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Normal tissue complication probability models for severe acute radiological lung injury after radiotherapy for lung cancer

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ABSTRACT

Purpose: To derive Normal Tissue Complication Probability (NTCP) models for severe patterns of early radiological radiation-induced lung injury (RRLI) in patients treated with radiotherapy (RT) for lung tumors. Second, derive threshold doses and optimal doses for prediction of RRLI to be used in differential diagnosis of tumor recurrence from RRLI during follow-up.
Methods and materials: Lyman-EUD (LEUD), Logit-EUD (LogEUD), relative seriality (RS) and critical volume (CV) NTCP models, with DVH corrected for fraction size, were used to model the presence of severe early RRLI in follow-up CTs. The models parameters, including α/β, were determined by fitting data from forty-five patients treated with IMRT for lung cancer. Models were assessed using Akaike information criterion (AIC) and area under receiver operating characteristic curve (AUC). Threshold doses for risk of RRLI and doses corresponding to the optimal point of the receiver operating characteristic (ROC) curve were determined.
Results: The α/βs obtained with different models were 2.7–3.2 Gy. The thresholds and optimal doses curves were EUDs of 3.2–7.8 Gy and 15.2–18.1 Gy with LEUD, LogEUD and RS models, and μ_d of 0.013 and 0.071 with the CV model. NTCP models had AUCs significantly higher than 0.5. Occurrence and severity of RRLI were correlated with patients' values of EUD and μ_d.
Conclusions: The models and dose levels derived can be used in differential diagnosis of tumor recurrence from RRLI in patients treated with RT. Cross validation is needed to prove prediction performance of the model outside the dataset from which it was derived.
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Introduction

Radiological radiation-induced lung injury (RRLI) is the increase in lung tissue density in patients treated with radiotherapy (RT) as seen on follow-up chest x-rays or computed tomography (CT) [1]. It is originated by the replacement of lung tissue with exudates or fibrotic tissues mostly confined into the radiation fields [2]. These changes are categorized as acute before 6 months (pneumonitis), and late after more than 6 months (lung fibrosis) [3–5]. The majority of patients with such radiographic changes remain asymptomatic [3].

Understanding dose–response relationship of tissues is essential for optimization and evaluation of RT treatment plans. Several studies indicated that appearance and degree of RRLI are correlated with dosimetric surrogates of the 3D dose distribution such as mean lung dose (MLD) or percent lung volumes receiving more than a certain dose [1,2,5–7]. Models of Normal Tissue Complication Probability (NTCP) correlate the occurring of side-effects after RT with dose-volume data, fractionation scheme and non-dosimetric variables [8–12]. For these reasons NTCP models are currently used as objective functions in the inverse planning process and to compare treatment plans [13]. A number of authors have investigated local dose–response relationships from changes in CT density in lung cancer RT patients [1,5,7,14] The dose–response for RRLI assessed from CT follow-up scans has been described in the past through NTCP modeling for breast cancer patients treated with 3D-conformal radiotherapy (3D-CRT) using the end-point of mild RRLI [10]. However, at best of our knowledge, appearance of severe patterns of early RRLI has never been described trough NTCP models.

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The aim of the present study was to derive threshold dose levels for early severe RRLI to be used as optimization constraints during planning of the treatment and for evaluation of the safety of proposed treatment plans. For this purpose, we modeled the risk of severe patterns of early RRLI using previously established NTCP models with DVHs corrected for fraction size. The best-fit parameters of dose–response models, including the fractionation parameter, α/β, were derived from fitting observed incidences of severe patterns of acute RRLI in patients treated with RT for lung tumors. The capability of models to predict severe RRLI was then tested through a series of statistical tests.

The second aim was to derive dose levels for classification of patients at high risk of RRLI. In highly conformal RT the differential diagnosis between benign changes on follow-up CT from progression or recurrence is a difficult task because areas of dense consolidation usually develop around the treated tumor [4]. Identification of patients at high risk for RRLI can help the physician in differential diagnosis of RRLI from tumor recurrence or persistence.

Methods and materials

Patient treatment

Forty-five Non-small Cell Lung Cancer (NSCLC) patients were treated with radical RT at our institution. Each patient underwent simulation using a 32-slice CT (Toshiba Aquilion LB, Toshiba Medical Systems Europe, Zoetermeer, the Netherlands). During the planning CT scan, patients were lying on a flat table in a supine and overhead arm position and allowed to breathe freely. No intravenous contrast was used.

