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Adaptive radiotherapy for NSCLC patients: utilizing the principle of energy conservation to evaluate dose mapping operations

Hualiang Zhong and Indrin J. Chetty

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA

Abstract

Tumor regression during the course of fractionated radiotherapy confounds the ability to accurately estimate the total dose delivered to tumor targets. Here we present a new criterion to improve the accuracy of image intensity-based dose mapping operations for adaptive radiotherapy for patients with non-small cell lung cancer (NSCLC). Six NSCLC patients were retrospectively investigated in this study. An image intensity-based B-spline registration algorithm was used for deformable image registration (DIR) of weekly CBCT images to a reference image. The resultant displacement vector fields were employed to map the doses calculated on weekly images to the reference image. The concept of energy conservation was introduced as a criterion to evaluate the accuracy of the dose mapping operations. A finite element method (FEM)-based mechanical model was implemented to improve the performance of the B-Spline-based registration algorithm in regions involving tumor regression. For the six patients, deformed tumor volumes changed by $21.2 \pm 15.0\%$ and $4.1 \pm 3.7\%$ on average for the B-Spline and the FEM-based registrations performed from fraction 1 to fraction 21, respectively. The energy deposited in the gross tumor volume (GTV) was 0.66 Joules (J) per fraction on average. The energy derived from the fractional dose reconstructed by the B-spline and FEM-based DIR algorithms in the deformed GTV's was 0.51 J and 0.64 J, respectively. Based on landmark comparisons for the 6 patients, mean error for the FEM-based DIR algorithm was 2.5 ± 1.9 mm. The cross-correlation coefficient between the landmark-measured displacement error and the loss of radiation energy was -0.16 for the FEM-based algorithm. To avoid uncertainties in measuring distorted landmarks, the B-Spline-based registrations were compared to the FEM registrations, and their displacement differences equal 4.2 ± 4.7 mm on average. The displacement differences were correlated to their relative loss of radiation energy with a cross-correlation coefficient equal to 0.68. Based on the principle of energy conservation, the FEM-based mechanical model has a better performance than the B-Spline-based DIR algorithm. It is recommended that the principle of energy conservation be incorporated into a comprehensive QA protocol for adaptive radiotherapy.

Keywords

dose accumulation; deformable image registration; tumor regression; energy conservation

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Corresponding Author: Hualiang Zhong, Department of Radiation Oncology, Henry Ford Health System, 2799 W Grand Blvd., Detroit, MI, 48202, hzhong1@hfhs.org, Phone: 1 (313) 874-3954, Fax: 1 (313) 916-3264.

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INTRODUCTION

Tumor regression during the course of fractionated radiation treatment has been observed in many patients diagnosed with locally advanced non-small cell lung cancer (NSCLC) (Sonke and Belderbos, 2010, Lim et al., 2011). When tumor regression occurs during the course of radiation treatment, dose conformity of an initial treatment plan may be compromised. To address this issue, a second plan can be developed with a new dose prescription to the residual gross tumor volume (GTV), based on the dose already delivered to the planning GTV and organs-at-risk (OAR's). The delivered doses can be calculated on a reference image dataset by using deformable dose mapping and accumulation techniques (Mohan et al., 2005, Heath and Seuntjens, 2006). It has been demonstrated that adaptive radiotherapy incorporating deformable dose accumulation (DDA) may facilitate dose escalation and normal tissue sparing (Weiss et al., 2013). Among these techniques, image-intensity-based deformable registration incorporating dose interpolation is a widely used DDA method (Rosu et al., 2005). However, due to the lack of an efficient verification technique (Schultheiss et al., 2012), deformable image registration is not yet an accepted tool in clinic for dose accumulation (Kong et al., 2013b).

A key component in DDA is deformable image registration (DIR), which is required to map dose from a treatment image to a reference image. A variety of DIR techniques have been developed and spatial accuracy has been improved over the last two decades. For example, the original "demons" (Thirion, 1998) has been enhanced to be efficient (Wang et al., 2005), inverse consistent (Yang et al., 2008) and diffeomorphic (Vercauteren et al., 2009, Yeo et al., 2010); the B-spline-based algorithm (Rueckert et al., 1999) has been extended to be hierarchical (Klein et al., 2010), diffeomorphic (Rueckert et al., 2006), and with non-uniform knot placement (Jacobson and Murphy, 2011) or with simplified regularization forms (Chun and Fessler, 2009). These improvements have facilitated the functionality of DIR in clinical settings, such as efficient contour propagation (Hardcastle et al., 2013, Chao et al., 2007), and organ segmentation even in regions with low image intensity contrast (Liu et al., 2012, Yeo et al., 2013). While these DIR algorithms may deform a treatment image to a reference image with a high similarity, they cannot guarantee accurate dose to be reconstructed on the reference image, because the dose reconstructed at each image voxel also depends on the dose mapping method used (Siebers and Zhong, 2008).

