Published in final edited form as:

Phys Med Biol. ; 63(6): 065017. doi:10.1088/1361-6560/aab235.

Utilization of a hybrid finite-element based registration method to quantify heterogeneous tumor response for adaptive treatment for lung cancer patients

Hoda Sharifi^{1,2}, Hong Zhang³, Hassan Bagher-Ebadian¹, Wei Lu⁴, Munther I Ajlouni¹, Jian-Yue Jin³, Feng-Ming Kong³, Indrin Chetty¹, and Hualiang Zhong¹

¹Department of Radiation Oncology, Henry Ford Health System, Detroit MI, U.S.A

²Department of Physics, Oakland University, Rochester MI, U.S.A

³Department of Radiation Oncology, Indiana University, Indianapolis, IN, U.S.A

⁴Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, U.S.A

Abstract

Tumor response to radiation treatment (RT) can be evaluated from changes in metabolic activity between two positron emission tomography (PET) images. Activity changes at individual voxels in pre-treatment PET images (PET1), however, cannot be derived until their associated PET-CT (CT1) images are appropriately registered to during-treatment PET-CT (CT2) images. This study aimed to investigate the feasibility of using deformable image registration (DIR) techniques to quantify radiation-induced metabolic changes on PET images. Five patients with non-small-cell lung cancer (NSCLC) treated with adaptive radiotherapy were considered. PET-CTs were acquired 2 weeks before RT and 18 fractions after the start of RT. DIR was performed from CT1 to CT2 using B-Spline and diffeomorphic Demons algorithms. The resultant displacements in the tumor region were then corrected using a hybrid finite element method (FEM). Bitmap masks generated from gross tumor volumes (GTVs) in PET1 were deformed using the 4 different displacement vector fields (DVF). The conservation of total lesion glycolysis (TLG) in GTVs was used as a criterion to evaluate the quality of these registrations. The deformed masks were united to form a large mask which was then partitioned into multiple layers from center to border. The averages of SUV changes over all the layers were 1.0 ± 1.3 , 1.0 ± 1.2 , 0.8 ± 1.3 , 1.1 ± 1.5 for the B-Spline, B-Spline+FEM, Demons and Demons+FEM algorithms, respectively. TLG changes before and after mapping using B-Spline, Demons, hybrid-B-Spline, and hybrid-Demons registrations were 20.2%, 28.3%, 8.7%, and 2.2% on average, respectively. Compared to image intensity-based DIR algorithms, the hybrid FEM modeling technique is better in preserving TLG and could be useful for evaluation of tumor response for patients with regressing tumors.

Keywords

Treatment response; PET imaging; tumor regression; deformable image registration; adaptive treatment planning

Introduction

Patients with non-small cell lung cancer (NSCLC) often show substantial changes in tumor volume during the course of fractionated radiotherapy (RT). Consequently, pre-RT treatment plans may no longer be conformal and do not reflect the actual dose delivered to these patients. Assessing treatment-induced tumor changes during the course of RT makes it possible to re-plan the remaining treatment and consequently improve clinical outcomes for individual patients (van Elmpt *et al.*, 2012). With the aid of FDG-PET imaging, treatment regimens can be adapted in different tumor regions based on the measured metabolic activities and therapeutic response (Hicks, 2009). When metabolic activities in peripheral regions decrease or disappear after a number of treatment fractions, high dose can be delivered to the remaining tumor. This facilitates an iso-toxic dose escalation to the residual tumor for individual patients. To track the metabolic changes in individual tumor regions, PET images acquired during RT (PET2) have to be compared to pre-RT PET images (PET1). Due to anatomical and physiological changes as well as setup uncertainties, rigid image registrations are not sufficient to make such a comparisons accurate.

Deformable image registration (DIR) may assume an important role in assessment of the PET-based tumor response. Since PET-CT images are usually acquired sequentially with the patient at the same position, the coordinates of the two images are considered to be automatically aligned. This allows the deformation map between two PET images to be generated from a DIR of the two associated CT images. However, there are many challenges to perform accurate DIRs, especially in the case of tumor shrinkage (Sonke and Belderbos, 2010). While intensity-based DIR methods may help find a transformation that maximizes the similarity measure between the mapped CT1 and CT2 (Rueckert *et al.*, 2006), such DIRs methods usually do not preserve tumor volume and therefore a large tumor volume in the CT1 could be reduced after mapping. This may cause errors when the resultant deformation map is used to compare SUVs between the two associated PET images. As tumor volume regresses during the course of radiation treatment in patients with NSCLC (Kupelian *et al.*, 2005; Lim *et al.*, 2011; Seibert *et al.*, 2007; Zhang *et al.*, 2014; Arai *et al.*, 1994; Wilson *et al.*, 2012), conventional, image intensity-based DIR algorithms cannot be directly applied to assessment of this type of patients.

