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ORIGINAL ARTICLE

Efficacy of helical tomotherapy combined with CT-guided three-dimensional intracavitary brachytherapy in treatment of locally advanced cervical cancer

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Summary

Purpose: *We aimed to evaluate the efficacy and safety of helical tomotherapy (HT) combined with computed tomography (CT)-guided three-dimensional intracavitary brachytherapy (CT-ICBT) in the treatment of locally advanced cervical cancer.*

Methods: *A total of 96 patients with locally advanced cervical cancer (IIB-IIIB) treated were retrospectively analyzed. They underwent concurrent radiochemotherapy, and the chemotherapy regimen paclitaxel + cisplatin was given for 3 weeks. The patients were divided into HT+CT-ICBT group (n=48) and intensity-modulated radiotherapy (IMRT) + two-dimensional ICBT (IMRT+ICBT group, n=48) according to the different extracorporeal and intracavitary radiotherapies. The short-term clinical efficacy, and short- and long-term adverse reactions were compared between the two groups, the tumor recurrence and survival status were recorded through follow-up, and the overall survival (OS) and progression-free survival (PFS) rates were compared between the two groups.*

Results: *The patient general clinical characteristics were comparable in both groups. The short-term clinical effective rate was 91.7% (44/48) and 87.5% (42/48), respectively, in HT+CT-ICBT group and IMRT+ICBT group. In the two groups, the incidence rate of grade 3-4 chronic radiation proctitis was 4.2% (2/48) and 22.9% (11/48), while that of grade 3-4 chronic radiation cystitis was 2.1% (1/48) and 18.7% (9/48), respectively. According to the follow-up results, the 3-year OS was 85.4% (41/48) and 77.1% (37/48), and the 3-year PFS was 81.3% (39/48) and 70.8% (34/48), respectively, in the two groups. Log-rank test showed that the 3-year OS and PFS had no statistically significant differences (p=0.395, p=0.401).*

Conclusion: *HT+CT-ICBT is safe and effective in the treatment of locally advanced cervical cancer, and it has similar short-term clinical efficacy and long-term survival rate compared with IMRT+ICBT, which also significantly reduces the long-term incidence of radiation proctitis and cystitis, so it is worthy of popularization and application.*

Key words: *cervical cancer, helical tomotherapy, CT-guided three-dimensional intracavitary brachytherapy, efficacy, toxic reaction*

Introduction

Cervical cancer is one of the most common malignant tumors in gynecology, as well as the second major malignant tumor following breast cancer in females [1]. At present, there are approximately 100,000 new cases of cervical cancer every year in China, showing a trend for younger ages [2]. It is recommended by the National Comprehensive Cancer Network (NCCN) Guidelines that concurrent radiochemotherapy be the standard therapeutic regimen for patients with locally advanced cervical cancer [3].

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Radiotherapy includes extracorporeal radiotherapy and intracavitary radiotherapy. After traditional extracorporeal pelvic radiotherapy, the incidence rate of severe radiation reactions, such as radiation proctitis and radiation cystitis, is up to 35-40% [4, 5]. With the progress in imaging and computer technology, precision radiotherapy techniques, such as three-dimensional conformal radiotherapy (CRT) and intensity-modulated radiotherapy (IMRT), have been widely used. Helical tomotherapy (HT) is an image-guided IMRT technique that combines computed tomography (CT) and accelerator, with 360-degree rotatory irradiation, which realizes the highly conformal and uniform dose distribution. At the same time, MVCT image calibration can be performed before radiotherapy each time to reduce the setup error and conduct precision radiotherapy [6,7].

Intracavitary radiotherapy is an indispensable treatment means for cervical cancer. There are limitations in the two-dimensional dose system of traditional intracavitary radiotherapy. For example, the size of target region cannot be adjusted according to the changes in tumor volume, the organ-at-risk (OAR) dose for bladder and rectum cannot be accurately evaluated, and the dose distribution in the target region is non-uniform due to the distance-dose inverse law in brachytherapy [8]. In recent years, CT- or MRI-based three-dimensional intracavitary brachytherapy (ICBT) have been gradually applied in the clinic, realizing the precision intracavitary radiotherapy [9,10].

