ORIGINAL ARTICLE

Usefulness of target delineation based on the two extreme phases of a four-dimensional computed tomography scan in stereotactic body radiation therapy for lung cancer

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Abstract

Background: An evaluation of the usefulness of target delineation based only on the two extreme phases of a four-dimensional computed tomography (4D CT) scan in lung stereotactic body radiation therapy (SBRT).

Methods: Seventeen patients treated with SBRT via 4D CT scans for lung cancer were retrospectively enrolled. Volumetric and geometric analyses were performed for the internal target volumes (ITVs) and planning target volumes (PTVs) generated using different respiratory phases (all phases and 2 extreme phases) and setup margins (3 mm and 5 mm).

Results: As the setup margins were added to the ITVs, the overlap percentage between the PTVs based on all phases and the two extreme phases increased (85.1% for ITVs, 89.8% for PTVs_3 mm, and 91.3% for PTVs_5 mm), and there were no differences according to the tumor parameters, such as the gross tumor volume and 3D mobility. The missing-volume differences for ITVs derived from cone-beam CT images also decreased, with values of 5.3% between ITVs, 0.5% between PTVs_3 mm, and 0.2% between PTVs_5 mm. Compared with the plan based on all phases and a 3 mm margin, the average lung-dose differences found for the PTV based on the two extreme phases and a 5 mm margin were 0.41 Gy for the mean lung dose and 0.93% for V20.

Conclusions: Regardless of tumor characteristics, PTV construction based only on the two extreme phases and a 5 mm setup margin may be a useful tool for reducing the clinical workload involved in target delineation in SBRT for lung cancer.

Introduction

Stereotactic body radiation therapy (SBRT) has been widely adopted for early-stage non-small cell lung cancer (NSCLC) with a high local control rate in most studies.[1] This approach involves the delivery of an ablative dose to the tumor using highly conformal and hypofractionated radiation over a short time while limiting the doses to the surrounding normal tissues. Respiration-induced tumor motion in the lung can lead to large uncertainties in target delineation and localization. The consideration and correction of these uncertainties are especially important for the SBRT technique, which uses high doses in small fractions for a small target volume.

In radiotherapy for lung cancer, the patient-specific aspect of tumor motion suggests the need for an individualized margin that considers motions within the patient's breathing cycle. Report 62 from the International Commission on Radiation Units and Measurements (ICRU) introduced the concept of an internal target volume (ITV), which consists of the clinical target volume (CTV) plus an additional internal margin to account for tumor motion.[2] A recent adaptation of the four-dimensional computed tomography (4D CT) technique has allowed for the acquisition of 3D CT images in multiple phases of the respiratory cycle. This capability has proven very useful for individualized ITV delineation for moving lung tumors.[3] Currently, the use of 4D CT scanning, which is the gold standard for ITV delineation, is also strongly

preferred for SBRT planning in lung cancer.[4] Additionally, the American Association of Physicists in Medicine (AAPM) has generated a report on the methods for reducing the impact of respiratory motion.[5] Considering the magnitude of tumor mobility, motion-reducing methods, such as gating and abdominal compression, can be applied during SBRT for lung cancer. In a motion-encompassing method using the 4D CT scan, when the patient is allowed to breathe freely without a gating technique, the target volume must be adjusted to completely encompass the tumor in all phases of the respiratory cycle.

There are several methods for using 4D CT data to generate individualized ITVs.[6,7] One time-consuming method, which may be the most accurate method for the acquisition of ITVs using 4D CT, is the delineation of a composite volume that encompasses the gross tumor volumes (GTVs) from all eight to 10 respiratory phases. As a simple approach to reducing the workload involved in contouring on all 4D CT phases, methods using the maximum intensity projection (MIP) dataset and only the two extreme phases (end-exhalation and end-inhalation bins) of the 4D CT scan have been suggested. However, together with the drawback of the MIP-based ITV approach, some reports have suggested that ITV delineation using only the two extreme phases of a 4D CT scan may be inappropriate for small, highly mobile tumors because intermediate tumor positions are required to generate a reliable ITV.[6–9] Nevertheless, no studies have reported any detailed analysis regarding the usefulness of target delineation using only the two extreme phases according to the tumor characteristics in lung SBRT, except for results regarding the extent of geometric coverage for the ITV generated from all phases of the 4D CT scan in all tumors.[9] The planning target volume (PTV) is generated by adding a setup margin to the ITV that is institution-specific, based on the available image-guided techniques and a systematic assessment of the positioning reproducibility.[7] Regarding the size of the setup margin, a uniform expansion of 3 mm or 5 mm with a cone-beam CT (CBCT) for image guidance during lung SBRT has typically been applied to the ITV to generate the PTV in most institutions.[7,10–12] To evaluate the usefulness of target delineation based on the two extreme phases in SBRT planning for lung cancer, we focused on the volumetric and geometric differences in the PTVs, which are the reference target volumes used for beam configuration and dose prescription, instead of those between the ITVs generated using all phases and only the two extreme phases of the 4D CT scan. The addition of an isotropic 3D margin to the ITV generated from the two extreme phases may lead to changes in the geometric coverage of the PTV based on all phases and/or the ITV generated from CBCT.

