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Multiphase-computed tomography-based target volume definition in conventional fractionated radiotherapy of lung tumors: dosimetric and reliable comparison with the technique using addition of generic margins

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ABSTRACT

Aims and background. The aim of the present study was to compare radiotherapeutic plans based on internal target volume determined by between multiphase computed tomography and addition of a generic margin in lung tumors and to evaluate the reliability of ITV determined by multiphase computed tomography during conventional fractionated radiotherapy.

Methods and study design. The radiotherapeutic plans based on internal target volume determined by between multiphase computed tomography and addition of a generic margin in 10 patients with lung tumors were applied. The difference of two planning target volumes (PTV) and irradiated dose and volume of normal lung tissue were compared. Weekly new targets were delineated on repeated computed tomography scans, and weekly dose coverage of clinical target volume under two different treatment plans was evaluated.

Results. For all patients, PTV_{3CT} volume based on multiphase computed tomography was significantly smaller than that of PTV_{con} based on addition of a generic margin ($t = 6.831$, $P < 0.001$). The volume receiving more than 20 Gy in $Plan_{3CT}$ and $Plan_{con}$ was 16.7 ± 5.2% and 20.0 ± 5.2% ($t = 7.565$, $P < 0.001$), the volume receiving more than 5 Gy was 36.6 ± 7.2% and 42.7 ± 6.4% ($t = 7.459$, $P < 0.001$), and mean lung dose was 1037.5 ± 275.0 cGy and 1246.8 ± 271.0 cGy ($t = 8.078$, $P < 0.001$), respectively. Both $Plan_{3CT}$ and $Plan_{con}$ provided a satisfactory clinical target volume coverage weekly during conventional fractionated radiotherapy for 6-7 weeks, and the ratio of the volume receiving the prescription dose was 1.03 ± 0.02 and 1.04 ± 0.02, respectively.

Conclusions. The radiotherapeutic plan based on internal target volume determined by multiphase computed tomography can ensure weekly target coverage during conventional fractionated radiotherapy in lung tumors, and it is better than the plan based on the addition of generic internal target volume, which can effectively reduce normal lung tissue irradiation.

Introduction

It is well known that thoracic tumors exhibit significant intra-fractional motion due to respiration[1-4]. More than 2.5 cm tumor movement has been reported for lung cancer patients during a respiration cycle[5-7]. Tumor motion can lead to a geometric miss and consequent tumor under-dosage if it has not been properly managed during radiotherapy[8,9]. To address tumor motion, the International Commission on Radiation Units Report 62 introduced the concept of internal target volume (ITV)[8]. The traditional way to account for tumor motion is to add a safety generic margin

Key words: conventional radiotherapy, internal target volume, lung neoplasm, tumor motion.

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(on the order of 1-2 cm for lung tumors) to the clinical target volume (CTV) to get the planning target volume (PTV)[10,11]. However, many investigators have suggested that an individualized margin should be generated based on patient-specific tumor motion, which helps to improve the target dose coverage during radiotherapy[12-14].

Recent advances in imaging technology using four-dimensional (4D) computed tomography (CT) have made it possible to determine a reliable patient-specific tumor motion[3,14,15]. However, there has been some limited availability for clinical use in many radiotherapeutic centers[14]. Some investigators use multiphase CT scans taken during free breathing, end inspiration and end expiration to account for patient-specific tumor motion. The scans are fused for treatment planning[11,14,16]. Some research results have suggested that the simpler technique using multiphase CT scans may provide an acceptable alternative to 4D CT to determine patient-specific tumor motion[3,14].

Wang *et al.*[3] found that compared to the conventional approach using helical images for target definition, 4D CT and multiphase CT both had the advantage of providing patient-specific tumor motion, based on which the designed PTV could ensure daily target coverage in hypofractionated stereotactic body radiotherapy (SBRT) of lung cancer. However, the reliability of patient-specific ITV determined by multiphase CT is inconclusive during conventional fractionated radiotherapy for 6-7 weeks in lung tumors.

In the present study, we compared radiotherapeutic plans based on ITV determined by between multiphase CT and addition of a generic margin in lung tumors and evaluated the reliability of ITV determined by multiphase CT during conventional fractionated radiotherapy for 6-7 weeks.

