Predicting Residual Disease for NSCLC using Pre-radiotherapy 4D PET/CT

Introduction: PET 18F-deoxyglucose (FDG) has a high prognostic value for tumor targeting, staging and therapy response for non-small cell lung cancer (NSCLC). Recent PET imaging studies showed that the patient survival can be significantly improved if tumor has completed therapy response with smearing residual metabolic activity. A rational strategy to improve patient survival is to minimize residual disease by escalating radiation dose to the primary target tumor. Toward this goal, it is critical to know where the dose should be boosted to the area of the primary tumor corresponding to the residual disease. In this study, we first quantify PET treatment response using a novel image registration approach, and further investigate the impact of 4D PET/CT pre-radiotherapy scan for predicting residual areas where high-uptake will persist after radiotherapy.

Methods: FDG-PET/CT scans were obtained for ten patients with NSCLC approximately two weeks before the start of radiation therapy (pre-RT) and approximately one month following completion of therapy (post-RT). The primary tumors were located mostly in the lower and upper lobes. The patients were treated with regular and hypofraction radiotherapy with an average dose of 60±6 Gy. The 4D scan was taken immediately following a 3D PET scan, using a single FDG dose (approximately 20mCi). The data were binned in five phases to create the 4D PET image sequence. The voxel size is 4.1×4.1×5 mm³ for 3D and 2.7×2.7×2 mm³ for 4D PET.

The images of the pre-RT scans were registered with the images of post-RT scan using a novel rigid-penalized deformable registration. The global lung bronchi and chest wall were non-rigidly transformed to minimize the respiration effects between pre-RT and post-RT scans while the lesion target is rigidly transformed to preserve the volume and SUV values before and after registration. Fig.1 illustrates the performance of registration employed on pre- and post-RT CT images. By aligned with planning CT, a ROI was defined by internal tumor volume (ITV) for each lesion individually on the 3D PET scan and each phase of the 4D PET scan. The high uptake areas pre and post-RT were delineated and quantified within the ROI using the threshold 40% of the maximal SUV. For post therapy scans the maximum SUV intensity had fallen to levels close to the surrounding background the threshold was increased anywhere from 55% to 90% of the maximum SUV.

We measured the physiological and geometrical variations between pre- and post-RT PET scans. The measures include the maximal SUV within the ROI for the 3D scan, $SUV_{3D}$, and for each phase of the 4D scan, $SUV_{4D}$. The locations of the center mass and the volumes of lesions were calculated based on delineations. The geometrical variation between pre- and post-RT were measured by the volumetric overlap fraction (VOF), where was defined as the
volume of overlap divided by the residual volume in post-RT scans, such as VOF = \frac{V_{\text{pre}} \cap V_{\text{post}}}{V_{\text{post}}}.

**Results:** Fourteen distinct lesions from ten patients were identified and analyzed. Fig. 2 shows a typical patient with a large heterogeneous tumor. The residual metabolic active areas are superimposed onto the pre-RT scan. Visual evaluation shows that the location of the residual areas largely corresponds with the high uptake areas pre-RT. The correspondence can be observed in both 3D and 4D PET. Compared to 3D PET, the high uptake areas in 4D PET have larger areas for both primary and residual tumor.

Fig. 3 shows the comparison of maximal SUV pre and post-RT scans. Two trends of treatment response to the radiotherapy were represented by the linear fits: dash line for partial treatment response, solid line for completed response. The pre-to-post maximal SUV changes showed 57% lesions has nontrivial residual uptake (SUVmax>2.5) for 3D PET, and 64% for 4D PET. The maximal SUVs for 4D pre and post PET have a 16.3% increase compared to those in 3D PET. Further statistical analysis show that there was a statistically significant increase in SUV maximum (p-value<0.005) for the lesions as measured on the 4D compared to 3D PET for both the pre-RT and post-RT scans.

Fig. 4 depicts the volumetric overlap fractions of the uptake within the primary tumor pre-RT with the post-RT tumor. The residual areas were mainly located within the primary tumor volume. For 3D PET, the 92% maximum SUV of residual metabolic-active areas are mainly located within the primary tumor volume. The overlap fraction of 4D PET is much closed to values of 3D PET. A trend of discrepancy was observed among five phases of 4D PET, which is indexed using the location of center mass of the high-uptake areas. We further classified the heterogeneity of the primary tumor using different thresholds of maximum SUV, and calculated VOFs. As a result, the mean VOFs reduced to 75% for 60% SUV_{3D} and 73% for 60% SUV_{4D}. The results suggest that the high-uptake areas within the residue largely located within the corresponded primary tumor in both 3D and 4D PET.

**Conclusions:** Residual metabolic-active areas have strong physiological and geometric correspondence to the primary tumor. With better signal recovery than standard 3D PET, high uptake areas of 4D PET pre-RT can better predict areas where residual metabolic activity will be found after radiotherapy.