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Analysis of the setup errors of medical image registration-based cone-beam CT for lung cancer

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Abstract.
PURPOSE: This study aimed to investigate the feasibility of efficiently using a rigid image registration (RIR) algorithm or a deformable image registration (DIR) algorithm to match medical images and evaluate the impact of setup errors on intensity modulated radiation therapy of lung cancer patients.
METHODS: Ten lung cancer patients were chosen randomly each day and were subjected to image-guided radiotherapy. The clinical registration between cone-beam computed tomography (CBCT) images and treatment planning system CT images was performed by applying both RIR and DIR; the clinical registration was evaluated on the basis of the contour index, including dice similarity coefficient, sensitivity, and positive predictive value; the optimal scheme of image registration was selected to ensure that the actual irradiation isocenter was consistent with the treatment planning isocenter. In each patient, the translational errors in the right-left (x), superior-inferior (y), and anterior-posterior (z) directions and the rotational errors in the u, υ, and w directions formed by the x, y, and z directions were calculated and analyzed daily in the whole course of treatment; margins were calculated according to this equation: $M = 2.5\sum + 0.7\delta$.
RESULTS: The tumors and the surrounding soft tissues of the patients are shown more clearly in the CBCT images than in the CT images. DIR can be applied more efficiently than RIR to determine the morphological and positional changes in the organs shown in the images with the same or different modalities in the different period. The setup errors in translation in the x, y and z axes were 0.05 ± 0.16, 0.09 ± 0.32 and -0.02 ± 0.13 cm, respectively; by contrast, the setup errors in rotation in u, υ and w directions were $(0.41 \pm 0.64)^\circ$, $(-0.08 \pm 0.57)^\circ$ and $(-0.03 \pm 0.62)^\circ$, respectively. The setup errors in the x, y and z axes of the patients indicated that the margins expansions were 0.82, 1.15 and 0.72 cm, respectively.
CONCLUSION: CBCT with DIR can measure and correct the setup errors online; as a result, setup errors in lung cancer treatments can be significantly reduced and the accuracy of radiotherapy can be enhanced.

Keywords: Lung cancer, cone-beam CT, setup errors, rigid image registration, deformable image registration

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1. Introduction

Radiotherapy is the preferred treatment for inoperable and transferred pulmonary malignant tumor. Radiotherapy has been developed into intensity-modulated radiation therapy (IMRT) and image-guided radiotherapy (IGRT) from three-dimensional conformal radiation therapy (3D-CRT). Radiotherapy can be applied to reduce the irradiation dose applied to organs at risk (OARs) and normal tissues and to increase the irradiation dose administered to tumors. However, positioning accuracy is required for radiotherapy. A radiotherapy plan is generally designed on the basis of CT scans obtained before treatment is administered; however, CT images provide the location of tumors in a flash; as such, the exact tumor location cannot be fully revealed during treatment; thus, errors may occur. The three main errors are setup errors of fractional treatment, target volume displacement, and deformation of inter-fractional radiotherapy and target volume motion of the same fraction [1–4]. A large margin is created in the irradiation field to ensure that all of the lesions are detected; however, the clinical results of a large number of cases in current clinical practices have shown that this technique may cause excessive and unnecessary irradiation to normal tissues. Although the target volume margin is rather large, leakage and transmission radiation caused by the change and movement of the target volume may occur.

IMRT and IGRT treatment plans are designed reversely by using a computer on the basis of the irradiation dose to a target volume; the dose curve is extremely steep and is located around vital organs; thus, the effects of a small error in irradiation dose on a target volume and normal tissues may be significantly evident [5–7]. A film or electronic portal imaging device (EPID) was traditionally used to assess setup errors; although this device could display osseous anatomical boundaries, EPID could not obtain soft tissue images and could not evaluate the motion of internal organs. In contrast to EPID, cone-beam computed tomography (CBCT) can be directly incorporated into a linear accelerator, and the CT images within the scope of a volume are obtained and reconstructed after the gantry completely rotates. Moreover, this system is characterized by a high utilization efficiency of ray and low irradiation dose to patients; CBCT can also perform X-ray fluoroscopy, radiography, and volume imaging in the treatment position [8–10]. Setup error parameters are obtained after the three-dimensional images reconstructed with the CT images of the treatment plan are matched and compared.

