

## Original Article

# The influencing factors and precision improvement of IMRT head and neck tumor setup errors guided by CBCT imaging

Yan Dou<sup>1</sup>, Hongyan Yang<sup>1</sup>, Meili Sun<sup>1</sup>, Qian Sun<sup>2</sup>, Zhongzheng Ding<sup>1</sup>, Yu Li<sup>1</sup>, Guohong Zu<sup>1</sup>

<sup>1</sup>Department of Tumor Radiotherapy, Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, Jinan 250013, China; <sup>2</sup>Cancer Center, The Second Hospital of Shandong University, Jinan 250033, China

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**Abstract:** This study aimed to analyze the factors that affect and improve the accuracy in the setup errors of intensity-modulated radiotherapy (IMRT) for head and neck tumor using CBCT imaging. A retrospective analysis was performed using the Elekta synergy linear accelerator airborne imaging system. CBCT scanning was performed during the pre-treatment (pr), post-correction (pc), and post-treatment (pt) periods, respectively. CBCT image-guided setup error data and the affecting factors were analyzed, and the standardized process for enhancing IMRT precision was put forward accordingly. The setup errors in the X, Y, and Z directions during the pr period were (0.63±0.77), (0.93±1.01), and (0.72±0.92) mm, during the pc period they were (0.06±0.54), (0.07±0.59), and (0.02±0.32) mm, and during the pt period they were (0.07±0.90), (0.16±0.71), and (0.05±0.87) mm, respectively. The pr and pc showed significant differences in the setup errors in the X, Y, and Z directions (Fx=9.66, Fy=6.29, Fz=38.49), (P<0.05), and during the pr period the frequencies of the setup of ≥3 mm were 8, 20, and 8 in the X, Y, and Z directions, accounting for 4.6%, 11.6%, and 4.6%, respectively. The setup errors gained their maximum value in the Y direction. The setup errors for IMRT in head and neck tumors remained low and matched the contribution to reduce the setup error. There are multiple factors affecting the setup errors of head and neck tumors. The pre-intervention parts should emphasize the positioning of the plastic mask and the preparation of the radiotherapy planning and quality control should be strictly performed to standardize the treatment-processes and monitor the equipment.

**Keywords:** CBCT image guidance, IMRT for head and neck tumors, setup errors, influencing factors, precision improvement

## Introduction

In recent years, the incidence of head and neck tumors has been increasing, with about 20-30% more newly diagnosed patients annually [1-3]. The peripheral organs that are adjacent to head tumors are also at risk, making it difficult to protect organ function and morphology and provide radical treatment in a single surgery [4-6]. Clinically, radiotherapy, surgery, and medication together constitute the three major therapeutic strategies [7, 8], and 60-70% of patients with tumors need radiation therapy throughout the treatment [9]. With the development of radiotherapy technology, intensity-modulated radiotherapy (IMRT) is currently the mainstay of treatment for head and neck tumors. IMRT planning is an inversely designed process of CT reconstruction based on the required exposure dose of the target region, with a very steep

dose curve, especially for the vital organs that are present around the tumor. This means that small errors can have a significant impact on the target region and the normal tissues. In order to achieve a high-dose gradient regimen, millimeter-scale errors also seriously affect the actual therapeutic efficacy [10, 11]. According to ICRU24, a 5% deviation of the target plan might lead to the loss of control of the primary lesions, increasing the complications [10]. Radiation therapy experts at home and abroad are also committed to reducing setup errors and improving setup accuracy [12, 13]. Hunt [14] believed that these errors have a greater impact on precise radiotherapy than conventional radiotherapy. The dose distribution of the regimen design is an ideal model, and any errors in this might lead to differences in the actual dose distribution.

