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A new CT-based method to quantify radiation-induced lung damage in patients

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SUMMARY

A new method to assess radiation-induced lung toxicity (RILT) using CT-scans was developed. It is more sensitive in detecting damage and corresponds better to physician-rated radiation pneumonitis than routinely-used methods. Use of this method may improve lung toxicity assessment and thereby facilitate development of more accurate predictive models for RILT.

The risk of Radiation-induced lung toxicity (RILT) is the crucial clinical bottleneck limiting the treatment dose in locally advanced lung cancer [1,2]. Current models to estimate the risk of developing RILT are not very discriminative. This may be both due to the large diagnostic uncertainties of up to 48% in the assessment of radiation pneumonitis (RP) [3] and due to the absence of reliable objective tests to measure RILT. This diagnostic uncertainty may be decreased by using objective quantitative parameters by e.g. imaging of underlying biological effects [4], changes in density [5–7] or consequential changes in different aspects of pulmonary function [8,9].

Changes observed on CT-scans may reflect radiation-induced changes in lung tissue including parenchymal inflammation and fibrosis [10,11]. Besides direct measurements of biological changes, several studies therefore utilized quantitative analysis of CT-scans as a surrogate for histopathological changes after chest radiotherapy [12–14]. However to explain a broad range of radiation-induced histopathological changes only (regional) mean density changes of the lung were quantified. The relation between this quantity and clinical RP [15] as well as pulmonary function [16–18] is however weak. Similarly, a weak relation was observed between changes in mean (local) lung density and symptoms of RP such as dyspnea and inflammation in a rat model [19]. These findings suggest that the analysis of changes in mean lung density may be insufficiently sensitive to mirror clearly observable radiation induced histopathological sequelae.

While extensive fibrosis indeed changes local mean density, pulmonary inflammation has more influence on the uniformity of the density which can be quantified by changes in standard deviation of the density [19,20]. To improve the sensitivity of current methods we previously combined mean density changes with the standard deviation of the density into one single measure (ΔS) to assess CT-derived structural changes [19,20]. Contrary to the mean density alone, ΔS strongly correlated with post radiation pulmonary dysfunction and histopathological changes in rats [19]. Therefore, in the present study we tested whether our ΔS-method improves sensitivity to detect tissue damage in CT-scans and indeed corresponds to clinical RP in patients.

Materials and methods

Study design

Patients with NSCLC (UICC stage II/IIIA/IIIB) or limited-disease small cell lung cancer (SCLC) referred for chemoradiation were eligible. In the case of NSCLC, the radiation dose was 60 Gy in 25 fractions 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/25 fx concurrently with cisplatin and etoposide. Dose constraints used for treatment planning 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

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committee and all patients gave written informed consent prior to treatment.

CT-scans

Deep inspiration breath-hold scans were performed. Settings included a slice thickness of 1.5 mm, 1.5 mm inter-slice distance, 0.5 s rotation time, pitch 0.75, 512 × 512 pixels. Since typically radiation pneumonitis is diagnosed within 6 months after treatment, CT-scans were performed prior to the start of radiotherapy and at 6 and 24 weeks after completion of treatment. To allow optimal image registration, patient positioning was identical on all time-points. In brief, 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 intravenous contrast agents were used.

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 spatially aligned using deformable image registration implemented in Elastix [21]. The pre-treatment CT-scan was used as intra-individual reference-scan for every patient. More details can be found in the Supplementary methods section.

Quantification of local structural lung changes

Radiation induced-changes in the lung tissue were assessed locally (in $4.5 \times 4.5 \times 4.5\ mm^3$ cubes) either by quantifying local mean density (Δmean) or Δ*S* including changes in the structure [19]. The results from quantification of Δ*S* and Δmean were compared to test their sensitivity for detection of radiation-induced damage at different time points after radiotherapy. Cubes consisting of more than 95% of voxels with low density (HU $\leqslant$700) pre-treatment were assumed to be lung parenchyma and included in the analysis. Cubes inside the planning target volume (PTV) were excluded, to avoid inclusion of tumor 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). More details can be found in the Supplementary methods section.

