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Clinical study of acute toxicity of pelvic bone marrow-sparing intensity-modulated radiotherapy for cervical cancer

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ABSTRACT

Objectives: To compare the dose volume of the target area and the toxicity of pelvic bone marrow-sparing intensity-modulated radiotherapy (PBMS-IMRT) with routine IMRT in patients undergoing radiochemotherapy for cervical cancer.

Material and methods: Forty patients with indications for adjuvant radiochemotherapy after cervical cancer surgery were selected and randomly divided into IMRT (n = 20) and PBMS-IMRT (n = 20) groups to observe and record the toxicity and its severity in the blood, gastrointestinal tract, and genitourinary system.

Results: There was no significant difference in the target area conformity index (CI) or homogeneity index (HI) between the two groups ($p > 0.05$). The pelvic bone V10–V50 in the PBMS-IMRT group were lower than those in the IMRT group ($p < 0.05$), and there was lower hematological toxicity ($p < 0.05$) and fewer delays or interruptions in chemotherapy and/or radiotherapy ($p < 0.05$) in the PBMS-IMRT group. The toxicity to the gastrointestinal and genitourinary systems in the two groups was not significantly different ($p > 0.05$).

Conclusions: PBMS-IMRT significantly reduced the dose volume of the pelvic bone marrow, thereby reducing the incidence of bone marrow suppression. However, it had no significant impact on the gastrointestinal or genitourinary systems.

Key words: cervical cancer; confined pelvic bone marrow; intensity-modulated radiotherapy; toxicity

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INTRODUCTION

Cervical cancer is the third most common malignant tumor in women worldwide, and it has always ranked first among gynecological malignancies in China. In recent years, cisplatin-based concurrent radiochemotherapy has become the standard treatment for advanced cervical cancer. Compared with radiotherapy alone, concurrent radiochemotherapy can reduce mortality by 30–50% [1–3]; however, it is associated with increased toxicity, especially acute hematological toxicity that may cause Grade 3 or higher bone marrow suppression and force patients to stop radiochemotherapy [4, 5]. Approximately 50% of adult bone marrow hematopoiesis is concentrated in the pelvic bone marrow and lower vertebral body [6, 7]. Several studies have shown that effectively reducing the volume of bone marrow irradiated during radiotherapy can reduce the risk of bone marrow suppression in patients with concurrent cervical cancer chemoradiotherapy [6–10]. Based on the above studies, as well as on the need to ensure precise coverage of the tumor target area while protecting organs at risk (OAR), this study clinically observed whether pelvic bone marrow-sparing intensity-modulated radiotherapy (PBMS-IMRT) can reduce acute side effects and ensure the smooth progress of concurrent radiochemotherapy in patients with cervical cancer.

MATERIAL AND METHODS

General clinical information

Forty patients who were admitted to our hospital for the first time after surgery for early cervical cancer between May 2016 and May 2017 were selected and divided into PBMS-IMRT (n = 20) and IMRT (n = 20) groups using the random table method. All selected patients had undergone extensive hysterectomy + pelvic lymph node dissection, were pathologically diagnosed with cervical cancer (squamous cell carcinoma or non-squamous cell carcinoma), and had no preoperative radiotherapy or chemotherapy. The indications for postoperative radiotherapy included:

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(1) having one high-risk factor after surgery (positive lymph node metastasis, positive surgical margin, or parauterine infiltration) and (2) having two medium-risk factors after surgery (tumor diameter ≥ 4 cm, interstitial infiltration depth greater than one-third, lymphatic vascular interstitial infiltration, or adenocarcinoma). The postoperative stage was determined jointly by an associate chief physician or above from the Department of Oncology, the Department of Oncology, and the Department of Gynecologic Oncology. The exclusion criteria were as follows: (1) history of hypertension, diabetes, heart disease, liver disease, kidney disease, neurologic diseases, other serious diseases, other tumors, or had received radiotherapy or chemotherapy; (2) no routine blood tests or computed tomography (CT) examination before chemoradiotherapy, abnormal blood indicators before chemoradiotherapy, or distant metastasis on CT; or (3) contraindications to radiotherapy and chemotherapy. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the ethics committee of Wenzhou Medical University. Written informed consent was obtained from all participants.