Understanding the manner of tumor response to radiation may help adapt treatment plans. For example, in the case of tumor border regressing while the surrounding tissue stays unchanged, a B-Spline-based DIR algorithm stretches the lung in the moving image to match the border of the regressed tumor (Zhong *et al.*, 2015). This will cause errors in matching voxels near the border between the two registered images, and reduce the quality of dose accumulation in the gross tumor volume (GTV)(Zhong *et al.*, 2017; Zhong and Chetty, 2017). When this algorithm is used to compare two PET images, the response derived from the comparison would be mis-interpreted. Tumor regression compounded by patient repositioning and anatomical deformation makes it difficult to quantify region-specific SUV changes in PET images.

The purpose of this study was threefold: (a) to demonstrate the limitation of conventional image registration methods used for measuring treatment response of regressing tumors, (b)

to present a method to improve the performance of these registrations, and (c) to investigate the pattern of tumor regression during the course of RT for patients with lung cancer. A hybrid finite element method (FEM) was used to track radiation-induced SUV changes in PET images. With this method, the metabolic changes between the pre and during radiation treatment were estimated for a group of patients who were treated with adaptive RT (Kong *et al.*, 2013). The performance of the hybrid FEM registration in evaluation of region-specific tumor response was compared with that of intensity-based B-Spline and Demons registration algorithms, based on total lesion glycolysis (TLG). Tumor response was quantified as the difference between the SUV in the mapped pre-RT PET images and the SUV in the post or during-RT PET images. Patterns of the tumor response were investigated through the analysis of SUV means and profiles calculated in different layers of the GTVs, which were mapped from pre-RT PET images.

Materials and Methods

Patient Characteristics

From the RTOG 1106 Randomized Phase II Trial (RTOG1106/ACRIN6697), five patients with stage IIIA or IIIB, non-operable non-small-cell lung cancer (NSCLC), treated with 3D conformal RT, were investigated in this study. Two FDG-PET/CT image sets were acquired for each patient, two weeks before and 18 fractions (2.2 Gy/Fr) after the start of RT. The position of the lung tumors for all patients was in the upper lobe except one patient whose tumor was in the lower lobe. The pre-RT and during-RT tumor volumes were delineated on the correspondent PET-CT images with results shown in Table 1 for all the patients. The gross tumor volume delineated on the pre-treatment PET-CT image was denoted by CT-GTV.

Preprocessing data

Due to the difference in voxel spacing, the pre-RT CT (CT1) images were first resampled using bilinear interpolation to have the same voxel size as in the during-RT CT (CT2) images. The resultant CT1 were rigidly registered to the CT2 based on bony structures and then cropped to have the same image size. The PET images were also resampled and cropped to match the voxel spacing and dimension of the CT images. The CT1 images (moving image) for all patients were then registered to the CT2 images (fixed image) using the four deformation algorithms (B-Spline, Demons, B-Spline+FEM, Demons+FEM). The resultant displacement vector fields (DVs) of these registrations pointed from CT2 to CT1. These DVs were used to reconstruct the mapped PET1 (mPET1) images from the PET1 images. Specifically, for each image index i , the intensity value of mPET1 at i was assigned from the intensity value of PET1 at voxel j , where the displacement vector at voxel i in mCT1 pointed to voxel j in CT1. The resultant mPET1 images ($PET1_{BSpline}$, $PET1_{BSpline+FEM}$, $PET1_{Demons}$, $PET1_{Demons+FEM}$) were compared with the PET2 images to calculate SUV changes. For each patient, the GTV delineated on the PET image (PET-GTV), was exported as a bitmap mask and deformed using the DVs of the four algorithms. The four mapped GTV masks were combined to form a bitmap mask union ($mGTV_{union}$) which was partitioned into multiple layers. Activity changes were evaluated by subtracting

SUVs in PET2 images from those in the mPET1 with the difference averaged on each of these layers. Figure 1 shows the steps to calculate SUV changes using the four algorithms.

Deformable image registration methods

In this study, rigid registration was performed based on landmarks selected from lung structures, and deformable registration was performed using image intensity-based B-Spline and diffeomorphic Demons algorithms implemented in the open source software package Elastix (v4.8, Utrecht, Netherlands) and Insight Toolkit (ITK) (Shamonin *et al.*, 2014; Klein *et al.*, 2010; Avants *et al.*, 2014), respectively. The B-Spline registration algorithm maximized the mutual information between the intensities of the fixed and moving images, using 4 resolution scales with 10000, 10000, 5000, and 5000 iterations for each resolution, respectively. The Demons algorithm was implemented with a multi-resolution mode with gradient tolerance configured to (0.005 0.005 0.005 0.0001) (Zhong *et al.*, 2010). The low tolerance was chosen to ensure that the maximum number of iteration loops were reached in the registration. The standard deviation of the Gaussian smoothing function was set to 1.0.

