Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

# CT characteristics allow identification of patient-specific susceptibility for radiation-induced lung damage

Gilles Defraene [a,*], Wouter van Elmpt [c], Wouter Crijns [a,b,d], Pieter Slagmolen [d,e], Dirk De Ruysscher [a,b]

[a] KU Leuven – University of Leuven, Department of Oncology, Experimental Radiation Oncology, B-3000 Leuven, Belgium; [b] University Hospitals Leuven, Department of Radiation Oncology, B-3000 Leuven, Belgium; [c] Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; [d] KU Leuven Medical Imaging Research Center, B-3000 Leuven, Belgium; [e] KU Leuven, ESAT/PSI – UZ Leuven, MIRC – iMinds, Medical IT Dept, Belgium

ARTICLE INFO

*Article history:*
Available online xxxx

*Keywords:*
Radiation-induced lung damage
Density change
CT
Lung cancer
Stereotactic ablative radiotherapy
Radiosensitivity

ABSTRACT

*Background and purpose:* There is a huge difference in radiosensitivity of lungs between patients. The present study aims to identify and quantify patient-specific radiosensitivity based on a single pre-treatment CT scan.

*Materials and methods:* 130 lung cancer patients were studied: 60 stereotactic ablative radiotherapy (SABR) treatments and 70 conventional treatments (20 and 30 patients from external datasets, respectively). A 3 month-follow-up scan ($CT_{3M}$) was non-rigidly registered to the planning CT scan ($CT_0$). Changes in Hounsfield Units ($\Delta HU = HU_{3M} - HU_0$) inside lung subvolumes were analyzed per dose bin of 5 Gy. $\Delta HU$ was modeled as a function of local dose using linear and sigmoidal fits. Sigmoidal fit parameters $\Delta HU_{max}$ (saturation level) and $D_{50}$ (dose corresponding to 50% of $\Delta HU_{max}$) were collected for all patients.

*Results:* Sigmoidal fits outperformed linear fits in the SABR groups for the majority of patients. Sigmoidal dose–responses were also observed in both conventional groups but to a lesser extent. Distributions of $D_{50}$ and $\Delta HU_{max}$ showed a large variation between patients in all datasets. Higher baseline lung density ($p < 0.001$) was prognostic for higher $\Delta HU_{max}$ in one SABR group. No prognostic factors were found for $D_{50}$.

*Conclusions:* Baseline CT characteristics are prognostic for radiation-induced lung damage susceptibility.

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Lung toxicity is a limiting factor in high-dose radiotherapy for lung cancer. In clinical practice, the prescribed radiation dose is restricted according to prediction models for radiation-induced lung toxicity. These models are currently based on physical dose–volume histogram (DVH) parameters, such as the mean lung dose (MLD) and $V_{20}$ (volume of the lungs receiving 20 Gy or more) or more complex normal tissue complication probability (NTCP) models [1–3]. It is accepted to limit the MLD to about 20 Gy and the $V_{20}$ to 35% in order not to exceed a 15% incidence of clinically important radiation pneumonitis in the patient population [4]. However, this implies that 15% of patients still experience major toxicity. Moreover, for the other 85% the tumor dose is not maximized, resulting in a suboptimal probability of tumor control. Clearly, treatment dose prescription should ideally be individualized in every patient based on a personalized susceptibility assessment for lung toxicity. The currently available prediction models, however, are not discriminative enough for this purpose [1–3] and failed validation for various reasons. Firstly, there is a lack of standardization across studies in terms of toxicity scoring (grading systems (e.g. CTCAE 4.0) and their subjective interpretation), treatment techniques and dose calculation algorithms [1,5]. Secondly, the categorical nature of classical toxicity scoring systems adds to the models' limited usability. Finally, global dyspnea scores do not allow to dissect the causes of shortness of breath, which are multifactorial. A leap forward is therefore needed in the field of lung toxicity modeling.

