CHAPTER 5

A novel method for the assessment of radiation-induced damage to the lung

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A NEW METHOD TO ASSESS RADIATION-INDUCED LUNG DENSITY CHANGES

Abstract

Purpose: Thoracic intensity modulated radiotherapy may result in a low dose spread over a large volume of the lung. Animal studies showed irradiated volume to be an important determinant of radiation-induced lung toxicity with volume-dependent secondary damage in non-irradiated parts of the lung. So far, imaging analysis techniques could not detect such damage in patients. Recently, a novel CT analysis technique was developed in rats, incorporating both changes in local structure and density, making it more sensitive than frequently-used analysis based on density changes only. In the present study its sensitivity and potential to detect damage in parts of the lung receiving negligible or no dose was investigated in patients. Materials and methods: Twenty patients with advanced (non-)small cell lung cancer were included. Deep inspiration breath-hold CT-scans were performed before, at 6 and 24 weeks after radiotherapy. Scans from different time-points were geometrically aligned with the dose distribution. Subsequently, radiation-induced changes in the lung tissue were assessed locally (in 4.5x4.5x4.5 mm³ cubes) either by quantifying local mean density (Δmean) or our method including changes in structure (ΔS). The sensitivity of both methods in detecting radiation-induced damage and their correspondence to clinical endpoints were compared. Results: Significant increases in ΔS were observed already below 2.5 Gy, whereas increases in Δmean were not observed until 22.5 Gy and 27.5 Gy at 6 and 24 weeks after radiotherapy respectively. Receiver-operating characteristic (ROC) analysis showed that ΔS method is more sensitive (area under curve (AUC) 0.925) than Δmean (AUC 0.675) in detecting radiation pneumonitis. This indicates that our novel method is more sensitive than using density only. This increased sensitivity enabled the detection of lung damage in regions receiving no or a negligible dose, confirming observations in animals. Conclusions: The novel CT analysis technique using information on tissue structure (ΔS) is more sensitive than analysis based on mean lung density only. It may therefore be used to assess radiation-induced lung density changes, adding an important tool towards increased understanding radiation-induced lung toxicity in patients.
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1. INTRODUCTION

Concurrent chemoradiotherapy is the cornerstone in the management of locally advanced non–small-cell lung cancer (NSCLC). Unfortunately, locoregional control using conventional doses remains poor. Dose escalation is expected to increase locoregional control, but is hampered by the risk of radiation pneumonitis and lung fibrosis. In order to estimate the risk of developing radiation-induced lung toxicity (RILT), dose-volume parameters like V20 (the percentage of lung volume receiving ≥ 20 Gy) and mean lung dose (MLD) are routinely used. However, model performance in terms of the area under the curve (AUC) of a Receiver Operator Curve of these models is only 0.50-0.68, indicating a low predictive power. When these predictive models would be used to select patients for dose escalation, a proportion of patients may either be under-treated, as they would have tolerated a higher dose, or be over treated due to higher sensitivity. As such, the development of models to facilitate the identification of these subpopulations is critical.

Frequently used clinical end-points for RILT, such as dyspnea and use of corticosteroids, are subjective or non-specific. As a consequence, models based on these endpoints, may have weak predictive power. Adding objective quantitative parameters, such as Computed Tomography (CT) may improve their performance.

Radiation-induced changes in the lung involve edema, parenchymal inflammation, hyperinflation and parenchymal fibrosis. These may all lead to density changes as measured on CT-scans. Indeed, significant changes in CT density were observed three to six months after concurrent chemoradiotherapy for NSCLC. These density changes were most evident in regions receiving >30 Gy, with only minor density changes occurring at lower dose levels. Similarly, threshold doses for radiation-induced density changes between 27 Gy and 40 Gy have been reported. However, radiation-induced changes in the lung were not detected in the volume receiving a lower dose, such as the V5-V13, known to correlate with the development radiation pneumonitis. Moreover, from preclinical studies it is known that, depending on the irradiated volume, a low dose may result in lung damage throughout the entire lung, including non-irradiated regions. As such, part of the damage, although involved in the development of RILT, may not
be detected using mean CT density changes. Therefore, more sensitive methods need to be developed for more accurate assessment of the radiation-induced damage to the lung tissue.