A hybrid registration method was developed by integrating an in-house developed finite element method with the image intensity-based deformable registration techniques to improve the accuracy of the registrations in region of regressing tumor. In order to implement the hybrid method, a bounding box, extending 2 ~ 3 cm on each side of the tumor in the fixed CT image, was partitioned to generate a tetrahedral mesh using ICEM (Ansys Inc., Canonsburg PA). The B-Spline or Demons computed displacements on the surface of the bounding box were used as the constraints of the FEM model to calculate FEM displacements for voxels within the box. For voxels outside the bounding box, the displacements were equivalent to the results of the B-Spline and Demons registrations. The material parameters were assigned with Young's moduli of 1 MPa for bone, 1 kPa for lung, and 10 kPa for soft tissue. The Poisson ratio was 0.38 for lung and 0.49 for bone and normal tissue. Since the size of the mesh required to cover the bounding box was small, the FEM computation was completed within 30 seconds.

In this study, the geometrical correspondence was established based on the movement of those voxels and structures that are located on the surface of the FEM-based bounding box (Figure 2). Within the box, the deformation of the tumor and structures using the hybrid methods was mechanically consistent to the movement of the surface voxels. In general, radiation treatment may reduce image intensity of tumor voxels, and meanwhile cause tumor shrinkage. As illustrated in Figure 2, tumor shrinkage results in voxels and structures on the surface of the bounding box to follow the regression of the tumor boundary. The B-Spline or Demons-derived displacements at these surface voxels were taken as boundary conditions, thus the hybrid FEM allows the tumor to shrink slightly in order for the deformation of the tumor to be mechanically consistent with other structures within the bounding box. Note that while the mapped tumor volume mPET1 (mCT1) is slightly smaller than the original tumor volume in PET1 (CT1), it is larger than that in PET2 (CT2) (Figure 2). The activity (mass) in the mapped tumor should be equal to the activity in the original tumor because they both represent the activity (mass) before treatment.

Evaluation of Deformable Image Registration

Note that the purpose of this study was to calculate activity changes between two PET images. Due to tissue deformation, SUVs in PET1 and PET2 cannot be subtracted directly to get the changes until voxels in PET1 are moved to right positions by a registration map. The voxel moving or registration mapping process should not increase or decrease the amount of tumor activities in PET1 (or tumor mass in CT1); otherwise the subtracted SUVs do not represent the SUV changes at the registered image voxels. Based on this consideration, the quality of the DIR-based PET mappings was evaluated using two methods: landmarks comparison and total lesion glycolysis (TLG) conservation under the DIR-based deformations. Landmarks were selected within the bounding box but away from the tumor, since outside the bounding box the FEM-based displacements are the same as in the conventional registrations. Around 15 landmarks were chosen for each patient and most of the landmarks were selected from the normal lung structures and vessels. TLG is defined as the product of the PET-based metabolic tumor volume and the relative SUV_{mean} within that volume (Chen *et al.*, 2012). The conservation of TLG was used as a criterion to evaluate the integrity of the mapping from PET1 to mPET1. This mapping is required for comparing the PET1 and PET2 images.

In order to calculate TLGs for each of the PET images, the SUV_{mean} on PET-GTV was calculated by overlaying the mapped PET1 images with the derived bitmap masks. By multiplying the SUV_{mean} with the volume of the mapped bitmap masks, the TLGs (TLG_{Bspline}, TLG_{Bspline+FEM}, TLG_{Demons}, TLG_{Demons+FEM}) were calculated for the mapped PET1. Similarly, the TLG was also obtained for the original PET1, and compared to the mapped TLGs for the consistency evaluation.

Response Calculation

GTVs were delineated on both CT and PET images. For all patients, PET-GTV was delineated using thresholds of 15–42% relative to the maximum standardized uptake value (SUV_{max}). The threshold for each patient was selected based on the size of the tumor: 15% for tumors larger than 5cm, 24% for tumors between 3–5 cm, and 42% for tumors less than 3 cm (Biehl *et al.*, 2006; Feng *et al.*, 2009). The tumor size was estimated by the mean of the maximum tumor diameter in any direction on the CT image. Since the absolute number of metabolic activities could be influenced by multiple factors (e.g. blood glucose level, tracer injection and scanning time), SUVs in PET1 and PET2 were normalized with respect to their means in the liver. Tumor response was calculated as the changes in the normalized SUV (nSUV) from the mapped PET1 to the PET2 image:

$$\Delta = \sum_{i \in V} \left(nSUV_{\varphi(PET1(i))} - nSUV_{PET2(i)} \right),$$

where i is a voxel index of the respective PET images, V is mask volume, and φ represents the map of a registration from CT1 to CT2 using the B-Spline, Demons or hybrid-FEM methods. The differences between the mapped PET1 and PET2 images represent the tumor response assessed by these DIR algorithms.

Generation of different layer sets for tumor response assessment

Partitioning a tumor volume into different layers may help to get a better understanding of tumor regression patterns, and may be useful for designing treatment margins for adaptive planning. In this study, the PET1-GTV bitmap mask was mapped by the four registration algorithms for each patient, and the mapped masks were divided into different layers using the two following methods. The first method was to combine the four mapped-GTVs to form a union of the bitmap masks, $mGTV_{union}$. The $mGTV_{union}$ was partitioned into different layers by creating rings of one voxel thickness from the 3D surface to the center until no interior voxel was left. This generated a set of layers, starting from the center of the $mGTV_{union}$ to the peripheral region (Figure 5f). The performance of the four DIR algorithms was evaluated on these layers. We divided a union of the 4 mapped GTVs into different layers so that the different DIR algorithms can be compared on the same layers.

