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Evaluation of adaptive treatment planning for patients with non-small cell lung cancer

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Abstract

The purpose of this study was to develop metrics to evaluate uncertainties in deformable dose accumulation (DDA) for patients with non-small cell lung cancer (NSCLC). Initial treatment plans (primary) and cone-beam CT (CBCT) images were retrospectively processed for seven NSCLC patients, who showed significant tumor regression during the course of treatment. Each plan was developed with IMRT for 2 Gy×33 fractions. A B-spline-based DIR algorithm was used to register weekly CBCT images to a reference image acquired at fraction 21 and the resultant displacement vector fields (DVF) were then modified using a finite element method (FEM). The doses were calculated on each of these CBCT images and mapped to the reference image using a tri-linear dose interpolation method, based on the B-spline and FEM-generated DVFs. Contours propagated from the planning image were adjusted to the residual tumor and OARs on the reference image to develop a secondary plan. For iso-prescription adaptive plans (relative to initial plans), mean lung dose (MLD) was reduced, on average from 17.3 Gy (initial plan) to 15.2, 14.5 and 14.8 Gy for the plans adapted using the rigid, B-Spline and FEM-based registrations. Similarly, for iso-toxic adaptive plans (considering MLD relative to initial plans) using the rigid, B-Spline and FEM-based registrations, the average doses were 69.9 ± 6.8 , 65.7 ± 5.1 and 67.2 ± 5.6 Gy in the initial volume (PTV₁), and 81.5 ± 25.8 , 77.7 ± 21.6 , and 78.9 ± 22.5 Gy in the residual volume (PTV₂₁), respectively. Tumor volume reduction was correlated with dose escalation (for isotoxic plans, correlation coefficient=0.92), and with MLD reduction (for iso-fractional plans, correlation coefficient=0.85). For the case of the iso-toxic dose escalation, plans adapted with the B-Spline and FEM DVFs differed from the primary plan adapted with rigid registration by 2.8 ± 1.0 Gy and 1.8 ± 0.9 Gy in PTV₁, and the mean difference between doses accumulated using the B-spline and FEM DVFs was 1.1 ± 0.6 Gy. As a dose mapping-induced energy change, energy defect in the tumor volume was $20.8 \pm 13.4\%$ and $4.5 \pm 2.4\%$ for the B-spline and FEM-based dose accumulations, respectively. The energy defect of the B-Spline-based dose accumulation is significant in the tumor volume and highly correlated to the difference between the B-Spline and FEM-accumulated doses with their correlation coefficient equal to 0.79. Adaptive planning helps escalate target dose and spare normal tissue for patients with NSCLC, but deformable dose accumulation may have a significant loss of energy in regressed tumor volumes when using image intensity-based DIR algorithms. The metric of energy defect is a useful tool for evaluation of adaptive planning accuracy for lung cancer patients.

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Keywords

tumor regression; adaptive treatment planning; dose escalation; deformable image registration; finite element method

INTRODUCTION

Lung cancer is the leading cause of cancer death for both men and women in the world. In the context of locally advanced non-small cell lung cancer (NSCLC), dose regimens in the range of 60–66 Gy produce 5-year overall survival rates of 10–15% (Kong et al., 2014). While higher radiation doses have been shown to potentially improve tumor local control and survival rates (Kong et al., 2005, Kong et al., 2014, Hansen et al., 2006), the ability to escalate dose on treatment targets is often limited by the increased risk of normal tissue toxicities (Movsas et al., 1997, Yamashita et al., 2014) (Bradley et al., 2010). Adaptive Radiotherapy (ART) enables mid-treatment plan modification in response to changes in gross tumor volume (GTV) and patient setup, ultimately to improve the therapeutic ratio over the course of fractionated radiotherapy (Kong et al., 2005, Sonke and Belderbos, 2010). Adaptation of planning margins as a result of tumor regression facilitates iso-toxic dose escalation to the target volume (Guckenberger et al., 2011b) (Feng et al., 2009). While ART incorporating deformable dose accumulation (DDA) has the potential to influence outcomes for patients with locally advanced NSCLC (Machtay et al., 2012, Kong et al., 2005, Ma et al., 2014, Nielsen et al., 2014), there are challenges with regard to proper validation of the accuracy of deformable image registration (DIR) algorithms, as well as limitations in dosimetric accuracy in situations where the tumor undergoes mass changes during the course of fractionated radiotherapy. These limitations are somewhat mitigated by the use of a constant planning treatment volume (PTV) during treatment (Tvilum et al., 2015) or the application of rigid registration for adaptive radiotherapy (Kong et al., 2013b) (Ma et al., 2014). Clearly these approaches are approximate, as they do not accurately account for changes in the tumor and normal tissue anatomy during the course of fractionated radiotherapy. Furthermore, response-based ART for individual patients will depend on quantitative assessment of tumor radiation responses, which requires accurate estimates of the total accumulated dose to each voxel within the image dataset.

