Title: Long term radiological features of radiation-induced lung damage.

Running title: Radiological features of RILD

Authors:

Catarina Veiga[1], David Landau[2,3], Jamie R. McClelland[1], Jonathan A. Ledermann[4], David Hawkes[1], Sam M. Janes[5], and Anand Devaraj[6]

Affiliations:

[1]Centre for Medical Image Computing, Department of Medical Physics & Biomedical Engineering, University College London, London WC1E 6BT, UK
[2]Deparment of Oncology, Guy's & St. Thomas' NHS Trust, London SE1 7EH, UK
[3]Department of Oncology, University College London Hospital, London NW1 2PG, UK
[4]Cancer Research UK and UCL Cancer Trials Centre, UCL Cancer Institute, London W1T 4TJ, UK
[5]Lungs for Living Research Centre, UCL Respiratory, University College London, London, WC1E 6JF, UK
[6]Department of Radiology, Royal Brompton Hospital, London SW3 6NP, UK

Keywords: lung, radiation-induced lung damage, computed tomography, fibrosis

ABSTRACT

Purpose: To describe the radiological findings of radiation-induced lung damage (RILD) present on CT imaging of lung cancer patients 12 months after radical chemoradiation.

Material and Methods: Baseline and 12-month CT scans of 33 patients were reviewed from a phase I/II clinical trial of isotoxic chemoradiation (IDEAL CRT). CT findings were scored in three categories derived from eleven sub-categories: (1) parenchymal change, defined as the presence of consolidation, ground-glass opacities (GGOs), traction bronchiectasis and/or reticulation; (2) lung volume reduction, identified through reduction in lung height and/or distortions in fissures, diaphragm, anterior junction line and major airways anatomy, and (3) pleural changes, either thickening and/or effusion.

Results: Six patients were excluded from the analysis due to anatomical changes caused by partial lung collapse and abscess. All remaining 27 patients had radiological evidence of lung damage. The three categories, parenchymal change, shrinkage and pleural change were present in 100%, 96% and 82% respectively. All patients had at least two categories of change present and 72% all three. GGOs, reticulation and traction bronchiectasis were present in 37%, 52% and 44% of patients.

Conclusions: Parenchymal change, lung shrinkage and pleural change are present in a high proportion of patients and are frequently identified in RILD. GGOs, reticulation and traction bronchiectasis are common at 12 months but not diagnostic.

MANUSCRIPT

Introduction

Radiation-induced lung damage (RILD) is a side effect of radical radiotherapy (RT) and a significant cause of reduced quality of life in cancer survivors[1]. While the early, acute phase has been extensively investigated, the late, chronic phase of RILD is less well studied and described [2–6]. The historically poor prognosis of lung cancer patients has led to a lack of objective and standardised criteria to describe and quantify the process [4,7,8], leading to variable reporting across centres and trials. As lung cancer survivorship improves, the importance of long term treatment side effects grows [9–14].

Repetitive or severe lung injuries result in permanent radiological scarring, often referred to as fibrosis, that impairs lung function [15]. CT imaging is a sensitive indicator of RILD [16–22]. In addition to parenchymal density changes many other related abnormalities exist that are under-reported in the literature and poorly understood [5,17,20,21,23–29]. These include more obvious changes such as segmental collapse and pleural effusions, and more subtle changes such as traction bronchiectasis, elevation or tenting of the hemidiaphragm, mediastinal shift and rotation, distortion of major airways and pleural thickening.

Using patient data from the completed IDEAL CRT trial we studied the incidence of anatomical abnormalities found on CT imaging of lung cancer patients 12 months after RT, compared to their pre-treatment CT. This study is the first step toward developing a CT-based scoring system for RILD. The aim was to describe key radiological findings to inform the diagnosis of RILD.

