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Setup errors in cone-beam computed tomography and their effects on acute radiation toxicity in cervical cancer radiotherapy

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ABSTRACT. This study aimed to evaluate cone-beam computed tomography setup errors during cervical cancer treatment and the effects of these errors on acute radiation toxicity and treatment efficacy. A total of 170 cervical cancer patients were randomly divided into image-guided radiation therapy (IGRT; 86 patients) and intensity-modulated radiation therapy (IMRT; 84 patients) groups to receive IGRT and IMRT, respectively. After correcting setup errors for the 86 patients in the IGRT group, the X-, Y- and Z-axis errors were smaller than the corresponding errors before correction ($P < 0.01$, $P < 0.05$, and $P < 0.05$, respectively). The setup errors unevenly influenced the affected organs and dosage distributions in the targeted regions. The frequencies of patients with grade 0 or I urinary toxicity were 86.0% (74/86) and 44.0% (37/84) in the IGRT and IMRT groups, respectively ($P < 0.01$), whereas the frequencies of patients with grade 0 or I gastrointestinal toxicity were 83.7% (72/86) and 53.6% (45/84) in the IGRT and IMRT groups, respectively ($P < 0.01$). The two groups had similar response rates ($P > 0.05$). IGRT significantly corrected and reduced setup errors during cervical cancer treatment and enhanced the dosage distribution

accuracy within the affected organs and targeted regions. IGRT can reduce the adverse effect of radiotherapy, thereby achieving improved efficacy during cervical cancer treatment.

Key words: Cervical cancer; Cone-beam computed tomography; Image-guided radiation therapy; Setup error

INTRODUCTION

Cervical cancer, the most common malignancy of the female reproductive system, has a slow developmental process. At early stages, the treatment of cervical cancer is relatively easy. It takes many years for atypical hyperplasia to develop into invasive cervical cancer. Therefore, an early diagnosis of cervical cancer will enable timely treatment and a potential cure for patients (Wang et al., 2012, 2013). Radiotherapy has been used to treat cervical cancer. Despite recent progressive improvements in radiotherapy, the number of deaths caused by cervical cancer remains high. This high mortality rate is primarily due to an advanced disease stage at diagnosis, because such cases are difficult to treat. In addition, at an advanced disease stage, radiotherapy is prone to large setup errors that will affect the therapeutic efficacy. Image-guided radiation therapy (IGRT) is a four-dimensional radiotherapy technology that adds a time factor to basic three-dimensional radiotherapy. Previous studies have demonstrated that the use of IGRT for the treatment of cervical cancer reduced setup errors and had fewer side effects and better efficacy when compared with intensity-modulated radiation therapy (IMRT) (Yuan, 2011; Liu et al., 2011). The present study aimed to investigate setup errors when using cone-beam computed tomography (CBCT) to treat cervical cancer and the effects of these setup errors on treatment efficacy and acute radiation toxicity.

MATERIAL AND METHODS

General information

A total of 170 cervical cancer patients who were admitted to our hospital for treatment between July 2011 and December 2012 were enrolled in the present study. These patients, aged 45-68 years, were randomly divided into the IGRT and IMRT groups. All 86 patients in the IGRT group received IGRT-based treatment; these patients had an average age of 49.12 ± 7.76 years and an average disease course of 4.92 ± 3.71 years. All 84 patients in the IMRT group underwent IMRT-based treatment; the patients had an average age of 49.11 ± 7.72 years and an average disease course of 5.12 ± 3.79 years. No statistically significant differences were observed between the groups in terms of general patient characteristics such as age, disease stage, and disease course of disease ($P > 0.05$). The present study protocol was reviewed and approved by the Ethics Committee of our hospital, and informed consent was obtained from all participating patients.

Methods

Computed tomography (CT) scanning

Enhanced CT scanning was conducted by using a Philips 17-row spiral CT simulator

(Philips Healthcare, Cleveland, OH, USA) specifically designed for radiotherapy. The patients underwent scanning in a supine position.

Delineation of the target region and affected organs

Systematic optimization was utilized to select the radiation dose, radiation field layout, and dose distribution.

Verification and implementation

Doses were verified by using the Metrics system. The absolute dose difference at the isocenter was ≤4%, and the distance to agreement was ≤5 mm.

CBCT scanning and image fusion

Acquisition of the CBCT images was performed as follows: in the accelerator chamber, the initial linear accelerator gantry angle was set at 21°, optional half-bow was turned counterclockwise to 177°, and co-rotating frame was set at 200°. Image fusion was completed via automatic soft-tissue matching. Three-dimensional CBCT image reconstruction was performed automatically by using an optimal band imaging system. The automatic image fusion was completed according to the originally designed bony registration points via the use-match-points fusion method.

