Chapter 11

Lung density changes after stereotactic radiotherapy: A quantitative analysis in 50 patients

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International Journal of Radiation Oncology, Biology, Physics, 2010 Oct 5
[Epub ahead of print]
Abstract

Purpose
Radiologic lung density changes are observed in more than 50% of patients following stereotactic body radiotherapy (SBRT) for lung cancer. We studied the relationship between SBRT dose and post-treatment CT density changes, a surrogate for lung injury.

Materials/Methods
The SBRT fractionation schemes used to treat stage I lung cancer with RapidArc (Varian Medical Systems) were 3 fractions of 18 Gy, 5 fractions of 11 Gy or 8 fractions of 7.5 Gy, prescribed at the 80% isodose. Follow-up CT scans performed at less than 6 months (n=50) and between 6-9 months (n=30) post-SBRT, were reviewed. Post-treatment scans were co-registered with baseline scans using a B-spline deformable registration algorithm (VelocityAI). Voxel-Hounsfield unit (HU) histograms were created for doses between 0.5-50 Gy. Linear mixed effects models were used to assess the effects of SBRT dose on CT density, and the influence of possible confounders was tested.

Results
Increased CT density was associated with higher dose, increasing PTV size, and increasing time post-SBRT (all p<0.0001). Density increases were apparent in areas receiving more than 6 Gy, most prominent in areas receiving more than 20 Gy, and appeared to plateau above 40 Gy. In regions receiving >36 Gy, the reduction in air-filled fraction of lung after treatment was up to 18%. No increase in CT density was observed in the contralateral lung receiving ≥3 Gy.

Conclusions
A dose-response relationship exists for quantitative CT density changes after SBRT. A threshold of effect is seen at low doses, and a plateau at highest doses.
Introduction

In patients presenting with stage I non-small cell lung cancer (NSCLC) who are unfit to undergo surgery, stereotactic body radiotherapy (SBRT) achieves three-year local controls rates in excess of 88% with a favorable toxicity profile (1-3). However, radiographic density changes are reported in more than 50% of patients (4-7). CT changes observed within 6 months include consolidation and ground glass opacities, and late changes include fibrosis, bronchiectasis, loss of lung volume, and further consolidation (5,8-10).

Although different classification systems for CT changes after lung SBRT have been proposed (5,6,10), no system is universally accepted, and scoring is qualitative and may be subjective. The use of CT density changes may allow for an objective measure of lung damage, and density changes have been shown to correlate with histological findings of inflammation (11). However, comparison of pre- and post-treatment CT densities is hampered by potential differences in positioning, scanner type, and use of intravenous contrast (12,13).

The relationship between radiation dose and quantitative changes in CT density post-SBRT has not yet been determined. Elucidating this relationship would be useful to guide clinicians and physicists in developing treatment planning constraints, and to help differentiate benign changes on follow-up CT from progression or recurrence. We previously demonstrated the utility of a quantitative CT density measurement technique using deformable registration for image matching (12,13). The aim of this current study was to determine if a relationship exists between SBRT dose and radiographic lung injury, as measured by CT density changes.

Methods

Patient Selection

Patients who were treated with SBRT for stage I NSCLC using RapidArc™ (Varian Medical Systems, Palo Alto, CA, USA) at the VU University Medical Centre (VUmc) prior to September 10, 2009 were assessed for eligibility for this study. Patients were excluded if they had no follow-up scans available from the VUmc or if they...
received previous radiotherapy for lung cancer. No patients received chemotherapy and no patients had local recurrence during the follow-up period of this study.

**Treatment Details**

Patients underwent four-dimensional (4D) CT scans for treatment planning (GE Medical Systems, Waukesha, USA), acquired at 140kVp and 100-110 mAs. Varian’s Real-time Position Management System (Varian Medical Systems, Palo Alto, USA) and an Advantage Workstation 4.1 (GE Healthcare) were used to sort scans into 10 breathing phases (0% to 90%), typically with 0% phase typically representing end inspiration and 50-60% phase bins typically representing end expiration. An internal target volume (ITV) was delineated, accounting for all tumor positions in the 4D dataset. The planning target volume (PTV) was obtained by uniformly expending the ITV with a 5 mm margin.