Methods and Materials

Study design

Patient data were derived from the IDEAL CRT trial cohort [11]. This was a stage I/II clinical trial of isotoxic chemoradiation for patients with stage II-III non-small cell lung cancer (NSCLC). Patients received 63-73Gy RT in 30 fractions over 6 weeks or 63-71Gy in 30 fractions over 5 weeks (with one day of twice daily RT weekly) with two concurrent cycles of cisplatin and vinorelbine. The lung EQD2mean dose was planned to be 18.2Gy in all patients, so that although the tumour dose varied between patients, the lung dose was homogeneous across the entire cohort. The protocol called for CT scans to be performed at 12 months post-RT in all patients. Median overall survival (OS) for the 6-

week protocol was 36.9 months. The 5-week outcomes are pending full follow-up. Baseline and 12 month CT scans were collected centrally. Information on tumour stage, recurrence status and patient characteristics are presented in Table 1.

CT scans

Each patient underwent a baseline PET/CT or diagnostic CT before treatment and a diagnostic CT 12 months after treatment. Pairs of baseline and follow-up CT images were rigidly co-registered using the open-source NiftyReg software [30]. The transformation was optimised to match the anatomy of the thoracic vertebrae.

Scoring of radiological findings of RILD

Analysis of CT abnormalities was achieved by consensus in a multidisciplinary team: AD, thoracic radiologist, DL, clinical oncologist and CV, medical physicist. Scans were inspected in pairs (baseline vs follow-up) to assess new findings indicative of lung damage. There was no knowledge of the patient's identity or RT treatment details. Window and level settings were the same for all images (W=1300, L=-350). The abnormalities identified were categorised as follows: (1) parenchymal, (2) lung volume reduction, and (3) pleural.

Classification of radiological changes

Parenchymal findings of four types were noted as defined in Gotway *et al* (2005) (Figure 1): ground-glass opacities (GGO), consolidation, reticulation and traction bronchiectasis [31]. Since rounded consolidation and residual masses may have a similar radiological appearance [32,33], residual masses were defined as opacities with rounded shape in the same anatomical location of the initial tumour. Follow-up clinical and imaging data from the trial were used to identify residual masses with local recurrence.

Lung volume reduction measurement was recorded in five ways (Figure 2): reduction in lung height, distortion of ipsilateral pleural fissure anatomy, changes in the position and shape of the ipsilateral hemidiaphragm [23], displacement and/or thickening of the anterior pleural junction line[34], and gross distortions of the anatomy of the main bronchi. Reduction in lung height was assessed on coronal reconstructed images. Fissure distortion was identified through changes in the relationship between the oblique fissure and diaphragm on axial images. Distortions of the bronchial tree were identified on coronal views.

Pleural changes included thickening and effusion (Figure 3). Effusion is a region of homogeneous liquid at the boundary between the lung and thoracic cage. Thickening is an increase in the size of the pleural reflection, with the intensity of soft tissue and occurring at any interface between lung and thoracic cage.

In total three categories and eleven sub-categories of lung damage were analysed. For each patient, the presence or absence of each category and sub-category was annotated. Qualitative details on sub-types of patterns of damage were also recorded for future analysis. For the purposes of this analysis changes were not empirically measured but were recorded as present or absent based on routine inspection.

Results

Out of 120 patients in IDEAL CRT, baseline and 12-month scans were available for central review in 33 patients at the time of this analysis. All available pairs of baseline and 12-month scans were reviewed by the multidisciplinary team. For a total of six patients there was radiological evidence of major radiation damage that did not correspond to typical RILD. In five patients there was partial lung collapse due to airways damage. One patient had a lung abscess with extensive inflammatory change. These anatomical changes obscure the described findings of RILD. 27 patients are included in this analysis. The median time from end of treatment to time of second scan was 353 days, range: 265-367 days.

The number of patients with each category and sub-category of change is shown in Figure 4. Parenchymal changes were detected in all patients and volume reduction in all patients but one. Pleural changes were found in 82% of patients. All patients had at least two categories of lung damage and all three categories were present in 78% of patients.

Within the parenchymal category, the sub-category of consolidation was most commonly present, affecting 93% of patients. GGOs, reticulation and traction bronchiectasis were present in 37%, 52% and 44% of patients respectively.