In the second method, the GTV mask was first mapped using each of the four DIR algorithms and then partitioned into a set of layers, resulting in different sets of layers for each of the four DIR algorithms (Figure 6f). nSUV changes between the mapped PET1 and PET2 images were calculated and averaged on each of these layer sets. The calculated nSUV changes were used to analyze the trend of tumor regression for each of these algorithms.

Results

Landmark-based evaluation of DIR

From the pre-RT to the during-RT, tumor volumes measured from CT images showed a reduction ranging from 9.2% to 50.1%, with an average of 30.1% for four out of the five patients, while patient 3 showed an increase of 9.7% in the volume of tumor. Patient 4 showed the largest regression (50%) among all the five patients. Results of the landmark-based evaluations for different registrations are shown in Table 2. The average displacement error over the five patients was 5.2 ± 0.6 mm for rigid registration, 3.5 ± 0.7 mm for B-Spline, 2.1 ± 0.4 mm for B-Spline+FEM, 1.6 ± 1.0 for Demons, and 2.1 ± 1.0 mm for Demons+FEM registrations. The large error in the rigid registrations and the significant changes in tumor volume make it necessary to perform a deformable image registration for measuring tumor response.

Figure 3 shows the results of the B-Spline and Demons registrations performed from the CT1 image to the CT2 image. When mapping the CT1 to the CT2, both the algorithms pressed the tumor surface in the moving image to match the fixed image, while the Demons algorithm resulted in more reduction in tumor volume than the B-Spline algorithm. When the resultant DVFs are used to map the PET1 image, the total metabolic activities in the PET1 would be different from those in the mapped PET1. This compromises the integrity of the SUV comparison between the mapped PET1 and the PET2. After applying the FEM algorithm, both the DIR methods better preserve the original tumor volume, as shown in Figure 3e and 3f.

The DVFs generated by the four DIR algorithms were used to warp PET1 images. The PET-based, original and mapped tumor volumes were calculated for the five patients. Tumor

volumes were calculated on both the original and mapped PET images. Their average differences were $2.8 \pm 1.5 \text{ cm}^3$, $1.8 \pm 1.4 \text{ cm}^3$, $5.1 \pm 3.4 \text{ cm}^3$, and $1.8 \pm 1.5 \text{ cm}^3$ for the B-Spline, B-Spline+FEM, Demons and Demons+FEM, respectively. Details for individual patients are shown in Table 3.

Consistency of TLG under deformation

TLG changes obtained from the B-Spline, Demons and hybrid FEM methods are shown in Table 4. The hybrid methods showed less changes in TLG than the B-Spline and Demons algorithms. Patient 1 had a small decrease in the size of the tumor between PET1 and PET2, so the hybrid method did not show significant improvement over the two image intensity-based DIR algorithms. Patient 3 had a tumor attached to chest wall with a small increase in tumor volume. The low gradient between the tumor and chest wall caused the Demons registration to perform poorly. This registration was corrected by the hybrid FEM algorithm. In Table 4, original PET1 (orgPET1) served as the reference was compared to the mapped PET1 (mPET1) using either a B-Spline, B-Spline+FEM, Demons, or Demons+FEM method. The closer the TLG of mPET1 to that of orgPET1, the more accurate the registration with respect to TLG consistency.

Heterogeneity of tumor response

The four DIR algorithms had large nSUV differences between their mapped PET images. Figure 4 shows the PET1, PET2, and mapped PET1 images (PET1_{B-Spline}, PET1_{B-Spline+FEM}, PET1_{Demons}, PET1_{Demons+FEM}) for patient 4. While the SUV profiles of the four algorithms along the green line have a similar variation pattern (Figure 4g), the magnitude of the profiles in PET1_{B-Spline+FEM} and PET1_{Demons+FEM} (yellow and orange lines) are higher than those in the PET1 images mapped by the B-Spline and Demons methods. The profiles of changes in Figure 4h showed the heterogeneous response of tumor to the treatment. It can be seen that the intensity-based Demons algorithm cannot identify the nSUV changes in the tumor region very well.

Comparison of tumor response measured on the union of mapped GTV masks

nSUV_{mean} changes averaged in mGTV_{union} over the five patients were 1.0 ± 1.3 , 1.0 ± 1.2 , 0.8 ± 1.3 , 1.1 ± 1.5 for the B-Spline, B-Spline+FEM, Demons and Demons+FEM algorithms, respectively.