Rigid image registration (RIR) is usually applied in medicine for transformation that requires six degrees of freedom; by contrast, deformable image registration (DIR) requires more dimensions for transformation in space. In DIR, several algorithms, including feature space description, similarity measurement, transformational model, and optimization algorithm, are used [11, 12]. DIR is mainly applied to determine an optimal conversion algorithm and to provide the maximum similarity structural outline or the smallest difference to images requiring registration based on reference images. In this study, RIR and DIR were compared and the setup errors in translation and rotation were investigated through DIR in the radiotherapy guided by kilo-voltage CBCT (KV-CBCT) for patients with pulmonary malignant tumor. The clinical target volume (CTV) margin was also calculated to provide a reference for clinical physicians.

2. Materials and methods

2.1. Case selection

In this study, 10 lung cancer patients treated in a hospital from January 2015 to May 2015 (8 males and 2 females; age range, 36–75 years old; median age, 51 years old) were randomly selected for IGRT in Elekta Synergy S Linear Accelerator. The tumors were located in the superior lobe of right lung (2 cases), middle lobe of right lung (1 case), inferior lobe of right lung (2 cases), superior lobe of left

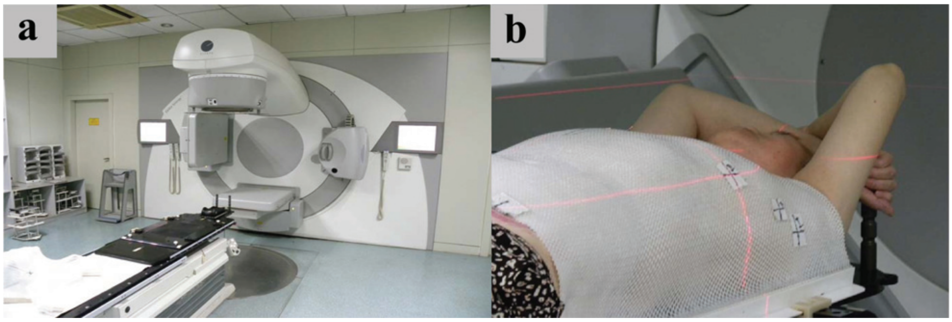

Fig. 1. Elekta Synergy S Linear Accelerator (a) and patient positioning on the couch (b).

lung (3 cases), and hilum of left lung (2 cases). The pathological types include 4 cases of pulmonary squamous-cell carcinoma, 3 cases of lung adenocarcinoma, and 3 cases of small cell lung cancer.

2.2. *Positioning method*

The 10 patients were treated in the supine position, with their C/B pillow placed in a comfortable position and with heads in their hands, and were fixed using a carbon fiber position fixing device and thermoplastic marks (Fig. 1). CT scans with a slice thickness of 5 mm were obtained from the cricothyroid membrane to the edge of the diaphragm using large-aperture 16 rows spiral CT of GE Medical Systems, and the CT images were transmitted into the treatment planning system.

2.3. *CBCT image acquisition and registration*

The CBCT scans of each patient were obtained using Elekta Synergy S Linear Accelerator before each treatment. The CBCT images were reconstructed at high resolution according to clinical requirements. Figure 2 depicts the image registration between CBCT and treatment planning CT of one patient for a certain level.

2.3.1. *RIR*

RIR was performed through automatic rigid registration fusion and rigid auxiliary calibration for both planning CT images and KV-CBCT images.

2.3.2. *DIR*

The planning CT images and KV-CBCT images both use pixel-based deformation registration at first and subsequently conduct adaptive contour delineation. Moreover, the deformation image contour automatically delineated well is compared with the contour delineated on the primary KV-CBCT images.

2.3.3. *Contour evaluation index*

DCS was qualitatively and quantitatively compared to obtain the effects of both DIR and RIR on organs or body registration. DCS is expressed as

$$DSC = 2 \times V_{ref} \cap V_{static}/(V_{ref} + V_{static}), \tag{1}$$

where V_{ref} is the organ volume of deformation contour of reference images and V_{static} is the organ contour volume delineated manually in the course of repeated KV-CBCT scanning. A DCS value closer to 1 indicates higher degree of similarity [13, 14].