As a simple method of moving target delineation in lung SBRT, the present study was undertaken to evaluate the usefulness of a method using only the two extreme phases according to the tumor characteristics, and the change in PTV margin through volumetric and dosimetric comparisons with the PTV based on all phases of the 4D CT scan.

Methods

Patient characteristics

Seventeen patients treated with SBRT via 4D CT scans for early-stage NSCLC (15 tumors) or for pulmonary metastases (2 tumors) at our institution were retrospectively enrolled. The median patient age was 68 years old (range, 57–86 years). The tumors were located in the upper ($n = 9$), middle ($n = 1$), and lower lobes ($n = 7$). Of the 17 tumors, 16 were peripherally located and one was centrally located. The Catholic University of Korea Daejeon St. Mary's Hospital institutional review board approved the study (IRB approval number: DIRB-00115_1-001).

Image acquisition and tumor motion analysis

A 4D CT technique using a multi-slice CT scanner (SOMATOM Sensation 64; Siemens Medical Solutions, Erlangen, Germany) was performed for SBRT planning in all patients. The patients were immobilized using a Wing board and a Vac-Lok body cushion (CIVCO Medical Solutions, Orange City, IA, USA) with their arms placed above their heads. The patients were advised to breathe freely and regularly, and abdominal compression to reduce breathing motion was not applied to any of the patients. A single helical 4D CT scan that included the entire lung was acquired with fixed acquisition parameters (pitch of 0.1, rotation time of 0.5 seconds, 120 kV, and 400 mA) using a commercially available motion-monitoring system (AZ-733V; Anzai Medical, Tokyo, Japan). A pressure sensor (AZ-733V), which was fixed to the upper abdominal region using an elastic belt, generated the external respiratory signal. Lower signal amplitudes (low pressure) corresponded to the exhalation (Ex) phase of the breathing cycle, and higher amplitudes (high pressure) corresponded to the inhalation (In) phase.[13] Using the Syngo software package (Siemens Medical Solutions), the projections were sorted retrospectively based on the corresponding breathing phases (Ex and In) and the relative amplitudes at 25% intervals from 0% to 100%, and the images were reconstructed into eight respiratory phase bins (100%, Ex 75%, Ex 50%, Ex 25%, 0%, In 25%, In 50%, and In 75%), which were equally distributed throughout the breathing cycle with a slice thickness of 3.0 mm. Immediately following the 4D CT scan, a modified slow CT scan with the same scanning range and slice thickness was obtained using the same scanner with the longest possible gantry rotation time (1.0 second) and a reduced pitch factor (0.5).[14] A free breathing CBCT was acquired prior to each fraction during the SBRT course using

a megavoltage (MV)-CBCT system (MVision; Siemens Medical Solutions) for all patients. This system, with a 6 MV beam and a 1024 × 1024 amorphous silicon (a-Si) detector, was used to acquire 200 projections over a 200°arc (270° to 110°, clockwise) in a 45 second interval, with 15 monitor units delivery for the chest region.[15]After the acquisition procedure, CBCT image reconstruction was immediately performed using the protocol for a reconstruction size of 512 × 512, a field size of 27.4 × 27.4 cm^2, and a slice thickness of 1 mm.