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In image-guided radiation therapy (IGRT), the requirement for the accurate and real-time measurement of deviations are fulfilled, achieving an automatic correction effect of the deviation using the system connection. This means that the real-time target position that is obtained during the treatment can be automatically corrected at the bed position by a connection between the system and the accelerator, so that the target region can be accurately and effectively treated, thus protecting the normal tissues to the maximum extent [15-17]. IGRT is another novel radiotherapy technique based on three-dimensional conformal radiotherapy and IMRT [18]. This can reduce the planning target volume, improve the irradiation accuracy, reduce the volume of sensitive tissues, increase the tumor exposure dose, achieve online or offline error correction, and increase the local tumor control rate [19]. Cone beam CT technology [20] is a novel imaging technology that is based on a large-area of amorphous silicon digital X-ray detection plates and is characterized by small volume, lightweight, and open architecture. Furthermore, it can be directly integrated into the accelerator for the reconstruction of CT images, and the patients are only exposed to small doses. In addition, real-time online correction of the position deviation can be achieved, which thus improves the radiotherapy setup accuracy. During the treatment, not only can the inter-fractional errors be corrected, but also those in the treatment can be corrected. By repeated online corrections, a CT image of the setup can be obtained, and the changes in morphology and the size of the tumors, the normal tissues, and the organs can be tracked, thus assisting in the discontinuation of treatment plan at an appropriate time point. Hence, in the present study, a statistical analysis of IMRT errors was performed in 36 patients with head and neck tumors guided by kilovolt-scale cone-beam computed tomography (CBCT) images. Also the error results and the factors affecting the accuracy were analyzed, and the methods for reducing the setup errors and our experience in improving the quality control (QC) of the accuracy are summarized.

### Materials and methods

#### *Therapeutic equipment*

Swedish Elekta Synergy linear accelerator (Elekta Inc.), Elekta airborne three-dimensional co-

ne-beam CT (CBCT) (Elekta Inc.), German Siemens 64-slice CT (Siemens Inc.), Monaco (Elekta Inc.) and Finnish pinnacle (Philips Inc.) TM reverse intensity modulation planning system were obtained. Positioned head plates, and others, such as head masks and head neck shoulder masks, were also obtained.

#### *Clinical data*

*Basic case information:* Thirty-six patients with head and neck tumors undergoing IMRT were admitted in our department in 2018 and were retrospectively analyzed. These 36 patients were randomly enrolled, and 8 had glioma, 9 had nasopharyngeal tumors, 3 had salivary gland tumors, 8 had laryngeal cancer, 2 had tongue cancer, 2 had tonsillar cancer, 2 had maxillary sinus tumors, and 2 had meningiomas. There were 19 males and 17 females ranging in age from 32-75 years and with a median age of 54 years.

*Enrollment criteria:* a. patients with histologically confirmed malignant tumors of the head and neck; b. patients with Karnofsky performance scores (KPS) of  $\geq 70$ ; c. patients who were able to tolerate radiotherapy, and without severe heart, liver, kidney, or blood system dysfunctions; and d. patients with an estimated survival time of >6 months or more. One patient reported a poor fixation of the head mask during the initial positioning due to oral vial, so the patient was enrolled after re-positioning. Other patients who were uncooperative because of their young age or tension were excluded from the observation group.

#### *Position fixation and CT scan*

All the patients were placed in a supine position and fitted with a disposable mask or a head, neck, and shoulder thermoplastic mask. The CT was positioned, the scanning layer thickness was 3 mm, and the head was positioned from top of the head to the lower edge of the 7<sup>th</sup> cervical vertebra, and the head and neck positioning was from the geisoma to the manubrium. The target region was delineated using the Monaco software image, Monaco (Elekta Inc.) and the Pinnacle (Philips Inc.)<sup>TM</sup> reverse intensity modulated planning system.

#### *CBCT scan*

The treatment was performed using an Elekta Synergy linear accelerator and guided using an

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**Table 1.** Frequency change and the proportion of the automatic registration of setup errors in each period

Period Axes	0-<2 mm		2-<3 mm		≥3 mm		
	Number	Percentage	Number	Percentage	Number	Percentage	
pr	X	137	79.2	28	16.2	8	4.6
	Y	118	68.3	35	20.2	20	11.6
	Z	137	79.2	28	16.2	8	4.6
pc	X	104	97.2	3	2.8	0	0
	Y	103	96.2	4	3.8	0	0
	Z	107	100	0	0	0	0
pt	X	30	93.8	2	6.2	0	0
	Y	29	91	3	9.0	0	0
	Z	32	100	0	0	0	0

Note; the number of cases in the table was presented as n (%).