The nSUV_{mean} changes in different layers for the four methods are graphed in Figure 5. The x-axis represents the number of layers generated from mGTV_{union}, starting from the center of the mGTV_{union}. Note that this center is not necessarily the center of the GTVs mapped by each of individual DIR algorithms. Among the 5 patients, patient 1 (Figure 5a) had the smallest tumor volume with little regression, and therefore not much difference was observed between the different methods. Patient 3 (Figure 5c) had an increase in nSUV_{mean} during RT, and consequently the average change in nSUV_{mean} was negative. Due to the impact of tumor regression, the B-Spline and Demons showed lower nSUV_{mean} changes in the outermost layers than the hybrid algorithms. The nSUV_{mean} changes measured by the two hybrid registrations were generally consistent to each other in each layer for all the

patients, showing their potential to be used to measure $nSUV_{mean}$ changes for lung cancer patients.

Comparison of tumor response measured on individual mapped GTV masks

$nSUV_{mean}$ changes were evaluated on the mapped GTV by each of the registration algorithms. Each mapped GTV was partitioned into different layers with $nSUV_{mean}$ changes calculated on each layer for individual patients (Figure 6). The x-axis represents the number of the layers generated by each of these DIR algorithms, where the same layer number may indicate different geometric regions in each of these mapped GTVs (Figure 6f). For each of these algorithms, the patients with tumor regression (patient 2, 4, and 5) showed a similar pattern in the $nSUV_{mean}$ changes, and the largest changes appeared in the middle layers located between the center and the periphery of the tumor. Among the four algorithms, Demons has mapped the image to closely match the target image, resulting in the smallest differences between the mapped $nSUV$ s and the target $nSUV$ s. This may help explain why the Demons method has the largest deviations between PET1 and mPET1 in Table 4.

Discussion

Patients with locally advanced stage NSCLC often have large tumor volumes. Tumor response within these volumes is not uniform during the course of fractionated radiotherapy. As a result, part of the tumor disappears after a number of treatment fractions and the original treatment plan is no longer conformal to the remaining tumor. Accurate measurements of region-specific tumor response may be useful in future studies for re-designing treatment margins and optimizing target dose for the rest of the treatment course. As an important functional imaging modality, PET images acquired on two different days can be compared to quantify tumor response to radiation treatment after an appropriate registration of the two images. Since there are no obvious anatomical structures in PET images, the registration is usually performed between the CT images, acquired at the same time as the corresponding PET images. It should be mentioned that the intensity-based registration of two PET (CT) images should not cause bias in the evaluation of tumor response. Suppose PET1 was acquired at time t_1 and PET2 acquired at time t_2 . Due to tumor regression and tissue deformation, PET1 cannot be compared directly with PET2 to get tumor response, so PET1 is reconstructed to form a mapped image, mPET1, which still represents the metabolic activities at time t_1 . Regardless of the pattern of tumor regression (shrinkage or shedding), the reconstructed activities (mass) in mPET1 (mCT1) must equal to the activities (mass) in PET1 (CT1) so that the activities (mass) between PET1 (CT1) and PET2 (CT2) can be fairly compared.

For a given deformation map, the activities (mass) in a target voxel can be reconstructed from its source voxels (Zhong and Siebers, 2009), based on the principle of activity (mass) conservation. However, the impact of registration errors on the reconstructed activity map is still unknown. In this study, we use the conventional interpolation method to reconstruct the mapped activities, and use the activity conservation principle to evaluate the mapped results. The generation of the geometrical deformation map, however, will in general be influenced by the pattern of tumor regression. Due to the complexity of the radiobiological process, the

underlying mechanism of tumor regression cannot be determined or quantitatively modeled. As shown in Table 4, the hybrid FEM algorithms showed an improvement over the B-Spline and Demons algorithms in the TLG conservation, while the geometrical accuracy of the hybrid method still needs to be verified in future studies.

In this study the image intensity-based B-Spline and Demons methods were initially used for comparison of two PET images. Unfortunately, due to changes in tumor volume during the course of treatment, the B-Spline and Demons methods may map a large tumor volume to its regressed one, resulting in the metabolic activity, represented as TLG, not being conserved under these registrations. Consequently, if we compare the mPET1 with PET2, in order to assess the changes in SUV, the metabolic activity in mPET1 will not represent the metabolic activity in initial PET1, and this will induce errors in the tumor response quantified as the changes in SUV. The FEM-based method however, is independent of image intensity and less influenced by the change in the volume of the tumor (Zhong *et al.*, 2015) and therefore allows for a better evaluation of regional SUV changes. Table 3 showed that while the Demons-based method reduced the TLG more than the B-Spline-based method, the hybrid Demons method is superior to the hybrid B-Spline method in the TLG conservation. This is likely due to the fact that compared to the B-Spline registrations, the displacements of the Demons registrations on the bounding box of the FEM model are less influenced by the tumor regression. With the hybrid registration methods, the region-specific $nSUV_{mean}$ changes were derived, showing that the tumor response varies from the center to the outer border of the tumor, and that halfway through the treatment $nSUV_{mean}$ decreased by about 40~50%. This is consistent to the significant reduction of tumor metabolic activity reported in (Massacesi *et al.*, (2012)). Since regional textural variations in PET images are related to treatment outcome (Lovinfosse *et al.*, 2016), accurate assessment of region-specific tumor response may help optimize adaptive plans and consequently improve the efficacy of radiation treatment (Trani *et al.*, 2015).

