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ORIGINAL ARTICLE

Dosimetric consequences of tumor volume changes after kilovoltage cone-beam computed tomography for non-operative lung cancer during adaptive intensity-modulated radiotherapy or fractionated stereotactic radiotherapy

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Abstract

Objective The aim of this study was to investigate tumor volume changes with kilovoltage cone-beam computed tomography (kV-CBCT) and their dosimetric consequences for non-operative lung cancer during intensity-modulated radiotherapy (IMRT) or fractionated stereotactic radiotherapy.

Methods Eighteen patients with non-operative lung cancer who received IMRT consisting of 1.8–2.2 Gy/fraction and five fractions per week or stereotactic radiotherapy with 5–8 Gy/fraction and three fractions a week were studied. kV-CBCT was performed once per week during IMRT and at every fraction during stereotactic radiotherapy. The gross tumor volume (GTV) was contoured on the kV-CBCT images, and adaptive treatment plans were created using merged kV-CBCT and primary planning computed tomography image sets. Tumor volume changes and dosimetric parameters, including the minimum dose to 95% (D_{95}) or 1% (D_1) of the planning target volume (PTV), mean lung dose (MLD), and volume of lung tissue that received more than 5 (V_5), 10 (V_{10}), 20 (V_{20}), and 30 (V_{30}) Gy were retrospectively analyzed.

Results The average maximum change in GTV observed during IMRT or fractionated stereotactic radiotherapy was –25.85% (range, –13.09% – –56.76%). The D_{95} and D_1 of PTV for the adaptive treatment plans in all patients were not significantly different from those for the initial or former adaptive treatment plans. In patients with tumor volume changes of >20% in the third or fourth week of treatment during IMRT, adaptive treatment plans offered clinically meaningful decreases in MLD and V_5, V_{10}, V_{20}, and V_{30}; however, in patients with tumor volume changes of < 20% in the third or fourth week of treatment as well as in patients with stereotactic radiotherapy, there were no significant or clinically meaningful decreases in the dosimetric parameters.

Conclusion Adaptive treatment planning for decreasing tumor volume during IMRT may be beneficial for patients who experience tumor volume changes of >20% in the third or fourth week of treatment.

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Key words: lung cancer; kilovoltage cone-beam computed tomography (kV-CBCT); intensity-modulated radiotherapy (IMRT); stereotactic radiotherapy; tumor changes; adaptive planning

Lung cancer has become the most common cancer and the leading cause of cancer-related death in China [1]. Radiotherapy is commonly considered the main therapeutic modality for non-operative lung cancer. During the course of radiation treatment, tumor regression has been observed using electronic portal images, repetitive computed tomography (CT) scanning, and mega-voltage CT (MVCT) [2–5]. Adaptive radiotherapy for tumor volume changes, in which one adjusts a treatment plan to account for patient anatomical variations over a treatment course, has been proposed to improve tumor dose coverage or better spare normal structures [6]. However, adaptive planning is a very time-consuming process that may increase resource utilization and physician work-

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Table 1 Patient and treatment characteristics

Patient No.	Age (y) / Sex	Histology	Stage	Prescription dose / frations	kV-CBCT fractions	Initial GTV (mL)	Maximum GTV changes (%)
1	55 / M	NSCLC	T2N0M0	60 Gy / 30 F	6	74.7	–56.76
2	60 / M	NSCLC	T2N0M0	62 Gy / 31 F	6	33.1	–38.36
3	62 / F	NSCLC	T2N0M0	60 Gy / 30 F	6	103.2	–32.75
4	63 / M	Sq	T2N0M0	60 Gy / 30 F	6	42.0	–26.91
5	49 / M	NSCLC	T2N0M0	63 Gy / 31 F	6	59.3	–14.67
6	64 / F	NSCLC	T2N0M0	60 Gy / 30 F	6	38.2	–13.09
7	65 / F	Sq	T2N0M0	64 Gy / 32 F	6	85.4	–20.32
8	62 / M	NSCLC	T2N0M0	60 Gy / 30 F	6	117.5	–13.45
9	66 / M	Sq	T2N0M0	60 Gy / 30 F	6	156.4	–29.54
10	66 / M	NSCLC	T2N0M0	60 Gy / 30 F	6	177.2	–28.05
11	78 / F	Sq	T2N0M0	62 Gy / 31 F	6	123.4	–30.95
12	82 / M	Ad	T2N0M0	60 Gy / 31 F	6	78.2	–48.59
13	74 / M	NSCLC	T2N0M0	60 Gy / 30 F	6	97.3	–38.23
14	69 / M	NSCLC	T1N0M0	64 Gy / 8 F	8	18.1	–13.81
15	70 / M	NSCLC	T1N0M0	56 Gy / 8 F	8	21.9	–15.52
16	71 / F	Ad	T1N0M0	60 Gy / 8 F	8	26.4	–15.91
17	77 / M	NSCLC	T2N0M0	50 Gy / 10 F	10	41.3	–13.80
18	68 / F	NSCLC	T1N0M0	64 Gy / 8 F	8	12.3	–14.63
Mean	67					72.55	–25.85
SD	8					47.4	12.84