The low sensitivity of the analysis of mean density changes in the lung may be attributed to compensatory hyperinflation of lung tissue, which is also a common feature of radiation-induced lung damage observed on CT-scans. As a consequence, the mean density may remain constant even though clear changes in the tissue have occurred. Thus, it seems important to take into account the spread in density changes represented by the standard deviation to describe structural changes as well. As such, using a rat model a new method to assess CT-derived structural changes ($\Delta S$) of lung tissue was developed. It uses local (1 mm$^3$ sub-volumes) mean density changes with the corresponding standard deviation. Interestingly, $\Delta S$ strongly correlated with loss of lung function and histopathological changes, unlike the mean density alone.

The aim of this pilot-study was to test the sensitivity of the $\Delta S$ method in detecting damage to the lung tissue in patients.

### 2. MATERIALS AND METHODS

#### 2.1 Study Design:

Patients with NSCLC (UICC stage II/IIIA/IIIB) or limited-disease small cell lung cancer (tumor confined to hemithorax without evidence of distant metastases or malignant pleural effusion) referred for radiotherapy or chemoradiotherapy were eligible. Diagnostic work-up included bronchoscopy with bronchoalveolar lavage and biopsy, $^{18}$F-FDG-PET/CT-scan and lung function testing. All tumours were pathologically confirmed by cytology or histology. Patients had to have a WHO performance score of 0-2 and a life-expectancy of at least 6 months. Radiotherapy was delivered according to the institutional protocol. Briefly, after acquisition of a planning 4D-CT-scan incorporating breathing motions, the target volume (primary tumour and pathological lymph nodes) was delineated. A margin of 0.5 cm for CTV and an additional margin of 0.6 cm for PTV were used. In the case of NSCLC, the radiation dose was 60 Gy/25fx with weekly low dose gemcitabine (300 mg/m$^2$) after two induction courses of cisplatin and...
gemcitabine. SCLC patients were treated at a dose of 45 Gy/25fx concurrently with cisplatin and etoposide. Conventional 3D-conformal radiotherapy or IMRT was delivered using a linear accelerator (Elekta). Constraints were V20<35% and MLD<20 Gy for the lungs and V35<65% for the esophagus. The study was approved by the local medical ethics committee and all patients gave written informed consent prior to treatment.

2.2 **CT-scans:**

CT-scans were performed on a Siemens Somatom Sensation Open. Scans comprised of a deep inspiration breath-hold scan, enabling optimal quantification of lung density. Settings included a slice thickness of 1.5 mm, 1.5 mm inter-slice distance, 0.5 seconds rotation time, pitch 0.75, 512x512 pixels. CT-scans were performed prior to the start of radiotherapy and at 6 and 24 weeks after completion of treatment. This time course covers acute radiation pneumonitis (6-26 weeks after treatment). To allow optimal image registration, patient position was identical on all time-points. In short, patients were positioned supine, with the arms placed in an elbow support above the head. The head was placed in retroflexion on a head base, and a knee support was used. No IV contrast agents were used.

2.3 **Deformable image registration:**

For comparison of the pre- and post- treatment CT scans and incorporation of the dose distribution data, CT data from different time-points were geometrically aligned. The control situation of each patient lung was defined based on the pre-treatment CT-scan, so that each patient served as its own control. Subsequently, to evaluate the dose-effect relation in lung tissue, corresponding regions in the post- and pre-treatment images were aligned using deformable image registration implemented in Elastix, a tool for image registration.

