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Radiation induced lung damage

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.

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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 ΔS including changes in the structure [19]. The results from quantification of ΔS 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 ΔS methods were applied to the deformed scans.

Local values of Δmean and ΔS 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 ΔS.

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 ΔS 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 ΔS, respectively, see Methods and Materials). In each patient, voxels were grouped based on their ΔS value falling in the same range. Subsequently, ΔS and Δmean values of these groups of voxels were averaged. Finally, these Δmean and ΔS 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
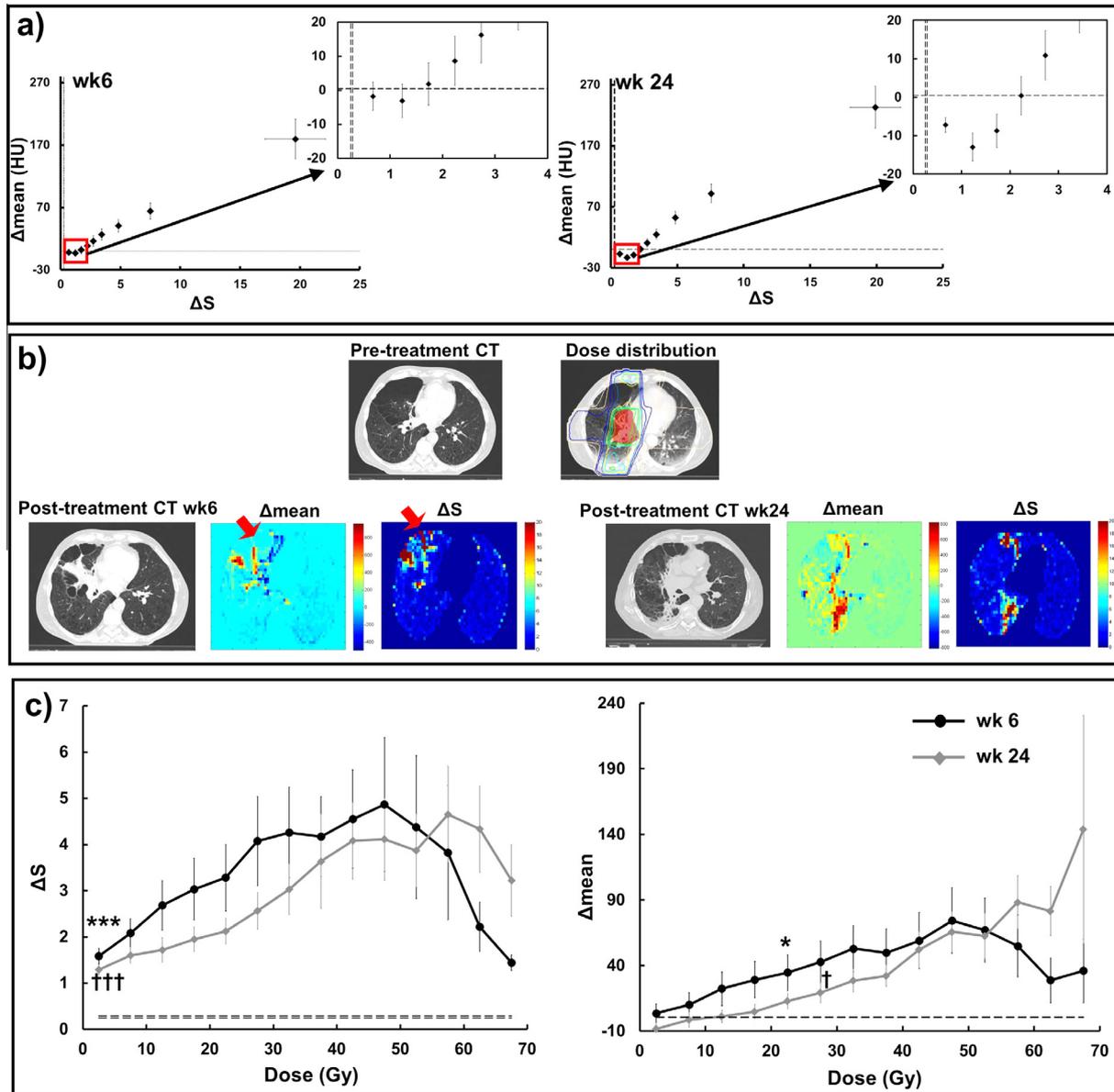
Fig. 1. ΔS method is more sensitive in detecting structural lung changes than Δmean method. (a) The sensitivity of Δmean and ΔS methods was compared quantitatively regarding the detection threshold and irrespective of the given dose at week 6 (left) and 24 post-treatment (right). The horizontal and vertical dotted lines: level of the detection threshold of the damage by Δmean and ΔS methods, respectively. (b) ΔS and Δmean sensitivities in detecting damage were visualized in patient #4 at 6 (left) and 24 (right) weeks post-RT. Six weeks post-treatment, dense consolidation of lung tissue is observed suggestive of radiation pneumonitis (left) which resolved at 24 weeks but then fibrosis developed according to the beam arrangement (right). Six weeks post-RT, ΔS, incorporating non-uniformity of the density, could detect structural changes that were not detected using Δmean, only based on the density itself (indicated by the red arrows). (c) Dose response of ΔS (left) and Δmean (right) was shown in the patient population at weeks 6 and 24 post-RT. A clear steep dose-dependent increase of ΔS was observed. Regarding the detection threshold of ΔS method (dotted line) the increase in ΔS is significant starting already at 0–2.5 Gy regions at both time-points ([***]$p < 0.001$ wk-6 and [†††]$p < 0.001$ wk-24). Changes in Δmean 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 weeks 6 and 24 respectively. Data are presented as mean ± SEM. Dotted lines: detection threshold of the damage. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the combination patient-averaged Δmean and ΔS values. Unlike Δmean, all values of the ΔS were above its detection threshold (vertical dotted lines), indicating the higher sensitivity of the ΔS method, both at week 6 and week 24 (Fig. 1a). This higher sensitivity was visualized in an example (Fig. 1b). Here, in the post-treatment CT-scan of week 6, ΔS could detect structural changes that were not detected using Δmean (indicated by the red arrows).