Material and methods

Patients

Approval for the current project was obtained from the local ethics committee together with written informed consent from each patient. Ten patients with lung tumors were recruited for the study between August 2009 and June 2010. The patients who had pleural effusion, pleural adhesion, atelectasis and obstructive pneumonia were excluded from the study. Patient characteristics are summarized in Table 1.

All patients went on to receive either radical radiotherapy or high-dose palliative radiotherapy. Radiotherapy was administered five times a week at 2 Gy/day. The prescribed total dose for non-small cell lung cancer and pulmonary metastases was 70 Gy. The prescribed total dose was 60 Gy to small cell lung cancer. Four patients received chemotherapy concurrently.

Table 1 - Patient characteristics

Characteristics	No. of patients
Patients	10
Age (yr), median (range)	67 (52-78)
Gender	
Male	9
Female	1
Tumor type	
Primary lung cancer	8
Pulmonary metastases	2
Tumor location	
Upper pulmonary lobe	8
Middle pulmonary lobe	1
Lower pulmonary lobe	1
Lymph node metastases of the mediastinum	
Yes	4
No	6

CT scanning protocol, target volume generation and treatment planning before radiotherapy

Before undergoing the CT scanning protocol, each patient underwent an individual coaching session with a radiation oncologist according to the description by Hughes *et al.*[14] Briefly, it consisted of: 1) explaining the rationale behind the protocol with the aid of diagrams; 2) explaining the instructions for normal breathing and end-tidal breath holds (inspiration and expiration); 3) assessing how long the patient could comfortably hold their breath to help to determine the time for the breath-hold CT; 4) a practice run with the patient lying on a couch in the CT scanning position; 5) the patients were also instructed to try to breathe regularly throughout their treatment, i.e. avoiding deep-breath holding, and atypically large tidal volumes. After receiving the coaching session, the patient would be able to fulfill the protocol satisfactorily.

All patients were positioned supine and immobilized in a body cushion with their arms raised above their heads. For each patient, a helical CT scan was acquired under normal free breathing followed by two breath-hold helical CT scans taken at end-inspiration and expiration. The slice thickness of CT scans was 5 mm for all patients.

For each patient, the gross tumor volume (GTV) was delineated in all three scans by an experienced radiation oncologist. Treatment plans were performed using two different methods: 1) One is the $Plan_{3CT.}$ The GTV from all three scans were superimposed to form GTV_{3CT}. A clinical target volume (CTV_{3CT}) was defined by GTV_{3CT} plus an isotropic margin for each direction of 8 mm to account for microscopic spread. Furthermore, a planning target volume (PTV_{3CT}) was performed by CTV_{3CT} plus an isotropic margin of 5 mm to account for repositioning inaccuracies in all directions; 2) another is the $Plan_{con.}$ The GTV under normal free breathing was defined by GTV_{con}. A CTV_{con} was defined by GTV_{con} plus an isotropic margin for each direction of 8 mm, and a PTV_{con}

was performed by CTV_{con} plus a generic margin for longitudinal direction of 15 mm and axial direction of 10 mm according to the experience from St. Thomas' Hospital[3]. Two treatment plans dedicated to $Plan_{3CT}$ and $Plan_{con}$ were generated for each patient by a three-dimensional conformal radiotherapy technique. Planning parameters including beam numbers and angles were kept constant to allow for accurate comparison. In the study, we recommended comparison of parameters GTV and PTV for the radiation target and V_{20} (volume receiving more than 20 Gy), V_5 (volume receiving more than 5 Gy) and mean lung dose (MLD) for normal lung tissue between $Plan_{3CT}$ and $Plan_{con}$. The difference was tested by the paired *t*-test.

Weekly CT scanning protocol, target delineation and dose coverage during conventional fractionated radiotherapy

Each patient received CT scanning every week randomly. The weekly helical CT scan was acquired under normal free breathing, and the weekly GTV was delineated. The weekly CTV was generated by the weekly GTV plus an isotropic margin for each direction of 8 mm. Furthermore, we superimposed $Plan_{3CT}$ and $Plan_{con}$ onto the weekly CT images to investigate dose coverage for each weekly CTV. The ratios of Vp of the weekly CTV was recommended to evaluate the reliability of $Plan_{3CT}$ and $Plan_{con}$ during conventional fractionated radiotherapy in lung tumors.