In the present study, the clinical data of 96 patients with locally advanced cervical cancer in our hospital were retrospectively analyzed, and the short-term efficacy, adverse reactions and survival were compared between HT+CT-ICBT and IMRT+ICBT in the treatment of locally advanced cervical cancer, so as to provide more bases for the treatment of this disease.

Methods

General data

A total of 96 patients with locally advanced cervical cancer (IIB-IIIB) treated in our hospital were retrospectively analyzed. They underwent concurrent radiochemotherapy, and the chemotherapy regimen of paclitaxel + cisplatin was given for 3 weeks. The patients were divided into HT+CT-ICBT group (n=48) and IMRT+ICBT group (n=48) according to the different extracorporeal and intracavitary radiotherapies. All patients underwent pathologic, gynecologic and hematologic examinations, tumor marker estimation and related imaging examinations before radiochemotherapy. Inclusion criteria: patients with cervical cancer (IIB-IIIB) according to the criteria of International Federation of Gynecology and Obstetrics (FIGO, 2009) (pathological type: squamous carcinoma, adenocarcinoma, etc.), and those with the Karnofsky performance scale (KPS) score ≥70 points. Exclusion criteria: patients with contraindications for radiochemotherapy. CT, MRI or PET-CT confirmed that the patients had no pelvic and para-aortic lymph node metastasis. The patients were aged 26-62 years old with a median of 43 years. All patients enrolled conformed to the *Declaration of Helsinki* and signed the informed consent form. This study was approved by the Ethics Committee of Lishui City People's Hospital (ZJMS-0215LSPH-0552).

Treatment methods

Extracorporeal radiotherapy: Meglumine diatrizoate (80 mL of 60% meglumine diatrizoate was diluted to 1200 mL) was orally taken to display the intestinal tract and fill the bladder. Iohexol was used to strengthen the blood vessels. The patients were fixed using vacuum pad or body film in supine position, and the pelvic-abdominal cavity was scanned using the Philips large-aperture CT simulated positioner (slice thickness: 5 mm). The markers on the body surface or body film were determined using the stereotactic frame. The large-aperture CT positioning images were sent to the physics room. The target region was delineated according to the Radiation Therapy Oncology Group (RTOG) guideline [10]. In extracorporeal radiotherapy, field-shrinking treatment was performed, namely extracorporeal total pelvic radiotherapy (DT: 2880 cGy), and field-shrinking irradiation to lymph node drainage region and parametrial tissues (DT: 2160 cGy). The fraction dose was 1.8 Gy, and the radiotherapy was performed 4 times per week. Extracorporeal radiotherapy was not conducted on the day of ICBT.

CT-ICBT: The patients lay on the carbon fiber treatment table in lithotomy position. After routine disinfection and draping, gynecological examination and anal examination were performed again to determine the size of cervical tumor, the location of the uterus and the distance between the cervix and the anus. Foley urethral catheter was placed to empty the bladder, and 5-7 mL of iohexol was injected into the saccule. A three-cavity catheter was placed into the rectum using the dedicated guide wire at 15-20 cm away from the anus. It was confirmed via anal examination that the end of the guide wire was above the cervix. The cervix was exposed using the vaginal speculum and disinfected again. After the location of the uterus and the depth of uterine cavity were determined using the probe, the standard Fletcher uterine applicator and vaginal applicator for CT (Nucletron) were placed and fully filled with the gauze, and the bladder and rectum were pushed away to reduce the bladder and rectal pressure. The applicators were fixed, followed by total pelvic scanning (slice thickness: 3 mm), and the images were collected and sent to the Oncentra TPS (Elekta). Then the gross tumor volume (GTV), high-risk clinical tumor volume (HR CTV), intermediate-risk CTV (IR CTV) and low-risk CTV (LR CTV) were delineated in three-dimensional ICBT for cervical cancer according to the recommendations of GEC European Society of Radiotherapy & Oncology (ESTRO) GYN treatment group in 2005. The images were imported into the Oncengtra-

Plan4.1 system to develop the ICBT plan. The applicators were reconstructed and the plan was optimized based on the guidelines of GEC ESTRO GYN treatment group in 2006, 2010 and 2012 [11,8,12]. In three-dimensional ICBT, HR CTV prescription dose was 500 cGy/time, and the dose curve was optimized geometrically and manually. The optimization target was 90% HR-CTV, namely D90 was greater than the prescription dose (500 cGy), and the OARs D2cc were reduced as far as possible. The dose at point A in each fraction of irradiation was recorded, and the cumulative total dose at point A was 45-50 Gy.