Dose mapping methods such as center-of-mass or tri-linear dose interpolation were developed to map dose from a source image to a reference image (Rosu et al., 2005). While accuracy of these approaches was improved in heterogeneous tissues regions using energy transfer methods (Siebers and Zhong, 2008, Li et al., 2014), dose interpolation remains a popular approach for dose mapping due to its computational efficiency (Guckenberger et al., 2011, Hugo et al., 2011, Zhang et al., 2014). However, since there are currently no methods to quantitatively validate mapped dose in the clinical setting, even without issues associated with tumor regression, the dose mapping process is still considered technically challenging and even controversial (Schultheiss et al., 2012). Examples of the complexity faced in clinical datasets, include rectal filling for pelvic or genitourinary treatments, and tumor mass changes for patients with locally advanced NSCLC. In the case of physiology-induced volumetric changes (e.g. rectum or bladder filling), it is reasonable to align organ boundaries

during the image registration process. However, for patients where the tumor may undergo regression during treatment (e.g. locally advanced NSCLC), the visible tumor mass might change, reflecting a possible destruction of tumor (Lim et al., 2011). In such situations, it may not be appropriate to simply align tumor boundaries during the DIR process. These two scenarios demonstrating mass changes may indeed require different registration and dose mapping techniques.

It is crucial to compute the actual dose delivered to tumor regions in order to accurately estimate tumor local control and treatment response (Taylor et al., 2013). It is therefore of paramount importance to develop an accurate dose mapping technique for patients with tumor regression. In this study, we will investigate the accuracy of dose reconstruction methods for NSCLC patients with tumor regression. Specifically, we will introduce the principle of energy conservation as a criterion for evaluation of deformable dose mapping. We will evaluate the accuracy of an image-intensity-based, B-Spline registration algorithm implemented in a clinical software package, and explore the dosimetric difference between this algorithm and an in-house implemented, fast finite element method (FEM) used in dose mapping operations.

METHODS AND MATERIALS

During the course of radiation treatment, dead tumor cells may be lost or replaced by new cells, resulting in mass and consequently image intensity changes in the tumor and its surrounding areas. As radiation dose (Gy) is a term defined on the top of irradiated mass, changes in the mass make this term no longer an objective quantity in measuring the amount of radiation energy deposited on a reference image.

2.1 The principle of energy conservation for dose mapping

Cell loss or replacement within the tumor volume is related to how many cells are destroyed by the total radiation energy delivered within each voxel. To assess such tumor cell destruction, it is necessary to track the coordinates of these voxels during the course of treatment so that the total energy deposited within each of these voxels can be correctly accounted for without any loss. This presents the requirement of energy conservation for dose mapping and accumulation operations.

Suppose a deformable registration ϕ is performed from a treatment image I_t to a reference image I_r with the delivered dose mapped to I_r . Based on the energy conservation principle, the radiation energy (RE) deposited in a geometric volume V_t in the image I_t must be equivalent to the radiation energy calculated from the reconstructed dose in the warped volume $\phi(V_t)$, i.e.

$$\sum_{v \in V_t} D_v \times \|v\| \times \rho_v = \sum_{w \in \phi(V_t)} D_w \times \|w\| \times \rho_w \quad (1)$$

where D_v is the dose calculated from the treatment plan at voxel v in V_t , $\|v\|$ represents the volume of the voxel v , and ρ_v is the mass density of the voxel v . D_w is the dose at voxel w ,

reconstructed using the tri-linear dose interpolation method (Rosu et al., 2005), and ρ_w is the mass density of voxel w . The mass density at each image voxel is converted from Hounsfield units (HU) using a scanned HU-to-mass-density table. The left and right sides of Eq. (1) are denoted by $RE(V_D)$ and $RE(\phi(V_D))$, respectively. The equivalence between $RE(V_D)$ and $RE(\phi(V_D))$ is termed as *the principle of energy conservation for the dose mapping operation* ϕ .

2.2. A hybrid finite element method

In common image intensity-based, B-Spline registration algorithms, the underlying B-spline functions are solved by maximizing the similarity of the image intensity distributions between the source and reference images (Rueckert et al., 1999). Under conditions of cell loss or replacement, those B-Spline functions in the region with mass density changed between the two images can be mis-calculated. To mitigate the related registration errors, we introduced a FEM-based, hybrid registration method. Compared to radiation-induced mass changes at tumor boundaries, those changes at locations distant to the regressed tumor volume are relative small. The B-Spline generated displacements at these distant locations can be incorporated into a FEM model to calculate tissue deformation in regions of tumor regression. As the deformation of the structures nearby the tumor is computed by the FEM-based mechanical model, independent of the regressed tumor volume, the regression-induced energy loss can be avoided in the FEM-based dose accumulation.

