Chapter 6

Time and dose-related changes in radiological lung density after concurrent chemoradiotherapy for lung cancer

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Abstract

Radiation pneumonitis is an important cause of morbidity after concurrent thoracic chemoradiotherapy (CCRT). However, asymptomatic changes in lung density on computed tomography (CT)-scans occur more commonly, and correspond to regions of inflammatory changes. Characterization of dose- and time-related changes in radiological lung density (RLD) may facilitate improved radiation planning, and allow for a more objective measure for assessing damage. We studied changes in RLD following CCRT with cisplatin–etoposide, using deformable registration to co-register follow-up scans. All CT-scans performed for up to 24 months post-treatment were evaluated in 25 patients treated with CCRT for stage III non-small-cell lung cancer. A total of 104 scans (median of 3 per patient) were co-registered with planning scans using a deformable registration tool (VelocityAI, Atlanta, USA). Last follow-up scan was at median 9.4 months (range 3.4–22.6 months). Seven patients developed clinical radiation pneumonitis. RLD changes (in Hounsfield units) were measured in regions receiving 3–66 Gy. Linear mixed models were used to study dose–density changes over time. No significant changes in RLD were observed in the first 3 months post-treatment. Increases in RLD were observed at 3–6 months ($p < 0.0001$) and 6–12 months ($p = 0.006$), but stabilized at 1 year. Increases were most evident in regions receiving >30 Gy, with only minor density changes at lower dose levels. Planning target volume size was significantly associated with RLD changes ($p = 0.03$). Limiting lung doses to ≤30 Gy during CCRT may limit sub-clinical damage, and the time-course of RLD changes may allow for early quantification of pulmonary damage when evaluating novel treatment strategies.

Introduction

Concurrent thoracic chemoradiotherapy (CCRT) is the standard of care in patients with stage III non-small-cell lung cancer (NSCLC) who have a good performance status [1]. Long-term survival remains disappointing, particularly in patients who present with large volume disease who are also at risk for increased pulmonary toxicity [2]. Some approaches for treatment intensification include the use of higher radiation doses and incorporation of novel systemic agents [3,4]. However, there is concern that more aggressive schemes will increase treatment-related toxicity including acute oesophagitis, neutropenia and anaemia, and radiation pneumonitis (RP) [1,5].

RP manifests as subacute toxicity as late as 1 year after treatment completion [6]. The radiological appearance of radiation-induced lung disease is usually confined to lung tissue within the radiation port and manifests as ground-glass opacity, attenuation or as consolidation in the acute phase, while in the late phase mainly traction bronchiectasis, volume loss and scarring are observed [7]. The risk of RP can be predicted by use of parameters such as the volume of lung tissue outside the planning target volume (PTV) receiving a dose ≥20 Gy (V_{20}), V_5 and mean lung dose (MLD) [8]. However, such parameters are imperfect predictors as fatal toxicity can also manifest in patients with low V_{20} [4]. Preclinical studies have shown that radiological lung density (RLD) changes correlate strongly with histopathological radiation damage and physical endpoints [9]. Available data examining the relationship between radiation dose and subsequently lung damage in humans were derived from older studies which did not use high-resolution computed tomography (CT)-scans and acceptable techniques for co-registration of images, and which were not restricted to patients with lung cancer [10–12]. Distinguishing between the phases of RP and the subsequent formation of fibrosis on CT-scan can be difficult, and both entities, therefore, are combined in the definition of ‘radiation-induced lung disease’ [13]. Objective and standardized methods for quantifying radiation-induced lung disease after CCRT could be useful in providing information on sub-clinical damage that occurs before the onset of overt clinical toxicity, and allow for improvements in radiotherapy planning and early detection of lung injury.

We previously evaluated quantitative changes in Hounsfield units (HU) in lung density on serial CT-scans performed after stereotactic radiotherapy [14,15], and found that RLD changes increased in a dose-dependent manner which correlated strongly with physician-scored radiological pneumonitis. In contrast, patients with stage III NSCLC constitute a more heterogeneous population than patients with stage I disease, with a range of tumour sizes and lymph node involvement. Consequently, large radiation fields are used in conjunction with chemotherapy, which increases the risk of symptomatic radiation-induced lung disease. In the present study, we retrospectively evaluated RLD changes after CCRT in patients with stage III NSCLC using the same technique.

