The Dosimetric and Clinical Comparison between Helical Tomotherapy and Fixed-Field Intensity-Modulated Radiotherapy in Radical Irradiation for Cervical Cancer

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Abstract

Background: To evaluate 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.

Methods: Between November 2016 and December 2018, 77 cervical cancer patients in radical irradiation were enrolled, 38 patients undergoing treatment with HT and 39 with f-IMRT. The dosimetry parameters, clinical complications, and efficacy were compared.

Results: The HT plans had superior homogeneity index (HI), conformity index (CI) ($P=0.000$), and resulted in a reduction in the dosimetry 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 radioactive cystitis, grade 2 or above rectal complication and acute bladder complication. The complete remission (CR) rates, effective rates (CR+PR) and local control rates of two years were 81.58%, 100% and 97.37%.

Conclusion: The HT plans showed advantages in dosimetry, and provided more superior clinical outcomes.

Background

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 a part of radical comprehensive treatment, or as palliative treatment. With the continuous development of technology, intensity-modulated radiotherapy (IMRT) has from the fixed-field developed to the rotating technology, such as volumetric modulated arc therapy (VMAT), helical tomotherapy (HT) [2]. Compared with the fixed-field technology, the rotating IMRT has a high freedom in the field direction, which is more conducive to protect the normal tissues ensuring a high dose in the tumor target volume at the same time [3-4]. HT, as a special rotating technology, has better treatment accuracy and organs at risk (OARs) protection [5-6], and is increasingly favored in the radiotherapy of cervical cancer. Many studies evaluated HT for cervical cancer in dosimetry [7-8], but the corresponding clinical results were scarcely reported.

In our institute, the HT system was used to treat cervical cancer patients from November 2016. This study focuses on the dosimetric parameters, clinical complications, and efficacy of HT and f-IMRT in radical radiotherapy for cervical cancer, and to evaluate the clinical application value of HT.

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 f-IMRT at our hospital were enrolled. 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.

Immobilization and CT Simulation

Patients were all immobilized in a supine position, following bladder filling and rectum emptying, and underwent CT simulation using a Philips BrillianceTM 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 EclipseTM Treatment Planning System via 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 TomoHDTM 2.1.2 reverse treatment planning system 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 EclipseTM 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

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 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/m²) combined with paclitaxel (60mg/m²) 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 1 month 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.

Follow-Up

The first evaluation took place 1 month after treatment completion; follow-up reviews were held every 2–3 months for the first year, then every 3–6 months during the second year. Outpatient follow-up and telephone follow-up were performed from the beginning of treatment. Careful gynecological examination , tumor marker tests, chest X-ray, magnetic resonance imaging (MRI) scans of the pelvic cavity and/or abdomen were conducted at each visit when appropriate. The deadline for follow-up was the end of November 2016.

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 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).

Table 1. Patient characteristics

Variable	HT	f-IMRT	<i>P</i>
Patients(n)	38	39	
Age(years)			0.858
Range	34-75	33-78	
Median	53	57	
Stage ^a (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	

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

Target dose evaluation, MUs and treatment time

The plans could both meet requirement of the prescribed dose. Both the HI and CI of HT plans were superior ($P=0.000$).The D_{99} was higher($P=0.006$), but the D_1 and D_{mean} were lower($P=0.024,0.000$) (Table 2).

The MUs of HT plans had a significant increase, 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).

Table 2 Parameters of HT and f-IMRT plans

Parameters	HT	f-IMRT	<i>t</i>	<i>P</i>
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.

OARs evaluation

The V_{10} , V_{20} , V_{30} and V_{40} of small intestine, rectum, bladder and femoral head for HT plans were all lower, except the V_{10} of small intestine, which showed no significant differences($P=0.682$)(Table 3).

Table 3 Dosimetric comparison of OARs

OARs	Parameters	HT	f-IMRT	<i>t</i>	<i>P</i>
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	93.79±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

Complications

The acute grade 1~2 complications of rectum for HT and f-IMRT patients were 28.95%(11/38) and 35.90%(14/39). The acute grade 1~2 complications of bladder were 5.26%(2/38) and 7.69%(3/39), respectively. The differences had all no statistics significance ($P=0.435, 0.665$). But the HT patients had no grade 2 or above acute rectum and bladder complications. The grade 1~2 myelosuppression were 57.89%(22/38) and 51.28%(20/39); the grade 3~4 were 39.47%(15/38) and 48.72%(19/39). The differences had no statistics significance ($P=0.265$) (Table 4).

The 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 the two groups had no statistics significance ($P=0.435$). But the HT group had no grade 2 or above radiation proctitis. The grade 1 radiation cystitis for f-IMRT patients were 7.69%(3/39); the HT patients had no radiation cystitis (Table 4).