The accuracy of dose accumulation is related to the accuracy of the underlying DIR algorithm (Mohan et al., 2005). Most commercially available DIR algorithms are based on the similarity of the two images being registered. Over time, the performance of these algorithms has improved significantly (Thirion, 1998, Wang et al., 2005, Nithiananthan et al., 2009, Rueckert et al., 2006). Unlike organ deformation, tumor regression may cause significant changes in the mass density of the tumor during the course of radiation treatment (Moller et al., 2014). Under such a condition, the accuracy of dose mapping with intensity-based DIR algorithms is limited because these algorithms register tumor volumes between the source and target images without considering the dosimetric consequence of the mass changes. When these algorithms were used for dose mapping, the total radiation dose delivered to the original tumor volumes could be mis-interpreted (Zhong and Chetty, 2017). Algorithms such as affine registrations or surface-based registration methods (Zhang et al.,

2014, Guckenberger et al., 2011b, Guckenberger et al., 2009, Sonke and Belderbos, 2010) have been used for dose accumulation for tumors undergoing mass changes to help circumvent the problems with intensity-based methods. However, the accuracy of these algorithms is limited, especially in the vicinity of the GTV. Recently Dial et al (Dial et al., 2016) employed synthetic image datasets produced by an image intensity-based DIR algorithm to evaluate the benefits of ART in terms of different replanning frequencies. The creation of synthetic CT datasets using DIR minimizes the impact of DIR uncertainties on dose reconstruction, While intensity-based registrations may still result in dose accumulation errors when the tumor has undergone significant mass regression, this study provided valuable information on the benefits of plan adaptation at different time points within the course of fractionated radiotherapy.

There have been several studies justifying the need for mid-treatment plan adaptation in response to tumor regression. For example, Guckenberger et al. (Guckenberger et al., 2011b) showed, using a surface model-based DIR algorithm, that a single mid-treatment plan adaptation was able to reduce mean lung dose (MLD) by 100 cGy on average, in cases where the GTV volume was reduced 39% on average at the end of week 4. Dial et al (Dial et al., 2016) used an image intensity-based DIR algorithm to demonstrate that mid-treatment plan adaptation reduced MLD by 38 cGy for patients who showed an average GTV reduction of 21% at the end of the treatment. Woodford et al. (Woodford et al., 2007) found that mid-treatment plan adaptation using rigid registrations produced a reduction in MLD ranging from 30 cGy to 160 cGy for three patients. It was suggestive that the major benefit from ART is achieved by implementation of a single mid-treatment adaptation (Dial et al., 2016), and that plan adaptation is recommended if a patient has tumor regression of 30% within the first 20 fractions (Woodford et al., 2007).

The above studies suggested that the accuracy of dose accumulation in ART is heavily dependent on its underlying DIR algorithm used. In this study, we have applied a commercially available B-Spline-based registration, as well as an in-house developed, finite element method (FEM) to perform DDA-based plan adaptations for seven patients with NSCLC. The accuracy of the dose accumulation was evaluated by computing energy and dose differences between the B-Spline and FEM-based plan adaptations, as well as by evaluating energy changes during the dose accumulation process. We have also investigated the potential to perform iso-toxic dose escalation for those cases where tumor mass regression was observed.

METHODS AND MATERIALS

As tumors respond to radiation, changes in the physical properties (e.g. mass density) within the tumor and surrounding areas occur over the course of fractionated treatment. These physical changes, sometimes manifested as tumor regression confound the accuracy of intensity-based registration algorithms for the purposes of deformable dose accumulation.

2.1 Image intensity-based registration under circumstances of tumor mass changes

An image intensity-based DIR algorithm implemented in Velocity AI (Varian Medical Systems, Palo Alto, CA) was employed in this study. Specifically, a navigator module in

Velocity AI was used for DIR of CBCT images. The procedure consisted of the following steps: manual alignment, selection of a region of interest, and rigid followed by deformable registrations. 3D “Deformable Multi-Pass” (DMP) was used for DIR. This algorithm uses a “Deformable Single-Pass” option with preprogrammed choices for grid settings for each pass. DMP is known to use mutual information (MI) as the similarity metric and a B-spline algorithm for interpolation (Stanley et al., 2013). By maximizing the similarity metric MI between the source and reference images, the coefficients of the B-Spline functions are derived, and the deformation field is then sampled with 3-D values for each voxel. When the MI of the two images is maximized, the tumor volume in the source image is changed to match that in the reference image. Consequently, in the case of tumor regression, the deformation map generated by this registration algorithm does not preserve the volume of the tumor.