Two-dimensional ICBT: It was performed using the integrated afterloading therapy equipment (Rongly, Shenzhen, China) once a week, and the prescription dose was 500 cGy. Extracorporeal radiotherapy was not conducted on the day of ICBT.

Observation indexes

The short-term efficacy was evaluated according to the evaluation criteria of the Union Internationale Contre Le Cancer (UICC): complete remission (CR): It was confirmed by gynecologic and imaging examination that all primary and metastatic lesions completely disappear for at least 4 weeks. Partial remission (PR): The product of the maximum and minimum diameters (double diameters) of the tumor was reduced by ≥50% for at least 4 weeks. Stable disease (SD): The product of the double diameters of the tumor was reduced by <50% or increased by <25%, and there were no new lesions. Progressive disease (PD): The product of the double diameters of the tumor was increased by ≥25%, or new lesions appeared. CR+PR indicated the effectiveness. After 4 weeks, the patients were followed up, including the recording of medical history, gynecologic examination and pelvic CT scan, and the follow-up rate was 100%.

The side effects include the acute toxic side effects and late toxic side effects. The toxic side effects of chemotherapy were graded based on the WHO acute and subacute toxic side effects, and those of radiotherapy were evaluated according to the criteria of RTOG.

The patients were reexamined in the outpatient clinic once every 1-2 months within 1 year after treatment, once every 3 months at 2-3 years and once every 3-6 months after 3 years, including general examination, pelvic examination, cervical cytology, pelvic B-mode ultrasound and chest X-ray, as well as CT or MRI scan if necessary. The patients were followed up until January 2019.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for the comparison between two groups. Enumeration data were expressed as rate (%), and x^2 test was performed for the comparison between two groups. P<0.05 suggested statistically significant difference. The survival curves were plotted using the Kaplan-Meier method and log-rank test was used to detect significant differences between two groups. P<0.05 suggested statistically significant difference.

Table 1. Baseline demographic and clinical characteristics of the studied patient

Characteristics	*HT+CT-ICBT group (n=48) n (%)*	*IMRT+ ICBT group (n=48) n (%)*	*p value*
Age, years	49.35±10.23	48.11±9.37	0.537
BMI (kg/m^2)	22.82±2.34	22.39±2.21	0.357
Histology			0.798
Squamous cell carcinoma	38(79.2)	40 (83.3)	
Adenocarcinoma	8 (16.7)	7 (14.6)	
Others	2 (4.1)	1 (2.1)	
Tumor size (cm)			0.529
≥4	31 (64.6)	28 (58.3)	
<4	17 (35.4)	20 (41.7)	
FIGO stage			0.647
II B	9 (18.8)	11 (22.9)	
III A	11 (22.9)	14 (29.2)	
III B	27 (56.3)	23 (47.9)	
Differentiation grade			0.576
High	15 (31.3)	13 (27.1)	
Middle	21 (43.7)	26 (54.2)	
Low	12 (25.0)	9 (18.7)	

HT+CT-ICBT: helical tomotherapy+ three dimensional CT-based intracavitary brachytherapy; IMRT+ ICBT: intensity-modulated radiation therapy+ intracavitary brachytherapy; BMI: body mass index; FIGO: Federation of Gynecology and Obstetrics.

Results

General patient conditions

In HT+CT-ICBT and IMRT+ICBT group, the main pathological type of cervical cancer was squamous carcinoma [38 cases (79.2%) and 40 cases (83.3%)], followed by adenocarcinoma [8 cases (16.7%) and 7 cases (14.6%)]. The tumor diameter was ≥4 cm in 31 cases (64.6%) and 28 cases (58.3%), and <4 cm in 17 cases (35.4%) and 20 cases (41.7%) in the two groups. In terms of FIGO stage, there were 9 cases (18.8%) and 11 cases (22.9%) in stage IIB, 11 cases (22.9%) and 14 cases (29.2%) in stage IIIA, and 27 cases (56.3%) and 23 cases (47.9%) in stage IIIB in the two groups. As for the tumor differentiation, 15 cases (31.3%) and 13 cases (27.1%) were well differentiated, 21 cases (43.7%) and 26 cases (54.2%) were moderately differentiated, and 12 cases (25.0%) and 9 cases (18.7%) were poorly differentiated in the two groups. It can be seen that there were no statistically significant differences in the age, body mass index, FIGO stage, pathologic type, grade of differentiation and tumor diameter between the two groups (p>0.05) (Table 1).