Materials and methods

Patient selection and treatment details

Patients with stage III NSCLC who were treated using thoracic radiotherapy and concurrent full-dose cisplatin–etoposide between 2003 and 2008 [16] were assessed for eligibility in this retrospective study. Eligible patients were required to have at least one CT-scan performed >3 months after completion of CCRT, and both chemotherapy and follow-up CT-scans had to be performed at our center. Treatment typically commenced with one course of cisplatin 80 mg/m^2 on day 1 with gemcitabine 1250 mg/m^2 on days 1 and 8, followed by 2–3 courses of cisplatin 80 mg/m^2 (days 21 and 42) and etoposide 100 mg/m^2 (days 21–23 and 42–44). Once-daily involved-field thoracic radiotherapy commenced at day 22 (5 days/week) in 2 Gy-fractions to a maximum of 66 Gy. During the time period of this study, doses of 50 Gy or higher were not routinely administered at our center to patients who presented with very bulky tumours and/or those with supraclavicular nodal metastases, as the technique of intensity-modulated radiotherapy (IMRT) was not (yet) available. A four-dimensional (4D) CT-scan was generally used for treatment planning and all doses were recalculated with the Analytical Anisotropic Algorithm (AAA) in Eclipse version 8.1 (Varian Medical Systems, Palo Alto, USA). Clinical RP (Grade ≥II) was retrospectively assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading system v3.0. Patients presenting with radiological signs of RP, and which was also accompanied by clinically troublesome symptoms such as dyspnea, were treated using steroids, typically prednisolone at a dose of 1 mg/kg for 6 consecutive weeks followed by tapering the dose of steroids to zero in the following 6 weeks.

Details of post-treatment CT-scans

Follow-up generally consisted of visits every 3–6 months until 2 years. All post-treatment diagnostic CT-scans were performed on one of three different scanners. Machine settings were 120 kVp, 100 mAs, with spiral acquisition and a 0.5 s rotation time. Seventy milliliter of contrast was administered for most patients with a delay of 25 s. Scans were acquired at inspiratory breath hold. All available scans after last radiotherapy fraction until 24 months post-treatment were used for analysis if adequate registration could be achieved. Two scans were excluded as they could not be registered accurately with the planning scan using the deformable registration technique, and one scan was excluded as it was repeated 3 days after a previous scan. In total, 104 follow-up scans were analyzed, with a median of 3 per patient (range 1–10 scans). Median radiological follow-up for all included patients within the study period of 24 months post-treatment was 9.4 months (range 3.4–22.6 months).

Image registration and lung density measurements

The method of image registration/deformation has been described previously [14,15]. Briefly, the post-treatment scans were co-registered with planning scans using a B-spline deformable registration algorithm (VelocityAI, Atlanta, USA). Contours of selected isodose levels (3 Gy, 5 Gy, 15 Gy, 30 Gy, 40 Gy, 50 Gy, 60 Gy) were exported from the planning system along with the contours of the lung, internal target volume (ITV), and the average-intensity CT dataset. The isodose lines were chosen so as to provide a wide range of doses and large enough volumes between isodose lines to allow for meaningful lung density measurements. Lung receiving <3 Gy was considered un-irradiated and as such was used to correct for baseline differences between scanners. After deformation of the follow-up scans to match the end-inspiratory phase of the planning scan, isodoses from the planning scan were then overlaid on the deformed follow-up scan, and checked for inconsistencies. The area within the target was not analyzed, to avoid confounding by changes in tumour density. Subsequently, changes in HU density were measured. **Figure 1** (colorfigure, page 114) demonstrates a central (A) and peripheral (B) primary tumour, showing the planning scan and deformed follow-up scans.

Statistical analysis

Linear mixed models were constructed to assess the association between RLD changes and radiation dose over time. Patient and CT-scan were implemented as the random grouping variables, thus adjusting for any within-patient correlations and the influence of different scanners. Radiation dose (3-5, 5-15, 15-30, 30-40, 40-50, 50-60 and 60-66 Gy), time post-treatment (0-3, 3-6, 6-12 and 12-24 months) and their interaction were taken as discrete fixed effects. Overall F tests were used to assess significance of the interaction term, and pairwise tests were performed to determine which regions differed between dose levels and time intervals. The association between RLD changes and patient characteristics; smoking (current vs. former/non/unknown), age (≤65 vs. >65 years), PTV (≤575 vs. >575 cm^3), V_{20} (≤30 vs. >30%), V_5 (≤50 vs. >50%), MLD (≤15 vs. >15 Gy), and clinical symptoms of RP (present vs. absent) was also assessed by including these variates as dichotomous fixed effects. In all analyses the restricted maximum likelihood estimates are reported, tests were two-sided when appropriate, and the significance level was taken at the 0.05 threshold. All analyses were performed in R (v2.10.1).