The amplitude of tumor motion was determined by measuring the tumor movement in the 8-phase 4D CT datasets using the InSpace 4D software package (Siemens Medical Solutions). The motion ranges of the tumor centroid in the superior-inferior (SI), anterior-posterior (AP), and left-right (LR) directions were measured on the transverse, sagittal, and coronal planes using a grid spacing of 1 mm for all eight phase bins registered by this software.

Target volume definitions

All datasets for planning CT and CBCT acquired for the first SBRT fraction were transferred to a commercial treatment-planning system (Pinnacle^3 version 8.0 m; Philips Medical Systems, Fitchburg, WI, USA), and, thereafter, the 4D CT and CBCT images were superimposed onto the modified slow CT images using an automated algorithm implemented in the Syntegra software package (Philips Medical Systems). The matched results were visually verified by reviewing the alignment of the spinal vertebrae. The GTVs in each of the eight phases of the 4D CT images and the GTV on the CBCT image were delineated by the same radiation oncologist using the lung window setting and were projected onto the modified slow CT image of the same slice.

We used the following to evaluate the ITVs and PTVs that were generated using different respiratory phases for target delineation and different setup margins: (i) the composite volume of the GTVs from all eight phases of the 4D CT (ITVall); (ii) the composite volume of the GTVs from the two extreme phases of the 4D CT (ITV2); (iii) the volume derived from the GTV on the CBCT image acquired for the first SBRT fraction (ITV_CBCT); (iv) the volumes generated by adding a 3 mm isotropic setup margin to ITVall and ITV2 (PTVall_3 mm and PTV2_3 mm); and (v) the volumes generated by adding a 5 mm isotropic setup margin to ITVall and ITV2 (PTVall_5 mm and PTV2_5 mm) (Table 1).

Volumetric and geometric analyses

Together with the absolute sizes of the ITVs and PTVs, the percentage of overlap volume (POV) between a pair of target volumes was measured to compare the geometric coverage of ITV2 or PTV2 with respect to the ITVall or PTVall. To

Table 1 Summary of the various ITVs and PTVs

Target volumes	Definition
ITVall	Volume generated by combining the GTVs from all 8 phases of 4D CT
ITV2	Volume generated by combining the GTVs from the 2 extreme phases of 4D CT
ITV_CBCT	Volume derived from the GTV on the CBCT image acquired for the first SBRT fraction
PTVall_3 mm	Volume generated by adding a 3 mm isotropic setup margin to the ITVall
PTV2_3 mm	Volume generated by adding a 3 mm isotropic setup margin to the ITV2
PTVall_5 mm	Volume generated by adding a 5 mm isotropic setup margin to the ITVall
PTV2_5 mm	Volume generated by adding a 5 mm isotropic setup margin to the ITV2

4D CT, four-dimensional computed tomography; CBCT, cone-beam CT; GTV, gross tumor volume; ITV, internal target volume; PTV, planning target volume; SBRT, stereotactic body radiation therapy.

evaluate the impact of the tumor parameters on the extent of geometric coverage, the POV values were correlated with tumor parameters, such as the mean GTV (mean value of the GTVs from all 8 phases), the 3D mobility, and the POV between the GTVs from the two extreme bins. The differences in POV were also compared within the tumor parameter groups, using a cut-off value. The geometric coverage of each planning volume was evaluated with respect to ITV_CBCT by determining the percentage of ITV_CBCT that was missed by the planning ITVs and PTVs and the number of tumors that exhibited any missing volume (>0%) for ITV_CBCT in each planning volume.

Dosimetric analysis

Three conformal SBRT plans for all 17 tumors were performed using three PTVs (PTVall_5 mm, PTV2_5 mm, and PTVall_3 mm) to assess the dosimetric effects on a normal lung that would result from the various target volumes. All plans used 10–14 coplanar and/or non-coplanar beams and were normalized such that 95% of the PTVs received the prescription doses. The dose-fractionation schedules were 48 Gy in four fractions (15 tumors), 56 Gy in four fractions (1 tumor), and 50 Gy in five fractions (1 tumor). The beam energies, weights, and gantry angles remained fixed for each tumor in the same beam configuration that was used for the actual patient treatment to allow for meaningful comparison. To ensure more realistic lung volume during treatment, the dose distributions were calculated on the modified slow CT images for all PTVs, with heterogeneity corrections applied using the Collapsed Cone Convolution Superposition algorithm. The dosimetric effects on a normal lung of SBRT planning using the three different PTVs were analyzed via

