



Correlation of Radiation-Induced Fibrosis and Local Dose-Related Parameters in Conformal Non-Small Cell Lung Cancer Radiation Therapy

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1. Introduction

Radiation therapy (RT) is an important therapeutic modality for the treatment of lung cancer. Although improved tumor control might require higher doses of radiation, dose escalation is often limited by the radiation tolerance of normal tissues. The lung parenchyma itself is one of the important dose-limiting organs for radiation therapy of tumors in the thoracic region. Despite the clinical importance of RT-induced pulmonary injury, methods to accurately predict the degree of RT-induced dysfunction are lacking¹. This article presents a tool for the automatic segmentation of RT-induced fibrosis. To illustrate the capabilities of the tool, the relation of different fibrosis grades is studied as a function of dose using both conventional as well as Monte Carlo dose calculations.

2. Patient and treatment characteristics

The study population for this trial consisted of 6 unselected patients (4 males, 2 females; median age: 68 years) with stage IIIA or IIIB, pathologically proven non-small cell lung cancer, homogeneously treated on an institutional research board approved Phase I/II study². Patients received neoadjuvant chemotherapy (carboplatin AUC 5 on day 1 and gemcitabine 1000 mg/m² on days 1 and 8 every 3 weeks for 2 cycles) followed by concomitant chemotherapy (paclitaxel 50 mg/m² and gemcitabine 100 mg/m² on days 1 and 8 every 3 weeks for 2 cycles) and thoracic RT, delivered using megavoltage energies (6-18 MV) in 2 Gy daily fractions for a total dose of 60 Gy. Three dimensional conformal radiotherapy techniques were used in all patients and their targets were defined in accordance with International Commission on Radiation Units and Measurements Report 50. RT was delivered in two plans. Plan one delivered a dose of 40 Gy and plan two (conned down fields) a dose of 20 Gy. Treatment plans were generated using CADPLAN (Varian) treatment planning stations and were performed without heterogeneity corrections. Radiation delivery was based on the plan generated in this way. In addition, retrospective Monte Carlo (MC) dose calculations were performed, and 3D MC dose distributions with the effects of tissue heterogeneity taken into account were calculated using the planning CT and the number of monitor units delivered. Patients underwent a standard CT simulation scan prior to radiotherapy and follow-up diagnostic CT scans, performed \leq 3 months, at 6 months and 12 months after completion of radiation treatment.

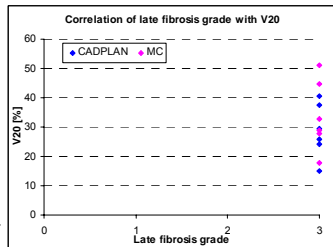
3. Correlation of various dose-volumetric parameters with physician-graded fibrosis

Lung contours delineated by the physicians on the planning CT images and CADPLAN and MC dose distribution were used to calculate *dose-volumetric parameters* potentially related to the risk of RT-induced fibrosis: MLD, V_{20} , as well as the MLD ($D50 = 30.8$ Gy, $m = 0.37$) and the Lyman-Kutcher-Burman ($D50 = 24.5$ Gy, $m = 0.18$, $n = 0.87$) models for the NTCP.

Radiation Therapy Oncology Group radiation morbidity scoring criteria were used, ranging from grade 0 (no change) to grade 5 (death).

No significant correlation was found between physician-graded fibrosis and any of the dose-volumetric parameters (see Fig. 1 for a typical result).

Figure 1. Correlation of physician-graded late fibrosis with V_{20} .



4. Pre- and post-RT image correlation

To investigate the association between dose distributions and RT-induced fibrosis, planning and diagnostic CT scans needed to be correlated. This correlation was realized using the affine registration feature of the Automatic Non-Linear Image Matching and Anatomical Labeling (ANIMAL) algorithm³.

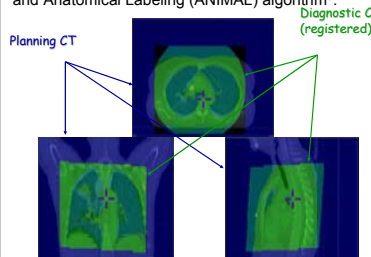


Figure 2. Diagnostic CT registered to planning CT.

5. Automatic fibrosis segmentation

A three-step process was carried out for automatic RT-induced fibrosis segmentation. The *first step* consists in the automatic segmentation of the lung volume, PTV excluded, on the CT image set acquired just before the beginning of the radiation therapy (pre-RT CT image set). In *step 2*, after tissue densities were determined for all CT image sets, difference image sets (Fig. 3c) were generated by subtracting the pre-RT CT image set (Fig. 3a) from the post-RT CT image sets (Fig. 3b) and pixel-by-pixel lung density changes were determined inside the segmented lung volume on the pre-RT CT image set. During the *last step*, mean lung density changes, corresponding to physician-identified radiographic fibrosis grades⁴, were used to identify different grades of fibrosis. Grades 1, 2 and 3 fibrosis were associated to lung density changes from 0.123 to 0.279 g/cc, 0.279 to 0.546 g/cc and 0.546 to 0.799 g/cc, respectively (Fig. 3d). Based on tissue densities alone differentiation between fibrosis and tumor recurrence is convoluted; therefore the automatic fibrosis segmentation (Fig. 3d) was performed outside the PTV.

