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Implementing Radiation Dose-Volume Liver Response in Biomechanical Deformable Image Registration

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Abstract

Purpose—Understanding anatomical and functional changes in the liver resulting from radiotherapy is fundamental to the improvement of normal tissue complication models needed to advance personalized medicine. The ability to link pre-treatment and post-treatment imaging is often compromised by significant dose-dependent volumetric changes within the liver that are currently not accounted for in deformable image registration (DIR) techniques. This study investigates using delivered dose, in combination with other patient factors, to biomechanically model longitudinal changes in liver anatomy for follow-up care and retreatment planning.

Methods—Population models describing the relationship between dose and hepatic volume response were produced using retrospective data from 33 patients treated with focal radiation therapy. A DIR technique was improved by implementing additional boundary conditions associated with the dose-volume response in series with a previously developed biomechanical DIR algorithm. Evaluation of this DIR technique was performed on computed tomography imaging from seven patients by comparing the model-predicted volumetric change within the liver to the observed change, tracking vessel bifurcations within the liver through the deformation process, then determining target registration error (TRE) between the predicted and identified post-treatment bifurcation points.

Results—Evaluation of the proposed DIR technique showed that all lobes were volumetric deformed to within the respective contour variability of each lobe. The average TRE achieved was 7.3 mm (2.8 mm LR and AP, 5.1 mm SI), with the SI component within the average limiting slice thickness (6.0 mm). This represented a significant improvement (Wilcoxon, $p < 0.01$) over the application of the previously published biomechanical DIR algorithm (10.9 mm).

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Conflict of Interest: None

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Conclusion—This study demonstrates the feasibility of implementing dose-driven volumetric response in deformable registration, enabling improved accuracy of modeling liver anatomy changes, which could allow for improved dose accumulation, particularly for patients who require additional liver radiotherapy.

I. Introduction

Liver cancer, including hepatocellular carcinoma (HCC) and intrahepatic biliary duct cancer, is the fifth most common cause of cancer related mortality in the United States with an estimated 27,170 cancer deaths in 2016 and has undergone a sustained increase in incidence over more than two decades [1, 2]. Additionally, the liver is also the dominant site of metastases from colorectal cancer (CRC) [1]. At the time of CRC diagnosis, 20% of patients will present with synchronous liver metastases, and an additional 35%–50% of patients diagnosed with CRC will develop liver metastases as the most prevalent mode of failure within 5 years of initial treatment [3, 4].

Advancements in imaging-based predictions of liver function have demonstrated the ability to analyze regional functional response due to radiation [5–7]. However, assessment and analysis of localized changes in liver function can be hindered by the inability to spatially correlate the subvolumes of tissue within the liver [5, 6]. In addition, significant non-uniform changes in liver volume can compromise the correlation of the dose delivered with the longitudinal changes in the liver function observed in functional imaging. Accurate correlation of functional imaging with delivered dose could lead to modifications of currently used liver normal tissue complication probability models to better account for the likelihood of spatially localized changes in liver function [5, 6].

Furthermore, stereotactic body radiation therapy (SBRT) is becoming an increasingly favored treatment method for patients with unresectable oligometastases in the liver [8–16]. Development of additional liver metastases can require multiple courses of SBRT, presenting a need to accurately map previously delivered dose to the subsequent treatment plan(s) for safe treatment planning. Although current dose mapping techniques can accurately account for respiratory and other anatomical motion between treatment courses, no current technique accounts for potentially significant hypertrophy/atrophy volume changes observed following radiation therapy (RT). [17]

