Dosimetric study of a respiratory gating technique based on four-dimensional computed tomography in non-small-cell lung cancer

Hui LIN[1], Heming LU[2,*], Liuyang SHU[3], Huixian HUANG[4], Huasheng CHEN[2], Jiaxin CHEN[2], Jinjian CHENG[2], Qiang PANG[2], Luxing PENG[2], Junzhao GU[2] and Zhiping LU[2]

[1]Department of Thoracic Surgery, People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Nanning City, 530021, Guangxi, China
[2]Department of Radiation Oncology, People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Nanning City, 530021, Guangxi, China
[3]Department of Medical Oncology, People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Nanning City, 530021, Guangxi, China
[4]Department of Clinical Medicine, Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, China
*Corresponding author. Department of Radiation Oncology, People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Nanning City, 530021, Guangxi, China. Tel: +86-771-218-6503; Email: luhming3632@163.com

This study sought to compare the differences in target volumes and dose distributions to the targets and organs at risk (OARs) between a four-dimensional computed tomography (4DCT)-based respiratory-gated intensity-modulated radiation therapy (IMRT) plan ($Plan_{EOE}$) and a three-dimensional CT (3DCT)-based IMRT plan ($Plan_{3D}$) in patients with non-small-cell lung cancer (NSCLC). For 17 patients with Stages I–III NSCLC, both 4DCT data and conventional 3DCT data were obtained. The $Plan_{3D}$ and $Plan_{EOE}$ were designed based on 3DCT data and 4DCT data, respectively. The displacements of the gross tumor volume (GTV) centroid were 0.13 ± 0.09 cm, 0.15 ± 0.1 cm, and 0.27 ± 0.27 cm in the right–left, anterior–posterior, and superior–inferior directions, respectively. The volume of the GTV_{EOE} was 3.05 ± 5.17 cm^3 larger than that of the GTV_{3D}. The volume of the PTV_{3D} was 72.82 ± 48.65 cm^3 larger than that of the PTV_{EOE}. There was no significant difference between the PTV_{3D} and PTV_{EOE} for V55.8, V60, V66 and the homogeneity index. The PTV_{3D} had a lower target conformity index than the PTV_{EOE} ($P = 0.036$). $Plan_{EOE}$ had a significantly lower lung V10, V20, V30, V40 and mean lung dose (MLD) than $Plan_{3D}$. For the heart, $Plan_{EOE}$ had a significantly lower V_{30} and mean dose. In conclusion, 4DCT is an appropriate method for assessing the displacement of the GTV centroid in three dimensions. $Plan_{EOE}$ has smaller PTVs and a decreased dose and volume for the normal lung and heart, as compared with $Plan_{3D}$.

Keywords: 4DCT; respiratory gating; non-small-cell lung cancer; intensity-modulated radiation therapy

INTRODUCTION

One of the challenges frequently encountered by radiation oncologists and medical physicists during a radiation treatment planning session is how to design an appropriate plan for a moving target. Traditionally, the margin created from the clinical target volume (CTV) to form the planning target volume (PTV) is determined by the physician's experience and literature report when there is no precise measurement available for evaluating the exact extent of the tumor motion. This margin includes various geometrical errors caused by tumor motion and daily patient set-up. However, the PTV margin is often too large or too small, since the extent of tumor motion in three dimensions is generally anisotropic. An increased risk of unnecessary irradiation to surrounding normal tissues may occur if the PTV margin is too large, which may result in severe side-effects associated with radiation therapy (RT). If the PTV margin is too small, however, a decreased local and/or regional control rate may occur as a consequence of the increased chance of missing targets.

Several researchers have investigated tumor motion and the impact of respiration-induced target motion on target

volume for patients with non-small-cell lung cancer (NSCLC) by using four-dimensional computed tomography (4DCT) and found that the gross tumor volume (GTV) moved anisotropically with breathing in each spatial dimension. Treatment planning based on 4DCT created smaller target volumes, compared with treatment planning based on three-dimensional computed tomography (3DCT) [1–3]. In addition, the plan based on 4DCT resulted in a lower radiation dose to the surrounding normal tissues, particularly the lungs [2–4].