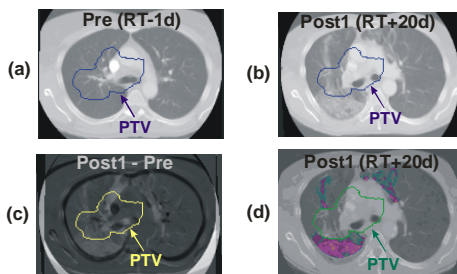


Figure 3. Illustration of the automatic fibrosis segmentation process: (a) Pre CT scan, acquired 1 day before the beginning of RT, (b) Post1 CT scan, acquired 20 days after the end of RT, (c) Post1 - Pre difference image set, (d) Grade 1 (blue), grade 2 (magenta) and grade 3 (red) fibrosis segmented on the Post1 CT image set.

6. Fibrosis-dose correlation

Fibrosis volume automatically segmented on the follow-up diagnostic CTs as well as CADPLAN and MC dose distributions were used to generate dose-response curves for RT-induced fibrosis. The probability of fibrosis was used as a measure of lung response to radiation:

- the probability of observing grade i fibrosis at dose D : $N(fibr_i, D) / N(lung, D)$ and
- the probability of observing any fibrosis at dose D : $\sum_{i=1}^3 N(fibr_i, D) / N(lung, D)$,

where $N(fibr_i, D)$ and $N(lung, D)$ are the number of voxels in fibrosis volume of grade i and lung, respectively, receiving a dose D .

7. Dose-response curves for fibrosis developed in the ipsilateral lung

Figure 4a shows the probability of fibrosis monotonically increasing as a function of the MC dose, while it shows an often irregular behavior for high CADPLAN dose. There is a threshold dose for the probability of fibrosis in Figure 4a and this threshold dose corresponds to the threshold dose in the differential dose-volume histogram (DVH) for the ipsilateral lung (Figure 4b).

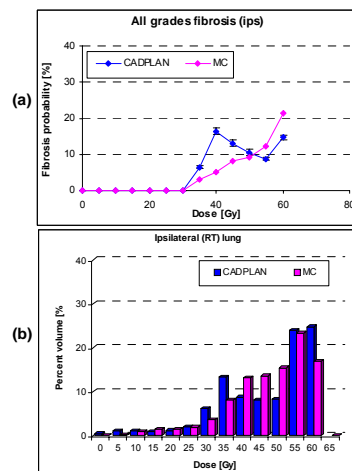


Figure 4. Probability of developing any grade of fibrosis in the ipsilateral lung as a function of CADPLAN and MC doses (a). Differential DVH for the ipsilateral lung (b).

8. Dose-response curves for fibrosis developed in the contralateral lung

Figure 5a shows radiological fibrosis spread over the entire dose range. As opposed to the ipsilateral lung, the differential DVH for the contralateral lung shows predominant irradiation to low doses (Fig. 5b) and this explains why the probability of fibrosis is spread over the entire dose range.

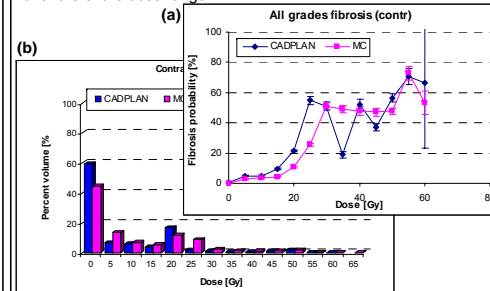


Figure 5. Probability of developing any grade of fibrosis in the contralateral lung as a function of CADPLAN and MC doses (a). Differential DVH for the contralateral lung (b).

For another patient, the residual fibrosis appearing in the contralateral lung at almost one year after RT (Fig. 6a) was very well correlated with a dose peak around 50 Gy in the differential DVH for the contralateral lung (Fig. 6b).

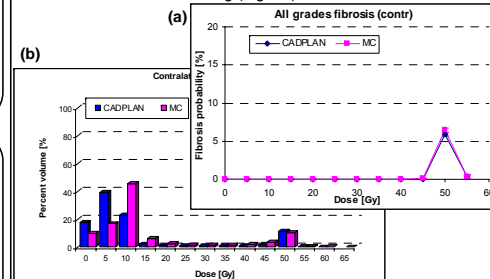


Figure 6. Probability of developing any grade of fibrosis in the contralateral lung as a function of CADPLAN and MC doses (a). Differential DVH for the contralateral lung (b).

9. Conclusions

An accurate, systematic numerical study of the relationship between RT-induced fibrosis and local dose-related parameters is presented. A strong patient-specific variation of fibrosis volumes was found during the follow-up period. A poor correlation existed between CADPLAN- and MC-based dose-volumetric parameters and physician-identified radiographic fibrosis. Overall, MC dose distributions correlated better with the probability of RT-induced fibrosis than do CADPLAN dose distributions.

References

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