Patients were treated with a risk-adapted strategy, and the fractionation schemes and treatment planning have been previously described (2,6,14). Choice of fractionation was based on tumor location and size as follows: i) T1 tumors surrounded by lung parenchyma were treated in 3 fractions of 18 Gy; ii) T2 tumors and T1 tumors with broad chest wall contact were treated in 5 fractions of 11 Gy. iii) centrally located tumors and tumors near the brachial plexus were treated in 8 fractions of 7.5 Gy. The dose was prescribed to the 80% isodose line, which covered the PTV. Doses to organs at risk were planned according to the criteria of the ongoing ROSEL study. All doses were calculated with the Analytical Anisotropic Algorithm (AAA) (15).

Routine patient follow-up consists of visits after 3, 6, and 12 months, with diagnostic CT scans performed at those visits. Clinical pneumonitis was assessed using the Common Terminology Criteria for Adverse Events, version 4.0 (16).

**Image Registration and Analysis**

Full details of imaging, registration, deformation and statistical analysis are provided in Appendix eI (online). Briefly, contours of selected isodose levels (0.5 Gy, 3 Gy, 6 Gy, 12 Gy, 18 Gy, 24 Gy, 36 Gy, and 50 Gy) were exported from the planning system along with the contours of the lung and internal target volume, and the average-intensity CT dataset. These isodose lines were chosen so as to provide a wide range of
doses and large enough volumes between lines to allow for meaningful density measurements. This resulted in a total of 8 evaluable dose-density regions in the ipsilateral lung. In the contralateral lung, only one dose-density region (receiving ≥ 3 Gy) was analyzed, as it was uncommon for contralateral lung to receive >5 Gy. Contralateral lung receiving <3 Gy was considered un-irradiated and as such was used to correct for baseline differences between scanners. The regions receiving >50 Gy were not analyzed since these volumes were small, and because small errors in registration could place a few millimeters of regressing or stable tumor within that volume, artificially increasing density measurements.

After deformation of the follow-up scans, isodoses from the end-inspiratory phase of the planning CT scan were then overlaid on the deformed follow-up scan (Figure 1), and changes in HU density were assessed.

**Figure 1.** Representative example of image registration and deformation with overlaid isodose lines. *Left*: baseline planning scan; *Centre*: follow-up scan after rigid registration and scaling, but no deformation, with misalignment evident; *Right*: follow-up scan after deformation, showing improved alignment. Isodoses are shown outside the internal target volume and range from dark blue (3-6 Gy) to red (>50 Gy). The target is indicated with a white arrow.
Stereotactic Radiation Therapy for Stage I Non-Small Cell Lung Cancer

Scans were classified as early (first follow-up scan, all <6 months) or late (second follow-up scan, at 6 months or later). The first day of treatment was considered day 0 of follow-up. Four patients had their second scan up to two weeks early, but these were classified as ‘6 month’ scans. No attempt was made to correct doses based on fractionation (e.g. using linear quadratic model) as substantial uncertainty exists as to which models and parameters are appropriate to calculate equivalent doses for SBRT (17-20).

Air-filled fraction ($f_{air}$) was calculated from HU density using the formula $f_{air} = -0.001 \times N_{CT}$, where $N_{CT}$ is the CT number in HU (21). $f_{air}$ represents the percentage of lung tissue that contains air, and it decreases with increasing CT density.

All statistical tests were two-sided with a threshold for statistical significance of 0.05, and were performed using the Statistical Package of Social Sciences (SPSS version 15.0, Chicago, USA) or R (version 2.9.2, Vienna, Austria).