In this study, we aimed to evaluate the impact of respiratory motion on displacement of the GTV centroid and to compare the differences in the size of GTVs and PTVs, and dose distribution to the PTVs and critical structures between an intensity-modulated radiation therapy (IMRT) plan based on 3DCT and a respiratory-gating plan based on 4DCT for 17 inoperable patients with NSCLC.

MATERIALS AND METHODS

Patient characteristics
From March 2010 to August 2012, 17 patients with newly diagnosed NSCLC were included in this study. Each patient underwent both a 3DCT helical scan and a 4DCT helical scan using a 24-slice CT scanner (Somatom Sensation Open, Siemens Medical Solutions, Erlangen, Germany) and was considered inoperable due to medical or other reasons (Table 1). Written informed consent was obtained for all patients. The study was approved by the institutional review board (IRB).

Immobilization and CT scans
Verbal coaching was required for all patients prior to, and during the 3DCT and 4DCT scans to achieve a regular and stable breathing pattern. Patients were positioned head first

Table 1. Patient characteristics

Characteristics	Value (%)
Number of patients	17
Male/Female	14/3 (82.3%/17.7%)
Histology	
Squamous cell carcinoma	6 (35.3%)
Adenocarcinoma	11 (64.7%)
Staging (AJCC 2002)	
I	2 (11.75%)
II	2 (11.75%)
III	13 (76.5%)
Tumor location	
Upper, middle lobe	10 (58.8%)
Lower lobe	7 (41.2%)

and supine in an individualized vacuum bag and were instructed to breath normally during the scans. The Respiratory Gating System AZ-733V (Anzai Medical, Tokyo, Japan) was used to monitor and coach the patient's breathing.

Non-contrast 3DCT imaging (effective mAs, 400 mAs; kV, 120 kV; rotation time, 0.5s; slice width, 4.0 mm; pitch, 1.2; reconstruction increment, 4.0 mm) was performed with a 4-mm slice thickness during free breathing from the cricoid cartilage to the lower edge of the liver. After that, intravenous contrast-enhanced 4DCT data with a 4-mm slice thickness were acquired (effective mAs, 400 mAs; kV, 120 kV; slice width, 4.0 mm; pitch, 0.1; reconstruction increment, 4.0 mm). For the 4DCT data, the acquired images were sorted by respiratory phases determined from the AZ-733V system to generate 8-phase 4DCT image datasets, namely 25% inhalation phase ($25\%_{in}$), 50% inhalation phase ($50\%_{in}$), 75% inhalation phase ($75\%_{in}$), 100% inhalation phase ($100\%_{in}$), 25% exhalation phase ($25\%_{ex}$), 50% exhalation phase ($50\%_{ex}$), 75% exhalation phase ($75\%_{ex}$), and 100% exhalation phase ($100\%_{ex}$). All 8-phase 4DCT datasets and the 3DCT datasets were imported to MiM Maestro V.5.6.1 (MIM Software Inc., Cleveland, OH) for contouring target volumes and organs at risk (OARs).

Target delineation and plan design
An appropriate window width and window level were selected for the lungs (window width, 1600 HU; window level, −600 HU) and the mediastinum (window width, 400 HU; window level, 20 HU) to better view and determine the targets. The target delineation was in accordance with the International Commission on Radiation Units and Measurements Reports 50 and 62, as well as an institutional treatment protocol, and reviewed by a radiation oncologist (H. Lu).

The GTV was contoured on the $25\%_{in}$ images and was then propagated automatically to the other 7-phase 4DCT image datasets through the VoxAlign Deformation Engine provided by the MiM Maestro software. Modification of the GTV was made whenever needed at the discretion of the treating physician. All GTVs created from the 8-phase images were used to evaluate the displacement of the GTV centroid in the three dimensions.

The GTV_{3D} was defined as the primary GTV contoured on the 3DCT datasets. It was then expanded with a 6–8 mm margin (squamous cell carcinoma, 6 mm; adenocarcinoma, 8 mm) to generate the CTV_{3D}. The PTV_{3D} was created by adding certain margins based on the tumor location to the CTV_{3D} (10 mm in the right–left and anterior–posterior directions; 10 mm in the superior–inferior direction for a tumor located in the upper and middle lobes; 15 mm in the superior–inferior direction for a tumor located in the lower lobe). A regional metastatic lymph node (GTV_n) was defined as any lymph node larger than 1 cm in the short axis in CT imaging study. It was expanded with a 5-mm margin to

generate the CTV_n. The PTV for the lymph nodes was formed by adding a 10-mm margin to the CTV_n. The delineation of the lungs was performed automatically and didn't include the trachea, hilum or any GTVs. Other OARs including the heart, esophagus and spinal cord were contoured manually. All contours of the target volume and OARs were sent to the CMS-XiO planning system (CMS, St Louis, MO) to design the IMRT plan ($Plan_{3D}$).