Note: M = male; F = female; NSCLC = non-small cell lung cancer; Sq = squamous cell; Ad = adenocarcinoma

load. Of the patients with lung cancer who are receiving radiation therapy, it is unknown who could benefit from adaptive planning for tumor shrinkage and when should it be implemented during the treatment course. In the present study, we investigated tumor volume changes using kilovoltage cone-beam CT (kV-CBCT) during intensity-modulated radiotherapy (IMRT) or fractionated stereotactic radiotherapy and analyzed their dosimetric consequences. We found that patients who had tumor volume changes of > 20% in the third or fourth week of treatment could benefit from adapted planning.

Patients and methods

Patients

Between December 2012 and November 2013, 18 patients with non-operative lung cancer were treated with IMRT (13 patients) or fractionated stereotactic radiotherapy (five patients) at Renmin Hospital of Wuhan University, China. All of these patients had histologically or cytologically proven lung cancer. Their median age was 66 years (range, 49–82 years). All patients had a World Health Organization performance status of 0 or 1. The patient characteristics were described in Table 1. The study was approved by the Wuhan University Committee on Human Resources.

Patient simulation and treatment planning

Each patient was immobilized in the supine position using a thermoplastic mask fixation system combined with a HipFix board (Med-Tec, Inc.). The mask perfectly followed the body contour without any free space between the patient's body and the mask. While breathing quietly, the patients were scanned in the treatment position by a high-speed spiral CT scanner (General Electric Medical Systems) from the fifth cervical vertebra to the second lumbar vertebra with contiguous 3-mm slices.

The planning CT images were transferred to an eclipse planning system 10.0 (Varian Medical Systems, Inc.) via a DICOM link. The gross tumor volumes (GTVs) were delineated on each image set. The GTVs were expanded uniformly by 0.8–1.2 cm to obtain the planning target volumes (PTVs). Normal tissues of interest including the spinal cord, lungs, heart, and esophagus were outlined depending on the proximity to the target volume. Thirteen patients received IMRT with a total dose of 60–64 Gy in 30–32 fractions of 1.8–2.0 Gy/fraction in five fractions per week; five patients underwent stereotactic radiotherapy with a total dose of 50–64 Gy in 7–10 fractions of 5–8 Gy/fraction in three fractions per week. All treatments were performed on a Varian Clinac 23iX (Varian Medical Systems, Inc.).

KV-CBCT and adaptive treatment planning

Patients underwent the kV-CBCT on a Varian Onboard Imaging system (Varian Medical Systems, Inc.) using a full-fan mode once every five fractions (weekly) during IMRT and at every fraction during stereotactic radiotherapy. For the kV-CBCT projection images, the

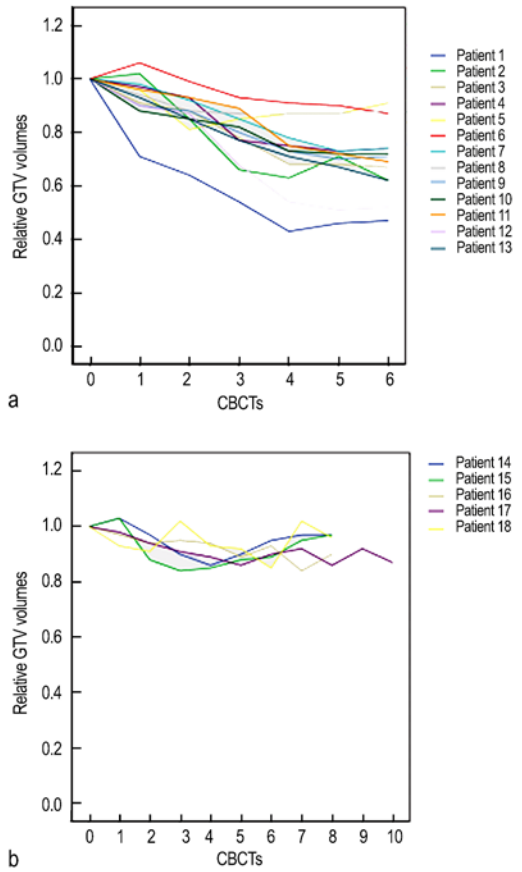

Fig. 1 Gross tumor volume (GTV) changes for patients treated with intensity-modulated radiotherapy (a) or fractionated stereotactic radiotherapy (b). CBCT, cone-beam computed tomography

