Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Regional variability in radiation-induced lung damage can be predicted by baseline CT numbers

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ARTICLE INFO

Article history:
Received 6 July 2016
Received in revised form 24 October 2016
Accepted 26 November 2016
Available online xxxx

Keywords:
Radiation-induced lung damage
Density change
CT
Regional heterogeneity
Lung cancer
Radiosensitivity

ABSTRACT

Background and purpose: Lung volumes are functionally heterogeneous but typically considered uniformly during radiotherapy planning. The present study aims to predict regional differences in radiation-induced lung damage based on pre-treatment CT information.

Materials and methods: For 42 lung cancer patients (including 15 from an external validation set), two 200 cc lung subvolumes (low-density (LD) and high-density (HD)) were auto-segmented in the ipsilateral lung of the planning CT_0. After non-rigid registration of 3 month follow-up CT scans, sigmoidal dose-density change ($\Delta HU = HU_{3M} - HU_0$) response curves were determined for all subvolumes. Predictive factors for the sigmoidal response parameters D_{50} and saturation level ΔHU_{max} were analyzed.

Results: The baseline density difference between LD (mostly in the upper lobe) and HD (mostly in the lower lobe) was on average 102 HU. The saturation level $\Delta HU_{max,LD}$ was significantly smaller than $\Delta HU_{max,HD}$ ($p = 0.03$). Expressed as mass density increase relative to the baseline density, saturation levels were 20.7% on average irrespective of baseline density, and they could be predicted in LD and HD subvolumes (AUC = 0.70–0.78). Intra-lung differences in D_{50} were significantly smaller than inter-patient differences.

Conclusions: Limited amount of damage was observed in LD subvolumes, while the relative density increase of all subvolumes was well predictable. This could allow dose redistribution preferentially targeting low-density lung regions.

Treatment dose prescription in (chemo)radiotherapy for stage III-IV non-small cell lung cancer is often limited by dose constraints applied on the normal lungs [1–3]. The resulting ad hoc lowered dose prescriptions often imply suboptimal tumor control probability. Widely accepted population-based dose constraints, limiting the incidence of significant radiation pneumonitis, are a mean lung dose (MLD) of both lungs below 20 Gy and a lung volume receiving 20 Gy (V_{20}) below 35% of the total lung volume [4–5]. Clinical risk factors for radiation pneumonitis development include age and smoking history [4–6].

A growing need for further lung toxicity risk-based individualization of the prescribed dose exists in the current era of modulated photon and particle treatments. In order to use these rapidly evolving treatment techniques to their full potential, better discriminating prediction models are required. This could partly be addressed by biomarkers of radiosensitivity [7]. While replicated results applicable in routine clinical practice are not yet available from the field of radiogenomics, imaging biomarkers could provide useful information on shorter notice, including relevant spatial information [8].

Another approach for treatment individualization is to exploit regional heterogeneity in the lung. Indeed, the lung was considered a parallel organ with uniform characteristics in aforementioned work. However, it is known that lungs can be extremely heterogeneous in their structural composition as well as in their functional capacity [9]. Observed examples were the increased lung radiosensitivity of lower lobe tumor treatments [10–12] and nuclear imaging ventilation and perfusion scans unveiling dramatic differences in regional functionality [13].

The presence of radiation-induced lung damage is an important cause of clinical lung toxicity. Lung damage was quantified by the magnitude of density increase of lung parenchyma, or by other features derived from follow-up CT scans [14–19]. A large inter-patient variability in dose response was observed for this lung damage endpoint [8,18]. Its correlation with clinical lung toxicity endpoints was shown in combination with the volume concerned

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http://dx.doi.org/10.1016/j.radonc.2016.11.021
0167-8140/

by the damage [18,20,21]. Clearly, along the lines of exploiting regional lung characteristics, sparing lung regions at higher risk for damage while preferentially targeting low-risk regions could be a promising strategy.

A prediction model for patient-specific radiation-induced lung damage, based on characteristics of the baseline CT, was previously presented [18]. The median density of irradiated lung tissue, reflecting the density of the local lung structure, was shown to be correlated to the absolute amount of damage measured 3 months after treatment. Our hypothesis was that the same behavior exists on the level of subregions within the same lung, i.e. that the lowest density regions (portions of less dense lung parenchyma, emphysema, lung bullae, etc.) might remain unchanged after treatment, in contrast to high density regions at risk of pulmonary infiltrations. Identification of such regions at the planning stage could then guide dose deposition in order to minimize the risk of radiation-induced lung tissue damage.

The goal of present work was thus to investigate the translation of the inter-patient prediction model to subregions within the lung. Therefore, the damage of two lung subvolumes, differing in median baseline density, was quantified. Predictive factors for this lung heterogeneity were studied, as they could help in patient selection for lung damage risk-based dose redistribution planning.

Materials and methods

Patient datasets

A total of 42 stage III–IV lung cancer patients treated with intensity-modulated radiotherapy (IMRT) were retrieved from 2 institutions, further referred to as dataset 1 and 2. The core of both datasets was an existing interinstitutional database described in detail in [18], from which all 30 IMRT treatments were selected.