online Elekta airborne CBCT scan image. The scanning time for the patients with head and neck tumors was as follows: CBCT scans were performed 173 times before the 3D IMRT treatment (pre-treatment, pr), and the tomographic images were automatically reconstructed by the system, matching the CT scan image of the treatment plan to obtain the patient's left-right (X axis), superior-inferior (Y axis), and anterior-posterior (Z axis) setup errors. When the linearity was  $\geq 2$  mm in either direction, an online correction was performed. The CBCT scanning was then performed again (post-correction, pc), and the scanning conditions and parameters remained unchanged. Next, the setup errors were obtained after correction 107 times, followed by an analysis of (post-treatment, pt) whether the patient moved or other factors affected the position, and then we performed a CBCT scan 32 times after the treatment. Each patient underwent a CBCT scan during the first three treatments and at one week after the treatment. The scanning conditions included  $200^\circ$  ( $100\text{-}260^\circ$ ) or  $360^\circ$  rotation; the acquisition included a selection of F0 ray filters for the head, an S20 scanning aperture; and if the head and neck (sometimes including supraclavicular lymph nodes) had a wide range, then an F1 ray filter was used, M20 scanning aperture, and the layer thickness was 3 mm; resolution ratio: reference value; and pixels:  $512 * 512$ .

### CBCT and CT image registration

The CBCT image was compared with the patient's planned CT image. The registration targets included the target regions, the critical organs, and the normal tissues. The gray re-

gistration was used, and automatic correction was performed after the registration, and the error data was setup in the X, Y, and Z directions after the registration was obtained.

### Statistical methods

The data were expressed as the mean  $\pm$  standard deviation (mean  $\pm$  SD), and the statistical analyses were performed using SPSS 20.0 statistical software. The measurement

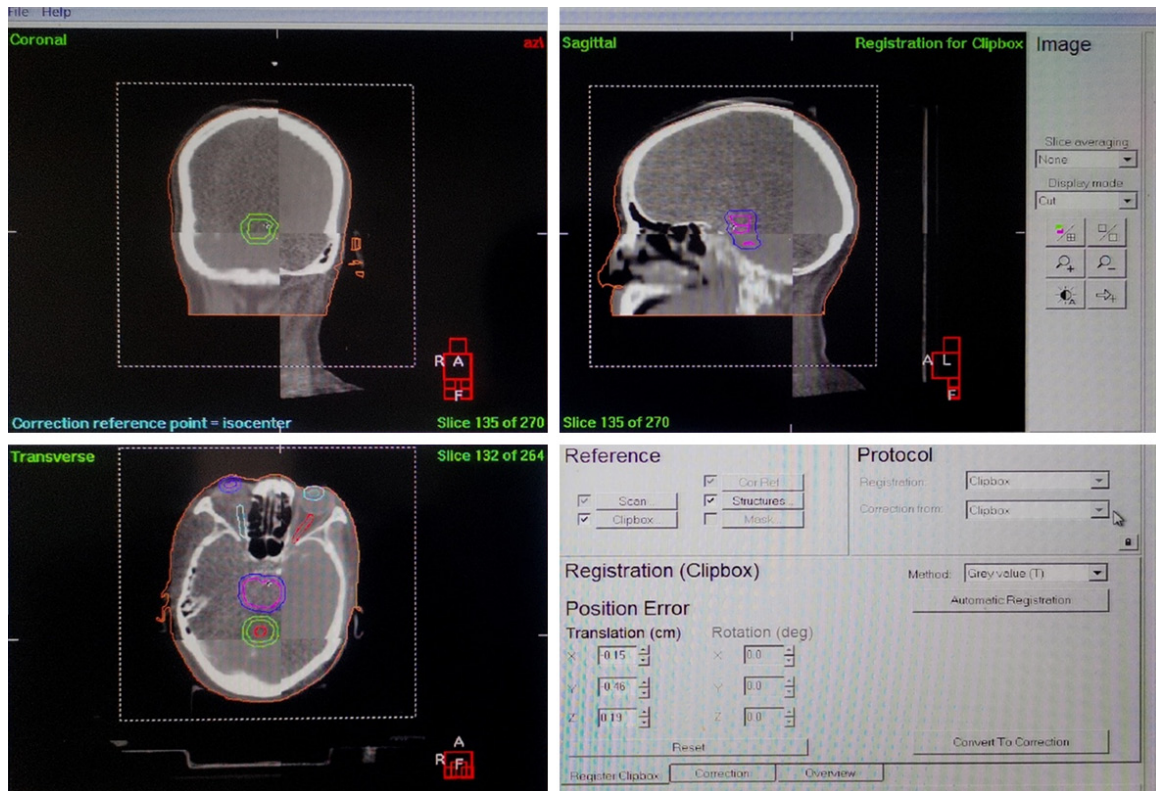
data were compared using F tests, and the count data were analyzed using chi-squared tests.  $P < 0.05$  was considered to be statistically significant.