The gating window was defined as three consecutive exhalation phases, namely $50\%_{ex}$, $75\%_{ex}$, and $100\%_{ex}$ [2–5]. The $100\%_{ex}$ images were used to design a treatment plan for the respiratory gating technique. A maximal intensity projection (MIP) dataset was created by assigning the highest density value for each pixel throughout the above three phase datasets and was used to define the GTV for the gating treatment plan (GTV_{EOE}). The GTV_{EOE} was expanded with an 8-mm margin for adenocarcinoma and a 6-mm margin for squamous cell carcinoma to generate the internal target volume (ITV), which is defined as a volume encompassing the CTV, taking into account the possibilities of the CTV variation in position, shape and size [6]. A 7-mm margin was added to the ITV to form the PTV_{EOE}. The criteria for determining the GTV_n and the CTV_n were the same as the above (except for the PTV_n, to which a 7-mm margin was addedz0. The OARs were contoured on the treatment planning images. All contours of the target volume and OARs were sent to the CMS-XiO planning system to design the gating treatment plan ($Plan_{EOE}$).

The prescribed radiation dose was 60 Gy in 30 fractions at 2 Gy per fraction delivered to the PTVs. The prescription criteria for the PTVs were as follows: 95% of the PTVs were covered by the prescription dose. Less than 10% of the PTVs received a dose >66 Gy, and less than 3% of the PTVs received a dose <55.8 Gy. A dose >66 Gy was not allowed to occur in any area outside the PTVs. Vx denoted the percentage of a specific structure exposed to a dose exceeding X Gy. Dose constraints for the OARs were as following: bilateral lungs, $V_{20} < 35\%$; mean lung dose, <20 Gy; heart, $V_{30} < 45\%$; mean heart dose, <26 Gy; esophagus, $V_{50} < 40\%$; mean esophagus dose, <34 Gy; spinal cord, maximum dose < 45 Gy.

Statistical analysis

The displacement of the GTV centroid in the right–left (RL), anterior–posterior (AP), and superior–inferior (SI) directions was calculated by using the MiM Maestro software, according three spatial coordinates of the 8-phase images. The size of the GTVs and the PTVs, radiation dose and volume of the targets and OARs were compared between the $Plan_{3D}$ and the $Plan_{EOE}$. The mean ± standard deviation was used for data with a normal distribution, whereas the interquartile range and median were used for data not normally distributed. Analysis of variance (ANOVA) was performed to determine whether there were any significant differences in the

displacements of the GTV centroid among the three dimensions. A paired sample T-test or Wilcoxon rank-sum test was chosen based on the data types. All P values were two-sided and considered significant at <0.05. The Statistical Package for Social Sciences, version 16.0 software (SPSS, Chicago, IL) was used for statistical analysis.

RESULTS

Displacement of the GTV centroid

The displacements of the GTV centroid in the RL, AP, and SI directions were 0.13 ± 0.09 cm, 0.15 ± 0.10 cm, and 0.27 ± 0.27 cm, respectively. Significant differences in the displacement of the GTV centroid were found between the SI and RL directions and between the SI and AP directions, with P-values of 0.023 and 0.048, respectively (Table 2).

Size of the GTVs and PTVs

The size of the GTV_{EOE} was 54.41 ± 47.96 cm^3, 3.05 ± 5.17 cm^3 larger than that of the GTV_{3D}, which accounted for $4 \pm 8\%$ of the total volume of the GTV_{EOE}. The size of the PTV_{EOE} was 314.41 ± 188.76 cm^3, 72.82 ± 48.65 cm^3 smaller than that of the PTV_{3D}, which accounted for $20 \pm 9\%$ of the total volume of the PTV_{3D} (Table 3).