Table 2 Comparisons of the target volumes obtained using the different ITV and PTV definitions and the POVs between pairs

Absolute volume (cc, Mean ± SD)	ITVall	ITV2	PTVall_3 mm	PTV2_3 mm	PTVall_5 mm	PTV2_5 mm
All tumors (*n* = 17)	14.4 ± 9.3	12.3 ± 8.1	29.2 ± 16.0	26.3 ± 14.7	41.1 ± 20.7	37.5 ± 19.3
POV according to tumor groups (%, Mean ± SD)		ITVall and ITV2	PTVall_3 mm and PTV2_3 mm		PTVall_3 mm and PTV2_5 mm	PTVall_5 mm and PTV2_5 mm
All tumors (*n* = 17)		85.1 ± 6.3	89.8 ± 5.1		74.0 ± 3.8	91.3 ± 4.6
Mean GTV ≤ 10 cc (*n* = 10)		83.8 ± 7.7	89.0 ± 6.4		71.5 ± 2.9	90.5 ± 5.7
>10 cc (*n* = 7)		87.1 ± 3.2	90.9 ± 2.4		77.6 ± 0.7	92.3 ± 2.1
		(*P* = 0.329)	(*P* = 0.770)		(*P* = 0.001)	(*P* = 0.626)
3D ≤ 10 mm (*n* = 10)		87.4 ± 3.9	91.0 ± 2.7		73.5 ± 4.0	92.1 ± 2.5
>10 mm (*n* = 7)		81.9 ± 7.9	88.1 ± 7.3		74.8 ± 3.7	90.1 ± 6.6
		(*P* = 0.079)	(*P* = 0.380)		(*P* = 0.380)	(*P* = 0.922)
Mean GTV > 10 cc and/or 3D ≤ 10 mm (*n* = 13)		87.1 ± 3.7	91.0 ± 2.6		74.6 ± 4.1	92.3 ± 2.3
Mean GTV ≤ 10 cc and 3D > 10 mm (*n* = 4)		78.9 ± 9.5 (*P* = 0.042)	85.8 ± 9.3 (*P* = 0.213)		72.2 ± 2.3 (*P* = 0.174)	88.0 ± 8.4 (*P* = 0.365)

3D, three dimensional mobility; GTV, gross tumor volume; ITV, internal target volume; POV, percentage of overlap volume, defined as the percentage ratio between the overlapping and encompassing volume; PTV, planning target volume; SD, standard deviation.

lung-dose parameters, such as the mean lung dose (MLD) and the percentage volumes of both lungs minus the PTVs receiving specific doses of 5, 10, and 20 Gy (V5, V10, and V20) according to dose-volume histogram estimations.

Statistical analysis

To compare the volumetric and dosimetric differences between each pair of target volumes, the POVs, and the lung-dose parameters, we used the Wilcoxon signed-rank test for each tumor. The correlations between the tumor parameters and the POVs were evaluated via Spearman's correlation analysis. Additionally, differences in POVs between the tumor parameter groups were assessed using the Mann-Whitney test. All statistical analyses were performed using the SPSS software package (version 15.0; SPSS Inc., Chicago, IL, USA). Values of $P < 0.05$ were considered to be significant.

Results

Tumor characteristics

The mean of the GTVs from all eight phases in all patients was 9.2 ± 6.1 cm^3 (range: 1.9–24.7 cm^3). The tumor motions were most extensive in the SI direction (7.7 ± 5.9 mm) and were approximately 1.6-1.8 times greater in this direction than in the AP (4.9 ± 3.8 mm) and LR (4.4 ± 3.6 mm) directions. The mean 3D mobility for all 17 tumors, which was calculated as $(SI^2+AP^2+LR^2)^{1/2}$, was 10.2 ± 7.7 mm, and all lower lobe tumors had a 3D mobility of >10 mm. The POVs, which were defined as the percentage ratios between the overlapping and

encompassing volumes, between the GTVs from the two extreme bins for tumors with 3D mobilities of ≤10 mm (upper/middle lobe tumors, *n* = 10) and >10 mm (lower lobe tumors, *n* = 7) were $63.7 \pm 16.8\%$ and $36.4 \pm 22.8\%$, respectively ($P = 0.025$).