Results

Of 89 stage III NSCLC patients described in our definite CCRT cohort [16], 50 were treated with both chemo- and radiotherapy at the VU University Medical Center. Of these, 25 patients were excluded for the following reasons: no available follow-up scans (n = 7); disease progression within 3 months after last radiotherapy (n = 7); difficulty with registration due to atelectasis (n = 4) or fistula/empyema (n = 2); previous pneumonectomy (n = 2); death during treatment (n = 2), and drop-out of CCRT after 40 Gy (n = 1). Baseline and treatment characteristics of the remaining 25 patients who were eligible are summarized in **Table 1**. Eight included patients were treated for a recurrent NSCLC in the ipsilateral lung (n = 2) or mediastinum (n = 6). Of these, 7 had undergone previous resection, while 1 had regional progression after stereotactic radiotherapy. After CCRT, 7 patients developed clinical RP; grade II (n = 5) or grade III (n = 2).

Table 1. Patient and treatment characteristics

Characteristic	Result	Range
Sex (n)		
Male	16	
Female	9	
Age (y)		
Median	65	48 - 78
Smoking (n)		
Current	10	
Former	12	
Non	2	
Unknown	1	
Comorbidities		
COPD	4	
Myocardial infarction	5	
Diabetes	2	
None	14	
Clinical stage (n)		
IIIA	14	
IIIB	11	
Primary location (n)		
Right upper lobe	10	
Middle lobe	1	
Right lower lobe	4	
Left upper lobe	3	
Left lower lobe	1	
Mediastinal	6	
Planning parameters (median)		
Total lung volume (cm^3)	3643	2461 – 7034
PTV (cm^3)	575	195 – 1258
V_{20} (%)	26.2	10.5 – 35.8
V_5 (%)	50.9	23.4 – 83
Mean lung dose (Gy)	14.1	6.6 – 23.5
Total radiation dose (Gy)		
46-58	10	
60	9	
66	6	

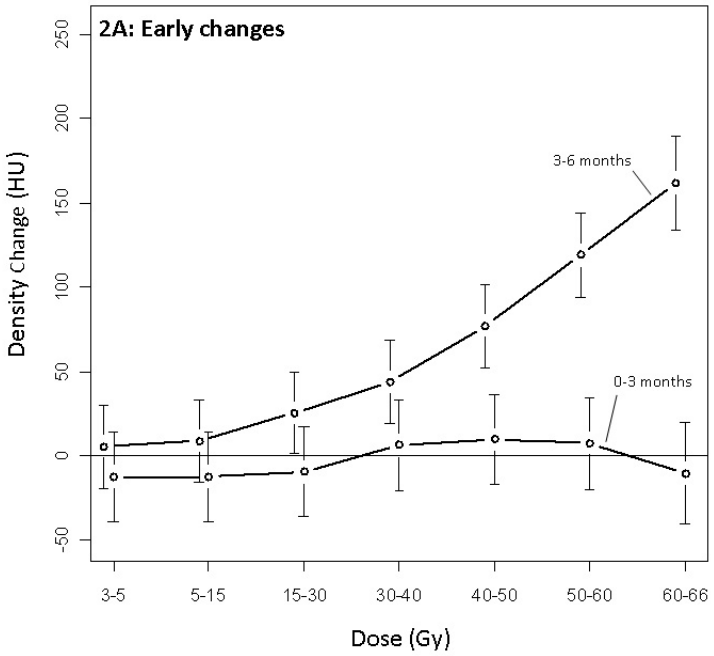
COPD, chronic obstructive pulmonary disease; PTV, planning target volume; V_n, percentage volume of lung tissue outside the PTV receiving indicated threshold dose or more.

