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ORIGINAL ARTICLE

Comparison of efficacy and safety between late-course and simultaneous integrated dose-increasing intensity-modulated radiation therapy for cervical cancer complicated with pelvic lymph node metastasis

Yi Cheng[1], Nan Huang[2], Jing Zhao[1], Jianhua Wang[1], Chen Gong[1], Kai Qin[1] (✉)

[1] Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[2] Allergy Department, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Abstract

Objective This study aimed to compare and analyze the clinical efficacy and safety of late-course and simultaneous integrated dose-increasing intensity-modulated radiation therapy (IMRT) for cervical cancer complicated with pelvic lymph node metastasis.

Methods Sixty patients with cervical cancer complicated with pelvic lymph node metastasis who were admitted to our hospital from January 2013 to January 2015 were enrolled. The patients were randomly divided into the late-course dose-increasing IMRT group and the simultaneous integrated dose-increasing IMRT group, with 30 cases included in each group, respectively. All patients were concurrently treated with cisplatin. After treatment, the clinical outcomes of the two groups were compared.

Results The remission rate of symptoms in the simultaneous integrated dose-increasing IMRT group was significantly higher than that in the late-course dose-increasing IMRT group ($P < 0.05$). The follow-up results showed that the overall survival time, progression-free survival time, and distant metastasis time of patients in the simultaneous integrated dose-increasing IMRT group were significantly longer than those in the late-course dose-increasing IMRT group ($P < 0.05$). The recurrent rate of lymph nodes in the radiation field in the simultaneous integrated dose-increasing IMRT group was significantly lower ($P < 0.05$) than in the late-course dose-increasing IMRT group. There was no significant difference in the incidence of cervical and vaginal recurrence and distant metastasis between the two groups ($P > 0.05$). The radiation doses of Dmax in the small intestine, D1cc (the minimum dose to the 1 cc receiving the highest dose) in the bladder, and Dmax in the rectum in the simultaneous integrated dose-increasing IMRT group were significantly lower ($P < 0.05$) than in the late-course dose-increasing IMRT group. There was no significant difference in intestinal D2cc (the minimum dose to the 2 cc receiving the highest dose) between the two groups ($P > 0.05$). The incidence of bone marrow suppression in the simultaneous integrated dose-increasing IMRT group was significantly lower ($P < 0.05$) than in the late-course dose-increasing IMRT group.

Conclusion The application of simultaneous integrated dose-increasing IMRT in the treatment of cervical cancer patients complicated with pelvic lymph node metastasis can significantly control tumor progression, improve the long-term survival time, and postpone distant metastasis time with high safety.

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Key words: simultaneous integrated dose-increasing intensity-modulated radiation therapy; late-course dose-increasing intensity-modulated radiation therapy; cervical cancer complicated with pelvic lymph node metastasis; clinical efficacy; safety

✉ Correspondence to: Kai Qin. Email: qinkaitj@126.com

Cervical cancer is one of the most common malignant tumors for Chinese women. The incidence of cervical cancer is increasing annually. A high proportion of young patients are affected by this disease; therefore, its Cervical Cervical cancer is one of the most common malignant tumors for Chinese women. The incidence of cervical diagnosis cancer is increasing annually. A high proportion of young patients are affected by this disease; therefore, its diagnosis and treatment has become increasingly important for doctors and researchers [1–2].Currently, most clinical guidelines recommend concurrent chemoradiotherapy as the preferred treatment for advanced patients. With thedevelopment of intensity-modulated radiation therapy (IMRT), precision radiotherapy has become the widely used treatment. However, there is no standard option [3–4]. This study aimed to compare the clinical efficacy and safety of late-course and simultaneous integrated dose-increasing IMRT for cervical cancer complicated with pelvic lymph node metastasis.