Results

Comparison between $Plan_{3CT}$ and $Plan_{con}$ before radiotherapy

We first compared GTV between $Plan_{3CT}$ and $Plan_{con.}$ As seen in Figure 1, the GTV_{3CT} for each patient is larger than the GTV_{con}. The percentage of the mean GTV_{3CT} was 151.2% (range, 116.6-228.9%) compared to that of GTV_{con} in all patients. However, the PTV_{3CT} for each patient is smaller than the PTV_{con} (Figure 2). PTV_{3CT} and PTV_{con} was 262.3 ± 170.5 and 374.2 ± 212.0 cm^3, respectively. A paired *t*-test confirmed that the difference was statistically significant ($t = 6.831$, $P < 0.001$).

The V_{20}, V_5, and MLD of normal lung tissue in $Plan_{3ct}$ and $Plan_{con}$ for all patients are summarized in Table 2. As seen in the Table, the V_{20} in $Plan_{3CT}$ and $Plan_{con}$ was 16.7 ± 5.2% and 20.0 ± 5.2%, respectively ($t = 7.565$, $P < 0.001$; Figure 3). The V_5 in $Plan_{3CT}$ and $Plan_{con}$ was 36.6 ± 7.2% and 42.7 ± 6.4%, respectively ($t = 7.459$, $P < 0.001$; Figure 3). The MLD in $Plan_{3CT}$ and $Plan_{con}$ was 1037.5 ± 275.0 and 1246.8 ± 271.0 cGy ($t = 8.078$, $P < 0.001$; Figure 4).

Weekly target coverage of $Plan_{3CT}$ and $Plan_{con}$

The weekly GTV for each patient was delineated in the weekly helical CT images acquired under normal free breathing. As seen in Figure 5A, the weekly GTV of each patient changed during conventional fractionated radiotherapy. The statistic results showed that the weekly GTV of all patients decreased gradually. The mean GTV in the last week was 48.9% (range, 31.6-73.9) compared to that of GTV_{con} before radiotherapy in all patients (Figure 5B). Moreover, $Plan_{3CT}$ and $Plan_{con}$ were superimposed onto the weekly CT images to investigate dose coverage for each CTV, respectively. V_p was 1.03 ± 0.02 and 1.04 ± 0.02 for $Plan_{3CT}$ and $Plan_{con}$, respectively (Figure 6). It was suggested that both $Plan_{3CT}$ and $Plan_{con}$ had good weekly CTV coverage.

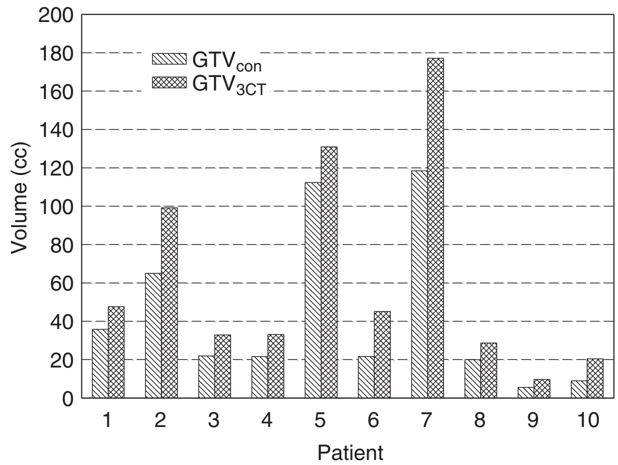

Figure 1 - Comparison of volumes between GTV_{3CT} based on multiphase CT scans and GTV_{con} based on CT scan in normal breathing. The GTV_{3CT} for each patient is larger than the GTV_{con} in 10 consecutive patients treated with conventional radiotherapy. GTV, gross tumor volume; CT, computerized tomography.