Simulative positioning and target area outline

Each patient was first placed in a fixed position using a vacuum air cushion and then enhanced CT scan positioning was performed using a Volume Zoom CT scanner (Smatom Series, Siemens Healthineers, Erlangen, Germany) with a scanning layer thickness of 5 mm and a scanning range of L3–5 cm under the pubic symphysis. The images were then transmitted to the therapy planning system (TPS) (Pinnacle 9.10 Radiation Therapy Planning System, Philips Healthcare, Amsterdam, Netherlands) to outline the target area. Referring to the Delineation Guidelines issued by the Tumor Radiation Therapy Cooperative Organization (RTOG) [11], the clinical target volume (CTV) of the target area was delineated in the TPS system, including that of the common iliac lymph nodes, internal and external iliac lymph nodes, anterior sacral lymph nodes, obturator lymph nodes, lymphatic cysts (if any), surgical stump, and 3 cm of the proximal vagina; the area 5 mm exterior to the CTV (2 mm to the rectal side) was defined as the planning target volume (PTV). The CTVs of the small intestines, bladder, rectum, spinal cord, and bilateral femoral heads were also delineated. For the PBMS-IMRT group, the CTV of the pelvic bone (all hip bones, sacrococcyx, and upper femurs in the radiation field) was delineated, and the area 5 mm exterior to it was defined as the PTV. The clinical goals of the dose-volume of the OAR were V30 < 38% for the small intestine, V40 < 45% for the bladder, and V50 < 20% for the rectum. The clinical goals of the dose-volume of the OAR in the PBMS-IMRT group were V20 < 76% and V40 < 35% [11]. All 40 patients were treated as planned.

Radiotherapy plan

The treatment plans in the two groups were designed in the TPS system, the 7-field irradiation method was used with an X-ray energy of 6 MV, and a Varian 23EX medical linear accelerator (Varian Medical Systems, Palo Alto, CA) was used to implement the radiotherapy plan. The prescribed dose of the PTV was 50 Gy over 25 fractions for five weeks with a 95% isodose curve surrounding the PTV. Acceptable evaluation plans were assessed by clinicians and physicists based on clinical requirements.

Dosimetric evaluation

Combined evaluation was performed by clinicians and physicists using dose-volume histograms. The homogeneity index (HI) and conformity index (CI) were as follows: HI = D5/D95, CI = V95/PTV, where D5 represents the PTV dose of 5% of the target area, D95 represents the PTV dose of 95% of the target area, and V95 represents the exposure volume enclosed by a 95% isodose surface of the prescribed dose. The HI indicates the dose distribution in the target area; the smaller the value, the more uniform the dose distribution in the target area. The CI indicates the consistency between the area surrounded by the isodose surface and the target area, in a range from 0 to 1; the larger the value, the better the fit.

Chemotherapy

Both the PBMS-IMRT and IMRT groups received concurrent chemotherapy during radiotherapy. The chemotherapy regimen consisted of weekly administration of cisplatin (CDDP) at 35–40 mg/m^2 and radiotherapy on days 1, 8, 15, 22, 29, and 36.

Classification criteria for acute radiation injury

Acute radiation reactions occurred during treatment or within three months after the completion of radiotherapy. The American Radiotherapy Collaborative Group acute radiation injury classification standard [4] was adopted.

Follow-up

The follow-up period was August 2017. Each patient was followed up for at least three months, and the follow-up rate was 100%. For each patient, blood tests were regularly performed in the clinic, and the patients were asked to self-report by telephone about radiation reactions in the digestive and genitourinary systems.

Statistical analysis

The statistical software package SPSS 20.0 (IBM, Armonk, NY) was used to analyze the data, and t-tests were used to compare the target area and the dose-volume parameters in OAR between the two groups. The corrected fourfold table χ^2 test was used to compare the delay and/or interruption rates of

chemotherapy and/or radiotherapy between the two groups. The non-parametric Mann-Whitney U test was used to compare acute reactions in the blood, digestive, and urinary systems. Statistical significance was established at $\alpha = 0.05$ and $p < 0.05$.

RESULTS

The patients were aged between 30–62 years, with a median age of 50 years and Karnofsky Performance Status (KPS) [12] scores of ≥ 90 points, including 12 cases of stage IB1, 9 cases of stage IB2, 8 cases of stage IIA1, and 11 cases of stage IIA2.

Evaluation of the PTV target area coverage

There was no significant difference in CI or HI values between the two groups ($p > 0.05$) (Tab. 1).

Comparison of the dose-volume parameters in OAR

There was a significant difference in dose-volume parameters of the pelvis at various levels between the two groups, but not in the dose-volume parameters of the small intestine, bladder, or rectum between the two groups (Tab. 2).

