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Original article

Extent and computed tomography appearance of early radiation induced lung injury for non-small cell lung cancer

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ABSTRACT

Background and purpose: The present study investigates the extent and appearance of radiologic injury in the lung after radiotherapy for non-small cell lung cancer (NSCLC) patients and correlates radiologic response with clinical and dosimetric factors.
Methods and materials: Eligible follow-up CT scans acquired up to six months after radiotherapy were evaluated for radiologic injuries in 220 NSCLC patients. Radiologic injuries were divided into three categories: (1) interstitial changes, (2) ground-glass opacity, or (3) consolidation. The relationship between the fraction of injured lung of each category and clinical or dosimetric factors was investigated.
Results: Radiological injuries of category 1–3 were found in 67%, 52%, and 51% of the patients, and the mean (and maximum) fraction of injured lung was 4.4% (85.9%), 2.4% (46.0%), and 2.1% (22.9%), respectively. Traditional lung dose metrics and time to follow-up predicted lung injury of all categories. Older age increased the risk of interstitial changes and current smoking reduced the risk of consolidation in the lung.
Conclusion: Radiologic injuries were frequently found in follow-up CT scans after radiotherapy for NSCLC patients. The risk of a radiologic response increased with increasing time and lung dose metrics, and depended on patient age and smoking status.

Radiation-induced lung injury is the main dose-limiting toxicity for lung cancer patients. It is typically divided into radiation pneumonitis (RP), occurring in a transient, acute phase up to 6 months after radiotherapy, and lung fibrosis, which is persistent in nature and develops in the following months or years in response to the initial tissue injury [1–3]. Symptomatic RP is observed in up to 10–20% of locally advanced lung cancer patients undergoing curatively intended radiotherapy [4]. The incidence of RP depends on the choice of grading system, and scoring is challenging due to confounding medical conditions [5]. Furthermore, patients may be asymptomatic, but still have radiologic evidence of lung injury [6]. In the acute phase, lung injuries manifest radiologically as ground-glass opacities (GGO) characterized by moderately increased densities in the lung parenchyma, or as consolidation, while lung fibrosis typically is characterized by volume loss, scarring, consolidation, and traction bronchiectasis [7]. In follow-up computed tomography (CT) images of lung cancer patients, intrapulmonary abnormalities have been reported in 63% of the cases [8]. The high incidence rate and the possibility to estimate the injury on an objective scale, makes it a suitable endpoint in radiobiological response modelling.

Several measures of radiological injury based on the relation between local dose and change in lung density after radiotherapy have been developed [9–12]. However, these require the use of advanced data processing including deformable image registration which may impair the analysis in many institutions. Simpler scoring systems have been devised based on the appearance of the pulmonary abnormalities and whether they conform to the radiation portals [13,14]. These methods were developed in the era of 2D conventional radiotherapy, but have been used to grade radiologic injuries in more advanced techniques [8,15–18]. The lower grades typically correspond to moderately increased density and higher grades involve consolidation. This poses a problem since massive lung injuries may be lethal in the acute phase where consolidation may not have had time to develop. Furthermore, the exact grade depends on whether the abnormality conforms to high dose areas. For patients treated with intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), it may be difficult to

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define which isodose line that should encompass the abnormality, and, fundamentally, an absolute grading scale should not depend on the lung volume irradiated but on the relative volume of the injury compared to the volume of the entire lung.

The current study introduces a simple grading system for radiologic lung injuries based on the CT appearance and the fraction of the lung involving the abnormalities. Early lung injuries of three different categories of appearance were graded retrospectively for a large cohort of non-small cell lung cancer (NSCLC) patients, and the relationship between injury grade and clinical or dosimetric factors was investigated.

Methods and materials

All 294 NSCLC patients treated to a prescribed dose of 60 or 66 Gy in 30–33 fractions using cone-beam image guide radiotherapy at Odense University Hospital in the period from 2007 to 2013 were considered for inclusion. For these patients, a follow-up CT scan was performed every third month for two years. For the present study, all follow-up CT scans acquired within six months from commencement of radiotherapy were retrieved. 258 patients had at least one follow-up scan acquired in this period. However, 22 of these patients were excluded as they did not have at least one follow-up scan without clinical or radiological evidence of local recurrence or thoracic metastases, while 16 patients were excluded because of unavailable dose plan objects. This resulted in a final cohort of 220 patients eligible for further analysis (see Table 1). In total 361 follow-up scans were analysed. 132 patients had scans acquired both before three months and between three and six months after commencement of radiotherapy.

