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Re-irradiation of lung cancer

Comparing rigid and deformable dose registration for high dose thoracic re-irradiation

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For patients with locally-recurrent lung cancer, high dose thoracic re-irradiation can prolong survival. Deformable image registration improves the accuracy with which initial treatments are accounted for compared to rigid image registration. Using deformable image registration will improve correlative toxicity data, and may reduce toxicity for selected patients undergoing re-irradiation.

Despite the use of concurrent chemoradiation (CRT) for locally advanced non-small cell lung cancer (NSCLC), isolated loco-regional recurrences develop in approximately 25% of patients [1,2]. Surgical salvage is generally not feasible in this setting as patients are unlikely to have been non-surgical candidates to begin with and subsequent surgery carries a high complication risk [3]. For such patients, high dose thoracic re-irradiation (Re-RT) can result in long-term survival [4,5], however the risk of toxicity limits the utilization of Re-RT.

Accurately accounting for the initial treatment is a primary concern when planning Re-RT. This is typically accomplished using rigid image registration (RIR). However, RIR may not account for anatomic changes, including changes in body weight, early and late normal tissue radiation responses, set-up and positioning or interval treatments such as surgery. Deformable image registration (DIR) is an image processing technique, with the potential to account for such changes [6]. DIR maps the individual components (voxels) of one scan to those of another thus attempting to resolve such differences. As manual clinician contours and planned radiotherapy doses are assigned to these voxels, DIR similarly attempts to correct the spatial distribution of these (Fig. 1).

We evaluated the use of DIR to account for initial treatment when planning curative-intent Re-RT. The objectives were to quantify the spatial difference between RIR and DIR and to determine if DIR enabled improved dose registration accuracy.

Material and methods

Between April 2003 and December 2011, all patients at the VU University Medical Center who received curative Re-RT, despite overlapping planning target volumes (PTV) were eligible for evaluation. No patients were excluded otherwise. Re-RT was only offered to patients after their case had been discussed and treatment recommended by, a thoracic multi-disciplinary tumor board. Medical ethics review was not sought as in The Netherlands, retrospective studies fall outside the scope of the Medical Research Involving Human Subjects Act.

Initial (CT1) and subsequent (CT2) planning CT scans and their respective planned doses (D1 and D2) were imported into VelocityAI (v2.8, Velocity Medical Solutions, Atlanta, Georgia). DIR was performed using a modified basis spline algorithm with Mattes' formulation for mutual information [7]. Registration methods were largely automated, with user interaction limited to defining the region of interest for registration. For RIR and DIR, the region of interest encompassed the thoracic vertebrae and entire lungs, respectively, with an additional 1 cm margin. In each case, the region of interest for DIR encompassed the entire initial dose distribution.

To determine the spatial differences in dose registration, the initial treatment (CT1 with D1) was registered to CT2 using both RIR and DIR. Within CT2, contours representing 100%, 90%, 80%, 70%,

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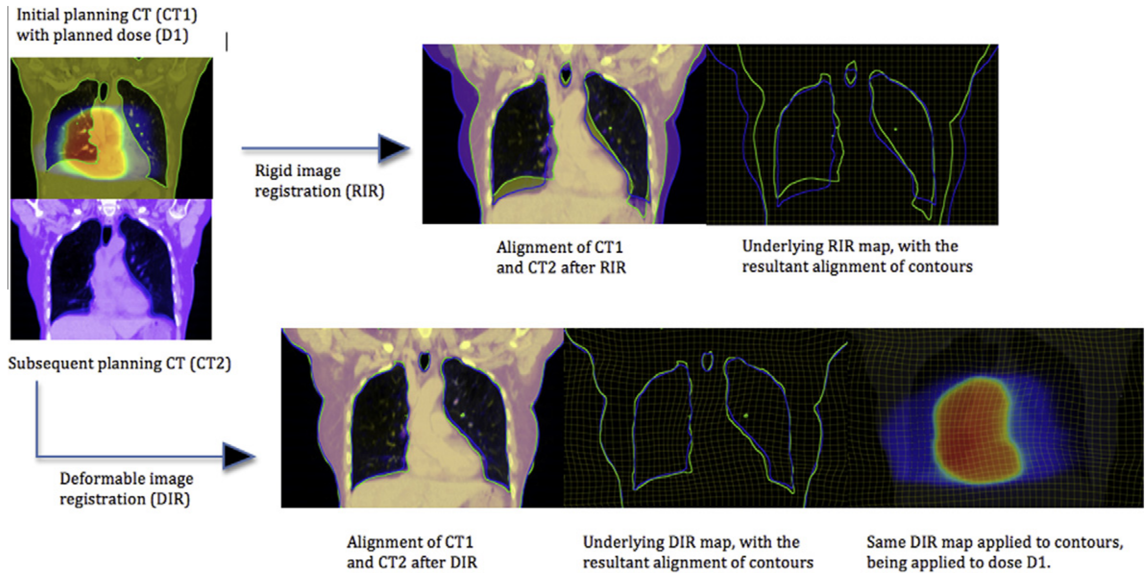