In the volume reduction category, fissure and diaphragm distortion were present in 78% and 67% of patients respectively. Lung height was reduced in 59%. Major airways distortion and anterior junctional change were present in 63% and 78% respectively, representing mediastinal change. Pleural thickening was present in 70% and pleural effusion in 19%.

Table 2 shows more information regarding the patterns of damage and incidence for each sub-category.

Discussion

We performed a systematic assessment of RILD changes on CT scans acquired 12 months following radical CRT for NSCLC. The analysis was performed on scans from a prospective cohort of homogeneously treated patients within the IDEAL CRT study. IDEAL CRT made use of modern RT technologies, namely planning on 3D or 4D-CT imaging based planning, 3D-CRT or IMRT treatment delivery, and limited mean lung dose. Based purely on radiological findings, all patients had evidence of lung damage at 12 month of follow-up, with variable levels of severity. RILD is a common but often asymptomatic consequence of lung RT. Our findings demonstrate the extent to which it is under-reported across centers and trials. While different sub-categories of damage can also be encountered in other diseases, the patterns of change are quite different from other forms of lung damage [31,35]. These findings will be useful in differentiating RILD from other lung diseases.

The presence of radiation damage in all patients is a key finding of this study. In IDEAL CRT, the target dose was escalated from 63 to 73 Gy, which might explain the high incidence of radiological findings of RILD. However, for the reported cohort, patients with higher prescribed doses did not have higher numbers of sub-categories of RILD. Further investigation, comparing the incidence and severity of RILD in larger cohorts with varying treatment prescriptions is required.

Three key categories of change were identified on CT: lung parenchymal changes, lung volume reduction and pleural effusion or thickening. These were present in 100%, 96% and 82% of patients respectively and 78% of patients had all three categories of change. These changes are therefore frequently identified in RILD. Specific forms of parenchymal CT change, such as GGOs, reticulation and traction bronchiectasis, occur with sufficient frequency to be consistent with RILD.

Mah et al (1986) reported 6-month changes after non-conformal radical RT. They found that parenchymal changes (air bronchograms, present in 25%), loss of lung volume (15%) and pleural thickening (15%) were common findings. CT scan slices were at 1cm thickness and the quality of the scans was likely not up to modern standards. Less than half of the patients were treated for NSCLC and there was no record of how reduction in lung volume was defined. Kroenig et al (2001) studied 19 NSCLC patients after radical conformal RT of 69.6Gy to 90Gy. They too found evidence of RT damage in all patients, concentrating on parenchymal lung changes.

Parenchymal damage is of core interest in RILD as the lung is the key organ at risk. We have described various parenchymal changes which likely manifest according to the predominant process of damage in individual patients. GGOs have been interpreted as inflammatory but might also be fibrotic [17,36,37]. Reticulation and traction bronchiectasis are interpreted as fibrotic and are core diagnostic findings in idiopathic pulmonary fibrosis [35]. Consolidation could represent either an inflammatory or fibrotic processes and might be a common radiological endpoint for both. It is likely that RILD is a process with both chronic inflammatory and fibrotic mechanisms reflected in the radiological findings. This has been described in diffuse pulmonary fibrotic diseases [15].

The distinction between radiotherapy induced inflammatory and fibrotic changes on CT has sometimes been defined by time. That is, changes before 6 months are described as most likely representing inflammation and those beyond 12 months most likely fibrotic [21,29]. The period of 6 to 24 months is often accepted as the period of stabilisation of fibrosis [17,38]. This paper describes CT changes 12 months following RT, a time point by which one might predict there to be little or no residual inflammatory changes. We have described significant consolidation and GGOs at 12 months. Whether these findings represent significant ongoing inflammation or areas of fibrosis is uncertain. A review of CT scans at 24 months is required to verify whether these changes persist or resolve. Identifying the presence of a chronic inflammatory process is important because it offers the possibility of successful intervention to reduce the extent of RILD even at a relative late stage.

Lung volume reduction as demonstrated by visible lung volume and mediastinal changes was evident in almost all patients (96%). Volume loss reflects fibrotic change including extensive microscopic fibrosis not apparent with standard CT imaging. It remains to be seen whether more quantitative measures of volume loss on CT necessarily correlate with clinical markers of lung damage.