The patients were treated with IMRT or VMAT on Elekta Synergy accelerators. For radiotherapy treatment planning purposes, 4D CT scans with a slice thickness of 2.5 or 3 mm plans were acquired. Treatment plans were created using Pinnacle DMPO or SmartArc segmentation algorithms for IMRT or VMAT planning, respectively. The Collapsed Cone algorithm with density correction was used for dose calculation.

The follow-up scans were acquired on a variety of CT scanners using slice thicknesses ranging from 0.6 to 7 mm. A single experienced radiographer examined each scan and compared it to the planning CT for the presence of new radiologic injuries. For each scan, the fraction of lung affected was estimated using the following methodology: In the planning CT, the volume of the bounding box surrounding the gross tumour volume (GTV), V_{GTV} was measured. In a follow-up CT, the combined volumes of the bounding boxes surrounding each lung, V_{Lung}, as well as the combined volumes of the bounding boxes surrounding the injured part of each lung, V_{Injury} was measured. In all cases, the bounding box was defined from the characteristic lengths of the structure in the three principle axes. The fraction of normal lung affected in a follow-up scan was estimated by

$$F_{est} = \frac{V_{Injury} - V_{GTV}}{V_{Lung} - V_{GTV}}.$$

The volume of the GTV was subtracted because the injuries often were found in the vicinity of the tumour area. Negative values of F_{est} were set to zero.

To investigate the validity of this method, the fraction of affected lung was also measured by delineating the lung and the injured part of the lung in Pinnacle for 20 patients selected to obtain a variety of estimated volume fractions. The Pearson correlation coefficient between estimated and delineated volume fractions was determined and deviations between methods were investigated using a Bland–Altman plot.

Table 1
Characteristics of the 220 patients.

Characteristic	n[a]	%
Gender		
Male	112	51
Female	108	49
Age		
Median	67	
Range	33–85	
Performance		
0	62	28
1	115	52
2	41	19
3–4	2	1
Stage		
1–2	42	19
3	152	69
4	6	3
Recurrence	20	9
Histology		
Squamous cell carcinoma	100	45
Adenocarcinoma	88	40
Other[b]	32	15
Current smoking status		
Smoking	106	48
Not smoking	114	52
FEV_1 [l/min]		
Median	1.8	
Range	0.6–4.5	
GTV volume (cm^3)		
Median	32	
Range	0–400	
Total radiation dose (Gy)		
60	56	25
66	164	75
Mean lung dose (Gy)		
Median	17	
Range	1–25	
Chemotherapy		
No	45	20
Only neoadjuvant	32	15
Only concomitant	4	2
Both neoadjuvant and concomitant	139	63

Abbreviations: GTV = Gross tumour volume.
[a] n denoted number of patients unless otherwise indicated.
[b] Large cell carcinoma, undifferentiated, atypical carcinoid, unspecified.

Radiologic injuries were divided into three categories based on appearance. Category 1 represented interstitial changes characterized by moderately increased densities in the lung parenchyma identified by pronounced vessels and borders. Category 2 represented ground-glass opacities (GGO) also characterized by moderately increased densities but appearing diffuse, amorphous, and with poorly defined vessel structures. Category 3 indicated patchy or confluent consolidation in the lung. See Fig. 1 for a case example. The amount of injury in each category for each scan was estimated by the radiographer as a fraction of V_{Injury} in steps of 0.05.

For outcome modelling, the CT scan with the highest fraction of lung affected of each category was selected. Injuries of each type were graded according to the following scale. Grade 0 represented no injury, Grade 1 corresponded to a fraction of lung affected in the range 0–0.05. For Grade 2 the range was 0.05–0.1, while Grade 3 corresponded to a fraction of lung affected above 0.1. The choice of the thresholds was based on examination of the final grading distributions (see Fig. 2b). The thresholds were chosen to result in distributions with a sufficient number of patients in each group to stabilize the following outcome models. Including grades higher than 3 would have resulted in groups with very few patients in the current patient cohort, but this may be relevant in other cohorts.

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