Results

A total of 50 patients stage I NSCLC patients met the inclusion criteria. All had a first follow-up scan within 6 months of treatment, and 38 patients had a second scan done at $\geq$ 6 months to measure late CT changes. Baseline clinical characteristics are shown in Table 1, and representative images of baseline and follow-up scans with isodoses are shown in Figure 1. Four patients had 2 primary tumors, and for these patients the total PTV volume is reported.

Eight patients (16%) developed symptoms consistent with radiation pneumonitis, six with grade 2 pneumonitis and 2 with grade 3 pneumonitis. Five of the eight patients with symptoms of pneumonitis had PTV volumes in excess of 100 cm$^3$.

CT Density Changes

The relationship between ipsilateral CT density changes and dose is shown in Figure 2. In general, in the low-dose regions (<10 Gy) density changes were small, and the majority of density increases were evident at doses >20 Gy, with a plateau at higher doses. Increased CT density was associated with increasing dose, time, and PTV size (all $p<0.0001$). An exploratory analysis showed that male gender was of borderline
significance for prediction of increased density changes, whereas age (p=0.34), upper vs.
lower tumor location (p=0.62), and central vs. peripheral tumor location (p=0.57) were
not. CT density changes did not correlate with clinical symptoms.

In patients with PTVs > 100 cc, large increases in late CT density were seen at
lower doses. For these patients, mean HU density changes of > 100 HU were detected in
all regions receiving more than 6 Gy. These changes were larger in magnitude than those
seen at any dose level in patients with smaller PTVs. However, due to the small number
of patients with large PTVs, the confidence intervals around the density estimates are
wide, making it more difficult to draw firm conclusions. the exact shape of the curve.

Table 1. Baseline clinical and treatment details characteristics for 50 patients treated with
stereotactic body radiation therapy for stage I NSCLC. Doses were calculated using an
Analytical Anisotropic Algorithm (AAA). PTV: planning target volume

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Range) or Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73 years (50-89 years)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Male</td>
<td>35 (70%)</td>
</tr>
<tr>
<td>PTV</td>
<td>43 mL (6-287 mL)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Upper</td>
<td>35 (70%)</td>
</tr>
<tr>
<td>Lower</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Dose and Fractionation</td>
<td></td>
</tr>
<tr>
<td>3 x 18 Gy</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>5 x 11 Gy</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>8 x 7.5 Gy</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>Time to first CT scan</td>
<td>3.3 months (1.8 – 5.6 months)</td>
</tr>
<tr>
<td>Time to second CT scan</td>
<td>6.7 months (5.7 – 9.3 months)</td>
</tr>
</tbody>
</table>
Table 2 shows the percent changes in air-filled fraction in the high dose regions (>18 Gy). The mean change in air-filled fraction at the highest dose region (36-50 Gy) ranged from 8-14% for early scans and 9-18% for late scans.

**Figure 2.** Estimated means and 95% confidence intervals for the changes in normal lung tissue relative to pre-treatment scans, stratified by planning target volume (PTV) size.

No increase in CT density was observed in the contralateral lung receiving ≥ 3 Gy. Density in the contralateral irradiated lung was not affected by time, PTV size, age, gender, or tumor location (all p>0.25).

**Discussion**

Our study demonstrates a clear dose-response relationship for CT density changes after SBRT. Although small changes in CT density were evident in areas receiving >6 Gy, most of the increase in density occurred at doses above 20 Gy, with a plateau evident above 30 Gy. In patients with PTVs larger than 100 cc, even low-dose regions developed late density changes. Despite the increases in density observed, the absolute decrease in lung aeration was small for most regions of the lung, and clinical symptoms of pneumonitis were uncommon. There was no increase in contralateral lung density due to low dose irradiation. Contralateral lung function may be of particular importance in compensating for ipsilaterial radiation pneumonitis (22).
Table 2. Percent change in air-filled fraction in high-dose regions, by dose levels and planning target volume (PTV) size, for CT scans done < 6 month (early) or 6-9 months (late) after treatment.