Materials and methods

Baseline

Sixty patients who were admitted to our hospital from January 2013 to January 2015 were enrolled this study, all of whom were diagnosed with cervical cancer complicated with pelvic lymph node metastasis. The patients were randomly divided into the following two groups: the late-course dose-increasing IMRT group and the simultaneous integrated dose-increasing IMRT group, 30 cases each, respectively. The patients in the late-course dose-increasing IMRT group were 34–61 years old, with an average of 54.6 (±5.8) years. According to the International Federation of Gynecology and Obstetrics (FIGO) staging system, 20 cases were categorized as having stage IIB; 7 cases, stage III A; and 3 cases, stage III B. The pathological classification of the patients included the following: 7 cases of adenocarcinoma, 22 cases of squamous cell carcinoma, and 1 case of adenosquamous cell carcinoma. The patients in the simultaneous integrated dose-increasing IMRT group were 34–63 years old, with an average of 54.2 (±5.9) years. According to the FIGO staging system, 22 cases were categorized as having stage II b; 6 cases, stage III A; and 2 cases, stage III B. The pathological classification of the patients included the following: 6 cases of adenocarcinoma, 23 cases of squamous cell carcinoma, and 1 case of adenosquamous cell carcinoma. There was no significant difference in the baseline between the two groups.

Inclusion and exclusion criteria

Inclusion criteria

All the patients who were diagnosed with cervical cancer by pathological biopsy, who had stage IIB–IIIB according to the FIGO staging system [5], and who were newly diagnosed without history of surgery or radiotherapy.

Exclusion criteria

Patients with history of pelvic and abdominal surgery, with organ dysfunction such as in the liver and kidney, and with cognitive impairment and patients who are pregnant or lactating.

Method

The IMRT conformed to standards of the Radiation Therapy Oncology Group (RTOG). GTV-n (Gross Target Volume for lymph nodes) included positive lymph nodes. CTV-n (Clinical Target Volume for lymph nodes) included the bilateral obturator, extrailiac, intrailiac, common iliac, and presacral lymph nodes. GTV-t (Gross Target Volume for tumor) included the primary tumor of cervical cancer. GTV-t (Clinical Target Volume for tumor) included the parametrium, cervix, uterine body, and vagina 3 cm below the lesion. Ondansetron was administered before chemotherapy to prevent nausea and vomiting. A total of 300 μg of recombinant human granulocyte colony-stimulating factor was injected subcutaneously per day when the white blood cell (WBC) count was detected to be $< 3.0 \times 10 \times 10^9$/L during chemotherapy, and it will be discontinued when the WBC count is within the normal range. In the late-course dose-increasing IMRT group, the prescription dose was 1.8 Gy/f × 25f firstly, followed by 2.2 Gy × 7f for GTV-n. The total dose was 60 Gy. In the simultaneous integrated dose-increasing IMRT group, the prescription dose for GTV-n was 2.4 GY/f × 25f, while the prescription doses for GTV-t, CTV-t, and CTV-n were 1.8Gy/f × 25f. The total dose was 60 Gy. Brachytherapy was performed after the patients were done with the external radiation for 15 times. The radiation dose at A point was 600 cGy/time (1 time/w for 5 times). Cisplatin 40 mg/m^2 was administered intravenously once a week for 6 times.

Endpoints

All patients were followed up for 30 months, and the clinical efficacy was recorded. Referring to the Response Evaluation Criteria in Solid Tumors criteria, the patients were divided into the following four grades: complete remission (CR), partial remission (PR), stabilization (SD), and progression (PD). The overall survival time, progression-free survival time, and distant metastasis time of the two groups were compared. Lymph node recurrence and distant metastasis were compared. The dosages of Dmax in the small intestine, D2cc in the small intestine, D1cc in the bladder, and Dmax in the rectum were recorded. The toxicity and side effects between the two groups were compared according to the RTOG/

European Organisation for Research and Treatment of Cancer standards of acute radiation injury.

Statistical analysis

Statistical Package for the Social Sciences version 16.0 was used to analyze the data. The numerical data were described as the mean (± standard deviation), and *t*-value test was used; the categorical data were described as percentage, and χ^2 test was used; $P < 0.05$ was considered to be statistically significant.

Results

Comparison of clinical efficacy between the two groups

A total of 20 CR, 9 PR patients, 1 SD patient, and 0 PD patients were enrolled in the simultaneous integrated dose-increasing IMRT group, while a total of 13 CR patients, 10 PR patients, 7 SD patients, and 0 PD patients were enrolled in the late-course dose-increasing IMRT group; the symptom relief rate of the simultaneous integrated dose-increasing IMRT group was significantly higher ($P < 0.05$) than in the late-course dose-increasing IMRT group, as shown in Table 1.