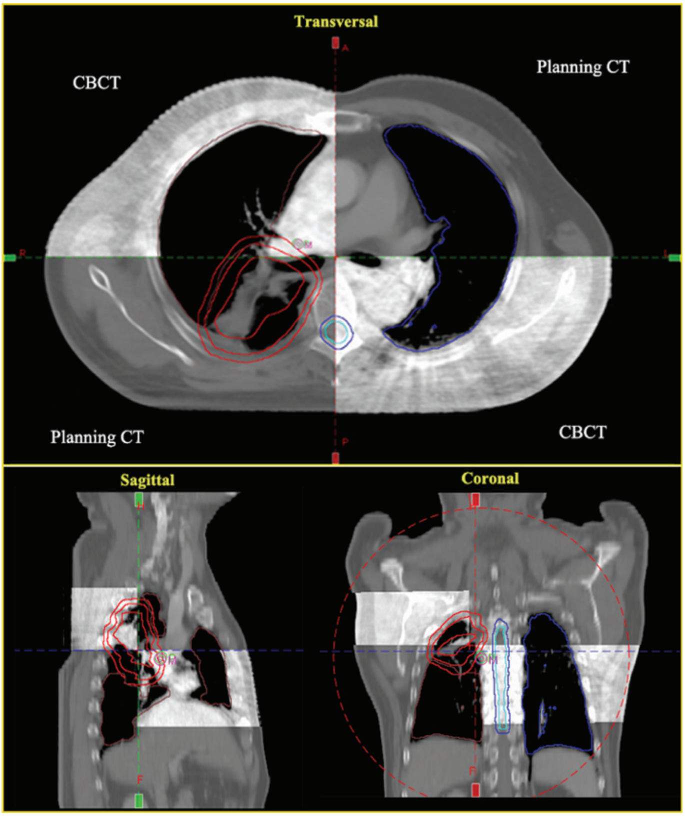

Fig. 2. Image registration between CBCT and planning CT. Cone-Beam Computed Tomography (CBCT): in the direction of leading diagonal. Planning Computed Tomography (CT): in the direction of minor diagonal.

The CBCT images obtained before treatment were automatically matched with the treatment planning CT images; the appropriate registration frame was initially selected for automatic registration using the osseous or gray registration method, and the manual registration was performed by physicians on the basis of automatic registration. Basing on the registration results, we collected and recorded the setup errors during translation in the left-right (x), superior-inferior (y), and anterior-posterior (z) directions, and the setup errors during rotation in the u, υ, and w directions formed rotationally by x, y, and z directions of the actual isocenter position of target volume and the isocenter position of target positioning CT scans, respectively.

2.4. Setup error analysis

The planning target volume (PTV) was delineated on the basis of the CTV expanded during treatment. The position errors of the treatment mainly come from the setup errors and organ motion, which also define the external margin of PTV. Moreover, the motion range of CTV external boundary is called internal margin owing to the respiratory/organ movement or to both the volume and shape changes of CTV during radiotherapy; by contrast, the CTV margin resulting from all the uncertainty between the patient and ray caused by position is known as setup margin. The external formula suitable for PTV delineated based on CTV expansion aims to calculate the M value in the x, y, and z directions using the formula $M = 2.5\sum + 0.7\delta$ [15, 16], where, $\sum$ stands for the whole systematic errors of all the patients' setup errors (i.e., the mean of the standard deviation of all the patients' systematic errors) and δ is the random error of all the patients' setup errors (i.e., the standard deviation of all the patients' systematic errors).

2.5. Statistical approach

Data were expressed as mean ± standard deviation $(\overline{X} \pm S)$, and the statistical analyses were performed using the IBM SPSS Statistic 19.0. Independent-samples *T*-test is used to design comparison, the threshold for statistical significance was $\alpha = 0.05$, $P \leq 0.05$.

3. Results

3.1. RIR and DIR comparison

The DSC of the organ contour in RIR was significantly different from that in DIR ($P < 0.05$). The DSC of DIR was higher than that of RIR in terms of body contour, double lungs, and heart (Table 1). Fig. 2 shows the comparison between RIR and DIR of a patient; Fig. 3 illustrates the image registration in CBCT and treatment planning CT of a patient at a certain level.

3.2. Setup errors

On the basis of the registration results, we selected 254 CBCT scans for the 10 lung cancer patients. Figure 4(a), (b), and (c) show the transversal, sagittal, and coronal scatter plots of the errors in x, y, and z directions, respectively. Figure 5 reveals the scatter plot of rotation errors in u, υ, and w directions.

Table 2 lists the setup errors in translation for each patient in three directions. The mean setup errors in translation in x, y, and z axes were 0.05 ± 0.16, 0.09 ± 0.32, and –0.02 ± 0.13 cm, respectively.

