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The dosimetric and clinical comparison between helical tomotherapy and fixed-field intensity-modulated radiotherapy in radical irradiation for cervical cancer

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► ***Original article***

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ABSTRACT

Background: To compare the dosimetric parameters, clinical complications, and efficacy of helical tomotherapy (HT) and fixed-field intensity-modulated radiotherapy (f-IMRT) in radical radiotherapy for cervical cancer. ***Materials and Method***: From November 2016 to December 2018, 77 cervical cancer patients in radical irradiation were selected, 38 patients undergoing treatment with HT and 39 with f-IMRT. The dosimetic parameters, clinical complications, and efficacy were compared. ***Results***: The homogeneity index (HI) and conformity index (CI) of HT plans were both superior to those of f-IMRT plans(P=0.000). HT plans resulted in a reduction in the dosimetric parameters of organs at risk (OARs) (P<0.05) except the V_{10} of small intestine (P=0.682). The incidence of myelosuppression showed no significant differences (P=0.265).The patients with HT had no radiocystitis, grade 2 or above radiation proctitis. The complete remission (CR) rates, efficacy rates (CR+PR) and local control rates of two years were 81.58%,100% and 97.37%. ***Conclusion***: HT showed advantages in dosimetry, and provided more superior clinical results. It has a good application prospect in radical irradiation for cervical cancer.

INTRODUCTION

Cervical cancer occupies the third place in cancer incidence among women worldwide and is a serious threat to women's health [(1)]. Radiotherapy plays an important role in the local treatment of cervical cancer, either as radical treatment, or as palliative treatment. With the continuous development of technology, intensity-modulated radiotherapy (IMRT) has progressed from the fixed-field to the rotational techniques like volumetric modulated arc therapy (VMAT) and helical tomotherapy (HT) [(2)]. Compared with the fixed-field technique, the rotational technique are featured by a high freedom in the field direction, and the protection of the normal tissues while ensuring a high dose in the tumor target volume at the same time [(3-4)]. HT is a special rotational technique, which is superb in its treatment accuracy and the protection of organs at risk (OARs) [(5)]. It is increasingly favored in the radiotherapy of cervical cancer [(6)].

Many studies had evaluated HT for cervical cancer in dosimetry [(7-8)], but the corresponding clinical results were scarcely reported. This study attempts to provide clinical guidance through the comparison of dosimetric parameters, clinical complications and efficacy between HT and f-IMRT, and to evaluate the clinical application value of HT.

MATERIALS AND METHODS

Patient's characteristics

From November 2016 to December 2018, 77 cervical cancer patients (Karnofsky performance status (KPS) ≥ 70) undergoing radical radiotherapy with HT or fixed-field intensity-modulated radiotherapy (f-IMRT) in Chongqing University Cancer Hospital were selected. All patients completed the following examinations: careful gynecological examination, tumor marker tests, chest X-ray or computed tomography (CT) scans, magnetic resonance imaging (MRI) scans or CT scans of the pelvic cavity. The staging of disease was according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. This study was approved by the ethics committee of Chongqing University Cancer Hospital, and the informed consent was acquired from each enrolled patient. The procedures followed were in accordance with the ethical

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standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

Immobilization and CT simulation

Patients were all immobilized in a supine position, with bladder filling and rectum emptying, and underwent CT simulation using a

Philips Brilliance™ 16-slice large aperture CT scanner (Philips, Amsterdam,

Netherlands) from the diaphragm to 5cm below the ischial tuberosities. The scanned images were transmitted to the Eclipse™ Treatment Planning System via local area network (LAN).

Delineation of target volumes

Delineation was according to Radiation Therapy Oncology Group (RTOG) 0418 protocol and the International Commission on Radiation Units (ICRU) and Measurements reports 62 recommendations [9], the clinical target volume (CTV) was defined as areas considered containing potential microscopic disease. The planning target volume (PTV) would provide a 7mm expansion of the CTV in all directions [10]. The target volumes were delineated by the same experienced radiation oncologist [11].