The commonly observed finding of pleural changes has not been previously recognised as a classic RILD finding [5,6]. Clinical pleural syndromes are not commonly reported after RT. It is unknown whether these changes are caused by direct RT damage or through a reaction to parenchymal lung changes.

RILD scoring systems are based on clinical, radiological and functional criteria, such as the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring system, and the Common Terminology Criteria for Adverse Events (CTCAE) [39,40]. Based on our findings the radiological components of these systems may be inadequate. RTOG/EORTC criteria score non-specified ‘radiological changes’ as either slight, patchy or dense. CTCAE scores pulmonary fibrosis radiologically on the extent of ‘radiological pulmonary fibrosis’ from <25% to <75% and adds ‘honeycombing’ in grade 4. These

criteria may well be appropriate for other causes of pulmonary fibrosis but seem inappropriate for use in RILD. Radiology-only scoring systems have been proposed based on qualitative assessments of CT intensity and texture changes. These have mostly been applied in the context of conventionally fractionated RT for early follow-up scans (≤6 months) [5,41] or multiple time-points over 36 months [6,18]. There are also studies following stereotactic RT that score RILD in terms of consolidation sub-types [20,22,42,43]. In these studies only parenchymal changes are considered. In stereotactic delivery the lung volumes irradiated are considerably smaller, and hence a radiological-system looking only at parenchymal consolidation is likely adequate. We have demonstrated that indirect signs of lung volume loss characterized by a variety of anatomical deformities, as well as the identification of pleural abnormalities, may be critical in diagnosing RILD following conventionally fractionated RT.

The spatial relationship between RILD and radiation dose is crucial and requires further detailed research investigating both local dose and global lung doses. We are exploring co-registration of images to propagate planning isodose surfaces [44,45]. Parenchymal changes seem to occur in areas of higher dose (approximately 40Gy and greater). Anatomical distortion and pleural reactions reflect dose delivered in distant anatomical locations. The lung doses in IDEAL CRT were relatively homogeneous, and dose relationship studies require advanced statistical methods such as principal component analysis of DVHs and permutation testing [46,47].

Our study has limitations. We have used an exhaustive examination of a relatively small cohort to define the key parameters with which to interrogate future large numbers. Another limitation is that the initial clinical trial was not designed to identify symptoms specific to the findings that we have now described. Lung function, MRC breathing score and performance status are available and will be investigated. More specific questions would be required to fully examine the clinical impact of RILD CT changes.

We have demonstrated that RILD changes occur in all patients following radical RT for NSCLC. We have purposely limited our study to clinically identifiable radiological changes aiming to describe them in a manner potentially transferrable to the clinic. We believe this is the first step towards generating a validated radiological scoring system that is objective, clinically sound, easily interpretable, repeatable and user independent that provides relevant information on RILD. To date there is still no objective scoring systems of long term RILD which leads to variability in reporting of toxicity amongst trials [48]. In the case of pneumonitis studies, other groups have worked on developing deformable image registration based methods to measure local changes in the parenchymal texture, which correlate well with radiologist scores of pneumonitis [49,50]. However, as found in this study, long term RILD causes both complex changes in the lung parenchyma and

distortions on thoracic anatomy. These changes pose a difficult challenge for image registration, described by our group elsewhere [45]. Next steps include developing objective quantification methods using image analysis techniques independent of image registration [51,52] and correlating radiological findings with clinical measures of respiratory function and with radiation dose distribution.

Acknowledgments

The authors would like to thank the Cancer Research UK and UCL Trials Unit, in particular Kate Frost, Yenting Ngai, Gita Parmer, and Ben Gallagher for data retrieval. The IDEAL CRT trial was funded by Cancer Research UK, grant number C13530/A10424. S.M.J. is a Wellcome Trust Senior Fellow in Clinical Science (WT107963AIA) and is supported by Rosetrees Trust, the Roy Castle Lung Cancer Foundation, The Mick Knighton Mesothelioma Research Fund, the Welton Trust, the Garfield Weston Trust and UCLH Charitable Foundation. This work was partially undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme and the CRUK Lung Cancer Centre of Excellence (S.M.J.). D.H. is supported by the CRUK/EPSRC Cancer Imaging Centre. J.R.M. and D.H. are supported by a Cancer Research UK Centres Network Accelerator Award Grant (A21993) to the ART-NET consortium.