Comparison of short-term clinical efficacy

The conditions of tumor were observed at 1 month after radiotherapy. It was found that there were 31 cases (64.6%) of CR, 13 cases (27.1%) of PR, 4 cases (42.6%) of SD and 0 case of PD in HT+CT-ICBT group, with an effective rate of 91.7% (44/48). In IMRT+ICBT group, there were 28 cases (58.3%) of CR, 14 cases (29.2%) of PR, 6 cases (12.5%) of SD and 0 case of PD, with an effective rate of 87.5% (42/48). The short-term clinical efficacy had no statistically significant difference between the two groups (p=0.504) (Table 2).

Comparison of short-term adverse reactions

In HT+CT-ICBT group and IMRT+ICBT group, the incidence rate of grade 3-4 acute blood system reactions was 14.6% (7/48) and 18.7% (9/48), re-

Table 2. Clinical effective rates of the two studied groups

	HT+CT-ICBT group (n=48) n (%)	*IMRT+ ICBT group (n=48) n (%)*	*p value*
CR	31 (64.6)	28 (58.3)	
PR	13 (27.1)	14 (29.2)	
SD	4 (42.6)	6 (12.5)	
PD	0 (0)	0 (0)	
RR	44 (91.7)	42 (87.5)	0.504

HT+CT-ICBT: helical tomotherapy+ three dimensional CT-based intracavitary brachytherapy; IMRT+ ICBT: Intensity-modulated radiation therapy+ intracavitary brachytherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RR: response rate

Table 3. Comparison of recent adverse reactions of patients in the two studied groups

Adverse reactions	*HT+CT-ICBT group (n=48) n (%)*	*IMRT+ ICBT group (n=48) n (%)*	*p value*
Hematologic			0.584
0-2 grade	41 (85.4)	39 (81.3)	
3-4 grade	7 (14.6)	9 (18.7)	
Gastrointestinal			0.563
0-2 grade	42 (87.5)	40 (83.3)	
3-4 grade	6 (12.5)	8 (16.7)	
Genitourinary			0.537
0-2 grade	43 (89.6)	41 (85.4)	
3-4 grade	5 (10.4)	7 (14.6)	
Cutaneous			
0-2 grade	44 (91.7)	42 (87.5)	
3-4 grade	4 (8.3)	6 (12.5)	

HT+CT-ICBT: helical tomotherapy+ three dimensional CT-based intracavitary brachytherapy; IMRT+ ICBT: intensity-modulated radiation therapy+ intracavitary brachytherapy.

spectively. The incidence rate of grade 3-4 acute gastrointestinal reactions was 12.5% (6/48) and 16.7% (8/48), respectively. The incidence rate of grade 3-4 acute urinary system reactions was 10.4% (5/48) and 14.6% (7/48), respectively. The incidence rate of grade 3-4 acute skin reactions was 8.3% (4/48) and 12.5% (6/48), respectively. It can be seen that there were no statistically significant differences in the incidence rate of short-term adverse reactions between HT+CT-ICBT group and IMRT+ICBT group (p>0.05) (Table 3).

Comparison of long-term adverse reactions

In HT+CT-ICBT group and IMRT+ICBT group, the incidence rate of grade 3-4 chronic radiation proctitis was 4.2% (2/48) and 22.9% (11/48), while that of grade 3-4 chronic radiation cystitis was 2.1% (1/48) and 18.7% (9/48), respectively. It can be seen that the long-term incidence of chronic radiation proctitis and chronic radiation cystitis had statistically significant differences between the two groups (p=0.007, p=0.008) (Table 4).

Follow-up results of patient survival

All 96 patients in both groups were followed up until January 2019, with a median follow-up time of 29.1 months (12-44 months). There was no loss to follow-up, and the follow-up rate was 100%. The median follow-up time was 28.4 months (12-43 months) in HT+CT-ICBT group and 29.5 months (12-44 months) in IMRT+ICBT group. The 3-year OS was 85.4% (41/48) and 77.1% (37/48), and the 3-year PFS was 81.3% (39/48) and 70.8% (34/48), respectively, in the two groups. The Kaplan-Meier survival curves of patients are shown in Figure 1. It was found via log-rank test that OS and PFS had no statistically significant differences between the two groups (p=0.395, p=0.401).