To the best of our knowledge, this is the first study that investigates the distribution and heterogeneity of tumor response using different image registration techniques. The layer-by-layer evaluation can help evaluate the differences in tumor response between the peripheral and central regions of the tumor, and provide regional information on $nSUV$ changes for precise modeling of tumor regression (Zhong and Chetty, 2014). Compared to voxel-wise comparisons, $nSUV_{mean}$ changes averaged on individual layers could be less sensitive to motion artifacts and DIR errors. It should be mentioned that due to the limited number of patients available for this study, the observed pattern of tumor regression may not be indicative for other patients. Also the radiation-induced inflammation and dosimetry impact on tumor response were not investigated. These issues as well as motion-induced artefacts should be further investigated in future studies. Nevertheless, as a proof of concept, this study demonstrated the potential of using PET images to measure region-specific tumor response, and could be useful for adaptive treatment planning for patients with NSCLC.

Conclusion

Region-specific tumor response measured using different DIR algorithms were compared for a group of lung cancer patients treated with adaptive radiotherapy. Compared to image

intensity-based DIR algorithms, the hybrid FEM modeling technique is less impacted by tumor regression, and could be useful for comparing PET images for patients with regressing tumors.

References

- Arai T, Kuroishi T, Saito Y, Kurita Y, Naruke T and Kaneko M 1994 Tumor doubling time and prognosis in lung cancer patients: evaluation from chest films and clinical follow-up study. Japanese Lung Cancer Screening Research Group Jpn.J.Clin.Oncol. 24 199–204 [PubMed: 8072198]
- Avants BB, Tustison NJ, Stauffer M, Song G, Wu B and Gee JC 2014 The Insight ToolKit image registration framework Frontiers in Neuroinformatics 8
- Biehl KJ, Kong F, Dehdashti F, Jin J, Mutic S, El Naqa I, Siegel B and Bradley JD 2006 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate? The Journal of Nuclear Medicine 47 1808–12 [PubMed: 17079814]
- Chen HH, Chiu Nt, Su WC, and Lee BF 2012 Prognostic value of whole-body total lesion glycolysis at pretreatment FDG PET/CT in non-small cell lung cancer Radiology 264
- Feng M, Kong F-M, Gross M, Fernando S, Hayman JA and Ten Haken RK 2009 Using Fluorodeoxyglucose Positron Emission Tomography to Assess Tumor Volume During Radiotherapy for Non-Small-Cell Lung Cancer and Its Potential Impact on Adaptive Dose Escalation and Normal Tissue Sparing International Journal of Radiation Oncology*Biophysics 73 1228–34
- Hicks RJ 2009 Role of 18F-FDG PET in assessment of response in non-small cell lung cancer The Journal of Nuclear Medicine 50 31S–42S [PubMed: 19380411]
- Klein S, Staring M, Murphy K, Viergever MA and Pluim JPW 2010 elastix: A Toolbox for Intensity-Based Medical Image Registration IEEE Transactions on Medical Imaging 29 196–205 [PubMed: 19923044]
- Kong FM, Machtay M, Bradley J, Ten Haken R, Xiao Y, Matuszak M, Hirsh V and Pryma D 2013 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).
- Kupelian PA, Ramsey C, Meeks SL, Willoughby TR, Forbes A, Wagner TH and Langen KM 2005 Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumor regression during treatment International journal of radiation oncology, biology, physics 63 1024–8
- Lim G, Bezjak A, Higgins J, Moseley D, Hope AJ, Sun A, Cho JB, Brade AM, Ma C and Bissonnette JP 2011 Tumor regression and positional changes in non-small cell lung cancer during radical radiotherapy Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 6 531–6
- Lovinfosse P, Janvary ZL, Coucke P, Jodogne S, Bernard C, Hatt M, Visvikis D, Jansen N, Duysinx B and Hustinx R 2016 FDG PET/CT texture analysis for predicting the outcome of lung cancer treated by stereotactic body radiation therapy European Journal of Nuclear Medicine and Molecular Imaging 43 1453–60 [PubMed: 26830299]
- Massacesi M, Calcagni M, Spitilli M, Cocciolillo F, Pelligro F, Bonomo L, Valentini V and Giordano A (2012) (18)F-FDG PET-CT during chemo-radiotherapy in patients with non-small cell lung cancer: the early metabolic response correlates with the delivered radiation dose Radiation Oncology 7 106 [PubMed: 22781363]
- RTOG1106/ACRIN6697:Randomized phase II trial of individualized adaptive radiotherapy using during treatment FDG-PET/CT and modern technology in locally advanced non-small lung cancer (NSCLC). Available at: <https://clinicaltrials.gov/show/NCT01507428>. Accessed: May 17, 2015
- Rueckert D, Aljabar P, Heckemann RA, Hajnal JV and Hammers A 2006 Medical Image Computing and Computer-Assisted Intervention – MICCAI 2006: 9th International Conference, Copenhagen, Denmark, October 1–6, 2006. Proceedings, Part II, ed Larsen R, et al. (Berlin, Heidelberg: Springer Berlin Heidelberg) pp 702–9

