditional treatment methods? Third, can the external dose be further improved to reduce adverse reactions and enhance the therapeutic effect?

Although improved effects of concurrent chemotherapy have been observed, the acute reaction remains noteworthy [15,16]. The improvement in acute adverse reactions by excellent intensity modulated plans is the focus of current clinical works. IMRT reduces radiation reaction and ensures the smooth progress of radiochemical synchronization. Chen *et al.* [17] studied cervical cancer patients after intensity-modulated therapy with synchronizal cisplatin, and found that intensity-modulated radiation reduces the acute response of the intestinal and urinary tract, indicating improved tolerability. This randomized control study for previously untreated patients with cervical cancer, radiotherapy, and concurrent chemoradiotherapy was completed in all patients. The present data showed that: IMRT significantly reduced acute intestinal reaction, which is its main advantage. No significant difference was observed in the overall survival and tumor-free survival of the first, second, and third years between the IMRT and 3D CRT groups. Furthermore, the intensity-modulated group did not reduce the effect of traditional conformal pelvic radiotherapy treatment. A significant difference was observed in diarrhea, suggesting that IMRT considerably protected the intestine and rectum, and reduce pain from radiation. Hematologic toxicity in the two groups was one of the major side effects of nedaplatin in clinical settings [18]. Moore *et al.* [19] noted that carboplatin can replace cisplatin to reduce the gastrointestinal response to chemotherapy. The present study also showed that nedaplatin was a better choice. In the IMRT group, nausea and vomiting, decreased hemoglobin, decreased neutrophils, and thrombocytopenia insignificantly differed from those in the 3D CRT group. Furthermore, more normal tissue was observed at low-dose levels in IMRT, and no serious effects on the hematopoietic function occurred.

This study confirmed that IMRT technology had obvious advantages in protecting sensitive tissue and reducing radiation reaction (especially the diarrhea incidence) over traditional conformal pelvic radiotherapy technology. In three years, the overall survival and recurrence-free survival indicated no disadvantages compared with traditional treatment, especially for large lumps or patients with Grade IIIb and above tumors. Thus, this treatment can replace traditional conformal pelvic radiotherapy technology for the treatment of cervical cancer.

Molla *et al.* [20] suggested that stereotactic radiotherapy can replace traditional brachytherapy and four Gy for non-surgical treatment. Grigsby *et al.* [21] observed that tumors with different sizes have significantly different local control rates and survival rates. Therefore, the excellent dose distribution formed by IMRT can partly replace traditional close-intracavity after loading therapy for previously untreated patients or individualized doses for larger tumors, which are all worthy of further research.

Acknowledgements

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