This complex dose-volume response of normal hepatic tissue has been observed in many studies [12–16]. Although precise causation remains unknown, it is hypothesized that this atrophy-hypertrophy radiation response is similar to the response commonly noted following surgical resection and other forms of liver treatment or injury [18, 19]. Despite these observations, currently available deformable image registration (DIR) techniques often cannot accurately account for large volumetric changes with localized mass loss or gain [20–22]. Previously, this has been demonstrated on head and neck cases with weight loss or disease progression and prostate cases with large deviations in bladder filling [21–23]. Studies have also shown that intensity-based DIR algorithms can fail in the presence of homogenous contrast (often observed in liver computed tomography (CT) images) and large deformations. [23–25]. Furthermore, many intensity-based DIR algorithms include

regularization terms to ensure that the deformation field is relatively smooth across an image. These regularization methods function to decrease roughness and irregularities within a deformation field, but may consequently restrict a deformation from accurately modeling localized volume changes [26]. Although biomechanical DIR algorithms often provide more physically plausible deformation fields in the presence of large volume changes, deformation is primarily driven by external organ boundaries (generated from contours) rather than intra-organ anatomy. In the application of liver registration, this can result in inadequate registration of liver subvolumes and intrahepatic anatomy even when the external boundary of the liver appears to be accurately registered.

In order to improve the correlation of subvolumes within the liver, this study proposes a modified biomechanical modeling method for hepatic tissue including independent dose-volume response deformation forces in addition to a previously developed spatially-constrained biomechanical DIR algorithm. Briefly, a relationship between dose and volume response, mimicking the thermal expansion relationship for non-biological materials, was developed for a population of patients using a subset of the total population. A two-step DIR algorithm was developed to include this dose-volume response in addition to spatial constraints. Using the patients excluded from the development of the population dose-volume response model, the newly developed algorithm including dose-volume response in addition to existing spatial constraints (Morpheus with Dose Boundary Conditions) was evaluated and compared to a rigid registration method and the previously developed spatially constrained DIR algorithm (Morpheus).

In summary, the purpose of this study is to improve longitudinal liver registration by developing a population-based dose-volume response model for normal liver tissue and implementing this dose-volume response as additional boundary conditions in series with previously developed biomechanical DIR algorithm. Volume and point based metrics were used to evaluate the performance of the newly developed DIR technique.

II. Materials and Methods

II. A. Data collection

Forty patients previously treated on an Institutional Review Board approved phase II trial of dose-escalated liver RT from 1998 to 2005, were retrospectively investigated [27]. In this clinical trial, previously described in detail [27], patients were treated with conformal high-dose RT (median dose was 60.75 Gy) in 1.5 Gy fractions twice daily (bid). Criteria for patient selection in this DIR development and evaluation study included having a single unresectable intrahepatic primary malignancy, HCC or biliary, or liver metastasis from CRC with a pre-RT planning CT and follow-up CT scans at least 49 days post-treatment. Potential effects of respiratory motion were mitigated by use of active breathing control and breath-hold CT scans when possible.

Liver images were previously contoured using stable anatomical landmarks to delineate the left lateral and medial segments, right anterior and posterior segments, and caudate lobe [28]. The gross tumor volume (GTV) was previously defined for clinical treatment planning purposes. The pre and post-RT volumes as well as mean radiation doses delivered to each

contoured region were obtained from the treatment planning software (XXXX, XXXX). Of the 40 patients selected, seven biliary and CRC patients were randomly chosen for accuracy evaluation while the remaining 33 were used to create a population model of normal tissue radiation response. HCC patients were not used for accuracy evaluation since the limited HCC patient cohort size did not allow enough data for both generation and evaluation the HCC-specific response model. For the seven patients used in accuracy evaluation, a radiation oncologist (XXXX) selected vessel bifurcations within the liver on both the pre and post-treatment CT scans to allow for calculation of the target registration error (TRE) to evaluate the accuracy of the model.

II. B. Liver Response Model

To generate explicit dose-response deformation forces for hepatic biomechanical modeling, termed Dose Boundary Conditions (Dose BCs) within the deformation process, a population model was created to relate liver volume response to dose in terms of a linear expansion coefficient (α_L). This methodology was chosen so that the volumetric response could be directly modeled using existing thermal expansion tools within commercial finite element modeling (FEM) software packages. By substituting dose for temperature change in a standard isotropic thermal linear expansion equation, we can utilize standard FEM thermal boundary conditions to achieve a direct relationship and mechanical-modeling method for volume change as a function of dose. To further clarify, this method is used to model the long-term biological-volumetric response (tissue atrophy/hypertrophy) and is not using dose as a surrogate for short-term temperature change associated with radiation dose deposition. For the 33 patients used in the population model, the linear expansion coefficient was computed for each of the previously defined segments of the liver using the equation (modified isotropic thermal linear expansion):