A bounding box of the tumor volume was defined in the overlay of the source and reference images which were rigidly registered such that the distance from the surface of the box to the surface of the original tumor is at least 2 cm. The box was then partitioned using the ICEM software (Ansys Inc., Canonsburg, PA) to generate a prototype tetrahedral mesh. A FEM model was formulated (Zienkiewicz and Taylor, 2000) with the algebraic equations represented by:

$$K * \begin{pmatrix} d_{k+1} \\ \dots \\ d_n \end{pmatrix} = \begin{pmatrix} F_{k+1} - \sum_{i=1, \dots, k} g_{k+1,i} d_i \\ \dots \\ F_n - \sum_{i=1, \dots, k} g_{n,i} d_i \end{pmatrix}, \quad (2)$$

where K is the global stiffness matrix consisting of the stiffness entry $g_{i,j}$ defined between two tetrahedral nodes i and j , $d_1, \dots, d_k$ are the displacements of the nodes located on the surface of the bounding box, and $d_{k+1}, \dots, d_n$ are the displacements of the free nodes. $F_{k+1}, \dots, F_n$ represent the external forces acting on the free nodes. These forces were assumed to be zero. The displacements $d_1, \dots, d_k$ were derived by interpolation of the displacement vector field (DVF) generated by a B-spline-based registration between the source and reference images. The material parameters were assigned with Young's moduli equal to 1 MPa for bone, 1 kPa for lung, and 10 kPa for other soft tissue (Zhong et al., 2010), and the Poisson ratio was assumed to be 0.35 for lung and 0.49 for the bone and normal tissue.

The equations were solved using a conjugated gradient method. The FEM generated displacements at each of the tetrahedral nodes were then interpolated to image voxels within the bounding box (Zhong et al., 2012). The FEM-computed displacements within the box

were combined with the displacements of the B-Spline registration outside the box to form a FEM DVF in the whole image domain. Since the FEM DVF is equivalent to the B-spline-computed displacements at the boundary of the box, the deformation map generated by the hybrid registration method is continuously defined in the domain of the reference image.

2.3 Spatial and dosimetric comparison of the two DIR algorithms

Six patients with locally advanced NSCLC were treated with 6MV photons and IMRT using a TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, CA). Weekly CBCT images were acquired for patient localization, and to help monitor tumor regression. An intensity-based B-Spline registration algorithm implemented in VelocityAI (Varian Medical Systems, Palo Alto, CA) was employed to register CBCT images from fraction 1 to fraction 21 (of 33 total fractions) for each of these patients. The derived DVFs were corrected by the hybrid FEM-based model. The spatial accuracy of these registrations was evaluated using landmarks, including vessels, carina and bony structures. These structures were selected only if they were distant from the tumor volume.

The quality of these registrations was also evaluated using the unbalanced elasticity energy (UEE), computed from their deformation maps (Zhong et al., 2007). Briefly, for each element j , the displacements $d_k^{(j)}$ at node k ($k=1, 2, 3, 4$) were generated from the deformation map of an image registration. The UEE of this registration in this element was calculated by

$$UEE(j) = \sum_{k=1, \dots, 4} \left| d_k^{(j)} E_j \sum_{l=1, 2, 3, 4} m_{kl}^{(j)} d_l^{(j)} \right| \quad (3)$$

where m_{kl} is defined to be equivalent to the stiffness entry g_{kl} except that the Young's modulus (E_j) was extracted out. The Young's modulus and Poisson ratio were assigned the same values as in Eq. (2). The displacements are in the unit of centimeters, and the resultant UEE is in the unit of milli-Joule. UEE reveals the mechanical compliance of the DVF generated by the B-Spline-based registrations. If a geometric volume has high UEE values, the corresponding DVF will have large errors in the associated region. Consequently, displacement profiles in these regions need to be further analyzed.

For the six patients, GTV and OAR contours were delineated on planning CT images, and rigidly propagated to CBCT₁ by using the Pinnacle planning system (Philips Radiation Oncology Systems, Fitchburg, WI). Adjustments were made on these contours if necessary. Treatment plans were re-optimized on CBCT₁. Computed doses were mapped to CBCT₂₁ using the dose interpolation method (Rosu et al., 2005), based on the DVFs generated by the B-spline and FEM-based registration algorithms. Dose mapping operations were evaluated using the principle of energy conservation described in Eq. (1).

RESULTS

3.1. Error of the B-Spline-based deformable registration and its correction

For the six patients, tumor volumes decreased by 40.5% on average from fraction 1 to fraction 21. A B-Spline-based DIR using VelocityAI was performed from an initial source image (CBCT₁) in Fig 1(a) to a reference image (CBCT₂₁) in Fig 1(b) for patient 1. The resultant DVF was used to deform the source image with the result shown in Fig 1c. Fig 1d represents the corresponding deformation grid.

Due to the tumor shrinkage, the surface of the original tumor volume (Fig 1a) was “pulled” toward that of the residual tumor volume (Fig 1b) by the intensity-based, B-spline algorithm. Such a surface-to-surface mapping generated by this registration algorithm induces large distortions in the structures surrounding the tumor, as illustrated in Fig 1(c–d). It can be found that the vessels (highlighted in the circled region outside the residual tumor) were inaccurately “stretched”, resulting in blurring of these structures. This example demonstrates that such unphysical “pulling and stretching” of the image dataset, using the B-spline algorithm, as a result of tumor regression, compromises registration accuracy in the vicinity of the tumor.