2.4 **Quantification of local structural lung changes:**

Radiation induced-changes in the lung tissue were assessed locally (in 4.5x4.5x4.5 mm$^3$ cubes) either by quantifying local mean density ($\Delta$mean) or $\Delta$S including changes in the structure. $\Delta$S analysis uses not only local $\Delta$mean but also changes in the local standard deviation of the density ($\Delta \sigma$) for quantification of the local structural changes in the lung tissue. The results from quantification of $\Delta$S and $\Delta$mean were compared
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to test their sensitivity in detecting radiation-induced damage at different time points
after radiotherapy. Cubes consisting of more than 95% of voxels with low density (HU < -700) were assumed to be lung parenchyma and included in the analysis. Cubes inside the planning target volume (PTV) were excluded, to avoid inclusion of tumour tissue. Dose distributions were pooled at 5 Gy intervals (i.e. 0-2.5 Gy, 2.5-7.5 Gy, ..., 62.5-67.5 Gy).

2.5 Quantification of the sensitivity of ∆mean and ∆S-based methods:

To establish the detection threshold for the ∆Mean and ∆S methods, two pre-
treatment deep-inspiration breath-hold scans were performed in three patients, not
included in the study. Subsequently, the pre-treatment scans were geometrically aligned
and ∆Mean and ∆S methods were applied to the deformed scans. Local values of ∆Mean
and ∆S maps (Figure.1) were averaged inside the lungs. The values obtained from these 3
patients were subsequently averaged. Detection thresholds were defined as the mean plus
two SD. Thresholds were 0.43±0.04 (HU) and 0.27±0.02 for ∆Mean and ∆S, respec-
tively. These were inserted in Figure.3 and Figure.4 as dotted lines. Secondly, radiation
pneumonitis was scored for each patient at 6 weeks after the completion of radiation
treatment, according to Southwest Oncology Group (SWOG) toxicity criteria. Grade
1 = radiographic changes only/symptoms, not requiring steroids, grade 2 = symptoms
requiring steroids, grade 3 = symptoms requiring oxygen. Area under the receiver oper-
ating characteristic curve (ROC curves) was used to assess the correspondence of both
methods with the SWOG criteria.

Figure.1: Determination of the detection threshold. Two deep inspiration CTs
of the same patient (left panel) were registered using deformable image registration.
Subsequently the ∆S and ∆Mean methods were applied to the deformed image and
the resultant maps are shown in the right panel.
2.6  **Statistics:**

To test whether the changes in ∆Mean and ∆S were statistically significant from the detection threshold, two-sided independent samples t-tests were performed. Calculations were performed using SPSS version 19.0. Statistical significance was set at \( p<0.05 \).

3.  **RESULTS**

3.1  **Patient characteristics**

Twenty patients were enrolled. Treatment parameters and patient characteristics are shown in Table 1.

**Table 1. Patients characteristics.**

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<th></th>
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<th>Pathology</th>
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<th>Mean Lung Dose (Gy)</th>
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Three patients refused further CT-scans after treatment, in two patients the pre-treatment CT was lost, two patients died within 6 weeks after completion and another four patients died 6–24 weeks after treatment. As such, 13 CT scans were available at week 6, and 9 CT scans were available at 24 weeks after treatment. Patient #5 received palliative radiotherapy, consisting of 39 Gy/13 fx instead of the planned 60 Gy/25 fx because of a deteriorated general condition.

3.2 Visual impression of ∆Mean and ∆S methods

Representative CT-scans made pre-treatment (deep inspiration) with the corresponding dose-distribution on the planning-CT-scan of patient #4 are depicted in Figure 2a.