### Results

The frequency of the proportion changes of the automatic registration by setup errors during the three periods was analyzed. During the pr period, the frequency of setup errors of  $< 2$  mm showed 137, 118, and 137 times, respectively in the X, Y, and Z directions, and the proportions were 79.2%, 68.3%, and 79.2%, respectively; the frequency of the setup errors of 2-<3 mm showed 28, 35, and 28, respectively in the X, Y, and Z directions, accounting for 16.2%, 20.2%, and 16.2%, respectively; the frequency of the setup errors of  $\geq 3$  mm showed 8, 20, and 8, respectively in the X, Y, and Z directions, accounting for 4.6%, 11.6%, and 4.6%, respectively. The setup error gained its maximum value in the Y direction. During the pc period, the frequency of setup errors of  $< 2$  mm showed 104, 103, and 107, respectively, accounting for 97.2%, 96.2%, and 100%; during the pt period, the frequency of setup errors of  $< 2$  mm showed 30, 29, and 32, respectively, accounting for 93.8%, 91%, and 100%, respectively, and the remaining number of cases showed a setup error of 2-<3 mm frequency (pc, pt) (Table 1).

In the quantitative analysis, the setup error in the X, Y, and Z directions during the pr period was  $(0.63 \pm 0.77)$ ,  $(0.93 \pm 1.01)$ , and  $(0.72 \pm 0.92)$  mm; the setup error in the X, Y, and Z directions during pc period was  $(0.06 \pm 0.54)$ ,  $(0.07 \pm 0.59)$ , and  $(0.02 \pm 0.32)$  mm; and the setup error in the

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**Figure 1.** Comparison of the planned CT image of the head tumor IMRT and the post-setup CBCT image in the pr period. Note: the above image was made during the pr period, with a deviation in the X, Y, and Z directions of (-1.5, -4.6, 1.9) mm.

X, Y, and Z directions during the pt period was  $(0.07 \pm 0.90)$ ,  $(0.16 \pm 0.71)$ , and  $(0.05 \pm 0.87)$  mm, respectively. A comparison of differences in the X, Y, and Z directions during the three periods (pr, pc, and pt) revealed significant differences in the setup errors of pr and pc in the X ( $F=9.66$ ), Y ( $F=6.29$ ), and Z ( $F=38.49$ ) directions ( $P < 0.05$ ). The setup error for IMRT in the head and neck tumors was low, and matching reduced the setup error. There was no significant difference between pc and pt in the X ( $F=0.03$ ), Y ( $F=0.01$ ), and Z ( $F=0.39$ ) directions (All  $P > 0.05$ ). Setup errors during pr and pt showed no statistical differences in X ( $F=3.69$ ) and Y ( $F=2.75$ ) directions ( $P > 0.05$ ), but showed a significant difference in Z ( $F=14.66$ ) direction ( $P < 0.05$ ) (Figures 1-3; Tables 2-4).

### Discussion

The setup error is considered to be an important factor affecting the precision and accuracy of precision radiotherapy, especially the high-precision IMRT. The influence of the different equipment fixations and different locations on

the setup errors is different. The application of the thermoplastic mask fixation technique, and the accuracy of radiotherapy for head and neck tumors have been greatly improved. According to the statistical data, the factors and rules of setup errors in the head and neck of each treatment unit are analyzed, and the process and technical improvements are performed based on these. The accuracy and safety of radiotherapy for head and neck tumors have shown further improvement.