Fig. 1. Rigid (RIR) and deformable (DIR) image registration and the resulting registration maps being applied to manual clinician contours and planned radiotherapy doses.

60% and 50% of the prescribed dose following RIR and DIR were generated and the spatial difference for each dose level determined. To determine the accuracy of RIR and DIR, a clinician (SAS) manually contoured thoracic normal organs at risk in CT1 and CT2 using published guidelines [8]. After both RIR and DIR of CT1 to CT2, the accuracy with which CT1 manual contours matched CT2 manual contours was determined. Registered CT1 contours matching CT2 manual contours more closely were considered more accurate. Manual contours included those for the lungs, heart, aorta, esophagus, spinal cord and the major airways (trachea and main bronchus).

Statistical analysis

Descriptive statistics were used for study outcomes. To determine the spatial differences in dose registration, the shortest surface-to-surface (sSSD) distance between every voxel assigned a given dose after RIR, and the voxels assigned the same dose after DIR, were determined. Using the average and standard deviation of all of these sSSD values, the distance accounting for 95% of these (sSSD-95) was considered the spatial difference in dose registration at that dose level. Thus outlying, non-representative voxels were excluded. As sSSD values were skewed rather than normally distributed, the sSSD-95 was calculated using logarithmic transformation. Similarly to compare the registration accuracy of RIR and DIR, the sSSD between every voxel constituting a given CT1 manual contour after each registration was compared to the respective CT2 manual contour. The sSSD-95 calculated for RIR and DIR was considered the registration accuracy and these were compared. All statistical analyses were two-sided and performed using SPSS version 18.0.

Results

Ten consecutive patients with recurrent NSCLC underwent curative-intent Re-RT despite PTV overlap. The median patient age was 59 years (range 49–71). Patients were all of good performance status (WHO 0–1), and had undergone re-staging whole-body positron emission tomography and brain magnetic resonance imaging to confirm the absence of distant recurrence. The median time to Re-RT was 25 months (range 8–70). The median PTV overlap was 165 cc (range 2–470), representing a median 35% (range 1–89%) of the initial PTV receiving Re-RT. The most frequently utilized initial and Re-RT dose schedules were 60 Gy delivered in once daily 2 Gy fractions, five times per week.

The spatial difference in dose registration between RIR and DIR was overall found to be 7 mm (95% confidence interval 6.2–7.9). This however was highly variable between patients, with values ranging between 2.4 and 31.8 mm. The patient with the largest spatial difference in dose registration (31.8 mm) had undergone interval surgery and radiotherapy simulation was in a different position between treatments. Patient-specific results are detailed in Table 1. For any given patient, the spatial difference in dose registration was similar throughout the entire dose distribution (50–100%), with the standard deviation ranging between 0.1 and 2.0 mm.

CT1 manual organ contours matched CT2 manual contours more closely after DIR compared to RIR almost universally (59/60). Overall, the registration accuracy improved using DIR by 3.0 mm (95% confidence interval 1.4–5.7). In four patients there was at least one organ contour which registered more accurately using DIR by more than 5 mm, while in two patients there was at least one instance where this was more than 10 mm. No organ specific trends were observed. For each patient, the average accuracy improvement with DIR across all organs showed a strong positive correlation with the spatial difference in registration between RIR and DIR (pearson 0.77, $p = 0.009$). The patient with the largest spatial difference in dose registration between RIR and DIR, had accuracy improvements in the registration of the esophagus, heart and major airways of more than 10 mm.

Discussion

Locally recurrent lung cancer is associated with extremely poor survival [9,10]. Although the majority of clinicians consider Re-RT for local recurrence [11], this is seldom high dose and with curative intent [12]. Toxicity concerns are likely the primary reason for this. In this report, we quantified the spatial difference between RIR and DIR, finding differences are patient-specific and that for selected cases these can be significant. Additionally, we found DIR to be almost universally more accurate than RIR and for patients with the greatest difference in registration between RIR and DIR, the accuracy improvement utilizing DIR was greatest. These differences call