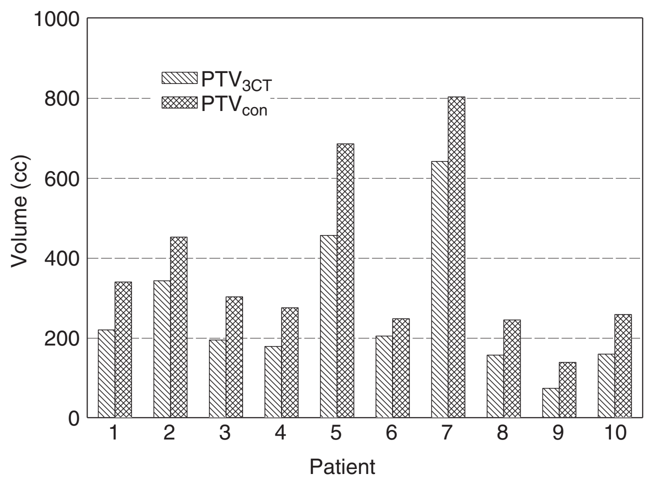

Figure 2 - Comparison of volumes between PTV_{3CT} based on multiphase CT scans and PTV_{con} based on addition of a generic margin. The PTV_{3CT} for each patient is smaller than the PTV_{con} in 10 consecutive patients treated with conventional radiotherapy. PTV, planning target volume; CT, computerized tomography.

Table 2 - V_{20}, V_5 and mean lung dose (MLD) of normal lung tissue in $Plan_{3CT}$ and $Plan_{con}$ for all patients

Patient no.	V_{20} (%)		V_5 (%)		MLD (cGy)	
	$Plan_{3CT}$	$Plan_{con}$	$Plan_{3CT}$	$Plan_{con}$	$Plan_{3CT}$	$Plan_{con}$
1	10.63	13.07	28.41	33.56	753	923
2	15.13	20.19	48.80	54.58	1170	1425
3	21.98	26.17	43.14	45.67	1206	1449
4	15.01	20.16	33.99	42.46	889	1227
5	20.83	24.71	35.71	42.17	1236	1511
6	18.97	19.80	41.80	43.70	1230	1274
7	26.11	28.36	42.70	48.59	1529	1680
8	11.26	13.44	29.02	35.15	749	904
9	11.44	15.09	27.83	36.95	698	938
10	15.77	18.99	34.64	44.56	915	1137
Mean ± SD	16.71 ± 5.15	20.00 ± 5.23	36.60 ± 7.22	42.74 ± 6.35	1037.5 ± 275.0	1246.8 ± 271.0
T	7.565		7.459		8.078	
P	<0.001		<0.001		<0.001	

V_{20}, volume receiving more than 20 Gy; V_5, volume receiving more than 5 Gy; SD, standard deviation.

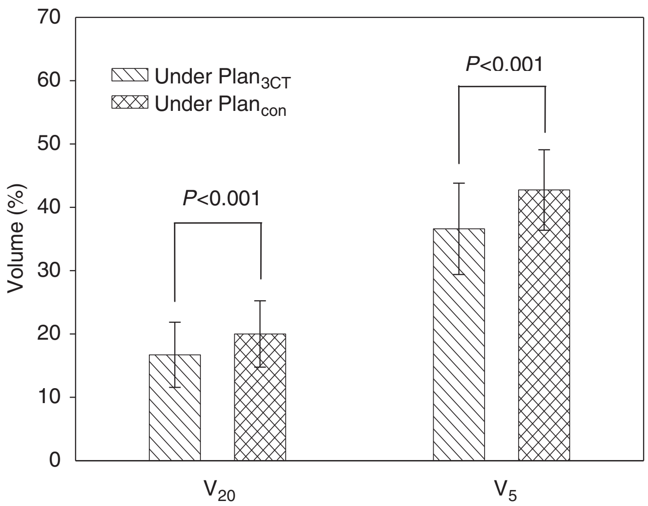

Figure 3 - The V_{20} and V_5 of $Plan_{3CT}$ were significantly lower than those of $Plan_{con}$. V_{20}, volume receiving more than 20 Gy; V_5, volume receiving more than 5 Gy.