Fig 2 illustrates the quantitative differences between the B-spline and FEM-based registrations across the horizontal ($y=280$) and vertical ($x=262$) lines marked in yellow. The profiles of the displacements of the B-Spline-based registration along the two lines are shown in Fig 2c and 2d. A bounding box was defined from voxel 200 to voxel 310 in both the x and y coordinates. Within the bounding box marked in the deformed source image (Fig 2a), with the B-Spline registration, the central voxels were displaced approximately 1.5 cm more than the boundary voxels. Consequently, soft tissues within the bounding box must be “stretched” at one end and “compressed” at the other end. Such unphysical “stretching and compression” (as shown by the deformed grid in Fig 2a), results in an unbalance of external forces, and consequently, high unbalanced energy as shown in Fig 2e. This contradicts the principle of elasticity energy equilibrium in soft tissue.

As shown in Fig 2(c) and 2(d), displacements for both algorithms were identical outside the bounding box, but the hybrid FEM method corrected the unphysical displacements of the B-spline-based registration within the box. The unbalanced energy within the box was also reduced with the hybrid FEM algorithm (Fig 2f). The FEM-deformed image superposed with the corresponding deformation grid is shown in Fig 2b. Note that since the FEM corrections were performed only within the bounding box, the number of the tetrahedral nodes required for such corrections was small, and each of these FEM corrections could be completed within 30 seconds. This allows efficient adjustments to be made on the shape of the bounding box. In general, a box with each face 2 cm away from the tumor may work well, but further investigations of optimal boundary constraints are warranted.

3.2. Deformation accuracy of the B-Spline and FEM-based registrations

Landmark points outside the tumor were selected to investigate the accuracy of the B spline and FEM-based registrations. As shown in Fig 3, the four points marked in the source image (Fig 3a) were found to be located slightly posterior in the reference image (Fig 3b), relative

to their positions in the source image. The B-Spline-based DIR performed from the source image to the reference image induced significant displacement of the landmark positions posteriorly in the deformed source image (Fig 3c), relative to the reference image (Fig 3b). This is because of the large scale deformation resulting from alignment of the original and residual tumor volumes with the B-spline-based registration. As a result, the deformed image is stretched and compressed in an unphysical manner, causing distortion of surrounding structures. On the other hand, it is clear that the vessels reconstructed by the FEM registration in Fig 3d are consistent with those in the reference image (Fig 3b).

Twenty landmark points outside the original tumor volumes were selected from each of the source images (CBCT₁). The difference in these landmark positions between the reference images (CBCT₂₁) acquired at fraction 21 and the deformed source images using the hybrid FEM-based DVF was 2.5 ± 1.9 mm on average for the six patients. Since the B-Spline-based registrations distorted these landmark structures, as illustrated in Fig 1c, the positions of these landmarks in the B-Spline warped source images cannot be assessed objectively. Alternatively, the B-Spline-based registrations were quantitatively evaluated through the comparison of their displacements with those of the hybrid FEM registrations at each image voxel. The average displacement difference between the B-Spline and FEM registrations is 4.2 ± 4.7 mm. The results of the comparison for each patient are shown in Table 1.

When the B-Spline-based registrations were performed from CBCT₁ to CBCT₂₁, the deformed GTV volumes changed $21.2 \pm 15.0\%$ on average. The corresponding change with the hybrid, FEM-based model was $4.1 \pm 3.7\%$. The FEM-based model therefore mitigated the volumetric inconsistency observed during the B-Spline-based registrations. Elasticity energy was calculated using Eq. (3) for each of the B-Spline and FEM displacement vector fields. The average UEE was 0.29 mJ for the B-Spline registrations and 0.06 mJ for the FEM registrations (Table 1). The FEM-based model reduced the deformation uncertainty of the B-Spline-based registrations.

3.3. Accuracy of dose mapping performed using the two DIR methods

The GTV dose per fraction calculated with the pre-treatment plans was 2.0 ± 0.03 Gy on average for the six patients. Using the formula shown in Eq (1), the dose was converted to radiation energy deposited in the GTV and its deformed volumes. The average energy deposited per fraction was 0.66 J within the GTV, and the average energies in the deformed GTV using the B-Spline and FEM registrations were 0.51 and 0.64 J, respectively. The ratio of the REs before and after the dose mapping was 78.0% for the B-spline registrations, and 95.7% for the FEM-based model. The RE loss in the B-Spline-based dose mapping, denoted by $L(BS)$, was defined as the difference between $RE(GTV)$ and $RE(\phi_{BS}(GTV))$, with respect to $RE(GTV)$. Similarly, the RE loss in the FEM-based dose mapping was denoted by $L(FEM)$. The relative loss (RL) of radiation energy for the B-Spline algorithm is defined as the difference between $RE(\phi_{BS}(GTV))$ and $RE(\phi_{FEM}(GTV))$. The computed results for the six patients are shown in Table 2.