For CT-based chest images, the B-spline registration algorithm is generally quite accurate. Based on benchmark tests for 4DCT and CBCT datasets, it was found that the errors of this algorithm are in the range of 1~3.1 mm in the lung (Stanley et al., 2013), and in the case of tumor shrinkage their difference from FEM-based DVFs is 4.2 ± 4.7 mm on average. However, when the original tumor volume is warped to the regressed tumor, the dose reconstructed by the B-Spline registration algorithm will be incorrect in the registered tumor volume because of the loss of deposited energy induced by tumor shrinkage (Zhong and Chetty, 2017). An in-house, fast FEM-based model was developed to correct for errors associated with B-Spline-based registrations in the tumor region. Briefly, the source and reference CBCT images were first rigidly aligned based on bony structures. A bounding box of the tumor was created in the source image with each face at least 2 cm away from the surface of the tumor. A tetrahedral mesh originally generated from a unitary cube was scaled to match the bounding box. A computational model was formulated on the mesh with the boundary constraints assigned from the displacements of the B-Spline registrations, and elasticity parameters assigned from the literature (Zhong et al., 2010). As anatomic structures distant to the regressing tumor are not displaced as much as those in the region surrounding the tumor, deformations in distant regions were taken as the boundary condition to guide a biomechanical model developed using the finite element method. The model-generated displacements at each of the tetrahedral nodes were then interpolated to image voxels located within the bounding box to generate the FEM-based deformation map. As this model is less influenced by image intensity changes, the FEM-based DIR can be accurate within ~2.5 mm. Since the FEM mesh covered only a small region around the tumor, the number of the tetrahedral nodes required for simulation was not substantial.

2.2 Metrics to evaluate dose accumulation error

Suppose that the dose delivered in week i is calculated on the weekly CBCT image (S_i). The map ϕ_i is generated by a deformable image registration, performed from S_i to a reference image (R), and ψ_i is the map generated by the corresponding FEM registration. A thorax-CBCT-density table was calibrated and used for CBCT dose calculation (Rong et al., 2010). Using the B-Spline and FEM-generated displacement vector fields (DVF), the doses on CBCT images were mapped to the reference image using trilinear dose interpolation (Rosu et al., 2005), and added together to compute the total dose delivered at each voxel.

Let $D(x,y,z)$ and $\rho(x,y,z)$ represent the calculated dose and mass density at point (x,y,z) in a source CBCT image S_i , respectively. Let V_i denote a tumor volume defined on S_i . Then the energy deposited in V_i can be derived using a volumetric integration:

$$E_{V_i} = \iiint_{V_i} D(x, y, z) * \rho(x, y, z) d\Omega. \quad (1)$$

Similarly, $E_{\varphi_i(V_i)} = \iiint_{\varphi_i(V_i)} D_{\varphi_i}(x', y', z') * \theta(x', y', z') d\Omega$, $D_{\varphi_i}(x', y', z')$ represents the reconstructed dose at point (x', y', z') in the target volume $\varphi_i(V_i)$ of the map φ_i , and $\theta(x', y', z')$ is the mass density which is converted from Hounsfield units (HU) using a HU-to-mass-density table calibrated for a CBCT scanner. Based on the energies integrated in the tumor volume V_i and the associated registration-deformed volume $\varphi_i(V_i)$, the following evaluation metrics were introduced:

The energy defect of the dose accumulation using the B-Spline-based deformation maps $\{\varphi_i\}$ is defined by:

$$\Delta_{BS}(V_i) := \frac{\sum_i |E_{\varphi_i(V_i)} - E_{V_i}|}{\sum_i E_{V_i}}. \quad (2)$$

The energy difference of the dose accumulation using the B-Spline-based maps $\{\varphi_i\}$, relative to the FEM-based deformation maps $\{\psi_i\}$, is defined by:

$$\delta_{BS,FEM}(V_i) := \frac{\sum_i |E_{\varphi_i(V_i)} - E_{\psi_i(V_i)}|}{\sum_i E_{\psi_i(V_i)}}. \quad (3)$$

The dose difference of the B-Spline-based dose accumulation, relative to the FEM-based dose accumulation, is defined as:

$$\varepsilon_{BS,FEM}(V_i) = \left| \widetilde{D}_{BS}(V_i) - \widetilde{D}_{FEM}(V_i) \right| \quad (4)$$

Where $\widetilde{D}_{BS}$ and $\widetilde{D}_{FEM}$ represent the doses accumulated by the B-Spline and FEM-based registrations, respectively, averaged over the volume V_i .