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
<i>P</i>	0.435		0.665		0.265		0.244		0.081	

Clinical efficacy

All the 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 effective rates(CR+PR) were 100%(38/38) and 97.44%(38/39). 5 cases lost to follow-up, the follow-up rate was 93.51%. The medium follow-up time was 20 months(the range was from 12 to 39 months).3 patients died in 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)

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]. HT, as a special intensity-modulated technology, equipped with a unique binary pneumatic multi-leaf Collimator (MLC) [14],has more advantages in dose distribution, and more flexible on shape and size of the tumor volume. It shows excellent in dose distribution and OARs protection [15].The organ deformation and positioning error are large in radical radiotherapy for cervical cancer. IMRT has a significantly reduced irradiation volume in order to protect OARs. But large positioning error may cause partial target volume radiation leakage, and affect the clinical efficacy[16]. HT has the megavolt CT scanning system to realize image-guided radiotherapy. It can overcome the large positioning error, and reduce the risk of missed irradiation in radical radiotherapy for cervical cancer[17].

This study compared the dosimetric parameters of HT and f-IMRT in radical radiotherapy for cervical cancer, and the results showed that the dose distribution of all plans could fulfill the prescription dose as well as all OARs limitation requirements. The HI and CI of HT plans increased by 2.7% and 5.9%, respectively, compared f-IMRT. HT was superior in terms of homogeneity and conformity in the target volumes. The D₉₉ of HT plans in PTV was 0.51Gy higher, while D₁ and D_{mean} were both lower 0.31Gy and 0.69Gy, respectively. 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 more steep. HT also has significant advantages in protecting OARs. The OARs are small intestine, rectum, bladder and femoral head in radical radiotherapy for cervical cancer. They are mainly parallel organs, and the radiation tolerance is related to the percentage volume dose. In our study, the dosimetry parameters of OARs in the HT plans were lower, except the V₁₀ of small intestine, which showed no significant differences(*P*=0.682). In the study of Marnitz et al. [18], both HT and conventional IMRT provide optimal

treatment of cervical cancer patients. The HT technique was significantly favored with regard to target conformity, homogeneity, and SB sparing. Chitapanarux et al. [19] 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 our study. In dosiology, HT has more advantageous in protecting OARs, which is beneficial to reduce the complications. However, the MUs of HT was 7740.42 ± 161.65 in this study, about 4 times of f-IMRT. It showed that HT had low ray utilization and high machine loss.

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. In this study, we assessed the bladder and rectum complications as well as bone marrow suppression. The results showed that the bone marrow suppression had no statistically significant difference between the two groups ($P=0.265$). It had been reported [20] 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. Our study did not limit on the pelvic bone marrow, which will be the next exploration of our research group. In this study, no patients had grade 3 or above acute rectum and bladder complications, suggesting that both HT and f-IMRT could effectively reduce OARs absorption while ensuring the dose distribution. The HT group had no radiation cystitis, grade 2 or above radiation proctitis and acute rectum and bladder complications. Although the differences had no statistics significance, it may need more sample size 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. In our study, the incidence rate of grade 1 ~ 2 radiation proctitis in the HT group was 5.26%, and no radiation cystitis happened. HT technology can reduce the incidence of chronic complications for rectum and bladder. This is consistent with the study of Chang et al [23].

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 [24]. In this study, patients were all treated with concurrent chemotherapy using TP weekly. The CR rates were 81.58% and 64.10%, respectively, and the effective rates (CR+PR) were 100% (38/38) and 97.44% (38/39), respectively. The local control rates at 2 years were 97.37% (37/38) and 94.87% (37/39), respectively. Both treatment regimens had both good clinical efficacy, while HT group was better.

In this study, all patients were able to complete radiotherapy as planned, that ensures the good clinical efficacy and local control rate. Results showed that HT had obvious advantages in dosiology and reducing complications, can obtain better clinical efficacy. Although there was no significant statistical difference for complications in clinic, it may be the clinically complicated multiple factors, insufficient follow-up time and limited cases.

Conclusions

As a high quality IMRT technique, HT is a better choice for external irradiation in cervical cancer and has a good application prospect. We look forward to longer term survival, follow-up of complications as well as further prospective randomized controlled studies.

Abbreviations

helical tomotherapy(HT)

fixed-field intensity-modulated radiotherapy (f-IMRT)

homogeneity index(HI)

conformity index(CI)

complete remission(CR)

intensity-modulated radiotherapy (IMRT)

volumetric modulated arc therapy(VMAT)

organs at risk(OARs)

computed tomography(CT)

magnetic resonance imaging (MRI)

International Federation of Gynecology and Obstetrics (FIGO)

Radiation Therapy Oncology Group (RTOG)

International Commission on Radiation Units(ICRU)

Clinical Target Volume(CTV)

Planning Target Volume (PTV)

the mean dose(D_{mean})

multi-leaf Collimator (MLC)

Declarations

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.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors carried out the study. RXQ, ZN collected the data, ZDL analyzed the data and GMF, LXF draft the manuscript. All authors read and approved the final manuscript.

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