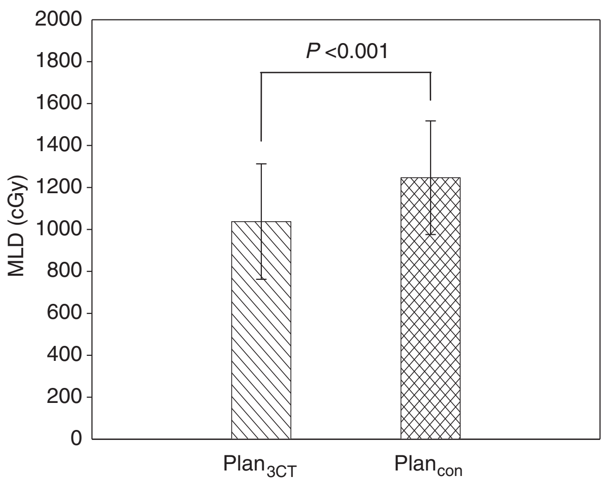

Figure 4 - The MLD of $Plan_{3CT}$ was lower than that of $Plan_{con}$. MLD, mean lung dose.

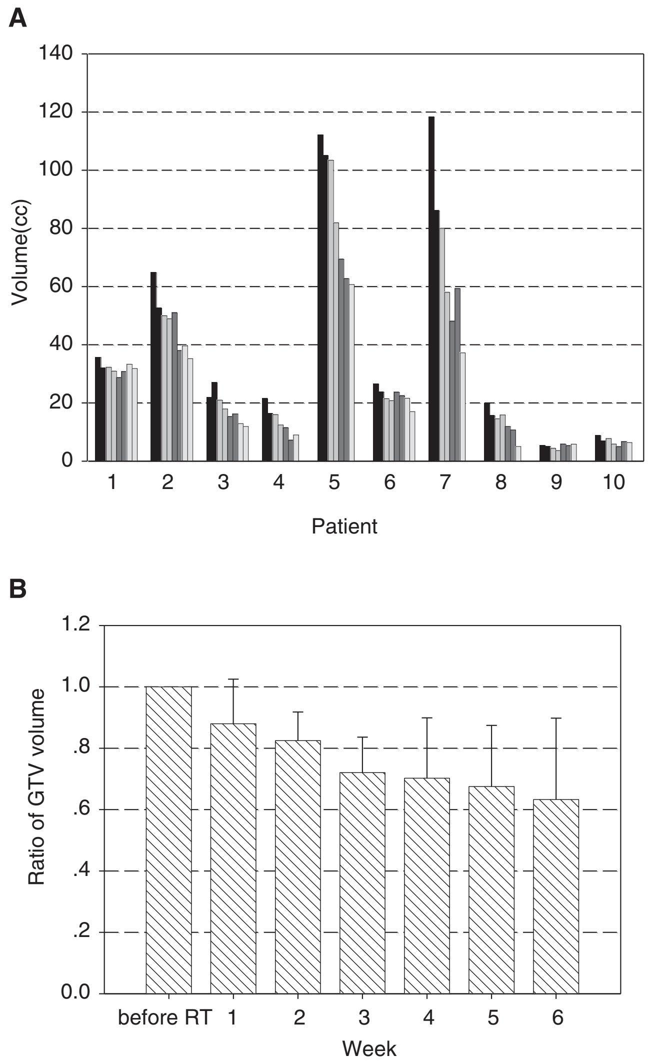

Figure 5 - A) The weekly GTV of each patient changed during conventional radiotherapy in 10 consecutive patients. B) The weekly GTV of all patients decreased gradually during conventional radiotherapy compared to the GTV before radiotherapy. GTV, gross tumor volume.