Density change of lung parenchyma is a known effect of radiation. It has extensively been studied qualitatively and quantitatively, using X-ray images [6–9], computed tomography (CT) scans [10–23] and even cone beam CT (CBCT) [24]. Many authors have described the time trend of dose-dependent density change [6–7,11,16–21,23–24]. Two phases could be unfolded: a transient phase peaking at 3–4 months and a stabilizing fibrotic phase after 9 months [7,21]. These coincide well with the timepoints of symptomatic radiation pneumonitis and fibrosis [21]. A negative impact of the tumor planning target volume (PTV) size on local density change has been described [18]. A density change plateau was shown above 30–50 Gy physical dose in different studies

* Corresponding author at: KU Leuven – University of Leuven, Department of Oncology, Experimental Radiation Oncology, B-3000 Leuven, Belgium.
*E-mail address:* gilles.defraene@uzleuven.be (G. Defraene).

http://dx.doi.org/10.1016/j.radonc.2015.07.033
0167-8140/

[16,18–20]. All previous studies, however, only reported population averaged dose–response curves. The large variation in interindividual dose–response was pointed out by some authors but not analyzed in detail [13,17,22,24].

There is no consensus about the correlation of density change with clinical symptoms [8,15,22,25]. Clinical symptoms like dyspnea are known to be multifactorial and thus governed by factors as age, baseline patient factors such as pulmonary function tests [5] and baseline inflammation [26]. However, density change most likely is an important driver for radiation-induced lung toxicity, especially when the affected volume becomes important [8].

This work focuses on a patient-specific description of radiation-induced lung damage assessed on CT through analysis of the dose–response and identification of prognostic factors. The Hounsfield Unit (HU) change 3 months after treatment was analyzed. The effect at 3 months has been described as the peak of the early phase and is strongly correlated to the late effect [20].

## Materials and methods

### *Patient datasets*

40 patients treated with stereotactic ablative radiotherapy (SABR) for single-lesion stage I non-small cell lung cancer (NSCLC) (SABR1 group) and 40 stage I–IV conventional radiotherapy lung cancer patients (CONV1 group), treated between 2010 and 2013, were retrieved from the University Hospitals Leuven database. Patients with previous radiotherapy in the chest region, including breast cancer, were excluded. SABR1 treatments prescribed doses of 48 Gy (4 fractions), 54 Gy (3, 4 or 8 fractions) or 60 Gy (5 or 8 fractions). Treatment plans consisted of 6–9 3D conformal beams. An internal target volume (ITV) defined on 4DCT with an additional 5 mm margin formed the PTV. The 25% expiration 4DCT frame was the planning CT ($CT_0$). A CBCT-based tumor match was performed before each fraction.

CONV1 patients were treated up to 66 Gy in 2.75 Gy fractions sequentially with chemotherapy or up to 70 Gy in 2 Gy fractions concurrently with chemotherapy. Margins of 10 mm from GTV to CTV and 7 mm from CTV to PTV were used. 3- and 4-field 3D conformal, 5 to 7-field intensity-modulated radiotherapy (IMRT) or 2-arc RapidArc plans were delivered. $CT_0$ was a free-breathing CT. The setup protocol involved planar kV–MV imaging with carina match.

All $CT_0$ scans were performed at the radiotherapy department using a Siemens Somatom Sensation scanner (Siemens Medical Solutions, Erlangen, Germany). The treatment was delivered by Clinac or TrueBeam linacs (Varian Medical Systems, Palo Alto, CA). Dose calculation was done with the Analytical Anisotropic Algorithm (AAA).

External validation sets of 20 SABR and 30 conventional patients treated at Maastro Clinic between 2008 and 2013 were studied (groups SABR2 and CONV2 respectively). Dose prescription for SABR was 54 Gy/18 Gy or 60 Gy/7.5 Gy and for fractionated treatment mostly 45 Gy/1.5 Gy twice per day, followed by a boost up to 24 Gy/2 Gy. Margin sizes were 5 mm (GTV–CTV) plus 3 and 5–10 mm (CTV–PTV) in SABR2 and CONV2, respectively. $CT_0$ was a 50% expiration 4DCT frame. 3D conformal and IMRT plans were calculated with a superposition algorithm from XiO (Elekta, Stockholm, Sweden), RapidArc plans were calculated with Acuros (Varian Eclipse).

Deep inspiration breath-hold diagnostic follow-up CT scans approximately 3 months after end of radiotherapy ($CT_{3M}$) were retrieved from the radiology departments or from peripheral centers. Dyspnea scores (CTCAE 4.0) at 6 months after the end of radiotherapy were retrospectively retrieved.