Measurement and correction of setup errors

CBCT scanning was performed three times each after the initial setup and after correction of the setup errors; online-guided postural correction was performed once after the initial setup. A total of 960 scanning procedures were performed on the study subjects.

Analysis of the effects of setup errors on dose distribution

Using computer simulation, the effects of the setup errors on dose distribution in the target region and affected organs were analyzed. Moving bed data from the CBCT scans were transferred to the planned CT scans.

Clinical evaluation indicators

The adverse reactions of patients in the two groups were assessed according to the United States Radiation Therapy Oncology Group scoring criteria. The response rate was calculated as the sum of the ratios of complete remission and partial remission. Complete remission was defined as the complete disappearance of all tumor masses with no appearance of neoplasms for 4 weeks. Partial remission was defined as a ≥30% reduction in tumor size with no appearance of neoplasms for 4 weeks. Stable disease was defined as no significant reduction in tumor size with the appearance of neoplasms within 1 week.

Statistical methods

Statistical analysis was performed by using the SPSS 17.0 software package (SPSS, Inc., Chicago, IL, USA). The measured data are reported as means ± standard deviations. A paired *t*-test was performed by using data obtained from two independent samples or intragroup measurement data. A *t*-test or rank-sum test was performed in the presence of heterogeneity of variance. The enumerated data were analyzed by using the chi-square test. A difference was considered statistically significant at $P < 0.05$ and statistically very significant at a $P < 0.01$.

RESULTS

Comparison of setup errors in the 86 patients in the IGRT group before and after correction

As shown in Table 1, the setup errors on the X-, Y-, and Z-axis in the 86 patients of the IGRT group were lower after correction than before correction ($P < 0.01$, $P < 0.05$, and $P < 0.05$, respectively).

Table 1. Comparison of 86 patients in the IGRT group before and after setup error correction (means ± standard deviations).

Corrected orientation	Before correction	After correction	*t* value	P value
X-axis	1.16 ± 2.71	0.35 ± 0.97	2.6097	0.0099
Y-axis	0.72 ± 2.11	0.14 ± 0.82	2.3760	0.0186
Z-axis	0.77 ± 2.31	0.07 ± 0.95	2.5990	0.0102

IGRT, image-guided radiation therapy

Dose distributions in the affected organs and target regions before and after correction of the setup errors

As shown in Table 2, the setup errors affected the dose distributions in the affected organs and target regions to different extents.

Table 2. Target dose distribution and organ placement data before and after error correction.

Target organ	Average dose (Gy)	Minimum dose (Gy)	Maximum dose (Gy)
Foci	-2.57 to 3.53	-10.22 to 7.30	-1.03 to 4.72
Small intestine	-3.05 to 15.31	-14.09 to 20.08	-2.13 to 15.67
Rectum	-10.52 to 12.82	-1.43 to 4.72	-4.52 to 10.37
Femoral head	-7.02 to 8.44	-10.19 to 3.78	-2.74 to 4.08
Bladder	-12.27 to 3.78	-2.40 to 11.52	-1.33 to 3.02

Comparison of the acute radiation reactions between both the groups

As shown in Table 3, the frequencies of patients with grade 0 or I upper respiratory tract toxicity were 86.0% (74/86) and 44.0% (37/84) in the IGRT and IMRT groups, respectively; the frequency in the IGRT group was significantly higher than that in the IMRT group ($\chi^2 = 33.08$, $P < 0.01$). The frequencies of patients with grade 0 or I upper gastrointestinal tract

toxicity were 83.7% (72/86) and 53.6% (45/84) in the IGRT and IMRT groups, respectively; the frequency in the IGRT group was significantly higher than that in the IMRT group ($\chi^2 = 18.00$, $P < 0.01$). The frequencies of patients with grade 0 or I skin toxicity were 89.5% (77/86) and 90.5% (36/84) in the IGRT and IMRT groups, respectively; the frequencies in the 2 groups were nearly identical ($\chi^2 = 0.04$, $P > 0.05$). No grade IV acute toxicity was observed in either group.

Table 3. Comparison of acute radiation reactions in the two groups of patients (N).

Group	No. of cases	Urinary tract				Gastrointestinal				Skin			
		Grade 0	Grade I	Grade II	Grade III	Grade 0	Grade I	Grade II	Grade III	Grade 0	Grade I	Grade II	Grade III
IGRT group	86	56	18	10	2	58	14	13	1	49	28	8	1
IMRT group	84	13	24	44	3	17	28	27	2	52	24	8	0
χ^2 value		52.46				42.58				1.38			
P value		<0.01				<0.01				>0.05			

IGRT, image-guided radiation therapy; IMRT, intensity-modulated radiation therapy.