$$\alpha_L = \frac{V_f - V_i}{3V_i D} \quad (1)$$

where V_f is the component's final volume, as measured on the post-treatment imaging study, V_i is the component's initial volume, as measured on the pre-treatment imaging study, and D is the mean absorbed dose of the component (dose replaces temperature change in the standard linear expansion equation). A log-logistic sigmoid function was selected to represent the data relationship between α_L and D since it captures the mean structure of the data well and is similar to formulas used in normal tissue complication probability and tumor control probability models. Using a least squares approach, the sigmoid function was fit to this data to get α_L as a function of D . For statistical comparison purposes, a corresponding linear fit was also generated.

Stratifications of the response model were investigated based on the hypothesis, formulated from previous studies, that dose response is correlated to tumor type (as a surrogate for the presence of underlying liver disease, e.g. cirrhosis and hepatitis) and spatial location of the tumor [19, 29–32]. To maintain statistical confidence within the stratifications, stratifications were only performed in groups that maintained at least 30 samples. The resulting seven stratifications included: all patients (HCC/Biliary/CRC), HCC, Biliary, CRC, Biliary/CRC,

right lobe Biliary/CRC, left lobe Biliary/CRC. Significance of these stratifications was determined using a statistical comparison of the stratified models to the all-inclusive response model based on Spearman's rank correlation coefficients, an assessment of how well the relationship of dose and linear expansion coefficient can be described using a monotonic function, and non-linear regression analysis from the sigmoid fit compared to a linear regression.

II. C. Liver Deformation

This study used Morfeus, an in-house developed biomechanical model-based deformable image algorithm, previously described in detail [33]. Briefly, two finite element models (FEM), representing the pre and post-RT livers, are generated using the CT contours of the complete livers. The pre-RT model is then deformed to the post-RT model via guided surface projections (HyperMorph, Altair Engineering, Troy MI). This biomechanical modeling technique incorporates linear-elastic material properties of liver tissue and GTV, and allows for the incorporation of additional boundary conditions within the finite element analysis (FEA).

In this study, pre-RT liver FEMs were deformed in a two-step process, shown in Figure 1. In Step 1, Dose BCs are applied using thermal expansion to describe the volumetric response of the liver to external beam RT (EBRT). In Step 2, surface constraints are applied, as previously published, to resolve anatomical deformation due to patient pose and physiological state [33].

In Step 1, Dose BCs were generated by grouping tetrahedral elements within the FEM into 1 Gy dose bins by calculating the mean dose received by that tetrahedron from the 3D dose grid produced from the commercial treatment planning software (Eclipse, v11, Varian Medical Systems). Each 1 Gy dose region was then assigned a single linear expansion coefficient calculated from a population-based liver response model. These coefficients were loaded into the FEM pre-processor as linear thermal expansion coefficients, and the dose delivered to the liver was applied as the boundary condition to model the atrophy and hypertrophy observed in the liver. Since the population dose-response model is not representative of GTV response, which varies significantly between patients due to many factors, tetrahedral elements representing the GTV were given a single patient-specific thermal expansion coefficient based on measured volumetric tumor response from the pre-RT to post-RT CT. Therefore, while the assignment of linear expansion coefficients to normal liver tissue is non-uniform and based on dose, the assignment of linear expansion coefficients to the GTV is uniform (representing an assumption of uniform volumetric response of the tumor).

Surface constraints, for Step 2 of the deformation process, were defined from guided surface projections generated after applying the FEA results from Step 1 (Dose BCs) to the FEM. The deformation results of this second FEA were applied in addition to the dose constraint analysis to spatially align the liver to the anatomical and physiological position of the liver in the follow-up image. Therefore, the final deformation vector field for complete DIR process is a summation of the tetrahedral displacement results of the Step 1 and Step 2 FEAs.