Discussion

Platinum-based concurrent radiochemotherapy is the currently standard therapeutic method for locally advanced cervical cancer [13,14], which makes the 5-year survival rate of patients reach

Table 4. Comparison of long-term adverse reactions of patients in the two studied groups

Adverse reactions	*HT+CT-ICBT group (n=48)* *n (%)*	*IMRT+ ICBT group (n=48)* *n (%)*	*p value*
Radiation proctitis			0.007
0-2 grade	46 (95.8)	37 (77.1)	
3-4 grade	2 (4.2)	11 (22.9)	
Radiocystitis			0.008
0-2 grade	47 (97.9)	39 (81.3)	
3-4 grade	1 (2.1)	9 (18.7)	

HT+CT-ICBT: helical tomotherapy+ three dimensional CT-based intracavitary brachytherapy; IMRT+ ICBT: intensity-modulated radiation therapy+ intracavitary brachytherapy.

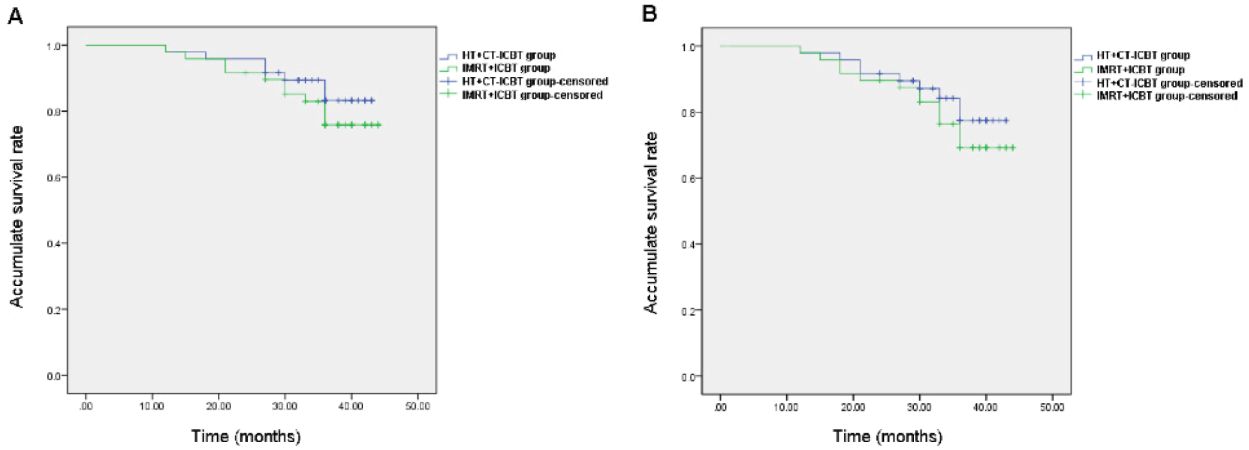

Figure 1. Kaplan-Meier survival curves of patients in HT+CT-ICBT group and IMRT+ICBT group. **A:** The difference of overall survival rate of patients in the two group had no statistical significance (p=0.395). **B:** The difference of progression-free survival rate of patients in the two group had no statistical significance (p=0.401).

70% [15]. Despite good therapeutic results, the acute and long-term adverse reactions associated with concurrent radiochemotherapy seriously affect the patient quality of life [16]. Therefore, how to improve the survival rate, reduce the adverse reactions and raise the quality of life of patients has always been a hotspot in the treatment of locally advanced cervical cancer.