Comparison of therapeutic efficacy between the two groups of patients

As shown in Table 4, the therapeutic efficiency was similar between the two groups ($P > 0.05$).

Table 4. Comparison of efficacy in the two groups of patients (N, %).

Groups	Number of cases	CR	PR	SD	Efficacy
IGRT	86	62	20	4	95.3% (82/86)
IMRT	84	58	22	4	95.2% (80/84)
χ^2 value					0.11
P value					>0.05

IGRT, image-guided radiation therapy; IMRT; intensity-modulated radiation therapy; CR, complete response; PR, partial response; SD, stable disease.

DISCUSSION

Cervical cancer is a common malignancy in women and is also the only cancer with a definitive cause. Conclusive evidence has demonstrated that cervical cancer is closely related to human papillomavirus (HPV) infection, that is, cervical cancer is a viral infection-related cancer caused by HPV infection. Because it takes several years for atypical hyperplasia to develop into malignant carcinoma, cervical cancer patients can be cured following early detection, diagnosis, and treatment. It is therefore recommended that women, especially those in high-risk populations, begin to undergo regular gynecological examination at a certain age to diagnose or exclude cervical cancer as early as possible.

Radiotherapy is among the primary treatments for cervical cancer and has improved in recent years along with the continuous development of medical technology (Zheng and Tian, 2009). However, the number of deaths due to cervical cancer continues to increase, principally because many patients are diagnosed with advanced-stage disease, which is difficult to treat (Lin et al., 2012b). In addition, setup errors during radiation therapy seriously affect the radiation level and therapeutic efficacy (Zhao, 2012). Setup errors can be caused by a variety of factors; systemic errors are primarily caused by equipment, whereas random errors are

closely related to the individual patient and skill of the operator (Lin et al., 2012a).

IGRT is a four-dimensional radiotherapy technology based on the addition of a time factor to three-dimensional radiation therapy. IGRT fully accounts for displacement errors due to respiratory motion and setup errors caused by anatomic tissue activity during treatment. Because these errors can lead to changes in the radiation dose distribution, the errors affect the patient's treatment throughout the therapeutic process. During IGRT, the tumor and involved organs are monitored and the radiation field is adjusted in a timely manner according to actual changes in position during radiotherapy to ensure an accurate radiotherapy process and achieve an optimal therapeutic effect.

A domestic study (Sun and Liu, 2013) involving 26 cases of patients who received IGRT treatment found that most setup errors that occurred during treatment were in the head-foot and front-back orientations; the left-right errors were smallest, with values of only 0.1-4.1 mm. This domestic study revealed that IGRT yielded good efficacy for the treatment of esophageal cancer. Setup correction during treatment maintained balance in the dose distribution in the target region, reduced the dose in the normal organs, and improved treatment efficacy with reduced toxicity.

The results of international and domestic studies (Chen et al., 2012; Zhai, 2012) have indicated that IGRT could correct and reduce setup errors during the treatment of cervical cancer, leading to more accurate dose distributions in the tumor lesions and affected organs, and consequently, to improved therapeutic effects and reduced adverse effects during radiation treatment for cervical cancer.

The present study showed that the 86 patients in the IGRT group exhibited markedly reduced errors on the X-, Y- and Z-axes after setup error correction ($P < 0.01$, $P < 0.05$ and $P < 0.05$, respectively). The setup errors were found to greatly influence the dose distributions in the targeted region and affected organs. The dose distribution was more accurate in the IGRT group, indicating that IGRT can correct and thus reduce setup errors during treatment to improve the dose distribution accuracy in the affected organs and target region.

The present study showed that the frequencies of grade 0 and I urinary tract and gastrointestinal toxicities were significantly higher in the IGRT group than in the IMRT group ($P < 0.01$). No grade IV acute toxicity was observed in either group. Similar response rates were observed in the patients from both groups ($P > 0.05$). These findings indicate that the use of IGRT for cervical cancer therapy significantly reduces mild and serious adverse effects during the treatment. Meanwhile, both IMRT and IGRT yielded high response rates in the treatment of cervical cancer.

In summary, the use of IGRT for the treatment of cervical cancer can remarkably correct and reduce setup errors and improve the dose distribution accuracy in the target region and involved organs. Consequently, IGRT can significantly reduce the adverse effects and achieve satisfactory therapeutic effects during the treatment of cervical cancer.

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