Conflict of interest statement

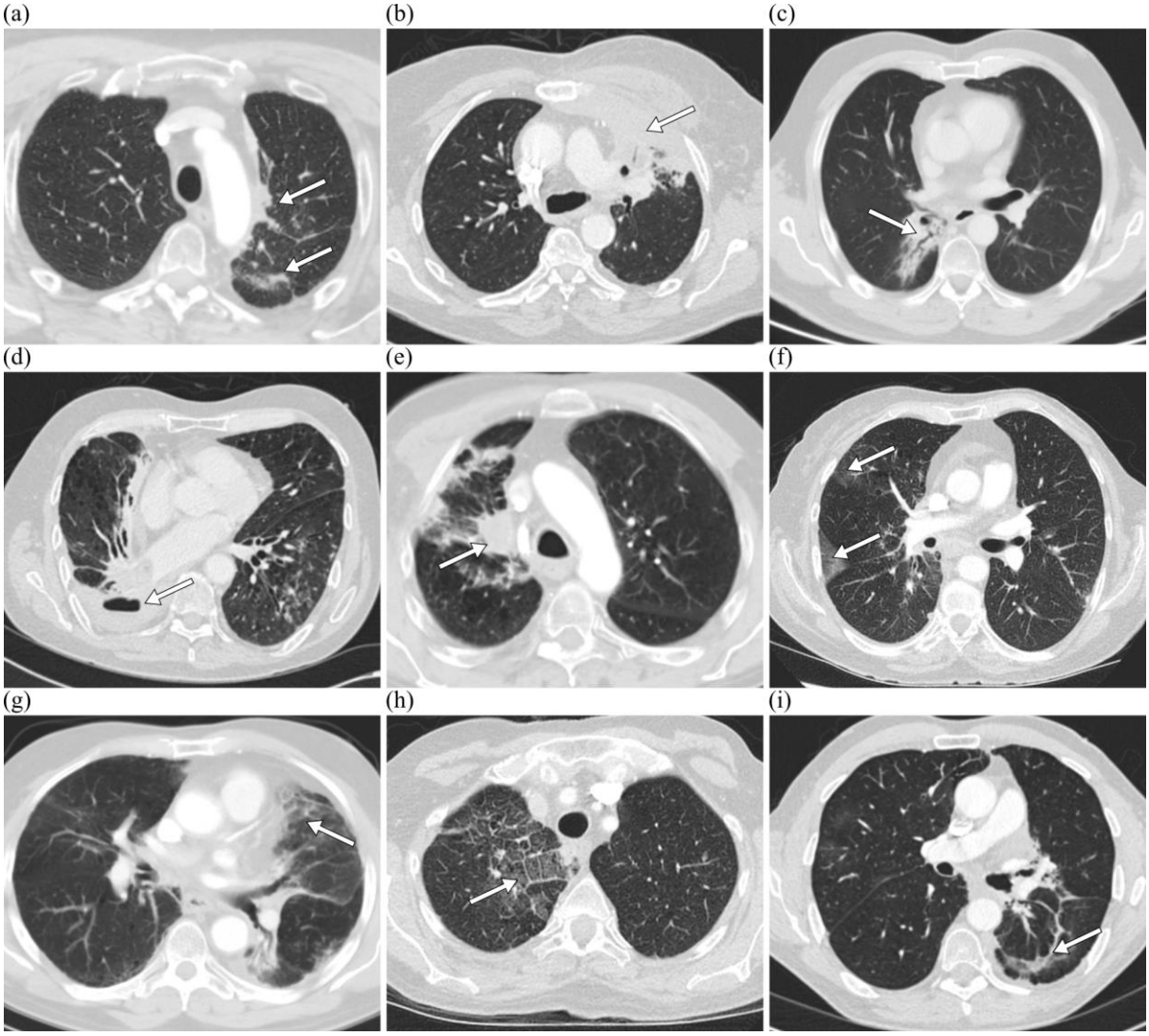
The authors declare that they have no conflicts of interest.