II. D. Accuracy Analysis and Comparison

Both volumetric response comparison and TRE were used to evaluate the accuracy of the model for the seven patients not included in the generation of the dose-response model. First, following the initial deformation from application of only the Dose BCs (Step 1), the volume of each deformed liver segment was compared to its actual post-treatment volume calculated from the contoured post-treatment imaging study. This comparison served as an analysis tool to determine whether the expansion and contraction generated from the population model accurately predicted the known volume change of each segment. Individual segment volume change was compared to previously reported intra-observer contouring reproducibility study for a similar liver segmentation methodology which gave the following 95% confidence intervals (CIs): left lateral segment 45 cc, left medial segment 56 cc, right lobe (superior and posterior) 84 cc, and caudate lobe 10 cc [34]. The magnitude and relative accuracy of the volumetric modeling was determined across three deformation methods: Morfeus, only Dose BCs (Step 1), and Morfeus with Dose BCs. Statistical significance of the volumetric modeling techniques was determined using a Wilcoxon signed-rank test.

TRE was calculated using the selected liver bifurcations for three registration methods: rigid, Morfeus, and Morfeus with Dose BCs. The bifurcations for the seven patients selected for accuracy analysis were selected a second time by the same observer on the follow-up image in order to quantify intra-observer variability. Statistical significance for the comparison of TRE between registration methods was determined using a Wilcoxon signed-rank test between individual corresponding point pairs.

III. Results

Characteristics for the seven patients excluded from the population response modeling and selected for accuracy analysis are shown in Table 1. The tumor type, location, and population response model used are provided. Due to varying Post-RT CT slice thickness and number of selected bifurcation points, the TRE analysis was performed on an individual patient level in addition to a population average.

III. A. Liver Response Model and Stratifications

Table 2 gives statistical and curve fitting analysis for the proposed stratifications. All stratifications resulted in significant Spearman correlation coefficients suggesting good negative correlation between linear expansion coefficient and dose. Stratifications of HCC, CRC, Right Lobe Biliary/CRC, and Left Lobe Biliary/CRC provided increased correlation compared to the all-inclusive model. In all stratifications, the log-logistic sigmoid fit gave an improved coefficient of determination when compared to a linear fit. Figure 2 shows the log-logistic sigmoid best-fit curves for each of the proposed stratifications. The seven patient accuracy analysis utilized the Biliary/CRC models. As noted in Table 1, for Patients 1 through 5, the location-specific stratification models were used since the tumors were confined to a single lobe, and for Patients 6 and 7, the general Biliary/CRC model was used since the tumors extended over both the right and left lobes. Location-specific models were

used instead of tumor-specific models since the average Spearman correlation coefficients were greater.

III. B. Liver Deformation Accuracy Analysis and Comparison

Volume Analysis and Comparison—Of the 29 segments modeled, 16 segments underwent volume changes exceeding the 95% CI for manual contouring of each segment location. For these 16 segments, the application of only Dose BCs resulted in 81% (13/16) of the segments modeled within the 95% CIs, whereas Morfeus (e.g. surface boundary conditions only) resulted in 63% (10/16). Application of the complete deformation process, Morfeus with Dose BCs, resulted in all (16/16) of the segments modeled to within the 95% CIs. This demonstrates that the proposed DIR technique performs volumetric modeling to within the variability of manual contouring.

Across all segments, the application of only Dose BCs resulted in final segment volumes with an average signed error of 2.3% (SD = 17.4%) and average absolute error of 14.5% (SD = 9.6%). The average signed and absolute volumetric errors were 20.0% and 32.3%, respectively, for rigid registration, 9.8% and 16% for Morfeus, and 0.5% and 9.5% for Morfeus with Dose BCs. The application of only Dose BCs showed significant improvement over rigid registration and regular Morfeus (Wilcoxon, $p < 0.01$ and $p = 0.03$ respectively). The volumetric difference between application of only the Dose BCs and Morfeus with Dose BCs was not significant (Wilcoxon, $p = 0.50$), demonstrating that the majority of the volumetric change is occurring during the application of the Dose BCs, as intended in Step 1 of the deformation process. Tumor response, using a uniform linear expansion coefficient calculated for each patient's specific tumor response, was modeled to an average absolute error of 7.3% (6 cc, SD = 9.3%) using the Dose BCs.