<table>
<thead>
<tr>
<th>PTV size</th>
<th>Change in air filled fraction</th>
<th>Change in air filled fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Dose (Gy)</td>
<td>50 cm³</td>
<td>50-100 cm³</td>
</tr>
<tr>
<td>18 - 24</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>24 - 36</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>36 - 50</td>
<td>8%</td>
<td>12%</td>
</tr>
</tbody>
</table>

These dose-response data could have several important applications: improvement of treatment planning constraints by identifying dose intervals likely to cause reduced aeration; comparisons of toxicity between different fractionation schemes or with the addition of systemic agents; or to help distinguish recurrence from benign changes based on the knowledge of likely locations and degree of normal density changes after SBRT.

CT density changes after lung radiotherapy have been the subject of increasing research interest (4-6,12,23,24), and our results build upon previously published data in several important ways. We assessed CT changes using objective, quantitative CT density measurements. This removes the subjectivity inherent to contouring CT abnormalities, and also avoids an “all-or-none” classification of CT changes. We used a deformable registration technique to improve accuracy in image alignment over rigid techniques (12,13), which is of paramount importance given the rapid dose-falloff with SBRT. We examined a large dose-range (<0.5 Gy to 50 Gy), using fractionation schemes in keeping with multi-institutional trials (15). Doses were calculated using the AAA algorithm, which is more accurate than pencil beam algorithms used in other studies (15).

Few studies have specifically examined the relationship between dose and CT changes after SBRT. After single-fraction lung radiosurgery, Hof et al showed that CT changes increase with dose and peak at 16 weeks after treatment. No threshold of dose for density changes was noted, although doses below 6 Gy were not analyzed (23). Areas of CT abnormalities were
contoured manually and density was not measured. Patients who did not develop CT changes were excluded, limiting the applicability of this data to the pre-treatment setting, since these patients cannot be identified before treatment.

Aoki et al evaluated the relationship between SBRT dose and CT changes by contouring abnormal areas and overlaying SBRT isodoses using registration of bony landmarks (25). The minimal dose associated with areas of CT change ranged from 16 to 36 Gy, with a median of 24 Gy, consistent with the results of our study in which most of the changes in CT density was noted in areas receiving >20 Gy.

Kyas et al assessed dosimetric factors predictive of CT changes in 64 patients treated with single-fraction treatments of 20-30 Gy (26). CT changes were defined as new hyperdense areas in the treated lung region. Factors predictive of development of these CT changes included volume of lung receiving 7 Gy or 10 Gy, mean dose, and equivalent uniform dose, all of which were closely correlated, but the isodose levels at which CT changes occurred were not examined.

We did not attempt to account for differences in fractionation between patients, or to convert doses to standard 2 Gy per fraction equivalents, since there is disagreement as to the best method of equating doses.(17-20) The linear-quadratic formula for calculating biologically equivalent doses is the most widely used, but could overestimate cell kill with large fraction sizes (> 6 Gy) (20). Nonetheless, the results of this study are generally in agreement with studies of CT density changes after conventionally fractionated RT, in which modest increases in CT density have been noted above 20-30 Gy, with more profound changes occurring above doses of 60 Gy (21,27-29).

The findings of this study must be considered in the context of its limitations. Although we have previously examined the feasibility of this technique for measuring changes in CT density (12,13), there are inherent uncertainties since scans may differ in time, patient position, use of contrast, degree of inspiration, and scanner type. Data was not available on many patient specific pre-treatment factors, such as smoking and comorbidities, although these factors do not appear to have a large impact on regional lung injury (30). Post-treatment pulmonary function data was not available. Density changes may continue to evolve with longer follow-up, although the peak density changes are expected to occur within the first 16 weeks (23). Finally, imaging modalities that could provide further information on lung injury, such as SPECT (27) or hyperpolarized 3-He MRI (22) were not available.
In conclusion, our study demonstrates a dose-response relationship for quantitative CT density changes after SBRT for stage I NSCLC. CT density changes exhibited a threshold at low doses, a plateau at high doses, and were significantly associated with PTV size and time after treatment.