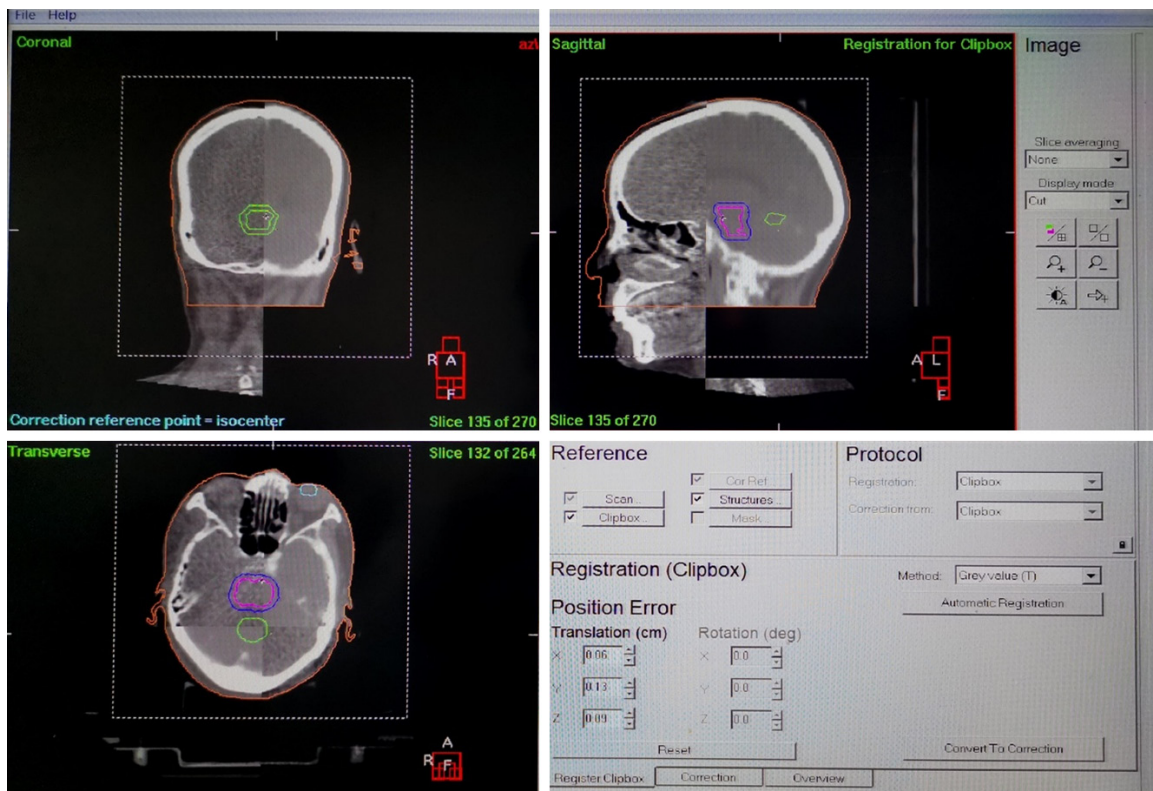
### Analysis of the results

*Analysis of the frequency changes and proportions in the three directions at each period:* In the pr period, the frequencies of the setup of  $\geq 3$  mm were 8, 20, and 8 in the X, Y, and Z directions, accounting for 4.6%, 11.6%, and 4.6%, respectively. The setup error gained its maximum value at the Y direction. This was due to the stretching and opening of the head neck shoulder mask in the Y direction. When performing the actual IMRT treatment of head and neck tumors, the verification was performed

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**Figure 2.** Comparison of the planned CT image of the head tumor IMRT and the post-setup CBCT image in the pc period. Note: the above image was made during the pc period, with a deviation in the X, Y, and Z directions of (-0.5, 0.2, 0.9) mm.



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**Figure 3.** Comparison of the planned CT image of the head tumor IMRT and the post-setup CBCT image in the pt period. Note: the above image was made during the pt period, with a deviation in the X, Y, and Z directions of (0.6, 1.3, 0.9) mm.

**Table 2.** Comparison of the setup deviations in the X, Y, and Z axes during the pr and pc periods, ( $\bar{x} \pm S$ ) unit (mm)

Axes	pr	pc	F value	P value
X	0.63±0.77	0.06±0.54	9.66	<0.05
Y	0.93±1.01	0.07±0.59	6.29	<0.05
Z	0.72±0.92	0.02±0.32	38.49	<0.05

**Table 3.** Comparison of the setup deviations in the X, Y, and Z axes during the pc and pt periods, ( $\bar{x} \pm S$ ) unit (mm)