Target Registration Analysis and Comparison—Average intra-observer variability for bifurcation selection on this seven patient data set, which is a limit for achievable TRE, was found to be LR: 0.9 ± 0.2 mm, AP: 0.9 ± 0.3 mm, and SI: 1.0 ± 1.0 mm, giving a total vector uncertainty of 2.1 ± 1.1 mm. Additionally, since a majority of follow-up scans had relatively large slice thicknesses (greater than 3 mm), precise localization of bifurcation points was limited axially and in-plane due to partial volume averaging affects. Figure 3 shows the average TRE vector for individual patients across the three registration methods: rigid, Morfeus, and Morfeus with Dose BCs. For all patients, the TRE improved with implementation of the Dose BCs.

Figure 4 shows the overall mean TREs for the three registration methods across all directions in addition to the overall TRE vector. In each direction, TREs were improved using Morfeus with Dose BCs, resulting in overall mean TREs of LR: 2.8 ± 0.4 mm, AP: 2.8 ± 1.0 mm, and SI: 5.1 ± 2.4 mm, and giving an overall TRE vector of 7.3 ± 1.3 mm. This represents a significant 44% and 30% improvement in the overall TRE vector when using Morfeus with Dose BCs as compared to rigid registration (Wilcoxon, $p < 0.01$) and Morfeus (Wilcoxon, $p < 0.01$), respectively.

IV. Discussion and conclusion

A biomechanical registration method has been proposed to more accurately model the complex liver deformations resulting from EBRT. The proposed DIR algorithm includes a newly developed dose-dependent volume response utilizing population-based normal tissue response models and modified FEA thermal expansion modeling to represent dose-based volume changes. The dose-volume response is applied in series with a previously developed spatial alignment biomechanical registration algorithm. This modified two-step deformation process has been evaluated for seven patients who were treated on the same treatment protocol as the patients used to generate the population dose-volume response model. In the future, this DIR technique could be applied to differing patient cohorts, such as SBRT patients, by modifying or regenerating the dose-volume response models presented in this study.

Generation of the population dose-dependent volume response model showed a significant negative correlation between planned dose and volumetric response of individual liver lobes. Of the six proposed population stratifications, four stratifications demonstrated improved negative correlation when compared to the all-inclusive population model. Additionally, four of the six stratifications demonstrated improved log-logistic curved fitting metrics when compared to the all-inclusive model. When a stratification did not improve these metrics, the results were similar to the baseline model. Future work involving new and refined stratifications, including biological factors beyond tumor type and location, will require a larger sample population.

The proposed registration method, Morfeus with Dose BCs, demonstrated significant improvements in both volumetric modeling and TRE. Volumetric analysis of individual lobes showed that this deformation method successfully modeled all lobes within the respective contour variability of each lobe. The average TRE achieved with the proposed method was 7.3 mm (2.8 mm LR and AP, 5.1 mm SD), representing a significant 30% improvement over the previously published biomechanical registration algorithm (Morfeus).

Remaining error in the overall TRE vector is largely due to the residual error in the SI direction, which should be taken in the context of relatively large slice thicknesses on post-treatment scans, up to 10 mm (shown in Table 1). This error measurement could be improved when applying this registration method to scans with improved slice thickness, in part because the reproducibility of manually selecting bifurcation points is dependent on slice thickness. Additionally, the modeling of the complex deformations observed in the liver might be improved by using corresponding vessel positions on the two CT scans as additional boundary conditions in the biomechanical model, as previously demonstrated in the lung [35]. However, this would rely on high-quality CT image contrast enabling visualization of vessels and the assumption of vessel preservation, which may not be a good assumption in the presence of large tumor response or cases of tumor induced thrombosis.

In this study, the development and evaluation of a population-based normal liver tissue dose-response model and application of the dose-volume response within a biomechanical DIR algorithm is reported. The use of the proposed liver registration algorithm is feasible and

may aid in future studies investigating improvement in the accuracy of biomechanical deformable registration algorithms. This work has the potential for clinical impact in improving the correlation of functional imaging with delivered dose and enabling accurate longitudinal mapping of previously delivered doses to planning images for subsequent treatments. Furthermore, the methodology of the proposed DIR algorithm could be used to improve registration in other treatment locations in which structures undergo dramatic volume changes as a result of radiation, such as the parotid gland in head and neck RT.