Dataset 1 contained 27 patients from the University Hospitals Leuven (15 from previous work, enriched by 12 patients with a lower lobe tumor) treated up to 66 Gy, in 2.75 Gy fractions sequentially with chemotherapy or in 2 Gy fractions concurrent with chemotherapy. 5- or 7-field IMRT or 2-arc RapidArc (RA) plans were delivered. The baseline planning CT (CT_0) was a free-breathing CT and dose calculation of treatment plans was done with an Analytical Anisotropic Algorithm (AAA 10.0.28) from Eclipse (Varian Medical Systems, Palo Alto, CA).

Dataset 2 consisted of 15 patients treated at Maastro Clinic (all from previous work). Dose prescription was 45 Gy in 1.5 Gy fractions twice per day, followed by a boost up to 24 Gy (2 Gy fractions). CT_0 was a 50% expiration 4DCT frame. IMRT plans calculated with a convolution superposition algorithm from XiO (Elekta, Stockholm, Sweden) were delivered.

Deep inspiration breath-hold diagnostic follow-up CT scans approximately 3 months after end of radiotherapy (CT_{3M}) were retrieved. All scans were taken in supine position with the arms raised above the head. Dyspnea scores (CTCAE 4.0) at the follow-up timepoint were retrospectively retrieved.

Lung subvolume generation and damage analysis

A predictive model for lung damage susceptibility on the patient level was previously designed. The model indicated that the median density calculated on CT_0 within the V_{20} volume, was highly predictive for the observed lung density increase 3 months after treatment [18]. The effect was most pronounced in SABR treatments (with small V_{20} volumes of on average 205 cc). This predictive factor was tested now for its ability to discriminate between damage susceptibility of different regions within the same lung. Two subvolumes of approximately 200 cc, named low-density (LD) and high-density (HD), were generated within the ipsilateral 'lung minus planning target volume (PTV)' using following user-independent strategy. The 'lung minus PTV' volume was sampled every 1.5 cm for voxels acting as seed points for region growing. The resulting region-growing volumes were expanded by a morphological closing operator. Only volumes were retained for which a dose–damage response analysis was possible at least from 20 Gy to 40 Gy. From the remaining volumes, the two non-overlapping volumes with maximal difference in median baseline density (HU_0) were selected for the susceptibility study. All image analysis steps were performed in MeVisLab 2.6.2 (MeVis Fraunhofer, Bremen, Germany). More details on this subvolume autogeneration are described in Appendix 1.

For both the LD and HD subvolumes, a dose–damage response analysis was performed as previously reported [18]. In short, CT_{3M} was non-rigidly registered to CT_0 using a free-form intensity-based registration algorithm of MIM 6.1.7 (MIM software, Cleveland, OH). Subsequently, a difference image was created by voxelwise subtraction of HU values ($\Delta HU = HU_{3M} - HU_0$). From this difference image, the median HU value within 5 Gy dose bins (between 0 Gy and 60 Gy) was calculated and plotted against the corresponding equivalent dose in 2 Gy fractions (EQD2, $\alpha/\beta = 4Gy$, repopulation rate = 0.44 Gy/day) [22,23]. Dose bins with a volume smaller than 1 cc were not taken into account. The HU difference in the lowest dose bin was used as a reference (i.e. negligible damage at low dose was assumed).

Sigmoidal least squares fits of dose versus ΔHU data were produced for every lung subvolume, resulting in subvolume-specific damage parameters D_{50} and ΔHU_{max}. Quality of the fit was expressed as the sum of squared residuals (SSR). The fit was qualified as acceptable when $SSR \leqslant 4000$, i.e. residuals being smaller than 20 HU on average.

Statistics

Differences between the LD and HD damage parameters were analyzed with a paired *t*-test for continuous variables and a McNemar test for proportions, while all comparisons between both datasets relied on unpaired *t*-tests and Z-score, respectively (0.05 significance level). The average intra-patient difference in damage parameters was compared to the previously observed inter-patient distribution. A lognormal distribution was fitted to the inter-patient data of Fig. 2b and d of [18]. Subsequently, for every patient, a datapoint pair was randomly generated from this inter-patient distribution. Repeating this 1000 times resulted in a distribution of average inter-patient damage parameter difference for our sample size.

Both dataset 1 and 2 were combined to find predictors (univariate linear regression) for HU_0 difference between LD and HD, and for the damage parameters (using acceptable fits). Following covariates were analyzed: gender, age, PTV volume, ipsilateral 'lung minus PTV' volume, lung laterality, upper/middle or lower lobe tumor location, smoking status (current versus never/previous smoker), overall treatment time (OTT), MLD, mean and maximal heart dose (D_{mean}, D_{max}), and CT_{3M} timepoint. Damage parameters and grade $\geqslant 2$ dyspnea Spearman's correlation coefficients were calculated.

Finally, multivariate logistic regression models predicted the saturation level of relative mass density increase ($\Delta HU_{max}/(1000 + HU_0)$) above thresholds of 10% and 20%. A forward selection procedure was performed on the combined dataset with the likelihood ratio test as comparison criterion (threshold $p = 0.10$). Predictive accuracy of the models was assessed with stratified 3-fold cross-validation repeated 100 times. Median value and 95% confidence interval (CI) of model performance on the unseen validation data were reported in terms of the area under the curve (AUC) of the

Please cite this article in press as: Defraene G et al. Regional variability in radiation-induced lung damage can be predicted by baseline CT numbers. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.11.021