Axes	pc	pt	F value	P value
X	0.06±0.54	0.07±0.90	0.03	>0.05
Y	0.07±0.59	0.16±0.71	0.01	>0.05
Z	0.02±0.32	0.05±0.87	0.39	>0.05

**Table 4.** Comparison of the setup deviations in the X, Y, and Z axes during the pr and pt periods, ( $\bar{x} \pm S$ ) unit (mm)

Axes	pr	pt	F value	P value
X	0.63±0.77	0.07±0.90	3.69	>0.05
Y	0.93±1.01	0.16±0.71	2.75	>0.05
Z	0.72±0.92	0.05±0.87	14.66	<0.05

only once in the first three times and every week, and so the error results during the pr reflected the true state of the radiotherapy setup errors for head and neck tumors. An error of <2 mm in each direction was regarded as the ideal goal of our treatment units. A study conducted by Wang [21] showed that in moving equivalent centers of intensity-modulated plans in 8 patients with nasopharyngeal carcinoma, the system of setup errors of 2 mm and 5 mm in 6 directions were separately simulated, and when the setup error was 2 mm, the GTV D98 and CTV D95 showed no dose reduction and was >3%. The rate of dose increases in the normal tissues of the spinal cord and brain stem exceeding 5% of the original plan were only 6.3% and 4.2%, and the rate of the left and right parotid glands exceeding 10% were 12.5% and 8.3%, respectively. But the specific dose effect should be considered according to the specific setup error of each radiotherapy unit. When the setup error was 2-<3 mm, then it was

considered to be within the range of CTV-PTV (3 mm) of the target region, so much attention should be paid to the results in this step, and if the setup error was  $\geq 3$  mm, then it acts as a warning to the results in this step. This was similar to the report put forwarded by Wang [22], in which the KV-CBCT was performed on 22 patients with nasopharyngeal carcinoma 754 times. Among the 505 scans before adjustment, the test number for setup deviations in the X, Y, and Z directions with an error of <2 mm was 386 (76.4%), 384 (76%), and 433 (85.7%), respectively, and the scan was performed 106 times after the correction. The number of errors of <2 mm in the three directions were 103 (97.2%), 103 (97.3%), and 106 (100%), respectively.

*Quantitative analysis and comparison of the setup errors in the three directions in each period:* In the quantitative analysis, the pr and pc showed significant differences in their setup errors in the X, Y and Z directions ( $P < 0.05$ ). The setup error for IMRT in the head and neck tumors was low, and the matching reduced the setup error. This suggested that the setup errors can be quickly detected and corrected by using CBCT image-guided treatment in patients with head and neck tumors. This further confirms that CBCT image-guided IMRT can improve its precision and accuracy. No significant difference was observed between the pc and pt periods ( $P > 0.05$ ). There was a significant difference between the pr and pt periods in the Z direction ( $P < 0.05$ ), but no significant differences were observed between X and Y ( $P > 0.05$ ). This suggests that the changes in the position and the corrected position after the treatment showed no significant differences, and the improvement in the Z direction was most significant before and after treatment.

*Calculation of the setup margin from clinical target volume (CTV) till planning the target volume (PTV) based on the errors during the three periods:* According to the setup margin equation  $M = 2.5\Sigma + 0.7\sigma$  recommended by Van Herk [23], the theoretical setup margin of the target region was calculated, where  $\Sigma$  was the standard deviation of the systematic error and  $\sigma$

was the standard deviation of the random error. However, when different diseases and stages of different patients were delineated in the target region, the actual setup margin remained different, and the three-dimensional directions for the same patient were also different [24]. According to the above equation, the maximum setup margins of PTV before and after the correction were 3.1 mm and 1.8 mm, respectively. According to the study by Wang [24], the maximum setup margin of PTV was 4.0 mm and 2.1 mm before and after adjustment. Therefore, the CBCT image-guided IMRT assisted in significantly reducing the setup margin of CTV-PTV.

### *Influencing factors of IMRT setup errors in head and neck tumors*

Setup errors include systematic errors and random errors. The systematic error occurs during the preparation of the treatment plan, which is different between the actual position and simulated positioning, and is specifically embodied when the treatment technique is difficult with regard to the position during repeated simulation positioning on the radiotherapy machine. Random errors occur during the execution of the treatment plan, and are also known as random (treatment execution) errors [25]. This is considered to be different in the daily repeated treatments, for the errors are mostly caused by the changes in the patient's position and organ motion. Setup errors are divided into inter- and intra-fractional errors, in which the results during pr period are considered inter-fractional errors, and those during pc and pt periods are considered intra-fractional errors.