- Seibert RM, Ramsey CR, Hines JW, Kupelian PA, Langen KM, Meeks SL and Scaperoth DD 2007 A model for predicting lung cancer response to therapy International journal of radiation oncology, biology, physics 67 601–9
- Shamonin D, Bron E, Lelieveldt B, Smits M, Klein S and Staring M 2014 Fast Parallel Image Registration on CPU and GPU for Diagnostic Classification of Alzheimer's Disease Frontiers in Neuroinformatics 7 1–15
- Sonke J-J and Belderbos J 2010 Adaptive Radiotherapy for Lung Cancer Seminars in Radiation Oncology 20 94–106 [PubMed: 20219547]
- Trani D, Yaromina A, Dubois L, Granzier M, Peeters SG, Biemans R, Nalbantov G, Lieuwes N, Reniers B, Troost EE, Verhaegen F and Lambin P 2015 Preclinical Assessment of Efficacy of Radiation Dose Painting Based on Intratumoral FDG-PET Uptake Clinical Cancer Research 21 5511–8 [PubMed: 26276892]
- van Elmpt W, Ollers M, Dingemans A, Lambin P and De Ruyscher D 2012 Response assessment using 18F-FDG PET early in the course of radiotherapy correlates with survival in advanced-stage non-small cell lung cancer The Journal of Nuclear Medicine 53 1514–20 [PubMed: 22879081]
- Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM and Weissfeld J 2012 Doubling times and CT screen-detected lung cancers in the Pittsburgh Lung Screening Study Am.J.Respir.Crit Care Med 185 85–9 [PubMed: 21997335]
- Zhang P, Yorke E, Hu YC, Mageras G, Rimner A and Deasy JO 2014 Predictive treatment management: incorporating a predictive tumor response model into robust prospective treatment planning for non-small cell lung cancer International journal of radiation oncology, biology, physics 88 446–52
- Zhong H and Chetty I 2014 A note on modeling of tumor regression for estimation of radiobiological parameters Medical Physics 41
- Zhong H and Chetty IJ 2017 Adaptive radiotherapy for NSCLC patients: utilizing the principle of energy conservation to evaluate dose mapping operations Physics in Medicine & Biology
- Zhong H, Kim J and Chetty IJ 2010 Analysis of deformable image registration accuracy using computational modeling Med.Phys 37 970–9 [PubMed: 20384233]
- Zhong H, Kim J, Gordon JJ, Brown SL, Movsas B and Chetty IJ 2015 World Congress on Medical Physics and Biomedical Engineering, June 7–12, 2015, Toronto, Canada, ed Jaffray AD (Cham: Springer International Publishing) pp 579–82
- Zhong H, Siddiqui S, Movsas B and Chetty I 2017 Evaluation of adaptive treatment planning for patients with non-small cell lung cancer Physics in Medicine & Biology 62 4346–60 [PubMed: 28072395]
- Zhong H and Siebers JV 2009 Monte Carlo dose mapping on deforming anatomy Phys.Med.Biol 54 5815–30 [PubMed: 19741278]

Figure 1:

A flowchart represents the steps to calculate SUV changes on the layers of mGTV_{union} using the four DIR algorithms. CT1, CT2, PET1, PET2 denote the rigidly registered, processed images. mPET1 represents the DVF-mapped PET1 image, and the mGTV_{PET1} is the DVF-mapped PET1-based GTV.

Figure 2:

The upper, left sub-figure illustrates the CT1/PET1 image with a bounding box extended around the tumor. The displacements of structures on the surface of the bounding box were derived from the B-Spline/Demons registrations. The upper, right sub-figure illustrates the CT2/PET2 image, where the tumor has experienced both shrinkage and shedding. The lower sub-figure shows the mPET1/mCT1 reconstructed by the hybrid FEM, where the bounding box and lung structures are deformed slightly towards the tumor as the tumor shrinks.

Figure 3:

a) The moving image (CT1) and b) the fixed image (CT2) for patient 4; c) the mapped CT1 using B-Spline algorithm, and d) the mapped CT1 using Demons algorithm, (e) and (f) the warped tumor volume after applying the hybrid-FEM algorithm to the B-Spline and Demons methods, respectively. The red circle shows the tumor region.

Figure 4:

a) original PET1, b) PET2, and mapped PET1 images using the four different DIR algorithms c) B-Spline, d) diffeomorphic Demons, e) the B-Spline + FEM, and f) the diffeomorphic Demons + FEM. g) Profiles of nSUVs generated along the green lines for the mapped PET1 images using the four different methods and PET2 (green line), and h) the response to treatment for the different registration methods.