Temporal changes in CT lung density (HU)

Figure 2 shows the relationship between RLD changes and dose levels during 4 time intervals after CCRT, and these were classified as early (0–6 months) vs. late (6–24 months). Compared to planning scan, RLD changes within the first 3 months post-treatment were not different for any dose level ($p = 0.13$). RLD increases after 3 months and stabilized at 1 year: the differences in RLD changes between the 0 and 3 vs. 3 and 6 month periods were highly significant ($p < 0.0001$), as were differences between the 3 and 6 vs. 6 and 12 month period ($p = 0.006$), but not between the 6 and 12 vs. 12 and 24 month periods ($p = 0.67$). RLD change was not evident in regions receiving <30 Gy ($p = 0.23$). A slight increase in RLD was evident in regions receiving 30–40 Gy ($p = 0.02$), with more pronounced RLD evident with increasing dose in higher dose areas (30–40 Gy vs. 40–50 Gy, $p = 0.003$; 40–50 Gy vs. 50–60 Gy, $p = 0.003$; 50–60 Gy vs. 60–66 Gy, $p < 0.0001$).

Table 2 summarizes the mean RLD changes in HU and 95% confidence interval (CI) for 5 dose levels during the different time intervals. Examining other variables by comparing patient groups, only large PTV (above the median of 575 cm^3) was associated with an increase in RLD (mean 64.9 HU; 95% CI: 11.0–118.7; $p = 0.03$). No association was found for: smoking ($p = 0.18$), age ($p = 0.56$), V_{20} ($p = 0.58$), V_5 ($p = 0.92$), MLD ($p = 0.67$), clinical RP ($p = 0.57$).

Figure 2. Early (A) and late (B) changes in radiological lung density. The mean values and 95% confidence intervals estimated from the linear mixed effects model are presented. HU, Hounsfield units.



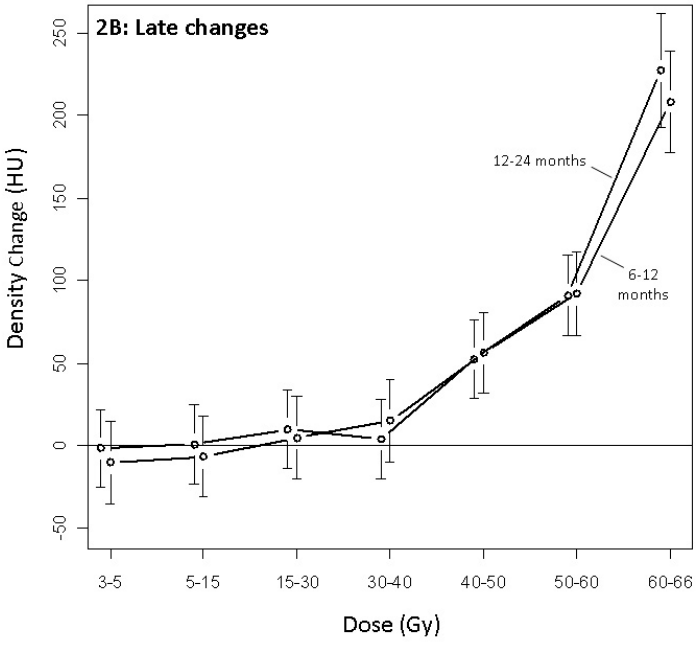


Table 2. Lung dose-density changes post-treatment (CCRT)

	0 – 3 months	3 – 6 months	6 – 12 months	12 – 24 months
Dose level (Gy)	**Mean change (HU)** *95% CI*	**Mean change (HU)** *95% CI*	**Mean change (HU)** *95% CI*	**Mean change (HU)** *95% CI*
3 – 30	**-12** *-34; 11*	**13** *-7.3; 34*	**- 4.1** *-25; 17*	**3** *-18; 24*
30 – 40	**6.3** *-20; 33*	**44** *19; 68*	**15** *-9.9; 40*	**3.9** *-20; 28*
40 – 50	**9.6** *-17; 36*	**77** *53; 100*	**56** *31; 81*	**53** *29; 76*
50 – 60	**7.3** *-20; 34*	**120** *94; 140*	**92** *67; 120*	**91** *67; 120*
60 – 66	**-10** *-41; 20*	**160** *130; 190*	**210** *180; 240*	**230** *190; 260*
Patients (n)	18	21	15	11
CT-scans (n)	20	25	26	33

CCRT, concurrent chemoradiotherapy; HU, Hounsfield units; CI, confidence interval; CT, computed tomography.