Volumetric and correlation analyses

Table 2 presents the measurements of the target volumes generated using different ITV and PTV definitions and the POVs between the pairs. The geometric coverage of ITV2 with respect to ITVall (the POV between ITV2 and ITVall) was $85.1 \pm 6.3\%$. However, when a setup margin was added or when the setup margin was increased, the value of the POV between the PTVall and PTV2 with the same setup margin also increased in all tumors ($P < 0.01$). With respect to PTVall_5 mm, the mean POV values for PTV2_5 mm, PTVall_3 mm, and PTV2_3 mm were $91.3 \pm 4.6\%$, $69.4 \pm 4.2\%$, and $62.3 \pm 5.2\%$, respectively. In the analysis of the correlation between the POV values and the tumor parameters, the POVs between ITVall and ITV2, between PTVall_3 mm and PTV2_3 mm, and between PTVall_5 mm and PTV2_5 mm did not exhibit significant correlations with any tumor parameters, such as the mean GTV, the 3D mobility, or the POV between the GTVs from the two extreme bins. Interestingly, for the tumors (*n* = 4) that had both high mobility (3D mobility > 10 mm) and a small volume (mean GTV ≤ 10 cm^3), although there was a significant difference in POV between the ITVs compared with the tumors (*n* = 13) that had low mobility and/or a large volume ($P = 0.042$), the differences in POV between the PTVs were not significant. Meanwhile, the POVs between PTVall_3 mm and
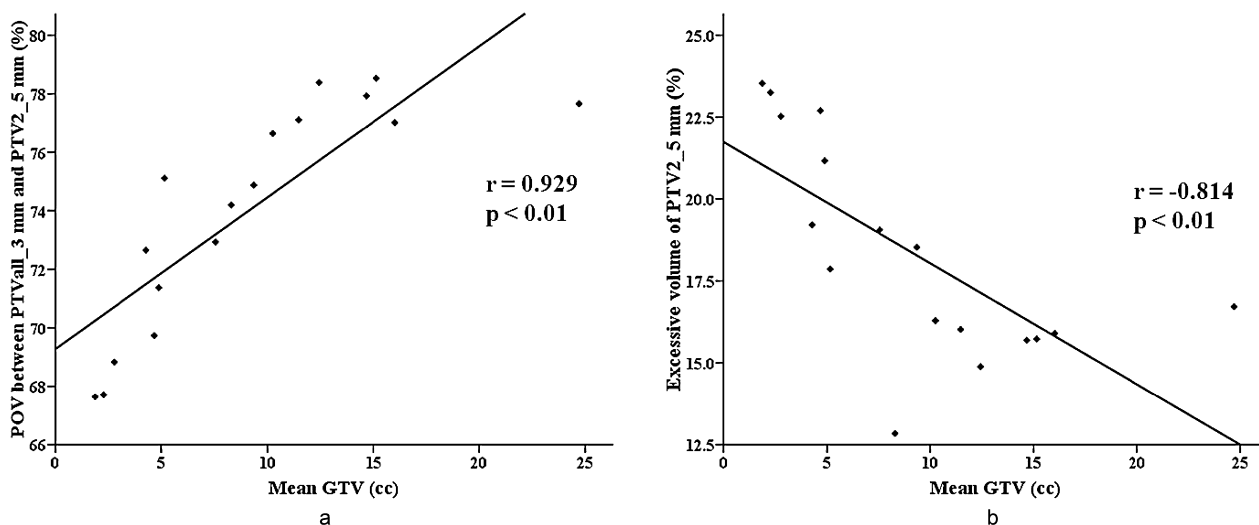
Figure 1 The relation between planning target volume (PTV)all_3 mm and PTV2_5 mm. (**a**) Correlations between the percentage of overlap volume (POV) between two PTVs and the mean gross tumor volume (GTV); (**b**) correlations between the excess volume of PTV2_5 mm with respect to PTVall_3 mm and the mean GTV. Here, r represents the correlation coefficient.

PTV2_5 mm were significantly correlated with the mean GTV, and this correlation was also strongly related to the difference in POV between the tumor parameter groups according to the mean GTV. Additionally, the excess volume of PTV2_5 mm with respect to PTVall_3 mm was $18.3 \pm 3.3\%$, which also decreased as the mean GTV increased, and a mean of 1.1% (range: 0.0–10.1%) of PTVall_3 mm was not encompassed in PTV2_5 mm (Fig 1).