Figure 5: $nSUV_{mean}$ changes between mPET1 and PET2 for a) patient 1, b) patient 2, c) patient 3, d) patient 4, e) patient 5 for the 4 DIR algorithms. f) The layers were generated from $mGTV_{union}$, starting from the center of the tumor (0) to the border of the tumor (N).

Figure 6:
(a-e) $nSUV_{mean}$ changes between PET1 and PET2 evaluated in the mapped GTVs by the 4 algorithms for the 5 patients, where the x-axis represents the layer number in each of these mapped GTVs; **(f)** the outermost layer of the mapped GTVs by the four algorithms for patient 4.

Table 1:

Tumor volume delineated on pre- and during- RT CT images for all patients. The fourth column represents the percentage of changes between the pre-RT and during-RT images.

CT volume [cm ³]	Pre-RT	During-RT	Percent change [%]
Patient 1	5.4	4.9	-9.2
Patient 2	62.3	39.7	-36.2
Patient 3	19.4	21.3	+9.7
Patient 4	103.9	51.8	-50.1
Patient 5	70.1	52.6	-24.9

Table 2:

Landmark errors for the B-Spline, Demons and hybrid FEM techniques for all the five patients. The landmark errors are represented by the difference of these landmarks positions (root mean square).

Displacement error (RMS)	Patient 1 (mean $\pm$ SD) [mm]	Patient 2 (mean $\pm$ SD) [mm]	Patient 3 (mean $\pm$ SD) [mm]	Patient 4 (mean $\pm$ SD) [mm]	Patient 5 (mean $\pm$ SD) [mm]	Average Displacement ($\pm$ Stdev) [mm]
Rigid	4.9 $\pm$ 3.7	5.9 $\pm$ 3.5	5.4 $\pm$ 2.1	5.5 $\pm$ 5.5	4.3 $\pm$ 3.1	5.2 $\pm$ 0.6
B-Spline	2.6 $\pm$ 1.4	3.7 $\pm$ 1.8	3.0 $\pm$ 2.5	4.1 $\pm$ 1.6	4.0 $\pm$ 2.1	3.5 $\pm$ 0.7
B-Spline+FEM	1.7 $\pm$ 1.2	2.1 $\pm$ 1.2	2.5 $\pm$ 2.5	1.8 $\pm$ 1.1	2.8 $\pm$ 1.2	2.1 $\pm$ 0.4
Demons	3.0 $\pm$ 3.0	2.1 $\pm$ 1.2	1.2 $\pm$ 0.5	0.7 $\pm$ 0.7	0.8 $\pm$ 0.2	1.6 $\pm$ 1.0
Demons+FEM	1.0 $\pm$ 0.2	2.2 $\pm$ 0.9	1.8 $\pm$ 1.2	2.2 $\pm$ 1.7	3.7 $\pm$ 0.6	2.1 $\pm$ 1.0

Table 3:

Original tumor volumes (orgVol) and mapped tumor volumes (mVol), measured on PET images for the five patients. The last column shows the average percent changes and standard deviations (Stdev) using the four methods.

Volume	Patient 1 [cm ³]	Patient 2 [cm ³]	Patient 3 [cm ³]	Patient 4 [cm ³]	Patient 5 [cm ³]	Average Percent change ± Stdev [cm ³]
orgVol	8.6	58.6	13.4	45.5	30.0	
mVol _{B-Spline}	5.1	57.3	14.4	41.0	26.6	14.3 (± 15.1)
mVol _{B-Spline+FEM}	7.2	60.2	13.4	49.4	32.3	7.0 (± 6.2)
mVol _{Demons}	9.1	48.7	18.8	39.7	25.9	17.9 (± 13.2)
mVol _{Demons+FEM}	8.6	59.9	14.4	49.0	33.0	5.5 (± 4.2)

Table 4:

Total lesion glycolysis values for original PET1 (orgPET1) and mapped PET1 (mPET1) were calculated using the 4 DIR algorithms for each patient. The last column shows the average TLG percent change and standard deviation of the percent changes over the five patients.

TLG ($\pm$ Stdev)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Average Percent change $\pm$ Stdev
orgPET1	4.5 (± 1.0)	235.0 (± 6.2)	39.1 (± 15.1)	123.4 (± 70.1)	140.2 (± 42.9)	
mPET1 (B-Spline)	2.0 (± 2.0)	220.0 (± 117.8)	39.3 (± 20.8)	96.1 (± 70.6)	117.3 (± 47.5)	20.2 (± 21.5)
mPET1 (B-Spline+ FEM)	3.3 (± 0.9)	222.2 (± 130.0)	36.3 (± 19.5)	119.6 (± 89.3)	139.0 (± 61.0)	8.7 (± 10.3)
mPET1 (Demons)	4.1 (± 1.2)	178.8 (± 105.8)	51.7 (± 27.5)	82.5 (± 69.0)	90.2 (± 53.8)	28.3 (± 11.0)
mPET1 (Demons+ FEM)	4.2 (± 1.3)	227.9 (± 125.1)	39.2 (± 20.9)	122.5 (± 87.0)	140.3 (± 6.2)	2.2 (± 2.8)