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Deformable image registration (DIR) of the liver after radiotherapy is challenging due to the complex radiation dose-dependent volume response of normal hepatic tissue. A modified biomechanical modeling method for hepatic tissue including independent dose-driven deformation forces was developed and implemented on a series of patients, then compared with a previously developed biomechanical DIR algorithm. This proposed DIR technique resulted in improved target registration and deformed segment volume accuracy.

Figure 1. Flow Chart the of Proposed Registration Method

Flow chart of the proposed biomechanical deformable image registration process with the inclusion of dose-dependent volumetric response. We first create a biomechanical liver model using the planning computed tomography (CT) image. Using the linear expansion dose-volume population model and the patient's radiation therapy (RT) dose distribution, we assign each tetrahedral element in the model with a linear expansion coefficient based on the mean dose to each element (shown prior to Step 1). We then preform a finite element analysis (FEA) run, Step 1, to account for dose volume changes (result shown after Step 1). Afterwards, we apply Step 2, another FEA run, using surface correlation boundary conditions to spatial align the Step 1 deformed liver with the liver contour on the follow up CT (result shown after Step 2).

Figure 2. Log-logistic Sigmoid Function Fits for each Stratification

Log-logistic sigmoid function fits for each of the proposed patient population stratifications. Please see Table 2 for more information on each stratification and statistical curve fitting results.

Figure 3. Mean Patient TRE for each Registration Method

Boxplot of the mean patient Target Registration Error (TRE) for each of the three registration approaches: Rigid, Morfeus, and Morfeus with Dose Boundary Conditions (Dose BCs). The newly developed method, Morfeus with Dose BCs, showed an improvement in overall vector TRE for each of the seven patients when compared to rigid and standard Morfeus registrations.

Figure 4. Mean Overall TRE for each Registration Method

Boxplot of the mean overall Target Registration Error (TRE) for each of the three registration methods: Rigid, Morfeus, and Morfeus with Dose Boundary Conditions (Dose BCs). The newly developed method, Morfeus with Dose BCs, improves in TRE for each direction and the overall vector when compared to rigid and standard Morfeus registrations.

Characteristics of the seven patients used for evaluation of the population dose-volume response models and proposed deformable image registration method.

Table 1

Patient	Tumor Type	Tumor Location (Lobe)	Population Response Model Used	CT Slice Thickness [mm]		# Bifurcation Points
				Pre-Tx	Post-Tx	
1	Biliary	Left	Left Lobe (Biliary/CRC)	3	2	16
2	CRC	Left	Left Lobe (Biliary/CRC)	3	5	10
3	CRC	Left	Left Lobe (Biliary/CRC)	3	7	14
4	Biliary	Left	Left Lobe (Biliary/CRC)	3	5	4
5	CRC	Right	Right Lobe (Biliary/CRC)	3	7	10
6	CRC	Left and Right	Biliary/CRC	3	10	6
7	Biliary	Left and Right	Biliary/CRC	3	5	7

Table 2
Correlation and curve fitting results for the proposed dose-volume response population stratifications.

Stratification	Sample Size	Spearman Correlation		Coefficient of Determination, r^2		
		ρ	[95% CI]	p	Linear-Fit	Sigmoid-Fit
All	117	−0.60	[−0.70, −0.47]	p < 0.01	0.37	0.45
HCC	32	−0.67	[−0.83, −0.42]	p < 0.01	0.55	0.64
Biliary	39	−0.57	[−0.75, −0.31]	p < 0.01	0.34	0.58
CRC	46	−0.66	[−0.80, −0.46]	p < 0.01	0.39	0.51
Biliary/CRC	85	−0.59	[−0.71, −0.43]	p < 0.01	0.33	0.43
Right Lobe (Biliary/CRC)	30	−0.64	[−0.81, −0.36]	p < 0.01	0.37	0.47
Left Lobe (Biliary/CRC)	55	−0.67	[−0.79, −0.49]	p < 0.01	0.33	0.41