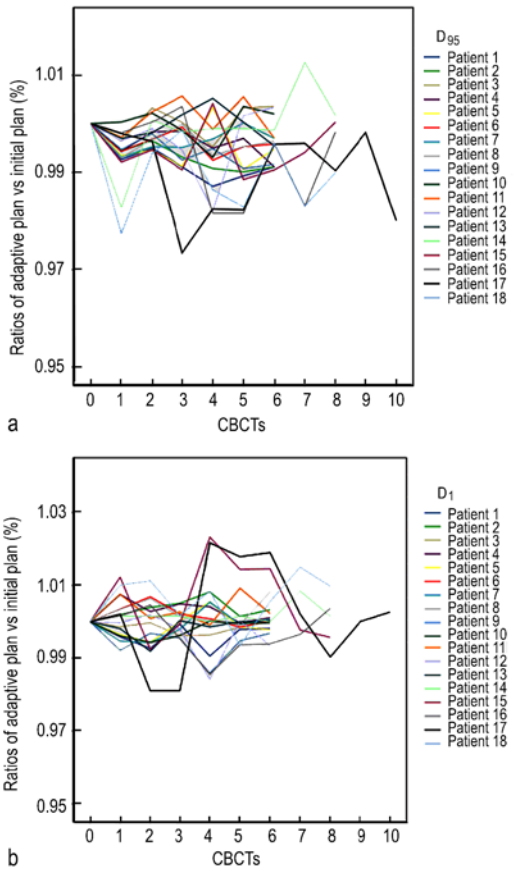

Fig. 2 Changes in D_{95} and D_1 of the planning target volume (PTV) for adaptive treatment plans in all patients. D_{95}, 95% of the PTV; D_1, 1% of the PTV; CBCT, cone-beam computed tomography

source to axis and source to detector distances were 100 cm and 150 cm, respectively. The detector size was 35 cm × 16 cm with a resolution of 512 × 512 pixels.

After the kV-CBCT images were imported into the Eclipse treatment planning system, the lung (partial since CBCT scanning cannot cover the entire lung) and the GTV were re-contoured. The kV-CBCT images were then fused with the primary planning CT images to replace their corresponding section. Adaptive treatment planning was created with reference to the primary treatment plan.

Dosimetric parameters

The minimum doses to 1% or 95% of the PTV volume (D_1 and D_{95}, respectively), along with mean lung dose (MLD), volume of lung tissue that received more than 5, 10, 20, and 30 Gy (V_5, V_{10}, V_{20}, and V_{30}), were calculated based on every adaptive treatment plan. Dose changes of more than 5% in D_1, D_{95}, and MLD or volume changes of > 10% in V_5, V_{10}, V_{20}, and V_{30} were considered clinically meaningful between two relevant treatment plans.

Statistical analysis

Data were analyzed using SPSS 14.0 software and a Wilcoxon matched-pairs test. A probability value ≤ 0.05 was considered significant.

Results

Tumor volume changes

As described in Table 1, the average initial GTV for the 18 patients was (72.55 ± 47.4) cm^3. Average maximal changes in GTV observed during IMRT or fractionated stereotactic radiotherapy were –25.85% (range, –13.09% to –56.76%). The trends of GTV changes were shown in Fig. 1. The majority of patients treated with IMRT showed a substantial decrease in tumor volume in the third or fourth week of treatment, followed by a plateau or slight increase; however, the all patients treated with stereotactic radiotherapy and a few patients treated with IMRT experienced variable tumor volume changes with no obvious decreasing trend.