Table 1

DSC comparison between RIR and DIR

Organ	RIR	DIR	*T*	*P*
Body contour	0.972 ± 0.025	0.980 ± 0.022	3.888	0
Left-lung	0.836 ± 0.103	0.873 ± 0.051	4.405	0
Right-lung	0.873 ± 0.072	0.888 ± 0.049	3.879	0
Heart	0.738 ± 0.089	0.764 ± 0.091	4.826	0
Spinal cord	0.666 ± 0.114	0.677 ± 0.116	2.041	0.047

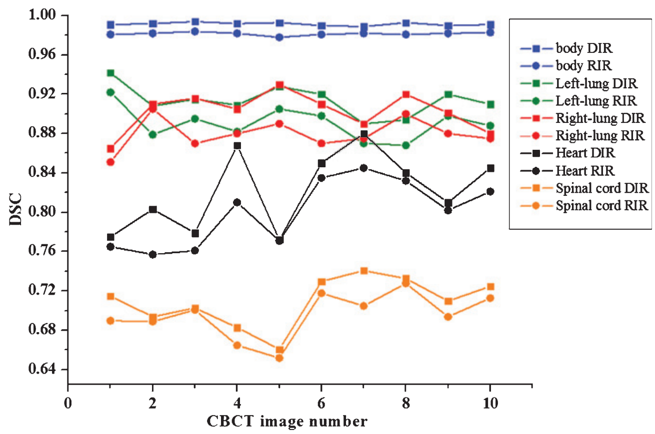

Fig. 3. Comparison between RIR and DIR for a certain patient. DCS: Dice Similarity Coefficient. DIR: Deformable Image Registration. RIR: Rigid Image Registration.

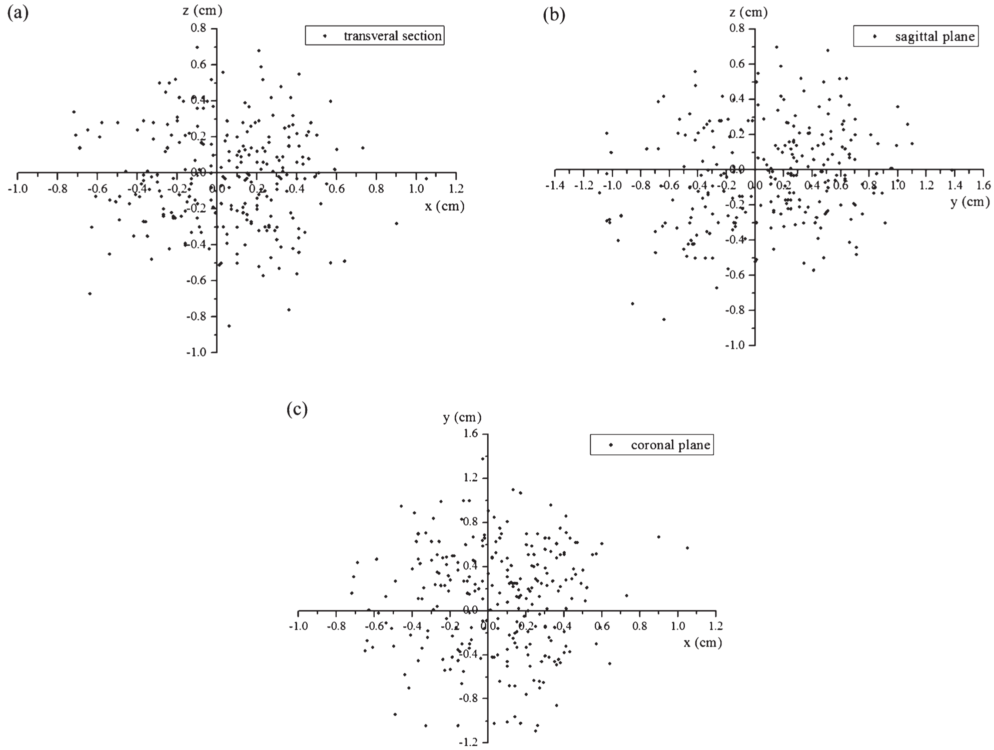

Fig. 4. (a) transversal, (b) sagittal (c) coronal scatter plots of the translational errors of the 254 CBCT scans. x, y, and z stand for right-left, superior-inferior, and anterior-posterior directions, respectively.