Geometric coverage of the internal target volumes (ITVs) and planning target volumes (PTVs) with respect to the ITV generated from cone-beam computed tomography

The mean value of ITV_CBCT for all 17 tumors was 11.2 ± 8.2 cm^3 (range: 1.6–29.7 cm^3). On average, the volumes could be ranked in the following order: mean GTV (9.2 ± 6.1 cm^3), < ITV_CBCT (11.2 ± 8.2 cm^3), $\approx$ ITV2 (12.3 ± 8.1 cm^3), and < ITVall (14.4 ± 9.3 cm^3). Regarding the geometric coverage with respect to ITV_CBCT, the missing volumes of the ITVs (13.9–19.2% of ITV_CBCT) were significantly larger than those of the PTVs (0.7-2.9% of ITV_CBCT). Moreover, missing volumes (>0%) were observed in >70% of patients when using the ITVs (16 of the 17 tumors) or PTV2_3 mm (12 of the 17 tumors), whereas fewer instances (5–8 of the 17 tumors) of missing volumes were observed when using PTVall_3 mm or PTVs_5 mm (Table 3, Fig 2). Moreover, as a setup margin was added or as the setup margin was increased, the missing-volume differences between PTVall and PTV2 decreased, with values of $5.3 \pm 2.4\%$ between the ITVs, $0.5 \pm$ 0.9% between the PTVs_3 mm, and $0.2 \pm 0.5\%$ between the PTVs_5 mm.

Dosimetric analyses of the three plans based on the different PTV definitions

The comparisons of the lung-dose parameters for the three SBRT plans based on the different PTV definitions are summarized in Table 4. Although there were statistically significant differences in the lung-dose parameters between each pair of plans, the magnitudes of the absolute differences among the plans were relatively small. The V20 values for the plans that used PTVall_5 mm, PTV2_5 mm, and PTVall_3 mm were $6.77 \pm 2.65\%$, $6.54 \pm 2.63\%$, and $5.61 \pm$

Table 3 Geometric coverage of the planning ITVs and PTVs with respect to the ITV generated from CBCT

Target volumes	Percentage of ITV_CBCT missed by target volumes (%, Mean ± SD)	No. of tumors exhibiting any missing volumes with respect to ITV_CBCT
ITV2	19.2 ± 12.3	16/17 (94.1%)
ITVall	13.9 ± 11.7	16/17 (94.1%)
PTV2_3 mm	2.9 ± 5.5	12/17 (70.6%)
PTVall_3 mm	2.4 ± 4.7	8/17 (47.1%)
PTV2_5 mm	0.9 ± 2.1	6/17 (35.3%)
PTVall_5 mm	0.7 ± 1.6	5/17 (29.4%)

CBCT, cone-beam CT; ITV, internal target volume; PTV, planning target volume; SD, standard deviation.
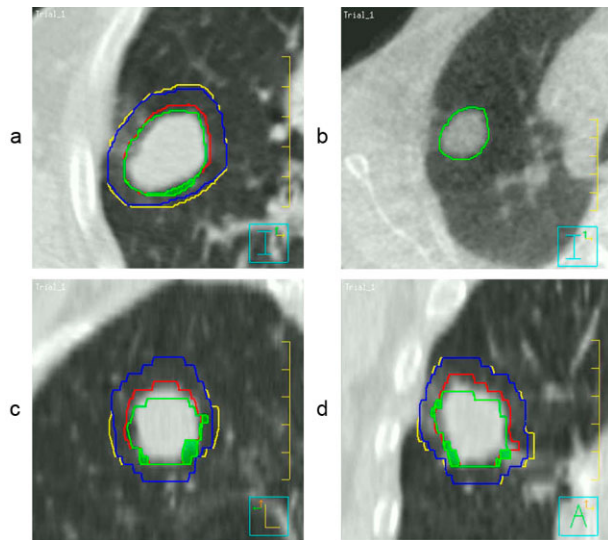
Figure 2 Example of the relations among the planning internal target volume (ITV) and planning target volume (PTV) and the ITV generated from cone-beam computed tomography (CBCT). (**a**) Transverse view of ITVall (red), ITV_CBCT (green), PTV2_5 mm (blue), and PTVall_5 mm (yellow) projected onto a modified slow CT scan; (**b**) delineation of ITV_CBCT on a CBCT image; (**c** and **d**) sagittal (**c**) and coronal (**d**) views of the target volumes. The geometric regions of ITV_CBCT that are missed by ITVall are displayed as green colored regions.