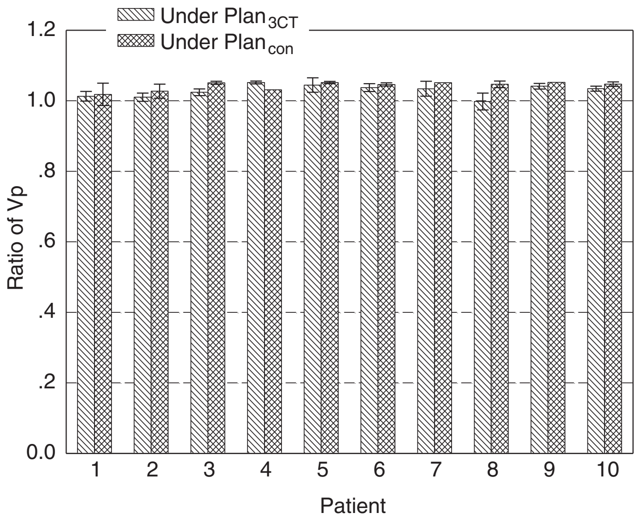

Figure 6 - The ratios of weekly V_p of $Plan_{3CT}$ and $Plan_{con}$ were more than 1.0. It was suggested that $Plan_{3CT}$ and $Plan_{con}$ both had good weekly CTV coverage. V_p, volume receiving the prescription dose; CTV, clinical target volume.

Discussion

Thoracic tumors exhibit significant intra-fractional motion due to respiration[1-4]. Ekberg *et al.*[17] found that the average GTV movement with quiet respiration was about 2.4 mm in the medio-lateral and dorso-ventral directions, and movement in the cranio-caudal direction was on average 3.9 mm with a range of 0-12 mm. In the present study, we found that the percentage of mean GTV_{con} was 151.2% (range, 116.6-228.9) compared to that of GTV_{3CT} in all patients. This result further confirms that significant tumor motion exists during radiotherapy for lung cancer.

How to manage a mobile tumor during radiotherapy is an interesting issue for radiation oncologist. The most commonly adopted technique is to apply an internal margin to the segmented tumor that incorporates its motion[14]. The traditional way to account for tumor motion is to add a safety generic margin (on the order of 1-2 cm for lung tumors) to the CTV to get the PTV[10,11]. However, if a large generic ITV is defined, it may increases the amount of normal tissue in the field, which could lead to an increased toxicity. Conversely, if a small ITV is defined, potentially insufficient irradiation doses are delivered to the tumor, as tumor mobility may extend beyond the previously targeted region[18-20]. Many investigators have therefore suggested that individualized margins should be generated based on patient-specific ITV, which helps to improve the target dose coverage during radiotherapy[12-14].

In the present study, we used a straightforward technique of three multiphase CT scans for generating a patient-specific ITV. The results showed that the PTV_{3CT} based on multiphase CT was significantly smaller than the PTV_{con} based on addition of a generic margin (P <0.001). Hughes *et al.*[14] also found that the patient-specific ITV based on multiphase CT was markedly smaller than the ITV based on addition of a generic margin, with a mean volume that was almost half of the ITV based on addition of a generic margin. At the same time, our study also revealed that V_{20} and V_5 of $Plan_{3CT}$ were both significantly lower than those of $Plan_{con}$ (P <0.001), and the MLD of $Plan_{3CT}$ was lower than that of $Plan_{con}$ (P <0.001). Wang *et al.*[3] found that 4D CT and three multiphase CT can reduce the amount of normal lung being irradiated compared to the conventional approach using addition of a generic margin. These research results suggested that the patient-specific definition of ITV was more reasonable than that of generic experience.

We further studied the reliability of ITV determined by multiphase CT during conventional fractionated radiotherapy for 6-7 weeks. Wang *et al.*[3] found that the designed PTV based on 4D CT and multiphase 3D CT could ensure daily target coverage in SBRT for lung cancer. However, tumor shape and size did not need to be considered because the period of SBRT is too short (only four fractions). Conversely, lung tumor shape and size may change significantly during conventional fractionated radiotherapy for 6-7 weeks. Kupelian *et al.*[21] found that tumor regression of non-small-cell lung cancer decreased by 1.2% (range, 0.6%-2.3%) everyday during treatment. In our study, we found that the weekly GTV of all patients decreased gradually during conventional radiotherapy. The mean GTV in the last week of radiotherapy was 48.9% (range, 31.6-73.9) compared to the GTV before radiotherapy. Furthermore, PTV based on multiphase CT and addition of a generic margin could ensure weekly target coverage in conventional radiotherapy for 6-7 weeks.

In conclusions, the radiotherapeutic plan based on ITV determined by multiphase CT can ensure weekly target coverage during conventional fractionated radiotherapy of lung cancer, and it is better than the plan based on addition of generic ITV, which can effectively reduce normal lung tissue irradiation.

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