Radiotherapy plans

The HT plans were calculated and optimized by TomoHD™2.1.2 reverse treatment planning system (Accuray, USA) combined with initial optimization parameters (field width of 2.5cm, modulation factor of 2.2-2.3, pitch of 0.287), performed using 360° spiral irradiation. The f-IMRT plans were designed with the Eclipse™ Treatment Planning System (version 10.0; Varian Medical Systems, Inc., Palo Alto, CA, USA), performed using 9 coplanar fields with the equational gantry angles. The prescribed dose to the PTV was 45Gy in 25 fractions. The prescribed dose covered at least 95% of the PTV for all plans. The limit dose for OARs as follows: the volume of small intestine receiving 40Gy (V_{40}) <50%; the same limitations were applied to the bladder and rectum. The mean dose (D_{mean}) of small intestine <30Gy. The volume of femoral head receiving 30Gy (V_{30}) <30%.

Dosimetric evaluation

Dose-volume histograms (DVHs) were used to evaluate the dose distribution in the PTV and OARs. To compare the approximate minimum/maximum dose (D_{99}/ D_1), D_{mean}, CI, and HI of the PTV, CI = $V_{t,ref}$/ $V_t \times V_{t,ref}/V_{ref}$, $V_{t,ref}$ was the target volume covered by the prescribed dose, V_t represented the target volume, V_{ref} was the whole volume covered by the prescribed dose; HI = $D_{5\%}/D_{95\%}$, $D_{5\%}$ and $D_{95\%}$ was respectively the dose of 5% and 95% for the target volume. The V_{10}, V_{20}, V_{30}, and V_{40} of the small intestine, rectum, bladder, and femoral head were evaluated. V_{10}, V_{20}, V_{30}, and V_{40} represented the volume of receiving 10Gy, 20Gy, 30Gy, and 40Gy.

Brachytherapy and chemotherapy

Intracavitary brachytherapy was added in the later stage of external irradiation: using iridium-192 high-dose-rate afterloading therapy system (Xinhua Medical Device Co. Ltd, Shandong) at Point A 6Gy/ time/week and 5 times in total. During the course of external radiotherapy, chemotherapy was conducted weekly with cisplatin (25-30 mg/m^2) (Gejiu Biological Pharmaceutical Co. Ltd, Yunnan) combined with paclitaxel (60mg/m^2) (Sichuan Taiji Pharmaceutical Co. Ltd, Sichuan) intravenously for 5-6 weeks.

Complications and efficacy

Acute and chronic complications were defined and graded according to the evaluation criteria of RTOG. Patients were directly assessed daily during treatment for acute rectum and bladder complication; Hematologic complications were assessed weekly. The chronic complications were collected retrospectively by follow-up. Clinical efficacy was evaluated 1month after completion treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and local control rate was evaluated at the last follow-up.

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences, version 22.0(SPSS, IBM Corp., Armonk, NY, USA). P<0.05 was considered statistically significant. The dosimetric parameters between HT and f-IMRT were analyzed by independent sample t test, and the patient characteristics, complications, and clinical efficacy were analyzed by chi-square test.

RESULTS

Patient's characteristics

38 patients undergoing radical radiotherapy with HT, and 39 patients with f-IMRT were included. The HT group had a median age of 53 years (range, 34-75 years). The f-IMRT group had a median age of 57 years (range, 33-78 years). All belong to FIGO Stage IB to IIIB. Differences between the 2 groups had no statistical significance (p>0.05) (table 1).

Target dose evaluation, MUs and treatment time

The plans could both meet requirement of the prescribed dose. The HI and CI of HT plans increased by 2.7% and 5.9% compared with f-IMRT, respectively (P=0.000). The D_{99} of HT plans in PTV was 0.51Gy higher (P=0.006), while D_1 and D_{mean} were both lower 0.31Gy and 0.69Gy, respectively (P=0.024, 0.000) (table 2, figure 1).

The MUs of HT plans had a significant increase,

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about 4 times of f–IMRT plans, the ray utilization was not high. The treatment times of HT were less (P=0.002) (table 2).