The three metrics were defined independently and used to evaluate dosimetric uncertainties in ART plans adapted with the B-Spline-based registrations.

2.3 Development of ART plans incorporating DDA

Treatment plans were retrospectively investigated in this study for seven NSCLC patients, whose characteristics are described in Table 1. Each patient was treated 2 Gy per fraction for 33 fractions using a 6MV TrueBeam linear accelerator (Varian Medical Systems, Palo Alto,

CA). The clinical treatment plans were developed with contours delineated on fan-beam CT and FDG-PET images in Eclipse (Varian Medical Systems, Palo Alto, CA). These plans were exported to the Pinnacle treatment planning system (Philips Radiation Oncology Systems, Fitchburg, WI). The original contours were propagated to CBCT₁, and modifications were made when necessary. A primary intensity-modulated radiation treatment (IMRT) plan for each of these patients was then developed on CBCT₁ using the Pinnacle. The GTV-to-PTV margin was set to 1 cm. The maximum dose constraint to the spinal cord was 45 Gy and the mean lung dose (MLD₁) for the primary plan was limited to 20 Gy. MLD₁ was calculated in bilateral lung with exclusion of GTV₁ which was delineated on CBCT₁. Weekly CBCT images were acquired at the beginning of each week and rigidly registered to CBCT₁ for calculating the weekly dose. The contours of the primary plan were propagated to CBCT₂₁ acquired at fraction 21, and adjusted, if necessary, to account for volumetric changes in the target and organs-at-risk (OAR). The resultant GTV₂₁ was extended 1 cm to generate PTV₂₁. A secondary plan was developed on CBCT₂₁ using the same constraints and beam configurations as for the primary plan. The mean lung dose (MLD₂₁) for the secondary plan was defined in CBCT₂₁ with exclusion of GTV₂₁.

There are two plan adaptation schemes investigated in this study. One is iso-prescription and the other is iso-toxic. The iso-prescription adaptive scheme consists of 20 fractions delivered with the primary plan, and 13 fractions with the secondary plan to give generally the same prescribed dose on the remaining target. The iso-toxic adaptive scheme also has 20 fractions delivered with the primary plan, but the number of the remaining fractions depends on the ratio of the mean lung doses between the primary and secondary plans.

For the iso-toxic dose escalation, if the primary plan was delivered for 20 fractions and a secondary plan was delivered for λ fractions, then λ can be found from relation $\lambda \times \text{MLD}_{21} = 13 \times \text{MLD}_1$, where MLD₁ and MLD₂₁ are the mean lung dose per fraction from the primary and secondary plans. The dose iso-toxically accumulated at voxel (x, y, z) from the two treatment plans can be computed by:

$$D_{\text{Total}}(x, y, z) = \sum_{i=1, \dots, 4} D_{\varphi_i}(x, y, z) + \lambda D_2(x, y, z) \quad (5)$$

where D_{φ_i} is the dose of the primary plan delivered in four weeks but warped by the map φ_i , and D_2 is the dose-per-fraction from the secondary plan. φ_i can be generated by the rigid, B-Spline or FEM-based registration methods. These registrations were performed from weekly CBCT images to CBCT₂₁, and dose mapping was performed using the tri-linear dose interpolation method (Rosu et al., 2005).

The B-spline-based dose accumulations were evaluated using the three metrics described in Eq (2–4). For patients with large energy defects (>10%) or large dose differences (>1 Gy) between different reconstruction methods, DIR errors were analyzed, and the dosimetric impact of these errors were illustrated by overlaying deformed grids on respective 3D dose distributions. The iso-toxic dose escalation on the tumor was evaluated using Eq. (5) with $\lambda = 13 \times \text{MLD}_1 / \text{MLD}_{21}$, and iso-prescription reduction in MLD was estimated using Eq. (5) with $\lambda = 13$.

RESULTS

3.1 Treatment plans developed for patients with tumor regression

The initial tumor volume (on CBCT₁) averaged over the 7 patients was $140.5 \pm 41.8 \text{ cm}^3$ (range = 93.2 to 262.2 cm³). The average tumor volume measured at the end of treatment was $64.6 \pm 35.7 \text{ cm}^3$. The reduction of tumor volumes, relative to CBCT₁ was $43.6 \pm 15.3\%$ at week 5 and $55.1 \pm 14.5\%$ at the end of treatment, respectively. These regression rates are slightly faster than those of Guckenberger (Guckenberger et al., 2011b), who reported tumor regression rates of 39% (week 5) and 49% (the end of treatment), as well as those of Lim who observed regression rates of 40.2% at week 5 and 51.1% at the end of treatment (Lim et al., 2011). The GTV regression trend for all patients is shown in Fig 1. The most significant regression was noted for patient 1 whose regression rate is similar to that of patient 2 reported by (Guckenberger et al., 2011b).