Table 1. Comparison of CI and HI between groups ($\bar{x} \pm s$)

Group	n	CI	HI
PBMS-IMRT	20	0.863 ± 0.025	0.103 ± 0.024
IMRT	20	0.852 ± 0.030	0.093 ± 0.015
t		1.260	1.580
p		0.215	0.122

CI — conformity index; HI — homogeneity index; PBMS-IMRT — pelvic bone marrow-sparing intensity-modulated radiotherapy; IMRT — intensity-modulated radiotherapy

Comparison of toxicity

The severity of hematological toxicity in the IMRT group was significantly higher than that in the PBMS-IMRT group ($Z = -2.186$, $p = 0.038$). There was no significant difference in the severity of toxicity in the lower digestive tract ($Z = -1.492$, $p = 0.136$) or the urinary tract ($Z = -1.399$, $p = 0.162$) (Tab. 3–5).

Impact on the completion of the chemotherapy and radiotherapy plans

The PBMS-IMRT group had a significantly better delay rate and/or discontinuation rate of chemotherapy and/or radiotherapy than the IMRT group ($p < 0.05$) (Tab. 6).

DISCUSSION

Concurrent radiochemotherapy is mainly used in patients with stage IIB-IVA cervical cancer. Multiple randomized controlled studies have shown that concurrent radiochemotherapy can reduce the risk of death by 30–50% compared to radiotherapy alone. However, concurrent radiochemotherapy can also cause severe bone marrow suppression, thus delaying the completion of treatment plans for cervical cancer, or even causing the suspension of treatment plans in cases with severe bone marrow suppression. This negatively affects the prognosis. Therefore, to reduce toxicity in the blood and ensure completion of the planned

Table 2. Comparison of dose-volume parameters in the endangered organs ($\bar{x} \pm s$)

Group	Dose-volume	PBMS-IMRT	IMRT	t	p
Pelvis	V_{10}	85.98 ± 3.01	90.07 ± 2.83	–4.427	< 0.001
	V_{20}	72.43 ± 4.98	80.02 ± 4.88	–4.868	< 0.001
	V_{30}	52.91 ± 4.34	58.72 ± 5.24	–3.819	< 0.001
	V_{40}	33.63 ± 4.23	38.12 ± 5.97	–2.744	0.005
	V_{50}	11.46 ± 1.33	16.21 ± 3.22	–6.097	< 0.001
Small intestine	V10	80.66 ± 5.30	82.67 ± 5.12	–1.220	0.231
	V20	60.37 ± 7.29	64.59 ± 8.00	–1.744	0.089
	V30	30.28 ± 6.03	30.96 ± 5.27	–0.380	0.706
	V40	11.34 ± 5.62	14.00 ± 5.94	–1.438	0.159
	V50	4.30 ± 1.18	4.27 ± 1.36	0.075	0.941
Bladder	V20	100 ± 0	100 ± 0	0	1.000
	V30	76.43 ± 8.32	75.99 ± 8.65	0.164	0.871
	V40	42.33 ± 7.32	42.20 ± 6.70	0.059	0.954
	V50	15.29 ± 2.02	14.72 ± 1.95	0.908	0.370
Rectum	V20	100 ± 0	100 ± 0	0	1.000
	V30	94.37 ± 2.49	94.11 ± 2.63	0.321	0.321
	V40	46.30 ± 10.34	45.29 ± 8.62	0.340	0.739
	V50	8.92 ± 2.46	8.99 ± 2.50	–0.089	0.929

PBMS-IMRT — pelvic bone marrow-sparing intensity-modulated radiotherapy; IMRT — intensity-modulated radiotherapy

Table 3. Comparison of toxicity in the blood system between groups

Group	n	Hematological toxicity			
		Level 0	Level 1	Level 2	Level 3
PBMS-IMRT	20	4	11	3	2
IMRT	20	2	9	5	4
Z	–2.186				
p	0.038				

PBMS-IMRT — pelvic bone marrow-sparing intensity-modulated radiotherapy; IMRT — intensity-modulated radiotherapy

Table 4. Comparison of toxicity in the lower digestive tract between groups

Group	n	Toxicity in lower digestive tract			
		Level 0	Level 1	Level 2	Level 3
PBMS-IMRT	20	3	12	3	2
IMRT	20	1	10	5	4
Z	–1.492				
p	0.136				

PBMS-IMRT — pelvic bone marrow-sparing intensity-modulated radiotherapy; IMRT — intensity-modulated radiotherapy

Table 5. Comparison of toxicity in the Urinary system between groups

Group	n	Toxicity in urinary system			
		Level 0	Level 1	Level 2	Level 3
PBMS-IMRT	20	4	11	3	2
IMRT	20	2	9	5	4
Z	–1.399				
i	0.162				

PBMS-IMRT — pelvic bone marrow-sparing intensity-modulated radiotherapy; IMRT — intensity-modulated radiotherapy

Table 6. Comparison of delay or discontinuation rates of chemotherapy and/or radiotherapy between groups

Group	Cases with delayed or discontinued chemotherapy and/or radiotherapy	Cases without delay or discontinuation rates of chemotherapy and/or radiotherapy	Sum	Delay or discontinuation rate
PBMS-IMRT	1	19	20	5%
IMRT	8	12	20	40%
X^2	5.161			
p	0.023			

PBMS-IMRT — pelvic bone marrow-sparing intensity-modulated radiotherapy; IMRT — intensity-modulated radiotherapy

concurrent radiochemotherapy, it is necessary to study how to reduce the irradiation volume of the hematopoietic bone marrow [4, 13–16].