Comparison of follow-up between the two groups

The follow-up results showed that the overall survival time, progression-free survival time, and distant metastasis time of the patients in the simultaneous integrated dose-increasing IMRT group were significantly longer than those patients in the late-course dose-increasing IMRT group ($P < 0.05$). In the simultaneous integrated dose-increasing IMRT group ,there was 1 case of lymph node recurrence in the radiation field, 3 cases of cervical and vaginal recurrence, and 2 cases of distant metastasis . In the late-course dose-increasing IMRT group, there were 10 case of lymph node recurrence in the radiation field, 4 cases of cervical and vaginal recurrence, and 2 cases of distant metastasis. The recurrence rate of lymph nodes in the simultaneous integrated dose-increasing IMRT group was significantly lower ($P < 0.05$) than in the late-course dose-increasing IMRT group. There was no significant difference in the incidence of cervical and vaginal recurrence and distant metastasis between the two groups ($P > 0.05$). Data were shown in Table 2.

Comparison of radiation dose between the two groups

The Dmax dose in the small intestine, D1cc in the bladder, and Dmax in the rectum in the simultaneous integrated dose-increasing IMRT group were significantly lower than that in the late-course dose-increasing IMRT group ($P < 0.05$). There was no significant difference in D2cc in the small intestine between the two groups ($P > 0.05$), as shown in Table 3.

Comparisons of toxicity and side effects between the two groups after treatment

The incidence of bone marrow suppression was significantly lower in the simultaneous integrated dose-increasing IMRT group than that in the late-course dose-increasing IMRT group ($P < 0.05$); there was no significant difference in the incidence of gastrointestinal reaction, liver injury, radiation-induced rectitis, and radiation-induced cystitis between the two groups ($P > 0.05$). Data were shown in Table 4.

Table 1 Comparison of clinical efficacy between the two groups

Group	Cases	CR	PR	SD	PD	Symptom relief rate
Late-course dose-increasing IMRT	30	13	10	7	0	76.67%
Simultaneous integrated dose-increasing IMRT	30	20	9	1	0	96.67%
χ^2	–	–	–	–	–	5.192
P	–	–	–	–	–	< 0.05

Table 2 Comparisons of follow-up between the two groups

Group	Cases	Overall survival time (months)	Progression-free survival time (months)	Distant metastasis time (months)	Lymph node recurrence in the radiation field (*n*)	Cervical and vaginal recurrence (*n*)	Distant metastasis (*n*)
Late-course dose-increasing IMRT	30	18.6 ± 2.7	13.1 ± 1.2	15.7 ± 2.3	10	4	2
Simultaneous integrated dose-increasing IMRT	30	22.7 ± 2.4	17.2 ± 1.5	19.4 ± 1.7	1	3	2
χ^2/t	–	6.216	11.690	7.086	9.017	0.162	0.000
P	–	< 0.05	< 0.05	< 0.05	< 0.05	> 0.05	> 0.05

Table 3 Comparison of radiation dose between the two groups (Gy)

Group	Cases	Dmax dose in the mall intestine	D2cc in the small intestine	D1cc in the bladder	Dmax in the rectum
Late-course dose-increasing IMRT	30	62.75 ± 6.20	53.51 ± 5.65	67.43 ± 5.89	66.14 ± 7.02
Simultaneous integrated dose-increasing IMRT	30	53.22 ± 5.84	54.26 ± 5.73	54.20 ± 6.17	54.21 ± 5.08
t	–	6.128	0.510	8.495	7.541
P	–	< 0.05	> 0.05	< 0.05	< 0.05

Table 4 Comparisons of toxicity and side effects between the two groups after treatment

Group	Cases	Bone marrow suppression	Liver injury	Gastrointestinal reaction	Radiation-induced rectitis	Radiation-induced cystitis
Late-course dose-increasing IMRT	30	25	3	20	14	10
Simultaneous integrated dose-increasing IMRT	30	11	3	17	13	8
χ^2	–	13.611	0.000	0.635	0.067	0.317
P	–	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Discussion