The primary IMRT plans were developed for each of these patients with an average PTV dose of 1.96 Gy per fraction and a MLD of 0.52 Gy per fraction. The secondary plans had an average dose of 1.94 Gy per fraction to the adapted target volume (PTV₂₁) and 1.58 Gy per fraction to the original target volume (PTV₁). MLD for the secondary plans was reduced to 0.37 Gy per fraction on average. The doses computed for these plans for individual patients are shown in Table 2.

3.2 Adaptive planning

The iso-prescription and iso-toxic adaptive schemes were used to create adaptive plans for the seven patients, respectively.

3.2.1 Iso-prescription dose accumulation—The two plans in Table 2 were summed in an iso-prescription manner to the primary plan for each patient. The MLD was reduced from 17.3 Gy for the primary plan to 15.2, 14.5 and 14.8 Gy for the summed plan adapted with the rigid, B-Spline and FEM-based registrations, respectively. The MLD of the summed plan for patient 1 was 13.8 Gy, and the plan adaptation reduced the MLD by 5.6 Gy.

Guckenberger et al (Guckenberger et al., 2011b) showed a reduction of ~3 Gy in MLD for a patient with a similar rate of tumor regression. The different MLD reductions between the two patients could be due to their tumor locations. Note that the same amount of tumor regression may spare more lung tissues for a peripheral tumor, as shown in Fig 2, than for a central, island one. Apart from patient 1, the reduction in MLD was about 1.8 Gy on average for the other patients.

3.2.2 Iso-toxic dose accumulation—Primary plans were calculated on the weekly CBCT images with the resultant doses mapped to the secondary planning images using the B-Spline and FEM-based registrations. Mapped doses were added to the doses of the secondary plans in an iso-toxic manner as described by Eq. (5). Accumulated doses using the B-Spline and FEM DVFs differed from the rigidly summed weekly doses by $2.8 \pm 1.0 \text{ Gy}$ and $1.8 \pm 0.9 \text{ Gy}$ for PTV₁, respectively (Table 3). The difference between the doses warped by the two types of the deformable registrations was $1.1 \pm 0.6 \text{ Gy}$ for PTV₁. The differences were based on the 40 Gy dose delivered within the first 20 fractions.

3.3 Accuracy of dose mapping

Among the seven patients, patients 1, 3 and 6 showed large dose differences between the ART plans adapted with the two DIR algorithms. The deformable registrations for these three patients are illustrated in Fig. 2, where the first two columns are the CBCT images acquired at fractions 1 and 21. The distortion of the B-spline registrations is illustrated in the deformed grids in Fig. 2. Due to an upstream bronchial obstruction, part of the lung volume for patient 6 showed high mass density at the beginning of the treatment (Fig 2(a3)). After two weeks of radiation treatment, the upstream obstruction was alleviated, allowing re-ventilation of the collapsed lung structure, as shown in the reference image (Fig 2(b3)). However, such a telestatic changes confounded the B-Spline registration algorithm resulting in the high density mass in the lung being pushed toward the front of the chest-wall. As a result, the high density mass was compressed in the deformed image as illustrated in Fig 2(c3). The FEM-based model was not influenced by such changes in image intensity, and produced accurate registration relative to the B-spline algorithm. It is observed that the FEM registration aligned the spinal cord in the source image to that in the reference image shown in Fig 2(b3), but did not distort the high density lung volume and structures toward the front of the chest wall. The FEM deformed image is shown in Fig 2(d3).

The dose volumes of the primary plans for the three patients are shown in red in Fig 3(a–c) and the B-Spline deformed grids are overlaid on the dose volumes to illustrate how the distortions of the B-Spline-based registrations impact the dose deformation. For patient 1, the distortion of the B-Spline-based registration occurred at the homogeneous, central dose region (Fig 3a), and for patients 3 and 6, the distortions of the B-Spline-based registrations appeared in regions with high dose gradients as shown Fig 3(b,c). Consequently, the dosimetric differences between the B-Spline and FEM-based plan adaptations for patient 3 and 6 were greater than that for patient 1. This was demonstrated in the DVHs of the B-Spline and FEM reconstructed doses shown in Fig 3(d–f). In general, dose accumulation errors depend not only on the scale of distortions in the image registrations, but also are related to the locations of these distortions.