2.42%, respectively. Compared with the plans that used PTVall_5 mm and PTVall_3 mm, the average dose differences in the normal lung compared with the plan based on PTV2_5 mm were 0.10 Gy and 0.41 Gy, respectively, for the MLD and 0.22% and 0.93%, respectively, for V20.

Discussion

Because of its significant correlation ($r = -0.770$, $P < 0.01$) with the 3D mobility, the POV between the GTVs from the two extreme bins may be associated with the possibility of reliable ITV construction. If the GTVs for these bins are completely separated, the POV will be 0%, indicating a need for motion information from the middle portion. However, this

scenario is expected to be fairly rare because of the influence of the tumor volume factor on this POV, although the magnitude of respiration-induced tumor motion in the lung can be greater than 2 cm. In our study, the mean value of the POV between the GTVs from the two extreme bins was $52.5 \pm 23.4\%$ (range: 16.9–85.1%), with a mean value of 36.4% for lower lobe tumors. Indeed, the tumor with the lowest value in POV (16.9%), the highest 3D mobility (33.8 mm), and a relatively large GTV (14.7 cm³) had a high POV value of 82.2% between ITVall and ITV2 and even higher POV values between the PTVs (88.2% and 90.9% for 3 mm and 5 mm margins, respectively). In addition, the difference in POV between ITVall and ITV2 for tumors with POVs of ≥30% ($n = 13$) and <30% ($n = 4$) was not significant ($85.4 \pm 7.0\%$ vs. $84.4 \pm 4.0\%$, $P = 0.428$).

Other studies concerning target volumes have employed only the two extreme phases of the 4D CT scan. Ezhil *et al.*[9] reported results similar to ours in 17 patients with stage I lung tumors; they found that the ITVs based on the two extreme phases covered 83.9% of the ITVs generated using all 10 phases. Furthermore, Rietzel *et al.*[16] reported that 10 patients with stage I–III lung cancer exhibited a 93.7% overlap between the PTVs generated using only the two extreme tumor positions and those generated using 10 respiratory phases. Through correlation and subgroup analyses, we found that the geometric coverage of ITV2 or PTV2 with respect to the ITVall or PTVall with the same margin was consistent for all tumors, regardless of the tumor parameters, such as the GTV and the range of tumor motion. In combination with the observation of an increasing overlap ratio between PTVall and PTV2 as the setup margin was added or increased, the POVs for the tumors with both high mobility and a small volume were found to be not significantly different from those of other tumors when the overlap between two such PTVs was assessed after the 3 mm or 5 mm setup margin was added to the two ITVs. These findings indicate that the respiratory tumor motions were sufficiently reflected by ITV2, suggesting that target delineation based on the two extreme phases could be suitable even for small, highly mobile tumors.

Table 4 Absolute differences in the lung-dose parameters for the three SBRT plans ($n = 17$) based on the different PTV definitions

Parameters	PTVall_5 mm (Mean ± SD)	PTV2_5 mm (Mean ± SD)	PTVall_3 mm (Mean ± SD)	PTVall_5 mm vs. PTV2_5 mm		PTVall_5 mm vs. PTVall_3 mm		PTV2_5 mm vs. PTVall_3 mm	
				Mean (range)	P	Mean (range)	P	Mean (range)	P
MLD (Gy)	4.34 ± 1.14	4.24 ± 1.13	3.83 ± 1.06	0.10 (0.02–0.55)	0.000	0.51 (0.32–0.76)	0.000	0.41 (−0.04–0.69)	0.000
V5 (%)	19.73 ± 5.05	19.41 ± 5.08	17.89 ± 4.56	0.32 (−0.06–2.15)	0.001	1.84 (0.94–3.20)	0.000	1.52 (0.10–3.05)	0.000
V10 (%)	14.07 ± 3.83	13.81 ± 3.86	12.49 ± 3.58	0.26 (−0.05–2.06)	0.001	1.58 (0.95–2.61)	0.000	1.32 (−0.07–2.50)	0.000
V20 (%)	6.77 ± 2.65	6.54 ± 2.63	5.61 ± 2.42	0.22 (0.04–0.99)	0.000	1.15 (0.52–1.99)	0.000	0.93 (−0.23–1.83)	0.000

MLD, mean lung dose; PTV, planning target volume; SBRT, stereotactic body radiation therapy; V5, V10, and V20, percentage volumes of both lungs minus the PTVs receiving specific doses of 5, 10, and 20 Gy.