For the B-Spline-based registrations, tumor regression induced displacement errors in regions nearby the tumor and caused radiation energy lost during the dose mapping process. The cross correlation coefficient between the FEM-based displacement errors evaluated in

Table 1 and the relative RE loss shown in Table 2 is 0.68 (Fig 4a). The correlation coefficient between the displacement errors and the unbalanced elasticity energy evaluated in Table 1 is 0.93 (Fig 4b). The high correlation coefficients support these evaluation methods to be used for assessment of DIR and dose accumulation operations. Different from the B-Spline-based registration, the FEM-based registration is independent of tumor regression. Its displacement errors in Table 1 are not directly related to the RE loss in the FEM-based dose mapping, and their correlation coefficient is only -0.16 (Fig 4c). While the landmark comparison for assessment of the FEM-based registrations might have uncertainties, these uncertainties do not impact the correlation coefficients shown in Fig 4 for the B-Spline-based registration which is independent of the assessment uncertainties for the FEM-based registrations.

3.5 Accuracy of reverse dose mapping

In cooperative group clinical protocols, such as RTOG 1106 (Kong et al., 2013a), the dose computed from an adaptive plan must mapped from the during-treatment image to the reference image in the initial treatment plan. To evaluate the impact of tumor regression on the two DIR-based dose mapping methods performed in the inverse or opposite direction, tumor contours were delineated on CBCT₂₁. The adaptive plan was retrospectively developed on CBCT₂₁ with a dose of 2 Gy per fraction prescribed to the residual tumor. The resultant iso-dose volumes are shown in color-wash in Fig 5(a). The blue contour represents the original tumor volume. Rigid registration was first performed from CBCT₂₁ to CBCT₁; the 2-Gy iso-dose volume (volume in red) of the adaptive plan is displayed on CBCT₁ (Fig 5b). It is noted that the 2 Gy iso-dose volume remains in the vicinity of the spine. The corresponding B-spline-based registration (Fig 5c) shows that the 2 Gy iso-dose volume (in red color wash) displaced toward the interface between the lung and the initial tumor volume.

DIR was also performed using the hybrid, FEM algorithm with the resultant DVF used to deform the residual tumor volume to CBCT₁. As shown in Fig 5d, the 2 Gy iso-dose volume (in red color wash) was deformed to the central region of the initial tumor volume, which is approximately midway between the two extreme positions mapped by the rigid and B-Spline-based registrations (Fig 5b and 5c).

The DVHs of the residual tumor volume for the adaptive plan and for the deformed doses by the B-Spline and FEM DVFs are shown in Fig 6a. These DVHs are consistent with the 2 Gy isodose distributions in Fig 5, where the large displacement in the dose reconstructed using the B-Spline-based registration is due to the unphysical stretching and compression of the image canvas. This deviation has been mitigated using the hybrid-FEM method (Fig 5d).

For comparison, a primary treatment plan was developed on CBCT₁. The forward registrations from CBCT₁ to CBCT₂₁ were performed using the rigid, B-Spline and hybrid, FEM-based algorithms. The corresponding DVHs for the doses deformed using these registrations are shown in Fig 6b. The difference in the doses deformed using the three methods in the forward direction is smaller than that in the reverse direction. In both directions, the hybrid, FEM-based model has improved the accuracy, and mitigated the errors associated with the B-Spline-based registrations.

DISCUSSION

To evaluate the response of a tumor, the total radiation energy deposited in the initial volume of the tumor must be correctly assessed throughout the fractionated radiation treatment. As tumor cells essentially respond to the total radiation energy released by all the particles in the tumor volume, the dose derived by dose accumulation should therefore represent the total radiation energy. If there is no mass change, the total dose, as the ratio of energy to mass, correctly represents the total energy delivered. If there is any loss of mass, dose mapping algorithms used to reconstruct the delivered dose on a reference image should follow the principle of energy conservation as described by Eq. (1).

The accuracy of the dose mapping operation is often assessed through the underlying DIR. However, verification of the DIR itself is difficult, especially in regions with low image contrast or with tumor regression (Guckenberger et al., 2011). The criterion of energy conservation proposed in this study is a convenient and rigorous metric for direct evaluation of the dose reconstructed by dose interpolation methods. This criterion can be complemented using DIR assessment metrics such as landmarks comparisons as shown in Fig 3, to assess the overall accuracy of a dose mapping function. It should be mentioned that the energy transfer method (ETM) of Siebers and Zhong (Siebers and Zhong, 2008) preserves radiation energy during the energy mapping process, so it automatically follows the principle of energy conservation. However, under circumstances of tumor mass regression, the spatial accuracy of the mass mapping using the ETM algorithm should be verified. This issue needs to be explored further in future studies.

In this work, we have demonstrated that an intensity-based registration algorithm produces inaccurate results, under conditions of tumor mass regression; the image was compressed and stretched in an unphysical way to align tumor boundaries (Figs 1 and 2). This is also evidenced by the high unbalanced elasticity energy shown in the tumor region (Fig 2). The FEM-based algorithm, in contrast, is not driven by the similarity of the two images, and therefore is not directly influenced by the regression of the tumor, as shown in Figs 2 and 3. Figure 6 showed that the dosimetric error associated with the B-Spline registration was mitigated using the hybrid, FEM-based model. In general, the hybrid FEM-based mechanical modeling does not depend on the similarity of the two images, and therefore, is preferred to be used for dose accumulation in the case of tumor regression, whilst conventional image intensity-based registration algorithms have advantages in other applications such as contour propagation. It is also possible that intensity-based DIR algorithms could be improved by incorporating volume-invariant constraints for dose accumulation in the case of tumor regression.