The lung was segmented on the CT images automatically in the Oncentra Masterplan (Elekta, Stokholm, Sweden) treatment planning system (TPS) by use of a thresholding method at a CT density between −300 and −400 Hounsfield units and edited manually based on visual inspection. The intrathoracic gross tumor was therefore automatically excluded from the lung during the segmentation. The planning target volume (PTV) included the gross tumor volume with an additional margin of 10 mm in the craniocaudal and 5 mm in the axial directions. Patients and RT treatment characteristics are shown in Table 1.

Forty-two patients were treated with Helical Tomotherapy (HT) [15] delivered with the Hi-Art II System (Accuray Inc, Sunnyvale, CA). Three patients were treated with IMRT delivered with a Varian CLINAC Trilogy system (Varian Medical Systems, Palo Alto, CA). Intensity modulation was achieved using a sliding window technique. Before treatment, each patient underwent kilovolt cone-beam CT imaging for set-up correction.

Tomotherapy treatments were planned using the Tomotherapy TPS (Accuray Inc, Sunnyvale, CA), and IMRT and 3D-CRT treatments using the Eclipse (Varian Medical Systems, Palo Alto, CA). In order to derive differential dose volume histograms (DVHs) of all the treatments in the same format, the Tomotherapy treatment plans were exported to Eclipse. DVHs of the ipsilateral lung and PTV were calculated within Eclipse and exported in text format with a dose resolution of 5 cGy. Dose received from imaging procedures was not considered in calculations.

All of the Tomotherapy treatment plans were exported to the Eclipse TPS. Differential dose-volume histograms (DVHs) of the ipsilateral lung were calculated with the Eclipse TPS and exported with a dose resolution of 5 cGy.

The following dosimetric parameters were recorded for each patient: percent volumes of the lung receiving more than 5 Gy and 20 Gy, mean dose to the lung, average total dose to the PTV, average dose per fraction to PTV.

Patient follow-up

The dosimetric and follow-up data were reviewed with the approval of our Institutional Review Board and after obtaining informed consent from each patient. Diagnostic CT scans were acquired during follow-up at 45 days, 3 months and 6 months after the end of RT and were read by a radiologist and a radiation oncologist in consensus. The lung injuries occurring within 6 months from the completion of radiation therapy were defined as acute RRLI and were classified into 5 categories [4,16]: (1) diffuse consolidation; (2) patchy consolidation and ground-glass opacities (GGO); (3) diffuse GGO; (4) patchy GGO; (5) no evidence of increasing density.

Diffuse consolidation (Fig. 1a) and patchy consolidation and GGO (Fig. 1b) were defined as patterns of severe RRLI in this study. When more than one CT scan within the first 6 months from RT were available on the same patient, the patient outcome was assumed as the lowest category of RRLI seen on the CT scans.

The following patient characteristics that were previously studied as risk factors for RRLI [2,3,14,16] were recorded for each patient: sex, age, smoking status at the time of treatment (smoker vs non-smoker), tumor location (right vs left lung, lower vs upper/middle), administration of chemotherapy or corticosteroids.

The Mann–Whitney *U* test and the chi-square tests were used to assess the correlation between radiographic lung injury and pretreatment clinical or dosimetric variables. Tests of statistical significance were two-sided. Bivariate correlation of dosimetric factors and grade of RRLI were assessed using Spearman's rank correlation. A 5% significance level was considered for the analysis.

Models for NTCP

In order to account for the variability in dose fractionation, the doses D_i in the differential ipsilateral lung DVHs of were corrected into equivalent doses at 2 Gy/fraction, $EQD_{2,i}$, using the linear quadratic model [17]:

$$EQD_{2,i} = D_i \left(\frac{\frac{D_i}{N} + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}} \right) \quad (1)$$

where N is the number of fractions in the treatment, i is the sub-volume of the organ irradiated with dose D_i in the differential DVH, and α/β ratio the parameter of the linear-quadratic model for the lung. To account for the effect of irradiated volume and dose distribution on risk of side effect, we used the equivalent uniform dose (EUD). This is the dose that, when delivered uniformly to the organ or tissue, is assumed to produce the same NTCP as the inhomogeneous dose distribution [18].

$$EUD = \left(\sum_i v_i \cdot EQD_{2,i}^{\frac{1}{n}} \right)^n \quad (2)$$

where v_i is the i-th fractional sub-volume of the organ irradiated with dose $EQD_{2,i}$ and the parameter n describes the volume effect of the irradiated organ or tissue.

For dose response modeling, we used previously established NTCP models [8,9,19] whose equations are described in appendix A. Two models based on EUD were chosen to model RRLI: the Lyman-EUD (LEUD) and the Logit-EUD (LogEUD) [9] models. These models rely on the hypothesis that all volume elements inside an organ have the same importance for the appearance of the side effect.

The relative seriality (RS) or Kallman s-model [19] and the population-averaged critical volume (CV) model [8] were also used.

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