### *Description of the dose–response for lung damage*

The $CT_{3M}$ was non-rigidly registered to $CT_0$ in MIM 6.1.7 (MIM software, Cleveland, OH) using a free-form intensity-based registration algorithm. 'Lungs minus PTV' contours were semi-automatically generated on the $CT_0$ and transferred together with the dose matrix to the registered image.

Image analysis was performed in MeVisLab 2.5 (MeVis Fraunhofer, Bremen, Germany). First an image subsampling led to isotropic pixel dimensions of approximately 3 mm. A difference image ($CT_{3M}$–$CT_0$) was then created by a voxel-by-voxel subtraction of HU values ($\Delta HU = HU_{3M} - HU_0$). Subvolumes of 'lungs minus PTV' receiving a certain dose (5 Gy dose bins between 0 Gy and 55 Gy) were segmented. From the difference image, the median $\Delta HU$ was calculated for each subvolume and plotted against the corresponding physical dose ($D$) and equivalent dose in 2 Gy fractions (EQD2 with $\alpha/\beta = 4$ Gy and repopulation rate = 0.44 Gy/day (radiation pneumonitis) and reference time = median overall treatment time (OTT) of the 33 fraction treatments) [27,28].

Linear and sigmoidal least squares $\Delta HU$-dose fits were produced for every patient, resulting in parameters M (linear), and $D_{50}$ and $\Delta HU_{max}$ (sigmoidal). The details of the procedure are outlined in Appendix 1.

### *Prognostic model for patient-specific radiosensitivity*

The patient-specific damage susceptibility was expressed as M (linear models), or $D_{50}$ and $\Delta HU_{max}$ (sigmoidal models). Per patient group, a multivariate linear regression of $D_{50}$ and $\Delta HU_{max}$ was performed with the following covariates: follow-up time of $CT_{3M}$, PTV volume, left or right lung, upper/middle or lower lobe, OTT, heart dose, chemotherapy (concurrent versus no/sequential), treatment technique (3D-CRT versus modulated treatments) and $HU_{0,Vx}$ (median baseline HU of $CT_0$ in volume $V_x$). The volume $V_x$ for which $HU_{0,Vx}$ was the most significant was first selected in univariate regression. A similar selection picked $D_{max}$ or $D_{mean}$ as heart dose parameter. All acceptable fits (sum of squared residuals (SSR) below 10 HU per datapoint on average) were used for the $\Delta HU_{max}$ predictions while only responding patients ($\Delta HU_{max} > 10$ HU) were retained for the $D_{50}$ predictions.

A multivariate logistic regression model predicts $\Delta HU_{max}$ above a certain threshold. All covariate combinations were tested for significance (likelihood ratio test between nested models). The area under the curve (AUC) of the receiver operating characteristic curve of the models was calculated.

Finally, Pearson correlation coefficients were calculated for the imaging-based parameters ($D_{50}$ and $\Delta HU_{max}$) and grade $\geqslant 2$ dyspnea.

## Results

$CT_{3M}$ was performed at a median of 2.8, 2.8, 2.3 and 2.9 months after end of radiotherapy, for SABR1, SABR2, CONV1 and CONV2, respectively. Treatment characteristics of the different datasets are listed in Table 1. Baseline patient and tumor characteristics can be found in Appendix 2.

Sigmoidal fits to EQD2 outperformed the other scenarios in the SABR datasets: median SSR (SABR2 between brackets) was 206.0 (146.6), 254.9 (171.0), 91.4 (115.2) and 85.0 (105.9) for linear fit to $D$, linear fit to EQD2, sigmoidal fit to $D$ and sigmoidal fit to EQD2, respectively. A linear fit scored best in only 9 out of 60 patients. For CONV1, the sigmoidal fit using $D$ scored slightly better than using EQD2: 409.7 versus 452.9, while linear fits performed worse (482.3 and 508.9, respectively). The CONV2 dataset presented similar results for the EQD2 fits (the combination of

Please cite this article in press as: Defraene G et al. CT characteristics allow identification of patient-specific susceptibility for radiation-induced lung damage. Radiother Oncol (2015), http://dx.doi.org/10.1016/j.radonc.2015.07.033