Note that when a visually perfect registration warps a regressed tumor volume back to its full size, the surface of the residual tumor is mapped to the surface of the original tumor. But the two surfaces are unlikely to be the same, so such a visually accurate registration is physically incorrect, resulting in the energy derived from the mapped dose different from what was actually delivered. To reduce the impact of tumor regression, Guckenberger (Guckenberger et al., 2009) employed a surface-based DIR algorithm to accumulate dose for regressing tumors, where the GTV surface points were excluded from control point selection

for registration. Based on the same consideration, an affine registration method was adopted by Zhang for adaptive RT studies (Zhang et al., 2014). These registration methods, however, do not have the same popularity as intensity-based DIR algorithms in the clinic, and may have limited accuracy in some anatomical regions. It is therefore important to develop a method to improve the accuracy of the intensity-based, B-Spline algorithm that is widely used in the clinic. In this study we implemented a hybrid FEM-based mechanical model to calculate the displacements of the interior points within a bounding box of the tumor. The surfaces of the box were located distant from the boundary of the tumor, and less influenced by tumor regression. The B-Spline-based displacements at these surface points therefore may serve as constraints for the FEM-based registration.

It should be mentioned that due to the loss of dead cells during the course of treatment, the surface of the tumor volume likely changes. The tumor surface cannot be used as a landmark to evaluate the B-Spline or FEM-based registrations. Instead, anatomical structures distant to the tumor volume are more reliable, and these structures may serve as landmarks for evaluation of these registrations. While different DIR and dose mapping algorithms could be used to accumulate radiation dose, the radiation energy derived from the accumulated dose in a registration-deformed tumor volume should equal to the radiation energy delivered to its original, un-deformed volume. Otherwise, quantitative relations such as cell-killing rates established between the tumor's response and the radiation energy deposited within the tumor would be inaccurate.

CONCLUSION

The principle of energy conservation is a valuable criterion for evaluation of dose mapping operations. Based on this criterion, it has been demonstrated that under circumstances of tumor regression, dose mapping using intensity-based B-Spline algorithm produces significant errors, which are mitigated using a hybrid FEM-based model. The hybrid FEM technique combined with the energy conservation evaluation criterion is likely to improve the quality of adaptive treatment planning for the benefit of lung cancer patients.

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Bibliography

- CHAO M, SCHREIBMANN E, LI T, WINK N, XING L. Automated contour mapping using sparse volume sampling for 4D radiation therapy. *Med Phys.* 2007; 34:4023–4029. [PubMed: 17985648]
- CHUN SY, FESSLER JA. A simple regularizer for B-spline nonrigid image registration that encourages local invertibility. *IEEE J Sel Top Signal Process.* 2009; 3:159–169. [PubMed: 21179392]
- GUCKENBERGER M, BAIER K, RICHTER A, WILBERT J, FLENTJE M. Evolution of surface-based deformable image registration for adaptive radiotherapy of non-small cell lung cancer (NSCLC). *Radiation Oncology.* 2009; 4:13. [PubMed: 19397824]
- GUCKENBERGER M, RICHTER A, WILBERT J, FLENTJE M, PARTRIDGE M. Adaptive radiotherapy for locally advanced non-small-cell lung cancer does not underdose the microscopic