Discussion

To our knowledge, this is the first study investigating radiation-induced lung disease by measuring RLD changes on serial CT-scans in patients receiving modern, standard of care CCRT with a platin-based doublet and 3D volumetric radiation treatment with inhomogeneity corrections. We applied a novel method that uses deformable registration, which significantly improves accuracy over rigid registration techniques [14]. Significant increases in RLD are observed as early as 3 months after the last fraction of radiotherapy, and at a dose threshold of 30 Gy. Furthermore, RLD increases become more apparent in higher dose regions, and are more pronounced in patients with larger target volumes.

This approach of measuring RLD changes on serial CT-scans after CCRT appears to be promising in several ways. Objective quantification of RLD changes may contribute to a better understanding of the development of all radiation-induced lung disease, and the identification of a threshold dose of 30 Gy when using full-dose cisplatin–etoposide suggests that it could be used as a constraint dose for treatment planning. Modern delivery technologies such as respiratory gated and intensity modulated radiotherapy can allow for appropriate redistribution of lung doses using such constraints [17]. Measurement of RLD in protocols could potentially be used to screen for unexpected increases in early radiological changes (especially in low-dose regions) when investigating new chemotherapy agents or higher radiation doses or fractionation schedules. An example of a change in chemotherapy that may have exacerbated RP was observed in the randomized HOG-LUN 01–24 trial of CCRT using cisplatin–etoposide, followed by treatment with or without consolidation docetaxel. Clinical RP was reported in 14.6% of patients receiving docetaxel, but only 3.6% in the other arm [18]. In a comparison between conventional radiotherapy and continuous hyperfractionated, accelerated radiotherapy (CHART), respectively 19% and 10% of study patients had clinically relevant RP within first 3 months post-treatment, however at longer follow-up analysis (2 years) there was a trend for more ‘troublesome’ clinical RP in the CHART study arm [19].

The use of CT-scans for quantitative measurement of radiation-induced lung disease was reported as early as 1988 [10]. A subsequent prospective study in 119 patients with breast cancer undergoing postoperative radiotherapy studied mean lung density changes on CT-scans [11]. A study in a heterogeneous group of patients who received thoracic radiotherapy or CCRT (mostly for lung cancer) found RLD changes to correlate with increasing dose, and which increased during the first 6 months post-treatment before

levelling off [12]. In patients treated with stereotactic radiotherapy, however, a threshold dose of 6 Gy was found to be associated with increased density of normal lung tissue, with changes increasing after 6 months and plateauing at 40 Gy [15]. Our present study builds upon this previously published data, providing further understanding of the spatial and temporal distribution of these changes using a more accurate dose calculation and image registration technique, in a group of patients treated with a modern CCRT regimen.

The findings of this study must be considered in the context of its limitations. The study is retrospective in nature, and patient inclusion was based on the availability of CT-scans. This may have resulted in a highly selected patient cohort, which could in turn limit the generalizability of the conclusions and introduce confounders. Furthermore, the median radiological follow-up of 9.4 months in the present cohort is less than median survival observed in patients treated using CCRT outside clinical trials [16]. The fact that correlations were not observed between RLD changes and patient factors, dosimetric parameters and clinical RP, is likely due to the limited power with this sample size and the lack of a longer follow-up. Only seven patients in this cohort experienced clinically relevant RP, which is a subjective diagnosis that can be difficult in this patient population. In addition, early medical intervention of RP with steroids improves both clinical and radiological appearance of the patient, which could influence lung density measurements and correlation with clinical endpoints. However, pre-clinical data indicates a good correlation between CT density changes and histopathological changes in lung tissue [9].

In conclusion, this study on serial CT-scans after full-dose CCRT in stage III NSCLC patients demonstrates a threshold dose of 30 Gy for increased lung dose–density changes, with RLD increasing 3 months after treatment and plateauing by 1 year. The relationship between radiation-induced lung disease and development of clinical toxicity is unclear, and further research is needed to correlate these quantitatively-measured RLD changes with clinical endpoints.

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Chapter 6 figure 1. Two study cases demonstrating a central and peripheral tumour on planning scan and deformed follow-up scans.