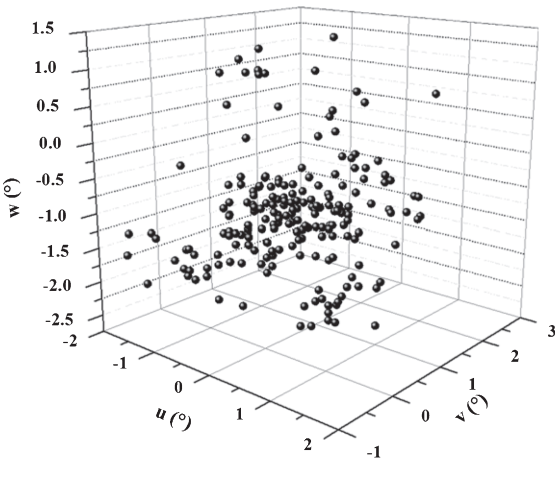

Fig. 5. Scatter plot of rotational errors in u, υ, and w directions. u, υ, and w refer to rotational degrees of freedom around the x, y, and z axes, respectively.

Table 3 lists the setup errors in rotation in three directions in each patient. The mean setup errors in rotation are $(0.41 \pm 0.64)^\circ$, $(-0.08 \pm 0.57)^\circ$, $(-0.03 \pm 0.62)^\circ$, separately.

3.3. PTV margin calculation

Table 4 shows the systematic errors in the x, y, and z directions in 10 patients; the result indicated that the maximum and minimum errors were obtained in y and z directions, respectively. Moreover,

Table 2
Setup errors in translation for ten patients with lung cancer in three directions

Case Number	x(cm)	y(cm)	z(cm)
1	–0.08 ± 0.35	–0.28 ± 0.50	0.19 ± 0.29
2	–0.02 ± 0.33	0.11 ± 0.32	–0.12 ± 0.19
3	0.18 ± 0.23	–0.29 ± 0.48	–0.18 ± 0.24
4	0.13 ± 0.30	0.33 ± 0.50	–0.12 ± 0.21
5	0.25 ± 0.28	0.34 ± 0.25	0.09 ± 0.17
6	–0.07 ± 0.21	0.21 ± 0.37	–0.02 ± 0.18
7	–0.14 ± 0.24	0.64 ± 0.32	0.10 ± 0.25
8	0.21 ± 0.19	0.25 ± 0.31	0.04 ± 0.30
9	–0.17 ± 0.37	–0.34 ± 0.24	–0.2 ± 0.35
10	0.11 ± 0.29	–0.12 ± 0.39	–0.03 ± 0.39

Table 3
Setup errors in rotation for ten patients with lung cancer in three directions

Case Number	u(°)	υ(°)	w(°)
1	0.68 ± 0.72	–0.20 ± 0.64	–0.73 ± 0.65
2	0.83 ± 0.57	0.32 ± 0.57	1.02 ± 0.73
3	1.01 ± 0.84	0.95 ± 1.04	0.25 ± 0.76
4	1.42 ± 1.21	–0.07 ± 0.89	–0.55 ± 1.38
5	–0.11 ± 0.51	–0.47 ± 0.49	0.46 ± 0.75
6	0.45 ± 0.49	–0.41 ± 0.85	0.41 ± 1.04
7	0.88 ± 0.49	–0.59 ± 0.66	–0.17 ± 0.71
8	–0.22 ± 0.54	–0.49 ± 0.36	0.72 ± 0.68
9	–0.32 ± 1.24	–0.57 ± 0.54	–0.09 ± 0.89
10	–0.58 ± 0.66	–0.43 ± 1.02	–0.75 ± 0.93

Table 4
The whole systematic error and margin evaluation for ten patients

Content	x(cm)	y(cm)	z(cm)
$\sum$ (systematic errors)	0.28	0.37	0.25
δ (random errors)	0.16	0.32	0.13
M (margin)	0.82	1.15	0.72

the specific external margins of CTV, which can form PTV, in x, y, and z directions are 0.82, 1.15, and 0.72 cm, respectively.

4. Discussion

With the development of precise radiotherapy technique, the precise acquisition of patients' images before treatment, localization, and delineation of target volume has become increasingly important; however, precise image acquisition can be affected by many uncertain factors during actual treatment. Studies have shown that during treatment, either the target volume is partly irradiated owing to setup position and organ motion or the OARs suffer from high-dose irradiation [17, 18]. Studies have also suggested that the inter-fractional error produced during lung cancer treatment reaches 5–40 mm [19–21]. Moreover, Balter et al. [22] found that a setup error of more than 1 cm will cause a loss of greater than 6 mm in the surrounding target volume. Therefore, a setup correction should be conducted during treatment for lung cancer patients [23–26].