- disease and has the potential to increase tumor control. *Int J Radiat Oncol Biol Phys.* 2011; 81:e275–82. [PubMed: 21497450]
- HARDCASTLE N, VAN ELMPT W, DE RUYSSCHER D, BZDUSEK K, TOME WA. Accuracy of deformable image registration for contour propagation in adaptive lung radiotherapy. *Radiat Oncol.* 2013; 8:243. [PubMed: 24139327]
- HEATH E, SEUNTJENS J. A direct voxel tracking method for four-dimensional Monte Carlo dose calculations in deforming anatomy. *Med Phys.* 2006; 33:434–445. [PubMed: 16532951]
- HUGO GD, WEISS E, BADAWI A, ORTON M. Localization accuracy of the clinical target volume during image-guided radiotherapy of lung cancer. *Int J Radiat Oncol Biol Phys.* 2011; 81:560–7. [PubMed: 21277096]
- JACOBSON TJ, MURPHY MJ. Optimized knot placement for B-splines in deformable image registration. *Med Phys.* 2011; 38:4579–82. [PubMed: 21928630]
- KLEIN S, STARING M, MURPHY K, VIERGEVER MA, PLUIM JP. elastix: a toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging.* 2010; 29:196–205. [PubMed: 19923044]
- KONG F, TEN HAKEN RK, SCHIPPER M, HAYMAN J, RAMNATH N, HASSAN KA, MATUSZAK M, RITTER T, BI N, WANG W, ORRINGER M, CEASE KB, LAWRENCE TS, KALEMKERIAN GP. A phase II trial of mid-treatment FDG-PET adaptive, individualized radiation therapy plus concurrent chemotherapy in patients with non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2013a; 31 abstr 7522.
- KONG FM, MACHTAY M, BRADLEY J, TEN HAKEN R, XIAO Y, MATUSZAK M, HIRSH V, PRYMA D. RTOG 1106/ACRIN 6697: Randomized Phase II Trial of Individualized Adaptive Radiotherapy Using During-Treatment FDG-PET/CT and Modern Technology in Locally Advanced Non-Small Cell Lung Cancer (NSCLC). 2013b
- LI HS, ZHONG H, KIM J, GLIDE-HURST C, GULAM M, NURUSHEV TS, CHETTY IJ. Direct dose mapping versus energy/mass transfer mapping for 4D dose accumulation: fundamental differences and dosimetric consequences. *Phys Med Biol.* 2014; 59:173–188. [PubMed: 24334328]
- LIM G, BEZJAK A, HIGGINS J, MOSELEY D, HOPE AJ, SUN A, CHO JB, BRADE AM, MA C, BISSONNETTE JP. Tumor regression and positional changes in non-small cell lung cancer during radical radiotherapy. *J Thorac Oncol.* 2011; 6:531–6. [PubMed: 21258244]
- LIU F, HU Y, ZHANG Q, KINCAID R, GOODMAN KA, MAGERAS GS. Evaluation of deformable image registration and a motion model in CT images with limited features. *Phys Med Biol.* 2012; 57:2539–2554. [PubMed: 22491010]
- MOHAN R, ZHANG X, WANG H, KANG Y, WANG X, LIU H, ANG KK, KUBAN D, DONG L. Use of deformed intensity distributions for on-line modification of image-guided IMRT to account for interfractional anatomic changes. *Int J Radiat Oncol Biol Phys.* 2005; 61:1258–66. [PubMed: 15752908]
- ROSU M, CHETTY IJ, BALTER JM, KESSLER ML, MCSHAN DL, TEN HAKEN RK. Dose reconstruction in deforming lung anatomy: dose grid size effects and clinical implications. *Med Phys.* 2005; 32:2487–2495. [PubMed: 16193778]
- RUECKERT D, ALJABAR P, HECKEMANN RA, HAJNAL JV, HAMMERS A. Diffeomorphic registration using B-splines. *Med Image Comput Comput Assist Interv.* 2006; 9:702–709. [PubMed: 17354834]
- RUECKERT D, SONODA LI, HAYES C, HILL DL, LEACH MO, HAWKES DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging.* 1999; 18:712–721. [PubMed: 10534053]
- SCHULTHEISS TE, TOME WA, ORTON CG. Point/counterpoint: it is not appropriate to “deform” dose along with deformable image registration in adaptive radiotherapy. *Med Phys.* 2012; 39:6531–3. [PubMed: 23127047]
- SIEBERS JV, ZHONG H. An energy transfer method for 4D Monte Carlo dose calculation. *Med Phys.* 2008; 35:4096–4105. [PubMed: 18841862]
- SONKE JJ, BELDERBOS J. Adaptive radiotherapy for lung cancer. *Semin Radiat Oncol.* 2010; 20:94–106. [PubMed: 20219547]