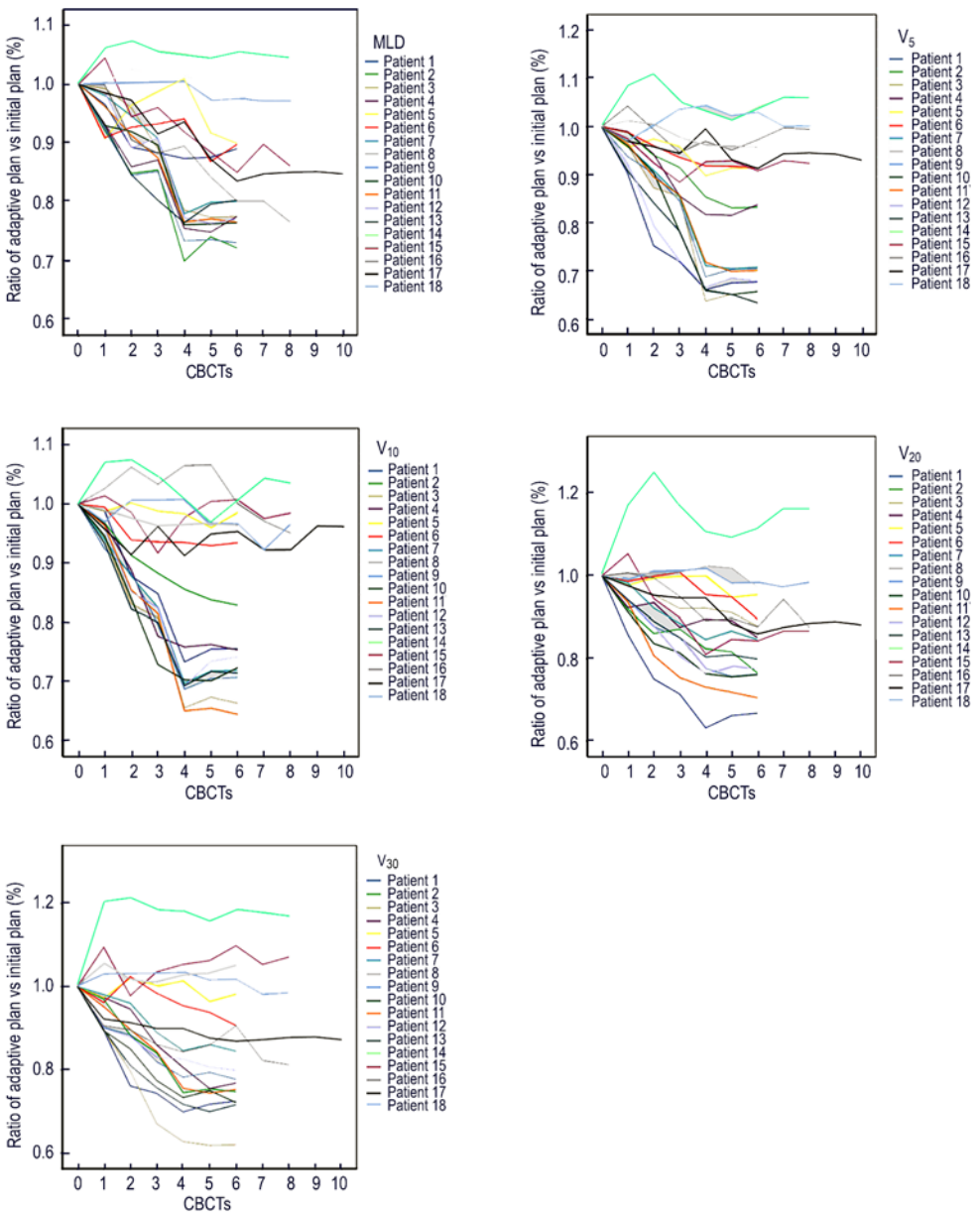

Fig. 3 Changes in mean lung dose (MLD) and volume of lung tissue that received more than 5 (V_5), 10 (V_{10}), 20 (V_{20}), and 30 (V_{30}) Gy for the adaptive treatment plans in all patients

Changes in dosimetric parameters for adaptive treatment plans

Although substantial changes in GTV were observed during the treatment course, there was no significant difference (< 5% of the initial plan) in D_{95} or D_1 of PTV between for the initial and adaptive treatment plans (all P > 0.1) in any of the patients (Fig. 2).

As shown in Fig. 3, clinically meaningful decreases in MLD and V_5, V_{10}, V_{20}, and V_{30} were observed in some patients in the third or fourth week of treatment during IMRT compared with the initial plans or adaptive treatment plans of the first two weeks; thereafter, a slight increase was seen in the fifth or sixth week. However, in the patients treated with stereotactic radiotherapy, there were no significant or clinically meaningful decreases in the above parameters. Those patients who showed clinically meaningful decreases in the above parameters had maximal changes in GTV in the third or fourth week of treatment, and the changes in GTV ranged from –19.3% to –56.76%; however, in the patients without clinically meaningful decreases in the above parameters, the maximum changes in GTV were –13.09% to –15.91%. These

facts suggest that adaptive planning for tumor changes can yield clinically meaningful sparing of normal structures without detrimental effects on PTV dose provided that the maximum changes in GTV reach 20% or more in the third or fourth week of treatment.