3.4 Energy conservation in dose accumulation

Doses were accumulated on the reference images for the seven patients, using the different DIR algorithms, and total energies within tumor volumes were calculated using Eq (1). It was found for patient 1 that the energy accumulated by the B-Spline-based registrations over the deformed tumor volume was 5.8 Joule (J), which is much smaller than the 10.2 J accumulated over the original tumor volume. For the FEM-based registration, the integrated energy in the deformed tumor volume was 9.9 J. The FEM-based registration produced the same displacements as the B-Spline-based algorithm in the region outside the bounding box, but conserved the tumor volume in the deformed images. This example demonstrates that in case where tumor regression is large, the B-Spline deformed dose is inaccurate relative to that of the FEM-based deformation.

The energy defect was 20.8% (averaged over 7 patients) for the B-Spline-based dose accumulation. It was 4.5% for the FEM-based dose accumulation. The energy difference δ ,

relative to the FEM-deformed dose, was 16.2% on average. Details of the energy changes in the dose accumulation operations for each of these patients are shown in Table 4.

When the dose difference $\epsilon_{BS,FEM}(PTV_1)$ in Table 3 was compared to the energy defect ϵ_{BS} in Table 4, the cross correlation coefficient was high as 0.79 (Fig 4b). The dose difference was also highly correlated to the energy difference $\delta_{BS,FEM}$ with a correlation coefficient of 0.86. Note that the dose difference $\epsilon_{BS,FEM}$ is the difference between the two accumulated doses averaged in PTV_1 , and the energy difference $\delta_{BS,FEM}$ was defined in the warped PTV_1 volumes by the B-Spline and FEM DVFs. ϵ_{BS} is a metric of energy conservation in the B-Spline-based dose accumulation, independent of the FEM-based registration. The results of the two comparisons are illustrated in Fig 4.

The fitted equation in Fig 4b shows that the energy defect $\epsilon_{BS} = 0.2$ with the B-Spline-based dose accumulation (in PTV_1 during the first 20 fractions), results in a dose difference of ~ 1.1 Gy (out of 40 Gy) on average. Note that for the tri-linear dose interpolation method, the average dose in PTV_1 in general is equivalent to the dose interpolated in the deformed PTV_1 . That means the energy defect is mainly due to the volume difference between PTV_1 and $\phi_{BS}(PTV_1)$. Note that the energy defect is a direct metric for measuring dose mapping errors, independent of the dose distribution. In contrast, volume or mass changes are not the only factor determining dose mapping errors because the latter also depends on how the dose was distributed (Saleh-Sayah et al., 2011). Nonetheless, as both the energy defect and volume or mass changes may be used to estimate dose accumulation errors in ART, these terms should be investigated further before recommendations for clinical use can be made.

3.5 Dosimetric benefits of adaptive planning

Iso-toxic (equivalent MLD) combination of the primary and secondary plans using the rigid, B-Spline and FEM-based registrations generated the total doses of 69.9 ± 6.8 , 65.7 ± 5.1 and 67.2 ± 5.6 Gy, respectively for PTV_1 , and 81.5 ± 25.8 , 77.7 ± 21.6 , and 78.9 ± 22.5 Gy, respectively for PTV_{21} . The results of the iso-toxic dose escalation in the original and residual tumor volumes are listed in Table 5.

Due to the rapid regression of the tumor volume for patient 1 (Fig 1), the adaptive planning has the potential for high escalation of dose to the residual tumor target (PTV_{21}), as shown in Table 5. Iso-toxic dose escalations for other patients are in the range of 1.4~16.9 Gy, depending on their tumor regression rates. As shown in Fig 5, the correlation coefficient between the GTV reductions and the changes in the target dose was 0.92.

The iso-toxic adaptive scheme may help improve tumor local control and overall survival rates (Kong et al., 2013b). In contrast, the iso-prescription scheme does not escalate dose on the treatment target, but reduces radiation toxicity in lung and other OARs. This is important for late stage NSCLC patients (Movsas et al., 2013). Fig 5b shows that the correlation coefficient between the reductions in GTV and MLD was 0.85, and perceptible reduction in MLD can be observed after the tumor volume regresses greater than 30%, which is comparable to the results of Woodford (Woodford et al., 2007). In general, the strong correlations shown in Fig 5 support the concept that adaptive planning facilitates either iso-

toxic tumor dose escalation or iso-fractional normal tissue dose reduction, for patients where tumor regression is observed.