To assess the sensitivity of the two methods in detecting radiation-dose-dependent lung damage, curves of ΔS and Δmean as a function of dose were generated for the entire population (Fig. 1c). In the highest dose bin (62.5–67.5 Gy), a steep rise or

decrease in lung density was observed in some patients. This phenomenon has been observed in other studies [22] and may be due to density increases complicating proper segmentation and registration of lung tissue. Comparing changes in ΔS with Δmean with reference to their detection levels (dotted horizontal lines), ΔS changes can be detected at lower dose levels than Δmean (Fig. 1c). Since the range of mean density changes measured in the present study was comparable with a study using similar radiotherapy techniques [12], our results suggest that the ΔS method is more sensitive in detecting radiation damage from CT scans than the Δmean method.

ΔS corresponds better to physician-rated score and symptoms

We next investigated whether the ΔS method corresponds better than the Δmean method to physician-rated pneumonitis. The outcomes of both methods at 6 weeks post-treatment were therefore related to RP SWOG scoring $\geqslant 1$ and RP SWOG scoring $\geqslant 2$. Although the number of patients in the current study was small, the ROC curve analysis showed that the ΔS method was more sensitive and specific than Δmean in detecting clinical assessment of RP SWOG scoring $\geqslant 1$ (Supplementary Fig. S4a) and SWOG scoring $\geqslant 2$ (Supplementary Fig. S4b). This suggests that inclusion of variation in the uniformity of the density (ΔS-method) may account for inflammation changes explaining the additive value of ΔS above Δmean for assessing the damage at 6 weeks post-treatment.

Discussion

Dose that can be administered to thoracic tumors is still limited by the risk of e.g. pulmonary complications. Better prediction of the risk of such complications would facilitate further individualization of the treatment of these tumors. The accuracy of predictive models for radiation pneumonitis, however, is determined by e.g. the quality of the data they are based on. Unfortunately the assessment of pulmonary toxicity is subject to considerable inter-observer variability [23].

To overcome this, various quantitative imaging methods have been proposed. Some focus on quantification of mechanisms involved in the development of the toxicity [4]. However, although related to the mechanism by which toxicity develops, the exact relationship to clinical symptoms is not straightforward. Moreover, the requirement of clearly non-routine investigations (e.g., hyperpolarized (1)(3)C-pyruvate Magnetic Resonance Spectroscopic Imaging) limits its clinical applicability, Alternatively the consequential changes in different aspects of pulmonary function [8,9] have been quantified. However, also here the relationship to patient complaints and physician assessment remains weak [8,9]. Others rather quantify the net outcome in terms of changes in density [5–7,24,25]. Since radiological change is one of the criteria of physician-rated toxicity, density changes are related to it, but this relation is not very strong [24,25]. To improve this, we investigated the incorporation of other features, such as the non-uniformity of the tissue into the quantitative analysis of CT images. Indeed, we found that the mean density and the non-uniformity were related to the fibrotic and inflammatory response respectively [19,20]. Moreover, in the present work we show that it relates well to the physician-assessed clinical toxicity based on the same images.

As such, we developed a new more sensitive and specific CT-based method to assess radiation-induced lung toxicity, results of which correspond better to physician-rated radiation pneumonitis than currently-used standard methods [19,20]. Use of this method may improve the assessment of RILT and thereby facilitate development of more accurate predictive models for the risk of RILT.

It should be noted, however, that the present study is a first clinical test to establish the usefulness of ΔS as a quantification of local tissue damage in the lungs. As such, the small number of patients included results in considerable uncertainties in the estimates of e.g. the area under the ROC curve (Fig. S4). Moreover, the optimal translation of local damage into a global score to be related to clinical symptoms may differ from the presently-used method of averaging ΔS over the whole lung. Achieving better estimates of the ROC curve as well as comparison of the presently used mean over the whole lung to alternatives, however, requires a considerably larger study.

Conclusion

We developed a new more sensitive and specific method to assess radiation-induced lung toxicity using CT-scans, that was significantly more sensitive than the most frequently used method (i.e. measuring differences in mean density). In addition, compared to the routinely used CT-based tools to detect RILT, the ΔS method corresponds better to physician-rated radiation pneumonitis.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.07.017.

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