OARs evaluation

The V_{10}, V_{20}, V_{30} and V_{40} of OARs for HT plans were all lower ($p<0.05$), except the V_{10} of small intestine, which showed no significant differences (P=0.682) (table 3, figure 1).

Table 1. Patient characteristics.

Variable	HT	f-IMRT	*P*
Patients (n)	38	39	
Age (years)			0.858
Range	34-75	33-78	
Median	53	57	
Stage*(n)			0.250
IB	4	5	
IIA-IIB	17	22	
IIIA-IIIB	17	12	
Pathology (squamous carcinoma) (n)			0.974
Well differentiated	3	3	
Moderately differentiated	27	28	
Poorly differentiated	8	8	
Tumor diameter≥4 cm (n)	18	16	

*According to the International Federation of Gynecology and Obstetrics.HT = helical tomotherapy. f-IMRT = fixed-field intensity-modulated radiotherapy.

Table 2. Parameters of HT and f-IMRT plans.

Parameters	HT	f-IMRT	*t*	*P*
HI	1.08±0.02	1.11±0.03	-4.437	0.000
CI	0.90±0.02	0.85±0.03	7.107	0.000
D_{99}(Gy)	44.65±0.88	44.14±0.66	2.849	0.006
D_1 (Gy)	47.45±0.57	47.76±0.60	-2.305	0.024
D_{mean} (Gy)	46.15±0.88	46.84±0.57	-4.119	0.000
MUs	7740.42±161.65	1996.59±94.16	189.892	0.000
Treatment times (mins)	8.04±0.21	8.47±0.24	-8.340	0.002

HT = helical tomotherapy; f-IMRT = fixed-field intensity-modulated radiotherapy; HI = Homogeneity index; CI = Conformity index; MUs = Monitor units; D = dose.

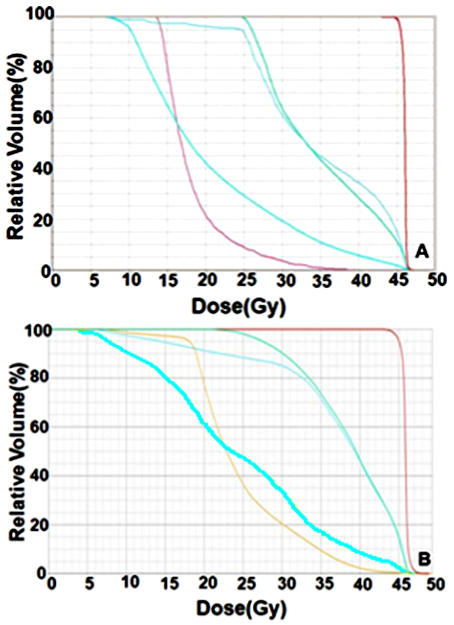


Figure 1. The DVHs curves of two plans. **A:** helical tomotherapy; **B:** fixed-field intensity-modulated radiotherapy.

Table 3. Dosimetric comparison of OARs.

OARs	Parameters	HT	f-IMRT	*t*	*P*
small intestine	V_{10}	88.71±2.38	88.44±3.20	0.412	0.682
	V_{20}	49.87±5.09	53.10±2.46	-3.557	0.001
	V_{30}	22.10±3.39	29.52±4.45	-8.214	0.000
	V_{40}	13.36±2.19	19.13±2.42	-10.943	0.000
rectum	V_{10}	96.57±3.12	98.62±1.53	-3.647	0.001
	V_{20}	89.31±4.85	3.79±4.89	-4.033	0.000
	V_{30}	68.37±5.38	79.86±4.89	-9.816	0.000
	V_{40}	42.32±3.71	47.84±2.23	-7.944	0.000
bladder	V_{10}	98.67±0.86	99.38±1.05	-3.271	0.002
	V_{20}	92.51±2.41	94.68±5.12	-2.369	0.020
	V_{30}	74.25±1.54	78.53±8.13	-3.191	0.002
	V_{40}	45.29±2.81	47.82±2.25	-4.346	0.000
femoral head	V_{10}	96.00±2.40	97.86±2.40	-3.401	0.001
	V_{20}	42.18±5.22	51.42±5.73	-7.399	0.000
	V_{30}	10.96±2.21	15.99±4.03	-6.780	0.000
	V_{40}	0.49±0.64	2.58±2.13	-5.872	0.000

HT = helical tomotherapy; f-IMRT = fixed-field intensity-modulated radiotherapy.