![Figure 2](image)

**Figure 2:** Comparison of ∆S and ∆Mean in patient #4 at 6 and 24 weeks post-RT. CT-slices of the deep-inspiration scan made before (a), 6 (b) and 24 (c) weeks post-treatment, are shown. The dose distribution is shown superimposed on a routinely-acquired 4D-CT-scan in panel a. Six weeks after treatment, dense consolidation of lung tissue is observed suggestive of radiation pneumonitis (b) which resolved at 24 weeks but then fibrosis developed according to the beam arrangement (c). ∆S and ∆Mean maps of patient #4 were compared 6 (b) and 24 (c) weeks post-RT.
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The post-treatment CT-scan (at 6 weeks) showed dense consolidation in the right lower lobe, suggestive of acute RILT, which was detected by both ∆Mean and ∆S quantification (Figure.2b). However, as indicated by the red arrows, ∆S could detect structural changes that were not detected using ∆mean. At 24 weeks, the dense consolidation resolved, however, fibrosis developed according to the beam arrangement (Figure.2c).

Comparison of both methods

Next, to show differences in sensitivity between the ∆Mean and ∆S methods quantitatively, individual values of ∆Mean and ∆S were pooled into bins, and the averages were correlated.

Figure.3: ∆S method is more sensitive than ∆Mean in detecting radiation-induced lung damage in the patient population at both 6 (a) and 24 weeks (b) post-treatment, as demonstrated quantitatively by comparing ∆S and ∆Mean values. Individual values of ∆Mean and ∆S were pooled into bins, and the averages were plotted. Different symbols represent different patients. The green and blue dotted lines are indicative of the level of the detection threshold of the damage by ∆S and ∆Mean methods respectively. Red points indicate the data of patient #4.

For both methods the detection thresholds as obtained from the pretreatment scans are shown (Figure.3 blue and green dotted lines for ∆Mean and ∆S methods,
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respectively). As shown in Figure.3 (red points = patient #4), all values of the ∆S method
were above the detection threshold (green dotted line), whereas for ∆mean, many values
were below within the detection threshold (blue dotted line), indicating the higher sensi-
tivity of the ∆S method, at week 6 (Figure.3a) and week 24 (Figure.3b), respectively.

3.3 ∆S method detects structural lung changes at no/low doses

To assess the sensitivity of the two methods with respect to dose, curves of ∆S
and ∆mean as a function of dose were generated for the entire population. Comparing
changes in ∆S (Figure.4a) with ∆Mean (Figure.4b) at week 6 and regarding to their detec-
tion levels (dotted lines) it can be seen that ∆S is capable of assessing density changes at
no/low dose levels (see in Figure.4a, *** p<0.001).

Figure.4: In contrast to ∆mean, ∆S detects radiation-induced lung damage
at no/low dose regions. Dose response of ∆S (a) and ∆mean (b) were shown in
the patient population at week 6 and 24 after radiotherapy. A clear steep dose-
dependent increase of ∆S was observed. Regarding to the detection threshold of
∆S method (dotted line) the increase in ∆S is significant starting already at 0-2.5
Gy regions at both time-points post-treatment (***p<0.001 wk-6 and †††p<0.001
wk-24). Changes in ∆mean are observed above threshold at 7.5 Gy and 22.5 Gy,
however they are not statistically significant above 22.5 Gy (*p<0.05) and 27.5
Gy (†p<0.05) at week 6 and 24 respectively. This indicates that ∆S method is
more sensitive in detecting small changes in the lung tissue. Data are presented as
mean values with standard error of the mean (SEM). The dotted lines represent the
methods detection threshold of the damage.
Consistent to literature\textsuperscript{8,17}, in the same dose-range (0-7.5 Gy), changes in mean lung density are still below the detection threshold and only become statistically significant above the detection threshold at 22.5 Gy (see in Figure.4b, * p<0.05). As such the ΔS method seems more sensitive and capable of detecting changes at lower dose levels. Also at 24 weeks, changes in ΔS were also already observed from 0 Gy (see in Figure.4a, ††† p<0.001), further increasing as a function of dose. In contrast, significant changes in mean lung density could only be observed above 27.5 Gy (see in Figure.4b, † p<0.05). Below that dose, density changes remained below the detection threshold. In the highest dose bin (62.5-67.5 Gy) a steep rise or a fall in lung density was observed in some patients.