Figure and table captions

	No. Patients (N=27)
Age (y)	
≥70	5
<70	22
Mean (±SD)	66 (±7)
Median (range)	65 (53-83)
Sex	
Male	20
Female	7
Stage	
IIA	0
IIB	1
IIIA	17
IIIB	9
Fractionation scheme	
6-weeks protocol	17
5-weeks protocol	10
Radiotherapy technique	
Conformal	24
IMRT/VMAT	3
GTV size* (cm^3)	
Mean (±SD)	104 (±57)
Median (range)	101 (14-211)
PTV size* (cm^3)	
Mean (±SD)	400 (±149)
Median (range)	358 (202-832)
Prescription dose (Gy)	
Mean (±SD)	67.9 (±3.8)
Median (range)	69.1 (63.0-73.0)

*calculated on 3D or 4D-CT used for planning. On 4D-CT a composite volume was formed by merging the GTV outlined on different phases.

Table 1- Demographics and baseline characteristics of all patients.



300

Figure 1- Patterns of parenchymal change. (a) Low volume of consolidation; (b) High volume of consolidation. (c) Consolidation accompanied by a distorted airway in keeping with traction bronchiectasis. (d) Cavitating consolidation. (e) Residual mass surrounded by consolidation. (f) Ground-glass opacities. (g)(h)(i) Examples of reticulation patterns.

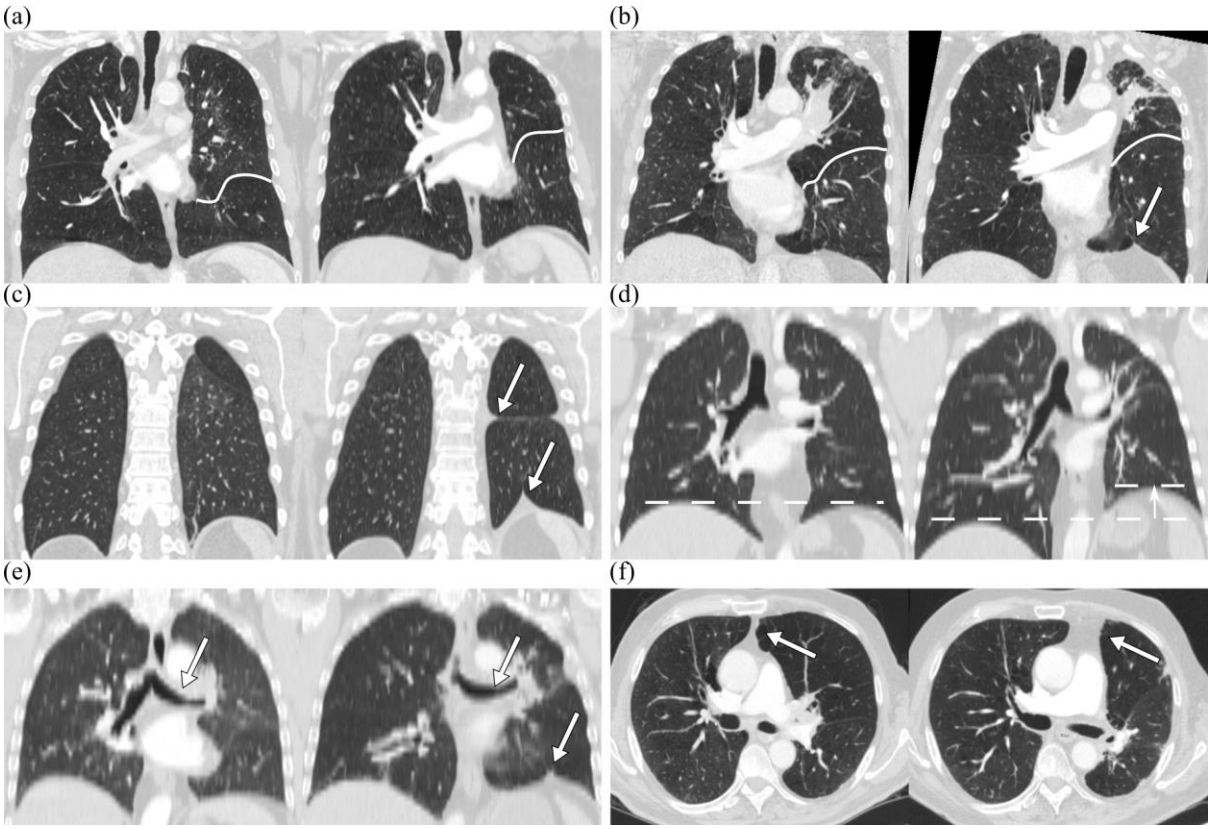
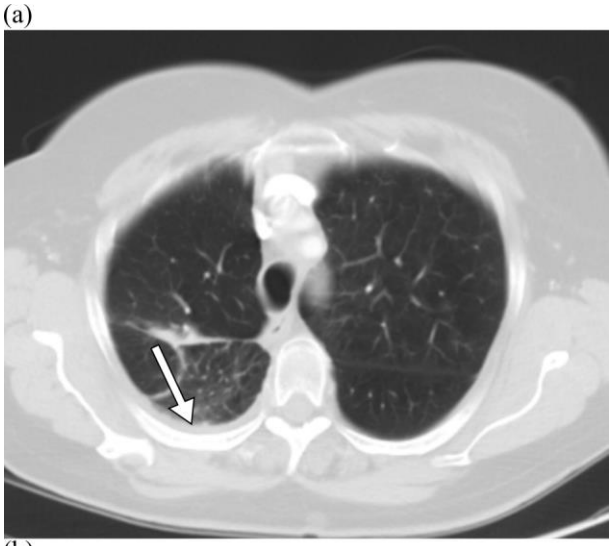