Our results showed that the DIR algorithm was superior over the RIR algorithm in obtaining better DSC value (including that of double lungs, spinal cord, heart, and body contour). A total of 254 IGRT scans were conducted in 10 lung cancer patients. The average setup errors in translation were 0.05 ± 0.16, 0.09 ± 0.32, and -0.02 ± 0.13 cm in the x, y, and z axes, respectively, demonstrating that the translational error was highest, intermediate, and lowest in the x, y, and z axes, respectively. In addition, the systematic errors in the right-left, superior-inferior, and anterior-posterior directions were 0.28, 0.37, and 0.25 mm, respectively; the systematic error was most distinct in the superior-inferior direction resulting from the conventional calibration for the accelerator, laser localized light, and CBCT. Considering the deformation of the body frame used in radiotherapy, we found that the random errors in the right-left, superior-inferior, and anterior-posterior directions were 0.16, 0.32, and 0.13 cm, respectively; the most distinct random error was found in the superior-inferior direction. Considering that the random error is associated with thermoplastic mask fixation, we immobilized the mask in the right-left and anterior-posterior directions to prevent relative displacement. However, the mask is open in the superior-inferior direction; therefore, if the skin becomes flabby or the position of the patient whose both arms were raised above his/her head slightly changes, a deviation in the superior-inferior direction may be produced. Moreover, our results are consistent with those of Guckenberger et al. [27], who revealed that the setup errors in three-dimensional directions in lung cancer before adjustment are large, that is, the inte-fractional setup error is considerably large; thus, CBCT is necessary to detect and adjust the setup before treatment is administered.

The inter-fractional radiotherapy error consists of setup error and organ motion-induced error; thus, PTV is delineated on the basis of CTV expansion [28]. Several computing schemes are suitable for PTV margin in clinic, and the CTV margin is mainly calculated by measuring the actual setup error of each unit. Langsenlehner et al. [29] reported that the PTV margins of head and neck tumor cannot exceed 3.6 mm in the three-dimensional directions; the setup errors of chest tumor is large, and 96.6% of the setup errors are greater than 2 mm in three-dimensional directions; the setup error can reach 18.9 mm in the superior-inferior direction; furthermore, the maximal setup errors of abdominal and pelvic reach 17.4 mm in the superior-inferior direction, the margins are approximately 5 mm in the right-left and anterior-posterior directions, and 90% of the setup errors are included in addition to 10 mm margins in the superior-inferior direction. Poulsen et al. [30] also corrected the setup errors in translation and rotation in radiotherapy positioning through CBCT; this process can significantly reduce systematic and random errors and enhance the radiotherapy accuracy. In our study, $M = 2.5\sum + 0.7\delta$ [31–33] was used to calculate the PTV margin, and the effects of systematic and random errors were considered; the results of this formula could guarantee 90% of patients that the minimum cumulative dose of CTV reaches to 95% of the prescription dose at least. The setup error in the lung cancer patients was determined through CBCT during radiotherapy to preliminarily calculate a PTV margin; this method can provide a basis of lung cancer treatment. The concrete margins in the x, y, and z directions were 0.82, 1.15, and 0.72 cm, respectively, which are nearly similar to those obtained by Masi et al. [34]. Considering the effect of organ motion (e.g., breathing and cardiac impulse) on the superior, middle, and inferior lung tumors, we should develop methods to obtain comparatively accurate PTV margins for the comprehensive consideration of setup errors and organ motion.

This study used a carbon fiber position-fixing device and a thermoplastic mask in all lung cancer cases. However, different radiotherapy isocenters may differ in terms of fixation techniques, such as vacuum pillow, stereotaxic frame, and respiratory gating technique. Different positioning technologies probably produce different errors in lung cancer patients. Masi et al. [34] demonstrated that a stereotactic body frame (Elekta, Crawley, UK) is relatively superior to carbon fiber plate and individualized thermoplastic positioning membrane; the stereotactic body frame also provides more advantages than active breathing control. However, a large difference resulting from diaphragm and heart movement is found between the left and right lungs; as such, a displacement difference in the target volume can be obtained; therefore, further research should be performed to investigate such differences.

Acknowledgments

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