Because the acquisition spans several respiratory cycles over a long period of time, the free breathing CBCT image should generate an ITV that captures the full range of motion and represents the time-averaged position of the target.[17] However, some studies have reported that the ITVs generated from such a CBCT scan could underestimate the target volume because of disparities in breathing or image quality depending on the target location.[17,18] In our results, the mean ITV_CBCT was smaller than ITVall by 22% ($P < 0.01$). However, a mean of 13.9% of ITV_CBCT was not encompassed in ITVall, and some missing volume was observed in 16 patients, with values of >10% for nine of them. This discrepancy between the ITVs from MV-CBCT and from 4D CT may be attributable to a difference in target delineation caused by different tumor contrast in these different CT images and/or some residual error in the process of fusing the images with the modified slow CT images. Another possible explanation could be a change in tumor motion caused by breathing pattern variations, a difference in the tumor centroid position, or some difference in the nature of image acquisition and reconstruction between the two CT techniques. At our institution, a PTV for lung SBRT planning is typically constructed by adding a 5 mm setup margin to ITVall or ITV2, and a treating physician checks the fusion accuracy and the inclusion of the visualized target volume on the CBCT image within this PTV using Adaptive Targeting software (Siemens Medical Solutions), which offers an image registration algorithm that is similar to the fusion that is performed on the planning system. Although there could be some residual or intrafractional setup error, the PTVs_5 mm were found to almost completely cover the ITV_CBCT in this study, as demonstrated by the mean missing-volume value of <1%. More importantly, the differences in ITV_CBCT coverage between the PTVs based on all phases and the two extreme phases decreased as the setup margin was added or increased, and this result was related to the result of POV between two such PTVs according to the setup margin. Regarding the number of tumors that exhibited any missing volume with respect to ITV_CBCT, the use of PTV2_3 mm led to considerable missing volume in 70.6% of patients; therefore, we excluded this PTV in further dosimetric analysis. For the three other PTVs, more than 50% of the patients who exhibited any missing volume exhibited missing volumes of <1%.

Recent studies have suggested that the MLD and the percentage of the total lung volume receiving a specific dose could serve as the main dosimetric predictors of symptomatic radiation pneumonitis after SBRT. For MLD ≤ 5 Gy and/or V20 ≤ 5–10%, the risk of grade ≥ 2 radiation pneumonitis has been reported to be only 10–15% in most studies.[19–22] Therefore, when selecting appropriate PTVs for lung SBRT, the relations between the dosimetric benefits of a smaller PTV and the clinical risk of radiation pneumonitis should also be considered. When compared with PTVall_5 mm, the use of PTV2_5 mm resulted in a high POV (91.3%) as well as very small differences in the missing volume (0.2% difference) and in the number of tumors exhibiting any missing volume (1 tumor difference) with respect to ITV_CBCT; moreover, nearly the same results were obtained for the lung-dose parameters. Additionally, the use of PTV2_5 mm instead of PTVall_3 mm led to improved coverage with respect to ITV_CBCT, together with more similar volumetric results between them as the mean GTV increased. However, the effects on the lung-dose parameters caused by this increase in the PTV were relatively small, with average differences of <0.5 Gy for the MLD and <1% for V20.

Conclusion

In conclusion, when a setup margin of 3 mm or 5 mm was added to the ITV, the POV between the PTVs based on all phases and the two extreme phases of the 4D CT scan increased, while the difference in coverage with respect to ITV_CBCT decreased. The construction of the PTV by adding a 5 mm setup margin to the ITV generated based on only the two extreme phases, regardless of tumor characteristics, such as the tumor volume and motion range, may be a useful tool for reducing the clinical workload involved in target delineation in SBRT for lung cancer.

Disclosure

None of the authors reports any conflicts of interest.

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