More than 50% of the hematopoietic activity in the bone marrow is located in the lumbosacral spine, ilium, ischium, pubis, and proximal femurs, and these areas are exposed to varying degrees during pelvic radiotherapy for cervical cancer. Most studies have confirmed that myelosuppression in patients undergoing pelvic radiochemotherapy is related to the volume of the bone marrow receiving 10 or 20 Gy doses [6, 7]. Zhu et al. [17] analyzed 102 cervical cancer patients receiving pelvic radiotherapy combined with cisplatin chemotherapy (40 mg/m^2/week) in three American centers, none of whom received granulocyte monocyte colony-stimulating factor (GM-CSF) or platelet transfusion therapy. Through the functional logarithmic transformation of time (weeks), they found that the weekly peripheral blood cell counts (*ln* [white blood cells (WBCs)] and *ln* [absolute neutrophil counts (ANC)]) were reduced and that there was a significant correlation between the increase in average photobiomodulation (PBM) radiation doses (V20, V30, and V40) and the weekly reduction of WBC and ANCs. With

each 1-Gy increase in PBM, *ln* (ANC) decreased by 9.6/μL/week (95% confidence interval, 1.9-17.3, p = 0.015). Subgroup analysis revealed a significant association between weekly decreases in *ln*(WBC) and *ln* (ANC) among the lumbosacral spine, ischium, and proximal femur. Therefore, the incidence of acute blood toxicity can be decreased by reducing the dose of pelvic radiation. Three-dimensional chemoradiotherapy (3D-CRT) and IMRT are the two technologies currently used to treat pelvic cancer. IMRT reduces the radiation dose to normal pelvic tissues. Compared with 3D-CRT, although the volume of bone marrow exposed to IMRT is lower, the incidence of bone marrow suppression in patients with cervical cancer undergoing concurrent IMRT and radiochemotherapy is still high. To date, there is no consensus on the ability of IMRT to reduce blood toxicity compared with 3D-CRT technology [18]. At present, most pelvic IMRT radiotherapy plans do not limit pelvis-endangering doses in the radiation field, and physicists have not paid enough attention to further reduce the radiation dose-volume of the pelvis. Lujan et al. [19] proposed a dosimetric study of bone-limited pelvic IMRT (BMS-IMRT) and concluded that it could reduce bone marrow toxicity. Mell et al. [20] conducted a phase II study on bone marrow-sparing RT and Huang et al. [21] reported that PBMS-IMRT reduced the incidence of hematologic toxicity in patients with cervical cancer receiving concurrent chemoradiotherapy. A single-center prospective randomized controlled trial from 2020 is also underway.

In this study, 40 patients with early-stage cervical cancer were divided into IMRT and PBMS-IMRT groups. The comparison of dosimetry and toxicity in the blood, digestive, and urinary systems between the two groups revealed that the severity of hematological toxicity in the IMRT group was significantly higher than that in the PBMS-IMRT group, and the on-time completion of the radiotherapy plan in the IMRT group was significantly worse than that in the PBMS-IMRT group ($p < 0.05$). There were no significant differences in the severity of digestive and urinary system toxicities ($p > 0.05$). The hematological toxicity results of this study are similar to those of Lujan et al. [22] and Gandhi et al. [23], but the results of Mundt et al. [24] could be useful in indicating the toxicity reported in the other studies as numbers. However, this study had a short study period and a small sample size, and signs of radiotoxicity in the lower digestive tract and urogenital system can take months to years to appear [4]. The impact on subacute and chronic toxic reactions, as well as on long-term survival, requires further study.

In summary, PBMS-IMRT significantly reduced radiation exposure to the pelvic bone marrow and reduced the incidence of bone marrow suppression, thus ensuring on-time completion of radiochemotherapy plans. This not only expands the body of research but is also clinically significant. The impact on subacute and chronic toxic reactions as well as on long-term survival requires further study.

Conflicts of interest

The authors declare no conflict of interest.

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