- TAYLOR ML, YEO UJ, KRON T, SUPPLE J, SIVA S, PHAM D, FRANICH RD. Comment on “it is not appropriate to ‘deform’ dose along with deformable image registration in adaptive radiotherapy” [Med Phys, 39: 6531–6533 (2012)]. Med Phys. 2013; 40:017101. [PubMed: 23298128]
- THIRION JP. Image matching as a diffusion process: an analogy with Maxwell’s demons. Medical Image Analysis. 1998; 2:243–260. [PubMed: 9873902]
- VERCAUTEREN T, PENNEC X, PERCHANT A, AYACHE N. Diffeomorphic demons: efficient non-parametric image registration. Neuroimage. 2009; 45:S61–72. [PubMed: 19041946]
- WANG H, DONG L, O’DANIEL J, MOHAN R, GARDEN AS, ANG KK, KUBAN DA, BONNEN M, CHANG JY, CHEUNG R. Validation of an accelerated ‘demons’ algorithm for deformable image registration in radiation therapy. Physics in Medicine and Biology. 2005; 50:2887–2905. [PubMed: 15930609]
- WEISS E, FATYGA M, WU Y, DOGAN N, BALIK S, SLEEMAN WT, HUGO G. Dose escalation for locally advanced lung cancer using adaptive radiation therapy with simultaneous integrated volume-adapted boost. Int J Radiat Oncol Biol Phys. 2013; 86:414–9. [PubMed: 23523321]
- YANG D, LI H, LOW DA, DEASY JO, EL, NI. A fast inverse consistent deformable image registration method based on symmetric optical flow computation. Phys Med Biol. 2008; 53:6143–6165. [PubMed: 18854610]
- YEO BT, SABUNCU MR, VERCAUTEREN T, AYACHE N, FISCHL B, GOLAND P. Spherical demons: fast diffeomorphic landmark-free surface registration. IEEE Trans Med Imaging. 2010; 29:650–68. [PubMed: 19709963]
- YEO UJ, SUPPLE JR, TAYLOR ML, SMITH R, KRON T, FRANICH RD. Performance of 12 DIR algorithms in low-contrast regions for mass and density conserving deformation. Med Phys. 2013; 40:101701. [PubMed: 24089891]
- ZHANG P, YORKE E, HU YC, MAGERAS G, RIMNER A, DEASY JO. Predictive treatment management: incorporating a predictive tumor response model into robust prospective treatment planning for non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2014; 88:446–52. [PubMed: 24315562]
- ZHONG H, KIM J, CHETTY IJ. Analysis of deformable image registration accuracy using computational modeling. Med Phys. 2010; 37:970–979. [PubMed: 20384233]
- ZHONG H, KIM J, LI H, NURUSHEV T, MOVSAS B, CHETTY IJ. A finite element method to correct deformable image registration errors in low-contrast regions. Phys Med Biol. 2012; 57:3499–3515. [PubMed: 22581269]
- ZHONG H, PETERS T, SIEBERS JV. FEM-based evaluation of deformable image registration for radiation therapy. Phys Med Biol. 2007; 52:4721–4738. [PubMed: 17671331]
- ZIENKIEWICZ, OC., TAYLOR, RL. Finite Element Method (5th Edition) Volume 1 - The Basis. Elsevier; 2000.

Figure 1.
(a) and (b) the initial and weekly CBCT images for patient 1; (c) the initial image deformed by the B-Spline based registration and (d) the deformed grid.

Figure 2.

(a) and (b) the deformed source images and their corresponding grids by the B-Spline and FEM registrations; (c) and (d) the norm of displacements along the cross lines at the center of the original tumor, parallel to the x- and y axes as shown in (a); (e) and (f) the unbalanced energy of the B-Spline and FEM-based registrations, respectively.

Figure 3. (a) and (b) the source and reference CBCT images; (c) and (d) the deformed source image by the B-spline and FEM-based DVFs, respectively.

Figure 4.

(a) The displacement difference between the B-Spline and FEM-based registrations compared with their relative loss of RE; (b) the displacement difference compared with the unbalanced elasticity energy of the B-Spline registration; (c) the displacement error of the FEM registrations compared with their RE loss.

Figure 5.

(a) An adaptive plan was developed on $CBCT_{21}$ with the 2 Gy dose prescribed to the residual tumor volume (blue contour); The iso-dose volumes were reconstructed on $CBCT_1$ using the rigid, B-Spline and FEM-based registrations in (b), (c) and (d), respectively, and displayed in the red color-wash volumes. The contours of the residual tumor volume in (b–c) were displayed after the rigid registration.

Figure 6.

(a) DVHs of CTV₂₁ for the adaptive plan and corresponding deformed plans using the B-Spline and FEM-based registrations from CBCT₂₁ to CBCT₁; (b) DVHs of CTV_p for the primary plan and its warped plans by the forward B-Spline and FEM-based registrations from CBCT₁ to CBCT₂₁.

The FEM error was measured through landmark comparison; The B-Spline error was defined as $\|BS-FEM\|$ that represents the mean differences between the B-Spline and FEM displacements; UEE-BS and UEE-FEM represent the unbalanced elasticity energy of the B-Spline and FEM registrations, averaged within the bounding box.

Table 1

	Pt1	Pt2	Pt3	Pt4	Pt5	Pt6	average
FEM error (mm)	3.0±2.1	2.4±1.7	2.6±2.3	2.6±1.9	2.3±2.1	2.2±1.5	2.5±1.9
$\ BS-FEM\ $ (mm)	5.2±5.9	4.0±3.2	5.5±5.9	2.0±1.3	2.6±1.8	6.0±7.1	4.2±4.7
UEE-BS (mJ)	0.44	0.23	0.42	0.15	0.14	0.38	0.29±0.14
UEE-FEM (mJ)	0.08	0.06	0.06	0.06	0.05	0.05	0.06±0.01

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Table 2

The radiation energies (RE) computed in the GTV and corresponding deformed volumes using the B-Spline and FEM-based registrations.

Joules	P1	P2	P3	P4	P5	P6	Mean
$RE(GTV)$	0.98	0.74	0.51	0.30	0.49	0.94	0.66
$RE(\phi_{BS}(GTV))$	0.64	0.59	0.29	0.28	0.41	0.83	0.51
$RE(\phi_{FEM}(GTV))$	0.94	0.70	0.49	0.28	0.44	0.92	0.64
L(BS)	0.35	0.20	0.43	0.07	0.16	0.12	0.22
L(FEM)	0.04	0.05	0.03	0.05	0.09	0.02	0.04
RL(BS)	0.31	0.15	0.40	0.01	0.06	0.10	0.17