Radiation dose to the targets and OARs

No significant differences were found in homogeneity index (HI), $V_{55.8}$, V_{60} or V_{66} between the PTV_{3D} and the PTV_{EOE}, with P-values of 0.705, 0.093, 0.550 and 0.499, respectively. The PTV_{3D} had a better conformity index (CI), compared with the PTV_{EOE} (1.06 ± 0.08 vs 1.09 ± 0.06, $P = 0.036$). There were significantly lower V_{10}, V_{20}, V_{30}, V_{40} and MLD for the bilateral lungs in the $Plan_{EOE}$, compared with the $Plan_{3D}$, with P-values of 0.047, 0.011, 0.013, 0.4006 and 0.013, respectively. However, no significant difference was found in V_5 for the lungs between the two plans ($P = 0.178$). For the heart, there was no significant difference in V_{40} between the two plans ($P = 0.161$). However, $Plan_{EOE}$ had a significantly lower V_{30} and mean dose, compared with

Table 2. Displacement of GTV centroid in three dimensions

Dimension	Mean ± SD	P-value
Left–right	0.13 ± 0.09	0.023*[a]
Anterior–posterior	0.15 ± 0.10	0.756[b]
Superior–inferior	0.27 ± 0.27	0.048*[c]

[a]Differences in the superior–inferior direction vs the left–right direction as analyzed by ANOVA.
[b]Differences in the anterior–posterior direction vs the left–right direction as analyzed by ANOVA.
[c]Differences in the superior–inferior direction vs the anterior–posterior direction as analyzed by ANOVA. *Significant difference.

Table 3. Volumes of GTVs and PTVs

Volume	Mean ± SD	*P*-value
GTV_{3D} (cm^3)	51.36 ± 45.99	0.019*
GTV_{EOE} (cm^3)	54.41 ± 47.96	
$GTV_{EOE} - GTV_{3D}$ (cm^3)	3.05 ± 5.17	
$(GTV_{EOE} - GTV_{3D})/GTV_{EOE}$ (%)	4.00 ± 8.00	
PTV_{3D} (cm^3)	387.23 ± 227.92	<0.001*
PTV_{EOE} (cm^3)	314.41 ± 188.76	
$PTV_{3D} - PTV_{EOE}$ (cm^3)	72.82 ± 48.65	
$(PTV_{3D} - PTV_{EOE})/PTV_{3D}$ (%)	20.00 ± 9.00	

*Significant difference.

$Plan_{3D}$. The V_{30} was 15.46 ± 12.15% in $Plan_{3D}$ and 13.30 ± 10.34% in $Plan_{EOE}$ ($P = 0.025$). The mean dose to $Plan_{3D}$ was 10.39 ± 8.56 Gy, while in $Plan_{EOE}$ this figure was dropped to 9.54 ± 7.94 Gy ($P = 0.009$). For the esophagus, no significant differences were found in V_{45}, V_{50} or V_{60} between the two plans. However, the mean dose to the esophagus was significantly lower in $Plan_{3D}$, compared with $Plan_{EOE}$ [14.05 (10.78–29.43) vs 15.60 (11.06–28.02) ($P = 0.025$)]. There was no significant difference in the maximum dose to the spinal cord (Table 4).

DISCUSSION

In lung cancer, respiration is considered as a major cause of target motion. It is also one of the biggest uncertainties during the whole treatment course [7]. An expanded target volume with a certain margin is often required such that adequate dose coverage can be achieved. However, this may increase the risk of treatment complications to the surrounding normal tissues.

The displacement of the GTV centroid was found to be different from one direction to another. Yu *et al.* [1] studied the tumor motions in 191 patients with NSCLC using 4DCT and found that the displacement of the primary disease was also associated with tumor stages. The largest motion range for early stage disease occurred in the RL direction, while the largest motion range for advanced stage disease occurred in the SI direction. Similarly, Britton *et al.* [8] found in locally advanced NSCLC the motion along the SI direction was significantly greater ($P < 0.001$), with mean ± SD values of 0.86 ± 0.19 cm, as compared with 0.39 ± 0.08 cm and 0.19 ± 0.05 cm in the AP and RL directions, respectively. These results were consistent with ours. In our study, the largest tumor motion was found in the SI direction, since 76.5% (13/17) of the patients had Stage III disease. However, patients in our study had a relatively smaller tumor motion in the SI direction, as compared with those in the other studies mentioned above. This may largely be attributed to the fact that fewer patients in our study had coexisting

disease, like chronic obstructive pulmonary disease (COPD), thus their regular breathing patterns were less likely to be interrupted by compromised pulmonary functions. Nevertheless, images obtained from 4DCT are more likely to represent the real status of patients as compared with 3DCT, since the respiratory signals are incorporated with the spatial 3DCT imaging during the image acquisition and reconstruction process. Therefore, 4DCT images could be used to evaluate the magnitude of the GTV variations in the three dimensions in the design of a treatment plan.