Quantification of the sensitivity of *Δmean* and *ΔS*-based methods

To establish the detection thresholds for either method, two pre-treatment deep-inspiration breath-hold scans were performed in three patients who were not included in the study. Subsequently, the pre-treatment scans were geometrically aligned and Δmean and Δ*S* methods were applied to the deformed scans. Local values of Δmean and Δ*S* maps were averaged inside the lungs. The values obtained from the 3 patients were subsequently averaged to define the threshold values: 0.43 ± 0.04 (HU) for Δmean, and 0.27 ± 0.02 for Δ*S*.

Clinical scoring of radiation pneumonitis

Patients were seen by the treating radiation oncologist on the days the CT scans were performed (6 weeks and 24 weeks after the completion of radiation treatment) and RP was scored according to the SWOG criteria. (Grade 1 = radiographic changes only/symptoms, not requiring steroids, grade 2 = symptoms requiring steroids, grade 3 = symptoms requiring oxygen.)

Statistics

To test whether the changes in Δmean and Δ*S* were statistically significant from the detection threshold, two-sided independent samples *t*-tests were performed. The area under the receiver operating characteristic curve (ROC curves) was used to assess the correspondence of both methods with the SWOG. The curves were then compared under a non-parametric assumption. Calculations were performed using SPSS version 19.0. Statistical significance was set at $p < 0.05$.

Results

Twenty patients were enrolled. Treatment parameters and patient characteristics are shown in Table 1. 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 without chemotherapy, consisting of 39 Gy/13 fx instead of the planned 60 Gy/25 fx because of deteriorating general condition.

ΔS method is more sensitive in detecting structural lung changes than Δmean method

The sensitivity to detect CT-changes of the two methods – irrespective of the given dose – was compared quantitatively employing the respective detection thresholds (0.43 ± 0.04 HU and 0.27 ± 0.02 for Δmean and Δ*S*, respectively, see Methods and Materials). In each patient, voxels were grouped based on their Δ*S* value falling in the same range. Subsequently, Δ*S* and Δmean values of these groups of voxels were averaged. Finally, these Δmean and Δ*S* values were again averaged over all the patients. Fig. 1a shows

Table 1
Patient characteristics.

N	Sex	Age	cTNM	Pathology	Radiation dose (total dose/fx)	Mean lung dose (Gy)	V5	V10	V15	V20	Concurrent chemotherapy	SWOG score radiation pneumonitis
1	M	62	cT3 N0 M0	NSCLC	60 Gy/25 fx	13.1	56	28	22	21	Yes	2
3	M	70	cT4 N3 M0	NSCLC	60 Gy/25 fx	17.7	74	60	41	32	Yes	0
4	M	82	cT4 N3 M0	NSCLC	60 Gy/25 fx	17.0	53	42	31	28	Yes	2
5	M	82	cT2 N2 M0	NSCLC	39 Gy/13 fx	12.2	51	35	30	27	No	1
6	M	60	cT2 N1 M0	NSCLC	60 Gy/25 fx	12.8	49	30	25	21	Yes	2
8	M	77	cTx N3 M0	NSCLC	60 Gy/25 fx	15.3	55	43	34	29	Yes	0
10	M	59	cT4 N3 M0	NSCLC	60 Gy/25 fx	14.7	53	42	30	26	Yes	0
11	M	72	cT2 N2 M0	NSCLC	60 Gy/25 fx	16.4	56	36	29	26	Yes	2
12	M	75	cTxN3 M0	SCLC	50 Gy/25 fx	17.3	65	50	38	33	Yes	1
14	M	79	cT4 N0 M0	NSCLC	60 Gy/25 fx	11.3	44	22	18	17	Yes	1
16	V	53	cT3 N0 M0	NSCLC	60 Gy/25 fx	3.7	10	7	6	5	Yes	0
19	V	52	cT2 N2 M0	NSCLC	60 Gy/25 fx	17.0	63	48	42	39	Yes	0
20	M	74	cT4 N2 M0	NSCLC	60 Gy/25 fx	10.7	38	20	18	17	Yes	1

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