Objective imaging biomarkers to quantify the evolution of radiation-induced lung damage

Catarina Veiga†, Joseph Jacob1,2, Natalie Yip1, Adam Szmul1, David Landau3 and Jamie McClelland1

1Centre for Medical Image Computing, University College London, WC1E 6BT London, UNITED KINGDOM.2Department of Respiratory Medicine, University College London, WC1E 6BT London. 3Department of Oncology, Guy's & St. Thomas' NHS Trust, SE1 7EH London, UNITED KINGDOM.

Introduction

Radiation-induced lung damage (RILD) is a common consequence of lung cancer radiotherapy (RT). RILD is the likely cause of loss of breathing function in lung cancer survivors. RILD is traditionally described as a two-phased process according to time since RT: the acute phase (pneumonitis) occurring during the first 6 months following RT, and the permanent phase (pulmonary fibrosis) that stabilises 6 to 24 months after RT. However, in clinical practice the distinction between pneumonitis and fibrosis is often unclear. Since RILD is visible on CT imaging, its evolution can be objectively monitored and quantified. Our group has recently proposed a suite of biomarkers extracted from CT imaging to objectively quantify RILD 12-months after RT [1]. In this short paper we investigate the use of four representative imaging biomarkers to study evolution of radiological RILD up to 24 months after RT.

Materials & Methods

Twenty subjects treated in a non-randomized phase I/II trial of isotoxic chemoradiation in stage II/III non-small cell lung cancer were analysed in our study[2]. CT imaging was available pre-RT and at fixed serial time-points following RT: 3, 6, 12 and 24 months. The average CT image resolution was 0.77×0.77×2.7 (±0.09×0.09×1.8) mm³. All scans were acquired at breath-hold with similar inhalation level across time-points for each subject. To investigate how RILD appears and develops, four CT-based biomarkers were calculated over serial time-points: volume of consolidation (RV), pleural change (ΔP [%]), normal lung volume shrinkage (ΔNV [%]), and anterior junction line rotation (Δβ [°]). These biomarkers were recently developed (full implementation details can be found here [1]) and are representative of parenchymal, pleural and lung volume change, and anatomical distortions after RT, respectively. The biomarkers (with the exception of RV) quantify the change in anatomical features between two time-points. For example, the biomarker “normal lung shrinkage” (ΔNV) is defined as the difference between the value measured for the anatomical feature “normal lung volume” at baseline and at follow-up (NV_B – NV_F). NV is normalized by the equivalent measure from the contralateral lung and converted to a percentage. The anatomical features are measured at each time-point from the CT images and corresponding manually edited segmentations (such as lung and chest wall) using semi-automated image analysis pipelines. Statistical analysis was performed using MATLAB 2016a Statistical Toolbox.

Results

The values measured for the four biomarkers varied according to time since RT (t={3, 6, 12, 24} months for all measures), providing complementary information on the evolution of RILD. Figure 1 presents the evolution of each biomarkers in full detail. RV peaked at 6 months and reduced at following time-points (RV={2.4±0.9, 2.9±1.4, 2.5±1.1, 2.5±1.1}). Pleural change was variable across the patient group (ΔP={10±14, 13±17, 10±13, 12±18} %). ΔNV became increasingly more severe over time, with the largest
variation occurring from 3 to 6-months ($\Delta NV=\{12\pm11, 24\pm14, 25\pm15, 27\pm16\}$%). $\Delta \beta$ continually increased over time ($\Delta \beta=\{1.4\pm2.0, 3.0\pm3.3, 5.0\pm3.5, 6.3\pm4.2\}$°). The variation of $\Delta \beta$ was statistically significant between all consecutive time-points (Wilcoxon paired two-sided signed rank test).

**Figure 1:** Variation in biomarkers measured over serial-timepoints. P-values shown for the Wilcoxon paired two-sided signed rank test between consecutive time-points.

**Discussion & Conclusions**

This study shows that CT-based imaging biomarkers provide quantitative information of the evolution of RILD on a set of homogeneously treated patients. The use of objective measures is advantageous as the evolution of RILD is not easily quantifiable by human observers. The findings across the whole patient group are indicative of an evolution of RILD from early acute inflammation phase (3-6 months), characterised by reversible parenchymal change into chronic inflammation (6-24 months), characterised by irreversible scarring, progressive lung volume loss and anatomical distortion. The biomarkers have the potential of allowing patient-specific distinction of acute and chronic RILD, which is important to identify personalised therapeutic interventions. One of the limitations of our study is the small number of subjects included. Our methodology also has limitations, namely uncertainties due to variation in inhalation level and resolution between serial scans, as well as uncertainties in segmentation. The severity measured for different biomarkers across time-points was variable between different patients, indicating sub-groups for the evolution of RILD. Hence, we plan to investigate the use of the biomarkers as a tool to distinguish different sub-groups of evolution of RILD. Further work is also on-going to extend the current analysis to a larger spectrum of anatomical changes commonly seen in RILD.

**References**


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†Corresponding Author: c.veiga@ucl.ac.uk