DISCUSSION

Different from dose escalation performed on the entire tumor volume (Bradley et al., 2010), ART with deformable dose accumulation allows high doses to be delivered to a reduced tumor volume without increasing radiation toxicity to lung and other healthy tissues. The potential of dose escalation may depend on the rate of tumor regression (Lim et al., 2011) as well as the accuracy of dose accumulation. As shown in Fig 5, the rate of tumor regression is highly correlated to the increase of the target dose and the reduction in MLD for the iso-toxic and iso-prescription adaptive schemes, respectively. The mid-treatment adaptation performed in this study reduced more MLD than those reported by Dial (Dial et al., 2016). This could be due to the different rates of tumor regression for patients in the two studies. The majority of the MLD reduction in this study was contributed by patient 1 who showed a rapid tumor regression within the first few weeks of treatment. Using the iso-toxic dose escalation approach specified by Eq (5), the average dose in the residual tumor volumes was increased from 64.7 Gy for the primary plan to 81.5, 77.7 and 78.9 Gy for the ART plans adapted by the rigid, B-Spline and FEM registration algorithms, respectively. The ART plans adapted by the three algorithms showed large dosimetric differences. The dosimetric differences are likely attributed to the fact that volume preserving deformation is not applied by these algorithms, and the changed volumes are inconsistent between these algorithms, in addition to the underlying registration uncertainties (Zhong and Chetty, 2017).

Due to the lack of an effective tool to measure the mapped dose, dose mapping errors usually are unknown. Quality assurance for ART was alternatively performed by evaluating the quality of image registrations used for the dose accumulation (Weiss et al., 2013) (Sonke and Belderbos, 2010) (Guckenberger et al., 2011a). However, this approach might be challenged when the tumor regresses, because dose reconstructed on the residual tumor will be incorrect even using an accurate registration map (Zhong and Chetty, 2017). In this study, we introduced the metric of energy defect to measure errors produced in the process of dose accumulation. Based on this metric, we found that errors in the FEM-based dose accumulation are much smaller than those produced by the B-Spline-based method (Table 4), and the dose difference between the two DIR-based ART plans is smaller than their differences from the plan adapted with a rigid registration algorithm (Table 3).

Since the FEM-based registration is not directly influenced by intensity changes, the distortion in the FEM-deformed grids is therefore small. Consequently, the FEM-accumulated doses were assumed to be more accurate, and used as a benchmark for evaluation of the B-Spline-based dose accumulation. Note that while the definition of the metric ϵ_{BS} is independent of the FEM-based dose accumulation, there is a strong correlation between the metrics ϵ_{BS} and $\epsilon_{BS,FEM}$, as shown in Fig 4b. This is because both the metrics reveal the uncertainties of the B-Spline-based dose accumulation. Different from $\epsilon_{BS,FEM}$, the metric ϵ_{BS} is independent of uncertainties in other benchmark registrations, and implementation of this metric is convenient. It is preferable to have ϵ_{BS} calculated for each of dose accumulation operations.

CBCT imaging serves as an important tool for adaptive planning and dose calculation for lung patients (Qin et al., 2013). In this study, CBCT doses were calculated using a CBCT-density table calibrated with a CIRS thorax phantom. It was reported that average differences between CT and CBCT dose calculations were 2%–3% for most dose metrics when a standard CT-density table was used, and a better agreement was observed when a thorax-CBCT-density table was used, with differences of 1%–2% (Rong et al., 2010, de Smet et al., 2016). Since in this study both the primary and secondary plans were calculated on CBCT images, the impact of CBCT dosimetric uncertainties on the evaluated metrics shown in Eq (2–4) should be minimized. Nevertheless, the 2% uncertainties may still exist in the estimated dose escalations. It is worth investigating the impact of the dosimetric uncertainties further on the metrics shown in Figure 5 in future studies.

Note that part of the PTV for the primary plan was not treated by the secondary plan, so the summed plan might not have a significant increase in the average dose in the entire PTV. Previous studies showed ~4 Gy dose escalation for the entire PTV (Guckenberger et al., 2011b, Gillham et al., 2008), and in this study, the dose escalation was in a range of 0.9–5.2 Gy, depending on the registration algorithm used. Furthermore, we showed that the summed plans may have heterogeneous dose distributions with significant dose increases to the residual tumors (Table 5). These results are supportive of the consensus that adaptive RT improves treatment outcomes for patients with locally advanced NSCLC (Kong et al., 2005, Kong et al., 2013a, Guckenberger et al., 2011a).

CONCLUSION

Adaptive planning helps escalate target dose and spare normal tissue for patients with NSCLC, but dose accumulation may have a significant loss of energy in regressed tumor volumes when using image intensity-based DIR algorithms. The metric of energy defect is a useful tool for evaluation of adaptive planning accuracy for lung cancer patients.

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Figure 1.
Relative tumor volumes during the course of radiation treatment for seven NSCLC patients.

Figure 2.

(a) The source image ($CBCT_1$) with GTV contoured; (b) the reference image ($CBCT_{21}$); (c) and (d) the source image warped the B-spline and FEM DVFs, respectively. Rows 1,2,3 are corresponding to patients 1, 3 and 6, respectively.

Figure 3.