Cover *et al.* [5] found that among CT datasets corresponding to different breathing phases, three consecutive phases (one end-exhalation and two adjacent phases) resulted in a reduced tumor motion. Residual tumor mobility in the three phases better correlated with residual mobility of the marker block than that of the diaphragm. This finding suggests that these three phases are suitable as a window for respiratory gating. In our study, 50%$_{ex}$, 75%$_{ex}$, and 100%$_{ex}$ phases were chosen as the gating window. The MIP dataset was created by assigning the highest density value for each pixel throughout the above three phase datasets and was used to define the GTV_{EOE}. We found that the size of the GTV_{EOE} was significantly larger than that of the GTV_{3D} ($P = 0.019$). However, the size of the PTV_{EOE} was significantly smaller than that of the PTV_{3D} ($P < 0.01$). The disadvantage of the 3DCT-based IMRT plan was that the PTVs were too large. The size of the PTV_{3D} was increased by 72.82 ± 48.65 cm^3, as compared with the PTV_{EOE}, which accounted for 20 ± 9% of the size of the PTV_{3D}. Underberg *et al.* [2] studied 31 consecutive patients with Stage I NSCLC undergoing a 4DCT scan, in which 3DCT datasets for 10-phase bins of the respiratory cycle were acquired during free breathing. Three PTVs were generated based on different criteria: PTV_{10bins} derived from an internal target volume (ITV) that incorporated all observed mobility, with a 3-mm isotropic setup margin; PTV_{gating} derived from an ITV generated from mobility observed in three consecutive phases during tidal-expiration plus a 3-mm isotropic margin; and PTV_{10mm} derived from the addition of a 10-mm isotropic margin to the most central gross tumor volume in the three bins selected for gating. They found that the PTV_{10mm} was the largest in all patients. Use of an individualized PTV_{10bins} resulted in an average volume of 48.2 ± 14.3% of the PTV_{10mm}. The PTV_{gating} was even smaller, with an average value of 33.3 ± 9.6% of the PTV_{10mm}. The mean PTV_{gating} was 70.5 ± 15.7% of the PTV_{10bins}. In another study conducted by Vlachaki *et al.* [3], 10 patients with thoracic malignancies who underwent gated and ungated CT scans were analyzed. It was found that the average PTV was 292.68 cm^3 for the gated plans, and 575.17 cm^3 for the non-gated plans. The average PTV generated from the non-gated plans was ~1-fold bigger than that generated from the gated plans. These findings were consistent with our results. Plans based on respiratory gating have the potential to reduce the target volume and, as a result, to

Table 4. Dose distributions to the PTV, lungs, heart, esophagus and spinal cord

Index	Plan$_{3D}$	Plan$_{EOE}$	P-value
PTV			
$V_{55.8}$ (%)	99.80 (99.37–99.92)	99.79 (99.32–99.97)	0.088
V_{60} (%)	95.41 (95.26–95.83)	95.57 (95.19–95.85)	0.550
V_{66} (%)	0.38 (0.07–1.32)	0.99 (0.06–2.55)	0.499
CI	1.06 ± 0.08	1.10 ± 0.05	0.036*
HI	1.09 ± 0.02	1.09 ± 0.02	0.705
Bilateral lungs			
V_5 (%)	50.61 ± 18.36	48.83 ± 17.61	0.178
V_{10} (%)	36.59 ± 14.25	34.89 ± 14.41	0.047*
V_{20} (%)	25.60 ± 12.67	24.13 ± 11.96	0.011*
V_{30} (%)	19.97 ± 10.36	18.48 ± 9.17	0.013*
V_{40} (%)	15.42 ± 7.69	13.93 ± 6.66	0.006*
MLD(Gy)	14.88 ± 5.88	14.03 ± 5.53	0.013*
Heart			
V_{30} (%)	15.46 ± 12.15	13.30 ± 10.34	0.025*
V_{40} (%)	10.18 ± 7.45	8.84 ± 6.05	0.161
MD(Gy)	10.39 ± 8.56	9.54 ± 7.94	0.009*
Esophagus			
V_{45} (%)	37.26 ± 29.33	35.01 ± 29.53	0.184
V_{50} (%)	34.16 ± 29.46	32.08 ± 29.31	0.193
V_{60} (%)	13.59 (3.93–44.62)	16.83 (12.87–31.82)	0.173
MD(Gy)	14.05 (10.78–29.43)	15.60 (11.06–28.02)	0.025*
Spinal cord			
Maximum dose	39.59 (33.28–42.43)	38.29 (34.34–42.36)	0.523