Cervical cancer is the most common cancer in the female reproductive system, and lymph node metastasis is a major risk factor for poor prognosis. In the past, the prescription dose of 45 Gy in the areas of the tumor and lymph nodes can only control the progression of the subclinical lesions, and the long-term recurrence risk of lymph node metastasis was still high [6–7]. Additional irradiation of positive lymph nodes was often used to prolong the overall survival time of patients and improve their quality of life. Increasing the dose of the traditional two-dimensional radiotherapy may lead to the aggravation of radiation-induced toxicity and side effects. Some patients chose to discontinue their treatment because of intolerance. In contrast, IMRT is the symbol of "precision radiotherapy," which can reduce the dose of organs at risk (OAR) and decrease the incidence and severity of radiation-induced toxicity and side effects. It is the preferred treatment for the positive lymph node area as a supplementary radiotherapy [8–9]. The results of long-term follow-up study showed that late-course dose-increasing IMRT may affect the long-term survival rate and quality of life of patients with cervical cancer, and the main reason was that the prolonged time of chemotherapy may induce more toxicity and side effects. In contrast, simultaneous integrated dose-increasing IMRT can give different doses to areas with different risks in the same region; therefore, it effectively increases the dose of target areas and reduces toxicity and side effects [6–9].

In this study, patients with cervical cancer complicated with pelvic lymph node metastasis were treated with late-course or simultaneous dose-increasing IMRT concurrently with cisplatin. The results of treatment and follow-up showed that the objective remission rate of the patients treated with simultaneous dose-increasing IMRT in the near future was higher than that of patients treated with late-course dose-increasing IMRT; the overall survival time, progression-free survival time, and distant metastasis time of the patients treated with simultaneous dose-increasing IMRT were higher than in the late-course dose-increasing IMRT. The recurrence rate of lymph nodes in the simultaneous integrated dose-increasing IMRT group was significantly lower than in the late-course dose-increasing IMRT group. There was no significant difference in the incidence of cervical and vaginal recurrence and distant metastasis between the two groups. The results suggest that [5, 10] simultaneous dose-increasing IMRT has more obvious advantages in controlling tumor proliferation, prolonging the long-term survival time, and reducing the metastasis and recurrence than late-course dose-increasing IMRT. At the same time, the overall radiation dose of simultaneous dose-increasing IMRT was significantly lower than in the late-course dose-increasing IMRT, suggesting that it has the advantage of reducing the radiation dose of pelvic and abdominal organs and reducing the damage to OAR; the Dmax dose in the small intestine, D1cc in the bladder, and Dmax in the rectum in the simultaneous integrated dose-increasing IMRT group were significantly lower than in the late-course dose-increasing IMRT group. There was no significant difference in D2cc in the small intestine between the two groups, which may be related to factors such as relatively longer peristalsis time, faster peristalsis rate, and the absence of the maximum dose point in the fixed part of the small intestine area [10]. Analysis of toxicity and side effects showed that the incidence of bone marrow suppression was significantly lower in the simultaneous integrated dose-increasing IMRT group than that in the late-course dose-increasing IMRT group. There was no significant difference in the incidence of gastrointestinal reaction, liver injury, radiation-induced rectitis, and radiation-induced cystitis between the

two groups. The study suggests that the simultaneous integrated dose-increasing IMRT can reduce the incidence of bone marrow suppression and improved the patients' compliance and tolerance. This can be attributed to the fact that only the high-risk areas and lymph node metastasis areas are supplemented in the treatment, and the pelvic radiation dose is reduced; thus, the incidence and severity of bone marrow suppression decrease [11–12].

In conclusion, compared with the late-course dose-increasing IMRT, the simultaneous integrated dose-increasing IMRT in the treatment of cervical cancer patients complicated with pelvic lymph node metastasis can significantly control tumor progression, improve patients' long-term survival time, and postpone distant metastasis time with higher safety.

Conflicts of interest

The authors declare no potential conflicts of interest.

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