Discussion

Tumor regression was studied in patients with lung cancer during the course of radiation treatment in several previous studies using various imaging modalities, such as electronic portal imaging, repetitive CT scanning, MVCT, and kV-CBCT. Erridge *et al* assessed tumor shrinkage in 25 patients with non-small cell lung cancer (NSCLC) during three-dimensional conformal radiotherapy using electronic portal images and showed that 40% of the patients had a projected area tumor regression of > 20% in at least one projection [3]. Juhler-Nøttrup *et al* evaluated 10 patients with locally advanced NSCLC using repetitive CT scanning and found a significant tumor reduction of 19% for lung tumors and 34% for mediastinal lymph node tumors during the course of radiation treatment [4]. MVCT and kV-CBCT were also utilized to quantitatively assess tumor shrinkage throughout the radiation treatment in patients with lung cancer and showed that some patients had a very large tumor change, whereas others had minor or no changes with reported variations of 12%–87% [7–8].

In the present study, we observed maximum changes in GTV ranging from –13.09% to –56.76% in patients treated with IMRT or fractionated stereotactic radiotherapy. Patients treated with stereotactic radiotherapy had less tumor regression (range, –13.8% to –15.91%) than patients treated with IMRT (the majority showed > 20%). The reason for this may be due to an insufficient treatment time for demonstrating a significant tumor regression with stereotactic radiotherapy. Analysis of the GTV change trends in the present study revealed that the majority of patients treated with IMRT experienced a substantial decrease in tumor volume in the third or fourth week of treatment, followed by a plateau or slight increase, while the other patients experienced variable tumor volume changes with no obvious decreasing trend. These results are similar to those of groups A (an initial period of a small tumor volume change, followed by a sharp decrease) and C (no clear decreasing trend) reported by Woodford *et al* [7]; however, no patients had a GTV change trends similar to that of group B (gradual linear decrease). Furthermore, we found that a few patients experienced a slight increase in tumor volume in the fifth and sixth week of treatment compared with that in the third or fourth week of treatment. The reason for this finding is unknown, but it may be due to radiation-induced inflammation of the normal lung tissue around the tumor.

Adaptive radiotherapy is an active feedback loop treatment process in which the treatment plan is modified based on updated information, i.e. changes in tumor size, shape, and position observed in images acquired at different times during the course of treatment. Adaptive planning has been shown to reduce normal tissue doses and prevent target misses, particularly for patients with large tumors that shrink substantially during therapy [9]. Woodford *et al* evaluated GTV changes using daily MVCT in 17 patients with NSCLC who were treated with helical tomotherapy at a total dose of 60–64 Gy in 2 Gy/fraction and demonstrated that adaptive planning for tumor shrinkage can improve the sparing of normal tissues if the tumor volume decreases by > 30% within the first 20 treatment fractions [7]. However, in the present study, we found that adaptive planning for tumor changes can yield clinically meaningful sparing of normal structures without affecting tumor dose if the maximum changes in GTV reach 20% or more in the third or fourth week of treatment. In patients treated with fractionated stereotactic radiotherapy, the maximum changes in GTV were much less than 20%; in such cases, adaptive planning for tumor changes proved to be of minimal benefit, a finding that is consistent with those of other reports [10]. However, despite the threshold of tumor changes for adaptive planning, reducing safety margins based on the individual patient's variation, e.g. setup uncertainties, remains valuable [11]. Microscopic disease associated with tumor shrinkage is a concern in adaptive planning for tumor changes, which may result in under-dosing of the microscopic disease around the visible tumor. Guckenberger *et al* evaluated doses delivered to the microscopic disease in adaptive radiotherapy for locally advanced NSCLC using the tumor control probability (TCP) model and showed that adaptive radiotherapy for tumor shrinkage does not compromise the dose coverage of volumes of suspected microscopic disease and has the potential to increase TCP by > 40% [12].

In conclusion, significant changes in target volumes may occur in patients with lung cancer during the course of radiation treatment consisting of IMRT or fractionated stereotactic radiotherapy. Adaptive treatment planning for tumor shrinkage may be beneficial for patients who experience tumor volume changes of > 20% in the third or fourth week of treatment.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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