Rectum acute grade 1~2 complications for HT and f-IMRT patients were 28.95% (11/38) and 35.90% (14/39).Bladder acute grade 1~2 complications were 5.26% (2/38) and 7.69% (3/39), respectively. The differences had no statistics significance between the 2 groups (P=0.435, 0.665). But the HT patients had no grade 2 or above acute rectum and bladder reaction. Grade 1~2 myelosuppression occurred in 57.89% (22/38) and 51.28% (20/39), and grade 3~4 were 39.47% (15/38) and 48.72% (19/39), respectively. Differences between groups had no statistics significance (P=0.265) (table 4).

Chronic grade 1~2 radiation proctitis for HT and f -IMRT patients were 5.26% (2/38) and 12.82% (5/39), respectively. Differences between two groups had no statistics significance (*P*=0.435). But the HT group had no grade 2 or above radiation proctitis. Grade 1 radiocystitis for f-IMRT patients were 7.69% (3/39), and the HT patients had no radiocystitis (table 4).

Clinical efficacy

All patients completed chemoradiotherapy as schedule. The CR rates of HT and f-IMRT groups were 81.58% (31/38) and 64.10% (25/39), respectively. The efficacy rates (CR+PR) were 100% (38/38) and 97.44% (38/39). 5 cases were lost to follow-up, the follow-up rate was 93.51%. The medium follow-up time was 20 months(range 12 -39 months).3 patients died in the HT group, and 2 patients died in f-IMRT group.1 year local control rates were both 100%;2 years local control rates were 97.37% (37/38) and 94.87% (37/39) (table 5).

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Table 4. Complications of HT and f-IMRT patients.

Grade	rectum		bladder		myelosuppression		radiation proctitis		radiation cystitis	
	HT	f-IMRT	HT	f-IMRT	HT	f-IMRT	HT	f-IMRT	HT	f-IMRT
0	27	25	36	36	1	0	36	34	38	36
1	11	12	2	3	4	3	2	4	0	3
2	0	2	0	0	18	17	0	1	0	0
3	0	0	0	0	12	13	0	0	0	0
4	0	0	0	0	3	6	0	0	0	0
P	0.435		0.665		0.265		0.244		0.081	

Table 5. Clinical efficacy.

	HT	f-IMRT
CR	81.58%(31/38)	64.10%(25/39)
PR	18.42%(7/38)	33.33%(13/39)
SD	0%(0/38)	2.38%(1/39)
Follow-up(month)	20(12~37)	22(13~39)
Recurrence/Metastasis(n)	2.63%(1/38)	5.13%(2/39)
Death(n)	0	2.38%(1/39)
Local control rate(1years)	100%	100%
Local control rate(2years)	97.37%(37/38)	94.87%(37/39)

DISCUSSION

With the development of radiotherapy, IMRT has been implemented widely in cervical cancer because it can better protect adjacent OARs while increasing the target dose and conformity [12-13]. Served as a special intensity-modulated technique, HT is equipped with a unique binary pneumatic multi-leaf Collimator (MLC) [14] that has more flexible on the shape and size of the tumor volume, and shows excellent in dose distribution and OARs protection [15]. The organ deformation and positioning error are very pronounced in the radical radiotherapy for cervical cancer. A big positioning error may cause partial leakage radiation of the target volume, and affect the clinical efficacy [16]. HT has the advantage of image guided radiation therapy based on daily 3D megavoltage CT imaging, and this advantage may overcome the issues with motion of the target and surrounding organs in the definitive treatment of cervical cancer [6].