Figure 2- Lung volume reduction (left: pre-treatment scan, right: 12-month follow-up scan). (a) Marked distortion of the fissure in the absence of consolidation. (b) Distortion of fissures accompanied by consolidation, volume loss and aggravation of pre-existing diaphragmatic tenting. (c) Diaphragmatic tenting combined with mild elevation, and pleural thickening at the fissure. (d) Elevation of the diaphragm, combined with elevation of the left upper main bronchus. (e) Left main bronchi pulled upward, together with minor diaphragmatic elevation and tenting. (f) Rotation and thickening of the anterior junction line.

(a)



(b)

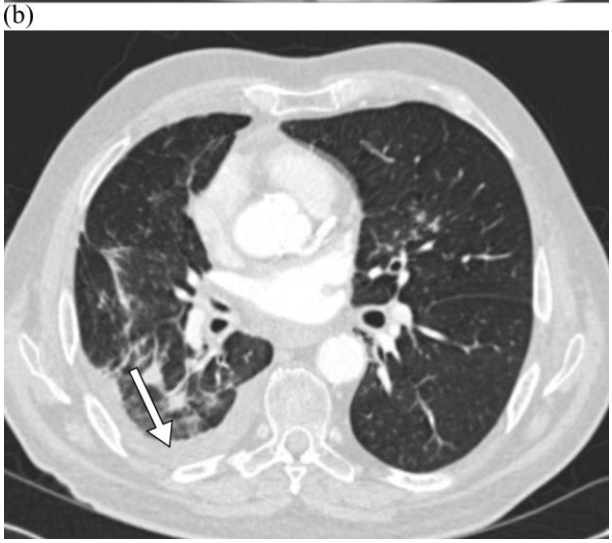


Figure 3- Pleural reactions. (a) Pleural thickening. (b) Pleural effusion.