This decrease in lung density may be explained by the fact that in some cases a ‘halo’ of less damage was observed around the tumour, as observed earlier\textsuperscript{8}. Similar results were found at 24 weeks after radiation although to a lesser extent (Figure.4a and b).

3.4 \textbf{ΔS method is more sensitive and specific in detecting radiation pneumonitis}

To determine whether the additional damage detected by the ΔS method relates to clinical radiation pneumonitis, ROC curve analysis was performed. The analysis showed that the ΔS method is superior to ΔMean method in detecting radiation pneumonitis at week 6 after radiotherapy (SWOG scoring, grade 1 and higher) with area under the curve of 0.925 vs 0.675 (Table 2).

In summary, our novel method using ΔS seems more sensitive to detect structural changes in the lungs when compared to the ΔMean method. This higher sensitivity enables ΔS method to detect radiation pneumonitis better than the ΔMean method.

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<th>AUC</th>
<th>95% confidence interval</th>
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<td>0.781 - 1</td>
</tr>
<tr>
<td>ΔMean</td>
<td>0.675</td>
<td>0.37 - 0.98</td>
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\textbf{Table 2. ΔS method detects radiation pneumonitis more accurately than does Δmean.} This was shown by ROC curve analysis. Radiation-induced lung damage which was quantified with both ΔS and Δmean method were related to grade 1 or higher radiation pneumonitis (SWOG scoring system). Area Under the Curve (AUC) for ΔS method is 0.925 compared to 0.675 for Δmean.
4. DISCUSSION

New developments in radiotherapy such as intensity modulated radiotherapy (IMRT) result in the deposition of a low dose to a large volume of normal lung tissue. Until now, imaging techniques such as CT-based lung density changes have been unable to non-invasively show changes in the lungs in the low dose regions (≤ 27-40 Gy) due to a lack in sensitivity.

Similarly, also in our study with comparable range of changes in mean lung density, we did not observe significant changes in mean lung density below 22.5 and 27.5 Gy at week 6 and 24 respectively. Our new ΔS method incorporating both changes in mean density and standard deviation of the density, was however capable of demonstrating structural changes in the lung throughout the entire lung, including regions receiving no/negligible dose. Interestingly, in a preclinical study it was recently reported that lung function is substantially compromised at very low doses if scattered over a large volume. Moreover, the observation of out-of-field effects, lead to the hypothesis that RILT may be a generalized lung disease, originating at the site of injury and then spreading throughout the lungs, rather than damage in the irradiated lung tissue only. Although from our present study, it is impossible to conclusively verify these observations in humans, the ΔS method was able to detect structural changes in the lung in areas where no dose was deposited. A more thorough investigation using the ΔS method in combination with e.g. perfusion scans in patients with a wide range of different dose distributions in the lung may shed some light on this.

Previously, it was shown in a preclinical model that ΔS is representative of radiation-induced morphological lung tissue damage. Moreover, in contrast to routinely used mean density changes that have weak correlations to pulmonary function, ΔS correlated well with changes in respiratory rate in rats as well as radiation pneumonitis in patients (present study). Noting that the range of mean density changes in our Δmean method is comparable with previous studies, this suggests that the ΔS method acquires more accurate information from CT scans than currently used methods. More sensitive tools such as ΔS method enable more accurate assessment of the relation between dose distribution and the resultant lung tissue damage and clinical endpoint (e.g. dyspnea).
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Inclusion of this information in the development of predictive models for the risk of RILT may improve their prediction power. First, however, the correlation of $\Delta S$ to radiation pneumonitis needs to be confirmed in a larger cohort of patients.

In conclusion, we showed that large inter-individual variation in lung density changes occur after (chemo)radiotherapy. Our highly sensitive $\Delta S$ method outperformed currently-used methods based on changes in mean lung density. It is more sensitive in detecting changes in the lung at low doses and relates better to radiation pneumonitis. Therefore, our novel method may be an important tool for the accurate and objective assessment of radiation-induced lung damage.
References


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