*Factors causing systematic errors:* This was related to the stretching and opening of the plastic film in the Y direction, especially during the preparation of the radiotherapy plan at the time of positioning, which included the fitness and comfort of the position, headrest, head mask, the difficulty level of repeated simulation positioning, and the accuracy of the equipment.

*Factors causing random errors:* This was related to the implementation of the current system norms and QC of the repeated setup in the fractionation. First, the factors associated with random error might be related to the breathing and swallowing movements; second, they may be related to the changes in the size, morphology, and position of the tumors, normal tissues, and

organs with increasing exposure to the dose and fractionation; third, they may be related to the positioning and treatment within a certain time span, and a change in the shape of the patient's body surface that caused the nonconformity between the head mask, the head neck shoulder mask, and the body; and fourth, it may be related to the factors, such as setup deviations caused by unclear marked lines and points, and without a strict verification of the position in the fractional treatment.

### *QC of the improved setup accuracy in the head and neck tumors*

*The effect of systematic error on accuracy and QC:* Systematic errors that are present throughout the patient's treatment process should be reduced and controlled using position fixtures and process optimization methods. Also the pre-intervention parts should emphasize positioning the plastic mask and the preparation of the radiotherapy planning, which includes the choice of mask and headrest, the improvement of the head mask's elasticity, and the technique of position fixation during the highly repetitive simulation positioning. The study on fixing the head neck shoulder thermoplastic mask showed that the neck-shoulder thermoplastic mask was used from the lower neck to the supraclavicular region, which in turn can control and reduce neck stretching, significantly reducing the setup errors [26, 27]. In addition, regular quality monitoring of machine equipment is needed, such as center point deviation, treatment bed and CT bed, CT simulation, deviation of the therapeutic machine's laser light positioning device, etc.

*The effect of random error on accuracy and QC:* Random errors are caused by body stretching during each treatment setup, movement of the organs, etc. QC should be strictly performed in standardizing the process, positioning and mask preparation, CT simulation positioning, planning design, and treatment by focusing on marked lines and points, and repeating the position of the first simulated positioning repeatedly and accurately. Through analysis, it was found that when preparing the masks for individual patients, it was difficult to reposition them due to the improper selection of the headrest and the improper fixation of the oral vial. Some patients undergo re-plasticization and positioning in time due to the increased number of treatments and doses, and changes in

their posture and external morphology. When all these conditions are satisfied, the patient should be treated soon, preferably within 1 week, to prevent the body changes due to the passage of time, avoiding the non-conformity between the body mask and the body, increasing the number of errors.

*Problems of CBCT image guidance:* CBCT images can display the target region, the organs at risk, and the normal tissues in the transverse, sagittal, and coronal directions. The radiation therapist should judge and match the superior-inferior, left-right, and anterior-posterior deviations of the above areas in real-time according to the planned image, quickly analyze the cause of the deviation, and accurately estimate the correction of the next setup displacement. This requires that the radiation therapist have a certain level of experience in image recognition and resolution.

The setup error of image-guided IMRT for head and neck tumors is affected by many factors. The best approach for reducing the errors during the actual operation is to regularly check the instruments and equipment for factors that influence the setup error, which thus assists in completing the correction in time. The pre-intervention design process should be emphasized during the preparation of the radiotherapy plan, and the positioning comfort and the head-rest should be improved. The elasticity of the head mask and the repeatability of the technique of position fixation during simulation positioning should also be noted. Under the guidance of the current rules and regulations, various other operational procedures should also be standardized, and QC should be strictly performed in all procedures from positioning and mask preparation, CT simulation positioning, and the planning design of the treatment, especially focusing on improving the levels of relevant technologists in mask preparation, setup, and image analysis. The improvement of treatment accuracy is the process involved in controlling and reducing these errors, which is also the future direction of each radiotherapy unit.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Guohong Zu, Department of Tumor Radiotherapy, Jinan Central Hospital,

Cheeloo College of Medicine, Shandong University, Jinan 250013, China. Tel: +86-13011719677; E-mail: guohongzu@163.com

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