This study showed that the dose distribution of all plans could fulfill the prescription dose as well as all OARs limitation requirements. Both the HI and CI of HT plans were superior (P=0.000), and the D_{99} was higher(P=0.006), but the D_1 and D_{mean} were lower (P=0.024,0.000) (table 2, figure 1). Those showed that HT could reduce the high dose of the target volume as much as possible while the minimum dose was close to the prescribed dose. It could make the dose gradient steeper. The OARs include the small intestine, rectum, bladder and femoral head in radical radiotherapy for cervical cancer. They are mainly parallel organs, and the radiation tolerance of them is related to the percentage volume dose. In this study, the dosimetry parameters of OARs in the HT plans were lower, except for the V_{10} of the small intestine, which did not show significant differences (P=0.682, table 3). HT has significant dosimetric advantages in protecting OARs. Marnitz *et al.* [17] showed that the HT technique was significantly favored with regard to target conformity, homogeneity, and SB sparing. Chitapanarux *et al.* [18] reported that HT had better uniformity in PTV coverage and better protection of bladder, rectum and small intestine than static IMRT. These dosimetric studies are similar to the results of this study. However, the MUs of HT was 7740.42±161.65 in this study, about 4 times of f-IMRT (table 2). It showed that HT had low ray utilization and high machine loss, in addition, the HT plans are more sophisticated. So that HT had high economic cost.

The complications of pelvic radiotherapy for cervical cancer are mainly from the bone marrow, bladder and rectum, which are categorized into acute or chronic events according to the occurrence time. This study showed that there was no significant difference in the myelosuppression between the two groups (*P*=0.265, table 4). It had been reported [19] that HT with bone marrow limited can reduce the bone marrow volume which received low-dose irradiation. It may help to prevent the acute hemotoxicity. This study did not limit on the pelvic bone marrow, which will be the next exploration of our research group. The filling state of the bladder and rectum could affect the radiation dose and side effect to the bladder and rectum. Patients were required bladder filling and rectum emptying in this study, controlling the consistency can guarantee the accuracy of the target location and the irradiation dose of the target, protect the bladder, small intestine and rectum, and alleviate the radiation-induced response [20]. In this study, patients in the HT group did not report radiocystitis, and grade 2 or above radiation proctitis. The incidence rate of grade 1~ 2 radiation proctitis in the HT group was only 5.26% (table 4). Although we did not obtain a significant difference, a large sample size is needed in the future study to reflect the statistical differences in case of lower incidence of rectum and bladder complications. In previous studies [21-22], the incidence of chronic complications in patients with local advanced cervical cancer treated with concurrent radiochemotherapy without HT technology was 9.4 ~ 13% and 3 ~ 14.5% in the gastrointestinal and urinary, respectively. HT technology can reduce the incidence of chronic complications for rectum and bladder.

NCCN has recommended pelvic radiotherapy combined with brachytherapy and concurrent chemotherapy as standard therapy method in radical treatment for cervical cancer. Concurrent platinum-based chemotherapy can increase the overall survival [23]. In this study, patients were all treated with concurrent chemotherapy using TP weekly. The CR rates, the effective rates (CR+PR) and the local control rates at 2 years were wonderful (table 5). Both treatment regimens had good clinical

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efficacy, while HT group was better.

In this study, all patients were able to complete radiotherapy as planned that ensured the good clinical efficacy and local control rate. It is shown that HT had obvious advantages in the dosiology and reducing complications, which could obtain a better clinical efficacy. No significant difference in the incidence of complications was yielded in the present study, which may be attributed to the clinically complicated multiple factors, insufficient follow-up time and limited sample size.

CONCLUSIONS

As a high-quality IMRT technique, HT is a better choice for external irradiation in cervical cancer and has a good application prospect. In the future, prospective randomized controlled studies with a longer term survival, and follow-up of complications are needed to validate our conclusion.

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***Ethics approval and consent to participate*:** This study was approved by the ethics committee of Chongqing University Cancer Hospital, and the informed consent was acquired from each enrolled patient. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

***Authors' contributions*:** All authors carried out the study. HY, CHDK collected the data, ZHXJ analyzed the data，and GMF, ZHN draft the manuscript. All authors read and approved the final manuscript.

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