With the progress in imaging and computer technology, precision radiotherapy techniques such as three-dimensional CRT and IMRT have been widely used since the 1990s. The three-dimensional CRT aims to make the dose distribution consistent with the target region in the three-dimensional direction. IMRT, based on achieving consistency between the shape of radiation field and the target region, makes the dose distribution consistent with the target region through adjusting the dose in the radiation field [17,18]. HT is an image-guided IMRT technique that combines CT and accelerator, with 360-degree rotatory irradiation, which realizes the highly conformal and uniform dose distribution. At the same time, MVCT image calibration can be performed before radiotherapy each time to reduce the setup error caused by the changes in bladder and intestinal volume and conduct precision treatment [6]. In a prospective randomized study involving 44 patients with cervical cancer (IIB-IIIB), the differences in therapeutic effects and adverse reactions were analyzed between total pelvic IMRT and conventional total pelvic radiotherapy. The results showed that at 27 months during follow-up, the DFS was 79.4% and 60% (p=0.651), and the OS was 76% and 85.7% (p=0.645), respectively, in WP-CRT group and WP-IMRT group. The incidence rate of acute gastrointestinal reactions in WP-IMRT group was lower than that in WP-CRT group (31.8% *vs.* 63.6%, p=0.034), and the same was true for the incidence rate of long-term gastrointestinal reactions (13.6% *vs.* 50%, p=0.011) [19]. According to the results of another international multicenter uncontrolled study, IMRT could reduce the acute hematologic and gastrointestinal adverse reactions in patients with stage IB-IVA cervical squamous carcinoma who underwent concurrent radiochemotherapy [20]. However, due to the influence of organ motion and setup error, the application of IMRT in cervical cancer is still controversial. HT can realize the highly conformal and uniform dose distribution, reduce the OAR dose, and lower the incidence of adverse reactions of radiotherapy, combined with the MVCT image calibration before radiotherapy each time, thus ensuring the setup accuracy. Moreover, some clinical studies have demonstrated that HT can reduce the incidence of treatment-related adverse reactions, such as hematologic, urinary system and gastrointestinal adverse reactions. For example, the incidence rates of grade III myelosuppression, and grade II and III diarrhea are reduced to 20%, 5% and 2.5%, respectively [21,22].

Currently, ICBT has developed to CT- or MRI-guided three-dimensional afterloading radiotherapy. In a multicenter non-randomized prospective study in France in 2005, the differences in the incidence of adverse reactions and survival rate were compared between two- and three-dimensional ICBT. At 24 months during follow-up, the local recurrence-free rate was 73.9% and 78.5%, and the incidence of grade 3-4 late adverse reactions was 22.7% and 2.6%, respectively, in two- and three-dimensional groups [23]. Although studies have proved that HT or CT-ICBT can improve the therapeutic effect on cervical cancer and reduce the incidence of adverse reactions, there have been no reports yet on the comparison of short- and long-term adverse reactions, short-term efficacy and survival rate between HT+CT-ICBT and IMRT+ICBT.

In the present study, the incidence rate of grade 3-4 chronic radiation proctitis was 4.2% (2/48) and 22.9% (11/48), while that of grade 3-4 chronic radiation cystitis was 2.1% (1/48) and 18.7% (9/48), respectively, in HT+CT-ICBT group and IMRT+ICBT group. It can be seen that the incidence rate of long-term adverse reactions had statistically significant differences between the two groups (p=0.007, p=0.008). There were no statistically significant differences in the short-term adverse reactions of the blood system, digestive system, urinary system and skin between the two groups (p>0.05). The short-term clinical efficacy was 91.7% and 87.5% in the two groups, showing no statistically significant difference (p=0.504). Moreover, according to the follow-up results, the 3-year OS was 85.4% (41/48) and 77.1% (37/48), and the 3-year PFS was 81.3% (39/48) and 70.8% (34/48), respectively, in the two groups. It can be seen that the 3-year OS and PFS had no statistically significant differences (p=0.395, p=0.401), indicating that OS and PFS have no obvious differences between HT+CT-ICBT and IMRT+ICBT, but the incidence rate of long-term adverse reactions obviously declines in HT+CT-ICBT.

This is a retrospective study, and there was certain data bias, small sample size and limited follow-up time, so the conclusions made in this study still need to be further verified by multicenter prospective randomized controlled studies in the future, so as to provide a reliable basis for the treatment of locally advanced cervical cancer.

Conclusions

HT+CT-ICBT is safe and effective in the treatment of locally advanced cervical cancer, and it has similar short-term clinical efficacy and long-term survival rate compared with IMRT+ICBT, which also significantly reduces the long-term incidence of radiation proctitis and cystitis, therefore it is worthy of popularization and application.

Conflict of interests

The authors declare no conflict of interests.

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