CI = conformity index, HI = homogeneity index, MLD = mean lung dose, MD = mean dose. *Significant difference.

avoid excessive normal tissues being involved in the PTV when compared with plans based on non-gated techniques.

In our study, all plans were evaluated and were considered suitable for treating patients, although no patients were acturally treated with either Plan$_{EOE}$ or Plan$_{3D}$. For the PTVs, the volume receiving <93% of the prescription dose was within 3%; the volume receiving 100% of the prescription dose was >95%; and the volume receiving more than 110% of the prescription dose was within 10%. The PTV$_{3D}$ was superior to the PTV$_{EOE}$ in terms of the CI. However, no significant difference was found in the HI between the two plans. Plan$_{EOE}$ provided more advantages in organ preservation than Plan$_{3D}$. Significant reductions were found in Plan$_{EOE}$ in the indices of V_{10}, V_{20}, V_{30}, V_{40} and MLD for the combined lungs. Similar results were found in the heart, where lower V_{30} and mean doses were observed in Plan$_{EOE}$. In Vlachaki's study [3], V_{10} and V_{20} were 26.26% and 30.96% for gated plans and 34.82%

and 40.16% for non-gated plans, respectively ($P < 0.0001$). Gated plans resulted in lower mean lung, esophageal, and heart doses compared with non-gated plans (14.27, 17.28 and 10.86 Gy vs 19.5, 21.85 and 16.45 Gy, respectively; $P \leq 0.003$). Underberg et al. [2] found that the mean volume of normal tissue that was encompassed by the 80% isodose line in the respiration-gated radiotherapy was only 39.1 ± 11.5% of that in the conventional radiotherapy, suggesting treatment plans based on gating technique have the potential for decreasing irradiated volumes of the normal tissues.

This study was initially designed to compare Plan$_{EOE}$ and Plan$_{3D}$ in a number of aspects. However, one may experience some dilemmas when doing this type of research, as there might be some inherent differences between the 3D and 4D techniques. For example, the scanning conditions may not be the same. Thus, the image quality and visibility of the tumor and normal structures between the two scans may be different,

which may subsequently result in discrepancies in the target volumes and the size of the OARs between the two plans. In addition, the OARs for Plan$_{3D}$ were outlined on the 3DCT images, which were actually the mixed-phase images, with different slices often being acquired from different respiratory phases. However, the OARs for Plan$_{EOE}$ were outlined on the images in 100% exhalation phase. This may cause some differences in size of the two OARs. Although the contouring based on the 3DCT and 4DCT images in the present study is a widely accepted strategy, more research is needed to find an optimal contouring approach for treatment planning sessions.

Theoretically, a reduction in the size of PTVs could result in a decreased risk of radiation-induced pneumonitis. Reports from the literature have concluded that the incidence of radiation-induced pneumonitis is 11–14% in patients with NSCLC treated with IMRT, whereas this figure was usually <10% in those treated with stereotactic body radiotherapy (SBRT) [9–13]. This could be largely explained by the fact that SBRT has smaller PTVs, compared with the IMRT technique. In the present study, neither Plan$_{EOE}$ nor Plan$_{3D}$ was used to treat patients. The incidence differences of complications associated with RT (including radiation-induced pneumonitis) between the two techniques were not available. This was another limitation of our study.

CONCLUSION

In conclusion, 4DCT is an appropriate method for assessing the displacement of the GTV centroid in three dimensions. The respiratory-gated IMRT plans based on 4DCT have smaller PTVs and decreased dose and volume for the normal lung and heart, compared with the IMRT plans based on 3DCT. The dosimetric advantage was mainly attributed to the 4DCT technique.

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