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Change	No. of Patients (N=27)
Parenchymal	**27**
Consolidation	25
of which	
Cavitation	2
Ground-glass opacities	12
Traction bronchiectasis	10
Reticulation	14
of which	
Focal linear opacities	11
Band opacities	3
Residual mass	7
of which	
Local recurrence	5*
Volume reduction	**26**
Reduction in lung height	16
Fissure distortion	21
of which	
Pulled forward	14
Pulled backward	5
Pulled upward	6
Pulled medially	2
Flipped	1
Diaphragm distortion	18
of which	
Elevation	7
Tenting	13
Changes in curvature	5
Anterior junction line distortion	21
of which	
Rotation	18
Thickening	15
Major airways distortion	17
of which	
Pulled upward	13
Pulled downward	2
Stenosis	1
Pleural reactions	22
Thickening	17
Effusion	3
Thickening and effusion	2

*confirmed with trial follow-up data

Table 2- Frequency of each sub-type of lung damage.

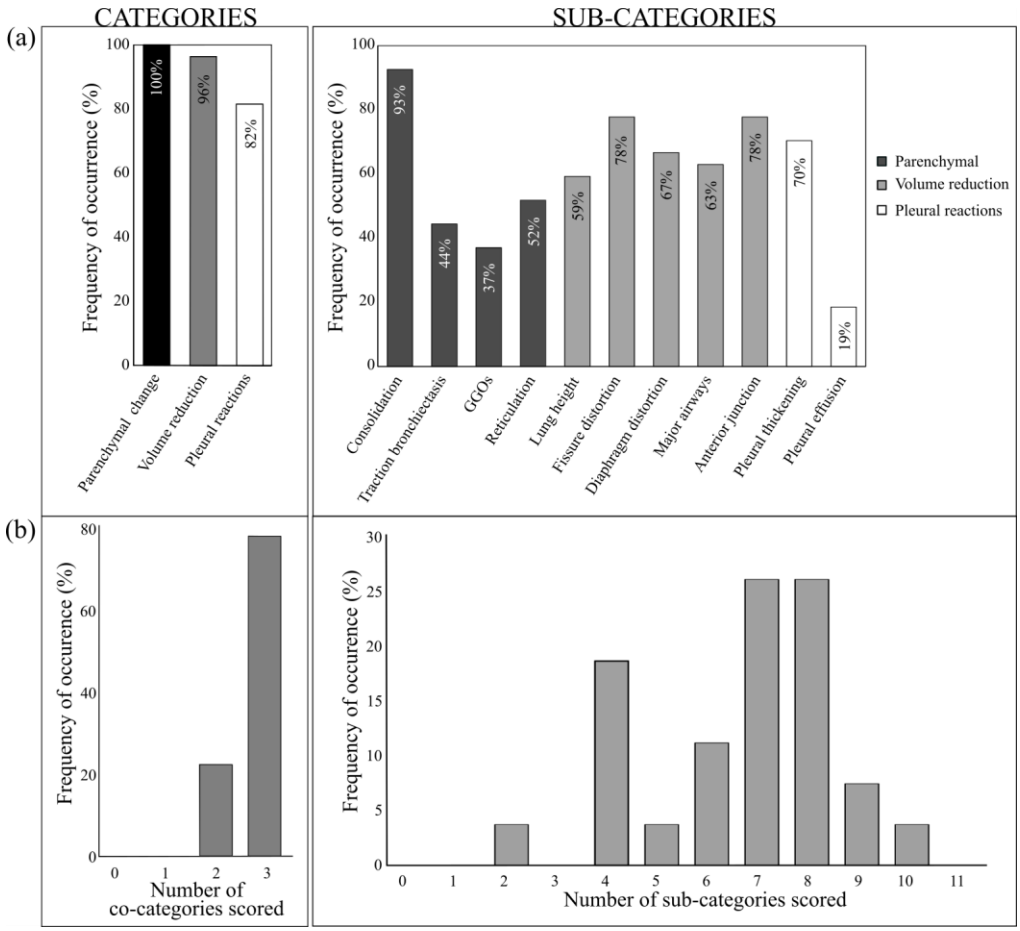

Figure 4 - (a) Incidence of different categories and sub-categories of change at 12-months after radiotherapy. (b) Incidence of categories and sub-categories of change scored per patient.

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