(a), (b) and (c) the B-Spline deformed grids overlaid on the dose distributions calculated by the primary plans, and (d–f) DVHs of the primary, B-Spline and FEM warped doses in PTV₁-PTV₂₁ for patients 1, 3 and 6, respectively.

Figure 4.

The dose difference $\epsilon_{BS,FEM}(PTV_1)$ of the B-Spline-based dose accumulation, relative to the FEM-accumulated dose, vs. (a) the energy difference $\delta_{BS,FEM}$ and (b) the energy defect Δ_{BS} of the B-Spline-based dose accumulation.

Figure 5. Relation between tumor volume reduction and (a) increased target dose in iso-toxic plans and (b) MLD reduction in iso-prescription plans.

Characteristics of the patients studied. R-GTV is the ratio between the volumes of GTV₂₁ and GTV₁, defined in CBCT₂₁ and CBCT₁, respectively.

Table 1

Patient	P1	P2	P3	P4	P5	P6	P7
Age	77	77	65	81	80	53	78
Stage	IIIA	IIIB	IIIA	IIIB	IIIA	IIIA	IIA
Histology	Adenoca	Adenoca	Squamous	Squamous	Squamous	NSCLC	Adenoca
GTV(cm ³)	162.5	238.8	115.9	173.6	93.2	262.2	99.4
R-GTV (%)	77.4	34.9	49.1	42.7	28.9	30.9	41.2
Location	LUL	RUL	RLL	LUL	RUL	LUL	RUL

Table 2

The dose per fraction averaged in the original and residual treatment targets, computed by the primary and secondary plans.

(G _y /fr)	P1	P2	P3	P4	P5	P6	P7	Aver±Std	
Primary Plan	PTV ₁	1.95	1.89	1.94	1.97	1.99	1.98	2.0	1.96±0.04
	PTV ₂₁	2.0	2.02	1.95	1.97	2.01	1.97	2.01	1.99±0.02
	MLD ₁	0.59	0.59	0.5	0.49	0.49	0.58	0.42	0.52±0.06
Secondary Plan	PTV ₁	0.91	1.27	1.72	1.78	1.93	1.66	1.76	1.58±0.36
	PTV ₂₁	1.95	1.98	1.76	1.98	1.99	1.92	2.01	1.94±0.08
	MLD ₂₁	0.16	0.38	0.36	0.36	0.46	0.53	0.31	0.37±0.12

Table 3

Dose differences averaged in PTV₁ between the ART plans adapted with the rigid, B-Spline and FEM-based registrations.

(Gy)	P1	P2	P3	P4	P5	P6	P7	Aver±Std
$\ ART_{BS}-ART_{rigid}\ $	3.2	1.8	4.1	1.9	3.6	3.1	1.7	2.8±1.0
$\ ART_{FEM}-ART_{rigid}\ $	2.2	1.1	1.9	1.7	3.3	0.6	1.4	1.8±0.9
$e_{BS,FEM}(PTV_1)$	1.2	1.0	2.4	0.7	0.5	1.3	0.9	1.1±0.6

Energy of the planned dose integrated in PTV₁ over the first 20 fractions for the seven patients and the energy indices δ and δ for the B-Spline and FEM-based dose accumulations.

Table 4

	P1	P2	P3	P4	P5	P6	P7	Aver±Std
E (J)	19.6	14.8	10.2	6.0	9.7	18.8	9.3	12.6±5.2
$\delta_{BS}(\%)$	34.8	20.3	43.2	6.6	15.5	11.7	13.0	20.8±13.4
FEM(%)	4.1	5.1	3.0	5.1	9.3	1.7	3.4	4.5±2.4
$\delta_{BS,FEM}(\%)$	30.8	15.1	40.2	1.5	6.1	9.9	9.7	16.2±14.1

Table 5

Average dose on the original and residual targets for iso-toxic plans developed using rigid, B-Spline and FEM-based registrations.

	Plan	P1	P2	P3	P4	P5	P6	P7	Aver±Std
PTV ₁	Rigid- ART	83.1	63.4	70.1	71.3	66.5	62.9	71.5	69.9±6.8
	BS- ART	74.5	61.6	62.1	67.2	61.8	62.3	70.1	65.7±5.1
	FEM- ART	77.3	62.6	66.6	67.8	62.3	63.8	69.6	67.2±5.6
PTV ₂₁	Rigid- ART	134.1	80.0	71.1	74.9	67.7	66.5	76.2	81.5±25.8
	BS- ART	120.9	78.8	66.3	71.6	64.2	66.8	75.1	77.7±21.6
	FEM- ART	124.4	79.5	68.9	72.2	64.7	67.9	74.6	78.9±22.5