Appendix e1

Image Registration

All follow-up diagnostic CT scans were performed on one of three different scanners at the VU Medical Center. Machine settings were 120 kVp, 100 mAs, with spiral acquisition and a 0.5 sec rotation time. 70 mL of contrast was administered for most patients with a delay of 25 seconds. Scans were acquired at inspiratory breath hold.

Image registration and deformation was performed using VelocityAI (version 2.2.1, Velocity Medical Solutions, Atlanta, Georgia, U.S.A) running on a Pentium dual core PC platform equipped with Windows XP (Microsoft Corporation, Redmond, Washington, U.S.A). Isodoses were transferred from the average-intensity dataset to the end-inspiratory breathing phase (to best match the follow-up scans). Artifacts can be common on 4DCT studies (31) and if the end-inspiratory scan had excessive artifacts, the scan closest in lung volume with minimal artifact was used.

Follow-up CT scans were then registered and deformed to match the end-inspiratory phase of the 4D-CT. Rigid registration of images with scaling was applied and manually inspected before deformation. Deformation was done using a modified B-spline-based calculation algorithm combined with the Mattes formulation of the mutual information metric (32). Deformable registration was performed first using ‘coarse’ settings (with relatively few control points), to maximize matching of normal structures while avoiding overfitting of differences between scans. After visual inspection, ‘fine’ deformation was applied if further deformation was needed.

After deformation, matching was assessed qualitatively by comparing locations of major structures (e.g. great vessels, vertebrae, major airways), with particular attention to accurate matching in the region immediately surrounding the tumor. The accuracy of this technique has been shown to be within 3-5 mm for most lung structures, and significantly better than rigid registration (12,13).
Voxel-HU density histograms were created for quantitative assessments of lung density in each of the dose regions described and the mean HU density recorded. Quantile-quantile plots were used to indicate that the densities (relative to air) were log-normally distributed. Subsequent analysis was performed on the log-transformed densities with results being back transformed onto the original scale. To account for possible differences in scanner sensitivity (i.e. comparing diagnostic scans with planning scans), observed lung densities were adjusted (by subtraction) so that the observed correction regions in the contralateral lung were equal (12,13). For patients with one lung (n=2), a remote section of ipsilateral lung was used for correction. Change from baseline in healthy lung tissue was assessed on the relative scale, equivalent to the difference in log transformed lung densities.

A linear mixed effects model was constructed to determine the relative change at different dose levels, for patients with different tumor volumes (0-49, 50-100, >100 cc). Given that only 8 ipsilateral dose levels were assessed and a sigmoid shape was expected, both fixed and random cubic response functions were implemented. The random effects were grouped by patient and a Gaussian spatial correlation structure applied. A simple bootstrap (selecting patients with replacement) was used to determine 95% confidence bands for the mean change. The Akaike information criterion was used to order the fits. The influence of possible confounders (age, gender, location upper vs. lower, location central vs. peripheral) were tested by including an interaction with the fixed effect cubic function and assessed using Wald tests.

To determine the relative change in the contra-lateral lung a similar, albeit simpler, linear fixed effects model was constructed. The primary difference being the absence of dose (both in fixed and random effects) as there was only one contra-lateral observation per patient (per measurement period).

Reference List


Chapter 12

Treatment of large stage I-II lung tumors using stereotactic body radiotherapy: Planning considerations and early toxicity

C.L. Ong, D. Palma, W. Verbakel, B. Slotman, S. Senan

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Radiotherapy and Oncology 2010 Dec;97(3):431-6.